(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199861327 B2
(10) Patent No. 746663

(54) Title
Terbenzimidazoles useful for medical therapy (topoisomerase inhibitors)

(51)[6] International Patent Classification(s)
C07D 235/18 C07D 401/14
A61K 031/415

(21) Application No: 199861327 (22) Application Date: 1998 .01 .21

(87) WIPO No: WO98/31673

(30) Priority Data

(31) Number	(32) Date	(33) Country
08/786629	1997 .01 .21	US

(43) Publication Date : 1998 .08 .07
(43) Publication Journal Date : 1998 .10 .08
(44) Accepted Journal Date : 2002 .05 .02

(71) Applicant(s)
Rutgers, The State University of New Jersey

(72) Inventor(s)
Edmond J. Lavoie; Leroy Fong Liu; Qun Sun

(74) Agent/Attorney
WRAY and ASSOCIATES,PO Box 6292,Hay Street,EAST PERTH WA 6892

CORRECTED VERSION*

61327/98

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONA pages 1/8-8/8, drawings, replaced by new pages 1/9-9/9; due to late transmittal by the receiving Office PERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 235/18, 401/14, A61K 31/415

A1

(11) International Publication Number: WO 98/31673

(43) International Publication Date: 23 July 1998 (23.07.98)

(21) International Application Number: PCT/US98/01005

(22) International Filing Date: 21 January 1998 (21.01.98)

(30) Priority Data:
08/786,629 21 January 1997 (21.01.97) US

(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application
US 08/786,629 (CIP)
Filed on 21 January 1997 (21.01.97)

(71) Applicant *(for all designated States except US)*: RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY [US/US]; Old Queens Building, Somerset and George Streets, New Brunswick, NJ 08903 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: LAVOIE, Edmond, J. [US/US]; 3 Guilford Court, Princeton Junction, NJ 08550 (US). LIU, Leroy, Fong [US/US]; 5 Fairacres Drive, Bridgewater, NJ 08807 (US). ~~QUN, Sun~~ [CN/CN]; Apartment 22, ReMian Road 201 Xiao Shan, Zhejiang 311200 (CN). Sun, Qun

(74) Agent: HOLLOWAY, Sheryl, S.; Schwegman, Lundberg, Woessner & Kluth, P.O. Box 2938, Minneapolis, MN 55402 (US).

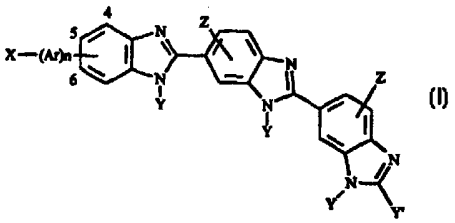
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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

(54) Title: TERBENZIMIDAZOLES USEFUL FOR MEDICAL THERAPY (TOPOISOMERASE INHIBITORS)

(57) Abstract

The invention provides a topoisomerase poision of formula (I) wherein Ar is aryl or a nitrogen–, sulfur– or oxygen–containing heteroaromatic group; X is H, CN, CHO, OH, acetyl, CF_3, $O(C_1–C_4)$alkyl, NO_2, NH_2, halogen or halo–$(C_1–C_4)$alkyl; each Y is individually H, $(C_1–C_4)$alkyl or aralkyl; Y' is phenyl, or methoxyphenyl; n is 0 or 1; and each Z is individually H, $(C_1–C_4)$alkyl, halogen or halo$(C_1–C_4)$alkyl; or a pharmaceutical acceptable salt thereof; for use in medical therapy (e.g. the treatment of fungal infection or cancer). The invention also provides novel compounds of formula (I); pharmaceutical compositions comprising compounds of formula (I); and therapeutic methods, comprising treating fungal infection or treating cancer by administering at least one compound of formula (I).



(I)

TERBENZIMIDAZOLES USEFUL FOR MEDICAL THERAPY (TOPOISOMERASE INHIBITORS)

Background of the Invention

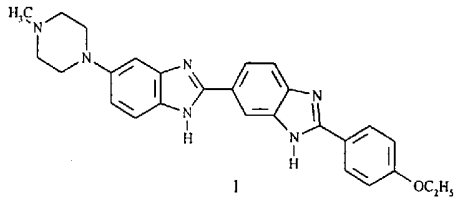
This invention was made with the support of the United States National Institutes of Health Grant CA 39962. The U.S. Government has certain rights in the invention.

DNA topoisomerases are nuclear enzymes that control and modify the topological states of DNA by catalyzing the concerted breaking and rejoining of DNA strands. See, for example, D'Arpa et al., Biochim. Biophys. Acta, 989, 163 (1989). Topoisomerase II enzymes alter the topological state of DNA by means of a double strand break in the DNA. By interfering with the breakage/reunion reaction of DNA topoisomerases, a number of agents have been shown to convert these enzymes into net DNA-breaking enzymes, resulting in efficient cell killing. See L. F. Liu, in Topoisomerases: topoisomerase targeting drugs, Adv. in Pharmacol., 29B (1994); L. K. Wang et al., Chem. Res. Toxicol., 6, 813 (1993). Thus, mammalian topoisomerase II represents an effective pharmacological target for the development of cancer chemotherapeutics. (A. Y. Chen et al., Annu. Rev. Pharmacol. Toxicol., 34, 191 (1994)). Among the clinical agents in use which are recognized as topoisomerase II inhibitors are etoposide (VP-16), teniposide (VM-26), mitoxantrone, *m*-AMSA, adriamycin (doxorubicin), ellipticine and daunomycin.

In comparison to topoisomerase II inhibitors, there are relatively few known topoisomerase I inhibitors. Camptothecin represents the most extensively studied mammalian topoisomerase I inhibitor. See R. C. Gallo et al., J. Natl. Cancer Inst., 46, 789 (1971) and B. C. Giovanella et al., Cancer Res., 51, 3052 (1991). The interference of camptothecin with the breakage/reunion reaction of topoisomerase I, results in accumulation of a covalent intermediate, in which topoisomerase I is reversibly trapped in a cleaved state, termed the cleavable complex (Y.-H. Hsiang et al., J. Biol. Chem., 260, 14873 (1985); S. E. Porter et al., Nucl. Acids Res., 17, 8521 (1989); C. Jaxel et al., J. Biol. Chem.,

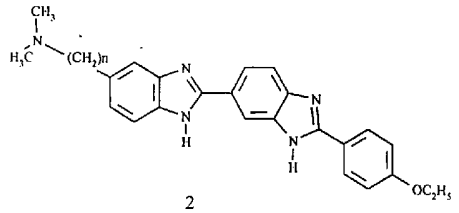
266, 20418 (1991)). The broad spectrum of potent antineoplastic activity observed for camptothecin has prompted further efforts to identify other agents which can effectively poison mammalian topoisomerase I.

It has recently been demonstrated that Hoechst 33342 (1), 2′-(4-ethoxyphenyl)-5-(4-methyl-1-piperazinyl)-2,5′-bi-1H-benzimidazole, is an inhibitor of topoisomerase I.



I

This agent, which binds to the minor groove of DNA, traps the reversible cleavable complex derived from DNA and topoisomerase I and produces a limited number of highly specific single-strand DNA breaks. For example, see A.Y. Chen et al., Cancer Res., 53, 1332 (1993) and A. Chen et al., PNAS, 90, 8131 (1993). A limitation of Hoechst 33342 as an anticancer agent is the previously reported observation that it is not effective against tumor cell lines which overexpress MDR1. While KB 3-1 cells are known to be quite sensitive to Hoechst 33342, with an IC_{50} of approximately 9 nM, this compound is approximately 130-fold less cytotoxic to KB V-1 cells, which are known to overexpress MDR1. Recently, several analogs of this bisbenzimidazole have been synthesized, to further investigate the structure activity relationships associated with their potency as mammalian topoisomerase I inhibitors and the related cytotoxicity. For example, Q. Sun et al., Biorg. and Med. Chem. Lett., 4, 2871 (1994) disclosed the preparation of bis-benzimidazoles of formula (2):



where n is 0, 1, 2, or 3. However, these compounds were found to be about one order of magnitude less cytotoxic than Hoechst 33342.

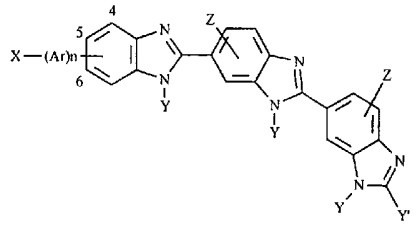
More recently, Q. Sun et al., in Abstract 2688, Scientific Proceedings–86th Annual Meeting of the AACR (Toronto, CA, March 18-22, 1995) disclosed that a trisbenzimidazole derivative, 5-(2-pyridyl)-2-[2′-benzimidazol-5″-yl benzimidazol-5′-yl]benzimidazole has similar potency as an inhibitor of human topoisomerase I as Hoechst 33342.

Mycotic infections have become increasingly important in the last two decades, causing high mortality among immunocompromised patients, such as transplant recipients and cancer and AIDS patients. The expanding patient population and some existing problems in current antifungal chemotherapy have created a demand for more effective and safe antifungal agents for the treatment of this increasingly important class of opportunistic infections. Based on studies in *Saccharomyces cerevisiae* and *Candida albicans*, nuclear fungal topoisomerase I shows promise as a molecular target for antifungal agents (see J. M. Fostel et al., Antimicrob. Agents Chemother., 39, 586 (1995); J. M. Fostel et al., Antimicrob. Agents Chemother., 36, 2131 (1992)). Studies in *S. cerevisiae* have established topoisomerase I to be a fungicidal target for camptothecin (J. Nitiss et al., PNAS USA, 85, 7501 (1988)). Studies in *C. albicans* have demonstrated differences in sensitivity of the human and *Candida* topoisomerase I to the aminocatechol A-3253 (J. M. Fostel (1995) cited above).

Aspergillus fumigatus and *A. niger* are two important life-threatening systemic human pathogens. There is an urgent need for more effective antifungal agents for the treatment of patients with these opportunistic infections.

Summary of the Invention

The invention provides a therapeutic method for the treatment of a fungal infection comprising administering to a mammal afflicted with a fungal infection, particularly a systemic fungal infection, an effective antifungal amount of a compound of general formula (I):



(I)

wherein Ar is aryl or a nitrogen-, sulfur- or oxygen-containing heteroaromatic group; X is H, CN, CHO, OH, acetyl, CF_3, $O(C_1-C_4)$alkyl, NO_2, NH_2, halogen or halo(C_1-C_4)alkyl; each Y is individually H, (C_1-C_4)alkyl or aralkyl; Y′ is H, (C_1-C_4) alkyl, phenyl or methoxyphenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof.

Preferably, Ar is a (C_6-C_{12})aryl, such as phenyl, or a 5- to 12-membered heteroaryl group, most preferably a 5-6 membered heteroaryl group, comprising 1-3 N, S or non-peroxide O, wherein each N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl. Ar can occupy the 4, 5, 6 or 7 position of the benzo ring, as shown, preferably the 5 position, and X can occupy any available position on Ar. Positions 4, 7 and 5, 6 are equivalent when Y is H. According to one embodiment, Ar is phenyl, and X is Cl or Br, preferably occupying the *para* position. As drawn, Z may occupy any position on the benzo moiety. Z is preferably H, halogen, CH_3 or CF_3.

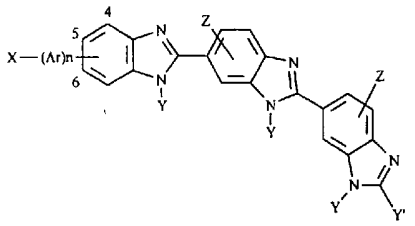
According to another embodiment, n is 0, and X is halogen, for example, F, Br, Cl or I, preferably Cl or Br, and preferably occupies the 5-

position of the benzo moiety. Y is preferably H or CH_3. Y' is preferably H, CH_3, ethyl or 4-methoxyphenyl.

While a number of known inhibitors of human topoisomerase I were found to be ineffective against a fungal topoisomerase I, including nitidine and coralyne, the compounds of formula (I) are inhibitors of fungal topoisomerase I, as demonstrated by their ability to promote DNA cleavage in the presence of *Aspergillus* topoisomerase I. As disclosed hereinbelow, it was unexpectedly found that the *Aspergillus* enzyme is completely resistant to some of the most potent human topoisomerase I poisons such as nitidine and coralyne, and to the less potent mono-benzimidazole human topoisomerase I poisons. Studies using yeast expressing human or yeast topoisomerase I also suggest similar resistance of the yeast topoisomerase I to these compounds. It appears that the fungal enzymes are substantially different in their drug sensitivity than their human counterpart.

Furthermore, compounds of formula (I) also are cytotoxic to mammalian tumor cells, including camptothecin-sensitive and camptothecin-resistant tumor cells and tumor cell lines exhibiting multi-drug resistance due to expression of the P-glycoprotein. Accordingly, the invention provides a therapeutic method for the treatment of cancer comprising administering to a mammal (i.e. a human), an effective anticancer amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The invention also provides novel compounds of formula (I). For example, the invention provides a compound of formula (I):



(I)

wherein Ar is (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CN, CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y′ is phenyl or methoxyphenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof. A peferred compound is a compound of formula (I) wherein Y' is methoxyphenyl. Another preferred compound is a compound of formula (I) wherein n is 1. Another preferred compound is a compound of formula (I) wherein X is CN, CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl, and n is 0. Yet another preferred compound is a compound of formula (I) wherein at least one Z is halogen or halo(C_1-C_4)alkyl, and n is 0.

The invention also provides pharmaceutical compositions adapted for both systemic and topical administration, comprising one or more compounds of formula (I), or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable vehicle.

The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof for use in medical therapy (i.e. treating fungal infections or cancer), as well as the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating fungal infections or for treating cancer.

Brief Description of the Drawings

Figure 1 is a schematic depiction of the synthesis of compounds 10-16.

Figure 2 is a schematic depiction of the preparation of intermediates 4-8 used to prepare compounds of the invention.

Figure 3 is a schematic depiction of the preparation of intermediate 9.

Figure 4 is a schematic depiction of the synthesis of compounds JSKIV-68, -37 and -47.

Figure 5 is a schematic depiction of the preparation of intermediate JSKIV-44.

Figure 6 is a schematic depiction of the preparation of analogs modified on the central benzimidazole moiety.

Figure 7 is a schematic depiction of the preparation of analogs modified on the terminal benzimidazole moiety, wherein Z and Y′ are as defined above.

Detailed Description of the Invention

The aryl groups (Ar) useful in the present compounds comprise (C_6-C_{18})aryl, preferably (C_6-C_{14}) aryl, e.g., systems containing aromatic rings, which systems comprise a total of 6 to 12 carbon atoms. Thus, as used herein, the term "aryl" includes mono- or bis-(C_1-C_4)alkyl-substituted aryl, such as tolyl and xylyl; ar(C_1-C_4)alkyl, such as benzyl or phenethyl; and alkaralkyl. Preferably aryl is phenyl, benzyl or naphthyl.

Heteroaromatic rings include aromatic rings containing up to 3 ring heteroatoms such as N, S or non-peroxide O, and up to 12 ring atoms. Representative aromatic rings include thiophene, benzothiophene, naphthothiophene, trianthrene, furan, benzofuran, isobenzofuran, pyran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, pyridine, pyrazine, triazole, tetrazole, pyrazine, triazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, phenazine, isothiazole, phenothiazine, oxazole, isoxazole, furazan, phenoxazine and the like. Preferred heteroaromatic rings have a 5- or 6-membered

heteroaromatic ring which may or may not be fused to an aromatic ring such as a benzo ring, e.g., the preferred 2-, 3- or 4-pyridyl substituents.

The term "alkyl" includes straight-chain or branched alkyl, as well as cycloalkyl and (cycloalkyl)alkyl, e.g., methyl, ethyl, i-propyl, cyclopropyl or cyclopropylmethyl.

Methoxyphenyl includes 2-, 3-, or 4-methoxyphenyl.

Pharmaceutically acceptable salts include the acid addition salts of basic NH with organic or inorganic acids, e.g., hydrochloride, carbonate, sulfate, bicarbonate, acetate, phosphate, tartarate, citrate, malate, maleate, and propionate salts, and the like.

The preparation of representative substituted trisbenzimidazoles is outlined in Figure 1. With the exception of phenylenediamine which was commercially available, the appropriately substituted phenylenediamines were synthesized by catalytic hydrogenation of the respective *o*-nitroaniline derivatives. These phenylenediamines were then coupled with 5-formyl-2-(benzimidazo-5′-yl)benzimidazole, 9, by heating them together in nitrobenzene at 150°C to provide the various trisbenzimidazoles, 10-16, in yields ranging from 43-96%, employing the general methodologies of M. P. Singh et al., Chem. Res. Toxicol., 5, 597 (1992) and Y. Bathini et al., Synth Comm., 20, 955 (1990).

The requisite nitroanilines, as outlined in Figure 1, with the exception of 3 which was commercially available, were synthesized from 4-bromo-2-nitroaniline, 17. Compound 17 was prepared from *o*-nitroaniline in good yield, 94%, using 2,4,4,6-tetrabromo-2,5-cyclohexadienone as the bromination reagent. G. J. Fox et al., Org. Syn., 55, 20 (1973). While allyltributyltin and phenyltributyltin are commercially available, the pyridyltributyltin derivatives were prepared from tributyltin chloride and 2-, 3-, and 4-bromopyridine, respectively. See D. Peters et al., Heterocyclic Chem., 27, 2165 (1990). These tributyltin derivatives were then coupled with 4-bromo-2-nitroaniline using $PdCl_2(PPh_3)_2$ as the catalyst in DMF as outlined in Figure 2 to provide compounds 4, 5, 6, 7, and 8, respectively, in accord with the methodology of M. Iwao et al., Heterocycles, 36, 1483 (1993). This

methodology can generally be applied to prepare 3-, 4-, 5- or 6-aryl- and heteroaryl-substituted 2-nitroanilines from the corresponding bromonitroanilines.

The preparation of 5-formyl-2-(benzimidazo-5′-yl)benzimidazole, 9, was accomplished as outlined in Figure 3. Reduction of 5-benzimidazolecarboxylic acid to 5-hydroxymethylbenzimidazole was accomplished using $LiAlH_4$. Oxidation of the resulting crude benzylic alcohol with tetrapropylammonium perruthenate (TPAP) and N-methylmorpholine N-oxide provided in two steps the desired 5-formylbenzimidazole in 32% an overall yield. See, A. Cherif et al., J. Med. Chem., 35, 3208 (1992). Coupling of 5-formylbenzimidazole with 4-cyano-1,2-phenylenediamine provided 5-cyano-2-(benzimidazol-5′-yl)benzimidazole, 19, which, when treated with Ni-Al catalyst in the presence of aqueous formic acid, gave 5-formyl-2-(benzimidazol-5′-yl)benzimidazole, 9, in 65% yield. (J. R. Pipier et al., J. Med. Chem., 31, 2164 (1988)).

The compounds of the present invention can be formulated as pharmaceutical compositions and administered to a mammalian host, such as an immunosuppressed human patient afflicted with a systemic or local fungal infection, in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit

dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion use can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusable solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate

dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersion or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be administered in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels,

optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers. The liquid compositions can also be employed as eyedrops, mouth washes, douches, etc. Antibacterial presaturated wipes are disclosed by Anderson (U.S. Pat. No. 4,896,768).

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Other examples of useful dermatological compositions which can be used to deliver the compounds of formula (I) to the skin are disclosed in Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of the present invention can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models, to that of an equivalent dosage of camptothecin (see, for example, B. C. Giovanella et al., Cancer Res., 51, 3052 (1991)) or Hoechst 33342 (see, A. Y. Chen et al., Cancer Res., 53, 1332 (1993)). Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of formula (I) in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt%, preferably about 0.5-2.5 wt-%. Single dosages for injection, infusion or ingestion will generally vary between 50-1500 mg, and may be administered, i.e., 1-3 times daily, to yield levels of about 0.5 - 50 mg/kg, for adults.

The present terbenzimidazoles are particularly useful to treat systemic fungal infections, or "deep mycoses." Such infections include

coccidiomycosis, chromoblastomycosis, cryptococcosis, systemic moniliasis, histoplasmosis, aspergillosis, rhodotorulosis, sporotrichosis, paracoccidiodosis, phycomycosis, blastomycosis, and candidiasis. Susceptible fungi include *candida (monilia) albicans*, which is a member of the normal flora of the mucous membranes in the respiratory, gastrointestinal, and female genital tracts. In these and other locations it may gain dominance and be associated with pathologic conditions. Sometimes it produces systemic progressive disease in debilitated or immunosuppressed patients. Candida may produce blood stream infection, thrombophlebitis, endocarditis, or infection of the eyes and other organs when introduced intravenously (tubing, needles, hyperalimentation, narcotic addiction, etc.). Other yeasts (e.g., torulopsis glabrata) may be pathogenic under similar circumstances.

The present compounds can also be used against *cryptococcus neoformans* infections. The fungus is free-living in the soil and is found frequently in pigeon feces. In man, it can cause primary pulmonary infection that is occasionally followed by fatal meningitis.

Blastomyces (Ajellomyces) dermatitidis infections can also be inhibited. This fungus causes a chronic granulomatous disease, North American blastomycosis, which may be limited to the skin or lung or may be widely disseminated in the body. The present compounds can also be used against *Blastomyces brasiliensis*, an ascomycete which causes South and Central American blastomycosis (paracoccidioidal granuloma), or to treat infection with *H. capsulatum*, which usually occurs through the respiratory tract, and can lead to clinical pneumonia and protracted illness.

Infections due to *Coccidioideo immitis* can also be treated, which can cause an influenza-like illness, with fever, malaise, cough, aches, pains and sweats, and which can progress to a highly fatal form called "coccidiodal granuloma." The compounds are also effective against *Geotrichum candidum*, a yeast-like fungus which produces geotrichosis, an infection of bronchi, lungs, and mucous membranes, and *Sporothrix (Sporotrichum) schenckii*, a fungus that causes sporotrichosis, a chronic granulomatous infection of skin, lymphatics, and

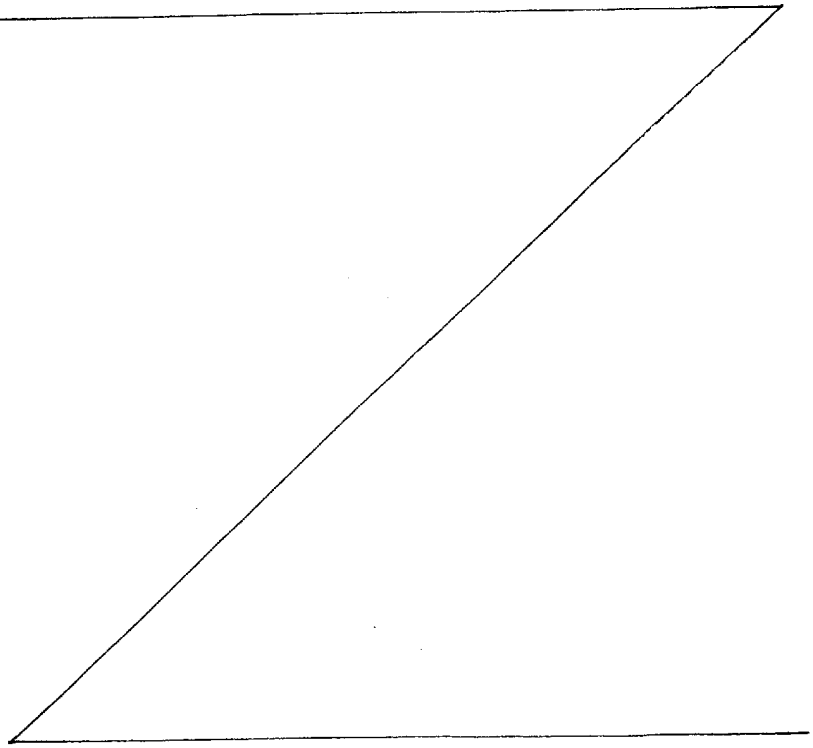
other tissues in animals and man. The present compounds can also be used to treat chromoblastomycosis, maduromycosis and phycomycosis, caused by *Rhizopus sp.* pr *Mucor sp.*

The present compounds are particularly effective against *Aspergillus* species. *Aspergillus fumigatus* and other *Aspergillus sp.* have become a frequent cause of systemic fungal infection in an altered host. Patients with leukemia or lymphoma, immunosuppressed persons (especially AIDS patients or patients undergoing organ transplants), and those receiving intensive corticosteroid therapy are particularly susceptible to aspergillosis. The portal of entry is the respiratory tract, and in most cases of aspergillosis pulmonary manifestations occur, predominantly necrotizing bronchopneumonia, hemorrhagic pulmonary infarction, or granulomas (aspergillomas).

The present compounds are also useful to inhibit the growth of fungi, including yeasts, on the skin of humans and animals such as household pets, farm animals and zoo animals. Such gram-positive microorganisms include *Propionibacterium acnes* which is the primary pathogen which causes human acne vulgaris. Mycotic skin infections of animals and humans can also be treated, including tinea capitis, tinea cruris (jock itch), tinea corporis (ringworm), tineal pedis (athlete's foot) and tinea unguium. Fungi associated with such dermatophytosis include *T. mentagrophytes, M. audevinii, T. rubrum, E. floccasum* and *M. pelineum.*

The present compounds are also effective against fungi associated with infections of the membranes of body cavities. Such infections include thrush, vaginitis and paronychia. See R. T. Yousef et al., Mykosen, 21, 190 (1978) and H. Gershon, J. Pharm. Sci., 68, 82 (1979). The present compounds can also be used in cosmetic and skin-cleansing compositions such as soaps, shampoos, deodorants, and skin-softening lotions, where they can function as deodorants, i.e., to control odor-causing bacteria on the skin. The present compounds can also be used in shampoos, rinses, and other haircare products, to inhibit *Pityrosporum ovale* (dandruff, skin lesions in immune-suppressed subjects).

The present analogs can also be used to treat cancers known to be susceptible to topoisomerase I inhibitors, including, but not limited to, Burkitt's tumor, chronic lymphocytic leukemia, multiple myeloma, squamous cell and large cell anaplastic carcinomas, adenocarcinoma of the lung, Ewing's sarcoma, non-Hodgkins lymphoma, breast tumor, colon tumor, stomach tumor, oat cell bronchogenic carcinoma, squamous cell carcinoma of the cervix, ovarian tumors, bladder tumors, testicular tumors, endometrial tumors, malignant melanoma and acute lymphocytic leukemia, and prostatic carcinoma. The present compounds can be administered as single agents, or in combination with other antineoplastic drugs commonly employed to treat these cancers.



The invention will be further described by reference to the following detailed examples, wherein melting points were determined with a Thomas-Hoover unimelt capillary melting point apparatus. Infrared spectral data (IR) were obtained on a Perkin-Elmer 1600 Fourier transform spectrophotometer and are reported in cm^{-1}. Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance were recorded on a Varian Gemini-200 Fourier Transform spectrometer. NMR spectra (200 MHz ^1H and 50 MHz ^{13}C) were recorded in $CDCl_3$ (unless otherwise noted) with chemical shifts reported in δ units downfield from tetramethylsilane (TMS). Coupling constants are reported in hertz. Mass spectra were obtained from Midwest Center for Mass Spectrometry within the Department of Chemistry at the University of Nebraska-Lincoln. Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA, and were with in ± 0.4%. THF was freshly distilled from sodium and benzophenone prior to use. Allyltributyltin and phenyltributyltin were purchased from Aldrich Chemical Company.

Aspergillus nidulans strain R21 *(pabaA1, yA2)* was used throughout the examples. The bibenzimidazole Hoescht dye 33342 (Ho33342), camptothecin, and berenil were purchased from Sigma Chemical Co. Mono-benzimidazoles (QS/II/9, 48, 50, 51, and 59A), terbenzimidazoles (11 and 13) and protoberberines (coralyne, DMII/33) and nitidine were synthesized as described below. and as by (Q. Sun et al., Biorg. & Med. Chem. Lett., 4, 2871

(1994), and J. Med. Chem., 38, 3638 (1995); Kim et al., Biorg. & Med. Chem. Lett., 4, 62 (1996); J. Med. Chem., 39, 992 (1996); D. Makhey et al., Med. Chem. Res., 5, 1 (1995); Biorg. & Med. Chem. Lett., 4 781 (1996)). (See Fig. 8 for structures.) All the drugs were dissolved in dimethyl sulfoxide (Sigma Chemical Co.) at a concentration of either 1, 5 or 10 mg/ml and kept frozen in aliquots at -20°C.

Example 1. **General Procedure for $PdCl_2(PPh_3)_2$-catalyzed Coupling Reaction of 4-Bromo-2-nitroaniline (13) with Tin Compounds.**

(A) 4-Phenyl-2-nitroaniline (5). A solution of 4-bromo-2-nitroaniline **17** (1.0 g, 4.67 mmol), tributylphenyl tin (2.2 g, 6.07 mmol), bis(triphenylphosphine)palladium (II) chloride (164 mg, 0.234 mmol), and triphenylphosphine (613 mg, 2.34 mmol) in DMF (15 ml) was heated under N_2 at 120°C overnight. After the solution was cooled to room temperature, the reaction mixture was directly chromatographed on silica gel eluting with 2-5% EtOAc/Hexane to give 752 mg (75%) of **5** as a yellow solid: mp 169-171 °C; IR ($CHCl_3$) 3517, 3398, 3022, 1635, 1525, 1250; ^1H NMR δ 8.38 (1H, d, J = 2.2), 7.66 (1H, dd, J = 8.7, 2.2), 7.59-7.54 (2H, m), 7.49-7.34 (3H, m), 6.90 (1H, d, J = 8.8), 6.13 (NH, brs); ^{13}C NMR δ 144.2, 139.3, 135.0, 130.9, 129.5, 127.8, 126.8, 124.4, 119.8, 112.8; Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.38, H, 4.76; N, 13.01.

(B) 4-Allyl-2-nitroaniline (4). Prepared from 4-bromo-2-nitroaniline **17** (1.70 g, 7.84 mmol) and allyltributyltin (3.38 g, 10.2 mmol) as a yellow solid in 96% yield as described above for **5**: mp 29-31 °C; IR (KBr) 3490, 3374, 1638, 1518, 1341, 1253; ^1H NMR δ 7.90 (1H, d, J = 2.0), 7.19 (1H, dd, J = 8.5, 2.0), 6.77 (1H, d, J = 8,5), 6.05 (NH, brs), 6.00-5.80 (1H, m), 5.11 (1H, dd, J = 1.4, 1.4), 5.04 (1H, ddd, J = 6.6, 3.0, 1.5), 3.28 (1H, d, J = 6.6); ^{13}C NMR δ 143.81, 137.13, 129.34, 125.59, 119.49, 116.95, 39.18; HRMS (EI) calcd for $C_9H_{10}N_2O_2$ 178.0742, found 178.0746.

(C) 4-(2'-Pyridyl)-2-nitroaniline (6). Prepared from 4-bromo-2-nitroaniline 17 (597 mg, 2.75 mmol) and 2-tributylstannylpyridine (1.01 g, 2.75

mmol) as a yellow solid in 52% yield as described above for **5**: mp 146-148 °C; IR ($CHCl_3$) 3516, 3397, 3020, 1634, 1524, 1341, 1250; ^1H NMR δ 8.74 (1H, d, *J* = 2.2), 8.63 (1H, dd, *J* = 4.9, 1.5), 8.13 (1H, dd, *J* = 8.8, 2.1), 7.78-7.66 (2H, m), 7.20 (1H, ddd, *J* = 4.8, 4.7, 1.9), 6.92 (1H, d, *J* = 8.8), 6.37 (NH, brs); ^{13}C NMR δ 155.6, 150.1, 145.6, 137.4, 134.5, 129.1, 124.7, 122.4, 119.8, 119.7; Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.53. Found: C, 61.29; H, 4.23; N, 19.43.

(D) 4-(3'-Pyridyl)-2-nitroaniline (7). Prepared from 4-bromo-2-nitroaniline **17** (1.42 g, 6.53 mmol) and 3-tributylstannylpyridine (3.60 g, 9.79 mmol) as a yellow solid in 32% yield as described above for **5**: mp 177-179 °C; IR ($CHCl_3$) 3515, 3399, 3052, 2983, 1638, 1524, 1341, 1259; ^1H NMR δ 8.68 (1H, d, *J* = 1.7), 8.42 (1H, dd, *J* = 4.8, 1.5), 8.22 (1H, d, *J* = 2.2), 7.74 (1H, ddd, *J* = 7.9, 2.4, 1.6), 7.50 (1H, dd, *J* = 8.7, 2.2), 7.23 (1H, ddd, *J* = 8.0, 4.8, 0.8), 6.92 (1H, d, *J* = 8.8), 6.56 (NH, brs); ^{13}C NMR δ 148.7, 147.8, 145.4, 135.0, 134.4, 133.8, 126.5, 124.4, 124.0, 120.4; Anal. Calcd for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.21; N, 19.53. Found: C, 61.28; H, 4.16; N, 19.40.

(E) 4-(4'-Pyridyl)-2-nitroaniline (8). Prepared from 4-bromo-2-nitroaniline **17** (165 mg, 0.76 mmol) and 4-tributylstannylpyridine (280 mg, 0.76 mmol) as a yellow solid in 25% yield as described above for **5**: mp 230-232 °C; IR ($CHCl_3$) 3518, 3398, 3032, 1636, 1528, 1344; ^1H NMR (CD_3OD) δ 8.55 (2H, d, *J* = 6.3), 8.52 (1H, d, *J* = 2.3), 7.84 (1H, dd, *J* = 8.9, 2.3), 7.71 (2H, d, *J* = 6.4), 7.13 (1H, d, *J*= 8.9); ^{13}C NMR (CD_3OD) δ 149.4, 133.4, 124.0, 120.7, 120.0; HRMS (EI) calcd for $C_{11}H_9N_3O_2$ 215.0695, found 215.0698.

Example 2. <u>5-Formyl-2-(benzimidazol-5'-yl)benzimidazole (9).</u>

A mixture of 5-cyano-2-(benzimidazol-5'-yl)benzimidazole **19** (148 mg, 0.57 mmol), Ni-Al catalyst (500 mg), formic acid (7 ml) and water (3 ml) was heated under refluxed under N_2 for 4h. The hot reaction mixture was immediately filtered through a plug of celite, and evaporated to give a yellow solid. The yellow solid was then dissolved in hot water (5 ml), and the solution was neutralized to pH 9 by 2N NaOH. The solid precipitated was collected by suction

filtration and further purified by flash chromatography on silica gel (15% MeOH/EtOAc) to give 142 mg (95%) of 9 as a white solid: mp > 275 °C; IR (KBr) 3106, 2835, 1685, 1618, 1432, 1293; ^{1}H NMR (CD_3OD) δ 10.01 (1H, s), 8.39 (1H, s), 8.35 (1H, s), 8.13 (1H, s), 8.06 (1H, dd, J = 8.6, 1.6), 7.83 (1H, dd, J = 8.4, 1.4), 7.77 (1H, d, J = 8.5), 7.71 (1H, d, J = 8.3); HRMS (FAB) calcd for $C_{15}H_{11}N_4O$ 263.0933, found 263.0932.

Example 3. <u>General Procedures for Preparing 5-substituted Trisbenzimidazoles.</u>

(A) 2-[2'-(Benzimidazol-5"-yl)benzimidazol-5'-yl]benzimidazole (10). A mixture of 5-formyl-2-(benzimidazol-5'-yl)benzimidazole **9** (121 mg, 0.46 mmol) and phenylenediamine (60 mg, 0.55 mmol) in nitrobenzene (8 ml) was heated at 150°C under N_2 overnight. The mixture was cooled to room temperature and chromatographed on silica gel (0-20% MeOH/EtOAc) to afford 155 mg (96%) of **10** as a solid: mp > 275 °C; IR (KBr) 3400, 3157, 1630, 1542, 1438, 1294; ^{1}H NMR (DMSO-d_6 + 3 drops of CF_3COOH) δ 9.71 (1H, s), 8.75 (1H, s), 8.65 (1H, d, J = 1.1), 8.48 (1H, dd, J = 8.7, 1.5), 8.21 (1H, dd, J = 8.6, 1.6), 8.14 (1H, d, J = 8.8), 8.08 (1H, d, J = 8.7), 7.90 (2H, dd, J = 6.2, 3.1), 7.61 (2H, dd, J = 6.1, 3.1); ^{13}C NMR (DMSO-d_6 + 3 drops of CF_3COOH) δ 154.4, 149.8, 133.2, 132.0, 131.7, 126.2, 125.5, 125.4, 123.9, 123.6, 116.3, 115.9, 114.23, 114.17, 114.13; HRMS (FAB) calcd for $C_{21}H_{15}N_6$ 351.1358, found 351.1367.

(B) 5-Cyano-2-[2'-(benzimidazol-5"-yl)benzimidazol-5'-yl]benzimidazole (11). Hydrogenation of **3** (70 mg, 0.43 mmol) was accomplished at 40 psi H_2 at room temperature for 1 h using 10% Pd-C (30 mg) in EtOAc (10 ml). The reaction mixture was filtered and concentrated *in vacuo* to afford a solid. The solution of this solid and **9** (87 mg, 0.33 mmol) in nitrobenzene (5 ml) was heated at 150 °C under N_2 overnight. The mixture was cooled to room temperature, and chromatographed directly on silica gel (0-10% MeOH/EtOAc) to give 107 mg (86%) of **11** as a solid; mp > 280 °C; IR (KBr) 3416, 3148, 2222, 1626, 1553, 1441, 1292; ^{1}H NMR (DMSO-d_6 + 3 drops of

CF_3COOH) δ 8.50 (1H, s), 8.46 (1H, s), 8.40 (1H, s), 8.18-8.11 (3H, m), 7.81-7.75 (3H, m), 7.62 (1H, dd, J = 8.3, 1.5); HRMS (FAB) calcd for $C_{22}H_{13}N_7$ 376.1310, found 376.1309.

(C) 5-Propyl-2-[2'-(benzimidazol-5"-yl)benzimidazol-5'-yl]benzimidazole (12). Prepared from 4-allyl-2-nitroaniline **4** (312 mg, 1.75 mmol) and 5-formyl-2-(benzimidazol-5'-yl)benzimidazole **9** (121 mg, 0.46 mmol) in 79% yield as described above for **11**: solid; mp > 270 °C; IR (KBr) 3421, 3068, 2957, 1434; ^{1}H NMR (DMSO-d_6 + 3 drops of CF_3COOH) δ 9.66 (1H, s), 8.73 (1H, s), 8.59 (1H, s), 8.48 (1H, dd, J = 8.7, 1.5), 8.13 (1H, dd, J = 8.7, 1.4), 8.11 (1H, d, J = 8.7), 8.02 (1H, d, J = 8.5), 7.79 (1H, d, J = 8.4), 7.66 (1H, s), 7.45 (1H, dd, J = 8.5, 1.3), 2.80 (2H, t, J = 7.0), 1.70 (2H, m), 0.96 (3H, t, J = 7.2); ^{13}C NMR (DMSO-d_6 + 3 drops of CF_3COOH) δ 153.84, 149.74, 141.64, 141.01, 139.37, 133.10, 132.26, 131.99, 130.34, 127.08, 126.26, 125.14, 141.64, 141.01, 139.37, 133.10, 132.26, 131.99, 130.34, 127.08, 126.26, 125.14, 122.91, 117.52, 116.32, 116.06, 115.76, 113.78, 112.99, 37.45, 24.73, 13.74.

(D) 5-Phenyl-2-[2'(benzimidazol-5"-yl)benzimidazol-5'-yl]benzimidazole (13). Prepared from 4-phenyl-2-nitroaniline **5** (247 mg, 1.15 mmol) and 5-formyl-2-(benzimidazol-5'-yl)benzimidazole **9** (201 mg, 0.77 mmol) in 89% yield as described for **11**: solid; mp 262-164 °C dec; IR (KBr) 3402, 3104, 1627, 1552, 1442, 1290; ^{1}H NMR (DMSO-d_6 + 3 drops of CF_3COOH) δ 9.66 (1H, s), 8.74 (1H, s), 8.65 (1H, s), 8.50 (1H, dd, *J* = 8.8, 1.1), 8.21 (1H, dd, *J* = 8.7, 1.4), 8.12 (1H, d, *J* = 8.8), 8.06 (1H,s), 8.05 (1H, d, *J* = 8.4), 7.97 (1H, d, *J* = 8.7), 7.89 (1H, dd, *J* = 8.7, 1.5), 7.80 (2H, d, *J* = 7.0), 7.61-7.47 (3H, m); HRMS (FAB) calcd for $C_{27}H_{19}N_6$ 427.1671, found 427.1666.

(E) 5-(2-Pyridyl)-2-[2'-(benzimidazol-5"-yl)benzimidazol-5'-yl]benzimidazole (14). Prepared from 4-(2'-pyridyl)-2-nitroaniline, **6** (110 mg, 0.50 mmol), and 5-formyl-2-(benzimidazol-5'-yl)benzimidazole **9** (51 mg, 0.25 mmol) in 84% yield as described above for **11**: solid; mp > 275 °C; IR (KBr) 3411, 3157, 1630, 1593, 1432; ^{1}H NMR (CD_3OD) δ 8.59 (1H, d, *J* = 4.8), 8.35 (1H, s), 8.31-8.25 (2H, m), 8.10 (1H, s), 8.04-7.94 (2H, m), 7.85-7.77 (3H, m),

7.72 (1H, d, J = 8.6), 7.68 (1H, d, J = 8.7), 7.64 (1H, d, J = 8.7), 7.30 (1H, m); HRMS (FAB) calcd for $C_{26}H_{18}N_7$ 428.1624, found 428.1611.

(F) 5-(3-Pyridyl)-2-[2'-(benzimidazol-5"-yl)benzimidazol-5'-yl]benzimidazole (15). Prepared from 4-(3'-pyridyl)-2-nitroaniline **7** (183 mg, 0.85 mmol) and 5-formyl-2-(benzimidazol-5'-yl)benzimidazole **9** in 46% yield as described above for **11**: solid; mp > 275 °C; IR (KBr) 3400, 3070, 2836, 1438, 1289; ^{1}H NMR (CD_3OD) δ 8.83 (1H, d, J = 1.6), 8.49 (1H, dd, J = 4.9, 1.5), 8.38 (1H, d, J = 1.1), 8.31 (1H, d, J = 1.1), 8.29 (1H, s), 8.11 (1H, ddd, J = 8.0, 2.3, 1.6), 8.05 (1H, dd, J = 8.5, 1.6), 8.00 (1H, dd, J = 8.5, 1.6), 7.81 (1H, d, J = 1.1), 7.77-7.68 (3H, m), 7.55-7.47 (2H, m); HRMS (FAB) calcd for $C_{26}H_{18}N_7$ 428.1624, found 428.1612.

(G) 5-(4-Pyridyl)-2-[2'-(benzimidazol-5"-yl)benzimidazol-5'-yl]benzimidazole (16). Prepared from 4-(4'-pyridyl)-2-nitroaniline **8** (35 mg, 0.16 mmol) and 5-formyl-2-(benzimidazol-5'-yl)benzimidazole **9** (50 mg, 0.19 mmol) in 43% yield as described above for **11**: solid; mp > 280 °C; IR (KBr) 3411, 3118, 1600, 1552, 1439, 1290; ^{1}H NMR (CD_3OD) δ 8.51 (2H, d, J = 6.2), 8.33 (1H, d, J = 1.1), 8.27 (1H, s), 8.25 (1H, d, J = 1.1), 8.01 (1H, dd, J = 8.6, 1.7), 7.96 (1H, dd, J = 8.9, 2.0), 7.87 (1H, d, J = 1.0), 7.74-7.56 (6H, m); HRMS (FAB) calcd for $C_{26}H_{18}N_7$ 428.1624, found 428.1625.

Example 4. **4-Bromo-2-nitroaniline (17).**

A solution of 2-nitroaniline (5 g, 36.2 mmol) in CH_2Cl_2 (100 ml) was cooled to -10°C, and treated by 90% 2,4,4,6-tetrabromo-2,5-cyclohexadienone (19.8 g, 43.5 mmol) in 5 portions. The mixture was stirred at -10°C – 0°C for 1 hr. After being warmed to room temperature, the reaction mixture was washed by 2N NaOH (60 ml) and brine (50 ml), dried over Na_2SO_4 and evaporated. Flash chromatography on silica gel (5% EtOAc/Hexane) gave 7.40 g (94%) of **17** as a yellow solid: mp 109-110 (lit. mp 112-113 °C); ^{1}H NMR δ 8.27 (1H, d, J = 2.3), 7.43 (1H, dd, J = 8.9, 2.4), 6.73 (1H, d, J = 8.8), 6.09 (NH, brs).

Example 5. **5-Formylbenzimidazole (18).**

A suspension of 5-benzimidazolecarboxylic acid (1.57 g, 9.7 mmol) in dry THF (50 ml) was cooled to -78°C under N_2, and treated with $LiAlH_4$ (736 mg, 19.4 mmol). After the addition, the mixture was allowed to warm slowly to room temperature and then stirred at r.t. overnight. The mixture was quenched by MeOH and H_2O cautiously, and passed through a short silica gel column eluting with 10% MeOH/EtOAc. The eluate was concentrated to give 876 mg crude alcohol as a solid. The crude alcohol (876 mg) was dissolved in a mixture of DMF (3 ml), THF (10 ml) and CH_2Cl_2 (40 ml). 4-Methylmorpholine N-oxide (2.25 g, 19.2 mmol), 4Å molecular sieves (5 g), and TPAP (169 mg, 0.48 mmol) were subsequently added to the crude alcohol solution. The mixture was stirred at room temperature overnight, and filtered through a pad of silica gel eluting with 10% MeOH/EtOAc. The elute was concentrated and further purified by flash chromatography on silica gel eluting with 0-10% MeOH/EtOAc to give 452 mg (32%, 2 steps) of **17** as a white solid: mp 164-166 °C; IR (KBr) 3087, 2818, 1690, 1292; ^{1}H NMR (CD_3OD) δ 9.95 (1H, s), 8.34 (1H, s), 8.08 (1H, d, J = 1.5), 7.74 (1H, dd, J = 8.4, 1.5), 7.63 (1H, d, J = 8.4); ^{13}C NMR (CD_3OD) δ 194.2, 146.0, 143.0, 139.8, 133.6, 124.9, 120.7, 116.6; Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.60; H, 4.17; N, 19.08.

Example 6. **5-Cyano-2-(benzimidazol-5'-yl)benzimidazole (19).**

A mixture of 5-formylbenzimidazole **18** (211 mg, 1.44 mmol) and 4-cyano-1,2-phenylenediamine (230 mg, 1.73 mmol) in nitrobenzene (10 ml) was heated at 150°C under N_2 overnight. The mixture was cooled to room temperature and directly chromatographed on silica gel eluting with 0-15% MeOH/EtOAc to give 244 mg (65%) of **18** as a solid: mp >270 °C; IR (KBr) 3110, 2826, 2224, 1627, 1426, 1294; ^{1}H NMR (CD_3OD) δ 8.41 (1H, s), 8.33 (1H, s), 8.07 (1H, dd, J = 8.6, 1.5), 7.98 (1H, s), 7.78 (1H, d, J = 8.4), 7.73 (1H, d, J = 8.4), 7.56 (1H, dd, J = 8.4, 1.5); ^{13}C NMR (DMSO-d_6 + 3 drops of CF_3COOH) δ 153.4, 140.4, 138.3, 132.9, 131.6, 127.0, 125.8, 125.3, 120.8,

119.8, 116.0, 115.8, 113.9, 105.5; HRMS (FAB) calcd for $C_{15}H_{10}N_5$ 260.0936, found 260.0935.

Example 7.

(A) 5-Bromo-2-[2'-(benzimidazol-5''-yl)benzimidazol-5'-yl]-benzimidazole (JSK IV-37) A mixture of 5-formyl-2-(benzimidazol-5'-yl)benzimidazole (118.8 mg, 0.45 mmol) and 5-bromophenylenediamine (169.6 mg, 0.90 mmol) in nitrobenzene (5 mL) was heated at 150°C under N_2 overnight. The mixture was cooled to room temperature and chromatographed using 0-10% methanol/ethyl acetate to afford 127.3 mg (66%) of brownish yellow solid: mp>280°C; IR (KBr) 3101, 1626, 1547, 1440; ^{1}H NMR (DMSO-d_6) δ 7.34 (dd, 1H, J=7.0, 2.0), 7.57 (d, 1H, J=9.0), 7.71-7.80 (m, 3H), 8.04-8.18 (m, 2H), 8.39 (s, 2H), 8.50 (s, 1H); ^{13}C NMR (DMSO-d_6 + 3 drops CF_3COOH) δ 114.1 115.8, 116.2, 116.4, 117.0, 118.6, 123.5, 125.3, 126.2, 128.7, 128.9, 131.8, 132.0, 132.3, 133.1, 134.4, 138.3, 140.6, 151.1, 153.4.

(B) 5-Chloro-2-[2'-(benzimidazol-5''-yl)benzimidazol-5'-yl]-benzimidazole(JSK IV-68) A mixture of 5-formyl-2-(benzimidazol-5'-yl)benzimidazole (160 mg, 0.61 mmol) and 5-chlorophenylenediamine (174 mg, 1.22 mmol) in nitrobenzene (5 mL) was heated at 150°C under N_2 overnight. The mixture was cooled to room temperature and chromatographed using 0-10% methanol/ethyl acetate to afford 167 mg (71%) of brownish yellow solid: mp>280°C; IR (KBr) 3103, 2826, 1427, 1293; ^{1}H NMR (DMSO-d_6) δ 7.24 (dd, 1H, J=8.5, 2.0), 7.60-7.81 (m, 4H), 8.07-8.17 (m, 2H), 8.40 (s, 2H), 8.50 (s, 1H); ^{13}C NMR (DMSO-d_6 +3 drops CF_3COOH) δ 114.3, 114.4, 115.3, 115.5, 115.6, 116.2, 118.5, 123.1, 125.4, 125.5, 125.6, 129.4, 132.4, 132.9, 133.0, 135.2, 138.9, 140.9, 151.8, 153.5.

(C) 5-(*p*-Chlorophenyl)- 2-[2'-(benzimidazol-5''-yl)benzimidazol-5'-yl]-benzimidazole (JSK IV-47) A mixture of 5-formyl-2-(benzimidazol-5'-yl)benzimidazole (99 mg, 0.38 mmol) and 5-(*p*-chlorophenyl)phenylenediamine (154 mg, 0.71 mmol) in nitrobenzene (5 mL) was heated at 150°C under N_2 overnight. The mixture was cooled to room temperature and chromatographed

using 0-10% methanol/ethyl acetate to afford 85 mg (49%) of brownish yellow solid: mp>280°C; IR (KBr) 3046, 2820, 1426, 1282; ^{1}H NMR (DMSO-d_6 + 3 drops CF_3COOH) δ 7.56 (d, 2H, J=8.5), 7.82 (d, 2H, J=8.5), 7.88-8.21 (m, 6H), 8.48 (d, 1H, J=8.8), 8.63 (s, 1H) 8.72 (s, 1H), 9.69 (s, 1H); ^{13}C NMR (DMSO-d_6 + 3 drops CF_3COOH) δ 111.8, 113.8, 114.7, 115.8, 116.1, 117.7, 123.0, 124.1, 125.2, 125.3, 129.2, 129.3, 131.9, 132.1, 133.0, 133.1, 137.2, 138,5, 139.3, 141.6, 150.8, 153.8.

(D) 4-Bromophenylenediamine (JSK IV-35) To 2-nitro-4-bromoaniline (340 mg, 1.57 mmol) in absolute ethanol (20mL) was added $SnCl_2$ (1.50g, 7.91 mmol) and refluxed overnight. The reaction mixture was then basified to pH 11 with 2N NaOH and extracted with ether to give 275 mg (94%) of product. This product was used without further purification for the synthesis of JSK IV-37.

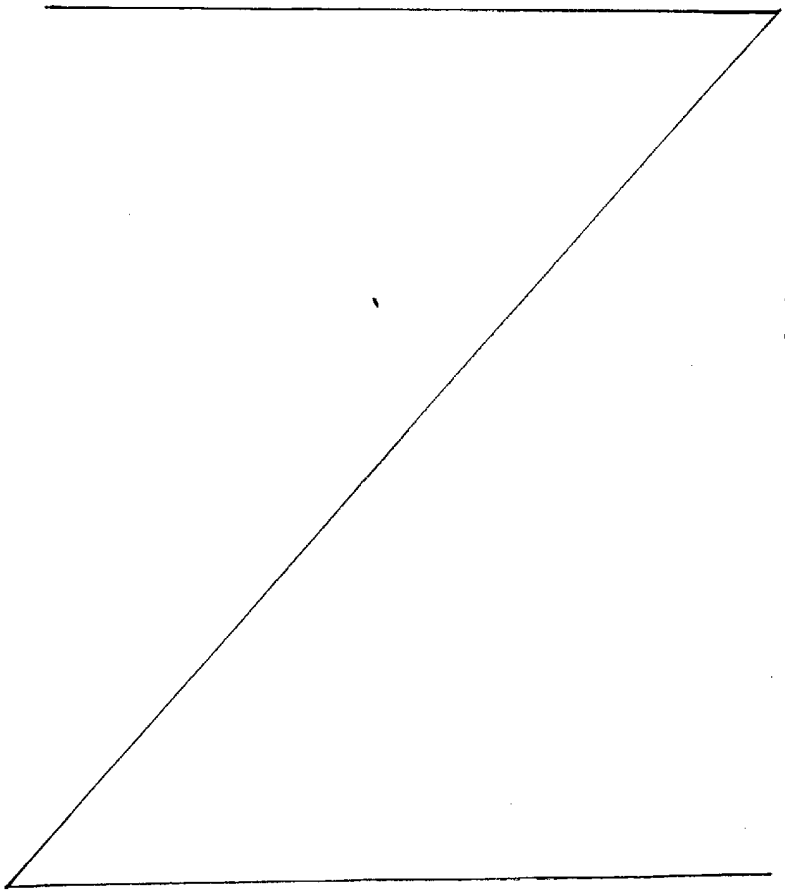
(E) 4-Chlorophenylenediamine (JSK IV-67) To 2-nitro-5-chloroaniline (304 mg, 1.76 mmol) in absolute ethanol (20 mL) was added $SnCl_2$ (1.68g, 8.86 mmol) and refluxed overnight. The reaction mixture was then basified to pH 11 with 2N NaOH and extracted with ether to give 250 mg (quantitative yield) of product. This product was used without further purification for the synthesis of JSK IV-68.

(F) *p*-Chlorotributylphenyltin (JSK IV-42) 4-Bromochlorobenzene (3.2 g, 16.62 mmol) was dissolved in dry THF (20mL). After bringing the reaction temperature down to -78°C with an acetone/dry ice bath, nBuLi (15.58 mL, 1.6M, 1.5 equiv.) was added slowly and stirred at -78°C for 30 min. Tributyltinchloride (6.77 mL, 1.5 equiv.) was added and stirred overnight while bringing the reaction to room temperature. Reaction mixture was quenched by stirring the reaction flask open in air for 1 hour after which THF was rotavaporated off. Product was obtained as an oil (7.35g, 97%) after passing the mixture through a quick silica gel column eluting with 100% hexanes.

(G) 2-Nitro-5-(*p*-chlorophenyl)aniline (JSK IV-44) To JSK IV-42 (2.02 g, 5.04 mmol) and 2-nitro-4-bromoaniline (730 mg, 3.36 mmol) in DMF (18 mL) was added $Pd(PPh_3)_2Cl_2$ (117.9 mg, 0.17 mmol) and PPh_3 (440.2 mg,

1.70 mmol) and heated at 120°C overnight. DMF was rotavaporated off and the mixture was separated on a silica gel column eluting with 5-10% ethylacetate/hexanes to give 270 mg (32%) of reddish solid.

(H) 4-(*p*-Chlorophenyl)phenylenediamine (JSK IV-46) JSK IV-44 (190 mg, 0.77 mmol) was dissolved in ethyl acetate (100 mL) and after adding 10% Pd-C (40 mg) was reduced by hydrogenation (45 psi). Product (quantitative yield) was used in JSK IV-47 without further purification.



Example 8 - Bioassays

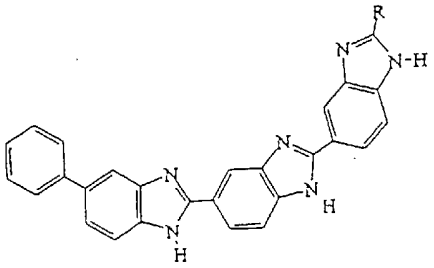
Cytotoxicity assay

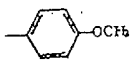
The cytotoxicity was determined using the as MTT-microtiter plate tetrazolinium cytotoxicity assay (MTA) following the procedures of F. Denizot et al., J. Immunol. Methods, 89, 271 (1986); J. Carmichael et al., Cancer Res., 47. 936 (1987) and T. J. Mosmann et al., Immunol. Methods, 65, 55 (1983). The human lymphoblast RPMI 8402 and its camptothecin-resistant variant cell line, CPT-K5 were provided by Dr. Toshiwo Andoh (Aichi Cancer Center Research Institute, Nagoya, Japan). See, for example, T. Andoh et al., Adv. Pharmacol., 29B, 93 (1994). The cytotoxicity assay was performed using 96-well microtiter plates. Cells were grown in suspension at 37°C in 5% CO_2 and maintained by regular passage in RPMI medium supplemented with 10% heat inactivated fetal bovine serum, L-glutamine (2 mM), penicillin (100 U/ml), and streptomycin (0.1 mg/ml). For determination of IC_{50}, cells were exposed continuously with varying concentrations of drug concentrations and MTT assays were performed at the end of the fourth day. The drug sensitive human epidermoid carcinoma KB3-1 cell line (S. Aliyamaet at., Somatic Cell Mol. Genet., 1-1, 117 (1985)) and its vinblastine-selected multidrug-resistant variant KBV- I cells (D. W. Shen et al., Science, 32, 643 (1986)) were provided by Dr. Michael Gottesmann (National Cancer Institute, Bethesda, ML). These cells were grown as monolayer cultures at in 5% CO_2 and maintained by regular passage in Dulbecco's minimal essential medium supplemented with 10% heat inactivated fetal bovine serum. KBV- I cells were similarly maintained except they were grown in the presence of 1 ug/ml vinblastine.

Results

As shown in Tables 1-3, compounds 87 and 88 according to the present invention demonstrated cytotoxicity in several cell lines.

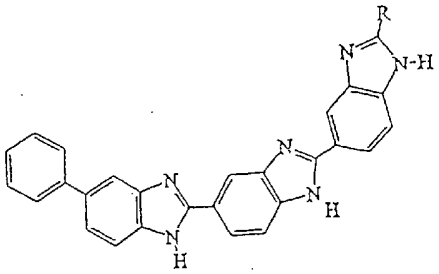
Resistance ratios of 2"-substituted 5-phenylterbenzimidazoles



Compound	R	IC_{50} (μM)		Resistance ratio[a]
		RPMI 8402	CPT-K5	
87		0.06	2.95	49
88		0.38	>90.00	>200

a)Resistance ratio is the ratio of IC_{50} in the RPMI 8402 cells to the IC_{50} in the CPT-K5 cells. Compounds are considered cross-resistant when the ratio is greater than 10.

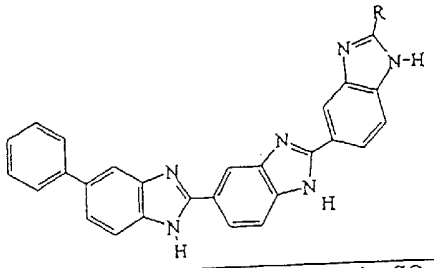
Cytotoxicity of 2"-substituted compounds in MDR1 cell lines

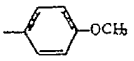


Compound	R	KB3-1[a]	KBV-1[a]	KBH1.0-(3-23)[a]
87		0.006	>40.00	>40.00
88		11.27	28.00	18.00

a) cytotoxicity in IC_{50} (μM) unless otherwise indicated.

Cytotoxicity of 2"-substituted compounds in various camptothecin resistant cell lines

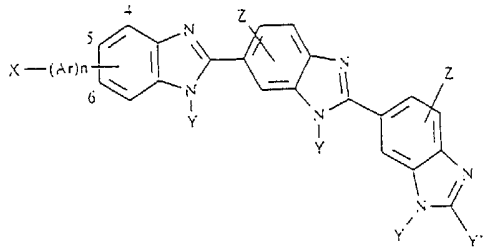


Compound	R	Cytotoxicity (IC_{50} in μM)			
		U937[a]	U937/CR[b]	A2780[c]	CPTR2000[d]0
87		0.02	0.01	-	0.002
88		0.13	0.56	13.15	9.39

a) Human myeloid leukemia cells:
b) Camptothecin-resistant variant of U937. Mutation at 361 Phenylalanine to Serine.
c) Human ovarian cancer cells.
d) Camptothecin-resistant variant of A2780. Mutation at 717 Glycine to Valine and 729 Threonine to Isoleucine.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein Ar is (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CN (when $n \neq 1$), CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C C_1-C_4)alkyl or aralkyl; Y' is phenyl or methoxyphenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof, when used in medical therapy.

2. Claim 1 wherein Y' is methoxyphenyl.

3. Claim 1 wherein n is 1.

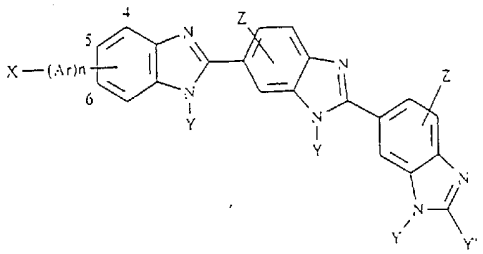
4. Claim 1 wherein X is CN, CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; and n is 0.

5. Claim 1 wherein at least one Z is halogen or halo(C_1-C_4)alkyl; and n is 0.

6. Claim 1, 2, 3, 4, or 5 wherein the medical therapy is the treatment of fungal infection.

7. Claim 1, 2, 3, 4, or 5 wherein the medical therapy is the treatment of cancer.

8. The use of a compound of formula (I):



(I)

wherein Ar is (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CN (when n ≠ 1), CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y' is phenyl or methoxyphenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating fungal infection.

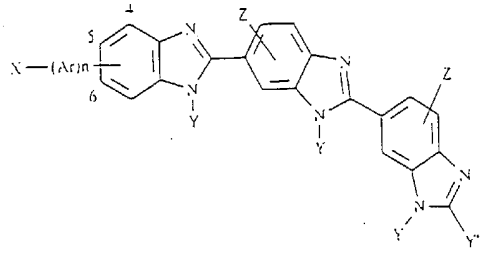
9. Claim 8 wherein Y' is methoxyphenyl.

10. Claim 8 wherein n is 1.

11. Claim 8 wherein X is CN, CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; and n is 0.

12. Claim 8 wherein at least one Z is halogen or halo(C_1-C_4)alkyl; and n is 0.

13. The use of a compound of formula (I):



(I)

wherein Ar is (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CN (when n ≠ 1), CHO, OH, acetyl, CF_3. O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y' is phenyl or methoxyphenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating cancer.

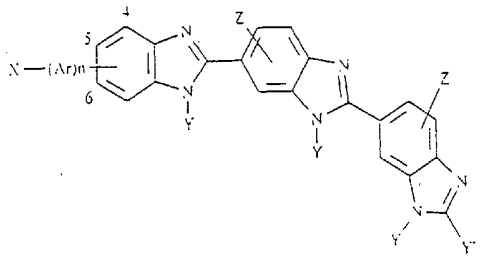
14. Claim 13 wherein Y' is methoxyphenyl.

15. Claim 13 wherein n is 1.

16. Claim 13 wherein X is CN, CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; and n is 0.

17. Claim 13 wherein at least one Z is halogen or halo(C_1-C_4)alkyl; and n is 0.

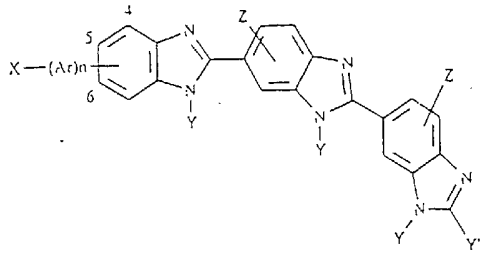
18. A compound of formula (I):



(I)

wherein Ar is benzo, (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CHO, OH, acetyl, CF_3. O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y' is methoxyphenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof.

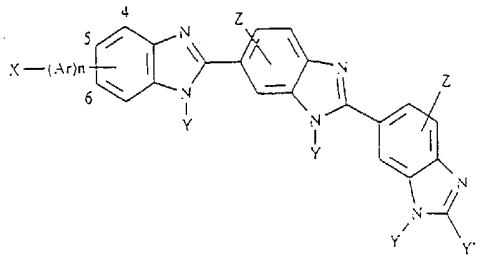
19. A compound of formula (I):



(I)

wherein Ar is benzo, (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CHO, OH, acetyl, CF_3. O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y' is methoxyphenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof.

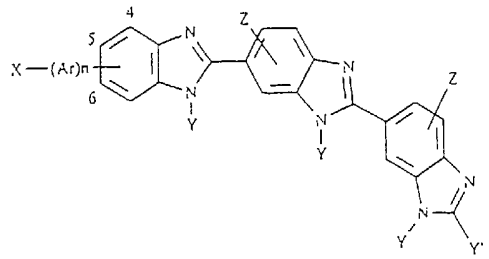
20. A compound of formula (I):



(I)

wherein Ar is benzo, (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CHO, OH, acetyl, CF_3. O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y' is phenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof.

21. A compound of formula (I):

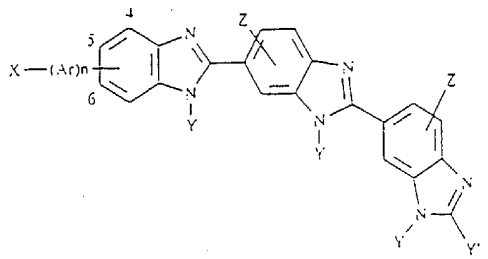


(I)

wherein Ar is benzo, (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CHO, OH, acetyl, CF_3. O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y' is phenyl;

each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof.

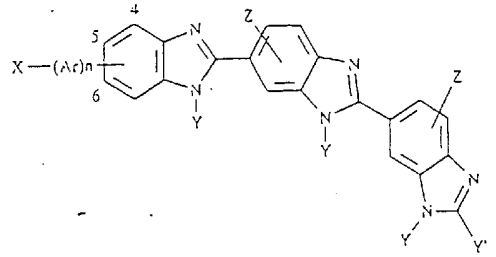
22. A compound of formula (I):



(I)

wherein X is CN, CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y' is phenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0; or a pharmaceutically acceptable salt thereof.

23. A compound of formula (I):



(I)

wherein X is H, CN, CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y' is phenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl, provided at least

one Z is halogen or halo(C_1-C_4)alkyl; and n is 0; or a pharmaceutically acceptable salt thereof.

24. The compound of claim 18, 19 or 20 wherein n is 1.

25. The compound of claim 21 or 22 wherein Ar is at the 5-position.

26. The compound of claim 21 or 24 wherein Ar is phenyl.

27. The compound of claim 21 or 24 wherein Ar is 2-pyridyl.

28. The compound of claim 18, 19, 20, 21, 22, 23 or 23 wherein X is halogen.

29. The compound of claim 28 wherein X is Cl.

30. The compound of claim 26 wherein X-Ar is *p*-chlorophenyl.

31. The compound of claim 30 wherein each Y is H; and each Z is H.

32. The compound of claim 18, 19 or 20 wherein n is 0.

33. The compound of claim 32 wherein X is Cl.

34. The compound of claim 33 wherein X is Br.

35. The compound of claim 33 or 34 wherein Y' is 4-methoxyphenyl; each Y is H; and each Z is H.

36. The compound of claim 18, 19, 20, 21 or 22 wherein at least one Z is halogen or halo(C_1-C_4)alkyl.

37. The compound of claim 36 wherein at least one Z is F or CF_3.

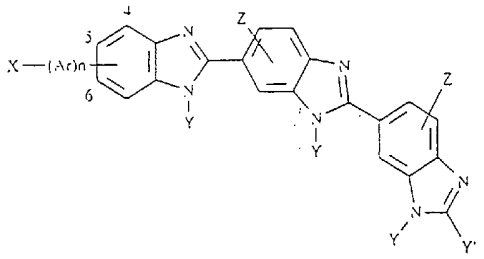
38. The compound of claim 21 or 24 wherein Ar is benzo.

39. The compound of claim 38 wherein Ar is 4,5-benzo.

40. The compound of claim 38 wherein Ar is 5,6-benzo.

41. A pharmaceutical composition comprising a compound of claim 18, 19, 20, 21, 22, 23 or 24 and a pharmaceutically acceptable carrier.

42. A therapeutic method comprising treating fungal infection by administering to a mammal in need of such therapy, an effective amount of a compound of formula (I):



(I)

wherein Ar is (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CN (when $n \neq 1$), CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C C_1-C_4)alkyl or aralkyl; Y' is phenyl or methoxyphenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof.

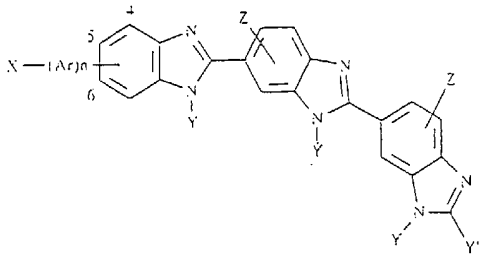
43. A therapeutic method comprising treating fungal infection by administering to a mammal in need of such therapy, an effective amount of a compound of claim 18, 19, 20, 21, 22, 23 or 24.

44. The method of claim 42 wherein the mammal is a human.

45. The method of claim 42 wherein the fungal infection is a systemic infection.

46. The method of claim 42 wherein the compound is administered in combination with a pharmaceutically acceptable vehicle.

47. A therapeutic method comprising treating cancer by administering to a mammal in need of such therapy, an effective amount of a compound of formula (I):



(I)

wherein Ar is (C_6-C_{12})aryl or (5- to 12-membered)heteroaryl comprising 1-3 N, S or non-peroxide O, wherein N is unsubstituted or is substituted with H, (C_1-C_4)alkyl or benzyl; X is H, CN, CHO, OH, acetyl, CF_3, O(C_1-C_4)alkyl, NO_2, NH_2, halogen or halo-(C_1-C_4)alkyl; each of Y is H, (C_1-C_4)alkyl or aralkyl; Y' is phenyl or methoxyphenyl; each Z is individually H, (C_1-C_4)alkyl, halogen or halo(C_1-C_4)alkyl; and n is 0 or 1; or a pharmaceutically acceptable salt thereof.

48. A therapeutic method comprising treating cancer by administering to a mammal in need of such therapy, an effective amount of a compound of claim 19, 20, 21, 22, 23 or 24.

49. The method of claim 47 wherein the mammal is a human.

50. The method of claim 47 wherein the compound is administered in combination with a pharmaceutically acceptable vehicle.

DATED this THIRTIETH day of JANUARY 2002

Rutgers, The States University of New Jersey
Applicant

Wray & Associates
Perth, Western Australia
Patent Attorneys for the Applicant.

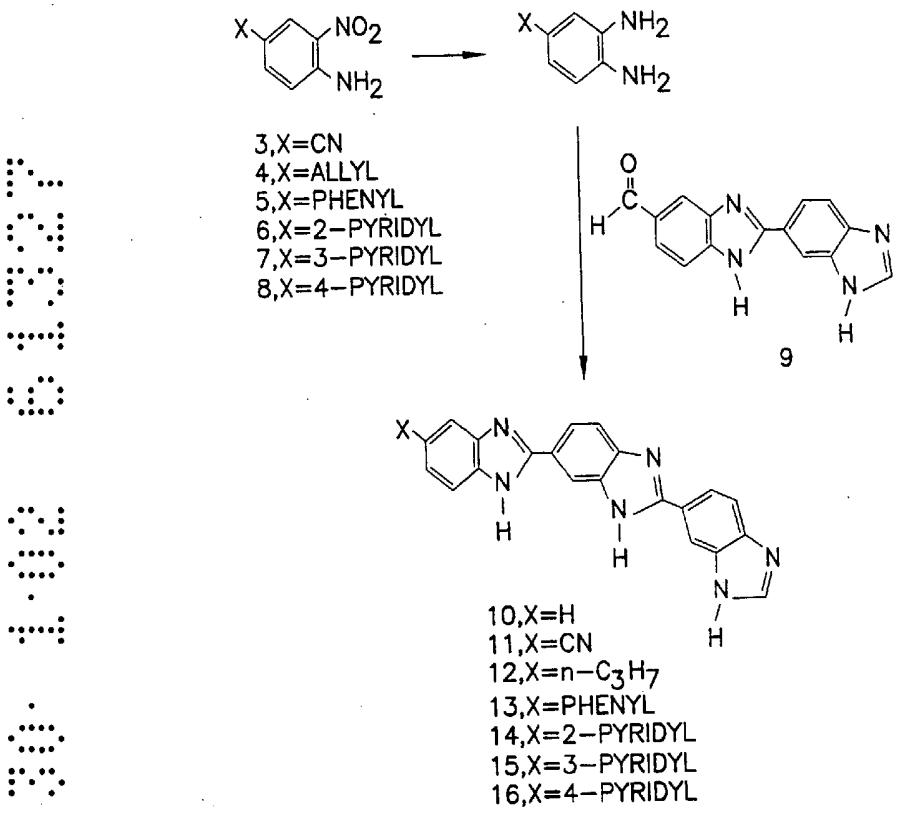

X
NO2
NH2
X
NH2
NH2
3,X=CN
4,X=ALLYL
5,X=PHENYL
6,X=2-PYRIDYL
7,X=3-PYRIDYL
8,X=4-PYRIDYL
O
C
H
N
H
9
X
10,X=H
11,X=CN
12,X=n-C3H7
13,X=PHENYL
14,X=2-PYRIDYL
15,X=3-PYRIDYL
16,X=4-PYRIDYL

FIG. 1

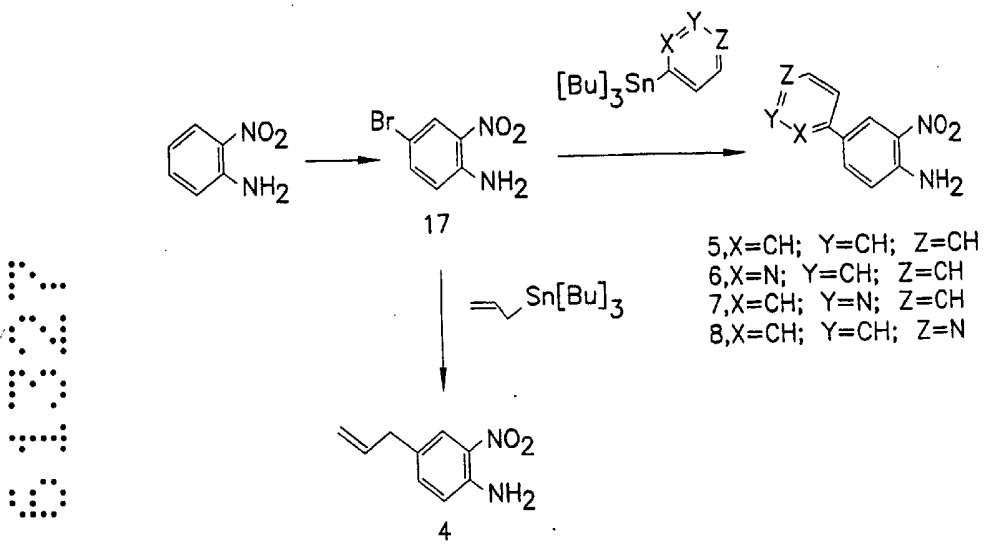

NO2
NH2
Br
NO2
NH2
17
[Bu]3Sn
X
Y
Z
Z
Y
X
NO2
NH2
5,X=CH; Y=CH; Z=CH
6,X=N; Y=CH; Z=CH
7,X=CH; Y=N; Z=CH
8,X=CH; Y=CH; Z=N
Sn[Bu]3
NO2
NH2
4

FIG. 2

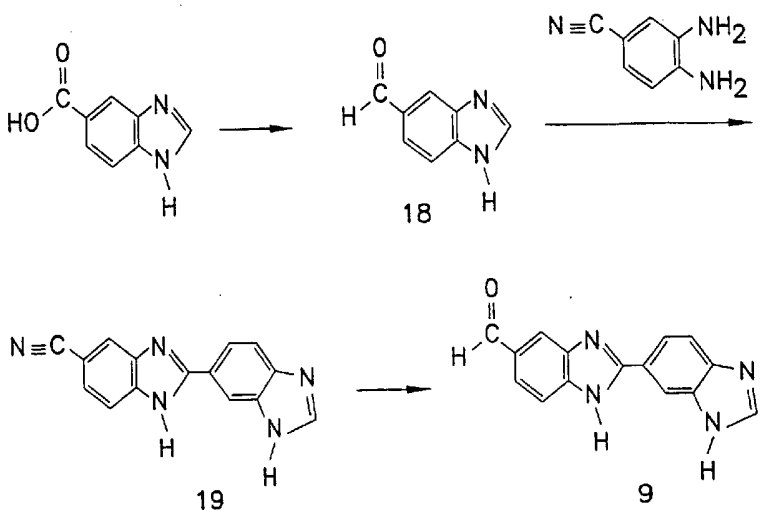
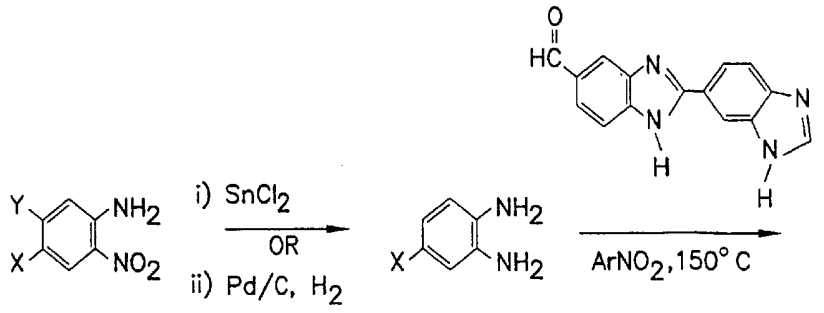
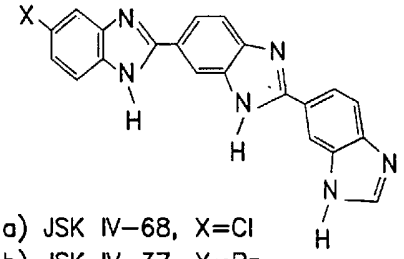


FIG. 3



a) X=H, Y=Cl
b) X=Br, Y=H
c) JSK IV-44

a) JSK IV-67, i), X=Cl
b) JSK IV-35, i), X=Br
c) JSK IV-46, ii), X=p-CHLOROPHENYL



a) JSK IV-68, X=Cl
b) JSK IV-37, X=Br
c) JSK IV-47, X=p-CHLOROPHENYL

FIG. 4

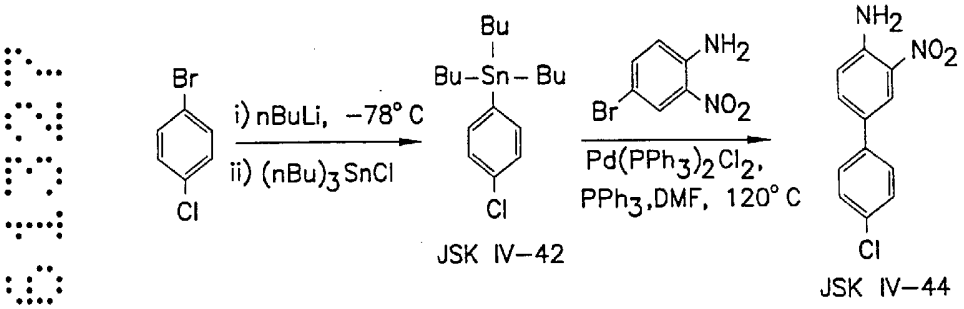

Br
Cl
i) nBuLi, −78° C
ii) (nBu)3SnCl
Bu
Bu–Sn–Bu
Cl
JSK IV–42
NH2
Br
NO2
Pd(PPh3)2Cl2,
PPh3,DMF, 120° C
NH2
NO2
Cl
JSK IV–44

FIG. 5

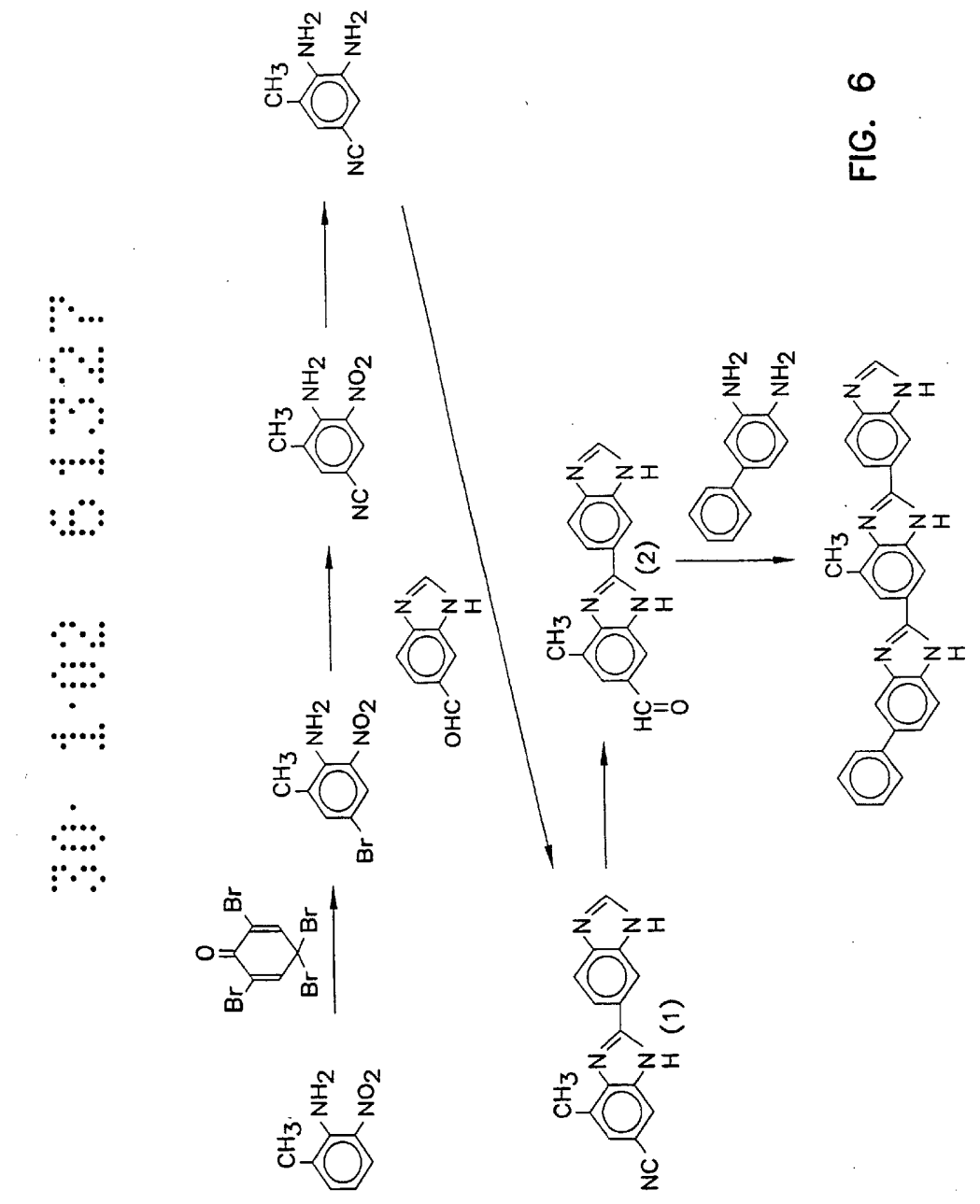


FIG. 6

FIG. 7

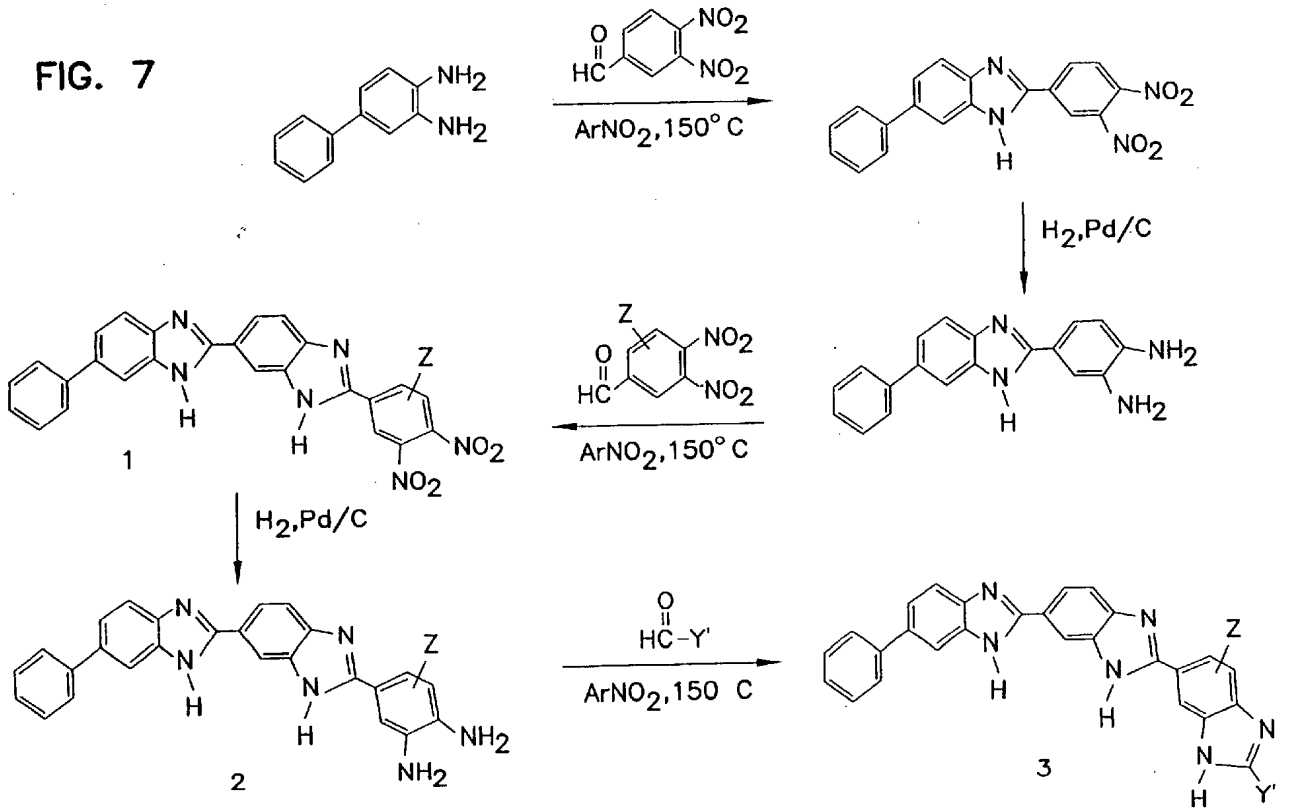
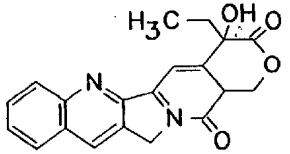
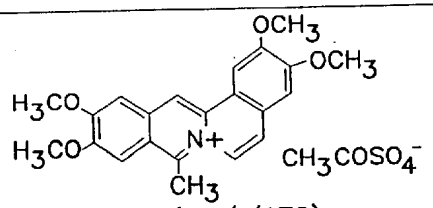
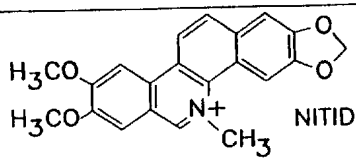
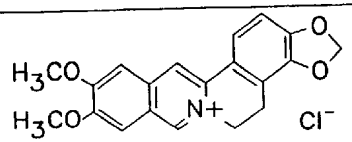
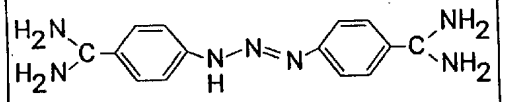
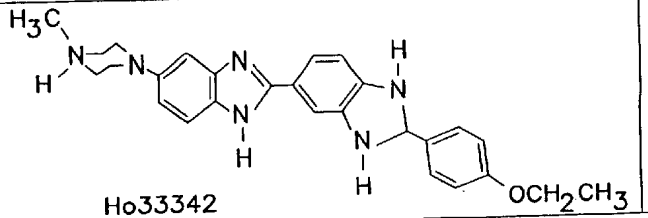
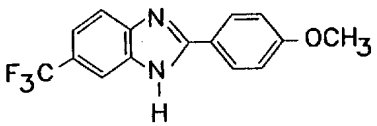
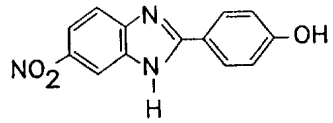
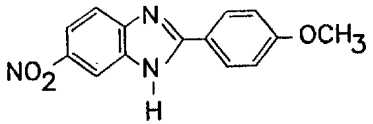
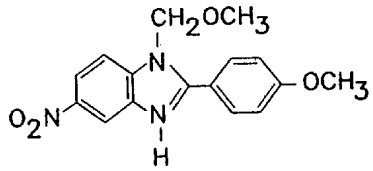
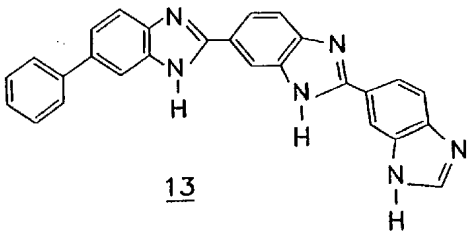
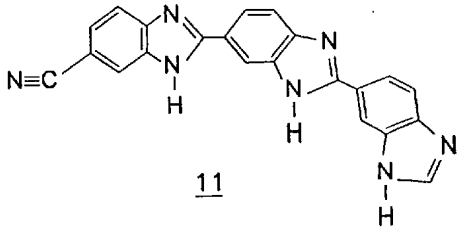

NH2
NH2
O
HC
NO2
NO2
ArNO2,150° C
N
N
H
NO2
NO2
H2,Pd/C
NH2
NH2
Z
NO2
NO2
ArNO2,150° C
1
H2,Pd/C
2
O
HC-Y'
ArNO2,150 C
3
Y'

FIG. 8

FIG. 8A
FIG. 8B

FIG. 8A

	H	A		H	A
 CAMPTOTHECIN	+	+	 CORALYNE (DM/I/170)	+	–
 NITIDINE	+	–	 DM/II/33	+	–*
 BERENIL	+	–	 Ho33342	+	+

	H	A		H	A
 QS/II/50	–	–	 QS–II–51	+	–
 QS–II–9	+	–	 QS/II/59 A	+	–
 13	+	+	 11	+	+

6/6

FIG. 8B