

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
12 June 2008 (12.06.2008)

PCT

(10) International Publication Number
WO 2008/070463 A2(51) International Patent Classification:
A61K 31/35 (2006.01)(74) Agents: CASIMIR, David, Ann, D. et al.; Casimir Jones,
S.C., 440 Science Drive, Suite 203, Madison, WI 53711
(US).(21) International Application Number:
PCT/US2007/085443(81) Designated States (*unless otherwise indicated, for every
kind of national protection available*): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH,
CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,
ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL,
IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK,
LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW,
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,
ZM, ZW.(22) International Filing Date:
21 November 2007 (21.11.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/860,420 21 November 2006 (21.11.2006) US
60/860,788 22 November 2006 (22.11.2006) US(71) Applicant (*for all designated States except US*): JINA
PHARMACEUTICALS, INC. [US/US]; 28100 North
Ashley Circle, Suite 103, Libertyville, IL 60048 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): AHMAD, Ateeq
[US/US]; 4795 West Pebble Beach Drive, Wadsworth,
IL 60083 (US). ALI, Shoukath, M. [US/US]; 29681
North Waukegan Road, #204, Lake Bluff, IL 60048 (US).
AHMAD, Moghis, U. [US/US]; 3050 North Forrest Hills
Court, Wadsworth, IL 60083 (US). SHEIKH, Saifuddin
[US/US]; 1059 South West Avenue, Waukegan, IL 60085
(US). AHMAD, Imran [US/US]; 4731 West Pebble
Beach Drive, Wadsworth, IL 60083 (US).(84) Designated States (*unless otherwise indicated, for every
kind of regional protection available*): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,
PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished
upon receipt of that report*

(48) Date of publication of this corrected version:

18 September 2008

(15) Information about Correction:
see Notice of 18 September 2008

(54) Title: ENDOXIFEN METHODS AND COMPOSITIONS

(57) Abstract: The present invention provides compositions containing endoxifen, formulations and liposomes of endoxifen, methods of preparation of such agents and formulations, and use of such agents and formulations for the treatment of breast cancer and other breast diseases and diseases susceptible to endoxifen. In particular, the compositions of the present invention include liposomes, complexes, vesicles, emulsions, micelles and mixed micelles of endoxifen in which the compositions further contain any of a variety of neutral or charged lipids and desirably, cholesterol and cholesterol derivatives, sterols, Z- and E- guggulsterones, phospholipids, fatty acids, vitamin D, and vitamin E. The present invention also provides methods of preparing endoxifen. The present invention provides methods for treating and preventing breast cancer and other breast related diseases by administering novel formulations or compositions comprising a therapeutically effective amount of endoxifen.

WO 2008/070463 A2

ENDOXIFEN METHODS AND COMPOSITIONS

This application claims priority to U.S. Provisional Applications Serial No. 60/860,420, filed November 21, 2006, and 60/860,788, filed November 22, 2006, both of which are incorporated herein by reference.

5

FIELD OF THE INVENTION

[0001] The invention relates to the use of endoxifen in the treatment of mammalian diseases. The invention also relates to liposomes and other formulations such as complexes, vesicles, emulsions, micelles and mixed micelles of endoxifen, methods of preparation, and
10 uses, *e.g.*, in the treatment of human and animal breast diseases. The invention in particular relates to compositions comprising endoxifen–lipid complexes, methods of preparation, and their use for the treatment of breast diseases, in particular benign and malignant breast disease, enhancing disease regression and reducing risk of patients developing breast cancer. The invention further relates to methods of preparing endoxifen and use of
15 endoxifen prepared by inventive method in the treatment of human and animal diseases.

BACKGROUND OF THE INVENTION

[0002] Every year more than 210, 000 women in the United States develop breast cancer. One in eight women in the US will develop breast cancer during their lives. Approximately
20 70 percent of breast cancers are fueled by estrogen, and many are treated with Tamoxifen, a drug designed to block the effects of estrogen in breast tissue.

[0003] Tamoxifen is an anti-estrogenic drug prescribed for long-term, low dose therapy of breast cancer. It has been widely used for more than 30 years for the endocrine treatment of all stages of hormone receptor-positive breast cancer (1-2). Tamoxifen has also been
25 approved for the prevention of breast cancer (3). In women, one of the adverse events associated with Tamoxifen is hot flashes. The risk of hot flashes is two to three-folds higher among women who take Tamoxifen than it is for those who do not (4). Selective serotonin-reuptake inhibitor (SSRI) antidepressants are prescribed to treat hot flashes. However, some SSRIs, such as paroxetine and fluoxetine, are known to inhibit cytochrome
30 P450 (CYP) 2D6 (5), an enzyme that is important for the metabolism of many drugs, including Tamoxifen. Our understanding of Tamoxifen metabolism and effect has changed clinical practice through the wide spread recognition that the co-prescription of drugs that inhibit CYP2D6 may compromise Tamoxifen efficacy. It is known that co-administration

of paroxetine decreases the plasma concentration of an active metabolite of Tamoxifen, 4-hydroxy-N-desmethyl-Tamoxifen (endoxifen).

[0004] Endoxifen is generated via CYP3A4-mediated N-demethylation and CYP2D6 mediated hydroxylation of Tamoxifen (see, *e.g.*, Figure 3). Any drug that can be substrate of CYP3A4 or CYP2D6, especially CYP2D6 *e.g.*, SSRIs, can decrease the level of endoxifen (6) and thus reduce the therapeutic benefits of Tamoxifen. Therefore, to avoid such drug-drug interactions, one should not give them together.

[0005] Recently, endoxifen has been shown to be anti-estrogenic in breast cancer cells and to be more potent than Tamoxifen (7). In patients treated with Tamoxifen, endoxifen is present in higher concentration (12.4 ng/mL) than 4-OH-tamoxifen (1 ng/mL) in the human plasma. The majority of genes affected by endoxifen are estrogen-regulated genes (8 -9). Use of endoxifen *e.g.*, in place of Tamoxifen, avoids several metabolic steps that rely on CYP2D6.

[0006] A strong need exists for methods to treat and to prevent breast diseases without significant adverse systemic side effects, particularly in the premenopausal population. In particular, there is a need for breast cancer treatments and preventatives that having reduced interactive effect with other medications.

SUMMARY OF THE INVENTION

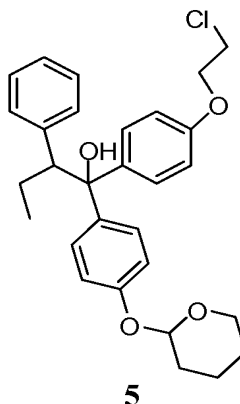
[0007] The present invention provides methods and compositions for the syntheses and use of active agents such as anticancer agents. The present invention relates to methods and compositions related to the formulations and uses of endoxifen, particularly in applications related to the treatment or prevention of cancer.

[0008] In some embodiments, the present invention provides a method of treating a disease, comprising, preparing a composition comprising a therapeutically active amount of endoxifen and administering the composition. In some embodiments, the endoxifen is a free base, or is in the form of a salt. In some preferred embodiments, the endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetate, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate. In some some embodiments, the endoxifen is predominantly in a form selected from the group consisting of *E*-isomer, *Z*-isomer, and a mixture of *E*- and *Z*-isomer.

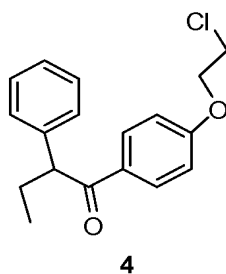
[0009] In some embodiments, method comprises preparing a complex comprising an anticancer drug and at least one lipid. In some embodiments, the anticancer drug is

endoxifen. In some embodiments, the compounds of the invention are not complexed with a lipid. In some embodiments, the compound is in the form of a free base or is in the form of a salt.

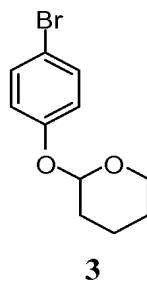
[0010] In some embodiments, the present invention provides methods of preparing endoxifen, comprising reacting a compound of Formula 5 with acid, wherein the compound of formula 5 has the structure:



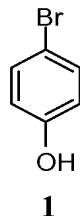
[0011] and, after the reaction of the compound of Formula 5 with acid, reacting the compound with methylamine. In some embodiments, the compound of Formula 5 is prepared by reacting compound of formula 4



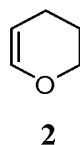
with a compound of Formula 3.



[0012] In some embodiments, the compound of Formula 3 is prepared by reacting compound of Formula 1



5 with a compound of Formula 2.



[0013] In some embodiments, the present invention provides methods of purifying the endoxifen as described above, comprising crystallizing the endoxifen and/or chromatographically treating said endoxifen to produce a purified preparation of endoxifen, wherein the purified preparation of endoxifen contains predominantly *E*-isomer, predominantly *Z*-isomer, or mixture of *E*- and *Z*-isomers of endoxifen.

[0014] As described above, in some embodiments, the invention provides endoxifen preparations comprising at least one lipid. In preferred embodiments, the at least one lipid is selected from the group consisting of egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylcholine (DPPC), distearylphosphatidylglycerol (DSPG), dipalmitoylphosphatidylglycerol (DMPG), cholesterol (Chol), cholesterol sulfate and its salts (CS), cholesterol hemisuccinate and its salts (Chems), cholesterol phosphate and its salts (CP), cholesterylphosphocholine and other hydroxycholesterol or amino cholesterol derivatives, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), coprostanol, cholestanol, cholestane, cholic acid, cortisol, corticosterone, hydrocortisone, and calciferol, *E*-guggulsterone, *Z*-guggulsterone, mixture of *E*- and *Z*-guggulsterone, monoglycerides, diglycerides, triglycerides, carbohydrate-based lipids selected from a group consisting of galactolipid, mannolipid, galactolecithin, β -sitosterol, stigmasterol, stigmastanol, lanosterol, α -spinasterol, lathosterol, campesterol, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, and

pegylated derivatives of distearoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, and dioleoylphosphatidylglycerol.

[0015] In some embodiments, a composition according to the present invention comprises endoxifen, cholesterol and/or cholesterol derivatives, and one or more
5 phospholipids. In some preferred embodiments, the composition comprises a cholesterol derivative, and the cholesterol derivative is cholesteryl sulfate. In some embodiments, at least one of the phospholipids is hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.

[0016] In some embodiments of the methods and compositions of the present invention,
10 the composition comprises a form selected from the group consisting of powder, solution, emulsion, micelle, liposome, lipidic particle, gel, and paste form. In some preferred embodiments, the preparing of the composition comprising a complex comprises preparing said complex in a lyophilized form. In some embodiments, the preparing the complex in a lyophilized form comprises using a cryoprotectant, wherein said cryoprotectant comprises
15 one or more sugars selected from the group consisting of trehalose, maltose, lactose, sucrose, glucose, and dextran. In some embodiments, the composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.

[0017] In some embodiments of the treatment methods of the present invention, the
20 disease is caused by cancer or by cancer-causing agents, while in some embodiments, the disease is benign breast disease.

[0018] In some embodiments, the administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

25 [0019] In some embodiments, the composition comprises a penetration enhancer, wherein said penetration enhancer comprises at least one saturated or unsaturated fatty acid ester.

[0020] In some embodiments, the composition comprising endoxifen is formulated in a
30 hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder or an oil.

[0021] In some embodiments, the composition comprising endoxifen is formulated in a hydroalcoholic composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

5 [0022] In some embodiments, the hydroalcoholic composition comprises a neutralizing agent.

[0023] In some embodiments, the hydroalcoholic composition comprises endoxifen at about 0.01% to 0.20% by weight; isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight; alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight; aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight. In some embodiments, the wherein the percentage of components is weight to weight of the composition.

[0024] In some embodiments, the alcohol is ethanol or isopropanol, and constitutes in absolute form.

15 [0025] In some embodiments, the aqueous vehicle is a phosphate buffered solution.

[0026] In some embodiments, the gelling agent is selected from the group consisting of polyacrylic acid, hydroxypropylcellulose and a cellulose derivative other than hydroxypropylcellulose.

20 [0027] In some embodiments, the hydroalcoholic composition further comprises a neutralizing agent, wherein said neutralizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, arginine, trolamine, and tromethamine, and wherein said neutralizing agent exists at a neutralizing agent/gelling agent ratio of about 1:1 to about 4:1.

25 [0028] In some embodiments, the invention provides methods of delivering endoxifen, comprising: providing any of the above described compositions and delivering the composition so as to expose the composition to a cell.

[0029] In some embodiments, the cell is *in vivo*.

[0030] In some embodiments of the invention, the host is a mammal.

30 [0031] The present invention also provides methods of inhibiting hormone-dependent breast carcinoma in a mammal comprising administering any of the above compositions to the mammal.

[0032] The present invention further provides methods of inhibiting a cancer in a mammal, said cancer including, but not limited to, lung cancer, colon cancer, breast cancer, leukemia, renal cancer, melanoma, cancer of the central nervous system, and prostate cancer

in a mammal; the method comprising administering any of the above compositions to said mammal (e.g., a human).

[0033] The present invention further provides compositions comprising a therapeutically active amount of a complex comprising endoxifen and at least one lipid, wherein said endoxifen is a free base or is in the form of a salt.

[0034] In some embodiments, the composition comprising endoxifen is formulated in a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder or an oil.

[0035] In some embodiments, the composition comprising endoxifen is formulated in a hydroalcoholic composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

[0036] In some embodiments, the hydroalcoholic composition comprises a neutralizing agent.

[0037] In some embodiments, the hydroalcoholic composition comprises endoxifen at about 0.01% to 0.20% by weight; isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight; alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight; aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight. In some embodiments, the wherein the percentage of components is weight to weight of the composition.

[0038] The present invention is not limited to the compositions and methods described above. It should be understood that variations of the above compositions and methods described elsewhere herein or that are understood by a skilled artisan in view of the present disclosure are included within the invention.

DESCRIPTION OF THE DRAWINGS

[0039] Figure 1 diagrams compound I.

[0040] Figure 2 diagrams embodiments for synthesis of compounds 3, 5, and I.

[0041] Figure 3 diagrams portions of Tamoxifen metabolic pathways.

DEFINITIONS

[0042] As used herein, the terms "host," "subject" and "patient" refer to any animal, including but not limited to, human and non-human animals (e.g., dogs, cats, cows, horses, sheep, poultry, fish, crustaceans, etc.) that is studied, analyzed, tested, diagnosed or treated.

As used herein, the terms "host," "subject" and "patient" are used interchangeably, unless indicated otherwise.

[0043] As used herein, the terms "subject at risk of cancer" refers to a subject identified as being at risk for developing cancer, *e.g.*, by prior health history, genetic data, etc.

[0044] As used herein, the term "anticancer drug" refers to an agent used to treat or prevent cancer. Such agents include, but are not limited to, small molecules, drugs, antibodies, pharmaceuticals, and the like.

[0045] As used herein, the term "effective amount" refers to the amount of an active composition (*e.g.*, a pharmaceutical compound or composition provided as a component in a lipid formulation) sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route.

[0046] As used herein, the terms "active" or "pharmaceutically active" as used in reference to an agent, drug, composition, or compound, refers to an agent that, upon administration or application, causes a beneficial, desired, or expected result. The administration may be in one or more administrations, applications or dosages and is not intended to be limited to a particular formulation or administration route. The term is not limited to any particular level of activity.

[0047] The terms "agent" and "compound" are used herein interchangeably to refer to any atom, molecule, mixture, or more complex composition having an attributed feature. For example, an "active agent" or "active compound" refers to any atom, molecule, preparation, mixture, *etc.*, that, upon administration or application, causes a beneficial, desired, or expected result.

[0048] As used herein, the term "treating" includes administering therapy to prevent, cure, or alleviate/prevent the symptoms associated with, a specific disorder, disease, injury or condition.

[0049] As used herein, the term "treatment" or grammatical equivalents encompasses the improvement and/or reversal of the symptoms of disease (*e.g.*, cancer), or reduction of risk of occurrence of disease. A compound which causes an improvement in any parameter associated with disease when used in the screening methods of the instant invention may thereby be identified as a therapeutic compound. The term "treatment" refers to both therapeutic treatment and prophylactic or preventative measures. For example, those who may benefit from treatment with compositions and methods of the present

invention include those already with a disease and/or disorder (*e.g.*, cancer, or symptoms or pathologies consistent with cancer) as well as those in which a disease and/or disorder is to be prevented (*e.g.*, using a prophylactic treatment of the present invention).

[0050] As used herein, the term "at risk for disease" refers to a subject (*e.g.*, a human) that is predisposed to experiencing a particular disease. This predisposition may be genetic (*e.g.*, a particular genetic tendency to experience the disease, such as heritable disorders), or due to other factors (*e.g.*, age, weight, environmental conditions, exposures to detrimental compounds present in the environment, *etc.*). Thus, it is not intended that the present invention be limited to any particular risk, nor is it intended that the present invention be limited to any particular disease.

[0051] As used herein, the term "suffering from disease" refers to a subject (*e.g.*, a human) that is experiencing a particular disease. It is not intended that the present invention be limited to any particular signs or symptoms, nor disease. Thus, it is intended that the present invention encompasses subjects that are experiencing any range of disease (*e.g.*, from sub-clinical manifestation to full-blown disease) wherein the subject exhibits at least some of the indicia (*e.g.*, signs and symptoms) associated with the particular disease.

[0052] As used herein, the terms "disease" and "pathological condition" are used interchangeably to describe a state, signs, and/or symptoms that are associated with any impairment of the normal state of a living animal or of any of its organs or tissues that interrupts or modifies the performance of normal functions, and may be a response to environmental factors (such as emotional trauma, physical trauma, malnutrition, industrial hazards, or climate), to specific infective agents (such as worms, bacteria, or viruses), to inherent defect of the organism (such as various genetic anomalies, or to combinations of these and other factors).

[0053] As used herein, the term "administration" refers to the act of giving a drug, prodrug, or other active agent, or therapeutic treatment (*e.g.*, compositions of the present invention) to a physiological system (*e.g.*, a subject or *in vivo*, *in vitro*, or *ex vivo* cells, tissues, and organs). Exemplary routes of administration to the human body can be through the eyes (ophthalmic), mouth (oral), skin (transdermal), nose (nasal), lungs (inhalant), rectal, vaginal, oral mucosa (buccal), ear, by injection (*e.g.*, intravenously, subcutaneously, intratumorally, intraperitoneally, *etc.*) and the like. Administration may be in one or more administrations, applications or dosages, and is not intended to be limited to a particular administration route.

[0054] As used herein, the term "co-administration" refers to the administration of at least two agent(s) (*e.g.*, two separate lipid compositions, containing different active compounds) or therapies to a subject. In some embodiments, the co-administration of two or more agents or therapies is concurrent. In other embodiments, a first agent/therapy is administered prior to a second agent/therapy. Those of skill in the art understand that the formulations and/or routes of administration of the various agents or therapies used may vary. The appropriate dosage for co-administration can be readily determined by one skilled in the art. In some embodiments, when agents or therapies are co-administered, the respective agents or therapies are administered at lower dosages than appropriate for their administration alone. Thus, co-administration is especially desirable in embodiments where the co-administration of the agents or therapies lowers the requisite dosage of a potentially harmful (*e.g.*, toxic) agent(s).

[0055] As used herein, the term "toxic" refers to any detrimental or harmful effects on a subject, a cell, or a tissue as compared to the same cell or tissue prior to the administration of the toxicant.

[0056] As used herein, the term "pharmaceutically purified" refers to a composition of sufficient purity or quality of preparation for pharmaceutical use.

[0057] As used herein, the term "purified" refers to a treatment of a starting composition to remove at least one other component (*e.g.*, another component from a starting composition (*e.g.*, plant or animal tissue, an environmental sample *etc.*), a contaminant, a synthesis precursor, or a byproduct, *etc.*), such that the ratio of the purified component to the removed component is greater than in the starting composition.

[0058] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent (*e.g.*, an active pharmaceutical compound) with a carrier, inert or active (*e.g.*, a phospholipid), making the composition especially suitable for diagnostic or therapeutic use *in vitro*, *in vivo* or *ex vivo*.

[0059] The terms "pharmaceutically acceptable" or "pharmacologically acceptable," as used herein, refer to compositions that do not substantially produce adverse reactions, *e.g.*, toxic, allergic, or immunological reactions, when administered to a subject.

[0060] As used herein, the term "topically" refers to application of the compositions of the present invention to the surface of the skin and mucosal cells and tissues (*e.g.*, alveolar, buccal, lingual, masticatory, or nasal mucosa, and other tissues and cells which line hollow organs or body cavities).

[0061] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers including, but not limited to, phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents, any and all solvents, dispersion media, coatings, sodium lauryl sulfate, isotonic and absorption delaying agents, disintegrants (*e.g.*, potato starch or sodium starch glycolate), and the like.. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers, and adjuvants. (See *e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, Pa. (1975), incorporated herein by reference). Moreover, in certain embodiments, the compositions of the present invention may be formulated for horticultural or agricultural use. Such formulations include dips, sprays, seed dressings, stem injections, sprays, and mists.

[0062] As used herein, the term "pharmaceutically acceptable salt" refers to any salt (*e.g.*, obtained by reaction with an acid or a base) of a compound of the present invention that is physiologically tolerated in the target subject (*e.g.*, a mammalian subject, and/or *in vivo* or *ex vivo*, cells, tissues, or organs). "Salts" of the compounds of the present invention may be derived from inorganic or organic acids and bases. Examples of acids include, but are not limited to, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, tartaric, acetic, citric, methanesulfonic, ethanesulfonic, formic, benzoic, malonic, sulfonic, naphthalene-2-sulfonic, benzenesulfonic acid, and the like. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts.

[0063] Examples of bases include, but are not limited to, alkali metal (*e.g.*, sodium) hydroxides, alkaline earth metal (*e.g.*, magnesium) hydroxides, ammonia, and compounds of formula NW_4^+ , wherein W is C_{1-4} alkyl, and the like.

[0064] Examples of salts include, but are not limited to: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, flucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, chloride, bromide, iodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, oxalate, palmoate, pectinate, persulfate, phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, undecanoate, and the like. Other examples of salts include anions of the compounds of the present invention

compounded with a suitable cation such as Na^+ , NH_4^+ , and NW_4^+ (wherein W is a C_{1-4} alkyl group), and the like. For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0065] For therapeutic use, salts of the compounds of the present invention are contemplated as being pharmaceutically acceptable. However, salts of acids and bases that are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0066] As used herein, the term "hydroalcoholic" as used in reference to a substance or composition indicates that said substance or composition comprises both water and alcohol.

[0067] As used herein, the term "gelling agent" refers to a composition that, when dissolved, suspended or dispersed in a fluid (*e.g.*, an aqueous fluid such as water or a buffer solution), forms a gelatinous semi-solid (*e.g.*, a lubricant gel). Examples of gelling agents include but are not limited to hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxypropyl guar, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, carbomer, alginate, gelatin, and poloxamer.

[0068] As used herein, the term "dried" as used in reference to a composition refers to removing the solvent component or components to levels that no longer support chemical reactions. The term is also used in reference to a composition that has been dried (*e.g.*, a dried preparation or dried composition). Those of skill in the art will appreciate that a composition may be "dried" while still having residual solvent or moisture content after, *e.g.*, lyophilization, or that a dried composition may, after the end of a drying process, absorb moisture hygroscopically, *e.g.*, from the atmosphere. The term "dried" encompasses a composition with increased moisture content due to hygroscopic absorption.

[0069] As used herein, the term "protective agent" refers to a composition or compound that protects the activity or integrity of an active agent (*e.g.*, an anticancer drug) when the active agent is exposed to certain conditions (*e.g.*, drying, freezing). In some embodiments, a protective agent protects an active agent during a freezing process (*i.e.*, it is a "cryoprotectant"). Examples of protective agents include but are not limited to non-fat milk solids, trehalose, glycerol, betaine, sucrose, glucose, lactose, dextran, polyethylene glycol, sorbitol, mannitol, poly vinyl propylene, potassium glutamate, monosodium glutamate, Tween 20 detergent, Tween 80 detergent, and an amino acid hydrochloride.

[0070] As used herein, the term "excipient" refers to an inactive ingredient (*i.e.*, not pharmaceutically active) added to a preparation of an active ingredient. The gelling and protective agents described herein may be referred to generally as "excipients."

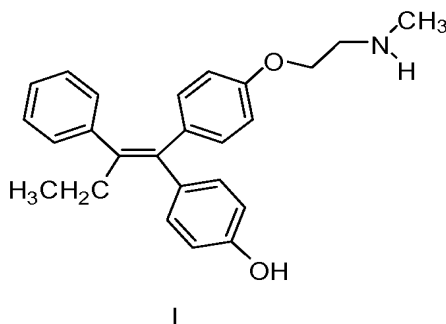
[0071] As used herein, the term "kit" refers to any delivery system for delivering

5 materials. In the context of kinase activity or inhibition assays, such delivery systems include systems that allow for the storage, transport, or delivery of reaction reagents and/or supporting materials (*e.g.*, buffers, written instructions for performing the assay etc.) from one location to another. For example, kits include one or more enclosures (*e.g.*, boxes) containing the relevant reaction reagents and/or supporting materials. As used herein, the
10 term "fragmented kit" refers to delivery systems comprising two or more separate containers that each contains a subportion of the total kit components. The containers may be delivered to the intended recipient together or separately. For example, a first container may contain an agent for use in an assay, while a second container contains standards for comparison to test compounds. The term "fragmented kit" is intended to encompass kits
15 containing Analyte Specific Reagents (ASR's) regulated under section 520(e) of the Federal Food, Drug, and Cosmetic Act, but are not limited thereto. Indeed, any delivery system comprising two or more separate containers that each contains a subportion of the total kit components are included in the term "fragmented kit." In contrast, a "combined kit" refers to a delivery system containing all of the components of a reaction assay in a single
20 container (*e.g.*, in a single box housing each of the desired components). The term "kit" includes both fragmented and combined kits.

DETAILED DESCRIPTION OF THE INVENTION

[0072] The present invention provides compositions and methods for delivering

25 endoxifen of Formula I, *e.g.*, to a mammalian host. In some embodiments of the present invention endoxifen is an *E*-isomer, while in other embodiments, it is a *Z*-isomer, while it is still in other embodiments, it is a mixture of *E*- and *Z*-isomers



[0073] An example of the present invention includes endoxifen, analogues of endoxifen, and derivatives of endoxifen, including but not limited to endoxifen, Tamoxifen, and 4-hydroxytamoxifen. The present invention also find use with other antineoplastic agents
5 such as paclitaxel, docetaxel, melphalan, chlormethine, extramustinephosphate, uramustine, ifosfamide, mannomustine, trifosfamide, streptozotocin, mitobronitol, mitoxantrone, methotrexate, fluorouracil, cytarabine, tegafur, idoxide, taxol, paclitaxel, daunomycin, daunorubicin, bleomycin, amphotericin, carboplatin, cisplatin, BCNU, vincristine, camptothecin, SN-38, doxorubicin, and etoposide. Also included are steroidal and non-
10 steroidal inhibitors used in cancer treatment, such as bicautamide, exemestane, formestane, letrozole, anastrozole and their analogues.

[0074] Endoxifen of Formula I can be prepared by any desired method for use in the treatments of the present invention but, in some embodiments, the present invention provides particular methods for the preparation of endoxifen. One preferred method of the
15 present invention is set forth in Figure 2. In this method, 4-bromophenol 1 is reacted with 3,4-dihydropyran 2 in the presence of acid (e.g., sulfuric acid and the like), to give compound 3. Compound 3 is then reacted with magnesium turning in a suitable anhydrous solvent (e.g., tetrahydrofuran and the like). This is followed by reaction with 1-[4-(2-chloroethoxy)phenyl]-2-phenyl-1-butanone 4 to provide compound 5 which, on
20 dehydration/deprotection in presence of acid in a suitable solvent (e.g., methanol and the like), produces compound 6. Reaction of yielded compound 6 with methylamine in a suitable solvent (e.g., isopropanol and the like) provides endoxifen I.

[0075] In some embodiments of the present invention, a mixture of *E*- and *Z*-isomers of endoxifen can be separated to provide the purified preparations of *E*- and *Z*-isomer of
25 endoxifen. The separation of *E*- and *Z*- isomers of endoxifen in the present invention can be done, e.g., by crystallization, or purification by liquid column chromatography (LC), or high pressure liquid column chromatography (HPLC).

[0076] Suitable solvents that can be employed in present invention for the separation of *E*- and *Z*-isomers of endoxifen include but are not limited to hexanes, heptanes, and the like,
30 benzene; toluene; ethyl acetate; acetonitrile; chlorinating solvents such as methylene chloride, chloroform, 1,2-dichloromethane, and the like, ketones, (e.g., acetone, 2-butanone, and the like), ethers such as diethyl ether, diisopropyl ether, methyl butyl ether, and tetrahydrofuran, alcohols such as methanol, ethyl alcohol, and isopropyl alcohol, and the like, and water. A solvent for crystallization can be used as a single solvent, or as

mixture of solvents such as hexane-ethyl acetate, chloroform-acetone, chloroform-methanol, dichloromethane-methanol, and the like. When a mixture of two solvents is used in the present invention, examples of ratios of one solvent to another are *e.g.*, in a range such as 9:1 to 1:9, (*e.g.*, 8:2, 7:3; 6:4; 5:5; 4:6; 3:7; 2:8; 1:9, and the like.) However, mixtures for use in the present invention are not limited to these ratios, or to mixtures comprising only two solvents.

[0077] Solvents that find use in the preparation of endoxifen according to the present invention include but are not limited to tetrahydrofuran, dichloromethane, chloroform, 1,2-dichloroethane, acetonitrile, *N,N'*-dimethylformamide, dimethylsulfoxide, toluene, pyridine, methanol, ethanol, isopropanol, acetone, 2-butanone, hexane, heptane, pentane, ethyl acetate, and the like.

[0078] Acids that find use in the preparation of endoxifen according to the present invention include, but are not limited to, sulfuric acid, hydrochloric acid, acetic acid, trifluoroacetic acid, phosphoric acid, *p*-toluenesulfonic acid, methanesulfonic acid, nitric acid, and the like.

[0079] Intermediates and final products of the present invention can be purified by column chromatography using a single or a mixture of common organic solvents such as hexane pentane, heptane, ethyl acetate, methylene chloride, chloroform, methanol, acetone, and the like.

[0080] As noted above, intermediates and final product of the present invention, may, in some embodiments, be purified by crystallization. Solvents that find use in the crystallization of intermediates and products include but are not limited to hydrocarbons such as pentanes, hexanes, heptanes, and the like, benzene; toluene; ethyl acetate; acetonitrile; chlorinating solvents such as methylene chloride, chloroform, 1,2-dichloromethane, and the like; ketones, for example, acetone, 2-butanone, and the like; ethers such as diethyl ether, diisopropyl ether, methyl butyl ether, tetrahydrofuran; alcohols such as methanol, ethyl alcohol, isopropyl alcohol, and the like. A solvent for crystallization can be used as a single solvent or mixture of solvents. Exemplary mixtures include, *e.g.*, hexane-ethyl acetate, chloroform-acetone, chloroform-methanol, dichloromethane-methanol, and the like. When a mixture of two solvents is used in the present invention, examples of ratios of one solvent to another are *e.g.*, in a range such as 9:1 to 1:9, (*e.g.*, 8:2, 7:3; 6:4; 5:5; 4:6; 3:7; 2:8; 1:9, and the like.) However, mixtures for use in the present invention are not limited to these ratios, or to mixtures comprising only two solvents.

[0081] One object of the present invention is to provide *E*-endoxifen or *Z*-endoxifen with at least 80% purity, such as at least 90% pure or at least 95% pure or at least 98% pure or at least 99% pure or at least 100% pure.

[0082] Another object of the present invention is to provide solubilized endoxifen in, *e.g.*, aqueous acid. Suitable acids for solubilizing endoxifen include but are not limited to formic acid, acetic acid, propionic acid, butyric acid, trifluoroacetic acid, lactic acid, tartaric acid, oxalic acid, malonic acid, succinic acid, and the like. The pH of the acidic solution comprising endoxifen can be adjusted with suitable base or buffers. Examples of base and buffers include but are not limited to sodium hydroxide, sodium acetate, sodium lactate, sodium succinate, sodium monophosphate, sodium diphosphate, sodium triphosphate, sodium oxalate, sodium tartrate, ammonium hydroxide, ammonium acetate, and the like. In some embodiments, a co-solvent can also be used to solubilize endoxifen. Examples of co-solvent include but are not limited to ethanol, isopropanol, detergents such as Tween 20 and Polysorbate, and the like

[0083] In certain preferred embodiments, the pH of a composition containing endoxifen according to the present invention are between about 4.0 and about 8.0, and preferably between about 5.0 and about 8.0, and most preferably between about 5.5 and about 7.5.

[0084] In some embodiments, the present invention relates to compositions and methods for delivery of endoxifen or endoxifen-lipid complexes to a mammalian host. Any suitable amount of endoxifen can be used in complex formation. Suitable amounts of endoxifen are those amounts that can be stably incorporated into the complexes of the present invention.

[0085] In some embodiments, the inventive composition comprises a lipid complex with endoxifen in which the complex desirably contains lipid or a mixture of lipids. Complexes can be in the form, *e.g.*, of micelles, vesicles or emulsions without exclusion of other forms.

The micelles of the present invention can be in the form of monomeric, dimeric, polymeric or mixed micelles. The complexes including micelles and emulsions are predominately in the size range of 50nm-20 micron, preferably in size range of 50nm-5 micron. In the complexes, the active agent can be bound to the lipid by covalent, hydrophobic, electrostatic, hydrogen, or other bonds, and is considered bound even where the drug is simply entrapped within the interior of lipid structures.

[0086] Endoxifen-lipid complexes may contain *e.g.*, cholesterol or cholesterol derivatives or a mixture of cholesterol and cholesterol derivatives. Cholesterol derivatives that find use in the present invention include cholesteryl hemisuccinate, cholesteryl succinate, cholesteryl oleate, cholesteryl linoleate, cholesteryl eicosapentenoate, cholesteryl

linolenate, cholesteryl arachidonate, cholesteryl palmitate, cholesteryl stearate, cholesteryl myristate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), water soluble cholesterol (for example, cholesterol methyl- β -cyclodextrin), coprostanol, cholestanol, or cholestane, cholic acid, cortisol, corticosterone or hydrocortisone and 7-dehydrocholesterol.

5 [0087] In some preferred embodiments, the compositions also include α -, β -, γ -tocopherols, vitamin E, calciferol, organic acid derivatives of α -, β -, γ -tocopherols, such as α -tocopherol hemisuccinate (THS), α -tocopherol succinate and/or mixtures thereof.

[0088] In other some preferred embodiments, endoxifen-lipid complexes of the present invention contain sterols. Sterols that find use in the present invention include β -sitosterol,
10 stigmasterol, stigmastanol, lanosterol, α -spinasterol, lathosterol, campesterol and/or mixtures thereof.

[0089] Compositions of the present invention also include endoxifen complexes with free and/or salts or esters of fatty acid. Preferred fatty acids range from those with carbon chain lengths of about C₂ to C₃₄, preferably between about C₄ and about C₂₄, and include
15 tetraoic acid (C_{4:0}), pentanoic acid (C_{5:0}), hexanoic acid (C_{6:0}), heptanoic acid (C_{7:0}), octanoic acid (C_{8:0}), nonanoic acid (C_{9:0}), decanoic acid (C_{10:0}), undecanoic acid (C_{11:0}), dodecanoic acid (C_{12:0}), tridecanoic acid (C_{13:0}), tetradecanoic (myristic) acid (C_{14:0}), pentadecanoic acid (C_{15:0}), hexadecanoic (palmatic) acid (C_{16:0}), heptadecanoic acid (C_{17:0}), octadecanoic (stearic) acid (C_{18:0}), nonadecanoic acid (C_{19:0}), eicosanoic (arachidic) acid
20 (C_{20:0}), heneicosanoic acid (C_{21:0}), docosanoic (behenic) acid (C_{22:0}), tricosanoic acid (C_{23:0}), tetracosanoic acid (C_{24:0}), 10-undecenoic acid (C_{11:1}), 11-dodecenoic acid (C_{12:1}), 12-tridecenoic acid (C_{13:1}), myristoleic acid (C_{14:1}), 10-pentadecenoic acid (C_{15:1}), palmitoleic acid (C_{16:1}), oleic acid (C_{18:1}), linoleic acid (C_{18:2}), linolenic acid (C_{18:3}), eicosenoic acid (C_{20:1}), eicosdienoic acid (C_{20:2}), eicosatrienoic acid (C_{20:3}), arachidonic acid (*cis*-5,8,11,14-
25 eicosatetraenoic acid), and *cis*-5,8,11,14,17-eicosapentaenoic acid, among others. Other fatty acids also can be employed in the compositions. Examples of such include saturated fatty acids such as ethanoic (or acetic) acid, propanoic (or propionic) acid, butanoic (or butyric) acid, hexacosanoic (or cerotic) acid, octacosanoic (or montanic) acid, triacontanoic (or melissic) acid, dotriacontanoic (or lacceroic) acid, tetratriacontanoic (or gheddic) acid,
30 pentatriacontanoic (or ceroplastic) acid, and the like; monoethenoic unsaturated fatty acids such as *trans*-2-butenic (or crotonic) acid, *cis*-2-butenic (or isocrotonic) acid, 2-hexenoic (or isohydrosorbic) acid, 4-decanoic (or obtusilic) acid, 9-decanoic (or caproleic) acid, 4-dodecenoic (or linderic) acid, 5-dodecenoic (or denticetic) acid, 9-dodecenoic (or lauroleic) acid, 4-tetradecenoic (or tsuzuic) acid, 5-tetradecenoic (or physeteric) acid, 6-

octadecenoic (or petroselenic) acid, *trans*-9-octadecenoic (or elaidic) acid, *trans*-11-octadecenoic (or vaccinic) acid, 9-eicosenoic (or gadoleic) acid, 11-eicosenoic (or gondoic) acid, 11-docosenoic (or cetoleic) acid, 13-decosenoic (or erucic) acid, 15-tetracosenoic (or nervonic) acid, 17-hexacosenoic (or ximenic) acid, 21-triacontenoic (or lumequeic) acid, and the like; dienoic unsaturated fatty acids such as 2,4-pentadienoic (or β -vinylacrylic) acid, 2,4-hexadienoic (or sorbic) acid, 2,4-decadienoic (or stillingic) acid, 2,4-dodecadienoic acid, 9,12-hexadecadienoic acid, *cis*-9, *cis*-12-octadecadienoic (or α -linoleic) acid, *trans*-9, *trans*-12-octadecadienoic (or linolelaidic) acid, *trans*-10, *trans*-12-octadecadienoic acid, 11,14-eicosadienoic acid, 13,16-docosadienoic acid, 17,20-hexacosadienoic acid and the like; trienoic unsaturated fatty acids such as 6,10,14-hexadecatrienoic (or hiragonic) acid, 7,10,13-hexadecatrienoic acid, *cis*-6, *cis*-9- *cis*-12-octadecatrienoic (or γ -linoleic) acid, *trans*-8, *trans*-10- *trans*-12-octadecatrienoic (or β -calendic) acid, *cis*-8, *trans*-10- *cis*-12-octadecatrienoic acid, *cis*-9, *cis*-12- *cis*-15-octadecatrienoic (or α -linolenic) acid, *trans*-9, *trans*-12- *trans*-15-octadecatrienoic (or α -linolenelaidic) acid, *cis*-9, *trans*-11- *trans*-13-octadecatrienoic (or α -eleostearic) acid, *trans*-9, *trans*-11- *trans*-13-octadecatrienoic (or β -eleostearic) acid, *cis*-9, *trans*-11- *cis*-13-octadecatrienoic (or puniic) acid, 5,8,11-eicosatrienoic acid, 8,11,14-eicosatrienoic acid and the like; tetraenoic unsaturated fatty acids such as 4,8,11,14-hexadecatetraenoic acid, 6,9,12,15- hexadecatetraenoic acid, 4,8,12,15-octadecatetraenoic (or moroctic) acid, 6,9,12,15- octadecatetraenoic acid, 9,11,13,15- octadecatetraenoic (or α -or β -parinaric) acid, 9,12,15,18-octadecatetraenoic acid, 4,8,12,16-eicosatetraenoic acid, 6,10,14,18-eicosatetraenoic acid, 4,7,10,13-docasatetraenoic acid, 7,10,13,16-docosatetraenoic acid, 8,12,16,19-docosatetraenoic acid and the like; penta- and hexa-enoic unsaturated fatty acids such as 4,8,12,15,18-eicosapentaenoic (or timnodonic) acid, 4,7,10,13,16-docosapentaenoic acid, 4,8,12,15,19-docosapentaenoic (or clupanodonic) acid, 7,10,13,16,19-docosapentaenoic, 4,7,10, 13,16,19-docosahexaenoic acid, 4,8,12,15,18,21-tetracosahexaenoic (or nisinic) acid and the like; branched-chain fatty acids such as 3-methylbutanoic (or isovaleric) acid, 8-methyldodecanoic acid, 10-methylundecanoic (or isolauric) acid, 11-methyldodecanoic (or isoundecylic) acid, 12-methyltridecanoic (or isomyristic) acid, 13-methyltetradecanoic (or isopentadecylic) acid, 14-methylpentadecanoic (or isopalmitic) acid, 15-methylhexadecanoic, 10-methylheptadecanoic acid, 16-methylheptadecanoic (or isostearic) acid, 18-methylnonadecanoic (or isoarachidic) acid, 20-methylheneicosanoic (or isobehenic) acid, 22-methyltricosanoic (or isolignoceric) acid, 24-methylpentacosanoic (or isocerotic) acid,

26-methylheptacosanoic (or isomonatonic) acid, 2,4,6-trimethyloctacosanoic (or mycoceranic or mycoserosic) acid, 2-methyl-*cis*-2-butenolic(angelic)acid, 2-methyl-*trans*-2-butenolic (or tiglic) acid, 4-methyl-3-pentenoic (or pyroterebic) acid and the like.

[0090] In some preferred embodiments, endoxifen-lipid complexes contain

5 phospholipids. Any suitable phospholipids or mixture of phospholipids can be used. For example, phospholipids can be obtained from natural sources or chemically synthesized. Suitable phospholipids include but are not limited to phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylserine (PS), phosphatidylcholine (PC), phosphatidylinositol (PI), phosphatidic acid (PA), sphingomyelin and the like, either used
10 separately or in combination. Phosphatidylglycerols may be having short chain or long chain, saturated or unsaturated such as dimyristoylphosphatidylglycerol, dioleoylphosphatidylglycerol, distearoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, diarachidonoylphosphatidylglycerol, short chain phosphatidylglycerol (C₆-C₈), and mixtures thereof. Examples of phosphatidylcholines
15 includes dimyristoylphosphatidylcholine, distearoylphosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, diarachidonoylphosphatidylcholine, egg phosphatidylcholine, soy phosphatidylcholine or hydrogenated soy phosphatidylcholine can be used, as can mixtures thereof.

[0091] According to one aspect, the present invention provides compositions comprising
20 endoxifen and derivatives of mono-, di- and tri-glycerides. Examples of the glycerides include 1-oleoyl-glycerol (monoolein) and 1, 2-dioctanoyl-*sn*-glycerol.

[0092] Another aspect of the invention provides forming complexes of endoxifen with functionalized phospholipids including but not limited to phosphatidylethanolamine, preferably dioleoylphosphatidylethanolamine, phosphatidylthioethanol, *N*-
25 biotinylphosphatidylethanolamine and phosphatidylethylene glycol.

[0093] Another aspect of the invention provides forming complexes of endoxifen with carbohydrate-based lipids. Examples of carbohydrate-based lipids include but are not limited to galactolipids, mannosyl lipids, galactolecithin and the like.

[0094] In other preferred embodiment, endoxifen-lipid complexes comprise sterols.

30 Sterols finding use in the present invention include but are not limited to β -sitosterol, stigmasterol, stigmasterol, lanosterol, α -spinasterol, lathosterol, campesterol and/or mixtures thereof.

[0095] Another aspect of the invention provides forming complexes of endoxifen with guggulipid and any suitable phospholipids. Guggulipid, or *guggul*, is a natural substance derived from the mukul myrrh tree. The mukul myrrh gives off a sticky resin, which is processed to obtain guggulipid. This extract has been used for thousands of years in
5 Aryurvedic medicine to treat arthritis and obesity. The guggulipid is a source of sterol compounds such as *Z*- and *E*-guggulsterones, generally present in an amount of at least 2.5% (10). *Z* and *E*-Guggulsterones can be synthesized chemically and thus can be used in drug formulations where the need is to have pure forms of these sterones. See, *e.g.*, U.S. Application Ser. No. 60/856,952, filed November 6, 2006, and PCT/US07/83832, filed
10 November 6, 2007, both incorporated herein by reference.

[0096] Yet another aspect of the invention provides forming complexes of endoxifen with derivatives of phospholipids such as pegylated phospholipids. Examples of pegylated lipids finding use in the present invention include but are not limited to the polyethylene glycol (Pegylated, PEG) derivatives of distearoylphosphatidylglycerol,
15 dimyristoylphosphatidylglycerol, dioleoylphosphatidylglycerol and the like.

[0097] In other aspects, the present invention provides compositions comprising endoxifen and polyethyleneglycol (PEG) and one or more lipids.

[0098] According to yet other aspects, the present invention provides compositions comprising endoxifen complexes with one or more lipids. Examples include but are not
20 limited to compositions comprising endoxifen, cholesterol or cholesterol derivatives and one or more phospholipids. Other examples of compositions include endoxifen, β -sitosterol, and one or more phospholipids. In some preferred embodiments, compositions of the present invention comprise endoxifen, and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.

[0099] The term "Polyethylene glycol (PEG)" includes polymers of lower alkylene oxide, in particular ethylene oxide (polyethylene glycols) having an esterifiable hydroxyl group at least at one end of the polymer molecule, as well as derivatives of such polymers having esterifiable carboxy groups. Polyethylene glycols of an average molecular weight ranging from 200-20,000 are preferred; those having an average molecular weight ranging
25 from 500-2000 are particularly preferred.

[00100] Another aspect of the invention provides forming complexes of endoxifen with carbohydrate-based lipids. Examples of carbohydrate-based lipids include but are not limited to galactolipids, mannanolipids, galactolecithin and the like.

[00101] In some embodiments of compositions of the invention, a complex is formed comprising endoxifen and preferably endoxifen in water at a concentration of about 0.5 mg/mL to about 25 mg/mL, such as between 1 mg/mL and about 20 mg/mL or between 1 mg/mL and 10 mg/mL, more preferably between 1 mg/mL and 5 mg/mL.

5 [00102] In some embodiments, compositions of the present invention contain about 2.5% to about 90% of total lipid, preferably about 2.5 to about 50% weight of total lipid or more, preferably about 10% to about 50% weight of total lipid.

[00103] In certain embodiments, compositions of the present invention preferably contain endoxifen, and lipid(s) in mole ratio between 1:1 to 1:100 such as in between 1:1 and 1:20 molar ratio or in between 1:1 and 1:30 molar ratio or in between 1:1 and 1:40 molar ratio or in between 1:1 and 1:50 molar ratio, in between 1:1 and 1:60 molar ratio, in between 1:1 and 1:70 molar ratios, and in between 1:1 and 1:80 molar ratios, and 1:90 molar ratios.

[00104] Ratios recited herein, *e.g.*, mole ratios of components in a composition, are provided by way of example and do not limit the invention to the precise incremental ratios recited, *e.g.*, to whole number ratios of the components in the composition. For example, a range of ratios of about 1:10 to 1:90 encompasses not only 1:11, 1:25, 1:89, *etc.*, but includes, without limitation, any ratio at or between about 1:10 to 1:90 (*e.g.*, 1:53.637).

[00105] In certain embodiments, compositions of the present invention preferably contain endoxifen and hydrogenated soy phosphatidylcholine, or soy phosphatidylcholine, and cholesterol or cholesterol derivative. Such composition includes endoxifen and cholesterol or cholesterol derivative preferably in from about 1:1-1:5 mole ratio, and more preferably at about 1:1 mole ratio to about 1:2 mole ratio.

[00106] Yet another aspect of the invention is to form complexes of endoxifen with derivatives of phospholipids, such as pegylated phospholipids. Examples include but are not limited to the polyethylene glycol (PEG) derivatives of distearoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, dioleoylphosphatidylglycerol and the like.

[00107] In some preferred embodiments, the mole ratio of endoxifen and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine, in a composition containing endoxifen and hydrogenated soy phosphatidylcholine or phosphatidylcholine is between about 1:10 and 1:90, *e.g.*, between about 1:10 and 1:80 or 1:10 and 1:70 or 1:10 and 1:60 or 1:10 and 1:50 or 1:10 and 1:40 and 1:10 and 1:30. Particularly preferred embodiments, the mole ratio of endoxifen and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine is between 1:10 and 1:60.

[00108] In some embodiments, compositions of the present invention preferably contain endoxifen and total lipids having weight to weight ratio between 1:1 to 1:100 ratio such as between 1:1 and 1:20 ratio or between 1:1 and 1:30 ratio or between 1:1 and 1:40 ratio or between 1:1 and 1:50 ratio, or between 1:1 and 1:60 ratio, or between 1:1 and 1:70 ratio, and between 1:1 and 1:80 ratio, or in between 1:1 and 1:90 ratio.

[00109] In some embodiments, the method of the present invention comprises solubilizing or suspending endoxifen and lipid(s) together in an aqueous solution, *e.g.*, water. Endoxifen-lipid complex solution can be filtered through suitable filters to control the size distribution of the complexes.

[00110] In some embodiments, the method may comprise mixing lipid(s) together in water and then adding endoxifen. Endoxifen-lipid complex solution can be filtered through suitable filters to control the size distribution of the complexes.

[00111] In some embodiments, the method also comprises mixing endoxifen and lipid(s) in an organic solvent(s), such as chloroform or ethanol or any other pharmaceutically acceptable solvents, and evaporating the solvent(s) to form a lipid phase or lipid film. The lipid phase is then hydrated with water or an aqueous solution. Examples of aqueous solutions include but are not limited to 0.9% sodium chloride, solutions containing sugars such as dextrose, sucrose, and the like. The hydrated solution can be filtered through suitable filters to control the size distribution of the complexes.

[00112] In some embodiments, the method comprises mixing lipid(s) in an organic solvent(s) and evaporating the solvent(s) to form a lipid phase or lipid film. The lipid phase is then hydrated with aqueous solution containing endoxifen. The aqueous solution in addition to endoxifen may further contain sodium chloride or sugars such as dextrose, sucrose and the like. The hydrated solution can be filtered through suitable filters to control the size distribution of the complexes.

[00113] In other embodiments, the method of the present invention comprises mixing endoxifen, one or more lipids in any suitable order and in any suitable solvents such that the resulting composition of the present invention contains endoxifen, and one or more lipids.

[00114] In some embodiments, the method of preparation of the present invention comprises heating the composition comprising endoxifen, and the lipid(s) at temperatures ranging from 30-100° C preferably between 30 - 80° C and more preferably between 30-60° C.

[00115] In some embodiments, the pH of the composition of invention ranges from about 3 to about 11, while a pH between 3.5 to about 8 is preferred and pH of between 4.0 to pH 7.5 are particularly preferred. Aqueous solutions having of a particular pH can be prepared from water having comprising appropriate buffers. Preferred buffers include but
5 are not limited to mixtures of monobasic sodium phosphate and dibasic sodium phosphate, tribasic sodium phosphate, disodium succinate. Other buffers that find use with the present invention include sodium carbonate, sodium bicarbonate, sodium hydroxide, ammonium acetate, sodium citrate, tris (hydroxy-methyl) aminoethane, sodium benzoate, and the like.

[00116] The mole ratio of endoxifen and hydrogenated soy phosphatidylcholine or
10 soy phosphatidylcholine in the composition containing endoxifen and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine is in between 1:10 and 1:90 such as in between 1:10 and 1:80 or 1:10 and 1:80 or 1:10 and 1:60 or 1:10 and 1:50 or 1:10 and 1:40 and 1:10 and 1:30. In preferred embodiments, the mole ratio of endoxifen and hydrogenated soy phosphatidylcholine or soy phosphatidylcholine is in between 1:5 and
15 1:60.

[00117] As noted above, compositions can be filtered to obtain a desired size range of complexes particle sizes from the filtrate. Filters that find use in the present invention include those that can be used to obtain the desired size range of the complexes from the filtrate. For example, the complexes can be formed and thereafter filtered through a 5
20 micron filter to obtain complexes, each particle having a diameter of about 5 micron or less. Alternatively, 1 μ m, 500 nm, 200 nm, 100 nm or other filters can be used to obtain complexes having diameters of about 1 μ m, 500 nm, 200 nm, 100 nm or any suitable size range, respectively.

[00118] When desired, the endoxifen-lipid complex can be dried, *e.g.*, by evaporation
25 or lyophilization. In certain embodiments of the invention, the endoxifen-lipid complex can be lyophilized with one or more cryoprotectants such as sugars. In preferred embodiments, sugars include but are not limited to trehalose, maltose, lactose, sucrose, glucose, and dextran. In particularly preferred embodiments, trehalose and/or sucrose are used. Lyophilization is accomplished under vacuum and can take place either with or without
30 prior freezing of the endoxifen lipid preparation. When desired, the complexes can be resuspended in any desirable solvent including water, saline, dextrose and buffer.

[00119] Pharmaceutical preparations that find use with the compositions of the present invention include but are not limited to tablets, capsules, pills, dragees, suppositories, solutions, suspensions, emulsions, ointments, and gels. For the oral mode of

administration, preferred forms of endoxifen or endoxifen lipid complex include tablets, capsules, lozenges, powders, syrups, aqueous solutions, suspensions and the like. For topical application and suppositories, preferred forms of endoxifen or endoxifen-lipid complex comprise gels, oils, and emulsions, such as are formed by the addition of suitable water-soluble or water-insoluble excipients, for example polyethylene glycols, certain fats, and esters, compounds having a higher content of polyunsaturated fatty acids and derivatives thereof. Derivatives include mono-, di-, and triglycerides and their aliphatic esters (for example, fish oils, vegetable oils etc.) or mixtures of these substances. Suitable excipients are those in which the drug complexes are sufficiently stable to allow for therapeutic use.

[00120] When desired, composition containing endoxifen or endoxifen-lipid complex can be encapsulated in enteric-coated capsules to protect it from acids in the stomach. The term "enteric" refers to the small intestine, and enteric coatings prevent release of medication before it reaches the small intestine. Most enteric coatings work by presenting a surface that is stable at acidic pH but breaks down rapidly at higher pH. Enteric coating of capsules filled with composition containing endoxifen or endoxifen-lipid complex can be done as methods known in the art.

[00121] The endoxifen -lipid complex of the present invention can be of varying size or can be of substantially uniform size. For example, the complex can have a mean diameter of about 1 mm or less, and more preferably are in the micron or sub-micron range. In some preferred embodiments, the complexes have an average diameter of about 5 μm or less, such as 0.2 μm or less or 0.1 μm or less.

[00122] The technology outlined in the present invention may also be used for any other water-insoluble drugs. The methods and compositions of the present invention find use in conjunction with the methods and compositions disclosed in U.S. Application Ser. No. 60/850,446, filed Oct. 10, 2006, PCT Application Ser. No. PCT/US07/80984, filed October 10, 2007, U.S. Application Ser. No. 60/856,952, filed November 6, 2006, PCT Application Ser. No. PCT/US07/83832, filed November 6, 2007, all of which are incorporated by reference herein in their entireties.

[00123] The compositions of the present invention can be employed to treat breast cancer and breast related diseases. For example, the compositions of the present invention may be administered to a patient diagnosed with benign breast disease. As used herein, the term "benign breast disease" refers to a constellation of non-malignant aberrations in breast tissue. The aberrations may be proliferative or non-proliferative in nature. The exemplary

benign breast diseases treatable by the present inventive compositions include adenosis, cysts, duct ectasia, fibroadenoma, fibrosis, hyperplasia, metaplasia and other fibrocystic changes. Each of these diseases, referred as "changes" or "conditions" due to their prevalence, have well-defined histological and clinical characteristics.

5 [00124] "Adenosis" refers to generalized glandular disease of the breast. It typically involves an enlargement of breast lobules, which contain more glands than usual. In "sclerosing adenosis," or "fibrosing adenosis," the enlarged lobules are distorted by scar-like fibrous tissue.

[00125] "Cysts" are abnormal sacs filled with fluid or semi-solid material. Cysts in
10 the breast are lined by breast epithelial cells, developing from lobular structures. They begin as excess fluid inside breast glands, but may grow to proportions that stretch surrounding breast tissue, causing pain. "Fibrocysts" are cystic lesions circumscribed by, or situated within, a conspicuous amount of fibrous connective tissue.

[00126] "Duct ectasia" refers to a dilation of mammary ducts by lipid and cellular
15 debris. Rupture of the ducts induces infiltration by granulocytes and plasma cells.

[00127] "Fibroadenoma" refers to benign tumors that are derived from glandular epithelium and contain a conspicuous stroma of proliferating fibroblasts and connective tissue.

[00128] "Fibrosis" simply refers to a prominence of fibrous tissue in the breast.

20 [00129] "Hyperplasia" refers to an overgrowth of cells, where several layers of cells line the basal membrane, without tumor formation. Hyperplasia increases the bulk of mammary tissue. In "epithelial hyperplasia," the cells lining breast ducts and lobules are involved, giving rise to the terms "ductal hyperplasia" and "lobular hyperplasia." Based on a histological determination, hyperplasia may be characterized as "usual" or "atypical".

25 [00130] "Metaplasia" refers to a phenomenon in which a differentiated tissue of one type transforms into a differentiated tissue of another type. Metaplasia often results from an environmental change, and enables cells better to withstand the change.

[00131] The compositions of the present invention may be administered in any dosage form and via any system that delivers the active compound endoxifen to breast
30 estrogen receptors *in vivo*. In some embodiments, a composition of present invention is delivered by "percutaneous administration", *e.g.*, delivering the drug from the surface of patient's skin, through the stratum corneum, epidermis, and dermis layers, and into the microcirculations. This is generally accomplished by diffusion down a concentration gradient. The diffusion may occur via intracellular penetration (through the cells),

intercellular penetration (between the cells), transappendageal penetration (through the hair follicles, sweat, and sebaceous glands), or any combination of the above.

[00132] Percutaneous administration of the endoxifen composition of the present invention may be advantageous because this may reduce systemic drug exposure and the risks from non-specifically activating estrogen receptors throughout the body. This is because in topical application of endoxifen will absorb primarily into local tissues. When the composition of invention containing endoxifen will be percutaneously applied to breasts, high concentration will accumulate in the breast tissues presumably due to many estrogen receptors therein. The composition of endoxifen may be applied to any skin surface, preferably to one or both breasts. The daily doses to be administered can initially be estimated based upon the absorption coefficients of endoxifen, the breast tissue concentration that is desired, and the plasma concentration that should not be exceeded. The initial dose may be optimized in each patient, depending on individual responses.

[00133] Percutaneous administration can be achieved in different ways, such as (i) by mixing the composition of endoxifen with suitable pharmaceutical carriers and, optionally, penetration enhancers to form ointments, emulsions, gel, lotion, creams or the like, where an amount of said preparation is applied onto a certain area of the skin, (ii) by incorporating the composition of endoxifen into patches or transdermal delivery systems according to the technology known in the art.

[00134] The effectiveness of percutaneous drug administration depends on many factors, such as drug concentration, surface area of application, time and duration of application, skin temperature, skin hydration, previous irradiation, physicochemical properties of the drug, and partitioning of the drug between the formulation and the skin. In some embodiments, *e.g.*, to enhance percutaneous effectiveness, the compositions or complexes comprise penetration enhancers that improve percutaneous absorption by reducing the resistance of stratum corneum by reversibly altering its physicochemical properties, changing hydration in the stratum corneum, acting as co-solvent, or changing the organization of lipids or proteins in the intracellular spaces. Such enhancers include but are not limited to organic solvents such as alcohol, acetone, dimethylsulfoxide (DMSO), polyethylene glycol, propylene glycol, fatty acids and fatty alcohol and their derivatives, hydroxyl acids, pyrrolidones, urea, vegetable oils, essential oils, and mixture thereof. In addition to chemical enhancers, physical methods can increase percutaneous absorption. For example, occlusive bandages induce hydration of the skin. Other physical methods include iontophoresis and sonophoresis, which use electrical fields and high-frequency ultrasound,

respectively, to enhance absorption of drugs that are poorly absorbed due to their size and ionic characteristics (12-13). Those who are in the pharmaceutical field can easily manipulate the various factors and methods to achieve right efficacious dosage for percutaneous delivery.

5 **[00135]** For percutaneous administration, the formulation or composition of the invention containing endoxifen may be delivered in the form of ointment, emulsion (lotion), cream, gel, powder, oil or similar formulation. In some embodiments, the formulation comprises excipient additives, including but not limited to vegetable oils such as soybean oil, mustard oil, almond oil, olive oil, groundnut oil, peanut oil, peach kernel oil, groundnut
10 oil, castor oil, canola oil, and the like, animal fats, DMSO, lanolin lipoids, phosphatides, hydrocarbons such as paraffin's, petroleum jelly, waxes, lecithin, detergent emulsifying agents, carotin, alcohols, glycerol, glycerol ether, glycerine, glycol, glycol ethers, polyethylene glycol, polypropylene glycol, non-volatile fatty alcohols, acids, esters, volatile alcoholic compounds, talc, urea, cellulose derivatives, coloring agents, antioxidants and
15 preservatives.

[00136] In some embodiments the formulation or composition of the invention containing endoxifen may be delivered as transdermal patch. The patch may comprise (i) a solution-impermeable backing foil, (ii) a layer like element having a cavity, (iii) a microporus or semipermeable membrane, (iv) a self-adhesive layer, and (v) optionally a
20 removable backing film. The layer-like element having a cavity may be formed by the backing foil and the membrane. Alternatively, the patch may comprise (i) a solution-impermeable backing foil, (ii) an open-pored foam, a closed pore foam, a tissue like layer or a fibrous web-like layer as reservoir, (iii) a self adhesive layer, and (iv) optionally a removable backing film.

25 **[00137]** In some preferred embodiments, the composition of the invention containing endoxifen is formulated in hydro alcoholic gel and the amount of endoxifen may vary from 0.001001 to 1.0 gram per 100grams of gel, most preferably in the range of 0.01-0.20 grams per 100 grams of gel.

[00138] In other embodiments, the composition of present invention comprises one
30 or more fatty acid esters as a penetration enhancer. One of the highly preferred examples of a fatty acid ester penetration enhancer is isopropyl myristate. When isopropyl myristate is used in gel, the amount may range e.g., from 0.11 to 5.0 grams per 100 grams of gel, preferably from 0.5 to 2.0grams per 100 grams of gel.

[00139] In another preferred embodiment the composition of invention containing endoxifen may also contain one or more nonaqueous vehicles, such as alcoholic vehicles. Examples of nonaqueous vehicles include ethyl acetate, ethanol, and isopropanol, preferably ethanol and isopropanol. These nonaqueous vehicles may be useful for dissolving both the active agent endoxifen and any other penetration enhancer used. They also preferably have a low boiling point, preferably less than 100° C at atmospheric pressure, to permit rapid evaporation upon contact with skin. In particular, ethanol may effectively contribute to the percutaneous absorption of endoxifen by rapidly evaporating upon contact with skin. The amount of absolute nonaqueous vehicle in a gel formulation ranges from 35% to 99% by weight, preferably between 50% to 85% and more preferably between 60% to 75%.

[00140] In another preferred embodiment, the composition or formulation of the invention comprises an aqueous vehicle that permits solubilization of hydrophilic molecules, and promotes moisturization of skin. An aqueous vehicle also can regulate pH. Aqueous vehicles include alkalinizing and basic buffer solutions, including phosphate buffer solutions, including phosphate buffer solutions (e.g., dibasic or monobasic sodium phosphate); citrate buffered solutions (e.g., sodium citrate or potassium citrate) and purified water. The amount of an aqueous vehicle preferably ranges between 0.1% to 65% by weight of the pharmaceutical composition, preferably between 15% to 50%, and more preferably between 25% to 40%.

[00141] In other embodiments, the composition of the invention comprises one or more gelling agents to increase the viscosity of the composition or formulation or to function as a solubilizing agent. It may constitute between 0.1% to 20% by weight of formulation depending on the nature of gelling agent, preferably between 0.5% to 10% and more preferably between 0.5% to 5%. The gelling agents may be carbomers, cellulose derivatives, poloxamers and poloxamines. The preferred gelling agents are chitosan, dextran, pectins, natural gums and cellulose derivatives such as ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and the like. The most preferred gelling agent is hydroxypropyl cellulose.

[00142] The composition of invention may comprise a gelling agent as described above, in particular a non-prenutralized acrylic polymer and also comprise a neutralizing agent. The ratio of neutralizing agent/gelling agent varies in between 10:1 to 0.1:1, preferably between 7:1 to 0.5:1, and more preferably between 4:1 to 1:1. A neutralizing agent

in the presence of polymer should form salts that are soluble in the vehicle. A neutralizing agent also should permit optimum swelling of polymer chains during neutralization of charges and formation of polymer salts. The neutralizing agents include ammonium hydroxide, potassium hydroxide, sodium hydroxide, aminomethylpropanol, trolamine, and tromethamine. Those skilled in the art will select a neutralizing agent according to the type of gelling agent used in the composition or formulation. However, no neutralizing agent is required when a cellulose derivative will be used as gelling agents.

[00143] In some embodiments, the compositions of present invention are employed to treat other diseases, and the medication is selected from a lipophilic or a compound made lipophilic by derivatization of the group consisting of antiasthma, antiarrhythmic, antifungals, antihypertensive, anticancer, antibiotics, antidiabetics, antihistamines, antiparasitics, antivirals, cardiac glycosides, hormones, immunotherapies, antihypotensives, steroids, sedatives and analgesics, tranquilizers, vaccines, and cell surface receptor blockers.

[00144] All references, including publications, patent applications, and patent cited herein, including those in the list below and otherwise cited in this specification, are hereby incorporated by reference to the same extent as if each reference was individually and specifically indicated to be incorporated by reference and were set forth in the entirety herein.

[00145] The use of terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising", "including", "having", and "containing" are to be construed as open-ended terms (i.e. meaning "including but not limited to") unless otherwise noted. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specifications should be constructed as indicating any non-claimed element as essential to the practice of the invention.

[00146] Preferred embodiments of this invention are described, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments can become apparent to those of ordinary skilled artisans to employ such variations as appropriate, and the inventors intend for the inventions to be practiced otherwise than specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as

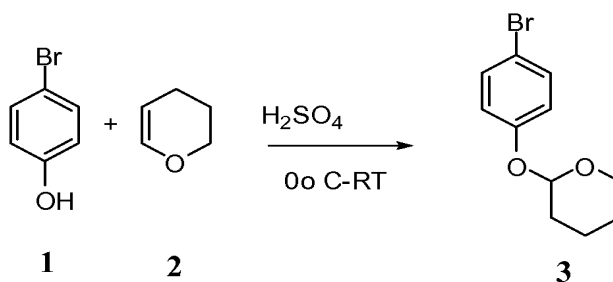
permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

5 EXAMPLES

[00147] The following examples further illustrate the invention and are not to be construed as in any way as limiting its scope.

10 EXAMPLE 1

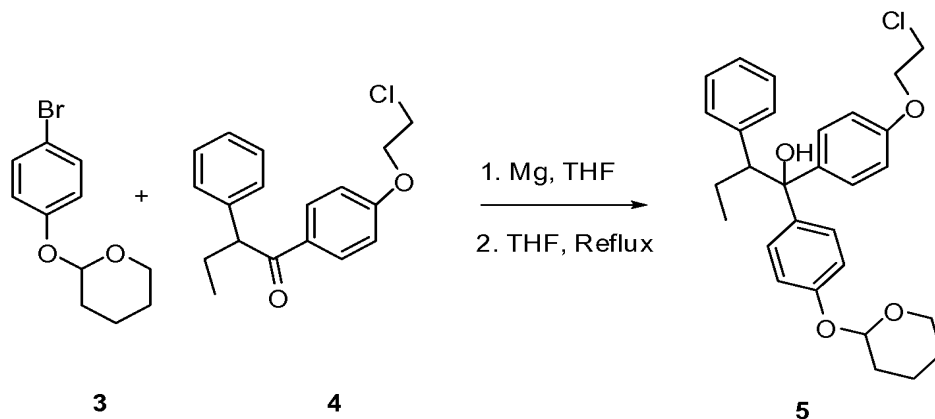
Synthesis of Compound 3



[00148] 4-Bromophenol (**1**, 1 kg) and 3, 4-dihydro-2H-pyran (**2**, 1.5 L) was mixed together in a round bottom flask and cooled to 0°C. Conc. Sulfuric acid (1 mL) was added drop wise while maintaining the temperature below room temperature. The solution was stirred at RT for 1 hr. The reaction solution was diluted with hexane and washed with water (1 L) followed by 5% sodium bicarbonate solution (1 L). The organic layer was dried over sodium sulfate, filtered and evaporated *in vacuo* at 50-55° C to give an oil (1.55 Kg). Hexane (300 mL) was added to the oil and triturated to give white solid **3**. The suspension was cooled to 0°C and stirred for 30 min before it was filtered and washed with cold hexane (100 mL) and dried. Yield 1.32 Kg.

EXAMPLE 2

Synthesis of Compound 5



5

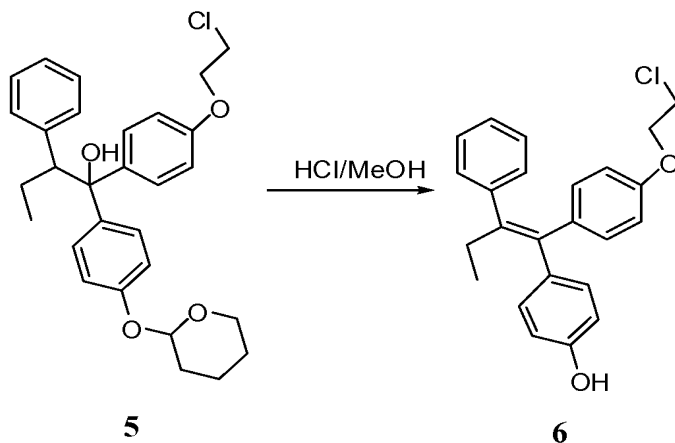
[00149] Magnesium turnings (115 g) were added to a 10_L 4-neck round bottom flask containing anhydrous tetrahydrofuran (1 L). The mixture was heated to 55°C. Iodine chips (approx. 5) were added in one lot followed by ethyl bromide (5 mL). Compound **3** (1.1 kg) was dissolved in THF (2 L). 200 mL of this solution was added at once to Mg-THF suspension. The reaction was initiated after 30 mins and reflux started. Remaining solution of compound **3** was added drop wise maintaining the reflux temperature over a period of 1.5 h. The reaction mixture was further refluxed for 2 hr and the cooled to RT. (2-Chloroethoxyphenyl) phenyl butanone (**4**, 870 g) in THF (1.5 L) was added drop wise over a period of 1 h maintaining the temperature between 30-35° C. The reaction mixture was refluxed for 4h and cooled to RT. The reaction mixture was poured into ice cold 50% hydrochloric acid (3L). The organic layer was separated and the aqueous layer was extracted with THF (3 x 500 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated to give **5** as oil which was carried over to next step without further purification. Yield – 1.57 kg.

20

25

EXAMPLE 3

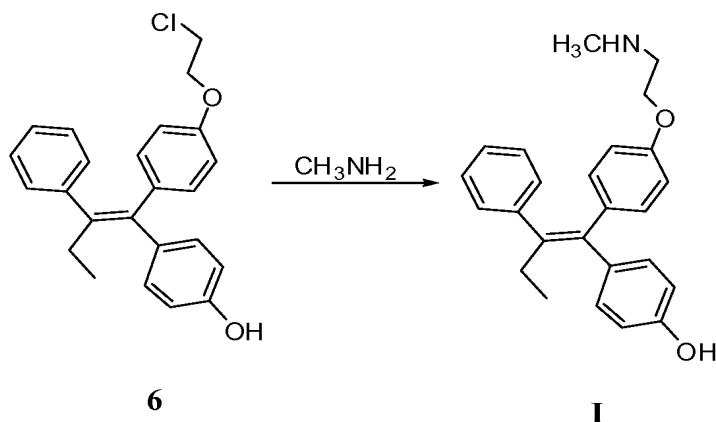
Synthesis of Compound 6



- 5 **[00150]** Compound (**5**, 1.57 kg) was dissolved in methanol (6 L) and conc. hydrochloric acid (1.57 kg) was added. The solution was refluxed for 5 h. Methanol was removed *in vacuo* and dichloromethane (5 L) was added. The organic layer was separated. The aqueous layer was extracted with dichloromethane (2 x 500 mL). The organic layers were combined and washed with water (2 L), 5% aq. NaHCO₃ (2 L), water (2L), dried over sodium sulfate. Charcoal was added and filtered. The solvent was removed under vacuum to give oil (1.38 kg). The oil was triturated with hexane (5 L) with vigorous stirring to yield
- 10 **6** as solid product which was filtered and dried. Yield 1.07 kg.

EXAMPLE 4

Synthesis of Compound I



- [00151]** To a solution of compound **6** (50 g) in isopropanol (500 mL), monomethyl amine (300 mL) was added and heated for 24 h maintaining the temperature between 70-

75°C. The completion of reaction was monitored by TLC (toluene:triethylamine, 7:3). The solvent was removed *in vacuo*. Water (500 mL) was added to the residue and extracted with diisopropyl ether (DIPE, 500 mL). The organic layer was separated and the aqueous layer was back extracted with DIPE (200 mL). The organic layers were combined and washed with water (500 mL), 5% aq. sodium bicarbonate (500 mL), dried over sodium sulfate and filtered. The solvent was removed *in vacuo* to give a gummy residue. Ethyl acetate (50 mL) was added and heated to dissolve the residue completely. The solution was cooled to RT and hexane (50 mL) was added and stirred for 12 h. The solid was filtered and washed with cold ethyl acetate-hexane (1:1, 10 mL) mixture. Product I was dried overnight under high vacuum. Yield 25 g.

EXAMPLE 5

Endoxifen Solution

[00152] Endoxifen solution (1 mg/mL) was prepared by solubilizing endoxifen (10.3 mg) in 0.2% glacial acetic acid (10 mL). The pH (~5.75) of the solution was adjusted with 1N sodium hydroxide (300 µL).

EXAMPLE 6

Endoxifen Solution

[00153] Endoxifen solution (5 mg/mL) was prepared by solubilizing endoxifen (100 mg) in 2% glacial acetic acid (8.6 mL). The solution was diluted with 5% dextrose (10.97 mL). The pH (~5.56) of the solution was adjusted with 5N sodium hydroxide (430 µL).

EXAMPLE 7

Endoxifen Complexes

[00154] A suspension of endoxifen, cholesteryl sulfate, and soy lecithin, is produced by mixing the components together in water and homogenizing using, *e.g.*, a high pressure homogenizer. The resulting suspension can be filtered through 0.2 µm filter and then mixed with 7.5% sucrose solution and lyophilized in either vials or in bulk. The particle size of the resulting complexes is determined using standard procedures, *e.g.*, using a Nicomp particle sizer 380.

EXAMPLE 8**Endoxifen Complexes**

[00155] A suspension of endoxifen and soy lecithin is produced by mixing the components together in water and homogenizing using, *e.g.*, a high pressure homogenizer..

5 The resulting suspension can be filtered through 0.2 μ m filter and then mixed with 7.5% sucrose solution and lyophilized in either vials or in bulk. The particle size is determined using standard procedures, *e.g.*, using a Nicomp particle sizer 380.

EXAMPLE 9**Toxicity Testing**

[00156] Endoxifen was formulated according to Example 6 and was tested for toxicity in male Balb/c mice. A single test dose at 100 mg/kg or 50 mg/kg was intravenously administered to mice. All the mice died at the 100 mg/kg dose level whereas all animals survived at the 50 mg/kg dose level with no significant loss of body weight. The mice also survived in the control group with a vehicle control that lacked endoxifen. Repeat dose toxicity study was conducted with a dose of 25 mg/kg administered consecutively for 3 days with accumulated dose of 75 mg/kg. All the animals in this group survived. The results are reported in the table below as the number of mice surviving per total.

Treatment	Dose (mg/kg)	Survival/Total
Single dose	100	0/2
	50	4/4
Repeat dose	25	4/4

EXAMPLE 10**Endoxifen exhibits anti-proliferative activity against different tumor cells**

[00157] Endoxifen was tested for antiproliferation activity against various cancer cell lines from Non Small Lung Cancer, Breast Cancer, Prostate Cancer, Melanoma Cancer, Ovarian Cancer, CNS Cancer, Renal Cancer and Colon Cancers. The cells were incubated for multiple days (3 - 7) with Endoxifen (10 nM to 10 μ M) and the inhibition of growth were measured by SRB or MTT staining method. The results indicated significant growth inhibition of cells in the presence of Endoxifen ranging from 10 to 100%. Endoxifen induce

growth inhibition or cell killing in different tumor cells indicates the usefulness of Endoxifen in the treatment of cancers in humans.

EXAMPLE 11

5 **Endoxifen Inhibits Estradiol Dependent Breast Tumor Growth**

[00158] It is known that Tamoxifen antagonizes estradiol-dependent breast cancer xenograft growth (15). Endoxifen base and endoxifen-citrate in oral dosage form can be similarly be tested for inhibition of estradiol dependent MCF-7 xenograft growth. For the animal experiments, female nude mice (Bom: NMRI-*nu/nu*) per xenograft experiment, ages
10 4 to 6 weeks and weighing 20 to 24 g, are used according to standard protocols. An example of such a procedure is as follows:

[00159] MCF-7 xenografts are developed by passage of transplantable tumor from a parent tumor established in oophorectomized athymic nude mice treated with estradiol (16-17).

15 [00160] Randomly bred female athymic mice are bilaterally ovariectomized and allowed a 2-week recovery period before the implantation of tumor material. The s.c. transplantation of the MCF-7 tumor fragments (size, $1 \times 1 \times 1 \text{ mm}^3$) is done under anesthesia. The diameter of the tumors is measured regularly, *e.g.*, once weekly, using a caliper-like mechanical instrument and the tumor volume (V) is calculated according to the
20 empirical equation $V = (\text{length} \times \text{width}^2)/2$. The median volumes of each group are normalized to the initial tumor volume resulting in the relative tumor volume. In all the experiments, tumor-bearing mice receive estradiol supplementation [estradiol valerate (E2D), 0.5 mg/kg once/wk i.m.]. This supplementation leads to physiologic levels of serum E2 (25-984 pg/mL) that are comparable to the human situation (25–600 pg/mL depending
25 on the follicular phase).

[00161] Substances: The following substances are used: E2D, Tamoxifen and endoxifen.

[00162] Treatment Modalities: All MCF-7 transplanted animals receive E2D (0.5 mg/kg) injections once a week. After 4 weeks, when hormone-supplemented tumors have
30 grown to ~0.7-0.8 cm in diameter ($180\text{-}250 \text{ mm}^3$), the mice are randomized into 4 treatment groups of 5-10 mice each. The 5-10 mice are sacrificed as baseline controls for E2D alone.

[00163] The treatment groups are: (i) E2D support (0.5mg/kg once/wk i.m); (ii) E2D support (0.5mg/kg once/wk i.m) plus Tamoxifen (0.5mg-2mg)/mouse per day, 5

days/week by gavage ; (iii) E2D support (0.5mg/kg once/wk i.m) plus endoxifen (0.5mg-2mg)/mouse per day, 5 days /week by gavage; (iv) withdrawal of E2D support.

[00164] Suppression of tumor growth in this breast cancer tumor model is indicative of therapeutic effect in the treatment of breast cancer in humans (15).

5

EXAMPLE 12

Endoxifen Minimizes Uterotrophic Effect of Estrogen

[00165] It is known that Tamoxifen is a non-steroidal agent with potent anti-estrogenic effect in animal and *in vitro* models. This pharmacologic property is related to the drug's ability to compete with estrogen for estrogen receptors in breast tissues, and to inhibit the stimulatory effect of estrogen on the uterus, vagina and ovaries (18).

[00166] Endoxifen (0.1 mg-2 mg) is administered orally once daily for 28 days to determine the reduction in utertrophic effect of estradiol; Female BALB/c mice approximately 50 days old and weighing 19-20 g are obtained (*e.g.*, from Charles-River, Inc.) and housed four to five per cage at a temperature (23+₋ 1 C) and light (12 h light/day). The atrophic changes are observed in the mice. There will be three groups such as vehicle control, Tamoxifen and endoxifen. The animals (5-10 mice) are randomly assigned to each group. Daily treatments of intact mice with a dose (*e.g.*, 0.1 mg-2mg) by gavage of Tamoxifen or endoxifen are expected to lead to progressive inhibition of uterine and vaginal weight.

[00167] Such results will show that endoxifen has better minimizing uterotrophic effect of estrogen than Tamoxifen, and that endoxifen finds use as an effective anti-estrogen. Endoxifen blocking of uterine weight gain stimulated by estrogen can also be demonstrated in immature rats. Endoxifen preparations showing the effects described above find use in the treatment of breast cancer as well as other estrogen-sensitive conditions, such as endometriosis, leiomyomata, and benign breast disease, as well as other estrogen-responsive conditions in men and women.

30

EXAMPLE 13

Endoxifen-Caused Decrease of Ki-67 Antigen Expression in Proliferating Breast Cancer Cells

[00168] Ki-67 is a nuclear non-histone protein. This antigen is absent in quiescent cells and is expressed in proliferating cells and is used as a biomarker (19-20). Endoxifen

base or endoxifen-citrate in oral or injectable form are given to xenograft breast cancer tumor models (*e.g.*, as described above), as well as to breast cancer patients.

Immunochemical determination of Ki-67 is done in tumor cells from breast cancer tissues from patients, as well as from mice bearing tumors as described in Example 11. The MIB-1 or similar antibody available from commercial sources such as DAKO, Carpinteria, CA is used for immunochemical localization of antigen. Decrease in Ki-67 antigen expression in animals and/or breast cancer patients demonstrate the applicability of endoxifen in treating breast cancers.

EXAMPLE 14

Endoxifen reduces IGF-1 levels in Breast Cancer

[00169] It is known for humans that Tamoxifen reduces the levels of circulating insulin-like growth factor I (IGF-1). IGF-1 has been used as a surrogate biomarker and predicts the effectiveness of Tamoxifen in treatments of breast cancer patients (21). To test the effects of endoxifen preparations of the present invention, endoxifen base or endoxifen-citrate are given orally or injected to experimental animals bearing breast cancer tumors. The concentration of IGF-1 levels in control and xenografted breast tumor is monitored by established assays (*e.g.*, ELISA Kit from Diagnostics Systems Laboratories, London, UK or DAKO, Carpinteria, CA). Endoxifen is administered by gavages at 0.5mg-2mg per mouse per day, 5 days/week. Decrease of IGF-1 levels and tumor growth reduction indicates the usefulness of IGF-1 as a surrogate marker for breast cancer.

EXAMPLE 15

Endoxifen Prevents Development of Bicalutamide –induced Gynecomastia and Breast Pain

[00170] Bicalutamide (CasodexR) is used for treating prostate cancer in men. There is growing evidence that IGF-1 may be involved in prostate cancer promotion and progression. It is also known that anti-estrogen agents such as Tamoxifen decrease IGF-1 levels and prevent bicalutamide –induced gynecomastia in prostate cancer patients (22). Since, endoxifen is an active metabolite of the Tamoxifen anti-estrogen, the silastic slow-release capsules containing endoxifen for implant or oral doses of endoxifen (1mg-10mg/day) with bicalutamide are expected to prevent development of bicalutamide –induced gynecomastia and breast pain.

REFERENCES

1. Furr BJ, Jordan VC. The pharmacology and clinical uses of Tamoxifen. *Pharmacol Ther* 1984; 25:127-205.
2. Osborne. Tamoxifen in the treatment of breast cancer. *N Engl J Med* 1998; 339:1609-18.
3. Fisher B, Costantino JP, Wickerham DL, Redmond CK, kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant and Bowel Project P-1 Study. *J. Natl Cancer Insts* 1998; 90:1371-88.
4. Stearns V, Ullmer L, Lopez JF, Smith Y , Issacs C, Hays D. Hot flushes. *Lancet* 2002; 360:1851-61.
5. Otton SV, Ball SE, Cheung SW, Inaba T, Rudolph RL, Sellers EM. Venlafaxine oxidation in vitro is catalyzed by CYP2D6. *Br J Clin Pharmacol* 1996; 41:149-56.
6. Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P, Hayes DF, Desta Z, Flockhart DA. Active Tamoxifen metabolite concentrations after co-administration of Tamoxifen and the selective serotonin reuptake inhibitor paroxetine. *J Natl Cancer Inst* 2003; 95:1758-1764.
7. YC, Desta Z, Flockhart DA and Skaar TC. Endoxifen (4-hydroxy-N-desmethyl-Tamoxifen) has anti-estrogenic effects in breast cancer cells with potency similar to 4-hydroxy-Tamoxifen. *Journal of Cancer Chemotherapy and Pharmacology* 2005; 55: 471-478.

9. Young Chai Lim, Lang Li, Zeruesenay Desta, Qianqian Zhao, James M. Rae, David A. Flockhart, and Todd C. Skaar. Endoxifen, a Secondary Metabolite of Tamoxifen, and 4-OH-Tamoxifen Induce Similar Changes in Global Gene Expression Patterns in MCF-7 Breast Cancer Cells; JPET, 2006, 318:503-512.

5

10. Matthew P. Goetz, James M. Rae, Vera J. et al. Pharmacogenetics of Tamoxifen Biotransformation Is Associated With Clinical Outcomes of Efficacy and Hot Flashes. JCO Dec 20 2005: 9312–9318.

10

11. Satyavati GV, Economic and Medical Plant Research, 5, 47(1991).

12. Indian Pharmacopeia, 1988.

15

13. Remington: The Science and Practice of Pharmacy (Lippincott Williams & Wilkins (2000), pages 836-58.

14. Percutaneous Absorption: Drugs Cosmetics Mechanisms Methodology edited by Bronaugh and Maibach, Marcel Becker Publisher (1999).

15. Stephen R.D. Johnston, Irene M. Boeddinghaus, Sharon Riddler, Ben P. Haynes, Ian R. Hardcastle, Martin Rowlands, Rachel Grimshaw, Michael Jarman, and Mitch Dowsett. Iodoxifen Antagonizes Estradiol-dependent MCF-7 Breast Cancer Xenograft Growth through Sustained Induction of Apoptosis, *Cancer Research*, 59, 3646-3651 (1999).
16. Iino, Y, Wolf, DM, Langan-Fahey SM, Johnson, DA, Ricchio, M, Thompson, ME, and Jordan VC. Reversible Control of Oestradiol-stimulated Growth of MCF-7 Tumours in the Athymic Mouse. *Br. J. cancer*, 64: 1019-1024 (1991)
17. Jann N Sarkaria, David FC Gibson, V C Jordan, John F Fowler, Mary J. Lindstrom, and R. Timothy Mulacahy. Tamoxifen-induced increase in the Doubling time of MCF-7 Xenografts as Determined by Bromodeoxyuridine Labeling and Flow Cytometry. *Cancer Research* 53, 4413-4417 (1993).
18. Nanjoo Suh, Andrew L. Glasebrook, Alan D. palkowitz, Henry U. Bryant, Lorris L. Burris, james J. Starling, Homer L. Pearce, Charlotte Williams, Christopher Peer, Yongping Wang and Michael B. Sporn. Arzoxifene, a New Selective Estrogen receptor Modulator For Chemo prevention of Experimental Breast Cancer. *Cancer Reseach* 61, 8412-8415 (2001).
19. Assersohn L, Salter J, Powles TJ, et al: Studies of the potential utility of Ki-67 as a predictive molecular marker of clinical response in primary breast cancer. *Breast Cancer Res Treat* 82:113-123, (2003).
20. Kenny FS, Willsher PC, Gee JM, et al: Change in expression of ER, bcl-2 and MIB-1 on primary Tamoxifen and relation to response in ER positive breast cancer. *Breast Cancer Res Treat* 65: 135-144, (2001).
21. Nahta R, Hartobagyi GN and Esteva FJ. Growth factor Receptors in Breast Cancer: Potential for Therapeutic Intervention, *Oncologist* 8: 5-17, (2003).
22. Saltstein D, Sieber P, Morris T, Gallo J. Prevention and Management of Biclutamide-induced gynecomastia and Breast Pain: Randomized Endocrinologic

and Clinical Studies with Tamoxifen and Anastrozole. Prostate cancer and Prostatic Diseases 8, 75-83 (2005).

Figure 1

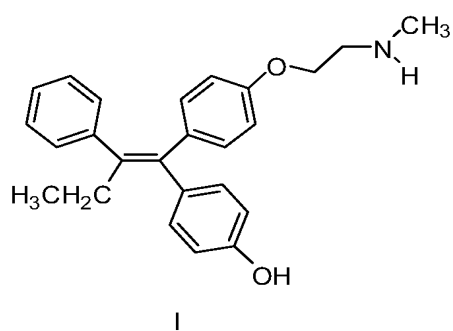


Figure 2

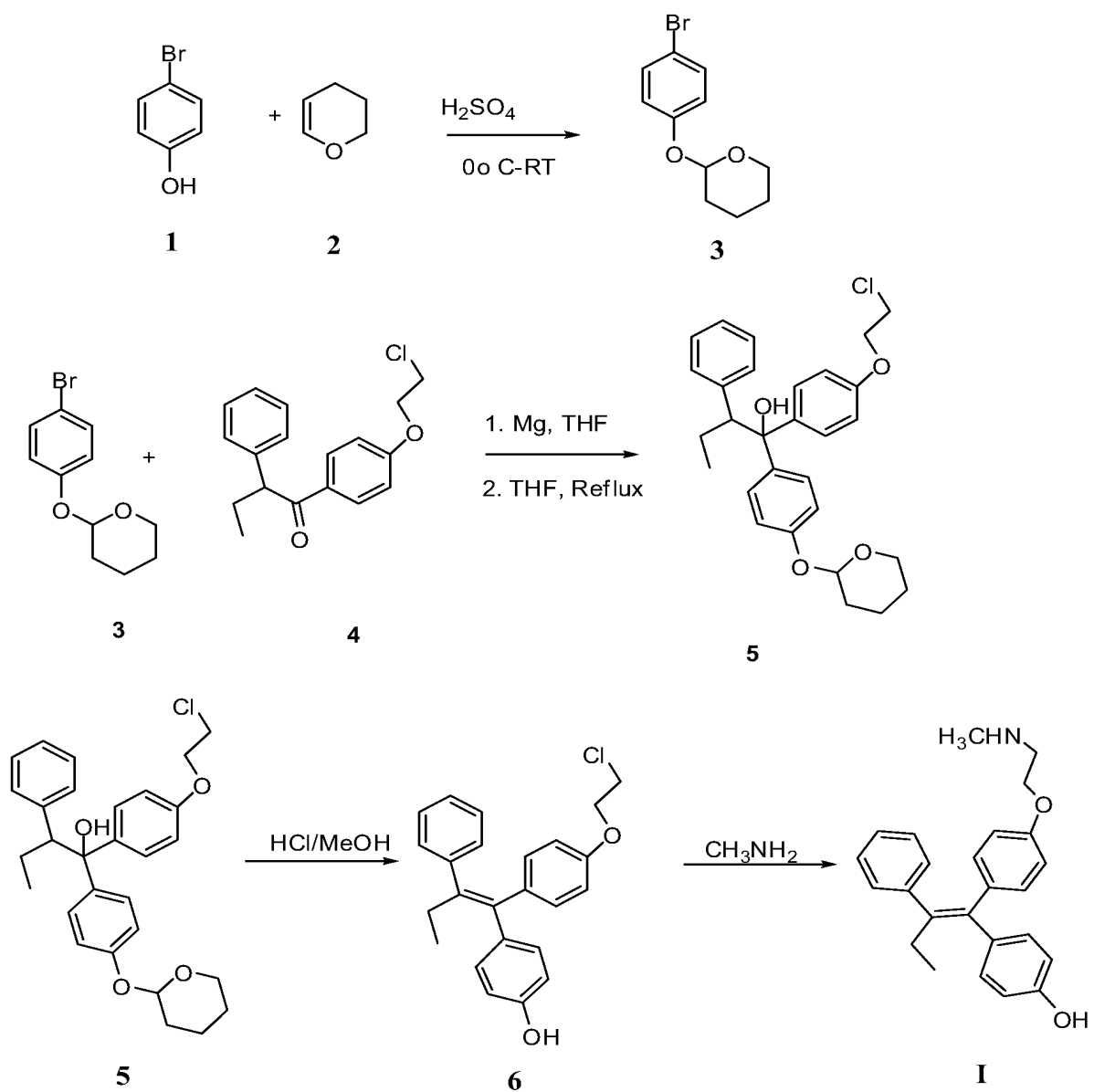
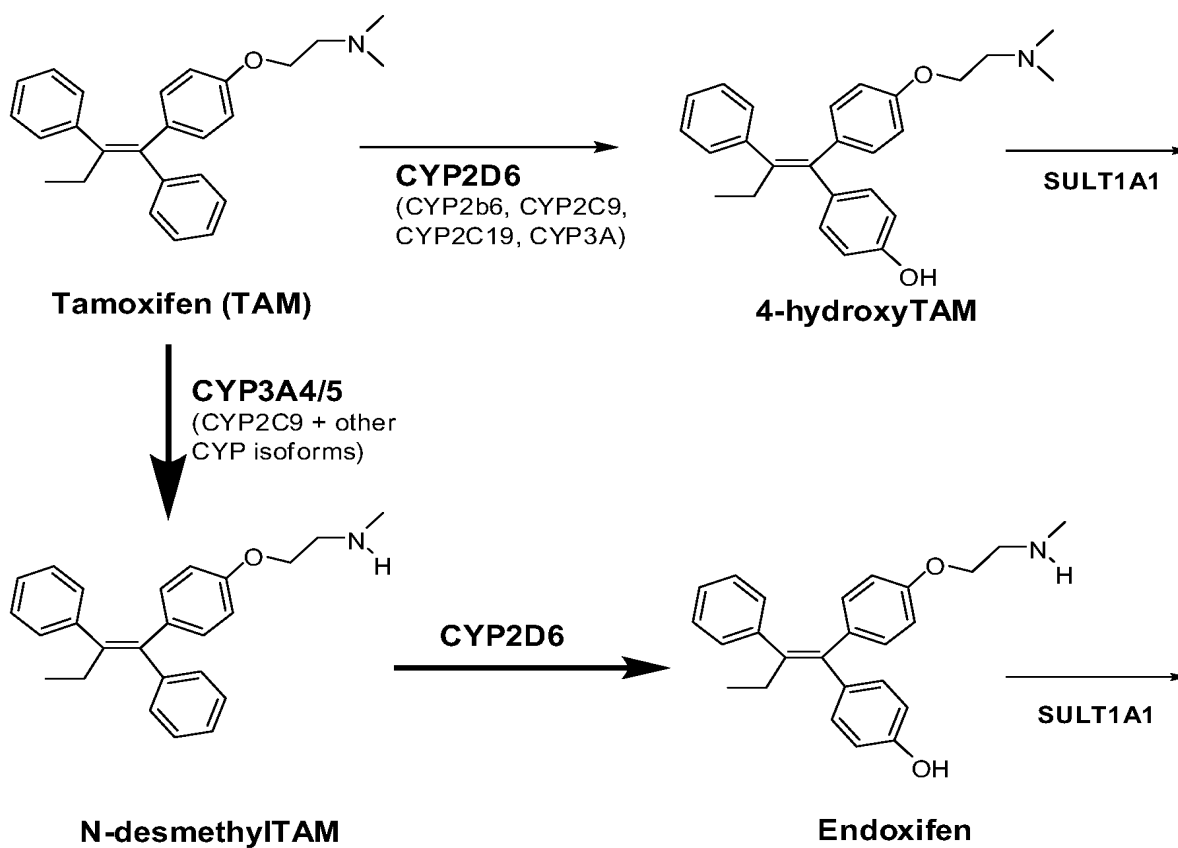


Figure 3



CLAIMS

1. A method of treating a disease comprising, preparing a composition comprising a therapeutically active amount of a complex comprising an anticancer drug and with or without at least one lipid.

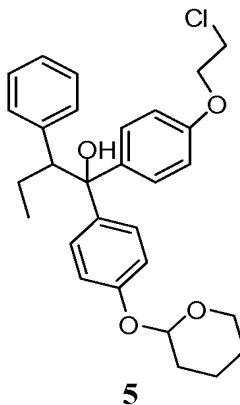
2. The method of claim 1, wherein the anticancer drug is endoxifen, and wherein said endoxifen is a free base or is in the form of a salt.

3. The method of claim 2 wherein said endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetane, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate.

4. The method of claim 2 or 3, wherein said endoxifen is predominantly in a form selected from the group consisting of *E*-isomer, *Z*-isomer, and a mixture of *E*- and *Z*-isomer.

5. A method of preparing endoxifen, comprising:

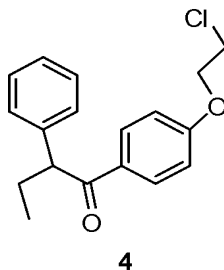
i. reacting a compound of Formula 5 with acid, wherein the compound of formula 5 has the structure:



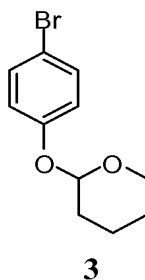
and

i. after said reaction of said compound of Formula 5 with acid,
reacting said compound with methylamine.

5 6. The method of claim 5, wherein said compound of Formula 5 is prepared
by reacting compound of formula 4

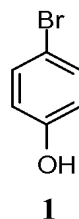


with a compound of Formula 3.



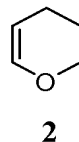
10

7. The method of claim 6, wherein said compound of Formula 3 is prepared
by reacting compound of Formula 1



15

with a compound of Formula 2.



8. A method of purifying the endoxifen of claim 5, comprising:
a. crystallizing said endoxifen; and/or

b.chromatographically treating said endoxifen;

to produce a purified preparation of endoxifen, wherein said purified preparation of endoxifen contains predominantly *E*-isomer, predominantly *Z*-isomer, or a mixture of *E*- and *Z*-isomers of endoxifen.

5

9. The method of claim 1 or 2, wherein said at least one lipid is selected from the group consisting of egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylcholine (DPPC), distearylphosphatidylglycerol (DSPG), dipalmitoylphosphatidylglycerol (DMPG), cholesterol (Chol), cholesterol sulfate and its salts (CS), cholesterol hemisuccinate and its salts (Chems), cholesterol phosphate and its salts (CP), cholesterylphosphocholine and other hydroxycholesterol or amino cholesterol derivatives, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), coprostanol, cholestanol, cholestane, cholic acid, cortisol, corticosterone, hydrocortisone, and calciferol, *E*-guggulsterone, *Z*-guggulsterone, mixture of *E*- and *Z*-guggulsterone, monoglycerides, diglycerides, triglycerides, carbohydrate-based lipids selected from a group consisting of galactolipid, mannosylphosphatidylcholine, β -sitosterol, stigmasterol, stigmasterol, lanosterol, α -spinasterol, lathosterol, campesterol, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, and pegylated derivatives of distearylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, and dioleoylphosphatidylglycerol.

15

20

25

10. The method of claim 2, wherein said composition comprises endoxifen, cholesterol and/or cholesterol derivatives, and one or more phospholipids.

11. The method of claim 10, wherein said composition comprises a cholesterol derivative, wherein the cholesterol derivative is cholesteryl sulfate.

30

12. The method of claim 10, wherein at least one of said phospholipids is hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.

13. The method of claim 1, wherein said composition comprises a form selected from the group consisting of powder, solution, emulsion, micelle, liposome, lipidic particle, gel, and paste form.

5 14. The method of claim 1 or 13, wherein said preparing of said composition comprising a complex comprises preparing said complex in a lyophilized form.

10 15. The method of claim 14, wherein said preparing said complex in a lyophilized form comprises using a cryoprotectant, wherein said cryoprotectant comprises one or more sugars selected from the group consisting of trehalose, maltose, lactose, sucrose, glucose, and dextran.

15 16. The method of claim 1 or 2, wherein, said composition comprises a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.

17. The method of claim 1 or 2, wherein said disease is cancer or caused by cancer-causing agents.

20 18. The method of claim 1 or 2, wherein said disease is benign breast disease.

25 19. The method of claim 1 or 2, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

20. The method of claim 1 or 2, wherein said composition comprises a penetration enhancer, wherein said penetration enhancer comprises at least one saturated or unsaturated fatty acid ester.

30 21. The method of claim 2, wherein said composition comprising endoxifen is formulated in a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder or an oil.

22. The method of claim 21, wherein said composition comprising endoxifen is formulated in a hydroalcoholic composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

5 23. The method of claim 21, wherein said hydroalcoholic composition comprises a neutralizing agent.

24. The method of claim 21, wherein said hydroalcoholic composition comprises

- 10 (i) endoxifen at about 0.01% to 0.20% by weight;
- (ii) isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight;
- (iii) alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight
- 15 (iv) aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and
- (v) gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight.

wherein the percentage of components is weight to weight of the composition.

20

25. The method of claim 24, wherein said alcohol is ethanol or isopropanol, and constitutes in absolute form.

26. The method of claim 24, wherein said aqueous vehicle is a phosphate
25 buffered solution.

27. The method of claim 24, wherein said gelling agent is selected from the group consisting of polyacrylic acid, hydroxypropylcellulose and a cellulose derivative other than hydroxypropylcellulose.

30

28. The method of claim 24, wherein said hydroalcoholic composition further comprises a neutralizing agent, wherein said neutralizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, arginine, trolamine, and tromethamine, and wherein said

neutralizing agent exists at a neutralizing agent/gelling agent ratio of about 1:1 to about 4:1.

29. A method of delivering endoxifen, comprising providing a composition according to any of the claims 1-28 and delivering said composition so as to expose the composition to a cell.

30. The method of claim 29, wherein the cell is *in vivo*.

31. The method of claims 1 and 30, wherein the host is a mammal.

32. A method of inhibiting hormone-dependent breast carcinoma in a mammal comprising administering composition of claim 1, 2 and 24 to said mammal.

33. A method of inhibiting a cancer in a mammal, said cancer selected from the group consisting of lung cancer, colon cancer, breast cancer, leukemia, renal cancer, melanoma, cancer of the central nervous system, and prostate cancer in a mammal, comprising administering a composition of claim 1, 2 or 24 to said mammal.

34. The method of claim 31, 32 or 33 wherein said mammal is human.

35. A composition comprising a therapeutically active amount of a complex comprising endoxifen and at least one lipid, wherein said endoxifen is a free base or is in the form of a salt.

36. The composition of claim 35, wherein said composition comprising endoxifen is formulated in a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder or an oil.

37. The composition of claim 36, wherein said composition comprising endoxifen is formulated in a hydroalcoholic composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

38. The composition of claim 36, wherein said hydroalcoholic composition comprises a neutralizing agent.

39. The composition of claim 36, wherein said hydroalcoholic composition comprises

- (i) endoxifen at about 0.01% to 0.20% by weight;
- (ii) isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight;
- (iii) alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight
- (iv) aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and
- (v) gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight.

wherein the percentage of components is weight to weight of the composition.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ateeq Ahmad, et al.	Confirmation No.:
Serial No.:	Group No.:
Filed: Herewith	Examiner:
Entitled: Endoxifen Compositions And Methods	

PRELIMINARY AMENDMENT

EFS WEB FILED
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATE OF EFS WEB TRANSMISSION UNDER 37 C.F.R. § 1.8	
I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being transmitted to the United States Patent and Trademark Office transmitted via the Office electronic filing system in accordance with 37 C.F.R. §1.6(a)(4).	
Dated: <u>May 15, 2009</u>	By: <u>/Mary Ann D. Brow/</u> Mary Ann D. Brow, Reg. No. 42,363

Sir or Madam:

Prior to examination of the instant application, please amend the application submitted herewith as follows.

Amendments to the Specification begin on page 2 of this communication.

Amendments to the Claims begin on page 3 of this communication.

Remarks are on page 8 of this communication.

The Commissioner is authorized by this paper to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No. JINA-13458/US-1/PCT. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

AMENDMENTS TO THE CLAIMS:

This listing of the claims will replace all prior listings and versions of claims in the application:

1-39 (cancelled)

40. (new) A composition comprising an effective amount of a complex comprising endoxifen, wherein said endoxifen is a free base or is in the form of a salt.

41. (new) The composition of claim 40, wherein said composition comprising endoxifen is formulated in a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder, a tablet, a capsule, an enteric-coated capsule, an enteric coated tablet, a lozenge, or an oil.

42. (new) The composition of claim 40, wherein said composition comprising endoxifen is formulated in a hydroalcoholic composition containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

43. (new) The composition of claim 40, wherein said hydroalcoholic composition comprises a neutralizing agent, wherein said neutralizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, arginine, tromamine, and tromethamine, and wherein said neutralizing agent exists at a neutralizing agent/gelling agent ratio of about 1:1 to about 4:1.

44. (new) The composition of claim 40, wherein said hydroalcoholic composition comprises

- (i) endoxifen at about 0.01% to 0.20% by weight;
 - (ii) isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight;
 - (iii) alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight
 - (iv) aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight;
- and
- (v) gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight.

wherein the percentage of components is weight to weight of the composition.

45. (new) The composition of claim 40, wherein said endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetate, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate salts.

46. (new) The composition of claim 40, wherein said composition comprises at least one lipid selected from the group consisting of egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylcholine (DPPC), distearylphosphatidylglycerol (DSPG), dipalmitoylphosphatidylglycerol (DMPG), cholesterol (Chol), cholesterol sulfate and its salts (CS), cholesterol hemisuccinate and its salts (Chems), cholesterol phosphate and its salts (CP), cholesterylphosphocholine and other hydroxycholesterol or amino cholesterol derivatives, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), coprostanol, cholestanol, cholestane, cholic acid, cortisol, corticosterone, hydrocortisone, and calciferol, *E*-guggulsterone, *Z*-guggulsterone, mixture of *E*-and *Z*-guggulsterone, monoglycerides, diglycerides, triglycerides, carbohydrate-based lipids selected from a group consisting of galactolipid, mannosyl, galactolecithin, β -sitosterol, stigmasterol, stigmasterol, lanosterol, α -spinasterol, lathosterol, campesterol, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, and pegylated derivatives of distearylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, and dioleoylphosphatidylglycerol.

47. (new) The composition of claim 40, wherein said composition comprises endoxifen, cholesterol and/or a cholesterol derivative, and one or more phospholipids.

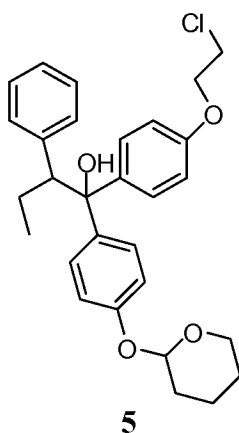
48. (new) The composition of claim 47, wherein at least one of said one or more phospholipids is hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.

49. (new) The composition of claim 40, wherein said composition comprises a form selected from the group consisting of powder, solution, emulsion, micelle, liposome, lipidic particle, gel, paste form, a lyophilized form, and a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.

50. (new) The composition of claim 40, wherein said composition is in a lyophilized form comprising a cryoprotectant, wherein said cryoprotectant comprises one or more sugars selected from the group consisting of trehalose, maltose, lactose, sucrose, glucose, and dextran.

51. (new) A method of preparing endoxifen, comprising:

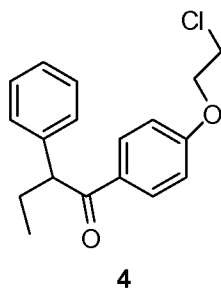
- i. reacting a compound of Formula **5** with acid, wherein the compound of formula **5** has the structure:



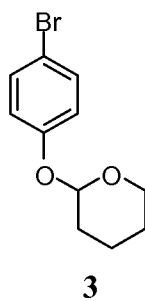
and

- ii. after said reaction of said compound of Formula 5 with acid, reacting said compound with methylamine.

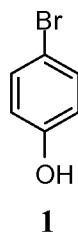
52. (new) The method of claim 51, comprising a step of preparing said compound of Formula **5** by reacting compound of formula **4**



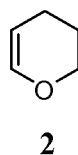
with a compound of Formula 3.



53. (new) The method of claim 52, further comprising a step of preparing said compound of Formula 3 by reacting compound of Formula 1



with a compound of Formula 2.



54. (new) The method of claim 51, comprising:
- a) crystallizing said endoxifen; and/or
 - b) chromatographically treating said endoxifen;
- to produce a purified preparation of endoxifen, wherein said purified preparation of endoxifen contains predominantly *E*-isomer, predominantly *Z*-isomer, or a mixture of *E*- and *Z*-isomers of endoxifen.
55. (new) A method of treating a cell, comprising, exposing said cell to a composition of claim 40.
56. (new) The method of claim 55, wherein the cell is *in vivo* in a host.
57. (new) The method of claim 56, wherein said host is a mammal.
58. (new) The method of claim 55, wherein said exposing comprises administering a composition of claim 40 to a subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.
59. (new) A method of treating a subject having cancer, comprising administering a composition of claim 40 to said subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject

REMARKS

Applicants respectfully request entry of this Preliminary Amendment prior to examination of the present application. These amendments do not contain new matter.

Dated: May 15, 2009

/Mary Ann D. Brow/
Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
440 Science Dr., Suite 203
Madison, WI, 53711
608-218-6900



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/515,261	01/08/2010	Ateeq Ahmad	JINA-13458/US-1/PCT	7363
72960	7590	11/08/2011		
Casimir Jones, S.C. 2275 DEMING WAY, SUITE 310 MIDDLETON, WI 53562			EXAMINER CHANNAVAJALA, LAKSHMI SARADA	
			ART UNIT	PAPER NUMBER
			1611	
			MAIL DATE	DELIVERY MODE
			11/08/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 12/515,261	Applicant(s) AHMAD ET AL.	
	Examiner LAKSHMI CHANNAVAJJALA	Art Unit 1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 40-59 is/are pending in the application.
 5a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☐ Claim(s) ____ is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☒ Claim(s) 40-59 are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Election/Restrictions

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 40-50, drawn to a composition comprising endoxifen.

Group II, claim(s) 51-54, drawn to a method of preparing endoxifen.

Group III, claim(s) 55-59, drawn to a method of treatment.

2. The groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The prior art of record (Johnston et al, 1991, Cancer Research submitted by applicants on IDS submitted on 11-9-09) teaches endoxifen containing compositions for breast cancer treatment, which breaks the unity of the invention of the instant groups. Therefore, instant claims lack the special technical feature and thus do not relate to a single general inventive concept.

3. This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

If Group III is elected, the species are as follows:

Route of administration: oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, or topical (claims 58, 59);

If Group I is elected, the species are as follows:

Form of the composition from: a hydroalcoholic gel, a hydroalcoholic solution, a patch, a cream, an emulsion, a lotion, an ointment, a powder, a tablet, a capsule, an enteric-coated capsule, an enteric coated tablet, a lozenge, or oil (claims 41 & 49).

Applicants are required to elect a "single" route and a "single specific" form.

Applicant is required, in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable. The reply must also identify the claims readable on the elected species, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered non-responsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise require all the limitations of an allowed generic claim. Currently, the following claim(s) are generic: claims 40, 41, 55, 58 and 59.

The above species are different because each of the routes of administration requires different formulations such as specific penetration vehicles, carriers, backing materials etc. For instance, a cream cannot be applied parenterally, and a patch for transdermal application requires additional backing materials or reservoirs etc., that is not necessary for intraperitoneal administration. In addition, these species are not obvious variants of each other based on the current record.

4. REQUIREMENT FOR UNITY OF INVENTION

As provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive

Art Unit: 1611

concept (“requirement of unity of invention”). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression “special technical features” shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. See 37 CFR 1.475(e).

WHEN CLAIMS ARE DIRECTED TO MULTIPLE CATEGORIES OF INVENTIONS

As provided in 37 CFR 1.475(b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

- (1) A product and a process specially adapted for the manufacture of said product; or
- (2) A product and process of use of said product; or
- (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4) A process and an apparatus or means specifically designed for carrying out the said process; or

(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Otherwise, unity of invention might not be present. See 37 CFR 1.475(c).

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species or invention to be examined even though the requirement may be traversed (37 CFR 1.143) and (ii) identification of the claims encompassing the elected invention.

The election of an invention or species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected invention or species.

Should applicant traverse on the ground that the inventions have unity of invention (37 CFR 1.475(a)), applicant must provide reasons in support thereof. Applicant may submit evidence or identify such evidence now of record showing the

Art Unit: 1611

inventions to be obvious variants or clearly admit on the record that this is the case.

Where such evidence or admission is provided by applicant, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

6. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not

Art Unit: 1611

commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKSHMI CHANNAVAJJALA whose telephone number is (571)272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1611

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ateeq Ahmad, et al.	Confirmation: 7363
Serial No.: 12/515,261	Group No.: 1611
Filed: 15-May-2009	Examiner: Channavajjala
Entitled: Endoxifen Compositions And Methods	

**RESPONSE TO RESTRICTION REQUIREMENT MAILED
NOVEMBER 8, 2011**

EFS WEB FILED

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

CERTIFICATE OF EFS WEB TRANSMISSION UNDER 37 C.F.R. § 1.8	
<p>I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being transmitted to the United States Patent and Trademark Office transmitted via the Office electronic filing system in accordance with 37 C.F.R. §1.6(a)(4).</p>	
Dated: <u>February 8, 2012</u>	By: <u>/Mary Ann D. Brow/</u> Mary Ann D. Brow, Reg. No. 42,363

Examiner Channavajjala:

This is responsive to the Office Communication mailed November 8, 2011, with response due on or before December 8, 2011. A two month extension of time, to February 8, 2012, is requested.

The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No. **JINA-13458/US-1/PCT**. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

In accordance with the procedure for Amendment Practice under 37 C.F.R. §1.121, please amend the above-identified application as follows:

Amendments to the Claims are reflected in a Listing of Claims that begins on page 3 of this communication.

Remarks begin on page 6 of this communication.

AMENDMENTS TO THE CLAIMS:

This listing of the claims will replace all prior listings and versions of claims in the application:

1-39. (cancelled)

40. (currently amended) A composition comprising an effective amount of a complex comprising a synthetic preparation of endoxifen, wherein said endoxifen is a free base or is in the form of a salt, wherein said composition comprising endoxifen is composition formulated in a hydroalcoholic gel, a patch, a cream, an emulsion, a lotion, an ointment, a powder, a tablet, a capsule, an enteric-coated capsule, an enteric coated tablet, a lozenge, or an oil.

41. (cancelled)

42. (withdrawn, currently amended) The composition of claim 40, wherein said composition comprising endoxifen is formulated in a hydroalcoholic ~~composition~~ gel containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

43. (withdrawn, currently amended) The composition of claim 40, wherein said hydroalcoholic ~~composition~~ gel comprises a neutralizing agent, wherein said neutralizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, arginine, tromamine, and tromethamine, and wherein said neutralizing agent exists at a neutralizing agent/gelling agent ratio of about 1:1 to about 4:1.

44. (withdrawn, currently amended) The composition of claim 40, wherein said hydroalcoholic ~~composition~~ gel comprises

- (i) endoxifen at about 0.01% to 0.20% by weight;
 - (ii) isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight;
 - (iii) alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight
 - (iv) aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight;
- and
- (v) gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight.

wherein the percentage of components is weight to weight of the composition.

45. (previously presented) The composition of claim 40, wherein said endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetate, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate salts.

46. (previously presented) The composition of claim 40, wherein said composition comprises at least one lipid selected from the group consisting of egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylcholine (DPPC), distearylphosphatidylglycerol (DSPG), dipalmitoylphosphatidylglycerol (DMPG), cholesterol (Chol), cholesterol sulfate and its salts (CS), cholesterol hemisuccinate and its salts (Chems), cholesterol phosphate and its salts (CP), cholesterylphosphocholine and other hydroxycholesterol or amino cholesterol derivatives, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), coprostanol, cholestanol, cholestane, cholic acid, cortisol, corticosterone, hydrocortisone, and calciferol, *E*-guggulsterone, *Z*-guggulsterone, mixture of *E*-and *Z*-guggulsterone, monoglycerides, diglycerides, triglycerides, carbohydrate-based lipids selected from a group consisting of galactolipid, mannosyl, galactosyl, sphingolipid, β -sitosterol, stigmasterol, stigmasterol, lanosterol, α -spinasterol, lathosterol, campesterol, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, and pegylated derivatives of distearylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, and dioleoylphosphatidylglycerol.

47. (previously presented) The composition of claim 40, wherein said composition comprises endoxifen, cholesterol and/or a cholesterol derivative, and one or more phospholipids.

48. (previously presented) The composition of claim 47, wherein at least one of said one or more phospholipids is hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.

49. (previously presented) The composition of claim 40, wherein said composition comprises a form selected from the group consisting of powder, solution, emulsion, micelle, liposome, lipidic particle, gel, paste form, a lyophilized form, and a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.

50. (previously presented) The composition of claim 40, wherein said composition is in a lyophilized form comprising a cryoprotectant, wherein said cryoprotectant comprises one or more sugars selected from the group consisting of trehalose, maltose, lactose, sucrose, glucose, and dextran.

51-54. (cancelled)

55. (previously presented) A method of treating a cell, comprising, exposing said cell to a composition of claim 40.

56. (previously presented) The method of claim 55, wherein the cell is *in vivo* in a host.

57. (previously presented) The method of claim 56, wherein said host is a mammal.

58. (previously presented) The method of claim 55, wherein said exposing comprises administering a composition of claim 40 to a subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

59. (previously presented) A method of treating a subject having cancer, comprising administering a composition of claim 40 to said subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

REMARKS

Claims 40-59 are pending in the present case. For business reasons and without acquiescing to the Examiner's arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claim 40 is herein amended to incorporate the features of Claim 41, and Claim 41 is cancelled.

In the Restriction Requirement mailed November 8, 2011, the Examiner restricted the claims into three groups:

Group I (Claims 40-50, drawn to a composition comprising endoxifen);

Group II (Claims 51-54, drawn to a method of preparing endoxifen); and

Group III (Claims 55-59, drawn to a method of treatment).

For business reasons, Applicants provisionally elect the claims of Group I, with traverse. Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. Applicants submit that the claims of Groups I and III relate to a single inventive concept. Each of the claims of Group III depends from Claim 40 and incorporates all the features thereof.

The Examiner points to a reference described as "Johnston et al., 1991, Cancer Research" as teaching endoxifen-containing compositions for breast cancer treatment. (Office Action page 2, paragraph 2). Applicants respectfully request clarification as no such reference has been cited in the IDS. A Johnston reference entitled "Iodoxifen Antagonizes Estradiol-dependent MCF-7 Breast Cancer Xenograft Growth through Sustained Induction of Apoptosis" Cancer Research, 59, 3646-3651 (1999) was cited in the IDS filed on 11/19/09. However, Johnston does not teach or suggest either preparation of endoxifen, or treatment with endoxifen. Applicants respectfully request withdrawal of the restriction requirement with respect to Group I and Group III claims.

Regarding the claims of Group I, the Examiner further requires election of a single form of composition. Applicants elect a tablet. Claims 42-44 are withdrawn in view of the present species election requirement, reserving the right to rejoin these claim in the event of allowance of a generic claim. Claims 40 and 45-50 read on the elected species.

Regarding the claims of Group III, the Examiner further requires election of a single route of administration. Applicants elect oral administration. Claims 55-57 are generic.

Claims 51-54 are cancelled without prejudice in view of the present Restriction Requirement, reserving the right to pursue these claims in one or more Divisional applications.

CONCLUSION

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608) 662-1277.

Dated: February 8, 2012

/Mary Ann D. Brow/
Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
2275 Deming Way, Suite 310
Middleton, Wisconsin 53562
608.662.1277



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/515,261	01/08/2010	Ateeq Ahmad	JINA-13458/US-1/PCT	7363
72960	7590	02/16/2012		
Casimir Jones, S.C. 2275 DEMING WAY, SUITE 310 MIDDLETON, WI 53562			EXAMINER CHANNAVAJALA, LAKSHMI SARADA	
			ART UNIT	PAPER NUMBER
			1611	
			MAIL DATE	DELIVERY MODE
			02/16/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

Receipt of amendment and response dated 2/8/12 is acknowledged.

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 40-50) in the reply filed on 2/8/12 is acknowledged. The traversal is on the ground(s) that where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. Applicants submit that the claims of Groups I and III relate to a single inventive concept. Each of the claims of Group III depends from Claim 40 and incorporates all the features thereof. This is not found persuasive because the common technical feature linking the claims is endoxifen. This element cannot be a special technical feature under PCT Rule 13.2 because the element is shown in the prior art. While examiner inadvertently cited the reference of Johnston et al., Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478) teaches synthetic endoxifen, thus breaking the unity of invention.

2. For the election of species, Applicants elect a tablet. Claims 42-44 are withdrawn in view of the present species election requirement, reserving the right to rejoin these claim in the event of allowance of a generic claim. Claims 40 and 45-50 read on the elected species.

The requirement is still deemed proper and is therefore made FINAL.

Applicants canceled claims 41 and 51-54 and claims 42-44 and 55-59 are withdrawn from further consideration.

Claims 40 and 45-50 have been considered for examination.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 40 and 45-46 and 49-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, submitted by applicants on IDS) in view of US 4,310,523 to Neumann and Zeisig et al (abstract, Anticancer Drugs, 2004).

Lim discloses synthetic preparation of endoxifen of the instant claims for anti-estrogenic effects and potency similar to that of 4-hydroxy tamoxifen. Page 472, col. 1

Art Unit: 1611

describes the use of synthetic, Endoxifen. Lim does not teach the claimed composition in the form of a tablet. While instant claim 40 requires a complex, the claim does not specify the components that form the complex.

Neumann teaches a composition comprising an anti-estrogen and anti-gonadotropically effective anti-androgen, wherein the former is tamoxifen (abstract). Neumann teaches administering the compositions by several routes including in the form of oral tablets (col. 9, l 9-21). The tablets containing tamoxifen are described in 1 and contain excipients/carriers such as lactose, PVP, Aerosil etc. Even though Neumann does not teach the composition claimed, it would have been obvious for one skilled in the art at the time of the instant invention was made to look to the teachings of prior art such as those of Neumann for preparing endoxifen compositions used for anti-estrogenic effect of Lim because Neumann teaches various routes of administering tamoxifen (compound related to endoxifen as suggested by Lim) including tablets with an expectation to provide effective delivery of the compound. Neumann further teaches salt forms of tamoxifen (examples) and therefore a skilled artisan would have been able to prepare a suitable salt form of endoxifen of Lim because preparing different salt forms of therapeutic compounds so as to improve their solubility is conventional in the art.

Zeisig investigated whether it is possible to reduce anti-estrogen resistance using liposomal encapsulated tamoxifen *in vivo*. Small liposomal vesicles containing up to 5.1 mg tamoxifen/ml liposomal suspension, together with an alkyl phospholipid to enhance the cellular uptake, were prepared and characterized. Mice transplanted with different

Art Unit: 1611

tumor models were treated with tamoxifen liposomes administered imp. or orally as a bolus dose of 50 mg/kg once a week or as a daily dose of 10 mg/kg/day, both during a 4-week period. After orally administered tamoxifen liposomes, tumor growth was significantly reduced for the 3366/tamoxifen (acquired resistance) and for the MCF-7 (inherent resistance) models to 47 and 16%, respectively (treated to control value of relative tumor volume). Intraperitoneal treatment with tamoxifen liposomes revealed similar results. Investigation of biodistribution revealed especially an accumulation of liposomal tamoxifen in MCF-7 tumors and livers of the treated mice. These liposomes had uterotrophic properties comparable to the dissolved compound. Zeisig states that the study demonstrates for the first time that a liposomal formulation of tamoxifen was able to induce pharmacological effects and to improve the therapeutic efficacy in several anti-estrogen-resistant xenografts.

Thus, it would have been obvious for one skilled in the art at the time of the instant invention was made to prepare a composition comprising endoxifen of Lim as an oral liposome formulation because Zeisig teaches that the liposomes had uterotrophic properties comparable to the dissolved compound. Zeisig states that the study demonstrates for the first time that a liposomal formulation had uterotrophic properties comparable to the dissolved compound and produce improved pharmacological effect. While Zeisig does not teach tamoxifen, Lim suggests that endoxifen as metabolite of tamoxifen and hence a skilled artisan would have expected endoxifen (of Lim) to be equally effective when administered as oral liposome formulation. Lim does not teach the claimed composition in the form of a tablet. While instant claim 40 requires a

Art Unit: 1611

complex, the claim does not specify the components that form the complex. However, the resulting encapsulation of endoxifen in the liposome formulation of Zeisig reads on instant complex.

5. Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, submitted by applicants on IDS) in view of US 4,310,523 to Neumann and Zeisig et al (abstract, Anticancer Drugs, 2004) as applied to claims 40 and 45-46 and 49-50 above, and further in view of US 6638767 to Unger et al (Unger).

Unger teaches methods of delivering various compounds including tamoxifen in to a cell using lipids as carriers. Unger teaches all of the claimed phospholipids (col. 11, l 59-col. 12 and also col. 18) and for delivering drugs such as tamoxifen (col. 29, l 61) or other drugs intracellularly, which may be otherwise resistant to delivery (col.2, l 53-62). Thus, it would have been obvious for one skilled in the art at the time of the instant invention was made to prepare endoxifen composition of Lim used for anti-estrogenic activity, as a liposome formulation employing one or more of the lipid carriers, including the instant claimed lipids and cholesterol, because Unger teaches that the liposomes have the ability to deliver the active agents effectively and selectively to a target cell. While Unger does not teach tamoxifen, Lim suggests that endoxifen as a metabolite of tamoxifen and hence a skilled artisan would have expected endoxifen (of Lim) to be equally effective when administered as liposome formulation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKSHMI CHANNAVAJJALA whose telephone number is (571)272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611

Application/Control Number: 12/515,261
Art Unit: 1611

Page 8

Notice of References Cited	Application/Control No. 12/515,261		Applicant(s)/Patent Under Reexamination AHMAD ET AL.	
	Examiner LAKSHMI CHANNAVAJJALA		Art Unit 1611	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,310,523	01-1982	Neumann, Friedmund	514/178
*	B	US-6,638,767	10-2003	Unger et al.	435/458
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Zeisig et al. Reduction of tamoxifen resistance in human breast carcinomas by tamoxifen containing liposomes in vivo. Anticancer Drugs. 2004 Aug;15(7):707-14. (abstract only)
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ateeq Ahmad, et al.	Confirmation: 7363
Serial No.: 12/515,261	Group No.: 1611
Filed: 15-May-2009	Examiner: Channavajjala
Entitled: Endoxifen Compositions And Methods	

**RESPONSE TO OFFICE COMMUNICATION
MAILED FEBRUARY 16, 2012**

EFS WEB FILED

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

CERTIFICATE OF EFS WEB TRANSMISSION UNDER 37 C.F.R. § 1.8	
<p>I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being transmitted to the United States Patent and Trademark Office transmitted via the Office electronic filing system in accordance with 37 C.F.R. §1.6(a)(4).</p>	
Dated: <u>May 16, 2012</u>	By: <u>/Mary Ann D. Brow/</u> Mary Ann D. Brow, Reg. No. 42,363

Examiner Channavajjala:

This is responsive to the Office Communication mailed February 16, 2012, with response due on or before May 16, 2012. Applicants respectfully request reconsideration in view of the following remarks.

The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No. **JINA-13458/US-1/PCT**. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Status of the Claims begins on page 2 of this communication.

Remarks begin on page 6 of this communication.

STATUS OF THE CLAIMS:

1-39. (cancelled)

40. (previously presented) A composition comprising an effective amount of a complex comprising a synthetic preparation of endoxifen, wherein said endoxifen is a free base or is in the form of a salt, wherein said composition comprising endoxifen is composition formulated in a hydroalcoholic gel, a patch, a cream, an emulsion, a lotion, an ointment, a powder, a tablet, a capsule, an enteric-coated capsule, an enteric coated tablet, a lozenge, or an oil.

41. (cancelled)

42. (withdrawn) The composition of claim 40, wherein said composition comprising endoxifen is formulated in a hydroalcoholic gel containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

43. (withdrawn) The composition of claim 40, wherein said hydroalcoholic gel comprises a neutralizing agent, wherein said neutralizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, arginine, trolamine, and tromethamine, and wherein said neutralizing agent exists at a neutralizing agent/gelling agent ratio of about 1:1 to about 4:1.

44. (withdrawn) The composition of claim 40, wherein said hydroalcoholic gel comprises

- (i) endoxifen at about 0.01% to 0.20% by weight;
- (ii) isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight;
- (iii) alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight
- (iv) aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight;

and

- (v) gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight.
- wherein the percentage of components is weight to weight of the composition.

45. (previously presented) The composition of claim 40, wherein said endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetate, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate salts.

46. (previously presented) The composition of claim 40, wherein said composition comprises at least one lipid selected from the group consisting of egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylcholine (DPPC), distearylphosphatidylglycerol (DSPG), dipalmitoylphosphatidylglycerol (DMPG), cholesterol (Chol), cholesterol sulfate and its salts (CS), cholesterol hemisuccinate and its salts (Chems), cholesterol phosphate and its salts (CP), cholesterylphosphocholine and other hydroxycholesterol or amino cholesterol derivatives, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), coprostanol, cholestanol, cholestane, cholic acid, cortisol, corticosterone, hydrocortisone, and calciferol, *E*-guggulsterone, *Z*-guggulsterone, mixture of *E*-and *Z*-guggulsterone, monoglycerides, diglycerides, triglycerides, carbohydrate-based lipids selected from a group consisting of galactolipid, mannosylphosphatidylcholine, galactosylphosphatidylcholine, β -sitosterol, stigmasterol, stigmasterol, lanosterol, α -spinasterol, lathosterol, campesterol, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, and pegylated derivatives of distearylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, and dioleoylphosphatidylglycerol.

47. (previously presented) The composition of claim 40, wherein said composition comprises endoxifen, cholesterol and/or a cholesterol derivative, and one or more phospholipids.

48. (previously presented) The composition of claim 47, wherein at least one of said one or more phospholipids is hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.

49. (previously presented) The composition of claim 40, wherein said composition comprises a form selected from the group consisting of powder, solution, emulsion, micelle, liposome, lipidic particle, gel, paste form, a lyophilized form, and a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.

50. (previously presented) The composition of claim 40, wherein said composition is in a lyophilized form comprising a cryoprotectant, wherein said cryoprotectant comprises one or more sugars selected from the group consisting of trehalose, maltose, lactose, sucrose, glucose, and dextran.

51-54. (cancelled)

55. (previously presented) A method of treating a cell, comprising, exposing said cell to a composition of claim 40.

56. (previously presented) The method of claim 55, wherein the cell is *in vivo* in a host.

57. (previously presented) The method of claim 56, wherein said host is a mammal.

58. (previously presented) The method of claim 55, wherein said exposing comprises administering a composition of claim 40 to a subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

59. (previously presented) A method of treating a subject having cancer, comprising administering a composition of claim 40 to said subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

REMARKS

Claims 40, 42-49 and 55-59 are pending in the present case. Claims 42-44 and 55-59 stand withdrawn in view of a prior species election requirement; Claims 40 and 45-49 are under examination.

In the Office Action mailed on February 16, 2012, the Examiner made the following rejections:

- I. Claims 40 and 45-46 and 49-50 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, hereinafter “Lim”) in view of US 4,310,523 to Neumann (hereinafter “Neumann”) and Zeisig et al (abstract, Anticancer Drugs, 2004, hereinafter “Zeisig”); and
- II. Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim Neumann and Zeisig as applied to claims 40 and 45-46 and 49-50 above, and further in view of US 6638767 to Unger et al (hereinafter “Unger”).

The Claims Are Not Obvious

I. Claims 40 and 45-46 and 49-50 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim in view of Neumann and Zeisig. The Examiner points to Lim for a teaching of a synthetic preparation of endoxifen having anti-estrogenic effects and potency similar to that of 4-hydroxy tamoxifen. Office Action, page 3. The Examiner admits that Lim does not teach the claimed composition in the form of a tablet, nor does Lim teach endoxifen in the form of a complex. The Examiner points to Neumann for a teaching of *tamoxifen* in tablet form, and asserts that a skilled artisan would have been able to prepare a tablet form of endoxifen. Office Action, page 4. The Examiner points to Zeisig as teaching liposome-encapsulated *tamoxifen* (Office Action, page 5) and asserts that it would have been obvious for one of skill in the art to prepare a composition comprising the endoxifen of Lim for oral administration. (Office Action, page 5).

Applicants respectfully disagree that the cited references render the claims obvious. Applicants point out that Lim is a basic research article examining the anti-estrogenic effects of tamoxifen metabolites, principally endoxifen and 4-hydroxytamoxifen, as a means of

understanding the activity of tamoxifen. As noted by Lim, endoxifen was known to be one of a number of metabolites of tamoxifen (Lim, Abstract). The endoxifen formulation disclosed by Lim was a 0.1% ethanol solution, suitable for use in testing the effects of the compound on MCF-7 cultured cells (Lim, page 472, paragraph bridging col 1 and col 2). Although endoxifen is characterized by Lim as “important . . . to the anti-estrogenic action of tamoxifen” (Lim, Abstract), and although Lim states that endoxifen may have an important role in *mediating* the responses to tamoxifen (Lim page 477, col 1), Lim does not teach or even suggest that preparations of endoxifen could or should be used directly in a therapeutic regimen, i.e., in place of tamoxifen. Neumann and Zeisig are both directed to formulations of tamoxifen and do not make any suggestions regarding the suitability of endoxifen in treatment formulations.

Lim’s omission of a suggestion that endoxifen could be used in a drug preparation for therapy is significant. At the time of the effective filing date of the instant application, there was an absence of information establishing the safety of endoxifen as a therapeutic, and there were good reasons to have concerns about its safety. Thus, there could be no reasonable expectation of success in formulating endoxifen for use in a therapeutic regimen.

The predictability of toxicity for tamoxifen metabolites is complicated by a several issues:

- 1) tamoxifen is understood to act as a selective estrogen receptor modulator that has both agonist and antagonist activities (Lim, page 473, col 2); and,
- 2) there are at least two important tamoxifen metabolites that each have recognized activity, as well as a host of other metabolites of less well defined activity (Lim, Abstract; and Introduction, page 471, col 2);

Kisanga, et al., (Clinical Cancer Research, Vol. 10, 2336-2343, April 1, 2004, provided herewith) discusses aspects of the foregoing uncertainties related to the toxicity of tamoxifen and its metabolites. Similarly, Mujumdar et al., (Journal of Biomedicine and Biotechnology, 1:3, 99-107, 2001, provided herewith) discusses the complex and uncertain state of the art regarding the cytotoxic mechanism of action of tamoxifen. In the face of the foregoing pharmacological complexities, the combination of references cited by the Examiner provides no clear delineation of the roles of even the principle metabolites in mediating the contradictory effects of tamoxifen, or in association with adverse tamoxifen side effects, such as lethal thromboembolism.

These uncertainties related to the pharmacology of tamoxifen would only be amplified when considering endoxifen, for which there was an absence of safety data prior to the present application. In contrast, Example 9 of the present application provides clear *in vivo* evidence of safety with both single and repeat dosages of synthetic endoxifen. In conjunction with the efficacy data presented in the specification, the teachings of the instant specification provide the missing basis for the reasonable expectation of success in using endoxifen therapeutically, e.g., in the treatment of breast cancer.

Endoxifen is of interest because tamoxifen is processed by CYP2D6 and CYP3A 4/5 into forms that include endoxifen and 4-OH-Tam. Tamoxifen is not effective in people with defective CYP2D6 genes, or who are taking other drugs or consuming foods that inhibit CYP2D6 and/or CYP3A 4/5 activity. Notably, grapefruit juice is a potent inhibitor of CYP3A 4/5, as are SSRI antidepressants. See, e.g., the attached paper by Sideras, et al., (Journal of Clinical Oncology, Vol. 28, Number 16; Jun 1, 2010) entitled Coprescription of Tamoxifen and Medications That Inhibit CYP2D6. The striking thing to be noted in the prior art is that, even recognizing the metabolic complications of tamoxifen treatment and the anti-estrogenic activity of endoxifen, and even though the chemical structure of endoxifen has been known for a number of years, the medical community did **not** propose treatment directly with endoxifen in place of tamoxifen until well after the effective filing date of the instant application. It is respectfully submitted that at least until 2009, the idea of testing endoxifen directly as a drug in clinical trials was not being pursued. See, for example, the attached article "NCI Plans Preclinical Testing Of Tamoxifen Metabolite Endoxifen For Breast Cancer" by Kirsten Boyd Goldberg in The Cancer Letter [on pages 4-6 of Vol. 35 No. 31 Aug. 7, 2009 (hereinafter "Cancer Letter"), particularly the following passages (with emphasis added)]:

"In theory, giving patients endoxifen rather than tamoxifen could increase the effectiveness of treatment by 15 to 20 percent, said James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis.

"The idea, which has yet to be tested, is that if you were to administer the metabolite – endoxifen - rather than the parent drug tamoxifen, you might get around genetic variations in drug metabolism," Doroshow said in an interview with The Cancer Letter.

...

"Because this metabolite has never itself been given directly to patients, we don't know, for example, if it is absorbed if you take it by mouth. What is its direct toxicity if you give it alone?" Doroshov said. "You have to do all of the preclinical studies in animals to understand its further metabolism and toxicity, and it's got to be produced in a fashion that can be administered to people, and under GMP conditions. The toxicological studies and the pharmacology studies are really quite expensive to support the filing of an IND for a phase I study, " Doroshov said. "Most academic centers, no matter how well positioned, don't have the resources to do that."

The Cancer Letter, v35(31) (2009), pages 4-5.

Nonobviousness is decided as a matter of law based on four factual inquiries as explained in *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) and reaffirmed in *KSR International, Inc. v. Teleflex, Inc.*, 550 U.S. 398 (2007). The patent examiner is responsible for evaluating the claimed invention against the most relevant prior art from the viewpoint of a person of ordinary skill in the field of invention. See *Graham*; *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009); see generally *In re Oetiker*, 977 F.2d 1443, 1445–47 (Fed. Cir. 1992).

A valid prima facie case requires the Office to present “articulated reasoning with some rational underpinning”, *KSR*, 550 U.S. at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)), that one of skill in the art would have been motivated to combine the elements to yield the claimed combination and that one would have done so having a reasonable expectation of successfully carrying out the claimed combination. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). A failure to establish either a motivation to combine or an expectation of success precludes finding a prima facie case of obviousness, and, without more, such failure entitles the applicant to allowance of the claims at issue. See MPEP § 2143.

For the reasons recited above, Applicants submit nothing in the cited references teaches or suggests that endoxifen might be safely administered as a therapeutic agent, or that endoxifen – in the absence of other metabolite components of tamoxifen – would be expected by one of skill in the art to exhibit suitable anti-estrogenic activity *in vivo*. As stated by Lim, the mechanism of action and basis for the variability of tamoxifen is poorly understood, as was the role of endoxifen in tamoxifen’s activity. Nothing in Lim suggests that endoxifen could be used

directly in therapeutic applications, and in the absence of such a suggestion, with an expectation of *predicable* results, one of skill in the art would simply have no motivation to modify the tamoxifen formulations of Neumann and Zeisig to produce therapeutic endoxifen formulations according to of the instant claims. The failure of those of skill in the art to pursue the use of endoxifen, even in the face of the variability of efficacy of tamoxifen, highlights the insufficiency of Lim, Neumann, and Zeisig in suggesting the claimed embodiments. The combination of Lim, Neumann and Zeisig thus fails to establish prima facie obviousness of Claims 40 and 45-46 and 49-50, and Applicants respectfully request that this rejection be withdrawn.

II. Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim, Neumann, and Zeisig as applied to claims 40 and 45-46 and 49-50 above, and further in view of Unger. The Examiner points to Unger for a teaching of methods for delivering various compounds, including tamoxifen, into a cell using lipids as carriers. Office Action, page 6.

For the reasons discussed above, the combination of Lim, Neumann, and Zeisig fails to establish prima facie obviousness of any therapeutic preparations of endoxifen, as recited in the instant claims. Unger, which does not teach or suggest therapeutic utility of endoxifen, fails to cure the deficiencies of Lim, Neumann, and Zeisig. For this reason, Applicants submit that the combination of Lim, Neumann, Zeisig and Unger fails to establish prima facie obviousness of Claims 47 ad 48, and respectfully request that this rejection be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for objection and rejection have been addressed and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 662-1277.

Dated: May 16, 2012

/Mary Ann D. Brow /

Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
2275 Deming Way, Suite 310
Middleton, Wisconsin 53562
608.662.1277



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/515,261	01/08/2010	Ateeq Ahmad	JINA-13458/US-1/PCT	7363
72960	7590	07/19/2012		
Casimir Jones, S.C. 2275 DEMING WAY, SUITE 310 MIDDLETON, WI 53562			EXAMINER CHANNAVAJALA, LAKSHMI SARADA	
			ART UNIT	PAPER NUMBER
			1611	
			MAIL DATE	DELIVERY MODE
			07/19/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	12/515,261	AHMAD ET AL.	
	Examiner	Art Unit	
	LAKSHMI CHANNAVAJJALA	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 May 2012.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 40,42-50 and 55-59 is/are pending in the application.
- 5a) Of the above claim(s) 42-44 and 55-59 is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 40 and 45-50 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>5/16/12</u> . | 6) <input type="checkbox"/> Other: ____. |

DETAILED ACTION

Receipt of response dated 5/16/12 is acknowledged.

Claims 40, 42-50 and 55-59 are pending in the instant application. Claims 42-44 and 55-59 have been withdrawn from consideration. Claims 40 and 45-50 have been considered for examination.

***Examiner note that the claim identifiers for claims 44 and 55-59 are improper and should state withdrawn.**

Claim Rejections - 35 USC § 103

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

. Claims 40 and 45-46 and 49-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, submitted by applicants on IDS) in view of US 4,310,523 to Neumann and Zeisig et al (abstract, Anticancer Drugs, 2004).

Lim discloses synthetic preparation of endoxifen of the instant claims for anti-estrogenic effects and potency similar to that of 4-hydroxy tamoxifen. Page 472, col. 1 describes the use of synthetic, Endoxifen. Lim does not teach the claimed composition in the form of a tablet. While instant claim 40 requires a complex, the claim does not specify the components that form the complex.

Neumann teaches a composition comprising an anti-estrogen and anti-gonadotropically effective anti-androgen, wherein the former is tamoxifen (abstract). Neumann teaches administering the compositions by several routes including in the

Art Unit: 1611

form of oral tablets (col. 9, l 9-21). The tablets containing tamoxifen are described in 1 and contain excipients/carriers such as lactose, PVP, Aerosil etc. Even though Neumann does not teach the composition claimed, it would have been obvious for one skilled in the art at the time of the instant invention was made to look to the teachings of prior art such as those of Neumann for preparing endoxifen compositions used for anti-estrogenic effect of Lim because Neumann teaches various routes of administering tamoxifen (compound related to endoxifen as suggested by Lim) including tablets with an expectation to provide effective delivery of the compound. Neumann further teaches salt forms of tamoxifen (examples) and therefore a skilled artisan would have been able to prepare a suitable salt form of endoxifen of Lim because preparing different salt forms of therapeutic compounds so as to improve their solubility is conventional in the art.

Zeisig investigated whether it is possible to reduce anti-estrogen resistance using liposomal encapsulated tamoxifen *in vivo*. Small liposomal vesicles containing up to 5.1 mg tamoxifen/ml liposomal suspension, together with an alkyl phospholipid to enhance the cellular uptake, were prepared and characterized. Mice transplanted with different tumor models were treated with tamoxifen liposomes administered imp. or orally as a bolus dose of 50 mg/kg once a week or as a daily dose of 10 mg/kg/day, both during a 4-week period. After orally administered tamoxifen liposomes, tumor growth was significantly reduced for the 3366/tamoxifen (acquired resistance) and for the MCF-7 (inherent resistance) models to 47 and 16%, respectively (treated to control value of relative tumor volume). Intraperitoneal treatment with tamoxifen liposomes revealed

similar results. Investigation of biodistribution revealed especially an accumulation of liposomal tamoxifen in MCF-7 tumors and livers of the treated mice. These liposomes had uterotrophic properties comparable to the dissolved compound. Zeisig states that the study demonstrates for the first time that a liposomal formulation of tamoxifen was able to induce pharmacological effects and to improve the therapeutic efficacy in several anti-estrogen-resistant xenografts.

Thus, it would have been obvious for one skilled in the art at the time of the instant invention was made to prepare a composition comprising endoxifen of Lim as an oral liposome formulation because Zeisig teaches that the liposomes had uterotrophic properties comparable to the dissolved compound. Zeisig states that the study demonstrates for the first time that a liposomal formulation had uterotrophic properties comparable to the dissolved compound and produce improved pharmacological effect. While Zeisig does not teach tamoxifen, Lim suggests that endoxifen as metabolite of tamoxifen and hence a skilled artisan would have expected endoxifen (of Lim) to be equally effective when administered as oral liposome formulation. Lim does not teach the claimed composition in the form of a tablet. While instant claim 40 requires a complex, the claim does not specify the components that form the complex. However, the resulting encapsulation of endoxifen in the liposome formulation of Zeisig reads on instant complex.

2. Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478,

Art Unit: 1611

submitted by applicants on IDS) in view of US 4,310,523 to Neumann and Zeisig et al (abstract, Anticancer Drugs, 2004) as applied to claims 40 and 45-46 and 49-50 above, and further in view of US 6638767 to Unger et al (Unger).

Unger teaches methods of delivering various compounds including tamoxifen in to a cell using lipids as carriers. Unger teaches all of the claimed phospholipids (col. 11, l 59-col. 12 and also col. 18) and for delivering drugs such as tamoxifen (col. 29, l 61) or other drugs intracellularly, which may be otherwise resistant to delivery (col.2, l 53-62). Thus, it would have been obvious for one skilled in the art at the time of the instant invention was made to prepare endoxifen composition of Lim used for anti-estrogenic activity, as a liposome formulation employing one or more of the lipid carriers, including the instant claimed lipids and cholesterol, because Unger teaches that the liposomes have the ability to deliver the active agents effectively and selectively to a target cell. While Unger does not teach tamoxifen, Lim suggests that endoxifen as a metabolite of tamoxifen and hence a skilled artisan would have expected endoxifen (of Lim) to be equally effective when administered as liposome formulation.

Response to Arguments

3. Applicant's arguments filed 5/16/12 have been fully considered but they are not persuasive.

Applicants argue that Lim is a basic research article examining anti-estrogenic effects of tamoxifen metabolites, endoxifen and 4-hydroxytamoxifen, for understanding the activity of tamoxifen; and characterizes endoxifen important for anti-estrogenic effects of tamoxifen. It is argued that Lim however does not teach or been suggest that

Art Unit: 1611

preparations of endoxifen for therapeutic regimen as a substitute for tamoxifen. It is argued that Lim's omission of such a teaching would be significant because there is no information establishing safety of endoxifen at the time of the effective filing date of instant invention and there were good reasons to have concerns about its safety.

Applicants cite Kisanga, et al., (Clinical Cancer Research, Vol. 10, 2336-2343, April 1, 2004, provided herewith) that discusses aspects of the foregoing uncertainties related to the toxicity of tamoxifen and its metabolites; and Mujumdar et al., (Journal of Biomedicine and Biotechnology, 1:3, 99- 107, 2001, provided herewith) discusses the complex and uncertain state of the art regarding the cytotoxic mechanism of action of tamoxifen. In the face of the foregoing pharmacological complexities, it is argued that the combination of references cited by the Examiner provides no clear delineation of the roles of even the principle metabolites in mediating the contradictory effects of tamoxifen, or in association with adverse tamoxifen side effects, such as lethal thromboembolism.

Applicants argue that in contrast, Example 9 of the present application provides clear in vivo evidence of safety with both single and repeat dosages of synthetic endoxifen; and the missing basis for the reasonable expectation of success in using endoxifen therapeutically, e.g., in the treatment of breast cancer. Applicants state that the striking thing to be noted in the prior art is that, even recognizing the metabolic complications of tamoxifen treatment and the anti-estrogenic activity of endoxifen, and even though the chemical structure of endoxifen has been known for a number of years, the medical community did not propose treatment directly with endoxifen in place of

Art Unit: 1611

tamoxifen until well after the effective filing date of the instant application. It is submitted that at least until 2009, the idea of testing endoxifen directly as a drug in clinical trials was not being pursued. See, for example, the attached article "NCI Plans Preclinical Testing Of Tamoxifen Metabolite Endoxifen For Breast Cancer" by Kirsten Boyd Goldberg in The Cancer Letter [on pages 4-6 of Vol. 35 No. 31 Aug. 7, 2009 (hereinafter "Cancer Letter"). Applicants submit nothing in the cited references teaches or suggests that endoxifen might be safely administered as a therapeutic agent, or that endoxifen - in the absence of other metabolite components of tamoxifen - would be expected by one of skill in the art to exhibit suitable anti-estrogenic activity & vivo. It is argued that nothing in Lim would have suggested directly in therapeutic applications, and in the absence of such a suggestion, with an expectation of predictable results, one of skill in the art would simply have no motivation to modify the tamoxifen formulations of Neumann and Zeisig to produce therapeutic endoxifen formulations according to of the instant claims. The failure of those of skill in the art to pursue the use of endoxifen, even in the face of the variability of efficacy of tamoxifen, highlights the insufficiency of Lim, Neumann, and Zeisig in suggesting the claimed embodiments. The combination of Lim, Neumann and Zeisig thus fails to establish prima facie obviousness of instant claims.

Applicants' arguments are not found persuasive because while applicants argue the toxicity of tamoxifen and its metabolites, instant claims do not recite the argued toxicity nor the claims require therapeutic activity. Instant claims are not directed to a method of treatment or providing therapy. Instant claims only require a composition. Even though the claims recite effective amount of endoxifen, the said claims do not

Art Unit: 1611

specify what effect is being achieved. Whereas claims 55-59 that are withdrawn as being non-elected are directed to a method of treatment. Thus, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, In response to applicant's argument that there is no teaching, suggestion, or motivation to combine the references, the examiner recognizes that obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, admittedly Lim teaches a significant anti-estrogenic effect of endoxifen, which meets the teaching, suggestion as well as motivation for one skilled in the art to substitute tamoxifen with endoxifen. Further, nothing in the teachings of Lim suggests about the toxicity of endoxifen and thus a skilled artisan would not be led away from employing endoxifen for tamoxifen.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper "functional approach" to

Art Unit: 1611

the determination of obviousness as laid down in *Graham*. Exemplary rationales that may support a conclusion of obviousness in the present case include:

- (A) Simple substitution of one known element for another to obtain predictable results; (F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; In the instant case, Lim, as explained above, suggests substitution of endoxifen for tamoxifen and their functions i.e., anti-estrogenic effect. Thus, one of ordinary skill in the art could have substituted endoxifen for tamoxifen, and the results of the substitution would have been predictable.
- (B) "Obvious to try" – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. In the instant case, Neumann and Zeisig provide the teaching of preparing oral compositions. If applicants argue the toxicity concerns, then certainly the same concerns are also present for tamoxifen since Kisanga et al shows higher serum levels of tamoxifen and its metabolites (p 2338, col. 2). However, such toxicity levels are dose responsive (Kisanga) and hence a skilled artisan would have taken in to consideration the doses or amounts of tamoxifen or its metabolites when preparing oral formulations that are effective as well as safe. In this regard, the "Cancer Letter" article supports the examiner's position that one of an ordinary skill in the art would have been motivated to

Art Unit: 1611

try endoxifen instead of tamoxifen because the former is thought to bypass the pharmacogenetic limitations of tamoxifen.

The teachings of Neumann and Zeisig have been cited to show that tamoxifen oral formulations, in particular comprising liposomal formulations are known in the art; and not cited for endoxifen. Applicants argue that Unger fails to cure the deficiencies of Lim, Neumann and Zeisig because Unger does not teach therapeutic utility of endoxifen. However, applicants argument is not persuasive because Unger is not cited for endoxifen and instead for phospholipids.

Conclusion

4. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKSHMI CHANNAVAJJALA whose telephone number is (571)272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Daniel M. Sullivan can be reached on 571-272-0779. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611

Application/Control Number: 12/515,261
Art Unit: 1611

Page 12

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**NOTICE OF APPEAL FROM THE EXAMINER TO
THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Docket Number (Optional)

JINA-13458/US-1/PCT

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

on _____

Signature _____

Typed or printed
name _____

In re Application of
Ateeq Ahmad et al.

Application Number
12/515,261

Filed
01/08/2010

For COMPOSITIONS AND METHODS FOR TREATING AND DIAGNOSING PANCREATIC CANCER

Art Unit
1611

Examiner
CHANNAVAJJALA

Applicant hereby **appeals** to the Board of Patent Appeals and Interferences from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 41.20(b)(1)) \$ 630

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: \$ 315

☐ A check in the amount of the fee is enclosed.

☐ Payment by credit card. Form PTO-2038 is attached.

☐ The Director has already been authorized to charge fees in this application to a Deposit Account.

☒ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 504302.

☐ A petition for an extension of time under 37 CFR 1.136(a) (PTO/SB/22) is enclosed.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

☐ applicant/inventor.

/Mary Ann D. Brow/

Signature

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed.
(Form PTO/SB/96)

Mary Ann D. Brow

Typed or printed name

☒ attorney or agent of record. 42363
Registration number _____

608.662.1277

Telephone number

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34. _____

01/22/2013

Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required.
Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 41.31. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11, 1.14 and 41.6. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ateeq Ahmad, et al. Confirmation: 7363
Serial No.: 12/515,261 Group No.: 1611
371(C) date: 01/08/2010 Office: Lakshmi Channavajjala
Entitled: **ENDOXIFEN COMPOSITIONS AND METHODS**

APPELLANTS' BRIEF
APPEAL NO:

VIA EFS WEB
Mail Stop Appeal Brief – Patents
Commissioner for Patents
BOX 1450
Alexandria, VA 22313–1450

CERTIFICATE OF EFS WEB TRANSMISSION UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being transmitted to the United States Patent and Trademark Office transmitted via the Office electronic filing system in accordance with 37 C.F.R. § 1.6(a)(4).

Dated: August, 22, 2013

By: /Mary Ann D. Brow/

Mary Ann D. Brow, Reg. No. 42,363

Madam,

This brief supports the appeal to the Board of Patent Appeals and Interferences from the Final Office Communication mailed July 19, 2012, in the application identified above, and is in furtherance of the Notice of Appeal filed January 22, 2013. Five months extension of time are requested.

The Commissioner is authorized to charge any fees required during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 and any extension of time fees, or credit any overpayment, to Deposit Account 50-4302, referencing Attorney Docket No: **JINA-13458/US-1/PCT**. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

This Brief contains the following items under the headings set forth below (in accordance with 37 C.F.R. § 41.37).

I.	REAL PARTY IN INTEREST	3
II.	RELATED APPEALS AND INTERFERENCES.....	3
III.	SUMMARY OF CLAIMED SUBJECT MATTER	3
IV	ARGUMENT	6
V.	CLAIMS APPENDIX.....	16
VI.	EVIDENCE APPENDIX.....	20

I. REAL PARTY IN INTEREST

The real party in interest is Jina Pharmaceuticals, Inc. of Libertyville, IL.

II. RELATED APPEALS AND INTERFERENCES

A Continuation-in-Part of the present application, Appl. Ser. No. 12/470,219, is under appeal. No other related appeals or interferences are known to Appellants or Appellants' legal representative.

III. SUMMARY OF CLAIMED SUBJECT MATTER

Claims 40, 42-50 and 55-59 are pending.

The claims are directed a synthetic preparation of endoxifen formulated as pharmaceutical compositions. The claims were subject to a species election requirement in the paper mailed 11/08/2011. Appellants elected claims directed the following:

1. tablet form of composition; and
2. oral route of administration.

Claims 42-44 and 55-59 stand withdrawn as being drawn to non-elected species.

Claim 40 is directed to a composition comprising an effective amount of a complex comprising a synthetic preparation of endoxifen (Specification at ¶8, Fig. 2; Examples 1-4), wherein the endoxifen is a free base or is in the form of a salt, wherein the composition is formulated as a tablet (Specification, ¶¶16, 45). Additional recited formulations stand withdrawn in view of a species election. These formulations are a hydroalcoholic gel, a patch, a cream, an emulsion, a lotion, an ointment, a powder, a capsule, an enteric-coated capsule, an enteric coated tablet, a lozenge, and an oil (Specification, ¶119).

Claim 45 is directed to a composition in which the endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetate, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate salts (Specification at ¶8).

Claim 46 is directed to the endoxifen composition comprising at least one lipid selected from the group consisting of egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylcholine (DPPC), distearylphosphatidylglycerol (DSPG), dipalmitoylphosphatidylglycerol (DMPG), cholesterol (Chol), cholesterol sulfate and its salts (CS), cholesterol hemisuccinate and its salts (Chems), cholesterol phosphate and its salts (CP), cholesterylphosphocholine and other hydroxycholesterol or amino cholesterol derivatives, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), coprostanol, cholestanol, cholestane, cholic acid, cortisol, corticosterone, hydrocortisone, and calciferol, *E*-guggulsterone, *Z*-guggulsterone, mixture of *E*-and *Z*-guggulsterone, monoglycerides, diglycerides, triglycerides, carbohydrate-based lipids selected from a group consisting of galactolipid, mannanolipid, galactolecithin, β -sitosterol, stigmasterol, stigmastanol, lanosterol, α -spinasterol, lathosterol, campesterol, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, and pegylated derivatives of distearylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, and dioleoylphosphatidylglycerol (Specification at ¶14).

Claim 47 is directed to a composition comprising endoxifen, cholesterol and/or a cholesterol derivative, and one or more phospholipids, and Claim 48 is directed to an embodiment in which one or more of the phospholipids is hydrogenated soy phosphatidylcholine or soy phosphatidylcholine (Specification at ¶15).

Claim 49 is directed to embodiments in which the endoxifen composition comprises a form selected from the group consisting of powder, solution, emulsion, micelle, liposome, lipidic particle, gel, paste form, a lyophilized form, and a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material (Specification at ¶16). Tablet form was elected as a species for prosecution in the paper filed February 8, 2012 and the other forms stand withdrawn in view of this election.

Claim 50 is directed to embodiments in which the endoxifen composition is in a lyophilized form comprising a cryoprotectant, wherein said cryoprotectant comprises one or more sugars selected from the group consisting of trehalose, maltose, lactose, sucrose, glucose, and dextran (Specification at ¶118).

Claim 55 is directed to a method of treating a cell, comprising, exposing said cell to a composition of claim 40 (Specification at ¶28, Example 9 starting at ¶156).

In the embodiment of claim 56, the cell is *in vivo* in a host (Specification at ¶29) and in claim 57, the host is a mammal (Specification at ¶30).

Claim 58 is directed to embodiments in which the exposing comprises administering a composition of claim 40 to a subject, wherein the administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject (Specification at ¶53; Example 9 starting at ¶156; and Example 11, starting at ¶158). Oral administration was elected as a species for prosecution in the paper filed February 8, 2012 and the other routes of administration stand withdrawn in view of this election.

Claim 59 is directed to a method of treating a subject having cancer, comprising administering a composition of claim 40 to said subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject (Specification at ¶123; and Example 11, starting at ¶158). Oral administration was elected as a species for prosecution in the paper filed February 8, 2012 and the other routes of administration stand withdrawn in view of this election.

IV. ARGUMENT

A. The Grounds of Rejection

Claims 40 and 45-46 and 49-50 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim (Cancer Chemother Pharamcol, 2005, 55, 471-478) in view of US 4,310,523 to Neumann and Zeisq (abstract only, Anticancer Drugs, 2004).

Claims 47 and 48 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim, Neumann, and Zeisq as applied above, further in view of US 6638767 to Unger. Appellants note that the claim identifiers for Claims 44 and 55-49 should state "withdrawn."

The present rejection over Lim, Neumann, Zeisq, and Unger is based on clear legal and factual deficiencies because:

- I.** The Office fails to establish a proper basis for combining the references
 1. The substitution is not a "simple substitution of one known element for another to obtain a predictable result;
 2. The skilled person had no expectation of success at the time of filing; and
 3. The selection of endoxifen to replace tamoxifen is not a "predictable solution" with a "reasonable expectation of success."
- II.** The Office uses impermissible hindsight reconstruction in making the rejection.

1. The cited art

The Office cites combination of Lim and Neumann, and this combination further in view of Zeisq or Unger, in alleging that the subject matter of the claims is obvious.

The Office points to the following teachings in the cited art:

- a) Lim, as teaching a synthetic preparation of endoxifen having anti-estrogenic effects and potency similar to that of 4-hydroxy tamoxifen (4-OH-Tam);
- b) Neumann for a teaching of *tamoxifen* in tablet form; and
- c) Zeisq as teaching liposome-encapsulated *tamoxifen*.
- d) Unger as teaching methods of delivering *tamoxifen* to cells using lipids.

The Office urges the substitution of the endoxifen of Lim in place of the tamoxifen in the formulations of Neumann or Zeisig or Unger to produce the compositions of the claims. The Office cites two rationales under which one of skill allegedly would make the substitutions. First, the Office argues that the substitution is a "simple substitution of one known element for another to obtain a predictable result." (Final Office Action mailed 07/19/12, hereinafter "Office Action," at page 9). Second, the Office argues that substituting endoxifen for tamoxifen is "obvious to try" in that it is "choosing from a finite number of identified predictable solutions, with a reasonable expectation of success" (Office Action, page 9). For the reasons discussed below, both of the asserted rationales fail.

2. The requirements for a finding of obviousness

Nonobviousness is decided as a matter of law based on factual inquiries as explained in *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966) and reaffirmed in *KSR International, Inc. v. Teleflex, Inc.*, 550 U.S. 398 (2007). "In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness." *In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993). Specifically, the examiner is responsible for evaluating the claimed invention against the most relevant prior art from the viewpoint of a person of ordinary skill in the field of invention. See *Graham*; *In re Kubin*, 561 F.3d 1351, 1355 (Fed. Cir. 2009); see generally *In re Oetiker*, 977 F.2d 1443, 1445–47 (Fed. Cir. 1992). While KSR relaxed some of the formalism accompanying earlier decisions requiring a "teaching, suggestion, or motivation" to combine prior art references, it did not eliminate the requirement to anchor the nonobviousness calculus in an explanation of how a person of ordinary skill would select and apply the teachings of the cited art. See, e.g., *KSR*, 550 U.S. at 417.

A valid *prima facie* case further requires the Office to present "articulated reasoning with some rational underpinning", *KSR*, 550 U.S. at 418 (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006)), that one of skill in the art would have been motivated to combine the elements to yield the claimed combination and that one would have done so having a reasonable expectation of successfully carrying out the claimed combination. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991). A failure to properly

establish either a motivation to combine references or a reasonable expectation of success in making the combination precludes finding a *prima facie* case of obviousness, and, without more, such failure entitles the Appellants to allowance of the claims at issue. See MPEP § 2143. Thus, the Office must provide an objective reason why one of skill in the art *would have*, not merely *could have*, combined or modified the teachings of the cited art.

1. The substitution is not a "simple substitution of one known element for another to obtain a predictable result."

Each of Neumann, Zeisig and Unger disclose only treatments with *tamoxifen* and do not suggest formulations containing endoxifen as an active drug. The only reference disclosing to the active agent of the instant claims, *endoxifen*, is the Lim reference.

As discussed in Lim and in the Amendment and Response filed on 05/16/12 ("Response"), tamoxifen is extensively metabolized in to a number of different metabolized in vivo into a number of different compounds that have different antiestrogenic and/or estrogenic effects (Lim p 471, col 2).

Lim's study is directed to examining the effects of the endoxifen metabolite as compared to the parent drug and to certain other metabolites. Lim provides a single formulation of endoxifen, a solution in 0.1% ethanol, and uses it solely for treating cultured cells in order to compare the anti-estrogenic activities of two major active metabolites of tamoxifen (Lim, page 472, paragraph bridging col 1 and col 2). *Inter alia*, Lim teaches that:

- i) Tamoxifen is extensively metabolized, producing a number of metabolites having anti-estrogenic activity, including 4-OH-Tam and endoxifen (Lim p 471, col 2);
- ii) 4-OH-Tam and endoxifen are of similar anti-estrogenic potency to each other but of much greater potency than tamoxifen (Lim p472, col 2);
- iii) 4-OH-Tam and endoxifen are both important to the action of tamoxifen (Lim Abstract, col 2);
- iv) 4-OH-Tam and endoxifen do not substantially inter-convert (Lim, Abstract col 2);
- v) 4-OH-Tam and endoxifen may interact *in vivo* and work in combination (Lim p474, col 2);

- vi) It is unknown whether the higher serum concentrations observed for endoxifen compared to 4-OH-Tam in patients influence treatment outcomes or toxicity (Lim p475-6, bridging paragraph);
- vii) Forms of 4-OH-Tam are both estrogenic and antiestrogenic (Lim, p476, col 2);
- viii) Endoxifen is the N-desmethylated form of 4-OH-Tam and this structural change causes significant pharmacokinetic differences between other tamoxifen-related compounds (Lim p 476, col 2).

In sum, Lim teaches that tamoxifen treatment produces a complex *mixture of metabolites* in patients, producing a mixture of anti-estrogenic and estrogenic effects and side-effects. Lim discloses similarities in activity and potency between endoxifen and 4-OH-Tam, and that both of these metabolites have much greater activity and potency than tamoxifen.

Lim does not suggest that either compound is *interchangeable* with tamoxifen in therapeutic applications or that either compound should be used in isolation. To the contrary, Lim teaches that *both* 4-OH-Tam and endoxifen are important for the activity of tamoxifen. Further, Lim further teaches that there is little inter-conversion between the metabolites, i.e., the use of endoxifen in a treatment would not provide 4-OH-Tam, and vice versa. Lim also teaches that structurally-similar tamoxifen-related compounds can display significantly different pharmacokinetics.

Thus, it is clear from Lim that use of endoxifen alone cannot produce the same spectrum of important metabolites provided by tamoxifen, and that the pharmacokinetics of endoxifen cannot be predicted from its structural similarities to tamoxifen or 4-OH-Tam.

2. The skilled person had no expectation of success at the time of filing

Lim's omission of a suggestion that endoxifen could be used alone in a drug preparation for therapy is significant. At the time of the effective filing date of the instant application, there was an absence of information establishing the safety of endoxifen as a therapeutic, and there were good reasons to have concerns about its safety. Thus, there

could be no reasonable expectation of success in formulating endoxifen for use in a therapeutic regimen.

As discussed in the Response, the predictability of toxicity for tamoxifen metabolites is complicated by a several issues:

- 1) tamoxifen is understood to act as a selective estrogen receptor modulator that has both agonist and antagonist activities (Lim, page 473, col 2); and,
- 2) there are at least two important tamoxifen metabolites that each have recognized activity, as well as a host of other metabolites of less well defined activity (Lim, Abstract; and Introduction, page 471, col 2);

Kisanga, et al., (Clinical Cancer Research, Vol. 10, 2336-2343, April 1, 2004, cited in the Response and provided herewith as Exhibit 1) discusses aspects of the foregoing uncertainties related to the toxicity of tamoxifen and its metabolites. Similarly, Majumdar et al., (Journal of Biomedicine and Biotechnology, 1:3, 99-107, 2001, cited in the Response and provided herewith as Exhibit 2) discusses the complex and uncertain state of the art regarding the cytotoxic mechanism of action of tamoxifen. In the face of the foregoing pharmacological complexities, the combination of references cited by the Examiner provides no clear delineation of the roles of even the principle metabolites in mediating the contradictory effects of tamoxifen, or in association with adverse tamoxifen side effects, such as lethal thromboembolism.

These uncertainties related to the pharmacology of tamoxifen would only be amplified when considering endoxifen, for which there was an absence of safety data prior to the present application. In contrast, Example 9 of the present application provides clear *in vivo* evidence of safety with both single and repeat dosages of synthetic endoxifen. In conjunction with the efficacy data presented in the specification, the teachings of the instant specification provide the missing basis for the reasonable expectation of success in using endoxifen therapeutically, e.g., in the treatment of breast cancer.

Endoxifen is of interest because tamoxifen is processed by CYP2D6 and CYP3A 4/5 into forms that include endoxifen and 4-OH-Tam. Tamoxifen is not effective in people with defective CYP2D6 genes, or who are taking other drugs or consuming foods

that inhibit CYP2D6 and/or CYP3A 4/5 activity. Notably, grapefruit juice is a potent inhibitor of CYP3A 4/5, as are SSRI antidepressants. See, e.g., Sideras, et al., (Journal of Clinical Oncology, Vol. 28, Number 16; Jun 1, 2010) entitled Coprescription of Tamoxifen and Medications That Inhibit CYP2D6, cited in the Response and attached hereto as Exhibit 3. The striking thing to be noted in the prior art is that, *even recognizing the metabolic complications of tamoxifen treatment* and the anti-estrogenic activity of endoxifen, and *even though the chemical structure of endoxifen has been known* for a number of years, the medical community did **not** propose treatment directly with endoxifen in place of tamoxifen until well after the effective filing date of the instant application. See, for example, the attached article "NCI Plans Preclinical Testing Of Tamoxifen Metabolite Endoxifen For Breast Cancer" by Kirsten Boyd Goldberg in The Cancer Letter [on pages 4-6 of Vol. 35 No. 31 Aug. 7, 2009 (hereinafter "Cancer Letter"), cited in the Response, particularly the following passages (with emphasis added)]:

"In theory, giving patients endoxifen rather than tamoxifen could increase the effectiveness of treatment by 15 to 20 percent, said James Doroshow, director of the NCI Division of Cancer Treatment and Diagnosis.

"The idea, which has yet to be tested, is that if you were to administer the metabolite – endoxifen - rather than the parent drug tamoxifen, you might get around genetic variations in drug metabolism," Doroshow said in an interview with The Cancer Letter.

...

"Because this metabolite has never itself been given directly to patients, we don't know, for example, if it is absorbed if you take it by mouth. What is its direct toxicity if you give it alone?" Doroshow said. "You have to do all of the preclinical studies in animals to understand its further metabolism and toxicity, and it's got to be produced in a fashion that can be administered to people, and under GMP conditions. The toxicological studies and the pharmacology studies are really quite expensive to support the filing of an IND for a phase I study, " Doroshow said.

"Most academic centers, no matter how well positioned,
don't have the resources to do that."

(Exhibit 4, The Cancer Letter, v35(31) (2009), pages 4-5.)

It is respectfully submitted that at least until 2009, well after the filing date of the instant application, the idea of testing endoxifen directly as a drug in clinical trials was not being pursued.

3. The selection of endoxifen to replace tamoxifen is not a "predictable solution" with a "reasonable expectation of success."

As discussed in the Response, the predictability of efficacy and toxicity for tamoxifen metabolites is complicated by the fact that, in addition to the two important tamoxifen metabolites discussed above (4-OH-Tam and endoxifen), tamoxifen produces a host of other metabolites of less well defined activity (Response, p 6). Lim teaches that there is substantial inter-patient variability in the occurrence of adverse reactions such as deep vein thrombosis, and that the mechanisms of the variability are poorly understood (Lim p471, col 2). Lim provides no clear delineation of the roles of any of the tamoxifen metabolites in association with the adverse side effects. Lim thus provides no clear or reasonable basis for selecting one particular active metabolite for use (as opposed to the other metabolite, or a mixture of the main active metabolites), or for assuming that this metabolite can be used to beneficial effect in place of tamoxifen, and in the absence of the other major and minor active metabolites.

The Neumann reference further teaches *away* from making the substitution urged by the Office. Like Lim, Neumann teaches that tamoxifen has a spectrum of activities (col 4, lines 66-68), including estrogenic and antiestrogenic activities (col 5, lines 7-8). Neumann further teaches that suitable antiestrogens [for use in the invention of Neumann] are those having a spectrum of activity that is *essentially the same as that of tamoxifen* (col 4, lines 56-58). As discussed above and in the Response, Lim teaches that the activities of tamoxifen may come from *the combination of active metabolites*, compounds that, as observed by Lim, provide a mixture of estrogenic and antiestrogenic effects. Nothing in these references teaches or suggests that a single isolated metabolite,

can provide the full "spectrum of activity" of tamoxifen, and nothing in these references suggests that it is safe or desirable to use an *isolated* metabolite of tamoxifen without the possible balancing effects of the other tamoxifen metabolites suggested by both Lim and Neumann.

There is simply no reasonable basis in the combination of references cited by the Office either to select a) endoxifen from among the metabolites to replace tamoxifen, or b) to produce endoxifen in the tablet form of Neumann or the liposome forms of Zeisig or Unger.

II. The Office uses impermissible hindsight reconstruction in making the rejection

In presenting the *prima facie* case, it is well established that deriving the claimed technology through *ex post* hindsight reasoning is impermissible. In particular, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 972 F.2d 1260, 1266, (Fed. Cir. 1992); *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998) ("obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention").

Consequently, an examiner absolutely must avoid using hindsight – the legal conclusion must be reached on the basis of the facts gleaned from the prior art. See MPEP § 2142. At the outset, hindsight must not be used to define the problem that the invention solves. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372 (Fed. Cir. 2012). Then, hindsight must not be used to gather or suggest the elements of the invention. See *In re Ochiai*, 71 F.3d at 1572 (Fed. Cir. 1995). Finally, "both the suggestion and the expectation of success must be founded in the prior art, not in the Appellant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

As the Office admits, Lim does not teach endoxifen in tablet or complex form (Office Action, p2). The Office seeks to address this deficiency by pointing to Neumann, urging the modification of Lim by substituting endoxifen for tamoxifen in the tablet of

Neumann (Office Action, p3). However, nothing in Neumann suggests endoxifen as a suitable replacement for tamoxifen in the disclosed tablets. Rather, as discussed above, Neumann teaches the use of anti-estrogens having the same *spectrum* of activity as tamoxifen. Endoxifen *does not have the same spectrum of activity* as tamoxifen because it lacks the activities provided by 4-OH-Tam and other metabolites.

Given the complete lack of teaching in the cited art suggesting selection of endoxifen from among the metabolites, the absence of any reason to produce the endoxifen in tablet form, and the absence of any predictable result or reasonable expectation of success in replacing tamoxifen with endoxifen in the compositions and methods of Neumann, it logically follows that the Office has impermissibly used the Appellants' own specification as a template to piece together the teachings of the prior art, and the rejection is thus improper.

Response to the Office's arguments of 07/19/2012

In the Office Action, the Office asserted that Appellants' arguments [regarding the potential toxicity of endoxifen, as discussed above] were not found persuasive because "while Appellants argue the toxicity of tamoxifen and its metabolites, instant claims do not recite the argued toxicity nor the claims require therapeutic activity. Instant claims are not directed to a method of treatment or providing therapy. Instant claims only require a composition."

The Office misstates Appellants' argument. Appellants have not argued toxicity or a lack thereof as a *claim element*, but as one of the reasons that the skilled person would lack motivation to make the combination urged by the Office. The Office's argument for combining the endoxifen of Lim with the tablet form taught by Neumann – i.e., that it the skilled person would be motivated to produce endoxifen in tablet form – is entirely dependent on a presupposition that the skilled person would be motivated to formulate endoxifen for oral administration to subjects. For the reasons discussed in the Response and above, Appellants maintain that the skilled persons in the medical community had significant uncertainty about the safety and efficacy of endoxifen. The lack of motivation to make the combination urged by the Office is evidenced by that fact that, until at least

2009, even in view of the possible advantages urged by the Office, those of skill in the art were not moved to formulate endoxifen for direct administration.

CONCLUSION

In view of the foregoing discussion of the deficiencies of the cited art and the Office's clear error, Appellants respectfully submit that the Office's rejection of Claims 40 and 45-46 and 49-50 under 35 U.S.C. § 103(a) was in error. Appellants request the Board to allow the claims.

Dated: August 22, 2013

/Mary Ann D. Brow/

Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
2275 Deming Way, Suite 310
Middleton, WI, 53562
608-662-1277

V. CLAIMS APPENDIX

1-39. (cancelled)

40. A composition comprising an effective amount of a complex comprising a synthetic preparation of endoxifen, wherein said endoxifen is a free base or is in the form of a salt, wherein said composition comprising endoxifen is composition formulated in a hydroalcoholic gel, a patch, a cream, an emulsion, a lotion, an ointment, a powder, a tablet, a capsule, an enteric-coated capsule, an enteric coated tablet, a lozenge, or an oil.

41. (cancelled)

42. (withdrawn) The composition of claim 40, wherein said composition comprising endoxifen is formulated in a hydroalcoholic gel containing a penetration enhancer, an aqueous vehicle, an alcoholic vehicle and a gelling agent.

43. (withdrawn) The composition of claim 40, wherein said hydroalcoholic gel comprises a neutralizing agent, wherein said neutralizing agent is selected from the group consisting of sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, arginine, trolamine, and tromethamine, and wherein said neutralizing agent exists at a neutralizing agent/gelling agent ratio of about 1:1 to about 4:1.

44. (withdrawn) The composition of claim 40, wherein said hydroalcoholic gel comprises

- (i) endoxifen at about 0.01% to 0.20% by weight;
- (ii) isopropyl myristate at about 0.1% to 2.0%, preferably 0.5% to 2.0% by weight;
- (iii) alcohol at about 50.0% to 80.0%, preferably about 60.0% to 75.0% by weight

(iv) aqueous vehicle at about 20.0% to 60.0%, preferably 25.0% to 50.0% by weight; and

(v) gelling agent at about 1.0% to 10.0%, preferably about 0.5% to 5.0% by weight.

wherein the percentage of components is weight to weight of the composition.

45. The composition of claim 40, wherein said endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetate, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate salts.

46. The composition of claim 40, wherein said composition comprises at least one lipid selected from the group consisting of egg phosphatidylcholine (EPC), egg phosphatidylglycerol (EPG), soy phosphatidylcholine (SPC), hydrogenated soy phosphatidylcholine (HSPC), dimyristoylphosphatidylcholine (DMPC), dimyristoylphosphatidylglycerol (DMPG), dipalmitoylphosphatidylcholine (DPPC), distearylphosphatidylglycerol (DSPG), dipalmitoylphosphatidylglycerol (DMPG), cholesterol (Chol), cholesterol sulfate and its salts (CS), cholesterol hemisuccinate and its salts (Chems), cholesterol phosphate and its salts (CP), cholesterylphosphocholine and other hydroxycholesterol or amino cholesterol derivatives, cholesteryl succinate, cholesteryl oleate, polyethylene glycol derivatives of cholesterol (cholesterol-PEG), coprostanol, cholestanol, cholestane, cholic acid, cortisol, corticosterone, hydrocortisone, and calciferol, *E*-guggulsterone, *Z*-guggulsterone, mixture of *E*-and *Z*-guggulsterone, monoglycerides, diglycerides, triglycerides, carbohydrate-based lipids selected from a group consisting of galactolipid, mannanolipid, galactolecithin, β -sitosterol, stigmasterol, stigmastanol, lanosterol, α -spinasterol, lathosterol, campesterol, phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidic acid, and pegylated derivatives of distearoylphosphatidylglycerol, dipalmitoylphosphatidylglycerol, dimyristoylphosphatidylglycerol, and dioleoylphosphatidylglycerol.

47. The composition of claim 40, wherein said composition comprises endoxifen, cholesterol and/or a cholesterol derivative, and one or more phospholipids.

48. The composition of claim 47, wherein at least one of said one or more phospholipids is hydrogenated soy phosphatidylcholine or soy phosphatidylcholine.

49. The composition of claim 40, wherein said composition comprises a form selected from the group consisting of powder, solution, emulsion, micelle, liposome, lipidic particle, gel, paste form, a lyophilized form, and a tablet or a filled capsule, wherein said tablet or filled capsule optionally comprises an enteric coating material.

50. The composition of claim 40, wherein said composition is in a lyophilized form comprising a cryoprotectant, wherein said cryoprotectant comprises one or more sugars selected from the group consisting of trehalose, maltose, lactose, sucrose, glucose, and dextran.

51-54. (cancelled)

55. A method of treating a cell, comprising, exposing said cell to a composition of claim 40.

56. The method of claim 55, wherein the cell is *in vivo* in a host.

57. The method of claim 56, wherein said host is a mammal.

58. The method of claim 55, wherein said exposing comprises administering a composition of claim 40 to a subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

59. A method of treating a subject having cancer, comprising administering a composition of claim 40 to said subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

VI. EVIDENCE APPENDIX

- Exh. 1. Kisanga, et al., *Clinical Cancer Research*, Vol. 10, 2336-2343, April 1, 2004
- Exh. 2. Majumdar et al., "In vitro investigations on the toxicity and cell death induced by tamoxifen on two non-breast cancer cell types," *Journal of Biomedicine and Biotechnology*, 1:3, 99-107, 2001
- Exh. 3. Sideras, et al., "Coprescription of Tamoxifen and Medications That Inhibit CYP2D6", *Journal of Clinical Oncology*, Vol. 28, No. 16, Jun 1, 2010.
- Exh. 4. Kirsten Boyd Goldberg, "NCI Plans Preclinical Testing Of Tamoxifen Metabolite Endoxifen For Breast Cancer," *The Cancer Letter*, Vol. 35 No. 31 Aug. 7, 2009.

Exhibits 1-4 were previously submitted to the Office with the Response filed on 05/16/12 and acknowledge by the Office in the Office Action of 07/19/2012.

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL (Submitted Only via EFS-Web)

Application Number	12/515,261	Filing Date	2009-05-15	Docket Number (if applicable)	JINA-132458/US-1/PCT	Art Unit	1611
First Named Inventor	Ateeq Ahmad			Examiner Name	Channavajjala		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.

Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☐ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☐ Other _____

☒ Enclosed

☒ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☒ Affidavit(s)/ Declaration(s)

☐ Other _____

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____
(Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to
Deposit Account No 504302

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

Signature of Registered U.S. Patent Practitioner			
Signature	/Mary Ann D. Brow/	Date (YYYY-MM-DD)	2015-04-14
Name	Mary Ann D. Brow	Registration Number	42363

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ateeq Ahmad, et al.	Confirmation: 7363
Serial No.: 12/515,261	Group No.: 1611
Filed: 15-May-2009	Examiner: Channavajjala
Entitled: Endoxifen Compositions And Methods	

**REQUEST FOR CONTINUED EXAMINATION AND
RESPONSE TO OFFICE COMMUNICATION
MAILED JULY 19, 2012**

EFS WEB FILED

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

CERTIFICATE OF EFS WEB TRANSMISSION UNDER 37 C.F.R. § 1.8	
<p>I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being transmitted to the United States Patent and Trademark Office transmitted via the Office electronic filing system in accordance with 37 C.F.R. §1.6(a)(4).</p>	
Dated: <u>April 14, 2015</u>	By: <u>/Mary Ann D. Brow/</u> Mary Ann D. Brow, Reg. No. 42,363

Examiner Channavajjala:

This paper is filed with a Request for Continued Examination and is responsive to the Final Office Communication mailed July 19, 2012. Also filed with this paper is a Declaration of Dr. Ateeq Ahmad under 37 C.F.R. §1.132. ("Ahmad Decl.") and a Form PTOL-413A Applicant Initiated Interview Request Form. Applicants respectfully request reconsideration in view of the following amendments and remarks.

The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No. **JINA-13458/US-1/PCT**. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Amendment to the Claims begins on page 3 of this communication.

Remarks begin on page 5 of this communication.

AMENDMENT TO THE CLAIMS:

This listing of the claims will replace all prior listings and versions of claims in the application:

1-39. (cancelled)

40. (currently amended) A solid pharmaceutical composition comprising an effective amount of ~~a complex comprising~~ a synthetic preparation of endoxifen, wherein:

i) said synthetic preparation of endoxifen is at least 80% Z-endoxifen;

ii) said synthetic preparation of endoxifen is in the form of a salt;

wherein said solid pharmaceutical composition is in the form of an enteric-coated tablet or enteric-coated capsule~~wherein said endoxifen is a free base or is in the form of a salt, wherein said composition comprising endoxifen is composition formulated in a hydroalcoholic gel, a patch, a cream, an emulsion, a lotion, an ointment, a powder, a tablet, a capsule, an enteric-coated capsule, an enteric-coated tablet, a lozenge, or an oil.~~

41- 44 (cancelled)

45. (currently amended) The solid pharmaceutical composition of claim 40, wherein said endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetate, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate salts.

46-57. (cancelled).

58. (currently amended) ~~The method of claim 55~~A method of treating a subject, wherein said exposing comprises comprising orally administering a solid pharmaceutical composition of claim 40 to a said subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

59. (currently amended) A The method of claim 58, wherein treating a said subject having is a mammal having cancer, comprising administering a composition of claim 40 to said subject, wherein said administering comprises oral, intravenous, subcutaneous, percutaneous, parenteral, intraperitoneal, rectal, vaginal, and/or topical delivery said composition to said subject.

REMARKS

Claims 40, 42-49 and 55-59 are pending in the present case. Claims 42-44 and 55-59 stand withdrawn in view of a prior species election requirement; Claims 40 and 45-49 are under examination.

In the Office Action mailed on February 16, 2012, the Examiner made the following rejections:

- I. Claims 40, 45-46 and 49-50 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, hereinafter “Lim”) in view of US 4,310,523 to Neumann (hereinafter “Neumann”) and Zeisig et al (abstract, Anticancer Drugs, 2004, hereinafter “Zeisig”); and
- II. Claims 47 and 48 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim, Neumann, and Zeisig as applied to claims 40, 45-46 and 49-50 above, and further in view of US 6638767 to Unger et al (hereinafter “Unger”).

Applicants disagree with these rejections for the reasons made of record in the Pre-Appeal Brief Review request filed on 01/19/13 and in the Appeal Brief filed on 08/22/13. Nonetheless, for business reasons and to advance prosecution, and without acquiescence and reserving the right to prosecute the original or similar claims in one or more future applications, Applicants by the present amendment cancel claims 42-44, 46-50, and 55-57. Claims 40, 45, and 58-59 remain pending. Claim 40 is amended herein to recite a solid pharmaceutical composition comprising an effective amount of a synthetic preparation of endoxifen, wherein the synthetic preparation of endoxifen is at least 80% Z-endoxifen, is in the form of a salt, and is in the form of an enteric-coated tablet or enteric-coated capsule. Method claims 58 and 59 as amended are directed to orally administering a composition according to claim 40.

Support for a solid preparation of endoxifen is provided in the specification, *e.g.*, in Example 4, bridging pages 32-33. Preparations of 80% or greater purity Z-endoxifen are disclosed, *e.g.*, in paragraph 81, and enteric coated tablets and capsules are disclosed, *e.g.*, in paragraph 120, and original claim 16. Salts of endoxifen are disclosed, *e.g.*, in claim 45.

The claims are not obvious

- I. Claims 40 and 45-46 and 49-50 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim *et al.* (Cancer Chemother Pharamcol, 2005, 55, 471-478, hereinafter “Lim”) in view of US 4,310,523 to Neumann (hereinafter “Neumann”) and Zeisig *et al.* (abstract, Anticancer Drugs, 2004, hereinafter “Zeisig”). In particular, the Examiner has asserted that it would be obvious to use endoxifen as disclosed by Lim in place of tamoxifen in preparations for oral administration, *e.g.*, in a tablet as disclosed by Neumann.

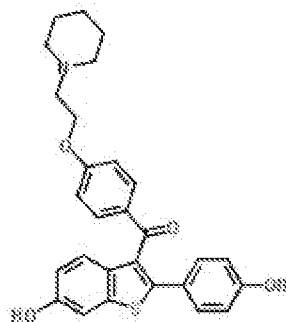
For the reasons discussed in detail below, Applicants respectfully submit that substitution of endoxifen for tamoxifen for oral administration was not obvious to a person skilled in pharmaceutical chemistry at time the application was filed. In particular, the specific chemical differences between endoxifen and tamoxifen suggest that such a substitution would not work.

Evaluation of different drugs for oral administration must include consideration of the effects of passage through the digestive system (*e.g.*, the gut and hepatic system) on the *particular* chemistries of the compounds. The effects of the digestive system can alter the bioavailability of different compounds in dramatically different ways, even if compounds *appear* to be structurally very similar. (Ahmad Decl., ¶6). As will be discussed herein below, at the time of Applicants’ filing, the skilled person would not have expected oral administration of endoxifen to be effective in delivering an active form of the drug systemically to a subject. (Ahmad Decl., ¶¶ 14-15).

a) It would have been expected that endoxifen would be glucuronidated and inactivated after oral administration

Endoxifen and 4-OH-Tam are both hydroxylated metabolites of tamoxifen, and members of the class of compounds referred to as “phenolics,” which is a class of chemical compounds consisting of one or more hydroxyl group(s) (-OH) bonded directly to an aromatic ring. Phenolic compounds are known to be substrates for intestinal modification, specifically glucuronidation. The intestinal glucuronidation system is recognized as a barrier to bioavailability of phenolic drug compounds. (Ahmad Decl., ¶8).

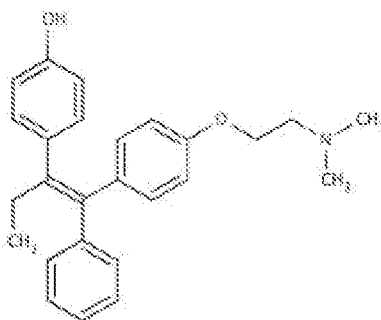
It is known that intestinal glucuronidation can inactivate drugs. Inactivation by glucuronidation has been observed, for example, with the selective estrogen receptor modulator (SERM) raloxifene, which has the structure shown below. (Ahmad Decl., ¶9).



Raloxifene

Despite the fact that orally administered raloxifene is quickly absorbed, its bioavailability is only 2%, and this low bioavailability is due to gastrointestinal glucuronidation. (Ahmad Decl., ¶9).

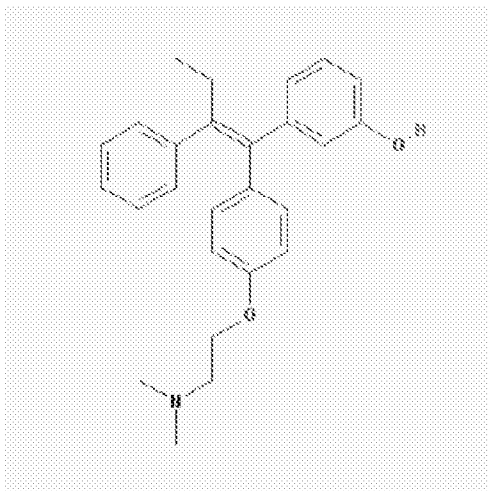
Endoxifen and 4-OH-Tam are similarly affected by intestinal glucuronidation. For example, Pierre Mauvais-Jarvis, *et al.* stated “ . . . 4-OHTAM cannot be used p.o. [*per os, i.e., by mouth*] because it is destroyed during its hepatic passage . . . ”. (Ahmad Decl., ¶10) The structure of 4-OH Tam is shown below:



4-OH-tamoxifen (4-OH-Tam)

Thus, it was understood at the time of filing that both endoxifen and 4-OH-Tam would be glucuronidated in the gut. Glucuronidation of 4-OH-Tam and of endoxifen effectively eliminates the antiestrogenic effects of these compounds. In fact, it has been determined that the glucuronidated form of endoxifen cannot bind estrogen receptors. (Ahmad Decl., ¶11).

Yet another hydroxylated active metabolite of tamoxifen, **3-OH tamoxifen** (“droloxifene”), having the structure shown below, was of interest because it has a 10- to 64-fold higher affinity for the estrogen receptor than tamoxifen. However, this drug, which is rapidly glucuronidated after administration, was abandoned as a possible therapeutic when it was shown to be less effective than tamoxifen. (Ahmad Decl., ¶ 12).



3-OH-tamoxifen (droloxifene)

Thus, it was understood at the time of filing of the present application that hydroxylated metabolites of tamoxifen, including active endoxifen and 4-OH Tam, if orally administered, would be expected to be glucuronidated, with the effect being reduction or elimination their antiestrogenic activities. In contrast, after oral administration of tamoxifen, these compounds are produced *in situ* by metabolism of tamoxifen, and are thus not exposed to these digestive system effects.

b) It would have been expected that endoxifen would have poor absorption after oral administration due to low lipophilicity

It was well established at the time the priority application was filed that hydrophilic drugs are often poorly absorbed when administered orally, and that greater lipophilicity enhances absorption. The hydroxyl group-containing metabolites 4-OH-Tam and endoxifen both have reduced lipophilicity as compared to tamoxifen, with endoxifen being even less lipophilic than 4-OH-Tam. Thus, endoxifen would be expected to be less effectively absorbed after oral administration than *either* tamoxifen or 4-OH-Tam. (Ahmad Decl., ¶14).

Thus, at the time the above-named patent application was filed, the art in the field pointed away from oral administration of endoxifen for at least the reasons that 1) it was expected that orally administered endoxifen would be modified by glucuronidation in the gut and/or the liver, as taught by Zheng, and would be rendered ineffective as an anti-estrogenic compound, and 2) it was expected that the low lipophilicity of endoxifen would result in limited absorption from the gut. Thus, a person skilled in the field of pharmacological chemistry would not be led to formulate endoxifen for oral administration, *i.e.*, they would not have used the endoxifen from Lim's ethanol solution to replace tamoxifen in a tablet formulation as described by Neumann, because the resulting compound would not have been expected to deliver an anti-estrogenic form of endoxifen systemically to a subject. (Ahmad Decl., ¶15).

c) Unexpected results

Surprisingly, Applicants have determined that a salt of endoxifen delivered orally as an enteric coated tablet has greater bioavailability than tamoxifen. (Ahmad Decl., ¶¶16-19, and Ahmad et al., Clin. Pharmacol. Ther. 88, 814-817, (2010), attached thereto). The single-doses of endoxifen citrate administered in humans indicates that the both rate and extent of absorption of endoxifen increased linearly, and in a manner proportional to the dose of endoxifen (tablets of 0.5, 1, 2, and 4 mg).

Table 1 of the Ahmad reference, reproduced below, lists the pharmacokinetic parameters observed during the study. The increase in C_{max} and AUC (area under concentration-time curve) appeared to be proportional to dose when consecutive dose increments were compared. Endoxifen administered at oral doses of 0.5, 1, 2, or 4 mg resulted in C_{max} values of 1.38, 3.98,

6.79, and 15.1 ng/mL respectively, and AUC_{0-Infinity} values of 100, 239, 401, and 801 ng.h/mL, respectively. When compared with endoxifen levels (C_{max} , 0417 ng/mL) in subjects who received 20 mg tamoxifen (Nolvadex), the doses of 0.5, 1, 2, and 4 mg endoxifen showed 231, 854, 1,528, and 3,521 % higher C_{max} values, respectively. It was surprising that the C_{max} was achieved faster with the administration of endoxifen than with tamoxifen. (Ahmad Decl., ¶17).

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	C_{max} (ng/ml)	AUC _{0-∞} (ng.h/ml)	$t_{1/2}$ (h)(CV%)	Vz (l)	Cl (l/h)
Endoxifen 0.5mg	1.38 ± 0.25	99.9 ± 13.6	58.11 (18.0)	427 ± 101	5.1 ± 0.7
Endoxifen 1.0mg	3.98 ± 1.7	239 ± 70	54.1 (10.6)	346 ± 88	4.5 ± 1.1
Endoxifen 2.0mg	6.79 ± 1.85	401 ± 113	55.4 (16.3)	428 ± 133	5.4 ± 1.8
Endoxifen 4.0mg	15.1 ± 4.24	801 ± 262	52.1 (12.9)	406 ± 119	5.5 ± 1.9
Tamoxifen 20mg	0.417 ± 0.013	381 ± 47.6	1.051 (16.4)*	Fixed	Fixed

The results obtained with endoxifen delivered as an enteric coated tablet are unexpected in view of the teachings Wu, Kemp, Mauvais-Jarvis, Zheng, and Buzdar, and in view of the knowledge in the field that hydrophilic drugs are often poorly absorbed when administered orally.

Historically, “obvious to try” was not permitted as an argument to support an obviousness rejection. The KSR v. Teleflex and follow-on Federal Circuit decisions made it clear that “obvious to try” would be permitted under certain limited circumstances—namely where there were a finite number of predictable options. That is not the case here, as the art at the time of filing predicted that endoxifen administered orally to a subject would fail to deliver an active, anti-estrogenic form of the drug systemically to the subject, and thus could not predict success in formulating endoxifen for oral administration. The claimed invention provides surprising and unexpected results (*e.g.*, efficacy of absorption, and unexpected bioavailability). In this context, the law insists that the claims are not obvious.

This point has been driven home by the recent Federal Circuit decision in *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharmaceuticals Inc.* (Fed. Cir. 2014) (the “Glenmark case”). In the Glenmark case, the Court reiterated that an “obvious to try” approach is only appropriate

where “there are a finite number of identified, *predictable* solutions” to a known problem and that it would **not** be obvious to try when “the prior art gave either no indication of which parameters were critical or no direction as to which of the many possible choices is likely to be successful.” Importantly, the Court re-iterated that in the medical arts “*potential solutions are less likely to be genuinely predictable.*” The Court deemed the patent claims non-obvious in the *Glenmark* case where they involved a drug combination of two known drugs, but where the specific combination had not been disclosed in the prior art and where evidence of surprising or unexpected results was present in the record. The Court compared and contrasted this conclusion to its previous drug combination cases and noted that like in *Pozen Inc. v. Pharmaceutical, Inc.* (Fed. Cir. 2012), “the court sustained a patent on a combination of the known compounds naproxen and sumatriptan for the treatment of migraine headaches, for this combination was not previously known or suggested, and was found to have longer-lasting efficacy than either component separately.”

In the present case, the prior art has shown that i) related hydroxylated tamoxifen metabolites display minimal bioavailability when administered orally due to glucuronidation; ii) active tamoxifen metabolites such as endoxifen and 4-OH Tam would predicted to be glucuronidated in the gut, rendering them inactive; and that iii) due to low lipophilicity, endoxifen should be poorly absorbed after oral administration. An expectation that endoxifen is not suited to oral administration is further strengthened by the fact that closely related, structurally similar hydroxylated tamoxifen metabolites *have been tried in oral therapeutic formulations and have failed.* (Ahmad Decl., 12).

In view of this knowledge in the art pointing to the likelihood of *failure*, it cannot be concluded that oral administration of synthetic endoxifen, or compositions for that purpose *e.g.*, oral tablets and capsules, meet the legal standards of “obvious to try” as re-iterated in *Glenmark*.

II. Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim, Neumann, and Zeisig as applied to claims 40 and 45-46 and 49-50 above, and further in view of Unger. Claims 47 and 48 are cancelled by the present amendment, rendering this rejection moot.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for objection and rejection have been addressed and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned at (608) 662-1277.

Dated: April 14, 2015

/Mary Ann D. Brow /

Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
2275 Deming Way, Suite 310
Middleton, Wisconsin 53562
608.662.1277

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Ateeq Ahmad, et al.	Confirmation:	7363
Serial No.:	12/515,261	Group No.:	1611
Filed:	15-May-2009	Examiner:	Channavajjala
Entitled:	Endoxifen Compositions And Methods		

**DECLARATION OF ATEEQ AHMAD, Ph.D.
UNDER 37 C.F.R. §1.132**

I, Ateeq Ahmad, declare the following:

1. I am the inventor of the invention disclosed and claimed in the present United States patent application.

2. I hold the position of Vice President of Jina Pharmaceuticals, Inc, in Libertyville, IL. I hold a Ph.D. and have been a research scientist in pharmaceutical chemistry since 1972, and have published over 60 scientific research articles in this field. I am the first author on Ahmad, *et al.*, Clin. Pharmacol. Ther. 88(6):814-817 (2010), which is provided herewith and discussed below.

3. In an Office Action in the above-named application mailed July 19, 2012 ("Office Action"), the Examiner asserted that it would be obvious to use endoxifen in place of tamoxifen in a tablet preparation for oral administration. The Examiner stated that Lim (Cancer Chemother Pharmacol, 2005, 55,471-478) discloses a synthetic preparation of endoxifen that has potency similar to that of 4-hydroxy tamoxifen (4-OH-Tam). (Office Action, page 2). The Examiner admits that Lim does not disclose endoxifen in tablet form, or salts of endoxifen, but asserts that Neumann (US 4,310,523) teaches a variety of preparations for administering tamoxifen, including oral tablets, and also discloses salts of tamoxifen. The Examiner concludes that it would have been obvious to prepare a composition comprising the endoxifen of Lim in a formulation for oral administration, with an expectation to provide effective delivery of the compound. (Office Action, page 3).

4. Knowledge in the art at the time of filing of the present application contradicts the Examiner's conclusion. As will be discussed in detail below, the art available at the time of filing indicated that formulation of endoxifen for oral delivery should not be expected to provide effective delivery of the compound to a subject.

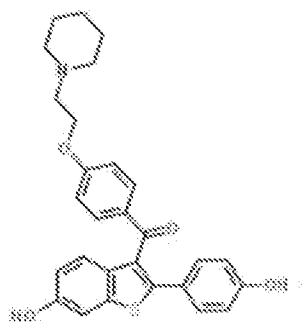
5. Lim discloses an ethanol solution of endoxifen comprising a mixture of 75% Z-isomers and 25% E-isomers (Lim, p. 472, col. 1). Lim exposed cancer cells in culture to the endoxifen solution, as well as to solutions of tamoxifen and 4-OH-Tam, and examined the production of metabolites released to the culture medium. Lim did not characterize these compounds in live animal models using oral administration.

6. Comparison of different drugs and evaluation for oral administration must include consideration of the effects of passage through the digestive system (the gut and hepatic system) on the specific chemistries of the compounds being compared. The effects of the digestive system can dramatically alter the bioavailability of different compounds, even if compounds are closely related and appear to be largely structurally similar.

7. The bioavailability of drugs administered orally can be influenced by a number of factors, including, *e.g.*, modification of the drug in the gut after ingestion, effects on the drug of different environments in the gut, the effect of lipophilicity/lipophobicity of the drug on absorption from the gut, and/or the effects of different foods present in the digestive system on absorption of the drug and the passage of the drug through the gut. See, *e.g.*, "Drug Absorption: Pharmacokinetics: Merck Manual Professional", provided herewith.

8. Endoxifen and 4-OH-Tam are both hydroxylated metabolites of tamoxifen, and members of the class of compounds referred to as "phenolics," which is a class of chemical compounds consisting of one or more hydroxyl group(s) (-OH) bonded directly to an aromatic ring. Phenolic compounds are known to be substrates for intestinal modification, specifically glucuronidation. The intestinal glucuronidation system is recognized as a barrier to bioavailability of phenolic drug compounds. See, *e.g.*, "First-pass metabolism via UDP-glucuronosyltransferase: a barrier to oral bioavailability of phenolics," Wu, *et al.*, J. Pharm. Sci., 100(9):3655-3681 (2001), provided herewith.

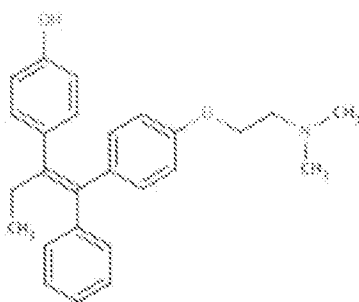
9. It is known that intestinal glucuronidation can inactivate drugs. Inactivation by glucuronidation has been observed, for example, with the selective estrogen receptor modulator (SERM) raloxifene, which has the structure shown below.



Raloxifene

Despite the fact that orally administered raloxifene is quickly absorbed, its bioavailability is only 2%, and this low bioavailability is due to gastrointestinal glucuronidation. See, *e.g.*, “Characterization of raloxifene glucuronidation *in vitro*: contribution of intestinal metabolism to presystemic clearance”. Kemp, *et al.*, Drug Metabolism and Disposition, 30(6):694-700 (2002), provided herewith.

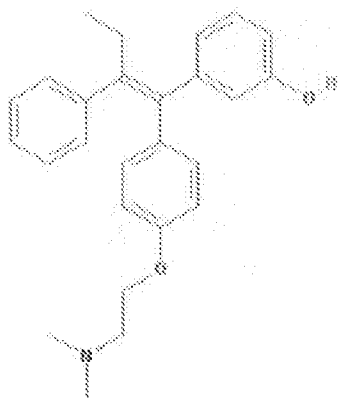
10. Endoxifen and 4-OH-Tam are similarly affected by intestinal glucuronidation. For example, Pierre Mauvais-Jarvis, *et al.* stated “... 4-OHTAM cannot be used p.o. [*per os*, *i.e.*, by mouth] because it is destroyed during its hepatic passage ...” (Mauvais-Jarvis, *et al.* Cancer Res. 46:1521-1525 (1986); see 2nd line of last paragraph, page 1525, emphasis added). The structure of 4-OH Tam is shown below:



4-OH-tamoxifen (4-OH-Tam)

11. Glucuronidation of 4-OH-Tam and of endoxifen effectively eliminates the antiestrogenic effects of these compounds. See, *e.g.*, "Elimination of antiestrogenic effects of active tamoxifen metabolites by glucuronidation." See, *e.g.*, Zheng, *et al.*, Drug Metabolism and Disposition 35(10):1942-48 (2007), provided herewith. In fact, it has been determined that the glucuronidated form of endoxifen cannot bind estrogen receptors.

12. Yet another hydroxylated metabolite of tamoxifen, 3-OH tamoxifen ("droloxifene"), having the structure shown below, was of interest because it has a 10- to 64-fold higher affinity for the estrogen receptor than tamoxifen (Buzdar, *et al.*, Cancer Chemother Pharmacol. 33(4):313-6 (1994), Abstract provided herewith). However, this drug, which is rapidly glucuronidated after administration, was abandoned as a possible therapeutic when it was shown to be less effective than tamoxifen in 2002 (Buzdar, *et al.*, Breast Cancer Res Treat 73(2):161-75 (2002), Abstract provided herewith).



3-OH-tamoxifen (droloxifene)

13. Thus, it was understood at the time of filing of the present application that hydroxylated metabolites of tamoxifen, including endoxifen and 4-OH Tam, if orally administered, would be expected to be glucuronidated, with the effect being reduction or elimination their anti-estrogenic activities.

14. It was well established at the time the application was filed that hydrophilic drugs are often poorly absorbed when administered orally, and that greater lipophilicity enhances absorption. See, e.g., "Drug Absorption: Pharmacokinetics: Merck Manual Professional", provided herewith. The hydroxyl group-containing metabolites 4-OH-Tam and endoxifen both have reduced lipophilicity as compared to tamoxifen, with endoxifen being even less lipophilic than 4-OH-Tam. Thus, endoxifen would be expected to be less effectively absorbed after oral administration than either tamoxifen or 4-OH-Tam.

15. Thus, at the time the above-named patent application was filed, the art in the field pointed away from oral administration of endoxifen for at least the reasons that 1) it was expected that orally administered endoxifen would be modified by glucuronidation in the gut and/or the liver, as taught by Zheng, and would be rendered ineffective as an antiestrogenic compound, and 2) it was expected that the low lipophilicity of endoxifen would result in limited absorption from the gut. Thus, a person skilled in the field of pharmacological chemistry would not be led to formulate endoxifen for oral administration, *i.e.*, they would not have used the endoxifen of Lim ethanol solution to replace tamoxifen in a tablet formulation as described by Neumann, because the resulting compound would not have been expected to deliver an anti-estrogenic form of endoxifen systemically to a subject.

16. Surprisingly, we determined that endoxifen delivered orally as an enteric coated tablet has greater bioavailability than tamoxifen. See Ahmad, *et al.*, Clin. Pharmacol. Ther. 88(6):814-817 (2010), which is provided herewith. The single-doses of endoxifen citrate administered in humans indicate that both rate and extent of absorption of endoxifen increased linearly, and in a manner proportional to the dose of endoxifen (tablets of 0.5, 1, 2, and 4 mg).

17. Table 1 of Ahmad, reproduced below, lists the pharmacokinetic parameters observed during the study. The increase in C_{max} and AUC (area under concentration-time curve) appeared to be proportional to dose when consecutive dose increments were compared. Endoxifen administered at oral doses of 0.5, 1, 2, or 4 mg resulted in C_{max} values of 1.38, 3.98, 6.79, and 15.1 ng/mL respectively, and $AUC_{0-\infty}$ values of 100, 239, 401, and 801 ng.h/mL, respectively. When compared with endoxifen levels (C_{max} , 0417 ng/mL) in subjects who

received 20 mg tamoxifen (Nolvadex), the doses of 0.5, 1, 2, and 4 mg endoxifen showed 231, 854, 1,528, and 3,521 % higher C_{max} values, respectively. It was surprising that the C_{max} was achieved faster with the administration of endoxifen than with tamoxifen (Ahmad et al., Clin. Pharmacol. Ther. 88, 814-817, 2010).

Table 1 Endoxifen doses and pharmacokinetic parameters

Dose	C_{max} (ng/ml)	AUC _{0-∞} (ng·h/ml)	$t_{1/2}$ (h) (CV%)	V_d (l)	Cl (l/h)
Endoxifen 0.5 mg	1.38 ± 0.25	99.9 ± 13.6	58.11 (18.0)	427 ± 101	5.1 ± 0.7
Endoxifen 1.0 mg	3.08 ± 1.7	239 ± 70	54.1 (10.6)	346 ± 88	4.5 ± 1.1
Endoxifen 2.0 mg	6.79 ± 1.85	461 ± 113	55.4 (16.3)	428 ± 133	5.4 ± 1.8
Endoxifen 4.0 mg	15.1 ± 4.24	801 ± 262	52.1 (12.9)	406 ± 119	5.5 ± 1.9
Tamoxifen 20 mg	0.417 ± 0.013	381 ± 47.6	1.051 (16.4) ^P	Fixed	Fixed

18. The results obtained with endoxifen delivered as an enteric coated tablet are unexpected in view of the teachings Wu, Kemp, Mauvais-Jarvis, Zheng, and Buzdar, and in view of the knowledge in the field that hydrophilic drugs are often poorly absorbed when administered orally.

19. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the above-captioned patent application.



Ateeq Ahmad, Ph.D.



Date

LIST OF REFERENCES ATTACHED

1. Drug Absorption: Pharmacokinetics: Merck Manual Professional
2. Wu, *et al.*, J. Pharm. Sci., 100(9):3655-3681 (2001)
3. Kemp, *et al.*, Drug Metabolism and Disposition, 30(6):694-700 (2002)
4. Mauvais-Jarvis, *et al.* Cancer Res. 46:1521-1525 (1986)
5. Zheng, *et al.*, Drug Metabolism and Disposition 35(10):1942-48 (2007)
6. Buzdar, *et al.*, Cancer Chemother Pharmacol. 33(4):313-6 (1994) (Abstract)
7. Buzdar, *et al.*, Breast Cancer Res Treat 73(2):161-75 (2002) (Abstract)
8. Ahmad, *et al.*, Clin. Pharmacol. Ther. 88(6):814-817 (2010)



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/515,261	01/08/2010	Ateeq Ahmad	JINA-13458/US-1/PCT	7363

72960 7590 06/04/2015
Casimir Jones, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER

CHANNAVAJJALA, LAKSHMI SARADA

ART UNIT	PAPER NUMBER
----------	--------------

1611

NOTIFICATION DATE	DELIVERY MODE
-------------------	---------------

06/04/2015

ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com
pto.correspondence@casimirjones.com

Office Action Summary	Application No.	Applicant(s)	
	12/515,261	AHMAD ET AL.	
	Examiner	Art Unit	
	LAKSHMI CHANNAVAJJALA	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 April 2015.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 40, 45, 58 and 59 is/are pending in the application.
- 5a) Of the above claim(s) 58 and 59 is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 40 and 45 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

Art Unit: 1611

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/14/15 has been entered.

Receipt of RCE, Declaration under 37 CFR 1.132 and response dated 04/14/15 is acknowledged.

Claims 40, 45, 58 and 59 are pending in the instant application.

Claims 58 and 59 have been withdrawn from consideration.

Claims 42 and 45 have been considered for examination.

***Examiner note that the claim identifiers for claims 58 and 59 are improper and should state withdrawn.**

In response to the cancellation of claims 47 and 48, the following rejection has been withdrawn:

3. Claims 47 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, submitted by applicants on IDS) in view of US 4,310,523 to Neumann and Zeisig et al (abstract, Anticancer Drugs, 2004) as applied to claims 40 and 45-46 and 49-50 above, and further in view of US 6638767 to Unger et al (Unger).

The following rejection of record has been maintained:

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Claims 40 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, submitted by applicants on IDS) in view of US 4,310,523 to Neumann.

Instant claim 40 has been amended to recite a solid pharmaceutical composition comprising an effective amount a synthetic preparation of endoxifen, wherein i) said synthetic preparation of endoxifen is at least 80% Z-endoxifen, ii) said synthetic preparation of endoxifen is in the form of a salt wherein said solid pharmaceutical composition is in the form of an enteric coated tablet or enteric-coated capsule. Claim 45 recites a salt form of endoxifen.

Lim discloses synthetic preparation of endoxifen of the instant claims for anti-estrogenic effects and potency similar to that of 4-hydroxy tamoxifen. Page 472, col. 1

Art Unit: 1611

describes the use of synthetic, Endoxifen. Lim does not teach the claimed composition in the form of a tablet. Lim does not teach the instant claimed solid composition in the form of a tablet or enteric-coated tablet and further requires 80% synthetic endoxifen.

Neumann teaches a composition comprising an anti-estrogen and anti-gonadotropically effective anti-androgen, wherein the former is tamoxifen (abstract). Neumann teaches administering the compositions by several routes including in the form of oral tablets (col. 9, l 9-21). The tablets containing tamoxifen are described in 1 and contain excipients/carriers such as lactose, PVP, Aerosil etc. Even though Neumann does not teach the composition claimed, it would have been obvious for one skilled in the art at the time of the instant invention was made to look to the teachings of prior art such as those of Neumann for preparing endoxifen compositions of Lim, used for anti-estrogenic effect, because Neumann teaches various routes of administering tamoxifen (compound related to endoxifen as suggested by Lim) including tablets with an expectation to provide effective delivery of the compound. Neumann further teaches salt forms of tamoxifen (examples) and therefore a skilled artisan would have been able to prepare a suitable salt form of endoxifen of Lim because preparing different salt forms of therapeutic compounds so as to improve their solubility is conventional in the art.

Response to Arguments

5. Applicant's arguments filed 4/14/15 have been fully considered but they are not persuasive.

Applicants argue that phenolic compounds, such as endoxifen and 4-OH-tamoxifen (metabolites of tamoxifen), are subject to glucuronidation in the intestine, which in turn inactivates the drugs and/or forms a barrier for bioavailability of the drugs. Applicants argue that it was understood at the time of filing that both endoxifen and 4-OH-Tam would be glucuronidated in the gut, which eliminates the antiestrogenic effects of these compounds and that the glucuronidated form of endoxifen cannot bind estrogen receptors. (Ahmad Decl., ¶11). Applicants refer to 3-OH tamoxifen ("droloxifene"), which is also rapidly glucuronidated after administration, and abandoned as a possible therapeutic when it was shown to be less effective than tamoxifen. (Ahmad Decl., ¶ 12). Hence, applicants argue that it would have been expected that endoxifen, a hydrophilic drug, would have poor absorption after oral administration due to low lipophilicity (Ahmad Decl., ¶ 12). Therefore, it was argued that a person skilled in the field of pharmacological chemistry would not be led to formulate endoxifen from the ethanol solution (of Lim) to replace tamoxifen in a tablet formulation, to prepare an oral tablet formulation. Applicants submit that a salt of endoxifen delivered orally as an enteric coated tablet unexpectedly presented greater bioavailability than tamoxifen, and the rate and extent of absorption of endoxifen increased linearly with the dose of endoxifen administered (Table 1 on page 10 of the response).

Applicants' arguments are not found persuasive because while applicants argue the bioavailability of tamoxifen and its metabolites, instant claims do not recite the argued toxicity nor the claims require therapeutic activity. Instant claims are not directed to a method of treatment or providing therapy. Instant claims only require a composition. Even though the claims recite effective amount of endoxifen, the said claims do not specify what effect is being achieved. Thus, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, obviousness may be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988), *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992), and *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 82 USPQ2d 1385 (2007). In this case, admittedly Lim teaches a significant anti-estrogenic effect of endoxifen, which meets the teaching, suggestion as well as motivation for one skilled in the art to substitute tamoxifen with endoxifen. Further, nothing in the teachings of Lim suggests about the lack of bioavailability of endoxifen

and thus a skilled artisan would not be led away from employing endoxifen for tamoxifen.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395-97 (2007) identified a number of rationales to support a conclusion of obviousness which are consistent with the proper “functional approach” to the determination of obviousness as laid down in *Graham*. Exemplary rationales that may support a conclusion of obviousness in the present case include: (B) “Obvious to try” – choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

In the instant case, applicants argue that the phenolic derivatives of tamoxifen are subject to glucuronidation resulting in the lack of bioavailability of the endoxifen and hence a skilled artisan would not have prepared an oral composition of endoxifen at the time of the instant invention was made. However, the arguments are not persuasive because the evidence for “obvious to try” standards come from the articles Buzdar et al., (1994) and Mauvais-Jarvis et al., (1996), which show that it is routine in the pharmacological art to test the active/potent metabolites of a drug for their bioavailability and absorption by various routes of administration, in order to determine and develop a most efficacious drug. Accordingly, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention was made to try to prepare a drug delivery system for endoxifen (of Lim) so as to provide an effective composition that is

Art Unit: 1611

more potent than tamoxifen (parent compound) because its potent estrogen receptor modulator effect. With respect to the comparative results of table I of the declaration, while the data presented shows significant differences, one of an ordinary skill in the art would have observed the argued difference in the plasma concentrations and bioavailability of endoxifen by employing endoxifen in a solid oral composition such as a tablet, capsule or other solid dosage form and further enteric coat the composition. While applicants argue that endoxifen is superior in performance to endoxifen, the comparison in Ahmad et al is not proper because it is noted that differences exist between the absorption and availability of tamoxifen versus endoxifen because it is noted that Ahmad et al described the plasma concentrations and bioavailability of single dose of tamoxifen (20 mg/day) versus multiple doses of endoxifen to show that endoxifen provides better PK and bioavailability. Additionally, Ahmad et al. states that endoxifen bypasses the CYP2D6 enzyme required for metabolic activation of tamoxifen and is therefore not likely to be affected by the CYP2D6 genetic polymorphisms or drug-drug interaction that inhibit CYP2D6 activity. While Ahmad proposes that endoxifen as a substitution of endoxifen for tamoxifen, the argued superiority is a result of the physiological response/reaction to the drug and not how endoxifen affects the physiology. Therefore, at the time of the instant invention was made, one of an ordinary skill in the art would not construe that endoxifen to be inferior to tamoxifen.

Art Unit: 1611

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKSHMI CHANNAVAJJALA whose telephone number is (571)272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bethany Barham can be reached on 571-272-6175. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ateeq Ahmad, et al.	Confirmation: 7363
Serial No.: 12/515,261	Group No.: 1611
Filed: 15-May-2009	Examiner: Channavajjala
Entitled: Endoxifen Compositions And Methods	

**RESPONSE TO OFFICE COMMUNICATION
MAILED JUNE 4, 2015**

EFS WEB FILED

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

CERTIFICATE OF EFS WEB TRANSMISSION UNDER 37 C.F.R. § 1.8	
I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being transmitted to the United States Patent and Trademark Office transmitted via the Office electronic filing system in accordance with 37 C.F.R. §1.6(a)(4).	
Dated: <u>September 4, 2015</u>	By: <u>/Mary Ann D. Brow/</u> Mary Ann D. Brow, Reg. No. 42,363

Examiner Channavajjala:

This is paper is responsive to the Office Communication mailed June 4, 2015. Applicants respectfully request reconsideration in view of the following remarks.

The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No. **JINA-13458/US-1/PCT**. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Remarks begin on page 3 of this communication.

STATUS OF THE CLAIMS:

1-39. (cancelled)

40. (previously presented) A solid pharmaceutical composition comprising an effective amount of a synthetic preparation of endoxifen, wherein:

- i) said synthetic preparation of endoxifen is at least 80% Z-endoxifen;
- ii) said synthetic preparation of endoxifen is in the form of a salt;

wherein said solid pharmaceutical composition is in the form of an enteric-coated tablet or enteric-coated capsule.

41-44. (cancelled)

45. (previously presented) The solid pharmaceutical composition of claim 40, wherein said endoxifen is in the form of a salt selected from the group of salts consisting of citrate, acetate, formate, oxalate, tartarate, trifluoroacetate, methane sulfonate, phosphate, sulfate, chloride, bromide, iodide, lactate, and formate salts.

46-57. (cancelled)

58. (withdrawn) A method of treating a subject comprising orally administering a solid pharmaceutical composition of claim 40 to a said subject.

59. (withdrawn) The method of claim 58, wherein said subject is a mammal having cancer.

REMARKS

Claims 40, 45, 58, and 59 are pending in the present case. Claims 58 and 59 stand withdrawn in view of a prior species election requirement. The claim identifiers for claims 58 and 59 are now shown as “withdrawn.” Claims 40 and 45 are under examination.

In the Office Action mailed on June 4, 2015, the Office rejected claims 40 and 45 under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, hereinafter “Lim”) in view of US 4,310,523 to Neumann (hereinafter “Neumann”). For the reasons discussed in detail below, Applicants request that the rejection be withdrawn because:

- a) The cited art does not disclose all the elements of Applicants’ claims;
- b) The claimed composition is not “obvious to try”; and
- c) The Office improperly failed to consider Applicants’ evidence of non-obviousness.

a) The cited art does not disclose all the elements of Applicants’ claims

The Office characterizes Applicants’ claims as reciting a solid composition that requires “80% synthetic endoxifen.” (Office Action, page 4) Applicants respectfully disagree with this restatement of the elements of Applicants’ claims. Claim 40 recites “said synthetic preparation of endoxifen is at least 80% Z-endoxifen.” Applicants respectfully submit that it is clear in the claim as worded that this element indicates the proportion synthetic endoxifen that is the Z-isomer of endoxifen, and the claim does not recite what portion of the entire composition, *e.g.*, of an enteric-coated tablet, is synthetic endoxifen.

The Office admits that “Lim does not teach the claimed composition in the form of a tablet. Lim does not teach the instant claimed solid composition in the form of a tablet or enteric-coated tablet and further requires 80% synthetic endoxifen.” (Office Action, page 4). Applicants note that Lim also does not disclose a synthetic preparation of endoxifen is at least 80% Z-endoxifen, as recited in Applicants’ claims, nor does Lim disclose a salt form of synthetic endoxifen.

The Office points to Neumann for a teaching of oral tablets as configured for tamoxifen (Office Action, page 4). The Office admits that Neumann does not teach the composition claimed (Office Action, page 4), but asserts that “it would have been obvious for one skilled in

the art at the time of the instant invention was made to look to the teachings of prior art such as those of Neumann for preparing endoxifen compositions of Lim.” (Office Action, page 4).

However, as noted above, Lim does not disclose a preparation of synthetic endoxifen that is at least 80% Z-endoxifen. Thus, even if one were to produce tablets as taught by Neumann containing the endoxifen preparation of Lim, as urged by the Office, (Applicants maintain that the skilled person would not have done so), one would still not arrive at a composition having all of the features recited in Applicants’ claims 40 or 45. Further, neither reference discloses enteric-coated tablets or capsules, an additional feature recited in all of Applicants’ claims.

It is well-settled law that establishing prima facie obviousness requires *at least* a suggestion of all of the features in a claim. See *In re Wada and Murphy, citing CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). See also MPEP §2143. The combination of Lim and Neumann does not teach or suggest all of the features of Applicants’ claims 40 and 45 and thus cannot establish prima facie obviousness of these claims. Applicants therefore request that the rejection be withdrawn.

Response to Arguments

b) The claimed composition is not “obvious to try”

The Office acknowledges that establishing that an invention is “obvious to try” requires, *inter alia*, that there had been a finite number of identified, predictable potential solutions to the recognized need or problem, and that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success. Regarding tamoxifen metabolites, however, Applicants’ claimed embodiments are not “obvious to try” for at least the reason that the cited art provides no reasonable expectation of success.

The Office asserts that Buzdar et al., (1994) and Mauvais-Jarvis et al., (1996) (provided with the Ahmad Declaration (Ahmad Decl.) filed in support of Applicants’ response of April 14, 2015) are evidence that it is obvious “to test the active/potent metabolites of a drug for their bioavailability and absorption by various routes of administration, in order to determine and develop a most efficacious drug.” (Office Action, page 7). Applicants disagree with the Office’s conclusion for at least the reasons that 1) Buzdar and Mauvais-Jarvis each teach only a single metabolite of tamoxifen (3-OH tamoxifen or 4-OH-tamoxifen, respectively), which is a far cry from suggesting routine screening of all active metabolites. Further each reference teaches

testing of its disclosed metabolite via a single route of administration (oral or transdermal, respectively). This combination of references simply does not suggest that it is routine in the pharmacological art to test all active/potent metabolites by all of the various routes of administration, as urged by the Office (Office Action, page 7).

Further, both Budzar and Mauvais-Jarvis specifically teach *away* from oral administration of their respective metabolites. Budzar demonstrated that orally administered of 3-OH Tam was “significantly less effective than tamoxifen”, and further development of the drug was stopped (see Ahmad Decl., ¶12, discussing Budzar 1994 and Budzar 2002), while Mauvais-Jarvis *did not use oral administration* and instead teaches that a percutaneous route was used because 4-OH tam is “**destroyed** during its hepatic passage” if taken orally (see Mauvais-Jarvis second line of last ¶ of page 1512, and, Ahmad Decl., ¶10). Thus, contrary to the Office’s assertion, Budzar and Mauvais-Jarvis both specifically teach that oral administration of an OH-bearing tamoxifen metabolite, e.g., via tablets as taught by Neumann, would be expected to fail in delivering tamoxifen-like anti-estrogenic activity to a treated subject.

c) The Office improperly failed to consider Applicants’ evidence of non-obviousness

The Office asserts that Applicants’ argument that the phenolic derivatives of tamoxifen are subject to glucuronidation resulting in the lack of bioavailability of orally administered endoxifen, and that a skilled artisan therefore would not have prepared an oral composition of endoxifen at the time of the instant invention was made are “not persuasive because the evidence for “obvious to try” standards come from the articles [Budzar and Mauvais-Jarvis]” and their purported teachings that it is routine to try metabolites. However, the Office points to Budzar and Mauvais-Jarvis *only* in so far as they allegedly suggest that it is routine to try metabolites by a variety of routes of administration (which, as discussed above, Applicants do not concede). An “obvious to try” argument, however, *also* requires a skilled person to have a reasonable expectation of success. Therefore, the Office’s dismissal of the Applicants’ evidence that that success would *not* be expected is improper, as the Office is obligated to consider all factual evidence provided in rebuttal. “When an applicant submits evidence, whether in the specification as originally filed or in reply to a rejection, the examiner must reconsider the patentability of the claimed invention. The decision on patentability must be made based upon consideration of all the evidence . . . A decision to make or maintain a rejection in the face of all

the evidence must show that it was based on **the totality of the evidence**". See MPEP §2142, citing *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990), emphasis added.

In omitting consideration of Applicants' proffered evidence that the skilled person contemplating routes of administration for a drug would consider the effects of the passage of a drug through the digestive system and, in view of the known intestinal glucuronidation of phenolics such as endoxifen and 4-OH-Tam, would have *followed* the teachings of Mauvais-Jarvis and avoided oral administration of endoxifen. In doing so, the Office effectively suggests that the person skilled in the art of pharmaceuticals and organic chemistry would ignore established knowledge in the field (*i.e.*, that phenolic metabolites such as 4-OH-Tam are *destroyed if taken orally*, as expressly stated by Mauvais-Jarvis), and would waste time and resources on testing oral administration of a compound that the literature clearly indicates should not succeed in delivering the anti-estrogenic activity to a subject to whom it is administered. The Office has shown no indication that Applicants' evidence had been considered, and provides no sufficient argument or evidence as to why a person of skill in the art would be moved to take this course of action. Applicants therefore submit that this continued rejection under 35 U.S.C§103 is improper in view of the evidence of record and Applicants request that the rejection be withdrawn.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that all grounds for objection and rejection have been addressed and Applicants' claims should be passed to allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 662-1277.

Dated: September 4, 2015

/Mary Ann D. Brow

Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
2275 Deming Way, Suite 310
Middleton, Wisconsin 53562
608.662.1277



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/515,261	01/08/2010	Ateeq Ahmad	JINA-13458/US-1/PCT	7363
72960	7590	12/09/2015		
Casimir Jones, S.C. 2275 DEMING WAY, SUITE 310 MIDDLETON, WI 53562			EXAMINER CHANNAVAJJALA, LAKSHMI SARADA	
			ART UNIT	PAPER NUMBER
			1611	
			NOTIFICATION DATE	DELIVERY MODE
			12/09/2015	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@casimirjones.com
pto.correspondence@casimirjones.com

Office Action Summary	Application No. 12/515,261	Applicant(s) AHMAD ET AL.	
	Examiner LAKSHMI CHANNAVAJJALA	Art Unit 1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 April 2015.
- 2a) ☒ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.
- 4) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 5) ☒ Claim(s) 40, 45, 58 and 59 is/are pending in the application.
- 5a) Of the above claim(s) 58 and 59 is/are withdrawn from consideration.
- 6) ☐ Claim(s) ____ is/are allowed.
- 7) ☒ Claim(s) 40 and 45 is/are rejected.
- 8) ☐ Claim(s) ____ is/are objected to.
- 9) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 10) ☐ The specification is objected to by the Examiner.
- 11) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>12/2/15</u> . | 6) <input type="checkbox"/> Other: ____. |

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Receipt of response dated 09/4/15 is acknowledged.

Claims 40, 45, 58 and 59 are pending in the instant application.

Claims 58 and 59 have been withdrawn from consideration.

Claims 40 and 45 have been considered for examination.

The following rejection of record has been maintained:

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 40 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, submitted by applicants on IDS) in view of US 4,310,523 to Neumann.

Instant claim 40 has been amended to recite a solid pharmaceutical composition comprising an effective amount a synthetic preparation of endoxifen, wherein i) said synthetic preparation of endoxifen is at least 80% Z-endoxifen, ii) said synthetic preparation of endoxifen is in the form of a salt wherein said solid pharmaceutical composition is in the form of an enteric coated tablet or enteric-coated capsule. Claim 45 recites a salt form of endoxifen.

Lim discloses synthetic preparation of endoxifen of the instant claims for anti-estrogenic effects and potency similar to that of 4-hydroxy tamoxifen. Page 472, col. 1 describes the use of synthetic, Endoxifen. Lim does not teach the claimed composition in the form of a tablet. Lim does not teach the instant claimed solid composition in the form of a tablet or enteric-coated tablet and further requires synthetic endoxifen that is 80% Z-endoxifen.

Neumann teaches a composition comprising an anti-estrogen and anti-gonadotropically effective anti-androgen, wherein the former is tamoxifen (abstract). Neumann teaches administering the compositions by several routes including in the form of oral tablets (col. 9, l 9-21). The tablets containing tamoxifen are described in 1 and contain excipients/carriers such as lactose, PVP, Aerosil etc. Even though Neumann does not teach the composition claimed, it would have been obvious for one skilled in the art at the time of the instant invention was made to look to the teachings of prior art such as those of Neumann for preparing endoxifen compositions of Lim, used for anti-estrogenic effect, because Neumann teaches various routes of administering tamoxifen (compound related to endoxifen as suggested by Lim) including tablets with an expectation to provide effective delivery of the compound. Neumann further teaches salt forms of tamoxifen (examples) and therefore a skilled artisan would have been able to prepare a suitable salt form of endoxifen of Lim because preparing different salt forms of therapeutic compounds so as to improve their solubility is conventional in the art.

Response to Arguments

3. Applicant's arguments filed 9/4/15 have been fully considered but they are not persuasive.

Applicants argue that instant claims do not claim 80% endoxifen by weight of the composition and instead requires at that synthetic preparation containing endoxifen is at least 80% is a Z-isomer endoxifen. Examiner agrees with applicants that instant claim requires percentage of z-isomer to be at least 80% and not the amount of endoxifen in the total composition.

Applicants argue that Lim does not teach the claimed at least 80% z-endoxifen and even if one were to produce tablets as taught by Neumann containing the endoxifen preparation of Lim, as urged by the Office, (Applicants maintain that the skilled person would not have done so), one would still not arrive at a composition having all of the features recited in Applicants' claims 40 or 45. It is argued that neither reference discloses enteric-coated tablets or capsules, an additional feature recited in all of Applicants' claims.

Applicants' arguments are not persuasive because even though Lim does not specifically mention a specific isomer, Lim teaches endoxifen (a mixture of 75% z-isomer and 25% E-isomer) (page 504, Materials & methods in col. 2, lines 1-9). Thus, employing the claimed at least 80% z-isomer in place of the endoxifen (of 75% z-isomer) would have been obvious for one of an ordinary skill in the art because the existence of a racemate is, in and of itself, sufficient to render obvious any individual

Art Unit: 1611

stereoisomers contained within; no express suggestion of isomer separation is needed. In re Adamson, 125 USPQ 233, 235 (CCPA 1960). Aventis v. Lupin, 84 USPQ2d 1197, 1205 (CAFC 2007). Pfizer Inc v. Teva Pharm. USA 109 USPQ2d 1652 Pfizer Inc. v. Apotex Inc., 82 USPQ2d 1321 (Fed. Cir. 2007). While Lim does not teach the claimed salts, employing a free base or a salt form of a compound depending on the solubility and the desired solubility of the compound would have been within the scope of a skilled artisan. In this regard, applicants have not provided unexpected advantage of employing at least 80% of z-endoxifen and a citrate salt of citrate.

Applicants argue the “obvious to try” standards of the examiner stating that the standard requires finite number of variables and a reasonable expectation of success. It is argued that the references Buzdar et al and Mauvais-Jarvis et al teach only a single metabolite of tamoxifen (3-OG and 4-OH) and only one route of administration, which is a far cry from suggesting routine screening of all active metabolites (such as that stated in Office Action), and does not teach or suggest that it is routine in the pharmacological art to test all active/potent metabolites by all of the various routes of administration.

Applicants’ arguments are not persuasive because Lim clearly teaches endoxifen (75% of which is z-endoxifen) and accordingly, does not require trying excessive number of compounds (metabolites of tamoxifen). Further, one of an ordinary skill in the art would not have to try excessive number of variables because one of an ordinary skill in the art would look to the teachings of Neumann and test for oral administration because Neumann suggests tamoxifen (parent compound) for its suitability for oral administration.

It is argued that because Buzdar et al teaches oral formulations are significantly less effective than tamoxifen and Mauvais-Jarvis uses a percutaneous route rather than oral administration, the tablets (suggested by Neumann) of endoxifen (Lim) would be expected to fail in delivering tamoxifen-like anti-estrogenic activity. Applicants further argue that the examiner does not seem to consider the unexpected results of record showing unexpected benefit of the enteric coated oral formulations comprising endoxifen as compared to those of tamoxifen, and that the rejection is not based on the totality of evidence. It is argued that the Office's position (without any evidence) amounts to stating that one of an ordinary skill in the art of pharmaceuticals and organic chemistry would ignore established knowledge in the field (i.e., phenolic metabolites of 4-OH tamoxifen are destroyed if taken orally) and still try to deliver the compounds orally.

Applicants' arguments are not persuasive because applicants' evidence of unobviousness of the instant claims has been considered fully. However, the claimed compositions are considered obvious because the prior art (Neumann) suggests that oral compositions of tamoxifen metabolites can be successfully employed in oral composition. In this regard, please refer to the examiner's rebuttal with respect to "obvious to try" standard. Thus, one of an ordinary skill in the art would have been able to try the limited number of endoxifen z-isomers in oral dosage formulations such as those suggested by Newman with an expectation to provide the desired therapeutic response.

In response to the unexpected results, the examiner notes that the results (Ahmad et al 2010) are not commensurate with the scope of the instant claims because while the compositions of Ahmad et al employ citrate salts, instant claims are not limited to citrate salts. Additionally, Ahmad does not specify if the endoxifen employed in the composition is at least 80% z-isomer. Hence, the argued results are not commensurate with the scope of claimed composition, particularly in light of the applicants' arguments that oral administration of endoxifen would have been expected to fail to provide any therapeutic efficacy owing to intestinal glucuronidation of phenolics such as endoxifen and 4-OH-Tam. Additionally, while the instant claims and the compositions of Ahmad et al describe enteric compositions, neither instant specification nor the experimental details of Ahmad describe any enteric formulation that would otherwise protect endoxifen from intestinal glucuronidation.

Therefore, the rejection of the instant claims has been maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

Art Unit: 1611

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKSHMI CHANNAVAJJALA whose telephone number is (571)272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bethany Barham can be reached on 571-272-6175. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Ateeq Ahmad, et al.	Confirmation:	7363
Serial No.:	12/515,261	Group No.:	1611
Filed:	15-May-2009	Examiner:	Channavajjala
Entitled:	Endoxifen Compositions And Methods		

**DECLARATION OF SAIFUDDIN SHEIKH, Ph.D.
UNDER 37 C.F.R. §1.132**

I, Saifuddin Sheikh, declare the following:

1. I am the inventor of the invention disclosed and claimed in the present United States patent application. I am the co-author on Ahmad, *et al.*, Clin. Pharmacol. Ther. 88(6):814-817 (2010) ("Publication"), which was provided in the above named application as part of the Declaration of Ateeq Ahmad, Ph.D. on April 14, 2015 ("Ahmad Declaration").
2. As described in the Ahmad Declaration, in the study reported in the Publication, we determined that endoxifen delivered orally as an enteric coated tablet has greater bioavailability than tamoxifen (see the Publication). The single-doses of endoxifen citrate administered in humans indicate that both rate and extent of absorption of endoxifen increased linearly, and in a manner proportional to the dose of endoxifen (tablets of 0.5, 1, 2, and 4 mg).
3. I understand that in an Office Action mailed December 9, 2015 ("Office Action"), the Examiner stated that the Publication does not specify whether the endoxifen employed in the composition is at least 80% *Z*-isomer, and that the experimental details of the Publication do not describe a particular enteric formulation that would protect endoxifen from intestinal glucuronidation.
4. The endoxifen contained in the enteric coated tablets used in the Publication was at least 80% *Z*-endoxifen and was in the form of a citrate salt of endoxifen.

5. The enteric coated tablets used in the Publication were formulated as follows:


Sr. No.	Ingredients
Dry Mixing	
1	Endoxifen Citrate eq. to Endoxifen, INH
2	Lactose Monohydrate (PHARMA 200M) DMV, USNF & Ph.Eur.
3	Lactose Monohydrate (DCL 11), Ph.Eur. & BP
4	Croscarmellose Sodium, USNF & Ph.Eur.
5	Magnesium Stearate, USNF & Ph.Eur.
Seal Coating	
6	Hydroxy propyl cellulose (Klucel EF), USNF & Ph.Eur.
7	Isopropyl Alcohol, USNF & Ph.Eur.
8	Purified water, USNF & USP
Enteric Coatings	
9	Acryl-EZE 93O18509 White, INH
10	Acryl-EZE 93O540016 Pink, INH
11	Acryl EZE 93O82960 Yellow, INH
12	Acryl-EZE 93O510003 Green
13	Purified water, USNF & USP

6. The different Acryl-EZE® enteric coatings listed above had no functional differences other than color, and different colors were used to distinguish tablets having different strength of endoxifen. A brochure for Acryl-EZE enteric coatings is provided herewith.

7. Enteric coatings for drugs are very well known in the field of pharmaceutical drug formulation and manufacturing. In addition to the Acryl-EZE coating, other materials commonly used for enteric coating of pharmaceutical tablets or capsules include Eudragit® coating, cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate succinate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, polyvinyl acetate phthalate, methacrylic acid ethacrylate co-polymer, and methacrylic acid methyl methacrylate polymer.

8. As discussed in the Specification of the above-named application, enteric coatings prevent release of medication before it reaches the small intestine (see, e.g., the Specification at paragraph 120). All of the materials listed in paragraph 6 above would be understood by a person skilled in pharmaceutical drug formulation to be suitable for enteric coating a tablet or capsule of endoxifen to prevent release of the medication before it reaches the small intestine.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the above-captioned patent application.



Saifuddin Sheikh, Ph.D.

March 07, 2016

Date

ACRYL-EZE®

Aqueous Acrylic Enteric System



Combining the benefits of a fully formulated coating system with the features and performance of a globally accepted enteric polymer, EUDRAGIT® L100-55, an Evonik product.



Delayed release oral solid dosage forms are widely formulated with enteric coating providing either protection of the gastric mucosa from irritating actives or protection of drugs unstable in gastric fluids. Delayed release products are also utilized for drug delivery to local sites in the intestine.

The Acryl-EZE® portfolio of products represents another breakthrough in coating technology that the pharmaceutical industry has come to expect.

Acryl-EZE is a world-class film coating product: an optimized, pigmented, aqueous acrylic system for the application of an enteric film coating for oral solid dosage forms. Acryl-EZE combines the benefits and performance of a globally accepted enteric polymer (EUDRAGIT® L100-55) with a fully formulated coating system, with or without plasticizer, providing significant time savings in both development and production. Acryl-EZE products have been optimized for tablet and multiparticulate applications, inclusive of proton pump inhibitors.

Time Savings in Development and Production

- Simple to dispense and disperse (20 minutes), with easy clean up
- Reduced raw material inventory and QC requirements
- Fully formulated or non-plasticized versions available for maximum formulator flexibility

Reliable and Reproducible Performance

- Simple coating procedure uses conventional processes
- No curing step required for most applications
- Backed by world-class technical service and manufacturing

Delayed Release for Wide Range of Oral Solid Dosage Forms

- Enteric polymer protects against acid media, solubilizes at pH 5.5
- Optimized formulations for tablet and multiparticulate applications at cost-efficient weight gains
- Formulations matched to customer's preference
- Specialized formulations available for acid-labile actives including proton pump inhibitors

Combined Service Offerings of Colorcon and Evonik

- On site scale-up and production assistance
- Regulatory support
- Formulation and development support
- Technical training

Deliver high-performance products — with Colorcon

Choose Colorcon, leader in pharmaceutical solid oral dose solutions, as a formulation partner in every phase of your product development. Our solution capabilities originate from two main areas of expertise:

Film Coatings:

- Optimized formulations specifically for your application and regulatory needs including customized colors and color matching
- Innovative products for mechanical integrity, gloss, pearlescence, and environmental protection
- Brand enhancement concepts, consulting and services to build a strong brand image and stand out from the competition

Formulation Technologies:

- Full range of functional excipients
- Technologies for development and production of delayed/enteric release and extended/controlled release tablets and multiparticulates
- HyperStart® service and extensive applications data to provide starting formulations to save you development time and money
- Extensive formulation know-how and technical support to achieve the exact drug release profile desired

From formulation and tablet design through product differentiation and branding, Colorcon gives you everything you need to deliver high-performance products.

ACRYL-EZE®
Aqueous Acrylic Enteric System
From **Colorcon®**

Powered by

Eudragit®
An Evonik product.

To contact Colorcon:

North America
+1-215-699-7733

Europe/Middle East/Africa
+44-(0)-1322-293000

Asia Pacific
+65-6438-0318

Latin America
+54-11-5556-7700

You can also visit our website at www.colorcon.com

To contact Evonik visit www.evonik.com/eudragit

Colorcon®

©BPSI Holdings LLC, 2013. The information contained in this document is proprietary to Colorcon and may not be used or disseminated inappropriately.

All trademarks, except where noted, are property of BPSI Holdings LLC.

EUDRAGIT® is a registered trademark of Evonik Röhm GmbH, Darmstadt, Germany.

PGR2023-00043 – Atossa

Ex. 2022 - Page 181

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Ateeq Ahmad, et al.	Confirmation: 7363
Serial No.: 12/515,261	Group No.: 1611
Filed: 15-May-2009	Examiner: Channavajjala
Entitled: Endoxifen Compositions And Methods	

**AMENDMENT UNDER 37 C.F.R. §1.116 AFTER
FINAL OFFICE ACTION MAILED DECEMBER 9, 2015
AND
REQUEST FOR AFTER-FINAL CONSIDERATION UNDER AFCP 2.0**

EFS WEB FILED

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

CERTIFICATE OF EFS WEB TRANSMISSION UNDER 37 C.F.R. § 1.8	
I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being transmitted to the United States Patent and Trademark Office transmitted via the Office electronic filing system in accordance with 37 C.F.R. §1.6(a)(4).	
Dated: <u>March 9, 2016</u>	By: <u>/Mary Ann D. Brow/</u> Mary Ann D. Brow, Reg. No. 42,363

This communication is an After Final Amendment under 37 C.F.R. §1.116, responsive to the Final Office Communication mailed December 9, 2015, and is filed with a Request for After-Final Consideration under AFCP 2.0. Also provided herewith is a Declaration of Dr. Saifuddin Sheikh under 37 C.F.R. §1.132. ("Sheikh Decl."). Applicants respectfully request entry of this amendment and reconsideration for the reasons set forth below.

The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4302, referencing Attorney Docket No. **JINA-13458/US-1/PCT**. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Amendment to the claims is reflected in the Listing of Claims on page 3 of this paper and **Remarks** begin on page 4 of this paper.

AMENDMENTS TO THE CLAIMS:

This listing of the claims will replace all prior listings and versions of claims in the application:

1-39. (cancelled)

40. (currently amended) A solid pharmaceutical composition comprising an effective amount of a synthetic preparation of endoxifen, wherein:

- i) said synthetic preparation of endoxifen is at least 80% Z-endoxifen;
- ii) said synthetic preparation of endoxifen is in the form of a citrate salt;

wherein said solid pharmaceutical composition is in the form of an enteric-coated tablet or enteric-coated capsule.

41-57. (cancelled)

58. (withdrawn) A method of treating a subject comprising orally administering a solid pharmaceutical composition of claim 40 to a said subject.

59. (withdrawn) The method of claim 58, wherein said subject is a mammal having cancer.

REMARKS

Claims 40, 45, 58, and 59 are pending in the present case. Claims 58 and 59 stand withdrawn in view of a prior species election requirement. The claim identifiers for claims 58 and 59 are now shown as “withdrawn.” Claims 40 and 45 are under examination.

In the Office Action mailed on December 9, 2015, the Office maintained rejection of claims 40 and 45 under 35 U.S.C. 103(a) as allegedly being unpatentable over Lim et al (Cancer Chemother Pharamcol, 2005, 55, 471-478, hereinafter “Lim”) in view of US 4,310,523 to Neumann (hereinafter “Neumann”).

In accordance with 37 CFR §1.116, Applicant seeks to amend the claims to address matters of form to put the claims in better form for appeal. Also provided herewith is a Declaration of Dr. Saifuddin Sheikh under 37 C.F.R. §1.132 (“Sheikh Decl.”).

Amendment to the claims

1. In maintaining the rejection over the cited art in view of the Declaration filed September 4, 2015, evidencing surprising results when endoxifen is provided in an enteric-coated tablet, the Examiner states that the results in Ahmad publication (“Publication”) are not commensurate with the scope of the instant claims because “while the compositions of Ahmad et al employ citrate salts, instant claims are not limited to citrate salts” (Office Action, page 7).

Applicants’ Response: For business reasons and without acquiescing to the Examiner’s arguments, and reserving the right to prosecute the original or similar claims in one or more future applications, Claim 40 is amended herein to recite that the endoxifen is in the form of a citrate salt. Claim 45 is cancelled in view of the amendment to claim 40.

Evidence of non-obviousness

2. The Examiner further asserts that the Publication “does not specify if the endoxifen employed in the composition is at least 80% z-isomer” and states that “while the instant claims and the compositions of Ahmad et al. describe enteric compositions, neither instant specification nor the experimental details of Ahmad describe any enteric formulation that would otherwise protect endoxifen from intestinal glucuronidation (Office Action, page 7).

Applicants' Response: As noted above, provided herewith is a Declaration of Dr. Saifuddin Sheikh under 37 C.F.R. §1.132. ("Sheikh Decl."). As noted in the Sheikh Decl., the endoxifen contained in the enteric coated tablets used in the Publication was at least 80% Z-endoxifen and was in the form of a citrate salt of endoxifen (Sheikh Decl., ¶4).

The enteric coated tablets used in the Publication were formulated as follows:

Sr. No.	Ingredients
Dry Mixing	
1	Endoxifen Citrate eq. to Endoxifen, INH
2	Lactose Monohydrate (PHARMA 200M) DMV, USNF & Ph.Eur.
3	Lactose Monohydrate (DCL 11), Ph.Eur. & BP
4	Croscarmellose Sodium, USNF & Ph.Eur.
5	Magnesium Stearate, USNF & Ph.Eur.
Seal Coating	
6	Hydroxy propyl cellulose (Klucel EF), USNF & Ph.Eur.
7	Isopropyl Alcohol, USNF & Ph.Eur.
8	Purified water, USNF & USP
Enteric Coatings	
9	Acryl-EZE 93O18509 White, INH
10	Acryl-EZE 93O540016 Pink, INH
11	Acryl EZE 93O82960 Yellow, INH
12	Acryl-EZE 93O510003 Green
13	Purified water, USNF & USP
Total	

(Sheikh Decl., ¶5)

The different Acryl-EZE® enteric coatings listed above had no functional differences other than color, and different colors were used to distinguish tablets having different doses of endoxifen (Sheikh Decl., ¶6).

Enteric coatings for drugs are very well known in the field of pharmaceutical drug formulation and manufacture. In addition to the Acryl-EZE coating, other materials commonly used for enteric coating of pharmaceutical tablets or capsules include Eudragit® coating, cellulose acetate phthalate, cellulose acetate trimellitate, cellulose acetate succinate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, polyvinyl acetate phthalate, methacrylic acid ethacrylate co-polymer, and methacrylic acid methyl methacrylate polymer (Sheikh Decl., ¶7).

As discussed in the Specification, enteric coatings prevent release of medication before it reaches the small intestine (see, e.g., the Specification at ¶120). All of the materials listed in above would be understood by a person skilled in pharmaceutical drug formulation to be suitable for enteric coating a tablet or capsule of endoxifen to prevent release of the medication before it reaches the small intestine (Sheikh Decl., ¶8).

Applicants respectfully submit that the claims as amended are commensurate in scope with the evidence of surprising results shown in the Ahmad publication and in the Ahmad Declaration filed on April 14, 2015, and that the claims are not obvious over the Lim in view of Neumann for the reasons set forth in the Response filed therewith. Applicants respectfully request that the present amendment be entered and that Applicants' claims be passed to allowance.

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 662-1277.

Dated: March 9, 2016

/Mary Ann D. Brow

Mary Ann D. Brow
Registration No. 42,363

CASIMIR JONES, S.C.
2275 Deming Way, Suite 310
Middleton, Wisconsin 53562
608.662.1277



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

72960 7590 03/29/2016
Casimir Jones, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

EXAMINER	
CHANNAVAJALA, LAKSHMI SARADA	
ART UNIT	PAPER NUMBER

1611

DATE MAILED: 03/29/2016

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/515,261	01/08/2010	Ateeq Ahmad	JINA-13458/US-1/PCT	7363

TITLE OF INVENTION: Endoxifen Compositions And Methods

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	06/29/2016

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: **Mail** **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

72960 7590 03/29/2016
Casimir Jones, S.C.
2275 DEMING WAY, SUITE 310
MIDDLETON, WI 53562

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/515,261	01/08/2010	Ateeq Ahmad	JINA-13458/US-1/PCT	7363

TITLE OF INVENTION: Endoxifen Compositions And Methods

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	\$480	\$0	\$0	\$480	06/29/2016

EXAMINER	ART UNIT	CLASS-SUBCLASS
CHANNAVAJALA, LAKSHMI SARADA	1611	424-464000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

- (1) The names of up to 3 registered patent attorneys or agents OR, alternatively, 1 _____
- (2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 _____
- 3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:

- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): (Please first reapply any previously paid issue fee shown above)

- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The director is hereby authorized to charge the required fee(s), any deficiency, or credits any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. Change in Entity Status (from status indicated above)

- ☐ Applicant certifying micro entity status. See 37 CFR 1.29
- ☐ Applicant asserting small entity status. See 37 CFR 1.27
- ☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
12/515,261	01/08/2010	Ateeq Ahmad	JINA-13458/US-1/PCT	7363
72960	7590	03/29/2016	EXAMINER	
Casimir Jones, S.C. 2275 DEMING WAY, SUITE 310 MIDDLETON, WI 53562			CHANNAVAJJALA, LAKSHMI SARADA	
			ART UNIT	PAPER NUMBER
			1611	
DATE MAILED: 03/29/2016				

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

<i>Examiner-Initiated Interview Summary</i>	Application No. 12/515,261	Applicant(s) AHMAD ET AL.	
	Examiner LAKSHMI CHANNAVAJJALA	Art Unit 1611	

All participants (applicant, applicant's representative, PTO personnel):

(1) LAKSHMI CHANNAVAJJALA. (3)_____.

(2) Mary Ann Brow. (4)_____.

Date of Interview: 16 March 2016.

Type: ☒ Telephonic ☐ Video Conference
 ☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
 If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
 (For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 40,58 and 59.

Identification of prior art discussed: _____.

Substance of Interview
 (For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Examiner informed the attorney that the composition claim 40 will be allowed upon cancellation of withdrawn claims 58-59 drawn to a different invention. Examiner was authorized by the attorney to cancel claims 58 and 59 (withdrawn claims) by examiner's amendment.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/LAKSHMI CHANNAVAJJALA/ Primary Examiner, Art Unit 1611	
--	--

Notice of Allowability	Application No. 12/515,261	Applicant(s) AHMAD ET AL.	
	Examiner LAKSHMI CHANNAVAJJALA	Art Unit 1611	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to 3/9/16.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are 40. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

- a) ☐ All b) ☐ Some *c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|--|
| 1. <input type="checkbox"/> Notice of References Cited (PTO-892) | 5. <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 2. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 6. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| 3. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 7. <input checked="" type="checkbox"/> Other <u>PTO-2323</u> . |
| 4. <input checked="" type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date _____. | |

/LAKSHMI CHANNAVAJJALA/
Primary Examiner, Art Unit 1611

The present application is being examined under the pre-AIA first to invent provisions.

EXAMINER'S AMENDMENT

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Mary Ann Brow on 3/16/16.

The application has been amended as follows:

Cancel claims 58 and 59

2. The following is an examiner's statement of reasons for allowance:

3. Instant claim 40 is allowable because the prior art of record as a whole does not teach or suggest employing a synthetic endoxifen in an oral composition, wherein the said synthetic compound is at least 80% z-endoxifen and is in a citrate salt form. Lim et al (closest prior art of record) suggests that endoxifen, a metabolite of tamoxifen, provides potent anti-estrogenic effects. However, Lim does not teach or suggest employing any particular salt form or a synthetic preparation containing at least 80% z-form of endoxifen citrate, in a solid pharmaceutical composition. Additionally, the prior art of record as a whole teaches away from preparing oral solid compositions of tamoxifen metabolites owing to their rapid glucouronidation upon oral administration and hence reduced bioavailability. On the contrary, applicants have provided evidence that

Art Unit: 1611

oral enteric coated preparations containing citrate form of z-endoxifen (containing at least 80% z-endoxifen) exhibits a greater bioavailability than that obtained higher amounts of tamoxifen.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKSHMI CHANNAVAJJALA whose telephone number is (571)272-0591. The examiner can normally be reached on 9.30 AM- 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bethany Barham can be reached on 571-272-6175. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1611

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/LAKSHMI CHANNAVAJJALA/
Primary Examiner, Art Unit 1611

<i>Examiner-Initiated Interview Summary</i>	Application No. 12/515,261	Applicant(s) AHMAD ET AL.	
	Examiner LAKSHMI CHANNAVAJJALA	Art Unit 1611	

All participants (applicant, applicant's representative, PTO personnel):

(1) LAKSHMI CHANNAVAJJALA. (3) ____.

(2) Mary Ann Brow. (4) ____.

Date of Interview: 16 March 2016.

Type: ☒ Telephonic ☐ Video Conference
 ☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
 If Yes, brief description: ____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☐Others
 (For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: 40,58 and 59.

Identification of prior art discussed: ____.

Substance of Interview
 (For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Examiner informed the attorney that the composition claim 40 will be allowed upon cancellation of withdrawn claims 58-59 drawn to a different invention. Examiner was authorized by the attorney to cancel claims 58 and 59 (withdrawn claims) by examiner's amendment.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/LAKSHMI CHANNAVAJJALA/ Primary Examiner, Art Unit 1611	
--	--