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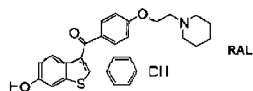
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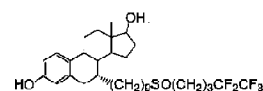
(54) Title: PURE ANTIESTROGENS FOR BREAST CANCER THERAPY

(57) Abstract: This invention provides. a compound having the structure
wherein R₁-R₁₅, q, and X are defined herein, or a salt thereof. A process for
preparing the above compound, a pharmaceutical composition comprising
the above compound, a method of inhibiting tumor proliferation in a mam-
mal, and a method of inhibiting and/or reducing loss of bone mineral den-
sity in a mammal are also provided.

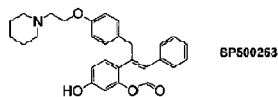
TAM:	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = H	X' = H	Z = H
4-OH ⁺ AM:	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = OH	X' = H	Z = H
TOR:	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = H	X' = Cl	Z = H
4-OH ⁺ TOR:	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = OH	X' = Cl	Z = H
GW 5638	X = CH=CHCOOH	Y = H	X' = H	Z = H
GW7004:	X = CH=CHCOOH	Y = OH	X' = H	Z = H
Idoxifene:	X = OCH ₂ CH ₂ N(CH ₃) ₄	Y = I	X' = H	Z = H
Ospemifene:	X = OCH ₂ CH ₂ OH	Y = H	X' = Cl	Z = H
TAT-59:	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = OPO ₃ H ₂	X' = H	Z = CH(CH ₃) ₂



RAL

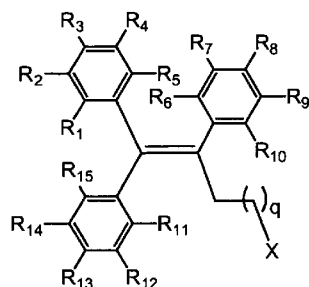


ICI 162,780



6P500263

Figure 2.





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, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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PURE ANTIESTROGENS FOR BREAST CANCER THERAPY

5 This application claims the benefit of U.S. Provisional Application No. 61/210,324, filed March 16, 2009, the content of which is hereby incorporated by reference in its entirety.

10 The invention disclosed herein was made with government support under grant number ES09418 awarded by the National Institute of Environmental Health Sciences. Accordingly, the U.S. Government has certain rights in this invention.

15 Throughout this application, certain publications are referenced in brackets. Full citations for these publications may be found immediately preceding the claims. The disclosures of these publications in their
20 entireties are hereby incorporated by reference into this application in order to describe more fully the state of the art to which this invention relates.

Background of the Invention

25 Breast cancer constitutes 32% of all female cancers in the United States [1]. Tamoxifen (TAM, Fig. 1a) is widely used as a first-line endocrine therapy for early-stage breast cancer patients with positive estrogen receptors (ERs) [2] and also as a prophylactic agent for women at
30 high risk of developing this disease [3]. Besides the significant benefit, long-term administration of TAM has serious side effects, including endometrial cancer [3-6]. The carcinogenic effect is thought to involve initiation and/or promotion. Studies of the genotoxic mechanism of

TAM [7] together with studies performed by other laboratories [8] established that TAM produces DNA adducts in rodent liver [9-11] and in the endometrium of women treated with TAM [12, 13]. Since TAM-DNA adducts are highly mutagenic [14] and not rapidly repaired [15, 16], the DNA adducts likely contribute to the initiation of endometrial cancer. Like estrogens, TAM is a partial ER agonist in uterine tissue [17] and such estrogenic effects may promote endometrial cancer [18, 19].

The genotoxic mechanism of TAM in animals and humans [7, 8] has been elucidated by several laboratories. As shown in Figures 1a and 1b, TAM and its metabolites are α -hydroxylated and undergo O-sulfonation catalyzed by hydroxysteroid sulfotransferase, after which they react with guanine residues in cellular DNA, forming primarily dG-N²-TAM and dG-N²-N-desmethylTAM adducts [7]. TAM-DNA adducts were detected in the liver of rodents treated with TAM [20-22] and in several tissues of monkeys, including the ovary and uterus [23]. In humans, TAM-DNA adducts have been detected in the endometrium of certain women treated with TAM [12, 13, 24] and in human endometrial explants exposed to α -OHTAM [25], although there is controversy about such findings in human tissues [26-28]. K-ras mutations were detected frequently in the endometria of women treated with TAM [29] and their mutational specificity was consistent with that of TAM-DNA adducts in mammalian cells [14]. TAM carcinogenicity may be due primarily to DNA damage induced by TAM through this mechanism. Therefore, TAM alternatives free of genotoxic and estrogenic potential are required to diminish such serious side-effects and to increase clinical efficacy.

Toremifene (TOR, Fig. 2), the chloroethyl analog of TAM, however, does not promote hepatic DNA adducts [10, 30, 31] and hepatocarcinoma in rats [10, 31], although the metabolic fate of TOR is similar to that of TAM. Previous studies indicate that this may be due to the steric hindrance caused by a bulky chlorine atom positioned at the ethyl moiety of TOR, which may reduce the ability of hydroxysteroid sulfotransferase to O-sulfonate α -OHTOR and consequently the amount of TOR α -sulfate available to react with DNA [32]. The field effect caused by the electron-withdrawing chlorine atom may also diminish the effective elimination of the α -sulfate group from the α -carbon and therefore inhibit the formation of the carbocation intermediate that reacts with DNA [32]. No K-ras mutation was observed in the endometria of patients receiving TOR [29].

Toremifene, raloxifene (RAL) and ICI 182,780 (structures shown in Fig. 2) are also currently used in the clinic for full or partial breast cancer therapy. TOR, a chlorinated TAM derivative, was approved in 1998 by the Food and Drug Administration (FDA) for breast cancer therapy. However, the estrogenic activity of TOR is similar to that of TAM and the clinical efficacy of TOR for breast cancer patients is also similar [33]. Therefore, this drug is not frequently used in the United States. Raloxifene (RAL) was approved by the FDA in 1998 for treating osteoporosis, but it was also found to reduce significantly the incidence of breast cancer in women at high risk of developing the disease [34]. Unlike for TAM, an increased incidence of endometrial cancer was not observed in women treated with RAL [35, 36]. In addition, hyperplasia and the incidences of thromboembolia and cataracts were significantly lower

than in RAL-treated patients than in TAM-treated patients [37]. Therefore, the FDA approved RAL in 2007 as a chemopreventive agent for postmenopausal women at high risk for invasive breast cancer [38]. However, RAL retains a weak proliferative effect on the uterus in postmenopausal women [39]. Moreover, venous thrombo-embolic events and liver dysfunction were still observed as adverse effects in patients treated with RAL [40]. Other adverse effects such as hot flashes, leg cramps and peripheral edema were also reported [41]. ICI 182,780 (Fig. 2) blocks the tropic action of 17β -estradiol (E_2) in the rat uterus and is free of estrogen agonist activity [42]. This drug has shown high response rates for advanced breast cancer [43] and was approved for treatment of post-menopausal breast cancer patients who fail to respond to TAM therapy [44]. However, since both RAL and ICI 182,780 have two hydroxyl moieties, the hydroxylated compounds can be conjugated rapidly through phase II metabolism and excreted [45, 46]. Moreover, ICI 182,780 is highly lipophilic and does not ionize under physiological conditions [47]. This makes it difficult to achieve adequate bioavailability by oral administration in humans [48]. As a result, higher doses must be administered to obtain an efficacy equivalent to that achieved with TAM [49]. Therefore, new alternative compounds having improved bioavailability and less harmful side-effects are required to provide better clinical efficacy.

More than seventy molecules classified by five chemical groups (triphenylethylene, benzothiophene, tetrahydronaphthylene, indole, and benzopyran) have been developed in the last four decades [50, 51]. Among them, several compounds have been applied in clinical studies

for treatment of breast cancer or osteoporosis [52-54]. However, TAT-59 (Fig. 2) was dropped because of anti-breast cancer efficacy inferior to that of TAM. Idoxifene (Fig. 2) and levormeloxifene [55] have been discontinued
5 from clinical testing due to undesirable effects on the uterus. In a phase III trial, arzoxifene did not show significant clinical benefit beyond TAM against advanced and metastatic breast cancer [56]. At present, ospemifene (Fig. 2), lasofoxifene, and bazedoxifene, in addition to
10 arzoxifene, are under clinical trials for treatment of osteoporosis. Clinical trials of GW5638 and SP500263 (Fig. 2) are also being considered for this purpose.

GW5638, with its novel carboxylic side chain (see X
15 position in Fig. 2), is a triphenylethylene compound that has been recognized as having powerful antiestrogenic activity. This compound is a selective estrogen receptor modulator, or SERM, that has estrogen-like actions to preserve bone density in OVX-rats but, unlike TAM, has
20 pure antiestrogenic activity in rodent uterus. Moreover, GW5638 does not promote tumor growth in rodent breast or endometrial cells [57, 58].

A major health concern for postmenopausal women is
25 osteoporosis, alluded to earlier, which results from a significant reduction in the production of estrogens by the ovaries [61]. Estrogen deficiency results in an imbalance between osteoblastic bone formation and osteoclastic bone resorption, leading to a net bone loss
30 and increased fracture risk. Several SERM compounds have shown anti-osteoporotic potential in the OVX-rat model. Ospemifene, lasofoxifene, bazedoxifene, and arzoxifene are under clinical trials for the treatment of osteoporosis. However, idoxifene and levormeloxifene [52-

54] have been discontinued from clinical testing for osteoporosis because of their undesirable effects on the uterus as mentioned earlier.

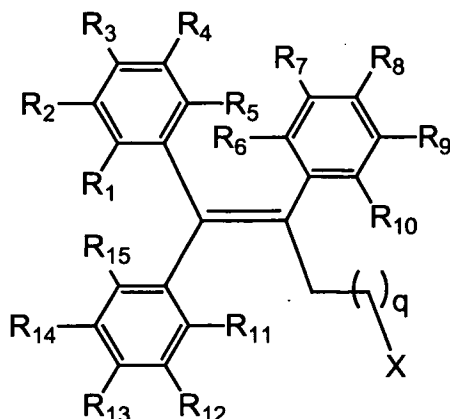
5 Estrogen has long been regarded as a beneficial factor in preventing cardiovascular diseases by keeping plasma cholesterol levels low in premenopausal women. Postmenopausal women lose this protection due to a reduction in estrogen levels as a result of natural
10 atrophy of the ovaries, resulting in a change in blood-lipid profile. All ER agonists, including TAM, RAL, and GW5638, examined to date that protect against bone loss are effective in suppressing OVX-induced increases in serum cholesterol [62-64], suggesting that the mechanisms
15 by which ER acts in bone and the cardiovascular system are biochemically linked. Although it is not clear whether the observed suppression of serum cholesterol levels is sufficient to explain the decrease in mortality from cardiovascular disease in postmenopausal women
20 receiving estrogen replacement therapy, cholesterol is accepted as a biomarker of estrogen action in the cardiovascular system [64]. A safer antiestrogen should have the capability of preventing osteoporosis and cardiovascular disease.

25
In light of the genotoxic and estrogenic potential of currently available compounds used for the treatment of breast cancer, osteoporosis, and some cardiovascular
30 genotoxic and estrogenic potential are required to diminish the serious side-effects associated with currently available compounds. Furthermore, while freedom from genotoxic and estrogenic potential is important, new alternatives should also possess improved bioavailability

and significant clinical benefits beyond those of currently available compounds, such as TAM and RAL, for the treatment and prevention of breast cancer.

Summary of the Invention

This invention provides a compound having the structure



5

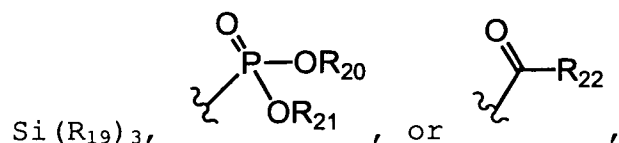
wherein

$R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14},$ and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -

10 SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



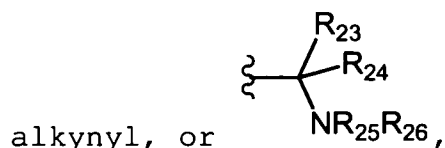
15

wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅

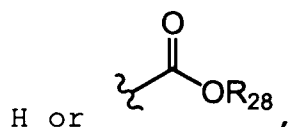
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wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -
(CH₂)₁₋₄-R₂₇,

wherein R_{27} is $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{NH}_2$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OH}$, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

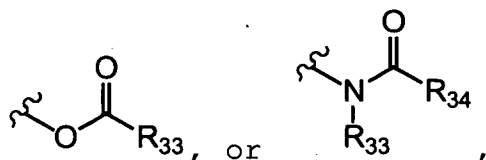
R_3 is Br, I, $-(\text{CR}_{29}\text{R}_{30})_2-\text{R}_{31}$, $-\text{CR}_{29}=\text{CR}_{30}-\text{R}_{31}$, $-\text{C}\equiv\text{C}-\text{R}_{31}$, $-\text{OSO}_2\text{H}$, $-\text{OSO}_2\text{R}_{31}$,

10 wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and
wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2\text{R}_{32}$, or $-(\text{CH}_2)_{1-6}-\text{CO}_2\text{R}_{32}$,

15 wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

20 X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,

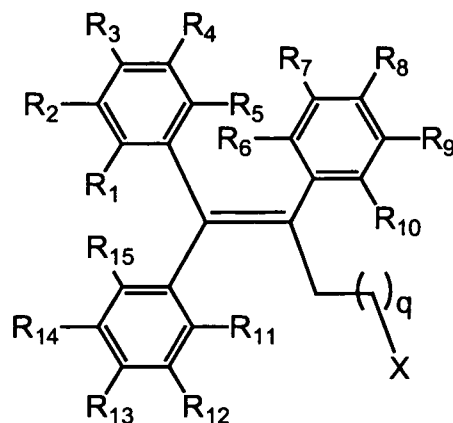


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

25 wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

This invention provides a process for preparing a compound having the structure

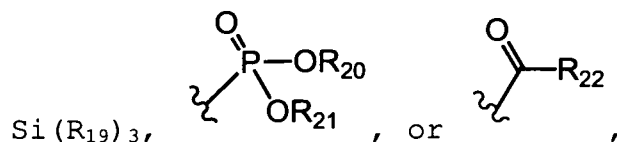


5 wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

10 wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,

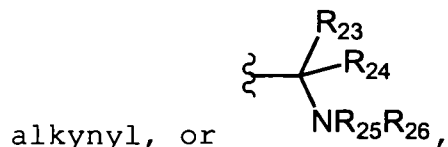


wherein each occurrence of R_{19} is,

15 independently, H, C₁₋₄ alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

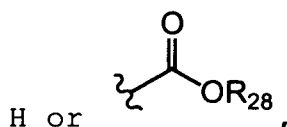
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



20 wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, - (CH₂)₁₋₄-R₂₇,

wherein R_{27} is $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{NH}_2$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OH}$, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

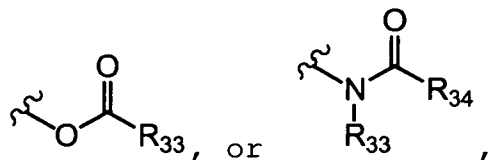
R_3 is Br, I, $-(\text{CR}_{29}\text{R}_{30})_2-\text{R}_{31}$, $-\text{CR}_{29}=\text{CR}_{30}-\text{R}_{31}$, $-\text{C}\equiv\text{C}-\text{R}_{31}$, $-\text{OSO}_2\text{H}$, $-\text{OSO}_2\text{R}_{31}$,

10 wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and
wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2\text{R}_{32}$, or $-(\text{CH}_2)_{1-6}-\text{CO}_2\text{R}_{32}$,

15 wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

20 X is H, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,

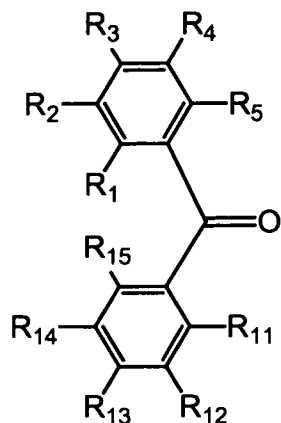


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

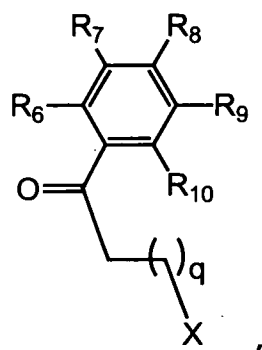
25 wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

comprising:

contacting a compound having the structure



with a compound having the structure



wherein

5 $R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14},$
and R_{15} are each, independently, H, halogen, -CN, -
NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -
CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

10 wherein R_{16} and R_{17} are each, independently, H,
C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;
 R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,
or Si(R₁₉)₃,

wherein each occurrence of R_{19} is,
independently, H, C₁₋₄ alkyl, or aryl;

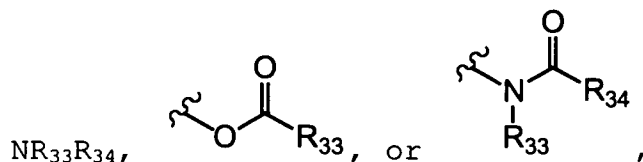
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R_3 is Br, I, -OSO₂H, or -OSO₂R₃₁,
wherein R_{31} is C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,
aryl, heteroaryl, or heterocyclyl; and

20

q is an integer from 1 to 5;

X is H, halogen, -CN, -NO₂, -OR₃₃, -SR₃₃, -OSO₂R₃₃, -



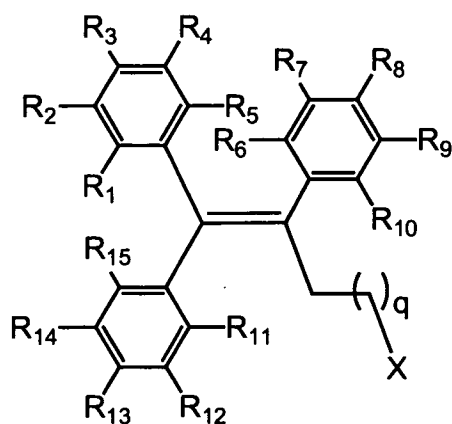
wherein R₃₃ and R₃₄ are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

5

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

10

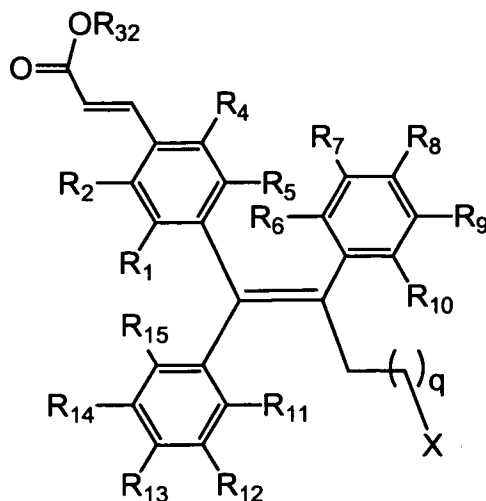
in the presence of a titanium reagent and a reducing agent so as to form a product having the structure



so as to thereby prepare the compound.

15

This invention provides a process of preparing a compound having the structure

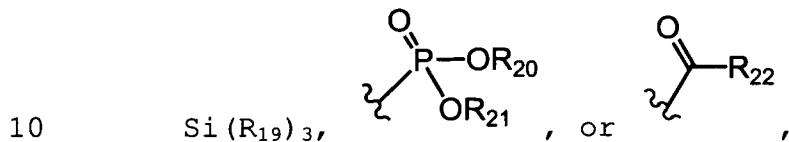


wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

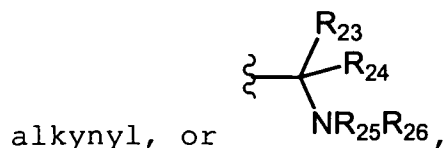
R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

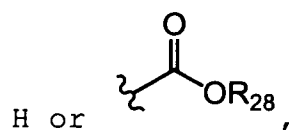
15 wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, or



wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, - (CH₂)₁₋₄-R₂₇,

wherein R_{27} is $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{NH}_2$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OH}$, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,

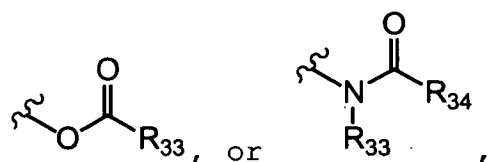


wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

10 q is an integer from 1 to 5;

X is H, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,



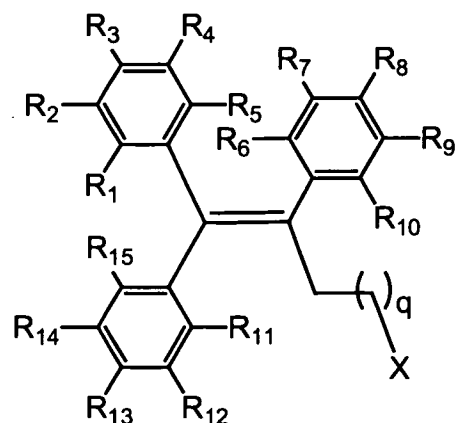
wherein R_{33} and R_{34} are each, independently, H, C_{1-10}

15 alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

20 comprising:

contacting a compound having the structure



wherein

$R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}$,
and R_{15} are each, independently, H, halogen, -CN, -
NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -
CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

5 wherein R_{16} and R_{17} are each, independently, H,
C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,
or Si(R_{19})₃,

10 wherein each occurrence of R_{19} is,
independently, H, C₁₋₄ alkyl, or aryl;

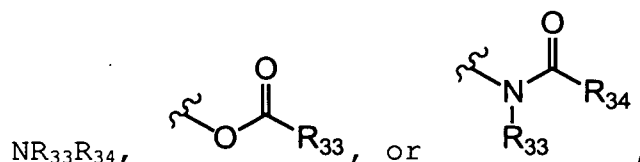
R_3 is Br, I, or -OSO₂R₃₁,

wherein R_{31} is C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀
alkynyl, aryl, heteroaryl, or heterocyclyl; and

15

q is an integer from 1 to 5;

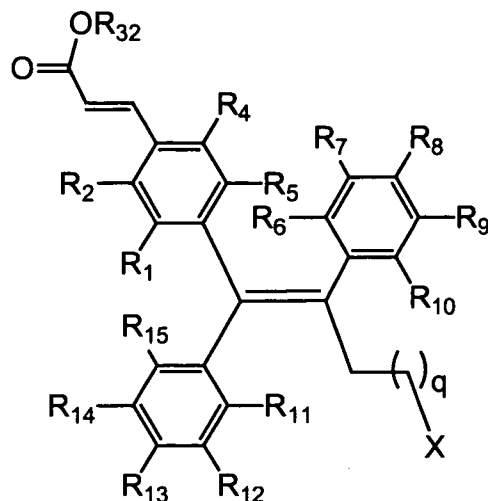
X is H, halogen, -CN, -NO₂, -OR₃₃, -SR₃₃, -OSO₂R₃₃, -



20 wherein R_{33} and R_{34} are each, independently, H,
C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

wherein each occurrence of alkyl, alkenyl, and
alkynyl is substituted or unsubstituted, branched or
25 unbranched;

with CH₂=CH₂-CO₂R₃₂, wherein R_{32} is C₁₋₁₀ alkyl, in the
presence of a palladium catalyst so as to form a
product having the structure



so as to thereby prepare the compound.

This invention provides a pharmaceutical composition
 5 comprising any one of the above compounds, or a
 pharmaceutically acceptable salt thereof, and a
 pharmaceutically acceptable carrier.

This invention provides a method of inhibiting tumor
 10 proliferation in a mammal comprising administering to the
 mammal a therapeutically effective amount of any one of
 the above compounds so as to inhibit tumor proliferation.

This invention provides a method of inhibiting and/or
 15 reducing the loss of bone mineral density in a mammal
 comprising administering to the mammal a therapeutically
 effective amount of any one of the above compounds so as
 to inhibit and/or reduce loss of bone mineral density.

20 This invention provides a method of delaying tumor
 formation in a mammal comprising administering to the
 mammal a therapeutically effective amount of any of the
 above compounds, or a salt thereof, so as to delay tumor
 formation.

This invention provides a method of prophylaxis against tumor formation in a mammal comprising administering to the mammal a therapeutically effective amount of any of the above compounds, or a salt thereof, so as to provide
5 prophylaxis against tumor formation.

Brief Description of the Figures

Figure 1a. Formation of TAM-DNA adducts via α -hydroxylation followed by O-sulfonation of TAM metabolites.

Figure 1b. Formation of TAM-DNA adducts via O-sulfonated TAM metabolites.

Figure 2. Structures of antiestrogens.

Figure 3. Formation of DNA adducts induced by antiestrogens in the liver of rats.

Figure 4. Uterotrophic potential of antiestrogens. Student t-test; $p < 0.05$ (SS1020 versus RAL, GW5638 or GW7604).

Figure 5. Effect of antiestrogens on uterine histology in OVX-rats. A, Sham; B, E2; C, TAM; D, GW5638; E, SS1020. Magnification: X10.

Figure 6a. Antitumor potential of antiestrogens on DMBA-induced mammary carcinoma. A. 1 mg/kg/day; **, $p < 0.01$ and ***, $p < 0.001$ versus (vs) Control (t-test). SS1020; a) $p < 0.05$ vs. TAM, RAL or GW5638; b) $p < 0.05$ vs. RAL, $p < 0.01$ vs. TAM or GW5638; c) $p < 0.01$ vs. RAL or GW5638, $p < 0.001$ vs. TAM; d) $p < 0.01$ vs. GW5638, $p < 0.001$ vs. TAM or RAL.

Figure 6b. Antitumor potential of antiestrogens on DMBA-induced mammary carcinoma. B. 0.33 mg/kg/day; **, $p < 0.01$ and ***, $p < 0.001$ versus (vs) Control (t-test).

Figure 7. Antitumor potential of SS1021 against DMBA-induced mammary.

5 **Figure 8.** HPLC analysis of the dephosphorylation of SS1021 by cytosol of rat intestine. A. No dephosphorylation observed when SS1021 incubated in inactivated cytosol; B. Conversion to SS1020 observed when incubated in cytosol.

10

Figure 9a. Antitumor potential of SS1020 in nude mice bearing ER-positive MCF-7 human breast cancer xenograft. A. MCF-7; Student t-test; *, $p < 0.05$ and **, $p < 0.01$ versus Control; a, b, and
15 c) $p < 0.01$ vs. TAM; d) $p < 0.001$ vs. TAM.

Figure 9b. Antitumor potential of SS1020 in nude mice bearing ER-negative MDA-MB-231 human breast cancer xenograft. B. MDA-MB-231. Student t-
20 test; *, $p < 0.05$ and **, $p < 0.01$ versus Control.

Figure 10. ER α binding assay for antiestrogens. The average of IC₅₀ was obtained from three
25 independent experiments.

Figure 11. Delaying effect of SS1020 against rat DMBA-induced mammary tumor.

30 **Figure 12.** Formation of mammary DMBA-DNA in rats pre-treated with SS1020. Control (corn oil only); α -NF (73 mg/kg); SS1020 (3.3 mg/kg).

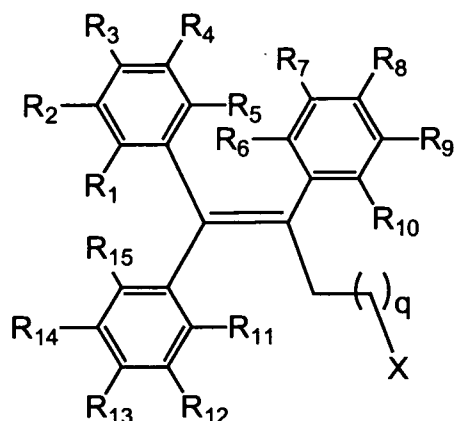
Figure 13. Antitumor potential of SS1020 against human MCF-7 breast cancer xenograft in athymic nude mice. OVX-nude mice bearing MCF-7 xenograft (4 mice/dose) were treated orally for 4 weeks with TAM or SS1020 at a dose molar equivalent to TAM (3.0 or 10 mg/kg). The control received vehicle only. The statistical analysis was performed similarly as described in Fig. 4. *, $p < 0.05$, ***, $p < 0.001$ vs Control; a) $p < 0.01$ vs TAM; b) $p < 0.0001$ vs TAM; c) $p < 0.05$ vs TAM.

Figure 14. Serum SS1020 or RAL concentration in rats.

Figure 15. Preventive potential of SS1020 against E_2 -induced mammary tumor in rats.

Detailed Description of the Invention

This invention provides a compound having the structure



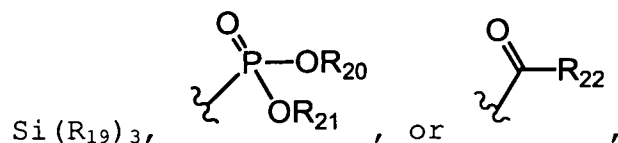
5

wherein

10 $R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14},$ and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



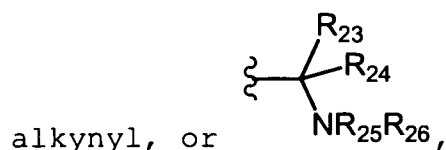
15

wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅

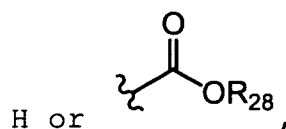
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wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, - (CH₂)₁₋₄-R₂₇,

wherein R_{27} is $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{NH}_2$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OH}$, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_3 is Br, I, $-(\text{CR}_{29}\text{R}_{30})_2-\text{R}_{31}$, $-\text{CR}_{29}=\text{CR}_{30}-\text{R}_{31}$, $-\text{C}\equiv\text{C}-\text{R}_{31}$, $-\text{OSO}_2\text{H}$, $-\text{OSO}_2\text{R}_{31}$,

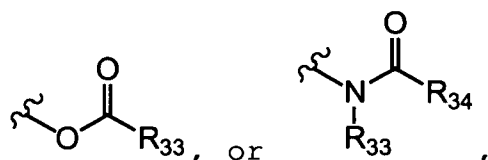
10 wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2\text{R}_{32}$, or $-(\text{CH}_2)_{1-6}-\text{CO}_2\text{R}_{32}$,

15 wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

20 X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,

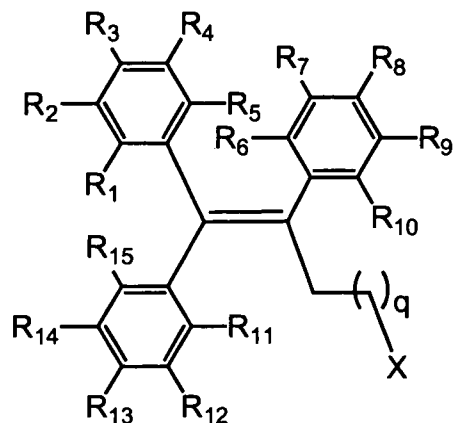


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

25 wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

30 In an embodiment, the compound has the structure

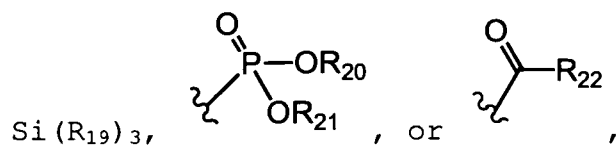


wherein

5 R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

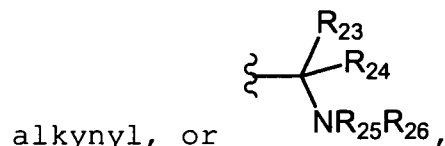
10 R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

15 wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

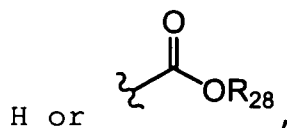
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -
20 (CH₂)₁₋₄-R₂₇,

wherein R_{27} is -CO₂H, -CONH₂, -NH₂, -SH, -SCH₃, -OH, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

5 R_3 is Br, I, $-\text{OSO}_2\text{H}$, or $-\text{OSO}_2\text{R}_{31}$,

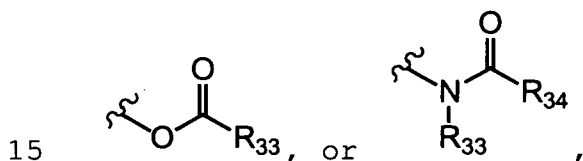
wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2\text{R}_{32}$, or $-(\text{CH}_2)_{1-6}-\text{CO}_2\text{R}_{32}$,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or

10 C_{2-10} alkynyl; and

q is an integer from 1 to 5;

X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,

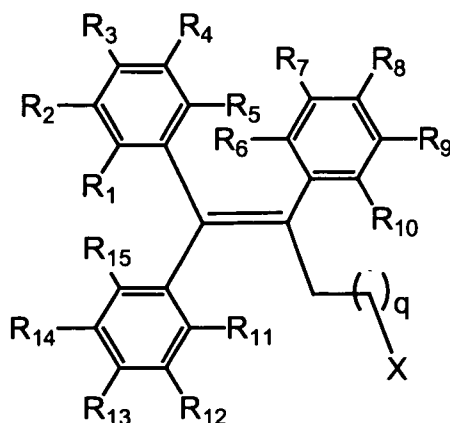


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is
20 substituted or unsubstituted, branched or unbranched;

or a salt thereof.

In an embodiment, the compound has the structure

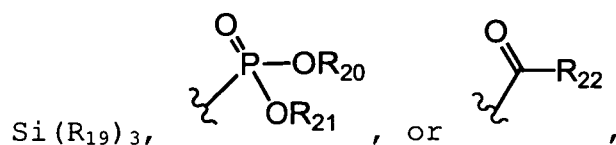


wherein

5 R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

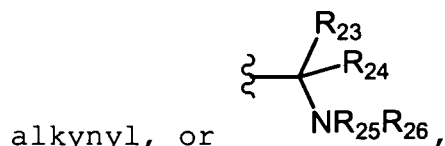
10 R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

15 wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

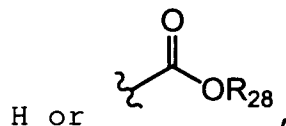
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -
20 (CH₂)₁₋₄-R₂₇,

wherein R_{27} is -CO₂H, -CONH₂, -NH₂, -SH, -SCH₃, -OH, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

5 R_3 is $-(CR_{29}R_{30})_2-R_{31}$, $-CR_{29}=CR_{30}-R_{31}$, or $-C\equiv C-R_{31}$,

wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2R_{32}$, or $-(\text{CH}_2)_{1-6}-$

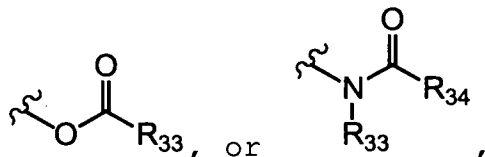
10 CO_2R_{32} ,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

15

X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2R_{33}$, $-\text{NR}_{33}R_{34}$,



wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

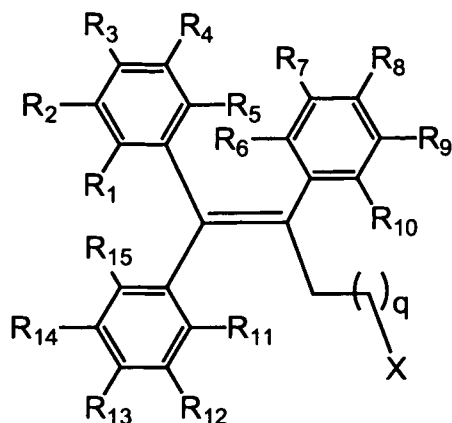
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wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

25

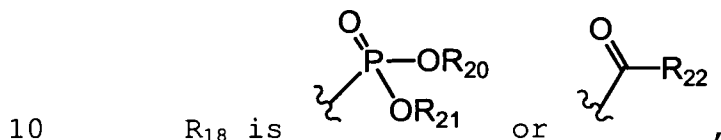
In an embodiment, the compound has the structure



wherein

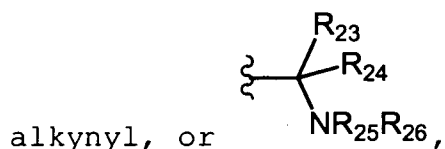
R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, and R₁₅
 5 are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀
 alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -
 SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R₁₆ and R₁₇ are each, independently, H, C₁₋₁₀
 alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;



wherein R₂₀ and R₂₁ are each, independently, H,
 C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

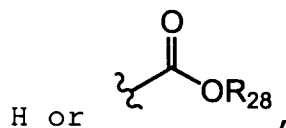
wherein R₂₂ is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



15 wherein R₂₃ and R₂₄ are each, independently,
 H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -
 (CH₂)₁₋₄-R₂₇,

wherein R₂₇ is -CO₂H, -CONH₂, -NH₂, -
 SH, -SCH₃, -OH, aryl, or heteroaryl;
 20 and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

5 R_3 is $-(CR_{29}R_{30})_2-R_{31}$, $-CR_{29}=CR_{30}-R_{31}$, or $-C\equiv C-R_{31}$,

wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2R_{32}$, or $-(\text{CH}_2)_{1-6}-$

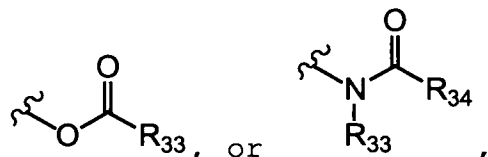
10 CO_2R_{32} ,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

15

X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2R_{33}$, $-\text{NR}_{33}R_{34}$,



wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

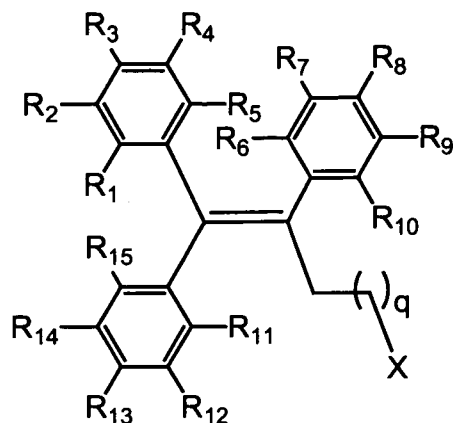
20

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

25

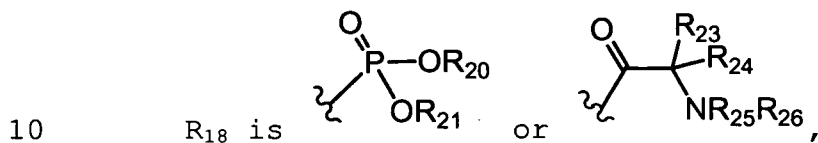
In an embodiment, the compound has the structure



wherein

5 R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

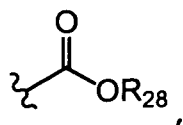


wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -(CH₂)₁₋₄-
15 R_{27} ,

wherein R_{27} is -CO₂H, -CONH₂, -NH₂, -SH, -SCH₃, -OH, aryl, or heteroaryl; and

wherein R_{25} and R_{26} are each, independently, H or



20 wherein R_{28} is C₁₋₁₀ alkyl or C₂₋₁₀ alkenyl;

R_3 is -(CR₂₉R₃₀)₂-R₃₁, -CR₂₉=CR₃₀-R₃₁, or -C≡C-R₃₁,

wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2R_{32}$, or $-(\text{CH}_2)_{1-6}-$

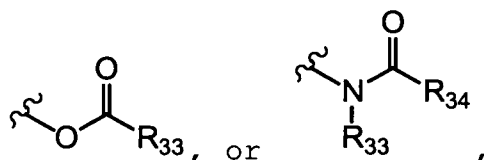
5 CO_2R_{32} ,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

10

X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2R_{33}$, $-\text{NR}_{33}R_{34}$,



wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

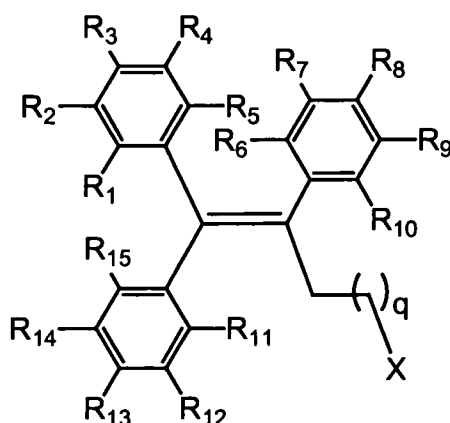
15

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

20

In an embodiment, the compound has the structure



wherein

25

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, $-\text{CN}$, $-\text{NO}_2$, C_{1-10}

alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R₁₆ and R₁₇ are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

5 R₁₈ is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, or Si(R₁₉)₃,

wherein each occurrence of R₁₉ is, independently, H, C₁₋₄ alkyl, or aryl;

10 R₃ is -(CR₂₉R₃₀)₂-R₃₁, -CR₂₉=CR₃₀-R₃₁, or -C≡C-R₃₁,

wherein R₂₉ and R₃₀ are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

wherein R₃₁ is C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, aryl, heteroaryl, heterocyclyl, -CO₂R₃₂, or -(CH₂)₁₋₆-

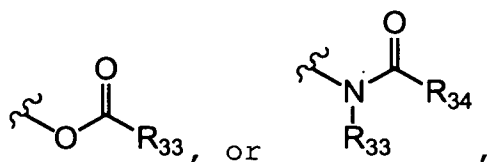
15 CO₂R₃₂,

wherein R₃₂ is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

q is an integer from 1 to 5;

20

X is halogen, -CN, -NO₂, -OR₃₃, -SR₃₃, -OSO₂R₃₃, -NR₃₃R₃₄,



wherein R₃₃ and R₃₄ are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

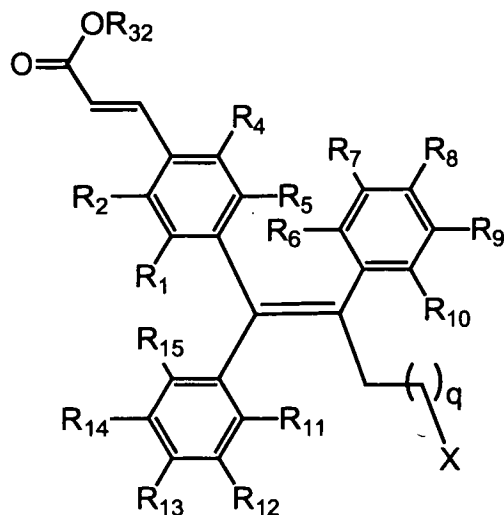
25

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

30

In an embodiment, the compound has the structure

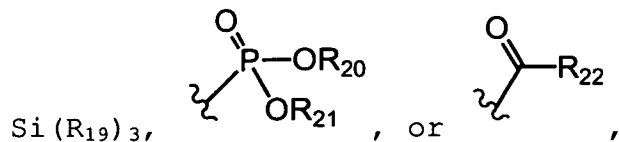


wherein

- 5 $R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14},$ and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

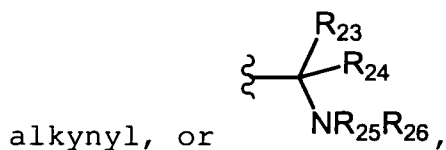
10 R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

15 wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

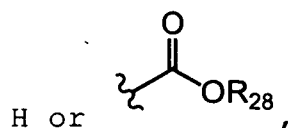
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -
20 (CH₂)₁₋₄-R₂₇,

wherein R_{27} is $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{NH}_2$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OH}$, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,

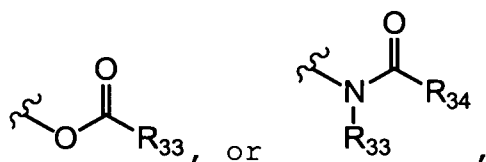


wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

10 q is an integer from 1 to 5;

X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,



15 wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

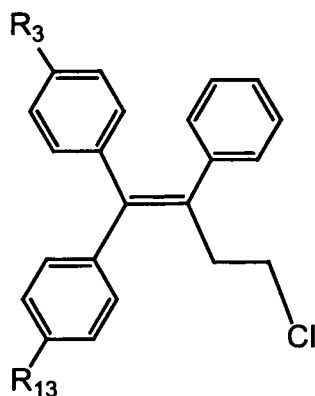
20 or a salt thereof.

In an embodiment, X is halogen or OR_{33} , or a salt thereof.

In an embodiment, X is halogen, or a salt thereof.

25

In an embodiment, the compound has the structure

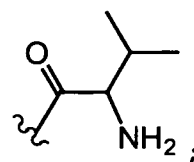
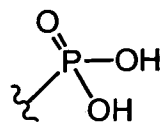
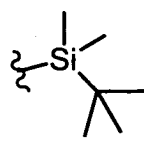


wherein

R_{13} is H or $-OR_{18}$,

5

wherein R_{18} is H,



, or

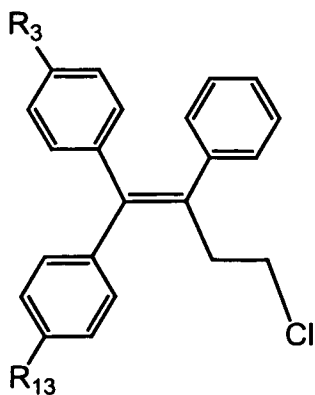
R_3 is Br, $-\text{CH}=\text{CH}-\text{CO}_2R_{32}$, or $-\text{OSO}_2\text{CF}_3$,

wherein R_{32} is H or t-butyl,

or a salt thereof.

10

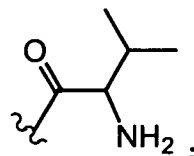
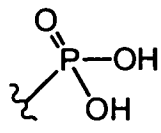
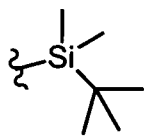
In an embodiment, the compound has the structure



wherein

15

R_{13} is H or $-OR_{18}$,



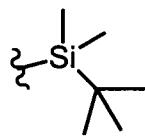
wherein R_{18} is H,

, or

R_3 is $-\text{CH}=\text{CH}-\text{CO}_2R_{32}$,

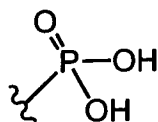
wherein R_{32} is H or t-butyl,
or a salt thereof.

5 In an embodiment, R_{18} is H or

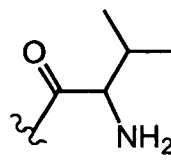


, or a salt thereof.

In an embodiment, R_{18} is

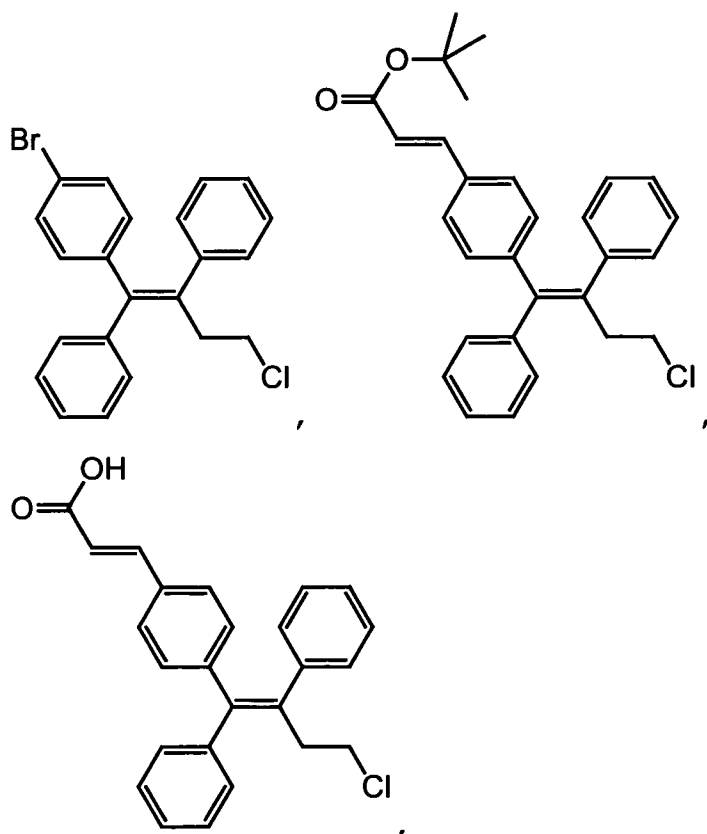


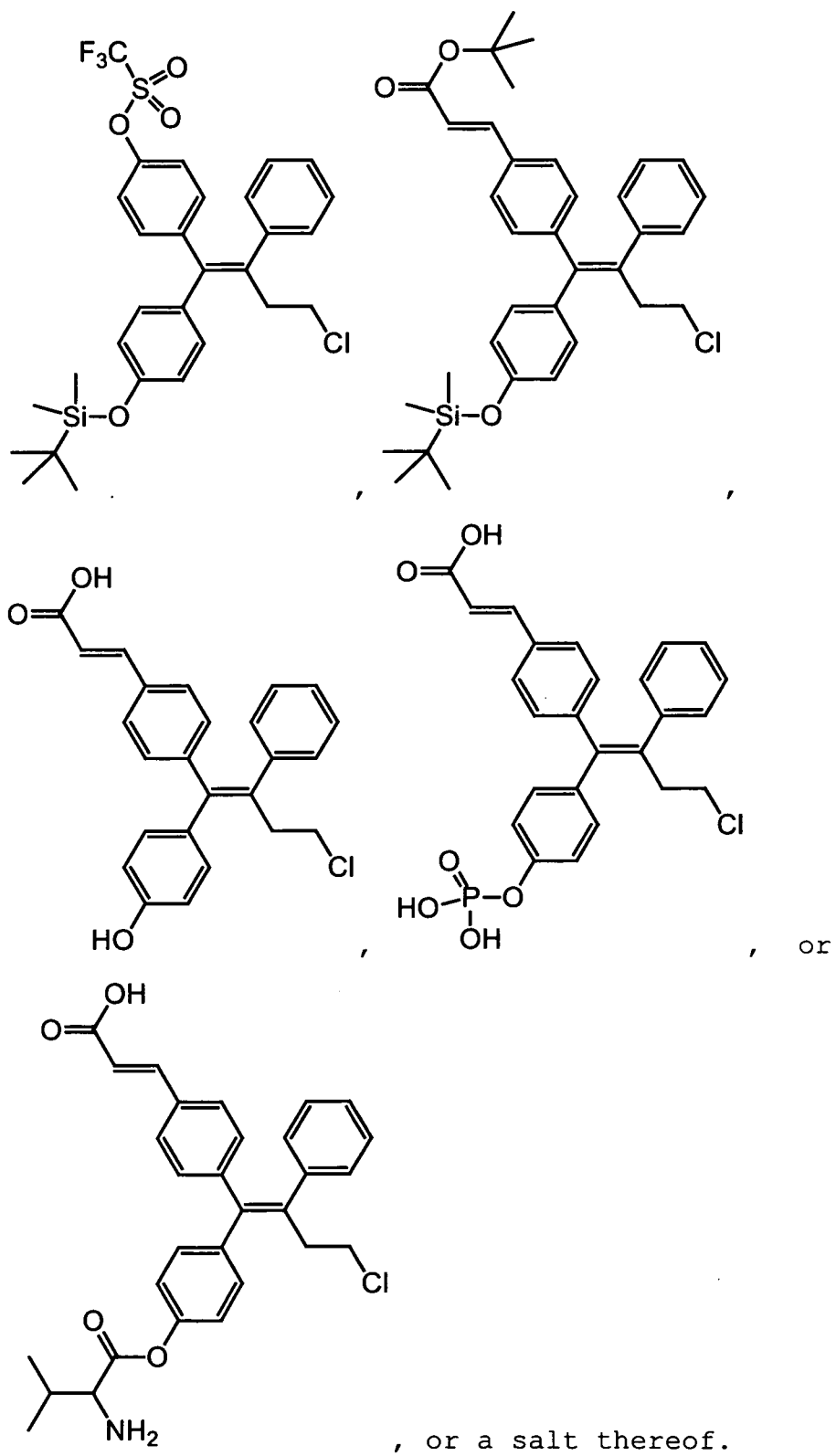
or



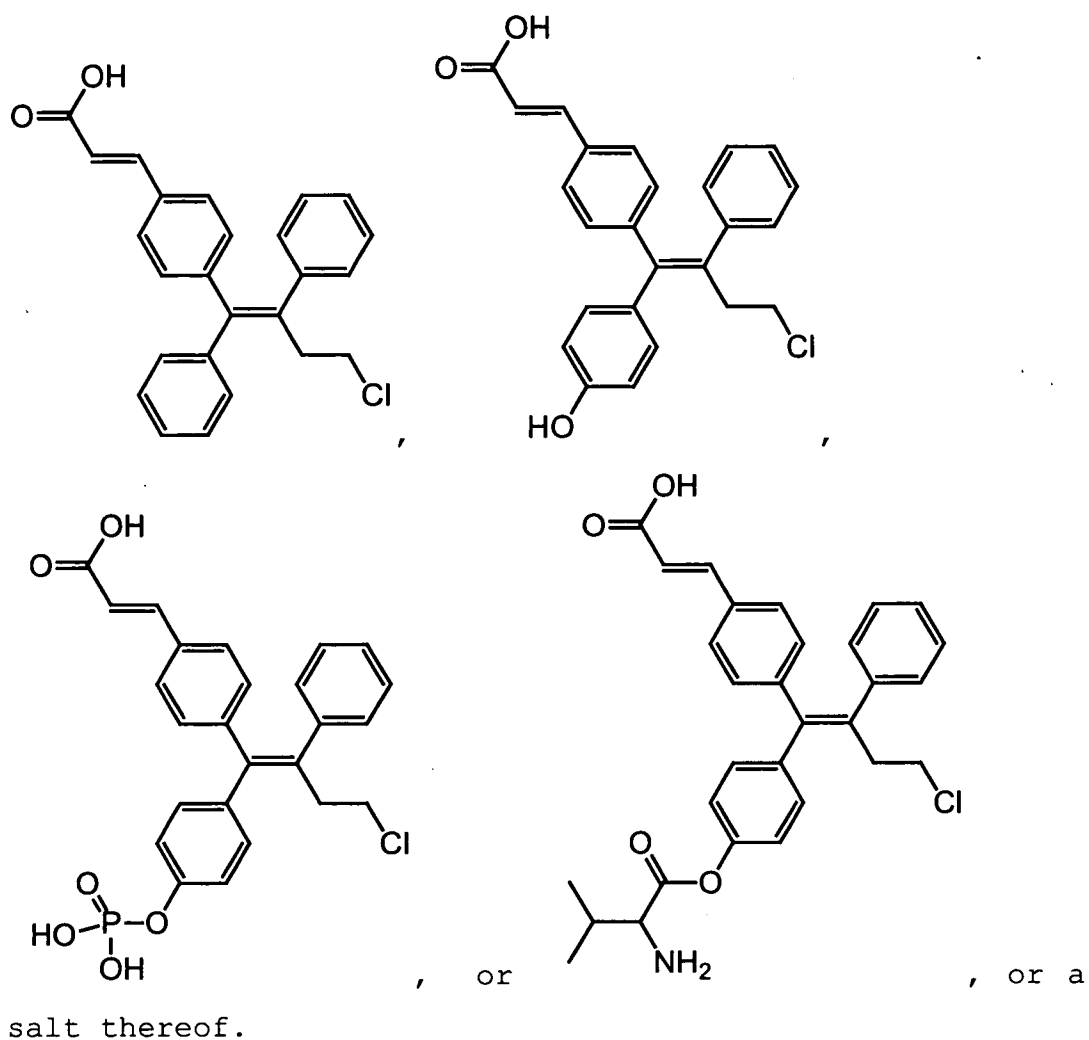
thereof.

10 In an embodiment, the compound has the structure

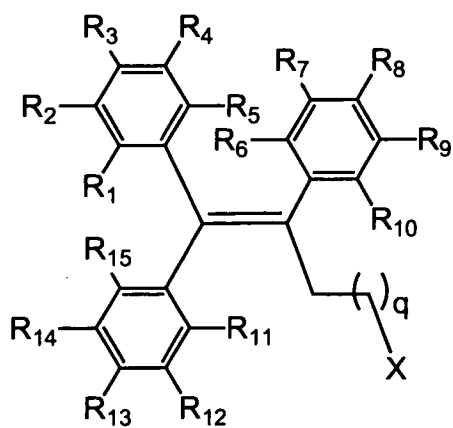




5 In an embodiment, the compound has the structure



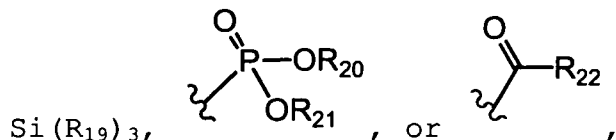
- 5 This invention provides a process for preparing a compound having the structure



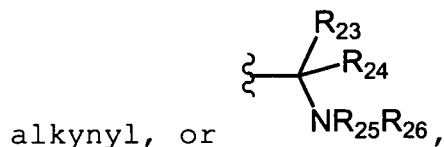
wherein

$R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14},$ and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

5 wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;
 R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



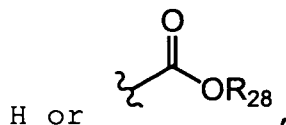
10 wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and
 wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and
 wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



15 wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -
 (CH₂)₁₋₄-R₂₇,

wherein R_{27} is -CO₂H, -CONH₂, -NH₂, -SH, -SCH₃, -OH, aryl, or heteroaryl;
 20 and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C₁₋₁₀ alkyl or C₂₋₁₀ alkenyl;

25 R_3 is Br, I, -(CR₂₉R₃₀)₂-R₃₁, -CR₂₉=CR₃₀-R₃₁, -C≡C-R₃₁, -OSO₂H, -OSO₂R₃₁,

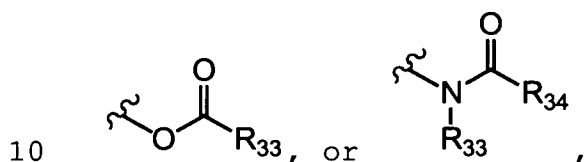
wherein R_{29} and R_{30} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-CO_2R_{32}$, or $-(CH_2)_{1-6}-CO_2R_{32}$,

5 wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

X is H, halogen, $-CN$, $-NO_2$, $-OR_{33}$, $-SR_{33}$, $-OSO_2R_{33}$, $-NR_{33}R_{34}$,

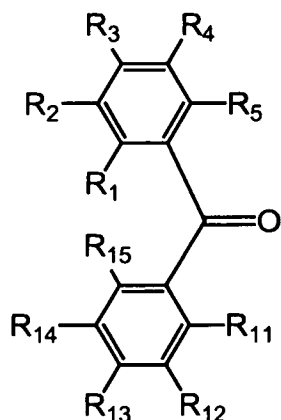


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

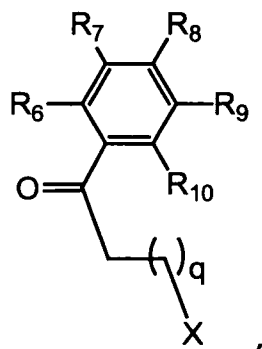
15 wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

comprising:

contacting a compound having the structure



20 with a compound having the structure



wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} ,
and R_{15} are each, independently, H, halogen, -CN, -
5 NO_2 , C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-\text{CO}_2\text{R}_{16}$, -
 $\text{CONR}_{16}\text{R}_{17}$, $-\text{SR}_{16}$, $-\text{NR}_{16}\text{R}_{17}$, $-\text{SO}_2\text{R}_{16}$, or $-\text{OR}_{18}$,

wherein R_{16} and R_{17} are each, independently, H,
 C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;

R_{18} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
10 or $\text{Si}(\text{R}_{19})_3$,

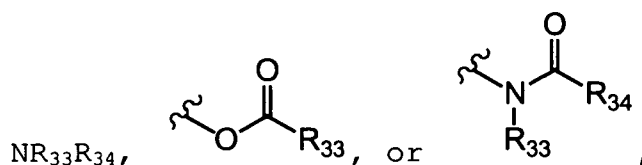
wherein each occurrence of R_{19} is,
independently, H, C_{1-4} alkyl, or aryl;

R_3 is Br, I, $-\text{OSO}_2\text{H}$, or $-\text{OSO}_2\text{R}_{31}$,

15 wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
aryl, heteroaryl, or heterocyclyl; and

q is an integer from 1 to 5;

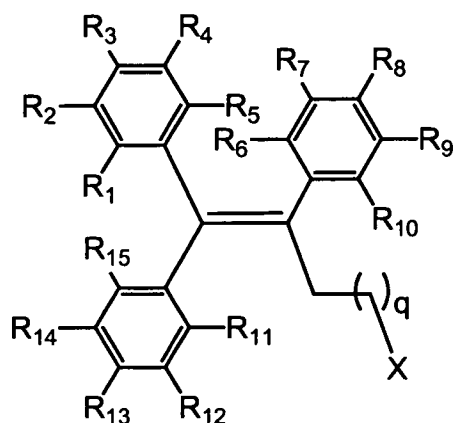
20 X is H, halogen, -CN, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, -



wherein R_{33} and R_{34} are each, independently, H,
 C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

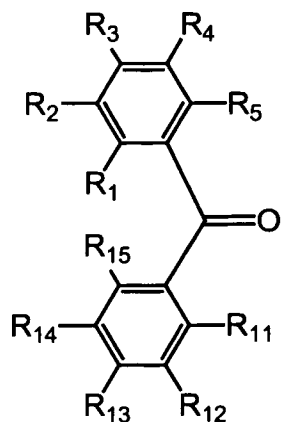
wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

- 5 in the presence of a titanium reagent and a reducing agent so as to form a product having the structure

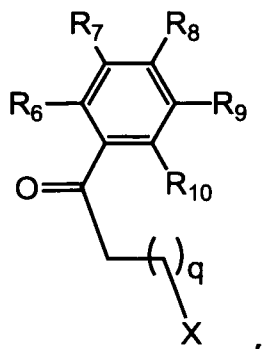


so as to thereby prepare the compound.

- 10 In an embodiment, the process comprises:
contacting a compound having the structure



with a compound having the structure



wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} ,
 and R_{15} are each, independently, H, halogen, -CN, -
 5 NO_2 , C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-\text{CO}_2\text{R}_{16}$, -
 $\text{CONR}_{16}\text{R}_{17}$, $-\text{SR}_{16}$, $-\text{NR}_{16}\text{R}_{17}$, $-\text{SO}_2\text{R}_{16}$, or $-\text{OR}_{18}$,

wherein R_{16} and R_{17} are each, independently, H,
 C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;

R_{18} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
 10 or $\text{Si}(\text{R}_{19})_3$,

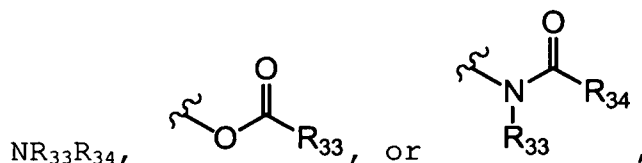
wherein each occurrence of R_{19} is,
 independently, H, C_{1-4} alkyl, or aryl;

R_3 is Br, I, $-\text{OSO}_2\text{H}$, or $-\text{OSO}_2\text{R}_{31}$,

15 wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
 aryl, heteroaryl, or heterocyclyl; and

q is an integer from 1 to 5;

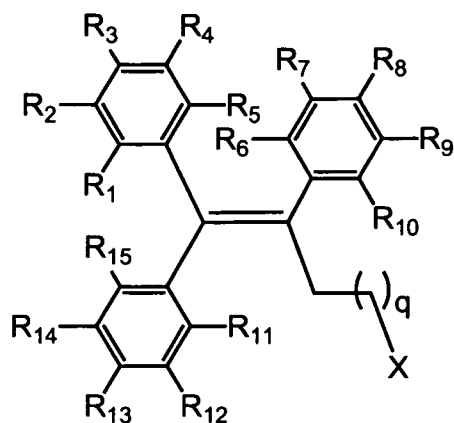
20 X is halogen, -CN, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, -



wherein R_{33} and R_{34} are each, independently, H,
 C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

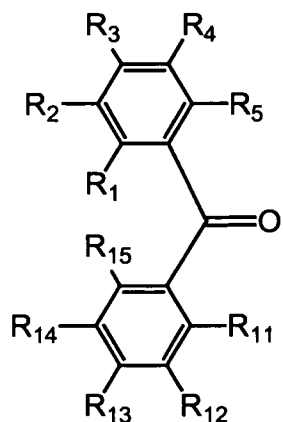
wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

- 5 in the presence of a titanium reagent and a reducing agent so as to form a product having the structure

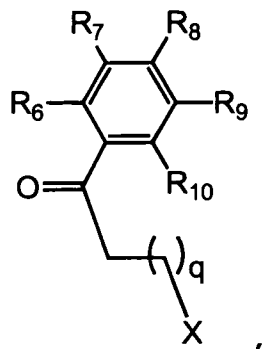


so as to thereby prepare the compound.

- 10 In an embodiment, the process comprises:
contacting a compound having the structure



with a compound having the structure



wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} ,
and R_{15} are each, independently, H, halogen, -CN, -
5 NO_2 , C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-\text{CO}_2\text{R}_{16}$, -
 $\text{CONR}_{16}\text{R}_{17}$, $-\text{SR}_{16}$, $-\text{NR}_{16}\text{R}_{17}$, $-\text{SO}_2\text{R}_{16}$, or $-\text{OR}_{18}$,

wherein R_{16} and R_{17} are each, independently, H,
 C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;

R_{18} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
10 or $\text{Si}(\text{R}_{19})_3$,

wherein each occurrence of R_{19} is,
independently, H, C_{1-4} alkyl, or aryl;

R_3 is Br, I, $-\text{OSO}_2\text{H}$, or $-\text{OSO}_2\text{R}_{31}$,

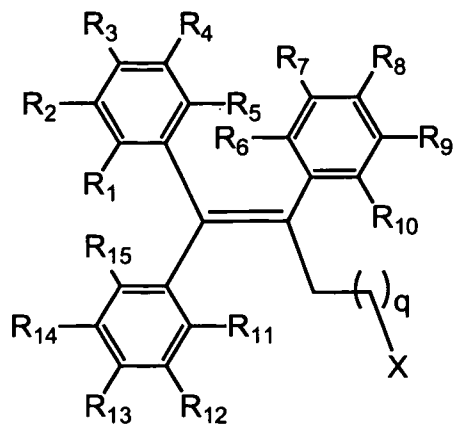
15 wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
aryl, heteroaryl, or heterocyclyl; and

q is an integer from 1 to 5;

20 X is H; and

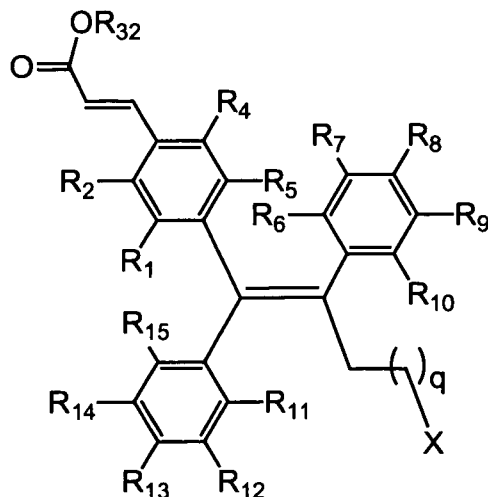
wherein each occurrence of alkyl, alkenyl, and
alkynyl is substituted or unsubstituted, branched or
unbranched;

25 in the presence of a titanium reagent and a reducing
agent so as to form a product having the structure



so as to thereby prepare the compound.

This invention provides a process of preparing a compound
5 having the structure



wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15}
are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀
10 alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -
SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀
alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

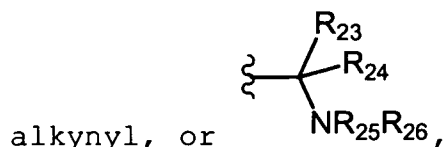
R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,

15 $\text{Si}(\text{R}_{19})_3$, $\text{P}(\text{OR}_{20})_2$, or $\text{C}(=\text{O})\text{R}_{22}$,

wherein each occurrence of R_{19} is, independently, H, C_{1-4} alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C_{1-5} alkyl, C_{2-5} alkenyl, or C_{2-5} alkynyl; and

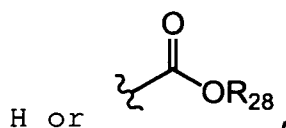
5 wherein R_{22} is H, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5}



wherein R_{23} and R_{24} are each, independently, H, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -
(CH_2) $_{1-4}$ - R_{27} ,

10 wherein R_{27} is $-CO_2H$, $-CONH_2$, $-NH_2$, -
SH, $-SCH_3$, $-OH$, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,



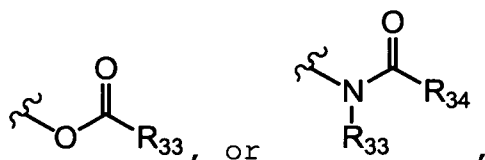
15 wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

20

X is H, halogen, $-CN$, $-NO_2$, $-OR_{33}$, $-SR_{33}$, $-OSO_2R_{33}$, $-NR_{33}R_{34}$,



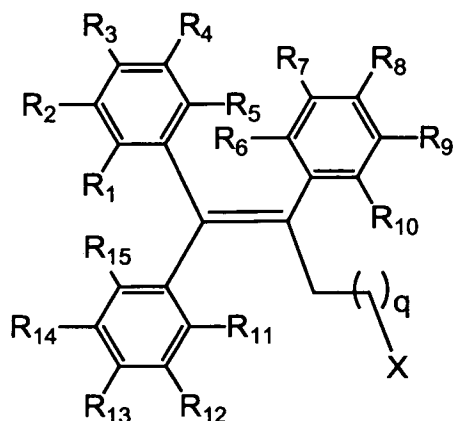
wherein R_{33} and R_{34} are each, independently, H, C_{1-10}
alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

25

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

comprising:

contacting a compound having the structure



wherein

5 R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

10 wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl; R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, or Si(R₁₉)₃,

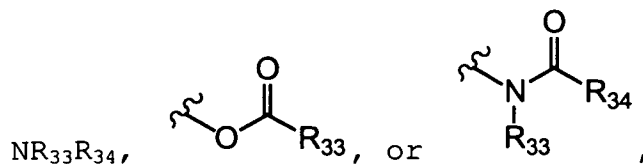
wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl;

15 R_3 is Br, I, or -OSO₂R₃₁,

wherein R_{31} is C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, aryl, heteroaryl, or heterocyclyl; and

20 q is an integer from 1 to 5;

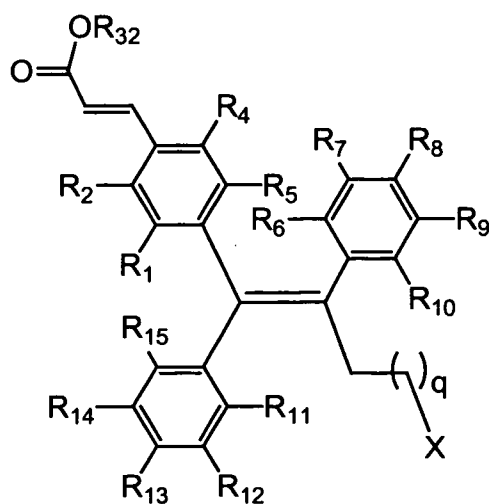
X is H, halogen, -CN, -NO₂, -OR₃₃, -SR₃₃, -OSO₂R₃₃, -



wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

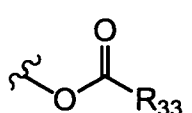
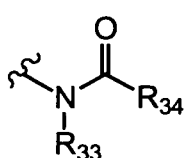
with $CH_2=CH_2-CO_2R_{32}$, wherein R_{32} is C_{1-10} alkyl, in the presence of a palladium catalyst so as to form a product having the structure



so as to thereby prepare the compound.

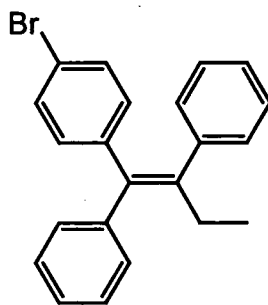
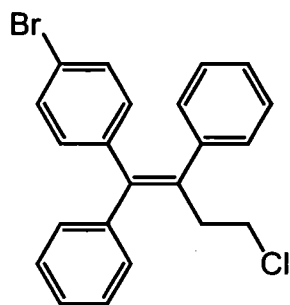
In an embodiment of the process, X is H.

In an embodiment of the process, X is halogen, -CN, -NO₂,

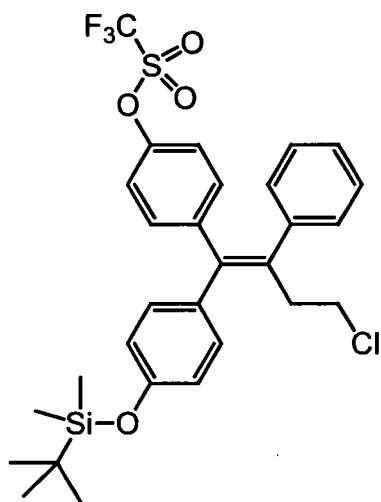
-OR₃₃, -SR₃₃, -OSO₂R₃₃, -NR₃₃R₃₄, , or ,

wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl.

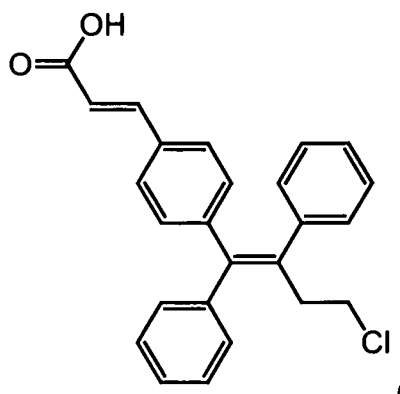
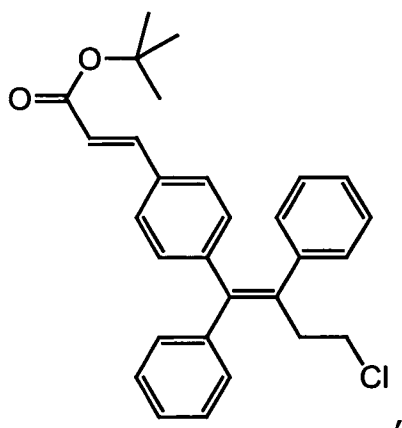
In an embodiment of the process, the compound prepared has the structure

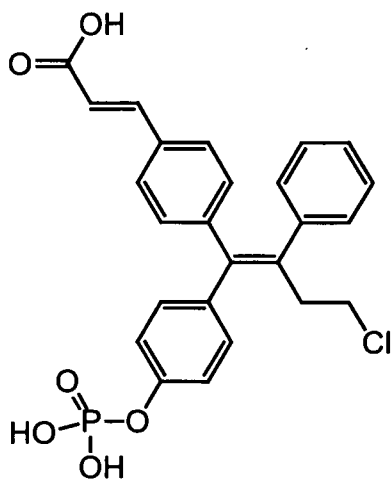
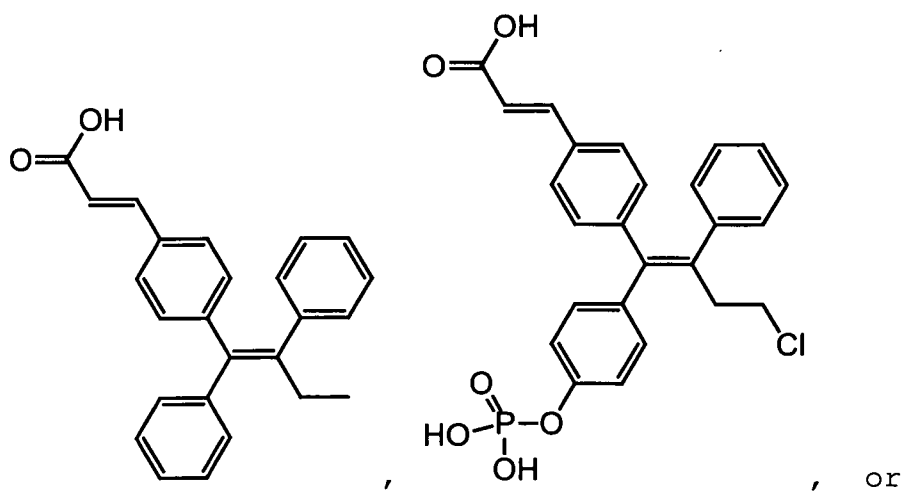
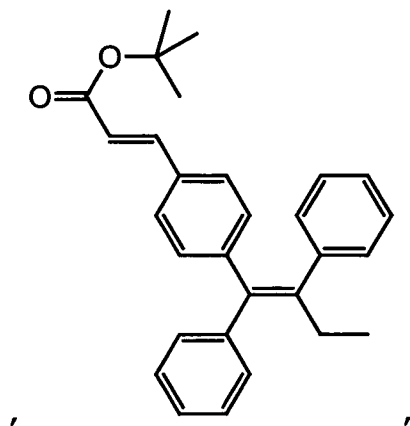
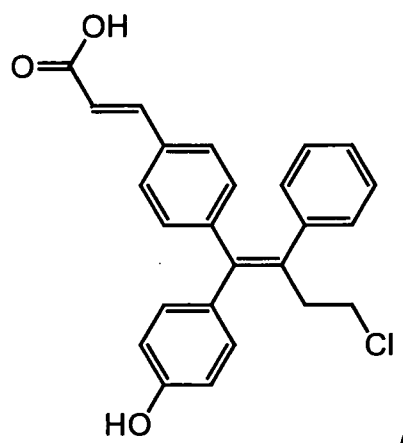
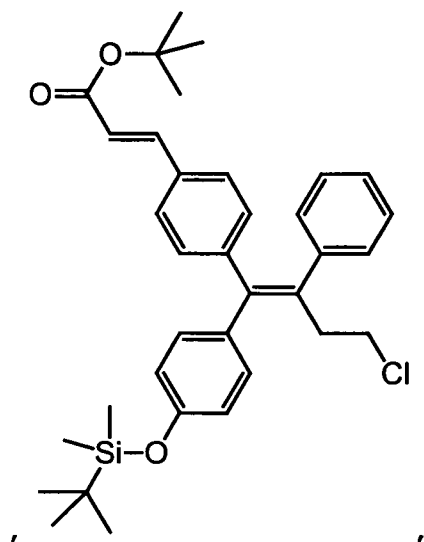


or

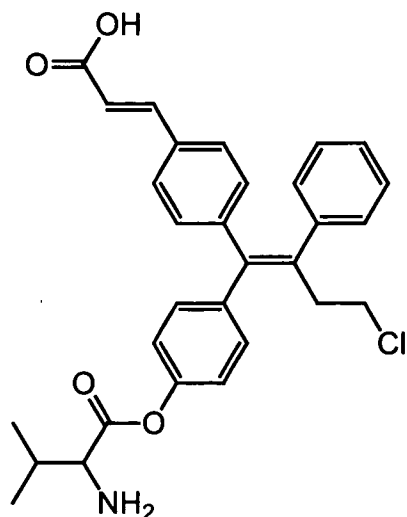


In an embodiment of the process, the compound prepared
5 has the structure





, or



This invention provides a pharmaceutical composition comprising any one of the above compounds, or a
5 pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

This invention provides a method of inhibiting tumor proliferation in a mammal comprising administering to the
10 mammal a therapeutically effective amount of any one of the above compounds, or a salt thereof, so as to inhibit tumor proliferation.

In an embodiment, the tumor is an estrogen-induced tumor.
15

In an embodiment, the tumor is an ER-positive tumor.

In an embodiment, the tumor is an ER-negative tumor.

20 This invention provides a method of inhibiting and/or reducing the loss of bone mineral density in a mammal comprising administering to the mammal a therapeutically effective amount of any one of the above compounds, or a salt thereof, so as to inhibit and/or reduce loss of bone
25 mineral density.

This invention provides a method of delaying tumor formation in a mammal comprising administering to the mammal a therapeutically effective amount of any of the
5 above compounds, or a salt thereof, so as to delay tumor formation.

This invention provides a method of prophylaxis against tumor formation in a mammal comprising administering to
10 the mammal a therapeutically effective amount of any of the above compounds, or a salt thereof, so as to provide prophylaxis against tumor formation.

The compounds described herein can be used in inhibiting
15 tumor proliferation in a mammal.

The compounds described herein can be used in inhibiting and/or reducing the loss of bone mineral density in a mammal.
20

The compounds described herein can be used in delaying tumor formation in a mammal.

The compounds described herein can be used in prophylaxis
25 against tumor formation in a mammal.

The compounds of the present invention include all hydrates, solvates, and complexes of the compounds used by this invention. If a chiral center or another form of
30 an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Compounds containing a chiral center may be used as a racemic mixture, an enantiomerically

enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. The compounds described in the present invention are in racemic form or as individual
5 enantiomers. The enantiomers can be separated using known techniques, such as those described in Pure and Applied Chemistry 69, 1469-1474, (1997) IUPAC. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the
10 scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

15

In the compound structures depicted herein, hydrogen atoms are not shown for carbon atoms having less than four bonds to non-hydrogen atoms. However, it is understood that enough hydrogen atoms exist on said
20 carbon atoms to satisfy the octet rule.

As used herein, "alkyl" includes both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms and may be
25 unsubstituted or substituted. Thus, C_1-C_n as in " C_1-C_n alkyl" is defined to include groups having 1, 2, ..., n-1 or n carbons in a linear or branched arrangement. For example, C_1-C_6 , as in " C_1-C_6 alkyl" is defined to include groups having 1, 2, 3, 4, 5, or 6 carbons in a linear or
30 branched arrangement, and specifically includes methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, pentyl, hexyl, and octyl.

As used herein, "alkenyl" refers to a non-aromatic hydrocarbon radical, straight or branched, containing at least 1 carbon to carbon double bond, and up to the maximum possible number of non-aromatic carbon-carbon double bonds may be present, and may be unsubstituted or substituted. For example, "C₂-C₆ alkenyl" means an alkenyl radical having 2, 3, 4, 5, or 6 carbon atoms, and up to 1, 2, 3, 4, or 5 carbon-carbon double bonds respectively. Alkenyl groups include ethenyl, propenyl, butenyl and cyclohexenyl.

The term "alkynyl" refers to a hydrocarbon radical straight or branched, containing at least 1 carbon to carbon triple bond, and up to the maximum possible number of non-aromatic carbon-carbon triple bonds may be present, and may be unsubstituted or substituted. Thus, "C₂-C₆ alkynyl" means an alkynyl radical having 2 or 3 carbon atoms and 1 carbon-carbon triple bond, or having 4 or 5 carbon atoms and up to 2 carbon-carbon triple bonds, or having 6 carbon atoms and up to 3 carbon-carbon triple bonds. Alkynyl groups include ethynyl, propynyl and butynyl.

"Alkylene", "alkenylene" and "alkynylene" shall mean, respectively, a divalent alkane, alkene and alkyne radical, respectively. It is understood that an alkylene, alkenylene, and alkynylene may be straight or branched. An alkylene, alkenylene, and alkynylene may be unsubstituted or substituted.

As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or polycyclic carbon ring of up to 10 atoms in each ring, wherein at least one ring is aromatic, and may be unsubstituted or substituted.

Examples of such aryl elements include phenyl, p-toluenyl (4-methylphenyl), naphthyl, tetrahydro-naphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. In cases where the aryl substituent is bicyclic and one ring is non-aromatic, it is understood that attachment is via the aromatic ring.

The term "arylalkyl" refers to alkyl groups as described above wherein one or more bonds to hydrogen contained therein are replaced by a bond to an aryl group as described above. It is understood that an "arylalkyl" group is connected to a core molecule through a bond from the alkyl group and that the aryl group acts as a substituent on the alkyl group. Examples of arylalkyl moieties include, but are not limited to, benzyl (phenylmethyl), p-trifluoromethylbenzyl (4-trifluoromethylphenylmethyl), 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl and the like.

The term "heteroaryl", as used herein, represents a stable monocyclic, bicyclic or polycyclic ring of up to 10 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Bicyclic aromatic heteroaryl groups include phenyl, pyridine, pyrimidine or pyridazine rings that are (a) fused to a 6-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom; (b) fused to a 5- or 6-membered aromatic (unsaturated) heterocyclic ring having two nitrogen atoms; (c) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one nitrogen atom together with either one oxygen or one sulfur atom; or (d) fused to a 5-membered aromatic (unsaturated) heterocyclic ring having one heteroatom selected from O,

N or S. Heteroaryl groups within the scope of this definition include but are not limited to: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, 5 benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, indolinyl, indolyl, indolaziny, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, 10 pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidiny, aziridinyl, 1,4-dioxanyl, hexahydroazepinyl, dihydrobenzoimidazolyl, 15 dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, 20 dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidiny, methylenedioxybenzoyl, tetrahydrofuranyl, tetrahydrothienyl, acridinyl, carbazolyl, cinnolinyl, 25 quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, furanyl, thienyl, benzothieryl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetra- 30 hydroquinoline. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively. If the heteroaryl contains nitrogen atoms,

it is understood that the corresponding N-oxides thereof are also encompassed by this definition.

The term "heterocycle" or "heterocyclyl" refers to a
5 mono- or poly-cyclic ring system which can be saturated
or contains one or more degrees of unsaturation and
contains one or more heteroatoms. Preferred heteroatoms
include N, O, and/or S, including N-oxides, sulfur
oxides, and dioxides. Preferably the ring is three to
10 ten-membered and is either saturated or has one or more
degrees of unsaturation. The heterocycle may be
unsubstituted or substituted, with multiple degrees of
substitution being allowed. Such rings may be optionally
fused to one or more of another "heterocyclic" ring(s),
15 heteroaryl ring(s), aryl ring(s), or cycloalkyl ring(s).
Examples of heterocycles include, but are not limited to,
tetrahydrofuran, pyran, 1,4-dioxane, 1,3-dioxane,
piperidine, piperazine, pyrrolidine, morpholine,
thiomorpholine, tetrahydrothiopyran, tetrahydrothiophene,
20 1,3-oxathiolane, and the like.

The alkyl, alkenyl, alkynyl, aryl, heteroaryl and
heterocyclyl substituents may be substituted or
unsubstituted, unless specifically defined otherwise.

25

In the compounds of the present invention, alkyl,
alkenyl, alkynyl, aryl, heterocyclyl and heteroaryl
groups can be further substituted by replacing one or
more hydrogen atoms with alternative non-hydrogen groups.
30 These include, but are not limited to, halo, hydroxy,
mercapto, amino, carboxy, cyano and carbamoyl.

As used herein, the term "halogen" refers to F, Cl, Br,
and I.

The term "substituted" refers to a functional group as described above in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms, provided that normal valencies are maintained and that the substitution results in a stable compound. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Examples of substituents include the functional groups described above, and, in particular, halogens (i.e., F, Cl, Br, and I); alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, and trifluoromethyl; hydroxyl; alkoxy groups, such as methoxy, ethoxy, n-propoxy, and isopropoxy; aryloxy groups, such as phenoxy; arylalkyloxy, such as benzyloxy (phenylmethoxy) and p-trifluoromethylbenzyloxy (4-trifluoromethylphenylmethoxy); heteroaryloxy groups; sulfonyl groups, such as trifluoromethanesulfonyl, methanesulfonyl, and p-toluenesulfonyl; nitro, nitrosyl; mercapto; sulfanyl groups, such as methylsulfanyl, ethylsulfanyl and propylsulfanyl; cyano; amino groups, such as amino, methylamino, dimethylamino, ethylamino, and diethylamino; and carboxyl. Where multiple substituent moieties are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties, singly or plurally. By independently substituted, it is meant that the (two or more) substituents can be the same or different.

It is understood that substituents and substitution patterns on the compounds of the instant invention can be

selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials. If a substituent is itself substituted with more than one group, it is understood that these multiple groups may be on the same carbon or on different carbons, so long as a stable structure results.

10

As used herein, a "titanium reagent" refers to elemental titanium, titanium salts and their complexes wherein the titanium atom can exist at various oxidation states. Suitable titanium reagents include, but are not limited to, TiCl_3 , TiCl_4 , $\text{TiCl}_3\text{-THF}$, and $\text{TiCl}_3(\text{DME})_{1.5}$.

15

The term "reducing agent" refers to an agent capable of reducing the oxidation state of another compound. Examples of reducing agents include, but are not limited to, aluminium hydrides, such as $(i\text{-Bu})_2\text{AlH}$, $(i\text{-Bu})_3\text{Al}$, LiAlH_4 , $\text{LiAlH}(\text{OMe})_3$, $\text{LiAlH}(\text{Ot-Bu})_3$, and $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$; boron hydrides such as 9-BBN, NaBH_4 , $\text{NaBH}_4\text{-CeCl}_3$, LiBH_4 , LiEt_3BH , $\text{Li}(\text{s-Bu})_3\text{BH}$, $\text{K}(\text{s-Bu})_3\text{BH}$, $\text{Na}(\text{s-Bu})_3\text{BH}$, KPh_3BH , $(\text{Ph}_3\text{P})_2\text{CuBH}_4$, $\text{Zn}(\text{BH}_4)_2$, $\text{Ca}(\text{BH}_4)_2$, $\text{Li}(\text{n-Bu})\text{BH}_3$, $\text{NaBH}(\text{OMe})_3$, $\text{NaBH}(\text{OAc})_3$, NaBH_3CN , Et_4NBH_4 , $\text{Me}_4\text{NBH}(\text{OAc})_3$, $(\text{n-Bu})_4\text{NBH}_3\text{CN}$, and $(\text{n-Bu})_4\text{NBH}(\text{OAc})_3$; (3) silicon hydrides such as Et_3SiH , PhMe_2SiH , Ph_2SiH_2 , and $\text{PhSiH}_3\text{-Mo}(\text{CO})_6$, (4) alkali and alkaline earth metals, such as Na, K, K/graphite, Li, Mg, and (5) transition metals and amalgams thereof, such as Zn and Zn(Cu) amalgam.

20

25

30

As used herein, the term "palladium catalyst" refers to elemental palladium and complexes thereof, wherein the palladium atom can be at various oxidation states and can

possess one or more ligands. Suitable palladium catalysts include, but are not limited to, tetrakis(triphenylphosphine)palladium(0), bis(tri-*t*-butylphosphine)palladium(0), palladium(II) acetate, 5 bis(tricyclohexylphosphine)palladium(0), palladium(II) chloride, bis(triphenylphosphine)palladium(II) chloride, tris(dibenzylideneacetone)dipalladium(0), bis(dibenzylideneacetone)palladium, (1,1'-bis(triphenylphosphino)ferrocene)palladium(II) chloride, 10 and bis(triphenylphosphine)palladium(II) acetate.

As used herein, abbreviations are defined as follows:

- Ac = acetyl
4-DMAP = 4-(dimethylamino)pyridine
15 DMF = *N,N*-dimethylformamide
EDC = *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide
TBAF = tetra-*n*-butylammonium fluoride
TBS = *tert*-butyldimethylsilyl
TMS = trimethylsilyl
20 Tf = trifluoromethanesulfonyl
KHMDS = potassium bis(trimethylsilyl)amide or potassium hexamethyldisilazide
AIBN = 1,1'-azobisisobutyronitrile
9-BBN = 9-borabicyclo[3.3.1]nonane
25 DIBAL = diisobutylaluminum
THF = tetrahydrofuran
MeOH = methanol
DCC = *N,N*-dicyclohexylcarbodiimide
DCE = 1,2-dichloroethane
30 DCM = dichloromethane
DME = dimethoxyethane
Ph = phenyl
Me = methyl
Et = ethyl

iPr = isopropyl

n-Bu = n-butyl

i-Bu = isobutyl

s-Bu = sec-butyl

5 t-Bu = tert-butyl

Ms = methanesulfonyl

Ts = p-toluenesulfonyl

SET = single electron transfer

DNA = deoxyribonucleic acid

10 RNA = ribonucleic acid

DMBA = 7,12-dimethylbenz[a]anthracene

Tris = tris(hydroxymethyl)aminomethane

OVX = ovariectomized

15 In choosing the compounds of the present invention, one of ordinary skill in the art will recognize that the various substituents, i.e. R₁, R₂, etc. are to be chosen in conformity with well-known principles of chemical structure connectivity.

20

The various R groups attached to the aromatic rings of the compounds disclosed herein may be added to the rings by standard procedures, for example those set forth in Advanced Organic Chemistry: Part B: Reaction and
25 Synthesis, Francis Carey and Richard Sundberg, (Springer) 5th ed. Edition. (2007), the content of which is hereby incorporated by reference.

The compounds of the instant invention may be in a salt
30 form. As used herein, a "salt" is the salt of the instant compounds which has been modified by making acid or base salts of the compounds. In the case of compounds used for treatment of cancer, the salt is pharmaceutically acceptable. Examples of pharmaceutically acceptable salts

include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as phenols. The salts can be made using an organic or inorganic acid. Such acid salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like. Phenolate salts are the alkaline earth metal salts, sodium, potassium or lithium. The term "pharmaceutically acceptable salt" in this respect, refers to the relatively non-toxic, inorganic and organic acid or base addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention, or by separately reacting a purified compound of the invention in its free base or free acid form with a suitable organic or inorganic acid or base, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts and the like. (See, e.g., Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19).

The compositions of this invention may be administered in various forms, including those detailed herein. The treatment with the compound may be a component of a combination therapy or an adjunct therapy, i.e. the subject or patient in need of the drug is treated or given another drug for the disease in conjunction with one or more of the instant compounds. This combination

therapy can be sequential therapy where the patient is treated first with one drug and then the other or the two drugs are given simultaneously. These can be administered independently by the same route or by two or more
5 different routes of administration depending on the dosage forms employed.

As used herein, a "pharmaceutically acceptable carrier" is a pharmaceutically acceptable solvent, suspending
10 agent or vehicle, for delivering the instant compounds to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind. Liposomes are also a pharmaceutically acceptable carrier.

15 The dosage of the compounds administered in treatment will vary depending upon factors such as the pharmacodynamic characteristics of a specific chemotherapeutic agent and its mode and route of
20 administration; the age, sex, metabolic rate, absorptive efficiency, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment being administered; the frequency of treatment with; and the desired therapeutic effect.

25 A dosage unit of the compounds may comprise a single compound or mixtures thereof with anti-cancer compounds, or tumor growth inhibiting compounds, or with other compounds also used to treat osteoporosis or
30 cardiovascular disease. The compounds can be administered in oral dosage forms as tablets, capsules, pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. The compounds may also be administered in intravenous (bolus or infusion),

intraperitoneal, subcutaneous, or intramuscular form, or introduced directly, e.g. by injection or other methods, into the cancer, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts.

5

The compounds can be administered in admixture with suitable pharmaceutical diluents, extenders, excipients, or carriers (collectively referred to herein as a pharmaceutically acceptable carrier) suitably selected
10 with respect to the intended form of administration and as consistent with conventional pharmaceutical practices.

The unit will be in a form suitable for oral, rectal, topical, intravenous or direct injection or parenteral administration. The compounds can be administered alone
15 but are generally mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid, and the type of carrier is generally chosen based on the type of administration being used. In one embodiment the carrier can be a monoclonal antibody. The

20 active agent can be co-administered in the form of a tablet or capsule, liposome, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to
25 swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms
30 include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules

and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

10

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in U. S. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975.

15

Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Pharmaceutical Dosage Forms: Tablets (Lieberman et al., 1981); Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976); Remington's Pharmaceutical Sciences, 17th ed. (Mack Publishing Company, Easton, Pa., 1985); Advances in Pharmaceutical Sciences (David Ganderton, Trevor Jones, Eds., 1992); Advances in Pharmaceutical Sciences Vol 7.

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(David Ganderton, Trevor Jones, James McGinity, Eds., 1995); Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms (Drugs and the Pharmaceutical Sciences, Series 36 (James McGinity, Ed., 1989); Pharmaceutical Particulate Carriers: Therapeutic Applications: Drugs and the Pharmaceutical Sciences, Vol 61 (Alain Rolland, Ed., 1993); Drug Delivery to the Gastrointestinal Tract (Ellis Horwood Books in the Biological Sciences. Series in Pharmaceutical Technology; J. G. Hardy, S. S. Davis, Clive G. Wilson, Eds.); Modern Pharmaceutics Drugs and the

30

Pharmaceutical Sciences, Vol 40 (Gilbert S. Banker, Christopher T. Rhodes, Eds.). All of the aforementioned publications are incorporated by reference herein.

5 Tablets may contain suitable binders, lubricants, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. For instance, for oral administration in the dosage unit form of a tablet or capsule, the active drug component can be
10 combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, gelatin, agar, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like. Suitable binders include starch,
15 gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include
20 sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

25

The compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of
30 phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines. The compounds may be administered as components of tissue-targeted emulsions.

The compounds may also be coupled to soluble polymers as targetable drug carriers or as a prodrug. Such polymers include polyvinylpyrrolidone, pyran copolymer, polyhydroxylpropylmethacrylamide-phenol, 5 polyhydroxyethylasparta-midephenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, 10 polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihdropyrans, polycyanoacylates, and crosslinked or amphipathic block copolymers of hydrogels.

15

The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the compound of the invention, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical 20 reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a compound of the invention.

The compounds of the subject invention can be converted 25 to prodrugs to optimize absorption and bioavailability. Formation of a prodrug include, but is not limited to, reaction of a free hydroxyl group with a carboxylic acid to form an ester, reaction of a free hydroxyl group with phosphorus oxychloride followed by hydrolysis to form a 30 phosphate, or reaction of a free hydroxyl group with an amino acid to form an amino acid ester, the reagents and process of which have been described previously by Chandran in WO 2005/046575, which is hereby incorporated by reference. The substituents are chosen and resulting

analogs are evaluated according to principles well known in the art of medicinal and pharmaceutical chemistry, such as quantification of structure-activity relationships, optimization of biological activity and
5 ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders, or
10 in liquid dosage forms, such as elixirs, syrups, and suspensions. It can also be administered parentally, in sterile liquid dosage forms.

Gelatin capsules may contain the active ingredient
15 compounds and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as immediate release products or as
20 sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective
25 disintegration in the gastrointestinal tract.

For oral administration in liquid dosage form, the oral drug components are combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as
30 ethanol, glycerol, water, and the like. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions,

solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, 5 preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance. In 10 general, water, a suitable oil, saline, aqueous dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water 15 soluble salt of the active ingredient, suitable stabilizing agents, and if necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid 20 and its salts and sodium EDTA. In addition, parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol. Suitable pharmaceutical carriers are described in Remington's Pharmaceutical Sciences, Mack Publishing 25 Company, a standard reference text in this field.

The compounds of the instant invention may also be administered in intranasal form via use of suitable intranasal vehicles, or via transdermal routes, using 30 those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will generally be continuous rather than intermittent throughout the dosage regimen.

Parenteral and intravenous forms may also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

5

The compounds and compositions of the invention can be coated onto stents for temporary or permanent implantation into the cardiovascular system of a subject.

10 As used herein, the term "tumor" refers to an uncontrolled growth of cells. A tumor may be benign or malignant. Benign tumors are not dangerous to health and are not considered cancerous. Malignant tumors are cancerous; they invade surrounding tissue, are usually
15 capable of producing metastases, may recur after attempted removal, and are likely to cause death of the host unless adequately treated. Left unchecked, malignant cells can eventually spread beyond the original tumor to other parts of the body. Various cancers result in the
20 formation of tumors, including, but not limited to, prostate cancer, breast cancer, endometrial cancer, and colon cancer. In particular, breast cancer is thought to be due to exogenous and endogenous factors. Typical exogenous factors are environmental mutagens and
25 carcinogens that induce DNA damage. Typical endogenous factors may be hormones, such as estrogen, that have estrogenic action and induce DNA damage. Such tumors are said to be estrogen-induced tumors. In addition, breast cancer tumors may express estrogen receptors ER α and/or
30 ER β . Tumors expressing any isoform of ER, i.e. ER α or ER β , are said to be ER-positive and tumors not expressing any isoform of ER are said to be ER-negative. Similarly, tumors expressing ER α are said to be ER α -positive and tumors not expressing ER α are said to be ER α -negative.

Tumors expressing ER β are said to be ER β -positive and tumors not expressing ER β are said to be ER β -negative.

As used herein, the term "bone mineral density" refers to
5 the density of minerals, such as calcium, found in bones.
Bone mineral density can be measured using several
different methods. These methods include, but are not
limited to, dual-energy X-ray absorptiometry (DEXA),
peripheral dual-energy X-ray absorptiometry (P-DEXA),
10 dual photon absorptiometry (DPA), ultrasound, or
quantitative computed tomography (QCT).

Design of safer antiestrogens

The results of studies of genotoxic mechanisms conducted
15 over the last 10 years [7], combined with the structures
and biological profiles of other new antiestrogens
developed by other laboratories [50, 51], have now made
it possible to design safer and more effective
triphenylethylene alternatives.

20

As mentioned earlier, long-term administration of TAM has
serious side effects, including endometrial cancer [3-6].
The carcinogenic effect is thought to involve initiation
and/or promotion. Studies of the genotoxic mechanism of
25 TAM [7] together with studies performed by other
laboratories [8] established that TAM produces DNA
adducts in rodent liver [9-11] and in the endometrium of
women treated with TAM [12, 13]. Since TAM-DNA adducts
are highly mutagenic [14] and not rapidly repaired [15,
30 16], the DNA adducts likely contribute to the initiation
of endometrial cancer. Like estrogens, TAM is a partial
ER agonist in uterine tissue [17] and such estrogenic
effects may promote endometrial cancer [18, 19].
Therefore, the rational design of safer antiestrogens

would encompass lowering both genotoxicity and estrogenic activity in order to circumvent these serious side effects.

5 Toremifene (TOR, Fig. 2), the chloroethyl analog of TAM, does not promote hepatic DNA adducts [10, 30, 31] and hepatocarcinoma in rats [10, 31], although the metabolic fate of TOR is similar to that of TAM. Previous studies indicate that this may be due to the steric hindrance
10 caused by a bulky chlorine atom positioned at the ethyl moiety of TOR, which may reduce the ability of hydroxysteroid sulfotransferase to O-sulfonate α -OHTOR and consequently the amount of TOR α -sulfate available to react with DNA [32]. The field effect caused by the
15 electron-withdrawing chlorine atom may also diminish the effective elimination of the α -sulfate group from the α -carbon and therefore inhibit the formation of the carbocation intermediate that reacts with DNA [32]. No K-ras mutation was observed in the endometria of patients
20 receiving TOR [29]. Therefore, the non-genotoxicity of TOR may stem from its inability to form DNA adducts as a result of replacing the ethyl group of TAM with a chloroethyl moiety.

25 GW5638 possesses a novel carboxylic acid side chain (see X position in Fig. 2) and has been recognized as having powerful antiestrogenic activity. This compound has estrogen-like actions to preserve bone density in OVX-rats but, unlike TAM, has pure antiestrogenic activity in
30 rodent uterus. Moreover, GW5638 does not promote tumor growth in rodent breast or endometrial cells [57, 58]. However, it was recently found that GW5638 does show estrogenic (uterotrophic) activity equivalent to that of RAL (see Fig. 4). GW5638 has an ethyl moiety that could

potentially undergo α -hydroxylation followed by O-sulfonation to produce an intermediate capable of reacting with DNA. A similar mechanism of DNA adduct formation may also be extended to idoxifene and TAT-59, both of which have an ethyl moiety [65, 71]. Therefore, triphenylethylene compounds having a chloroethyl moiety are proposed as possibly safer, nongenotoxic antiestrogens, as demonstrated in the studies described comparing TAM and TOR [32].

10

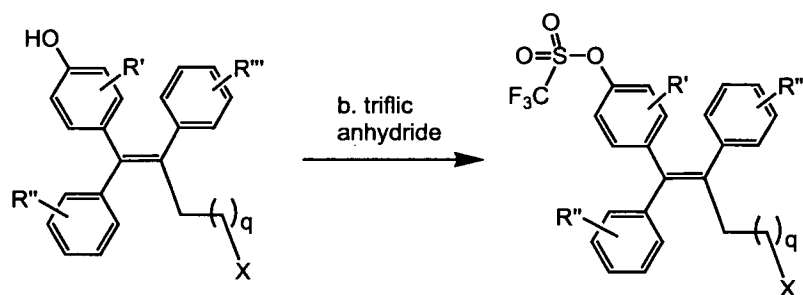
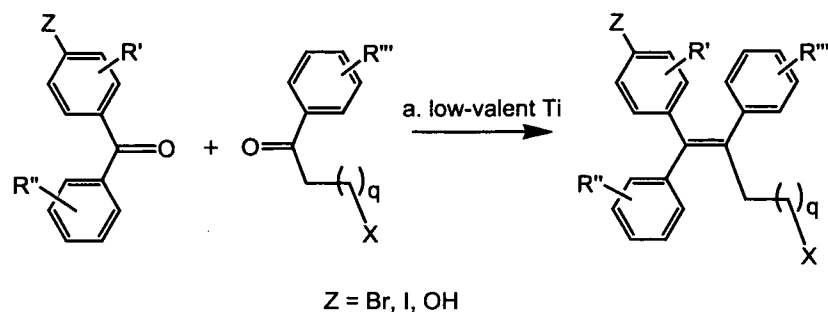
The moiety at the Y position (Fig. 2) affects the antiestrogenic activity. Since 4-OHTAM is a principal metabolite showing ~100-fold more antiestrogenic activity than TAM in vitro [65], the 4-OH moiety may confer high antiestrogenic activity.

15

Synthesis of triphenylethylene derivatives

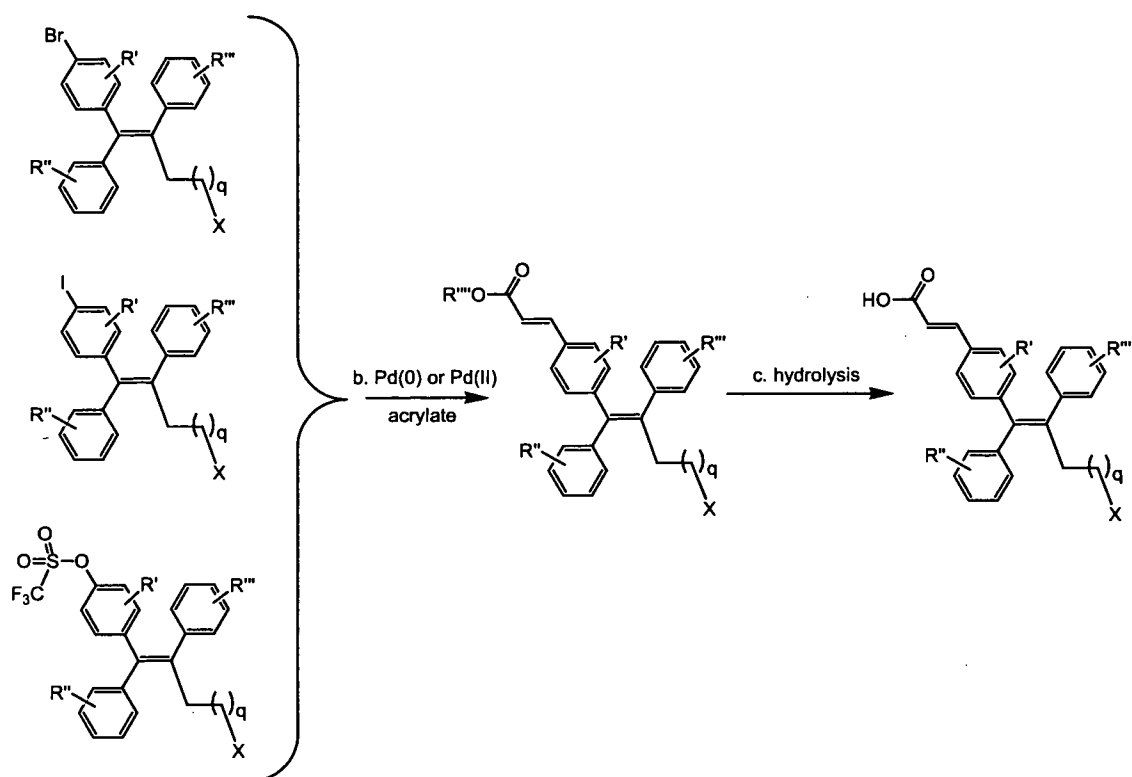
Synthesis of the triphenylethylene derivatives of the subject invention are initiated according to the general procedure shown in Scheme 1. The R groups represent generic substituents.

20



Scheme 1

In step a, the desired benzophenone is reacted with an alkyl phenone of desired length, as indicated by q, and substitution, as indicated by X, in the presence of low-valent titanium (typically synthesized *in situ* from a titanium reagent and a reducing agent) to produce the desired triphenylethylene intermediate. Use of low-valent titanium, also known as the McMurry reaction, to form similar triphenylethylene cores has been described by Södervall et al in WO 01/36360, which is hereby incorporated by reference. In the case where Z is a hydroxyl group, the triphenylethylene intermediate is then triflated (scheme 1, step b) using triflic anhydride (trifluoromethanesulfonyl anhydride) following the McMurry coupling reaction. The subsequent palladium-catalyzed coupling with an alkyl acrylate is achieved in the presence of Pd(0) or Pd(II). Hydrolysis of the coupled product yields the desired acrylic acid-functionalized triphenylethylene compound (Scheme 2).



Scheme 2

5

Those having ordinary skill in the art of organic synthesis will appreciate that modifications to the general procedure shown in schemes 1 and 2 can be made to yield structurally diverse triphenylethylenes. In step a, the requisite benzophenone and alkyl phenone may be obtained commercially with the desired substituents already in place. When the desired substituted benzophenone and alkyl phenone are not commercially available, substituents are installed onto the phenyl rings of the molecules using standard aryl substitution reactions well known in organic synthesis. Furthermore, the alkyl portion of the alkyl phenone may be

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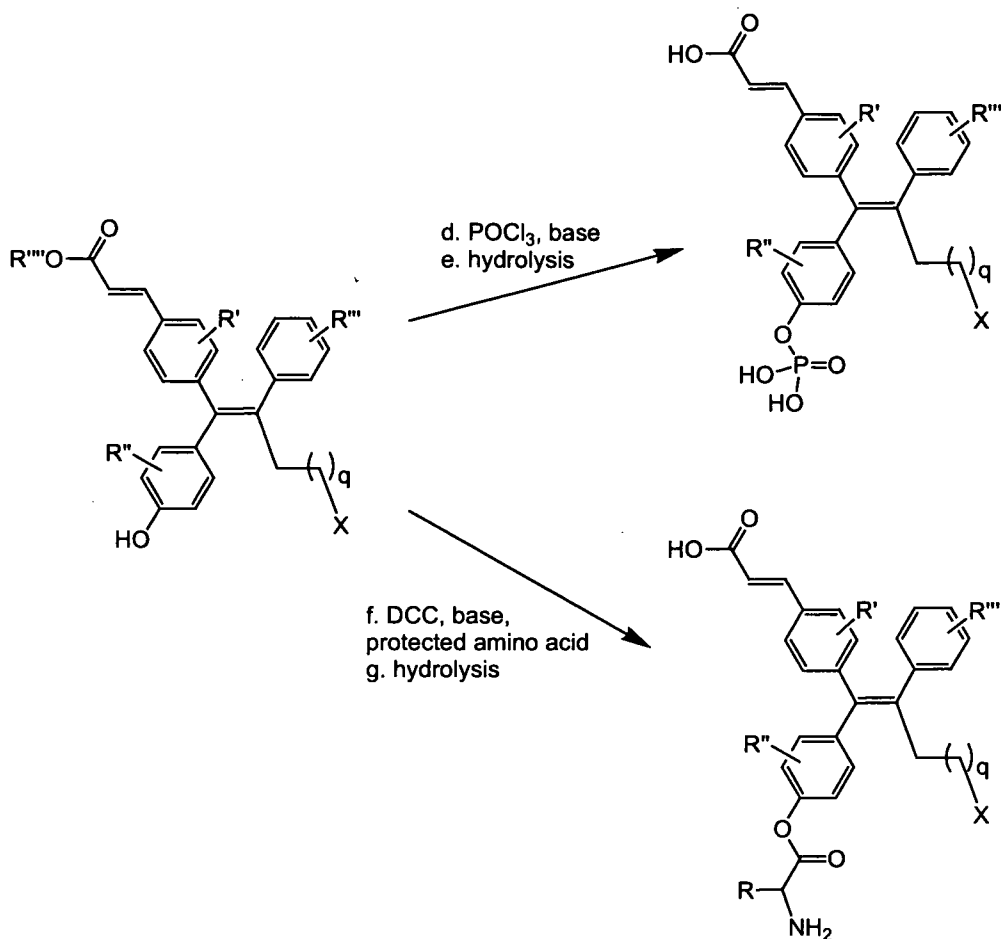
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unsubstituted or substituted using standard methods well known to the ordinarily skilled artisan.

5 In the palladium-catalyzed coupling reaction, the acrylic acid ester may be replaced by other unsaturated compounds capable of engaging in palladium-catalyzed coupling reactions. For example, terminal alkenes and alkynes of varying length and substitution may be used. Furthermore, the resulting coupled product may be reduced using well-
10 known reduction chemistry to yield the corresponding saturated product.

Phenolic compounds, such as the triphenylethylenes where the Y position is OH, may be rapidly conjugated through
15 phase II metabolism and detoxified. To minimize degradation and improve the oral bioavailability [66], the triphenylethylenes can be prepared as prodrugs. The prodrugs should be converted to the active parent during transportation by specific enzymes such as alkaline
20 phosphatase or carboxypeptidase A in the gastrointestinal tract [67]. If the prodrug is efficiently transported into the body and converted to the active drug, the concentrations of the prodrug and its active product should be higher than those obtained with the parent
25 compound alone. Therefore, the prodrug is expected to demonstrate higher efficacy both in inhibiting cancer growth and in preventing cancer development.

RAL diphosphate and TAT-59 were designed as a phosphate
30 ester prodrug and has shown improved oral bioavailability [66, 68]. O-Valinyl derivatives have been used as amino acid ester prodrugs [67, 69]. The formation of the phosphate and amino acid ester prodrugs is achieved according to the general procedure shown in Scheme 3.



Scheme 3

5 The phosphate prodrug is formed by reacting a triphenylethylene having a free hydroxyl group with phosphorus oxychloride (POCl₃) in the presence of a base, and the resulting product is hydrolyzed to form the desired phosphate prodrug (scheme 3, steps d and e). The

10 phosphate may also be further alkylated using standard alkylation methods, such as nucleophilic substitution of the deprotonated phosphate.

To determine the potential for dephosphorylation of the

15 phosphate prodrug, the prodrug can be incubated at 37 °C for 1 hr in a buffer containing cytosol (0.1 mg protein) of rat intestine. The cleavage of the phosphate group is

observed by using HPLC analysis and confirmed by comparison to the incubation of the phosphate prodrug in inactivated cytosol where no conversion is expected.

- 5 The amino acid ester prodrug is formed by reacting a triphenylethylene having a free hydroxyl group with an N-protected amino acid in the presence of DCC and a base followed by hydrolysis to form the desired amino acid ester prodrug (scheme 3, steps f and g).

10

Following synthesis, the triphenylethylenes of the subject invention are evaluated for activity against breast cancer, osteoporosis, and cardiovascular disease using various *in vitro* and *in vivo* assays and
15 experiments, some of which are briefly described hereinafter.

Biological evaluation

Uterotrophic potential

- 20 Safer antiestrogen alternatives to TAM and RAL should have little or no estrogenic activity in order to minimize the risks of developing uterine and endometrial cancers. The compounds of the invention are subjected to an animal uterotrophic assay for evaluating their
25 estrogenic potential. To measure the uterotrophic potential, OVX-rats (Sprague Dawley, 6-week-old females) are treated orally for 3 days with an antiestrogen and the uterine weight is measured 1 day after the final treatment, following an established protocol [62, 70].
30 Although a dose molar equivalent to TAM (0.33-0.66 mg/kg/day) is human equivalent (20-40 mg/60 kg woman/day), a high dose at a molar equivalent to TAM [10 mg (27 μ mol)/kg/day] suspended in 1.0 ml of corn oil is applied to ensure detection of estrogenic activity of

each compound (8 rats/group). The results are compared with those observed with their counterpart antiestrogens (TAM, TOR, GW5638, GW7064, ICI 182,780, and SP500263). Control rats (8 rats) receive only corn oil orally. The animals are euthanized 1 day after the final treatment by CO₂ asphyxiation. The uterine cervix is cut away from the vagina fornix. Since fluid imbibition is an estrogen response, care is taken to retain all uterine luminal fluid. The uterus is then removed by gently lifting tissue anteriorly and trimming away the mesometrium. Uterine wet weights and body weights are then measured, and uterine wet weight/body-weight ratios calculated and compared with those obtained for OVX-rats treated subcutaneously with E₂ (8 rats, 0.3 µg/100 µl corn oil/rat/day for 3 days) as a positive control. Statistical analyses are performed to evaluate the difference. Values of $p < 0.05$ are considered statistically significant. After weighing the uterus, the tissue is then fixed in 10% formalin solution for pathological determination. A cross-section of each uterine horn is processed, embedded in paraffin, sectioned into 5 µm slices and stained with hematoxylin and eosin for histological and morphometric evaluation.

25 Anti-uterotrophic activity

Anti-uterotrophic activity is determined by measuring the inhibitory effect of the compounds on the uterine weight of OVX-rats treated with E₂ [62, 70]. OVX-rats (Sprague-Dawley OVX 6-week-old females) are treated subcutaneously with E₂ (0.3 µg/100 µl corn oil/rat) for 3 days and simultaneously treated orally for 3 days with the selected compounds (8 rats/group) at doses molar equivalent to TAM (0.1, 1.0, and 10 mg/kg/day). Antiestrogens (TAM, RAL, GW5638, and SP500263) are used

as comparisons. The control OVX-rats (8 rats) are treated orally with corn oil. The animals are euthanized by CO₂ asphyxiation one day after the final treatment. Uterine wet weights and body weights are then measured to
5 determine the uterine wet-weight/body-weight ratios, as described above for the uterotrophic assay. The data are compared with those obtained from the OVX-rats (8 rats) treated subcutaneously with E₂ (0.3 µg/100 µl corn oil/rat, 8 rats) as a positive control.

10

Genotoxicity

The genotoxic potential of the compounds selected by uterotrophic evaluation is determined by measuring DNA damage in rodents. Rat liver contains a high level of
15 hydroxysteroid sulfotransferase (HST) that actively converts α-hydroxylated TAM metabolites to their O-sulfate forms, which in turn react with cellular DNA [15]. The enzymatic activity of rat HST is at least one order of magnitude higher than that of human HST (SULT
20 2A1); therefore, the rat is a good model animal to evaluate the genotoxicity of antiestrogens. The selected compounds are administered orally to rats for 7 days, as reported previously [17, 22]. TAM is used as a positive control [22]. Control animals receive corn oil only.
25 Since 20 mg/kg of TAM induce large amounts of hepatic DNA adducts in rats [22], the molar equivalent dose of TAM is applied for the selected compounds (5 rats/group). Five hours after the final treatment, the animals are then euthanized by CO₂ asphyxiation. The liver is removed
30 quickly, frozen in liquid nitrogen, and stored at -80°C until DNA extraction. DNA adduct analysis using ³²P-postlabeling methods have been established [1, 13].

Anti-breast cancer potential

The anti-breast cancer potential of the compounds of the subject invention that lack both estrogenic and genotoxic activities are determined using rats bearing DMBA-induced mammary carcinoma. Selected compounds displaying antitumor activity superior to TAM and RAL are subjected to further evaluation against human MCF-7 breast cancer xenograft in nude mice.

DMBA-induced mammary carcinoma in the rat is a widely used animal model to study the factors which control hormone-sensitive breast cancer in humans [62, 70]. Using this model, the antitumor activity of the selected compounds is determined. The results are compared with those observed for antiestrogens (TAM, RAL and ICI 182,780) currently in clinical use or GW5638 as a counterpart of the compounds of the invention. Following an established protocol [70, 71], mammary carcinoma is induced by treating rats (Sprague-Dawley, 8-week-old females) with a single oral dose (50 mg/kg) of DMBA in corn oil and an approximately 8-mm diameter tumor is expected to develop in 8 weeks. The rats are then treated orally for 4 weeks with each compound. The growth of animals is monitored twice a week as a marker of the host health. Since 20 or 40 mg TAM is generally used as a daily dose for women undergoing breast cancer chemotherapy and chemoprevention (20 and 40 mg/60 kg woman = 0.33 and 0.66 mg/kg/day, respectively), similar or slightly higher doses molar equivalent to that used for TAM (0.33, 1.0, or 3.0 mg/kg/day, p.o. for 4 weeks) are used. TAM and RAL are used as the positive controls. Controls receive corn oil only. The volume of the tumors is recorded twice a week, using the two perpendicular dimensions. The volume of the tumors (TV) are estimated from equation 1 $[TV \text{ (mm}^3\text{)} = (\text{length}) \times (\text{width})^2 / 2]$,

calculated by measuring the width (defined as whichever is the smaller dimension) and the length of the tumor. The relative tumor volume (RTV) is calculated as the ratio of TV on day n to that on day 1, according to equation 2 [RTV = (TV on day n)/(TV on day 1)]. Since tumors in the control rats grow rapidly to approximately 20~25 mm in diameter and/or promote necrosis after 4 weeks' treatment, such animals are euthanized according to established animal care regulations. Appropriate statistical analyses are performed. As the effect differences and variability for most of these experiments are unknown, some pilot experiments are initially run with 8 animals per group. Based on the results of these pilot experiments, needed sample sizes to achieve certain statistical power are then calculated and a confirmatory set of experiments is then conducted, if necessary.

Athymic nude mice implanted with human mammary tumor xenograft are widely used to evaluate the antitumor efficacy of antiestrogens against human breast cancer [70, 72]. Following an established protocol [70], OVX-nude mice (nu/nu-BALB/c, 8-week-old females) supplemented with an estrogen pellet (E₂, 0.72 mg/pellet) given subcutaneously are injected with MCF-7 cells (2 x 10⁷ cells in 0.2 ml saline) subcutaneously into the shoulder region; the tumors are then allowed to grow for 6 weeks (up to ~6 mm in diameter). The nude mice (8 mice/group) are then treated orally for 4 weeks with the selected compounds. Body weight is also measured twice a week to monitor the growth of the animals. Since it is often observed that drug metabolism in mice is faster than in rats, a dose (10 mg/kg) higher than that applied to the rat tumor model is used. To explore the dose response effects, the efficacy of lower molar doses equivalent to

TAM (1.0 and 3.0 mg/kg/day, p.o.) are also examined for the selected compounds, and the results are compared with those for TAM and RAL. Mice from which the estrogen pellets are removed before starting antiestrogen treatment are used as negative controls. As a further control, 8 mice receive corn oil only. Following an established protocol [73], as described for the DMBA-rats, the volume of the tumors are measured twice a week. TV and RTV are estimated from equations 1 and 2 above, respectively. Because studies using nude mice have previously been performed [68], the anti-breast cancer potential of the compounds of the invention is readily determined.

15 Estrogen receptor binding assay

ER β may play an important role in the antitumor action of the selected compounds. Other mechanisms such as apoptosis and cell arrest may also be involved in enhancing their antitumor potential. Thus, ER-binding specificity of the compounds of the invention is determined using an ER binding assay. The level of cell-cycle arrest and apoptosis induced by the compounds is also determined.

25 The differential binding affinity of antiestrogen to ER α and ER β may affect transcriptional regulation [57]; thereby, the antitumor activity of antiestrogens may vary. To explore the ER α - and ER β -binding properties of antiestrogens, the relative binding affinity (RBA) of each

30 compound to ER α and ER β are determined using a spin column assay with a commercially available full-length form of either ER α or ER β (PanVera Corp.), following a widely used the method [57]. Briefly, a range of

concentrations of each compound (10^{-11} - 10^{-4} M) is incubated in buffer containing ER (15 nM) and ^3H -labeled 17β -estradiol (E_2 , 3 nM). The mixture is then be applied to a micro spin column containing G-25 Sephadex according to the manufacturer's instructions. Bound E_2 is separated from free ligand by spinning. A fraction of the filtrate is used for counting in a liquid scintillation counter. A binding curve is then fitted using a single-binding-site competition model and statistical analysis software. Percent RBA is then determined by dividing the IC_{50} for unlabeled E_2 by the ligand IC_{50} and multiplying that value by 100. To evaluate the relative antiestrogenic potential and $\text{ER}\alpha$ or $\text{ER}\beta$ specificity of each of the compounds, the results are compared with those observed for other antiestrogens (TAM, 4-OHTAM, TOR, RAL, ICI 182,780, GW5638, GW7604, and SP500263). The results obtained from this assay may suggest the contribution of $\text{ER}\alpha$ and $\text{ER}\beta$ to the antitumor potency of antiestrogens. In addition, certain antiestrogens could act as estrogen agonists or antagonists to mimic estrogen's positive effects, depending on the specific tissue. Although the relative abundance of $\text{ER}\alpha$ and $\text{ER}\beta$ in bone cells has not been determined, human and mouse genetic studies suggest a predominant role for $\text{ER}\alpha$ in bone metabolism [74, 75]. Different affinities of antiestrogen to $\text{ER}\alpha$ and $\text{ER}\beta$ may also affect the results of anti-osteoporotic efficacy tests.

Cell-cycle and apoptosis

A mechanism other than an antiestrogenic one may also contribute to improving the antitumor potential of antiestrogens. In fact, weak cell-cycle arrest and apoptosis have been observed in cultured breast cancer cells exposed to TAM [76, 77]. Using flow cytometric

analysis and other techniques, the stages of the cell-cycle and apoptosis in cultured human breast cancer cells exposed to the compounds of the invention as well as in mammary tumors of rodents treated with the compounds are
5 determined.

Human MCF-7 breast cancer cells express both ER α and ER β but not the apoptotic factor caspase-3; in contrast, MDA-MB-231 cells do not express ER α but they do express
10 caspase-3. Therefore, if the compounds of the invention do have an apoptotic effect, it should be observable in MDA-MB-231 cells. With TAM as a positive control, alterations to the cell-cycle and apoptosis generated by the compounds with varying exposure times (1, 3, and 5
15 days) and several doses (0.01, 0.1, 1.0, 10, 25, 50 and 100 μ M) are evaluated. Cell viability is determined by using a trypan

blue exclusion assay to measure the percentage of viable cells under a field microscope. Briefly, both types of
20 human breast cancer cells exposed to antiestrogens are harvested from culture media, fixed in paraformaldehyde, incubated with DNA-labeling solution, and stained using propidium iodide (PI) working solution with RNase type2A. If the cell-cycle and apoptosis stages in mammary tumors
25 taken from rodents treated with antiestrogens can be determined, a more precise effect of the compounds could be investigated. At one day after 4 weeks of oral antiestrogen treatment, mammary tumors are collected from rats bearing DMBA-induced mammary carcinoma or from nude
30 mice bearing MCF-7 human breast tumor xenograft. Immediately after collecting the tumors, part of each tumor are homogenized and centrifuged to isolate the cell fraction, and then cultured overnight to harvest the attached cancer cells. The methods for analyzing the

cell-cycle and apoptosis follow the procedures described above for the cultured cells. Taken together with results from the cultured cell experiments, involvement of mechanisms other than estrogenic effects on antitumor potential can be explored.

Caspase-3 functions as a major mediator of apoptotic execution [78]. Involvement of caspase-3 in antiestrogen-induced anti-breast cancer potential is determined using Western-blot analysis [79] and immunohistochemical analysis. Immunohistochemical analysis is performed on BrdU-labeled (brown-stained nuclei) cells using caspase-3 antibody and an ABC kit. The slides are counter-stained with hematoxylin for identification of tumor morphology. The percentage of caspase-3 positive nuclei in the mammary tumor is determined using a semiquantitative histomorphometric evaluation. To confirm the effect of caspase-3 on antiestrogen-induced apoptosis, the cleavage of PARP, a common proteolytic marker of apoptosis [80], in mammary cells exposed to antiestrogens is also detected. When apoptosis is induced, a significant increase in PARP cleavage, as indicated by the production of the p85 subunit, should be detected, suggesting that caspase-3 sensitizes breast cancer cells to antiestrogen by inducing enhanced apoptosis. PARP cleavage is detected using Western-blot [79] and immunohistochemical analyses. β -Actin is used as a loading control.

MDA-MB-231 cells expressing caspase-3 are also implanted in nude mice for exploring the contribution of apoptosis to the antitumor potential of antiestrogens. Since MDA-MB-231 cells are ER α -negative, OVX and estrogen pellet implantation are not required for this experiment. Intact nude mice are injected with MDA-MB-231 cells (2×10^7

cells in 0.2 ml saline) subcutaneously into the shoulder region for the implantation, following an established protocol [81]. When the tumors grow to ~6 mm in diameter, the nude mice are treated orally for 4 weeks with compounds of the invention at a dose molar equivalent to TAM (1.0, 3.0 or 10 mg/kg/day, 8 mice/dose). TAM (1.0, 3.0, and 10 mg/kg/day) are used as a positive control. Eight control mice receive corn oil only. If apoptosis is primarily involved in the antitumor potential, then growth of MDA-MB-231 xenograft should be reduced more effectively than that of MCF-7 xenograft.

In addition, the stages of apoptosis and the cell cycle in MDA-MB-231 xenograft collected from nude mice are determined using flow cytometry and Western-blot analysis, as described earlier. If apoptosis is a major factor in suppressing the growth of mammary tumors, then it should be induced more in MDA-MB-231 xenograft expressing caspase-3, as compared with MCF-7. Results obtained from studies determining apoptotic potential provide insight into the anti-breast cancer mechanism.

Cancer Preventive Potency

The recent increased incidence of breast cancer is thought to be due to exogenous and endogenous factors. Typical exogenous factors are environmental mutagens and carcinogens that induce DNA damage. Typical endogenous factors may be hormones that have estrogenic action and induce DNA damage. Such factors may be involved in initiating and/or promoting mammary tumor. Compounds having the capability of preventing development of mammary tumors could be used as preventive agents. Therefore, the preventive activities of the selected compounds are determined in the following two animal

models. Chemical carcinogen (DMBA)-induced mammary tumor in rats is used as a model to evaluate the preventive effect against a typical exogenous factor. Hormone (E_2)-induced mammary tumor in rats is used as a model to evaluate the preventive effect against a typical endogenous factor. The incidence of mammary tumors may parallel the frequency of carcinogen-induced DNA adducts in the mammary gland, as observed with β -NF [82]. In fact, treatment with TAM prior to a single DMBA injection has been shown to reduce the formation of mammary DMBA-DNA adducts in rats [82]. Such treatment lowered the incidence of mammary carcinoma in mice [83, 84]. TAM or its metabolite is thought to inhibit the bioactivation of DMBA and/or to increase its rate of detoxification, thus lowering the level of adduct formation, as demonstrated by α -NF and β -NF [82,85]. However, RAL, with its higher antiestrogenic activity, did not show such a preventive effect on mammary tumor in mice [84], although this drug significantly reduced the incidence of breast cancer in women at high risk of developing the disease [34]. Thus, indicating that the preventive mechanism of each antiestrogen may involve other factors.

The carcinogen-induced rodent mammary tumor model has been widely used to explore the preventive effects of many compounds, including antiestrogens. To determine whether the preventive effect of antiestrogen is involved in the initiation stage or post-initiation (promotion) stage in DMBA-induced carcinogenesis, the following two experimental protocols are carried out, as demonstrated with β -NF [82]: a) The first protocol is used to evaluate the contribution of antiestrogen to the initiation stage. Rats (10 rats/dose) are treated orally with the compounds of the invention at molar equivalent doses to TAM (1.0,

3.0, or 10 mg/kg/day) 7 days prior to oral treatment with a single dose (50 mg/kg) of DMBA. Since DMBA is not rapidly excreted from the rat body, the antiestrogen treatment is continued 7 days after the DMBA injection;

5 b) The second protocol is used to determine the effect of antiestrogen on the post-initiation stage of carcinogenesis. Oral treatment with compounds at molar equivalent doses to TAM (1.0, 3.0. or 10 mg/kg/day) of rats (10 rats/dose) start 3 weeks after a single dose (50
10 mg/kg) of DMBA and continue for 3 weeks. For both protocols, the control rats receive a vehicle (corn oil) only. TAM (1.0, 3.0, 10 mg/kg/day) is used as a positive control [82, 86] and RAL will be used as a negative control [84]. Pretreatment with α -NF [85] or β -NF [82]
15 reduced the formation of DMBA-DNA adducts in rodents and/or the incidence of DMBA-induced mammary tumor; therefore, α -NF or β -NF (29 or 73 mg/kg/day) at doses molar equivalent to TAM (40 or 100 mg/kg/day) are also used. The development of mammary tumor is monitored
20 weekly; the number of tumors is recorded. To avoid exposure to dietary phytoestrogens having estrogenic activity, rats are given a phytoestrogen-free AIN-76A diet *ad libitum*.

25 If pretreatment with the compounds of the invention reduce the incidence of mammary tumor formation, this would indicate that the preventive mechanism involves the initiation stage of DMBA-induced carcinogenesis. Alternatively, if post-treatment with the antiestrogen
30 lowers the tumor incidence, then the post-initiation (promotion) stage is likely to be important to the prevention.

If interfering with the initiation process is involved in reducing DMBA-induced carcinogenesis, then the level of DMBA-DNA adducts in the mammary gland may correlate with the incidence of mammary tumors [82]. If pretreatment with the compounds of the invention shows a preventive effect against DMBA-induced mammary tumor formation, the level of DMBA-DNA adducts in the mammary gland (as a target organ) and the liver (as a major organ metabolizing DMBA) are determined as an end-point marker using ^{32}P -postlabeling analysis. Procedures for DNA extraction and ^{32}P -postlabeling analysis have been established [87]. Rats (5 rats/dose) are treated orally with the compounds at doses molar equivalent to TAM (1.0, 3.0, or 10 mg/kg/day) 7 days prior to a single oral dose (50 mg/kg) of DMBA. Positive controls (5 rats) receive corn oil only prior to a single oral dose of DMBA. Negative controls (5 rats) receive corn oil only without DMBA treatment. The results are compared with those observed with TAM or RAL (1.0, 3.0, or 10 mg/kg/day). Since pretreatment with α -NF [85] or β -NF [82] has been shown to reduce the formation of DMBA-DNA adducts in rodents, α -NF or β -NF (29 or 73 mg/kg/day) at doses molar equivalent to TAM (40 or 100 mg/kg/day) are used as a positive control. The rats are euthanized one day after the DMBA treatment by CO_2 asphyxiation. Mammary gland and liver are collected for analysis of DMBA-DNA adducts. Briefly, DNA is isolated from mammary gland or liver using phenol/chloroform extraction or a commercially available kit and digested using micrococcal nuclease and spleen phosphodiesterase to produce normal (dN3'P) and adducted deoxynucleoside 3'-monophosphate (dX3'P). By incubating with nuclease P1, dN3'P is 3'-dephosphorylated to form deoxynucleosides (dN) whereas dX3'P is generally resistant to the enzyme. Therefore, adducted nucleotides

are enriched during this process (nuclease P1 enrichment), labeled with ^{32}P using $[\gamma\text{-}^{32}\text{P}]\text{ATP}$ and T4 polynucleotide kinase, and resolved by 30% non-denaturing polyacrylamide gel electrophoresis (PAGE) or by using an HPLC/radioisotope detector. Active diol epoxide forms of DMBA [(±)anti-DMBADE and (±)syn-DMBADE] are prepared, following an established method [88], and reacted with 2'-deoxyguanosine monophosphate (dGMP) or 2'-deoxyadenosine monophosphate (dAMP) in a buffer [89]. The resulting DMBA-DNA adducts are used as markers for ^{32}P -postlabeling analysis. With this assay, the limit of detection for a 5 µg DNA sample is approximately 3 adducts in 10^9 nucleotides for ^{32}P -postlabeling/PAGE and 3 adducts in 10^{10} nucleotides for ^{32}P -postlabeling/HPLC. These methods have successfully been used to detect and quantify DNA adducts in rodents [33]. Alternatively, DMBA-DNA adducts can be determined using liquid chromatography electrospray tandem mass spectrometry (LC/MS/MS) [33]. Use of LC/MS/MS has the significant benefit of being able to identify the DMBA-induced DNA adducts. DNA is digested using micrococcal nuclease and spleen phosphodiesterase and incubated with alkaline phosphatase. The resulting nucleosides are subjected to LC/MS/MS. The detection limit is approximately 1 adduct in 10^8 bases using 25 µg of DNA. If the amount of DMBA-DNA adduct formed in the mammary gland parallels the incidence of developing mammary tumors generated by antiestrogens, this assay can be used to predict the preventive efficacy of compounds and also used as a screening system to find highly effective preventive agents.

The mechanism involved in reducing the level of DMBA-DNA adduct formation by antiestrogens, including TAM [86],

has not yet been investigated. CYP 1 family enzymes (CYP1A1, 1A2 and 1B1), regulated by the aryl hydrocarbon receptor (AhR) [90], are responsible for bioactivation of DMBA. In fact, pretreatment with α -NF, a potent inhibitor of CYP 1 family enzymes, reduced the formation of DMBA-DNA adducts in rodents [91]. If pretreatment with the selected compounds shows a preventive effect against DMBA-induced mammary tumor, then expression of CYP1 enzymes is determined. A fraction of mammary gland (as a target organ) and liver (primary site of DMBA metabolism) collected for studies for DMBA-DNA adduct formation (see above) are used for determination of CYP 1 and AhR expression using Western-blot analysis and relative reverse transcriptase-polymerase chain reaction (RT-PCR). Surprisingly, β -NF, a potent inducer of phase II enzymes, has also been shown to reduce the formation of DMBA-DNA adducts, indicating that rapid DMBA detoxification may be involved in reducing adduct formation [82]. The expression of GSTs and UDP-GT, typical phase II enzymes [92], is also determined.

Expression of CYP1, AhR, GSTs, and UDP-GT is measured in total mammary protein prepared using an RNA/DNA/protein isolation reagent, such as TRI REAGENT® (MRC), a monophasic solution comprising phenol and guanidine thiocyanate, according to the manufacturer's instructions [93]. Briefly, proteins are resolved on polyacrylamide gels and transferred to a hydrophobic polyvinylidene difluoride membrane, such as HYBOND™-P membrane (Amersham Pharmacia Biotech). Membranes are blocked 8 h at room temperature with shaking in Tris-buffered saline plus Tween (TBST) and then incubated with antibody to CYP1A1, CYP1A2, CYP1B1, AhR, GSTs, or UDP-GT in TBST plus milk powder overnight at 4°C with shaking. β -Actin is used as

a loading control. After washing, the membranes is incubated in TBST plus milk powder containing horseradish peroxidase-conjugated secondary IgG A. Membranes are washed three times in TBST, and the proteins are visualized using an enhanced chemiluminescence system, such as ECL PLUSTM (Amersham Pharmacia Biotech), and detected by autoradiography. Immunoquantitation is obtained by densitometric scanning of the resulting autoradiographs using a molecular imager.

10

For RT-PCR, total mammary gland RNA is extracted using an RNA/DNA/protein isolation reagent, such as TRI REAGENT® (MRC), according to the manufacturer's directions. First-strand complementary DNAs (cDNAs) are synthesized from total RNA using the Reverse Transcription System (Promega). PCR is performed using the primer sequences for CYP1A1, CYP1A2, CYP1B1, β -actin [93], for AhR [94], and for GSTs and UDP-GT [92, 95]. The PCR products are fractionated through an agarose gel and visualized by dual staining with ethidium bromide and SYBR green. The bands are analyzed by video densitometry; the areas of the peaks are calculated in arbitrary units. The relative value is generated by calculating the ratio of the arbitrary units of each enzyme amplicon to that of β -actin.

25

With regards to hormone (E_2)-induced mammary tumor, ACI rats have been used as model animals for studying human sporadic breast cancer [96]. The metabolic activation of human estrogen (E_2) by CYP 1A1 and 1B1 [97], the same enzymes that metabolize DMBA, may be related to the carcinogenicity [97]. Therefore, a hormone-induced rat mammary tumor model is also used to explore the preventive effect of antiestrogens. Following this

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protocol [96], mammary tumors have been successfully induced in approx. 3 months in ACI rats implanted under the skin with a pellet containing 2.5 mg of E₂. Oral treatment with selected compounds at molar equivalent doses to TAM (1.0, 3.0, or 10 mg/kg/day) of rats (10 rats per dose) are started 7 days prior to implanting the estrogen pellet under light isoflurane anesthesia and continue until the experiment is completed. Controls (10 rats) receive a placebo pellet. Tumor size and number are recorded once a week during the course of the study. The results are then compared with those observed with TAM or RAL (1.0, 3.0, or 10 mg/kg/day). If a preventive effect is observed against E₂-induced rat mammary tumors, the expression of mammary CYP 1, AhR, and PR is monitored during the period of antiestrogen treatment. Rats (10 rats/dose) are treated orally with selected compounds at doses molar equivalent to TAM (1.0, 3.0, or 10 mg/kg/day) prior to being implanted with an E₂ pellet. Controls (10 rats) receive a placebo pellet. Five rats are then euthanized 1.5 and 3.0 months after the pellet implantation by CO₂ asphyxiation. The fourth mammary gland is collected for analysis of CYP 1, AhR, and PR expression using Western blot and RT-PCR, as described earlier. The results are compared with those observed with TAM or RAL (1.0, 3.0, or 10 mg/kg/day). If the development of E₂-induced mammary tumor is reduced by the antiestrogen treatment, then the preventive activity may be associated with the inhibitory effect of antiestrogen on CYP 1, AhR, and/or PR expression. TAM treatment of ACI rats implanted with an E₂-pellet down-regulated ER expression in addition to PR [96]. Expression of ER α and ER β in ACI rats treated with selected compounds are also monitored using Western-blot analysis [79].

In parallel with Western-blot and RT-PCR studies, the skin containing the third mammary gland is collected from ACI rats 1.5 and 3 months after the E₂- or placebo-pellet implantation. Following an established protocol [98, 99],
5 the mammary gland is fixed in 10% neutral buffered formalin for 3 days and then dissected free from the skin and processed as a whole mount. The gland is defatted in ethanol, acetone, chloroform and ethanol again, 3 days for each solvent. After dehydration, the gland is stained
10 with hematoxylin and washed with distilled water. The stained gland is cleaned up under a stereomicroscope, dehydrated in ethanol, cleared in xylene and mounted. Photographs are taken using a digital color camera mounted on a microscope. If antiestrogens have the
15 capability of inhibiting the development of E₂-stimulated mammary gland, then the increase in size and number of end buds by E₂ treatment observed in normal mammary gland [100] should be reduced. Taken together with results obtained from the DMBA-induced mammary tumor model, the
20 preventive potential of compounds of the invention, and the preventive mechanism are evaluated. If the compounds protect against development of mammary tumors induced by the endogenous or exogenous carcinogen, such antiestrogens could provide potential benefits for women
25 in preventing the disease.

Preventive potency against osteoporosis

Antiestrogens act as selective estrogen receptor modulators (SERMs), exerting a broad spectrum of effects
30 on tissues, including maintenance of bone density and cardiovascular protection [101]. TAM, a first-generation SERM, revealed the efficacy of estrogen in preventing bone loss [102-104]. Several other antiestrogens, including RAL, were more effective than TAM in preventing

bone loss (35, 39, 62, 105]. If the compounds of the invention have a similar or higher preventive effect than RAL, such drugs could provide more benefits for patients to protect against osteoporosis. Three-dimensional high-resolution (20 micron) micro-computed tomography (μ CT) has been used to monitor changes in bone morphology and micro-architecture, including those induced by osteoporosis [106]. Importantly, fully-automated customized algorithms are available for time-efficient analysis of bone morphology [107]. Thus, changes in bone architecture in rats can be longitudinally monitored using the μ CT to determine the anti-osteoporotic potential of the selected compounds and compare the changes to those observed with RAL or TAM. Precise and accurate μ CT measures of bone quantity and quality are used as surrogate markers of bone strength. If necessary, the mechanical properties of the bone are computed directly via finite element modeling [108, 109]. To support these results, serum alkaline phosphatase level is determined as a biomarker of bone turnover [110].

To determine the cardiovascular protection, serum cholesterol levels are also determined as a biomarker in the cardiovascular system.

25

The OVX-rat is widely used as an osteopenic animal model that mimics the development of estrogen deficiency-induced osteopenia in humans [111, 112]. OVX-rats have been known to lose bone mineral content (BMC) [70]. Following a general protocol [73], OVX-rats, aged 13 weeks (Sprague-Dawley, females) are treated orally once daily for 3 months with each compound. Doses molar equivalent to TAM (1.0, 3.0, or 10 mg/kg/day in corn oil) are used for the compounds evaluated. To minimize the data variation for

30

statistical analysis, 10 rats per a dose are used. TAM and RAL are used as the positive control. E₂ (0.0073 µmol/kg/day) is administered subcutaneously to one group of OVX-rats as a positive control. Sham rats are treated with corn oil as a control. The vehicle volume is adjusted to 1.0 ml/kg rat body weight. Body weight is measured weekly. Three-dimensional bone quantity, quality, and architecture are monitored once every month for 3 months under a light anesthesia using a µCT. Blood is also taken from the tail before treatment of the compound and then once every month for 3 months to determine the serum alkaline phosphatase activity and total cholesterols. The animals are euthanized by CO₂ asphyxiation one day after the final treatment. Blood and tissues are taken and stored in a -80 °C deep freezer. To evaluate any long-term effects of the compounds on estrogenic potential, uteri are dissected free of fat, and the wet weights measured for determination of uterotrophic potential. A portion of each uterus is used for preparation of formalin-fixed tissue for pathological determination.

In parallel with the 3-month osteological experiments, to evaluate any long-term side-effects of the compounds on liver and uterus, normal Sprague-Dawley rats (10 rats per dose) are also treated orally once daily for 3 months with the selected compounds at doses molar equivalent to TAM (3.0 or 10 mg/kg/day). The body weight is measured twice a week to monitor the growth of the animals. The animals are then euthanized by CO₂ asphyxiation one day after the final treatment. Liver and uteri are dissected and subjected to pathological evaluation. The final pathological evaluation is performed. If abnormal effects

are found in comparison with the control, such compounds are excluded from the candidate compounds.

A μ CT scanner provides a high resolution imaging technique to quantify changes in bone morphology over time, including bone mineral density (BMD) and BMC [113]. Since bone metabolism is more active in trabecular bone than cortical bone, osteopenic abnormality generally appears on trabecular bone earlier than cortical bone [106]. Using this system, cortical and trabecular bone quantity and quality, and micro-architecture of the distal femur and the femoral diaphysis are measured. Three-dimensional images are also acquired and a Gaussian filter is used to partly suppress noise in the volumes [107]. The following parameters are calculated according to the manufacturer's software [114] for evaluation of bone loss: tissue volume (TV), bone volume, (BV), bone volume fraction (BV/TV), bone surface (BS), the structure model index (SMI, an estimation of the plate-rod characteristic of the structure), connectivity density (Conn.D), mean trabecular thickness (Tb.Th), mean trabecular separation (Tb.Sp), mean trabecular number (Tb.N) and the geometrical degree of anisotropy (DA, ratio between the maximal and minimal radii of the mean intercept length ellipsoid), and tissue mineral density (TMD, a measure of tissue mineralization). For example, trabecular bone loss has been successfully monitored in a mouse subjected to 3 weeks of bone disuse [115].

Since the level of serum alkaline phosphatase increases in parallel with bone loss, alkaline phosphatase levels have been used as a biomarker of bone turnover [110]. In fact, alkaline phosphatase levels increase in both OVX-rats [116] and postmenopausal women [117], indicating an

increase in bone turnover. Blood is taken from OVX-rats once every month during the 3 months of antiestrogen treatment. Serum total alkaline phosphatase activity is determined by commercially available kits [116]. Since
5 this assay is based on colorimetric estimation of p-nitrophenol formed after the breakdown of p-nitrophenylphosphate by the enzyme, both hepatic and bone alkaline phosphatases can be measured together. To obtain an accurate measure of bone turnover, changes in bone-
10 specific alkaline phosphatase in serum are determined electrophoretically using a commercially available kit. If long-term treatment with any of the antiestrogens does not increase the level of serum alkaline phosphatase, then such compounds may help prevent bone loss. These
15 data support the results derived from the μ CT study to evaluate the protective efficacy of new compounds against osteoporosis.

Serum cholesterol levels increase in postmenopausal women
20 and can be reversed by hormone replacement therapy [118]. Serum cholesterol levels also increase in OVX-rats [62]. Therefore, serum cholesterol level is accepted as a biomarker of estrogen action in the cardiovascular system. In fact, E_2 , TAM and RAL suppress the rise in
25 serum cholesterol associated with ovariectomy [119, 120]. E_2 lowers cholesterol by upregulating the hepatic low-density lipoprotein (LDL) receptor, resulting in an increased removal of serum cholesterol from the circulation [121]. Since, unlike human, rat high-density
30 lipoprotein (HDL) contains apoprotein E that binds to the LDL receptor, both HDL and LDL cholesterol levels are reduced in estrogen-treated rats [122]. Therefore, serum HDL and LDL cholesterol levels are also determined. Serum total cholesterol, LDL and HDL levels in OVX-rats treated with

selected compounds are determined once every month by commercially available kits [120]. If antiestrogen treatment does not increase the serum cholesterol level, such compounds may help prevent cardiovascular disease.

5

The compounds and compositions of the invention are useful for preventing and/or inhibiting the proliferation of tumors, particularly estrogen-induced tumors, as well as tumors expressing ER α . Furthermore, the compounds and compositions of the invention are also useful for the treatment of osteoporosis.

10

This invention will be better understood by reference to the Experimental Details which follow, but those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention as described more fully in the claims which follow thereafter.

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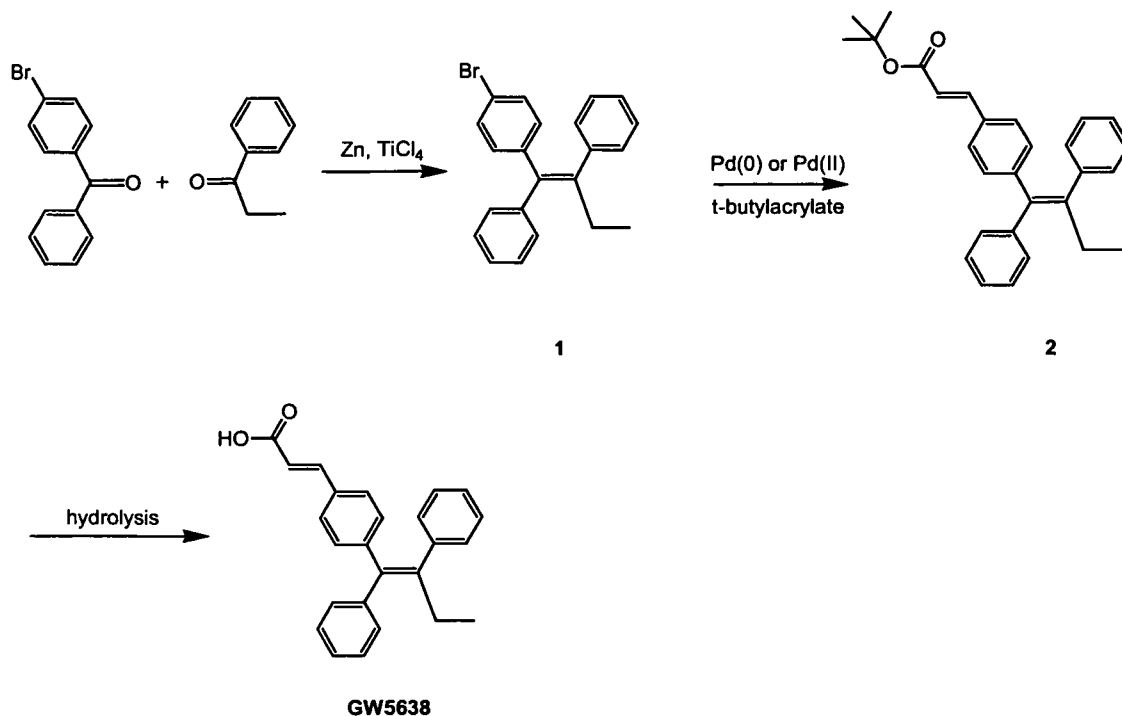
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Experimental Details

Example 1

Synthesis of GW5638

5 Most triphenylethylene antiestrogens are currently prepared using many synthetic steps. Therefore, the yield is low, which contributes to the high cost of the drugs. For example, GW5638 has been prepared through 9 steps [73]. To expedite the synthesis, GW5638 was prepared in
10 only 3 steps with good overall yield (~45%) according to the general procedure shown in schemes 1 and 2. The triphenylethylene core was synthesized according to a strategy similar to that described by Gaulthier and co-workers [123]. The McMurry reaction [124] was carried out
15 with commercially available 4-bromo benzophenone and propiophenone in the presence of TiCl_4 and Zn. The bromo olefin **1** was obtained as a mixture of *E* and *Z* isomers which were separated by column chromatography. The subsequent palladium-catalyzed coupling reaction [125] of
20 (*Z*)-bromo olefin **1** with *t*-butyl acrylate followed by hydrolysis gave (*Z*)-GW5638 (Scheme 4). The melting point, the ^1H -NMR and mass spectral data were identical to those reported earlier [73].



Scheme 4

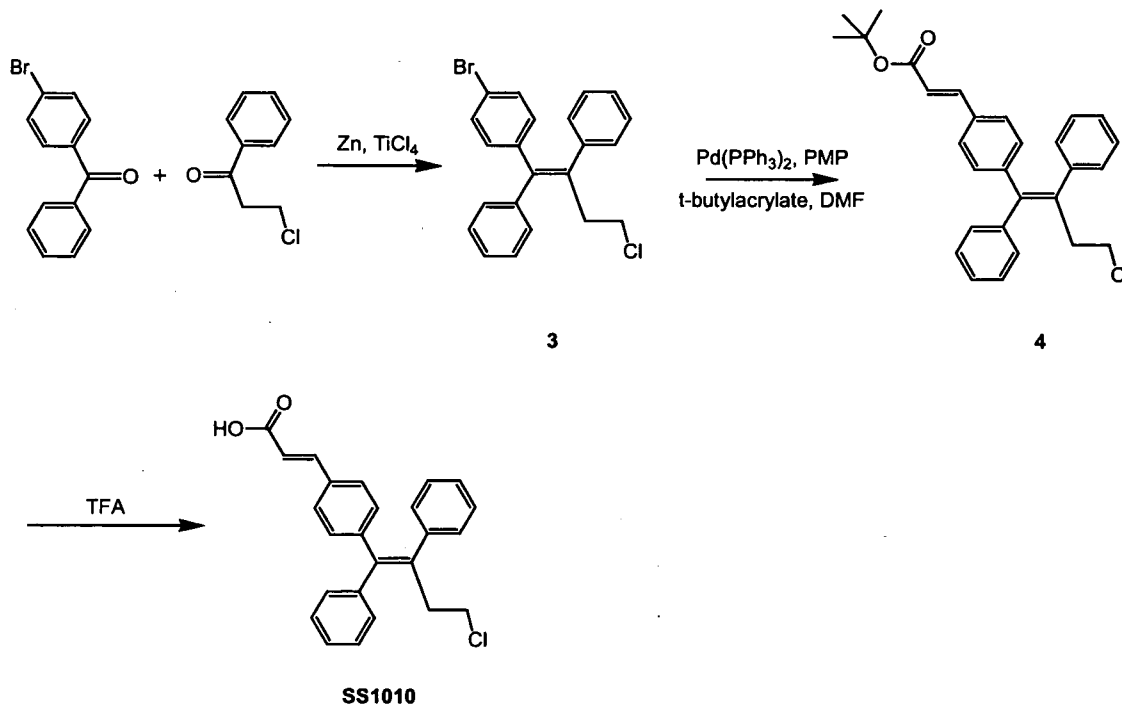
5 **GW5638**: $^1\text{H-NMR}$: δ (CDCl_3): 0.94 (t, $J=7.2$ Hz, 3H); 2.48 (q, $J=7.2$ Hz, 2H); 6.27 (d, $J=16$ Hz, 1H); 6.90 (d, $J=8.4$ Hz, 2H); 7.10-7.28 (m, 12H); 7.62 (d, $J=16$ Hz, 1H). $^{13}\text{C-NMR}$ data: δ (CDCl_3): 172.55 (C=O); 146.87 (-CH=CH-CO); 145.88; 143.62; 142.88; 121.74; 138.03; 131.31; 129.57; 129.48; 128.28; 128.01; 127.54; 126.87; 126.52 (aromatic and -C=C-); 116.39 (-CH=CH-CO); 29.14 (-CH₂CH₃); 13.47 (-CH₂CH₃). m/z : 354 (M^+); R_f = 0.3 (DCM:MeOH 95:5); melting point = 144-145°C.

15 **Example 2**

Synthesis of SS1010

SS1010 was synthesized according to scheme 5. The McMurry reaction was carried out with commercially available 4-bromo benzophenone and chloropropiophenone. The bromo olefin **3** was obtained as a mixture of *E* and *Z* isomers which were separated by column chromatography. The

- subsequent palladium-catalyzed coupling reaction of (Z)-bromo olefin **3** with t-butyl acrylate was achieved in the presence of $\text{Pd}(\text{PPh}_3)_2$ and 1,2,2,6,6-pentamethylpiperidine (PMP) in DMF solvent to form the coupled acrylate **4**.
- 5 Acrylate **4** was hydrolyzed in the presence of trifluoroacetic acid (TFA) to yield SS1010.



10

Scheme 5

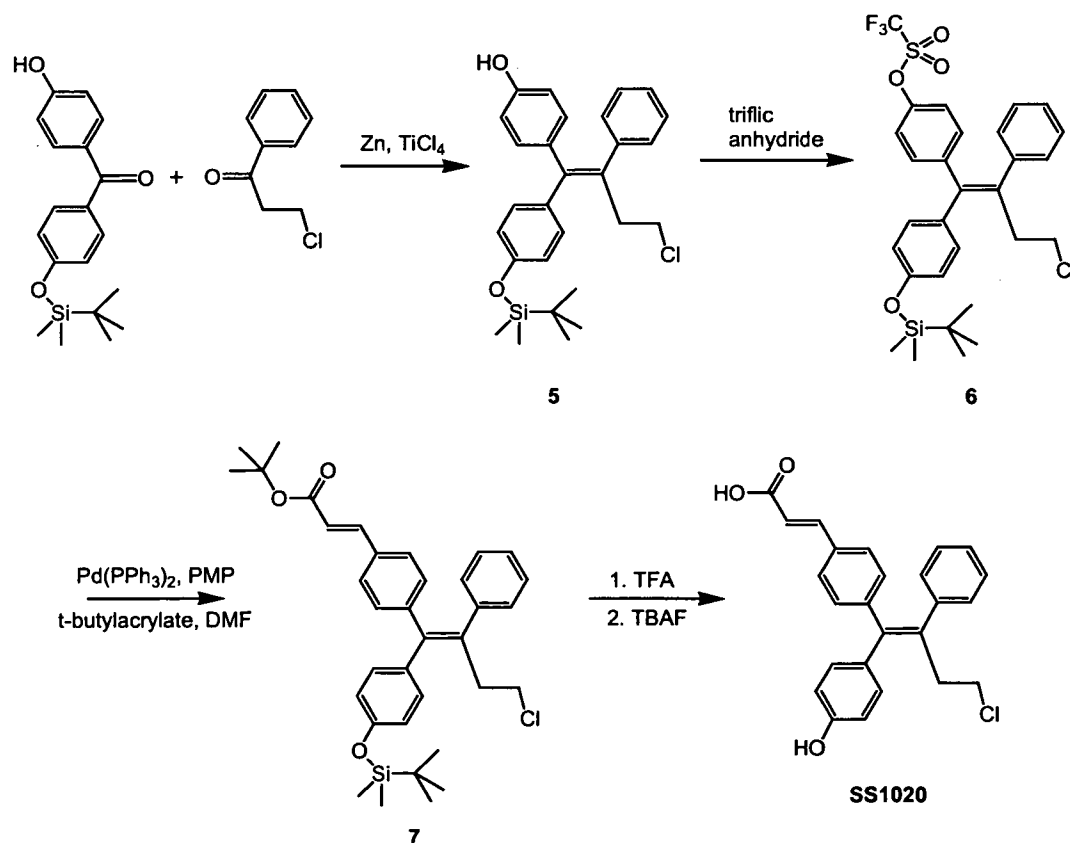
SS1010: ^1H -NMR: δ (CDCl_3): 2.95 (t, $J=7.2$ Hz, 2H); 3.42 (t, $J=7.2$ Hz, 2H); 6.28 (d, $J=16$ Hz, 1H); 6.91 (d, $J=8.8$ Hz, 2H); 7.20-7.37 (m, 12H); 7.59 (d, $J=16$ Hz, 1H). ^{13}C -NMR data: δ (CDCl_3): 173.01 (C=O); 147.06 (-CH=CH-CO); 145.51; 142.31; 141.83; 140.62; 137.74; 132.06; 131.41; 129.80; 128.87; 127.99; 127.62; 127.42 (aromatic and -C=C-); 117.08 (-CH=CH-CO); 42.97 (-CH₂CH₂Cl); 38.78 (=C-CH₂-). m/z : 354 (M^+); melting point = 170-172°C.

20

Example 3

Synthesis of SS1020

SS1020 was synthesized according to scheme 6. The McMurry reaction was carried out with a monosilylated dihydroxy benzophenone and chloropropiophenone. The resulting product **5** was obtained as a mixture of *E* and *Z* isomers and the mixture was subsequently triflated using triflic anhydride to give triflate **6**. Triflate **6** was purified by column chromatography to give the (*Z*)-triflate. The palladium-catalyzed coupling reaction of (*Z*)-triflate **6** with *t*-butyl acrylate was achieved in the presence of $\text{Pd}(\text{PPh}_3)_2$ and 1,2,2,6,6-pentamethylpiperidine (PMP) in DMF solvent to form the coupled acrylate **7**. Acrylate **7** was hydrolyzed in the presence of TFA and the silyl group was cleaved using tetrabutylammonium fluoride (TBAF) to yield SS1020.



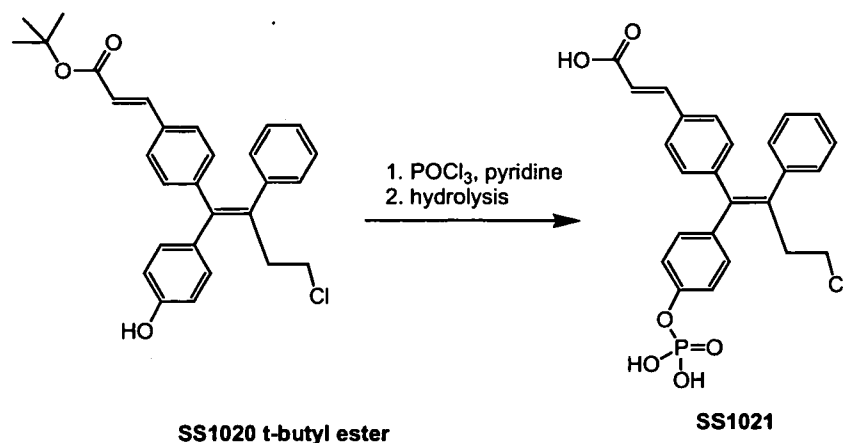
Scheme 6

SS1020: ^1H -NMR data: δ (CD_3OD): 2.97 (t, $J=7.2\text{Hz}$, 2H); 3.41 (t, $J=7.2\text{Hz}$, 2H); 6.32 (d, $J=16\text{Hz}$, 1H); 6.79 (d, $J=8.4\text{Hz}$, 2H); 6.92 (d, $J=8.4\text{Hz}$, 2H); 7.11-7.18 (m, 7H); 7.23 (d, $J=8\text{Hz}$, 2H); 7.49 (d, $J=16\text{Hz}$, 1H). ^{13}C -NMR data: δ (CD_3OD): 170.58 (C=O); 158.02 (O-C of Ph-); 146.98 (-CH=CH-CO); 146.08, 143.07, 142.43, 138.39, 134.85, 133.63, 132.41, 131.92, 130.93, 129.41, 128.46, 128.05 (aromatic and -C=C); 118.96 (-CH=CH-CO); 116.35 (carbons ortho to phenolic OH); 43.59 (C=C-CH₂CH₂Cl); 39.78 (C=C-CH₂CH₂Cl). m/z : 403 (M^+-1); R_f = 0.15 (DCM:MeOH: 95:5); melting point : 176-177°C.

Example 4

Synthesis of SS1021 (phosphate derivative of SS1020)

The phosphate derivative of SS1020 was obtained according to established procedures [126, 127] and is shown in scheme 7. The t-butyl ester of SS1020 was reacted with phosphorus oxychloride (POCl_3) in the presence of pyridine followed by hydrolysis to yield SS1021.



Scheme 7

SS1021, 3-{4-[4-Chloro-2-phenyl-1-(4-phosphonooxy-phenyl)-but-1-enyl]-phenyl}-acrylic acid: ^1H -NMR data: δ (CD_3OD): 2.97 (t, $J=7.0\text{Hz}$, 2H); 3.44 (t, $J=7.0\text{Hz}$, 2H);

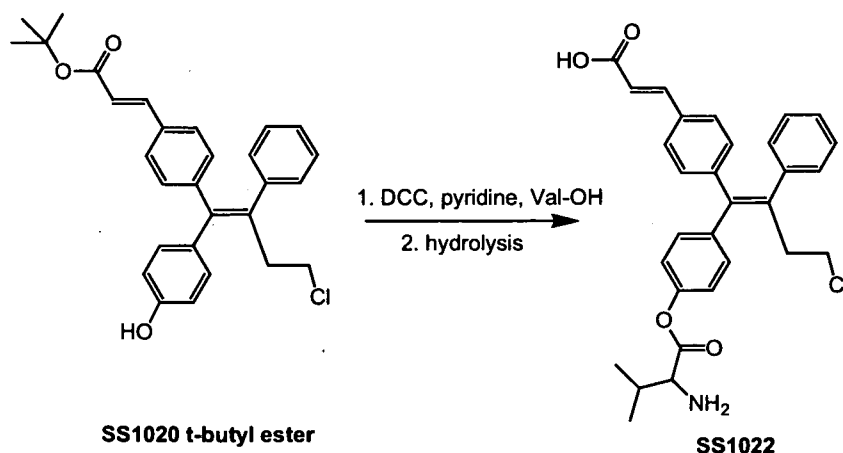
6.34 (d, $J=16\text{Hz}$, 1H); 6.95 (d, $J=8.5\text{Hz}$, 2H); 7.17-7.27 (m, 9H); 7.34 (d, $J=8.0\text{Hz}$, 2H); 7.52 (d, $J=16\text{Hz}$, 1H). ^{13}C -NMR data: δ (CD_3OD): 170.43 ($\text{C}=\text{O}$); 152.07 & 152.00 ($\text{O}-\text{C}$ of Ph-); 146.23 ($-\text{CH}=\text{CH}-\text{CO}$); 145.95, 142.14, 141.76, 140.00, 139.24, 133.72, 132.25, 132.01, 130.82, 129.44, 128.57, 128.23, 121.57, 121.53 (aromatic and $-\text{C}=\text{C}-$); 119.07 ($-\text{CH}=\text{CH}-\text{CO}$); 43.43 ($\text{C}=\text{C}-\text{CH}_2\text{CH}_2\text{Cl}$); 39.46 ($\text{C}=\text{C}-\text{CH}_2\text{CH}_2\text{Cl}$). ^{31}P -NMR data: δ (CD_3OD): -4.06. m/z : 483 & 485 (M^+-1); melting point: 112-115 $^\circ\text{C}$.

10

Example 5*Synthesis of SS1022 (valinyl derivative of SS1020)*

The valinyl derivative of SS1020 was obtained according to established procedures [128] and is shown in scheme 8. Reaction of the t-butyl ester of SS1020 with protected valine in the presence of N,N-dicyclohexylcarbodiimide (DCC) and pyridine followed by hydrolysis gave the desired valinyl product SS1022.

20



Scheme 8

SS1022 2-Amino-3-methyl-butyric acid 4-{1-[4-(2-carboxy-vinyl)-phenyl]-4-chloro-2-phenyl-but-1-enyl}-phenyl

ester: ^1H -NMR data: δ (CD_3OD): 1.22-1.24 (m, 6H); 2.49-2.53 (m, 1H); 2.97 (t, $J=7\text{Hz}$, 2H); 3.44 (t, $J=7\text{Hz}$, 2H);

25

4.25 (d, J=4.5Hz, 1H); 6.34 (d, J=16Hz, 1H); 6.96 (d, J=7.5Hz, 2H); 7.18-7.29 (m, 9H); 7.45 (d, J=8.5Hz, 2H); 7.52 (d, J=15.5Hz, 1H). ¹³C-NMR data: δ (CD₃OD): 170.1 (Ar-O-C=O); 169.04 (O=C-OH); 150.55 (O-C-C of Ar-);
5 145.96 (CH=CH-CO); 145.87, 142.22, 141.82, 141.58, 139.72, 133.91, 132.25, 132.18, 130.81, 129.47, 128.62, 128.33, 122.49 (aromatic and -C=C-); 119.22 (-CH=CH-CO); 59.64 (-OOC-CH-NH₂); 43.36 (C=C-CH₂-CH₂Cl); 39.39 (C=C-CH₂-CH₂Cl); 31.33 ((CH₃)₂-CH-); 18.61 & 18.47 ((CH₃)₂-CH-).
10 m/z: 504 & 506 (M⁺+1).

The compounds of Examples 1-5 were tested using one or more of the following assays.

15 *Determination of DNA adducts induced by antiestrogens in rats.*

Sensitive ³²P postlabeling/PAGE analysis [87] has been used for determination of the level of DNA adducts generated by antiestrogens. As studied previously with
20 TAM [33], three rats were treated orally for 7 days with SS1020 or TOR at a dose molar equivalent to TAM (20 mg/kg/day). Rats receiving corn oil only were used as the control. A high level (~1 adduct/105 nucleotides) of hepatic DNA adducts was observed with TAM while no DNA
25 adducts were detected with SS1020 or TOR (Fig. 3) and the control. Thus, SS1020 may be a compound free of genotoxic effects.

30 *Determination of the uterotrophic potential of antiestrogens*

The uterotrophic potential of SS1020 was determined using ovariectomized (OVX) rats and compared with those of antiestrogens being used clinically or considered for clinical trials. OVX-rats (Sprague-Dawley, 6-week old

females) were treated orally for 3 days with each compound and the uterine wet weight [mg/g body weight (B.W.)] was measured one day after the final treatment. A dose molar equivalent of TAM [10 mg (27 μ mol)/kg/day] suspended in 0.5 ml of corn oil was used for each antiestrogen (4 rats/group). The uterine weight of the untreated OVX-rats was 0.255 mg/gB.W. and the uterine weight of OVX-rats treated subcutaneously with E₂ (0.3 μ g/day for 3 days) was 1.074 mg/gB.W. As shown in Fig. 4, TAM had high uterotrophic activity, showing 54 % of that observed for E₂-treated OVX-rats; even using 0.1 and 1.0 mg/kg TAM, the uterotrophic activities were still 33 % and 34 %, respectively. Surprisingly, 4-OHTAM, recognized as a principal antiestrogenic TAM metabolite, showed uterotrophic activity (45 %) similar to TAM. The uterotrophic potentials of TOR (46 %), idoxifene (47 %) and ospemifene (41 %) were also similar to that of TAM. RAL showed partial estrogenic activity (14 %) similar to that observed with GW5638 (16 %), GW7604 (17 %), or SP500263 (15 %), indicating that these antiestrogens still have weak estrogenic activity. In contrast, the uterotrophic activity of SS1020 was significantly lower than that of RAL, GW5638 or GW7065 (see Fig. 4). SS1020 did not have significant uterotrophic activity, indicating that it lacks estrogenic function.

Histopathological examination of the uterus from rats treated with antiestrogens

Uterine tissue obtained from the uterotrophic assay was fixed in 4% neutral buffered formalin. The tissue was embedded in paraffin, and stained with hematoxylin and eosin. Samples for histopathological examination were taken from the midpoint of each uterine horn. In OVX-rats treated with E₂ (Fig. 5B), the uterine thickness was more

than twice that of the sham (5A) and marked hypertrophy was observed in uterine epithelial cells. The uterine thickness of TAM- or GW5638-treated OVX-rats (5C & 5D) was 1.9 and 1.6 times higher than that of the sham; 5 epithelial hypertrophy was also observed. The uterine histology of OVX-rats treated with SS1020 (5E) was not significantly different from that of the sham-treated rats.

10 *Antitumor effect of antiestrogens to DMBA-induced mammary tumor.*

Following an established protocol [85], mammary carcinoma was successfully induced in rats treated with DMBA (50 mg/kg, p.o.). Rats bearing mammary tumors (5 rats per a 15 dose) were treated orally for 4 weeks with TAM or SS1020 at the equivalent molar dose of TAM (1.0 mg/kg body weight/day). Controls (8 rats) received vehicle only. No significant effect was observed on the growth of rats treated with SS1020. Tumor volume was recorded, using the 20 two perpendicular dimensions and normalized to 100% on the first day of dosing. With SS1020, the tumor volume did not increase, as indicated by statistical analysis (t-test; ***, $p < 0.001$ versus the control) (Fig. 6a); indeed, the tumor size in 3 out of 5 rats was less than 25 10% after 4 weeks. In contrast, using the same molar dose for TAM, RAL or GW5638, tumor growth tended to be inhibited; but no statistical significance was observed versus the control (Fig. 6a). Statistical significance was observed for SS1020 versus TAM, RAL or GW5638 during 30 the entire time period of treatment; for example, at day 28, $p < 0.001$ for SS1020 vs. TAM and RAL, and $p < 0.01$ for SS1020 vs. GW5638. Thus, the antitumor potential of SS1020 was much stronger than those of other antiestrogens (TAM, RAL and GW5638).

At the human-equivalent dose of TAM (0.33 mg/kg body weight/day), the mammary tumors in rats treated with TAM grew rapidly, similar to that observed for the control; tumor size increased approximately 9.5-fold in 4 weeks (Fig. 6b). Strikingly, with SS1020 at the same dose, the tumors had only doubled in size by 11 days and showed no further growth over the next ~3 weeks, as indicated by statistical analysis (**, $p < 0.01$ and ***, $p < 0.001$ versus the control). Thus, SS1020 was strongly effective against rat mammary tumor at the human-equivalent dose of TAM.

Anti-tumor effect of SS1021 to DMBA-induced mammary tumor. With TAM, SS1020, or its phosphate derivative (SS1021) at the human-equivalent dose of TAM (0.33 mg/kg body weight/day), the mammary tumors in rats treated with TAM grew rapidly, similar to that observed for the control; tumor size increased approximately 9.5-fold in 4 weeks (Fig. 7). However, with SS1020, by 11 days the tumors had only doubled in size and showed no further growth over 4 weeks. Surprisingly, SS1021 (phosphate-derivative of SS1020) strongly inhibited tumor growth; the increase in tumor size in 4 weeks was less than 50 %. Therefore, SS1021, a prodrug of SS1020, was more effective against mammary tumor than the parent, SS1020.

Dephosphorylation of SS1021.

SS1021 (100 μ M) was incubated at 37 °C for 1 hr in a buffer including cytosol (0.1 mg protein) of rat intestine. The cleavage of the phosphate group of SS1021 was confirmed using HPLC analysis (Fig. 8B). However, when the cytosol was inactivated by heating before the

incubation with SS1021, the conversion was not observed (Fig. 8A).

Antitumor potential of SS1020 in athymic nude mice bearing ER-positive MCF-7 and ER-negative MDA-MB-231 human breast cancer.

SS1020 was administered orally for 4 weeks to athymic nude mice (5 mice/group) bearing an ER-positive MCF-7 human breast cancer xenograft (Fig. 9a). No significant effect was observed on the growth of mice treated with SS1020. The tumor volume of the untreated mice (control) became approximately 7 times larger in 4 weeks. TAM (10 mg/kg/day) did not significantly inhibit the tumor growth. In contrast, with SS1020 at an equivalent molar dose of TAM, no tumor growth was observed during the period of treatment (t-test; *, $p < 0.05$ and **, $p < 0.01$ vs. the control). Apparently, SS1020 has a much stronger antitumor potential than TAM. Similar antitumor activity was observed against ER-negative MDA-MB-231 human breast cancer xenograft (Fig. 9b). Since MDA-MB-231 expresses caspase-3 functioning in apoptosis while MCF-7 does not, this result may indicate that mechanism(s) other than antiestrogenic action are involved in suppressing the tumor growth.

Similarly, treatment at a lower dose of SS1020 (3 mg/kg vs. 10 mg/kg) also showed inhibition of tumor growth in athymic nude mice bearing ER-positive MCF-7 human breast cancer xenografts (Fig. 13).

Estrogen receptor binding assay for antiestrogens.
The ER α binding potential of SS1020 and other antiestrogens was determined using an established method [57]. The binding curve was fitted using a single binding

site competition model and PRISM® statistical analysis software (Fig. 10). The IC_{50} of 4-OHTAM was similar to that of E_2 and approximately 50 times higher than that of TAM, as reported earlier [65]. The relative binding affinity (RBA) of RAL was 44% of that of E_2 and 16 times higher than that of TAM. Therefore, 4-OHTAM and RAL have strong binding potentials for $ER\alpha$. The RBA of GW5638 was 0.06, relative to that of E_2 . However, the RBAs of the 4-hydroxylated forms (GW7604 and SS1020) were 70 and 60 times, respectively, higher than that of GW5638. This indicates that 4-hydroxylated compounds have at least one or two orders of magnitude higher binding activities to $ER\alpha$, as observed with 4-OHTAM.

15 *Preventive activity of SS1020 against DMBA-induced mammary tumors.*

Rats were treated orally with SS1020 [11 mg (27 μ mol)/kg], RAL [13.7 mg (27 μ mol)/kg], or vehicle (corn oil) 7 days prior to a single oral dose (50 mg/kg) of DMBA and 7 days after the DMBA injection. Tumors in the nonpretreated group were observed at 42.0 ± 5.7 days ($n = 7$) after the DMBA treatment (Fig. 11). Surprisingly, pretreatment of rats with SS1020 significantly delayed the tumor development to 65.8 ± 11.7 days ($p < 0.001$, student's t -test; $n = 5$). One rat did not develop a tumor even after 18 weeks. In contrast, with RAL, the significant delay was not observed [50.4 ± 9.1 days ($n = 5$), $p < 0.08$]. Thus, SS1020, but not RAL, has a delaying effect and possible preventive potency against the mammary tumor.

Preventive activity of SS1020 against hormone-induced mammary tumors

To determine the preventive potential of SS1020 against E2-induced mammary tumor, SS1020 was given to female ACI rats implanted under the skin with an E2 (2.5 mg) pellet and the development of mammary tumors was monitored.

5 SS1020 was dietary given *ad libitum* after implanting the pellet using phytoestrogen-free AIN-76A diet containing 50 ppm SS1020 (approximately equivalent to 3.0 mg/kg/day). Among 7 ACI rats not given SS1020, 3 rats developed a palpable mammary tumor in 13 weeks (Fig. 15).

10 In contrast, no tumors were observed in ACI rats given SS1020. Therefore, SS1020 has preventive effect against hormone-induced mammary tumors, indicating that this compound can be used as a safer prophylactic agent for women at high risk of developing breast cancer.

15

Effect of SS1020 pretreatment on the formation of mammary DMBA-DNA adducts.

Rats (3 rats) were treated orally with SS1020 [3.3 mg (8.1 μ mol)/kg], α -NF [73 mg (270 μ mol)/kg], or vehicle

20 (corn oil) 7 days prior to a single oral dose (50 mg/kg) of DMBA. The level of mammary DMBA-DNA adduct was determined using ^{32} P-postlabeling/PAGE analysis. The level of DMBA-DNA adduct in the control rats was 1.0 ± 0.32 adducts/ 10^8 nucleotides (Fig. 12). Pretreatment of rats

25 with SS1020 significantly reduced the formation of DMBA-DNA adducts by 41% ($p < 0.05$, *t*-test). Although α -NF also suppressed adduct formation, by 65%, the molar dose of SS1020 (8.1 μ mol/kg) used was 33 times lower than that of α -NF (270 μ mol/kg). Thus, a low dose of SS1020 is able to

30 reduce the formation of mammary DMBA-DNA adduct, predicting that this compound has preventive potency against breast cancer.

Determination of osteoporotic potential of antiestrogens.

To determine the osteoporotic potential of SS1020, OVX-rats (5 rats/group) were treated orally for 4 weeks with SS1020 at a dose equivalent to 10 mg/kg/day TAM. Bone mineral density (BMD) was measured using an X-ray bone densitometer (Model pDEXA, Norland Medical Systems Inc.). As compared with the sham rats, OVX-rats treated with vehicle lost approximately 10% of BMD in the femur, lumbar and whole body (Table 1), as reported previously [105]. The BMD of OVX-rats treated subcutaneously with E₂ (1.2 µg/kg/day) was similar to that of the sham-treated rats. The BMD of TAM-treated OVX-rats tended to decrease while the BMD of SS1020-treated OVX-rats was not significantly different from that of the sham. The results indicate that SS1020 may have higher anti-osteoporotic potential than TAM.

Table 1. Effect of TAM and SS1020 on the bone mineral density in OVX-rats

Compound	Whole body	Femur (g/cm ²)	Lumbar
Sham	0.133 ± 0.002 (100 %)	0.149 ± 0.003 (100 %)	0.145 ± 0.007 (100 %)
OVX	0.119 ± 0.004 (89.5 %)	0.133 ± 0.001 (89.3 %)	0.132 ± 0.003 (91.0 %)
E ₂	0.139 ± 0.006 (104 %)	0.153 ± 0.009 (102 %)	0.150 ± 0.010 (103 %)
TAM	0.126 ± 0.002 (94.7 %)	0.139 ± 0.007 (93.3 %)	0.136 ± 0.005 (93.8 %)
SS1020	0.129 ± 0.006 (97.0 %)	0.140 ± 0.010 (94.0 %)	0.143 ± 0.010 (98.6 %)

Bioavailability of SS1020 and RAL in rats

Rats were treated with a single dose of SS1020 or RAL at the equivalent molar dose of RAL (10 mg/kg, p.o.). Controls received corn oil only. Rats were euthanized by

CO₂ asphyxiation and blood was collected 1, 2, 4, 6, 8, 10, and 16 h after the treatment. The serum was incubated with β -glucuronidase/sulfatase in a buffer, extracted by methanol, and evaporated to dryness. Analysis of SS1020
5 and RAL was performed using HPLC/UV and LC/MS/MS, respectively.

The serum concentration of SS1020 was much higher than that observed with RAL (Fig. 14). The area under curve of
10 SS1020 was 32 times higher than that of RAL. Apparently, SS1020 has higher bioavailability than RAL.

As shown in the foregoing results, the compounds and compositions of the invention are useful for preventing
15 and/or inhibiting the proliferation of tumors, particularly estrogen-induced tumors, as well as tumors expressing ER. Furthermore, the compounds and compositions of the invention are also useful for the treatment of osteoporosis. The compounds and compositions
20 of the invention may also prove to be useful for the prevention and/or treatment of other cancers, such as prostate cancer.

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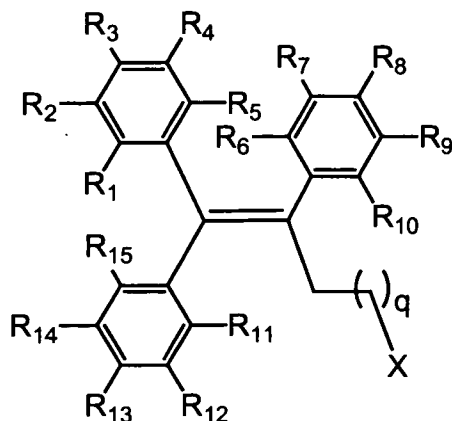
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Claims

What is claimed is:

1. A compound having the structure

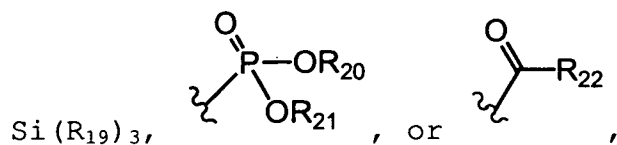


wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

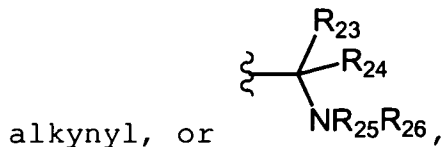
R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

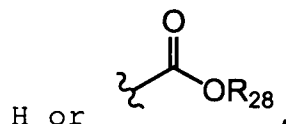
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



wherein R_{23} and R_{24} are each, independently, H, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, $-(CH_2)_{1-4}-R_{27}$,

wherein R_{27} is $-CO_2H$, $-CONH_2$, $-NH_2$, $-SH$, $-SCH_3$, $-OH$, aryl, or heteroaryl; and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_3 is Br, I, $-(CR_{29}R_{30})_2-R_{31}$, $-CR_{29}=CR_{30}-R_{31}$, $-C\equiv C-R_{31}$, $-OSO_2H$, $-OSO_2R_{31}$,

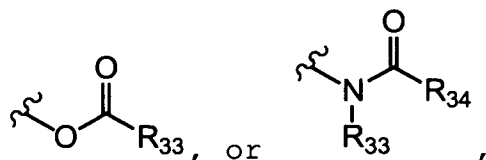
wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-CO_2R_{32}$, or $-(CH_2)_{1-6}-CO_2R_{32}$,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

$\bar{X}$ is halogen, $-CN$, $-NO_2$, $-OR_{33}$, $-SR_{33}$, $-OSO_2R_{33}$, $-NR_{33}R_{34}$,

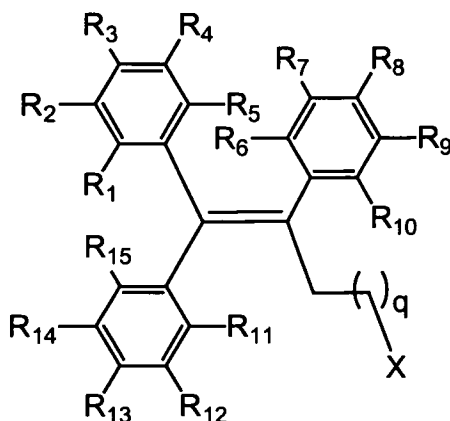


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

2. The compound of claim 1 having the structure

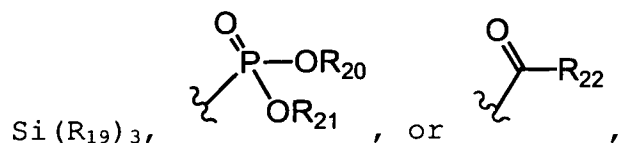


wherein

$R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14},$ and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

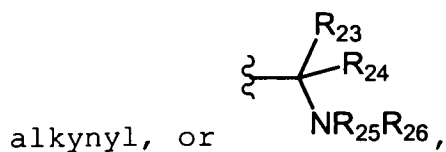
R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

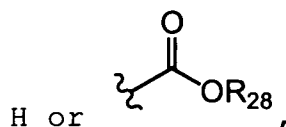
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -
(CH₂)₁₋₄-R₂₇,

wherein R_{27} is $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{NH}_2$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OH}$, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

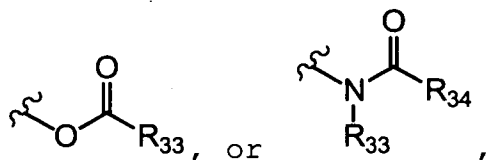
R_3 is Br, I, $-\text{OSO}_2\text{H}$, or $-\text{OSO}_2\text{R}_{31}$,

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2\text{R}_{32}$, or $-(\text{CH}_2)_{1-6}-\text{CO}_2\text{R}_{32}$,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,

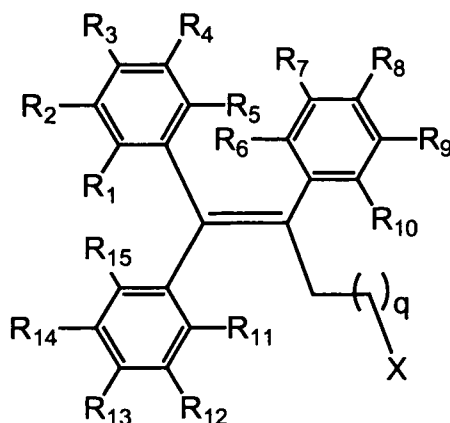


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

3. The compound of claim 1 having the structure

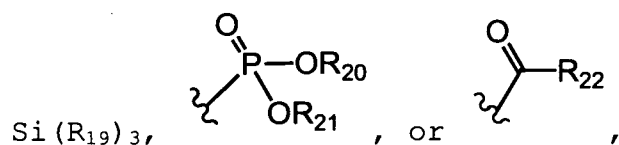


wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

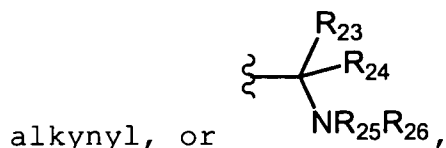
R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

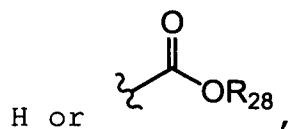
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, - (CH₂)₁₋₄-R₂₇,

wherein R_{27} is -CO₂H, -CONH₂, -NH₂, -SH, -SCH₃, -OH, aryl, or heteroaryl; and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_3 is $-(\text{CR}_{29}\text{R}_{30})_2-\text{R}_{31}$, $-\text{CR}_{29}=\text{CR}_{30}-\text{R}_{31}$, or $-\text{C}\equiv\text{C}-\text{R}_{31}$,

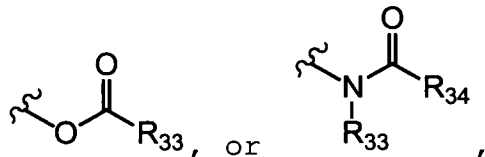
wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2\text{R}_{32}$, or $-(\text{CH}_2)_{1-6}-\text{CO}_2\text{R}_{32}$,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,

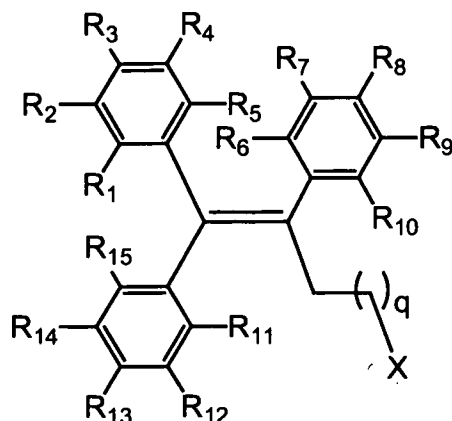


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

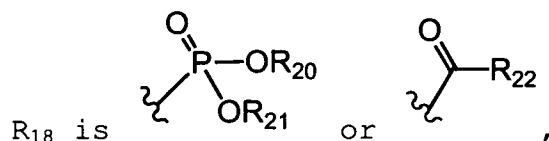
4. The compound of claim 3 having the structure



wherein

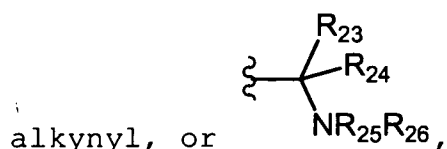
R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;



wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

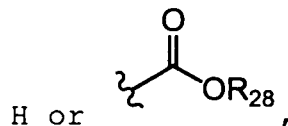
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, - (CH₂)₁₋₄-R₂₇,

wherein R_{27} is -CO₂H, -CONH₂, -NH₂, -SH, -SCH₃, -OH, aryl, or heteroaryl; and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_3 is $-(CR_{29}R_{30})_2-R_{31}$, $-CR_{29}=CR_{30}-R_{31}$, or $-C\equiv C-R_{31}$,

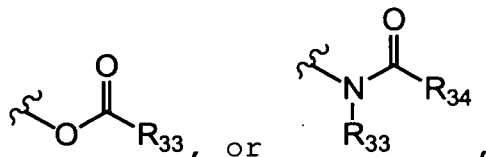
wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-\text{CO}_2R_{32}$, or $-(\text{CH}_2)_{1-6}-\text{CO}_2R_{32}$,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2R_{33}$, $-\text{NR}_{33}R_{34}$,

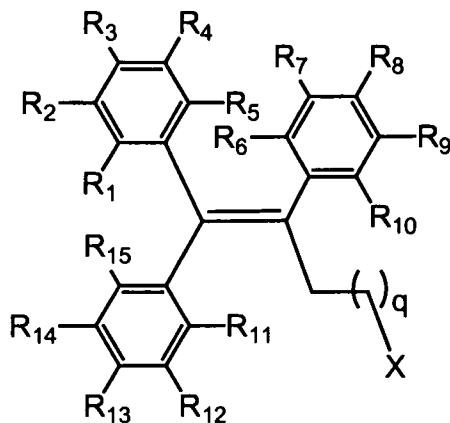


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

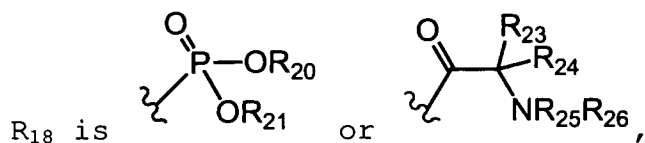
5. The compound of claim 4 having the structure



wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

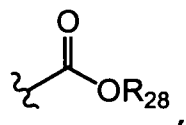


wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -(CH₂)₁₋₄-R₂₇,

wherein R_{27} is -CO₂H, -CONH₂, -NH₂, -SH, -SCH₃, -OH, aryl, or heteroaryl; and

wherein R_{25} and R_{26} are each, independently, H or



wherein R_{28} is C₁₋₁₀ alkyl or C₂₋₁₀ alkenyl;

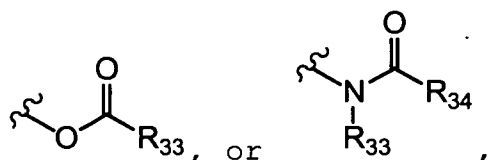
R_3 is -(CR₂₉R₃₀)₂-R₃₁, -CR₂₉=CR₃₀-R₃₁, or -C≡C-R₃₁,

wherein R_{29} and R_{30} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and
 wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, heterocyclyl, $-CO_2R_{32}$, or $-(CH_2)_{1-6}-CO_2R_{32}$,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

X is halogen, $-CN$, $-NO_2$, $-OR_{33}$, $-SR_{33}$, $-OSO_2R_{33}$, $-NR_{33}R_{34}$,

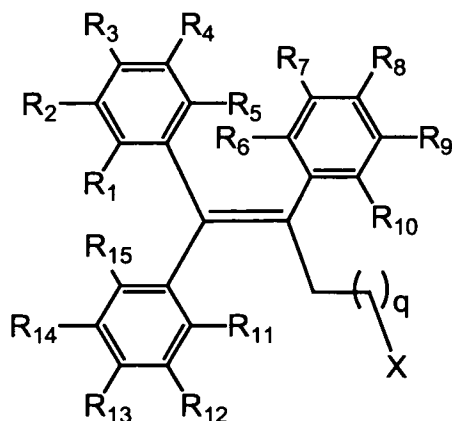


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

6. The compound of claim 3 having the structure



wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, $-CN$, $-NO_2$, C_{1-10}

alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R₁₆ and R₁₇ are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

R₁₈ is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, or Si(R₁₉)₃,

wherein each occurrence of R₁₉ is, independently, H, C₁₋₄ alkyl, or aryl;

R₃ is -(CR₂₉R₃₀)₂-R₃₁, -CR₂₉=CR₃₀-R₃₁, or -C≡C-R₃₁,

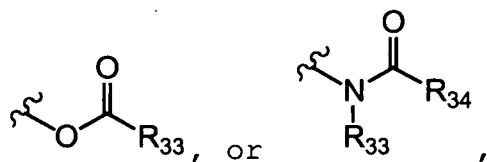
wherein R₂₉ and R₃₀ are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

wherein R₃₁ is C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, aryl, heteroaryl, heterocyclyl, -CO₂R₃₂, or -(CH₂)₁₋₆-CO₂R₃₂,

wherein R₃₂ is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

q is an integer from 1 to 5;

X is halogen, -CN, -NO₂, -OR₃₃, -SR₃₃, -OSO₂R₃₃, -NR₃₃R₃₄,

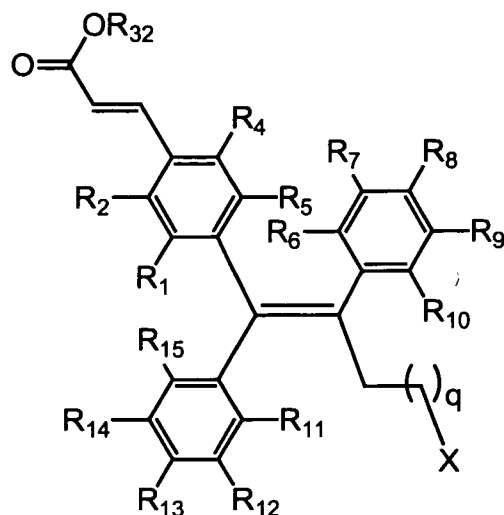


wherein R₃₃ and R₃₄ are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

7. The compound of claim 3 having the structure

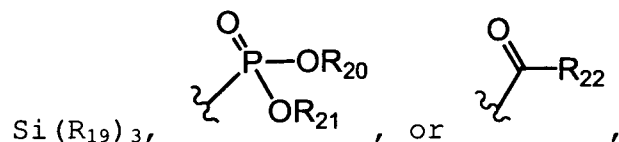


wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

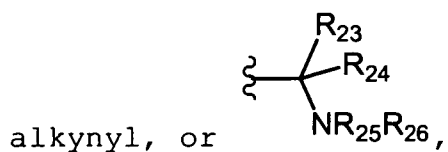
R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

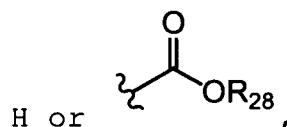
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, - (CH₂)₁₋₄-R₂₇,

wherein R_{27} is $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{NH}_2$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OH}$, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,

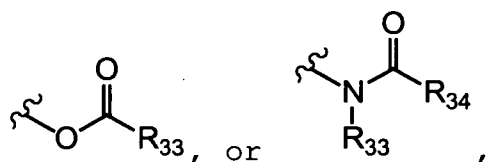


wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

X is halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,



wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

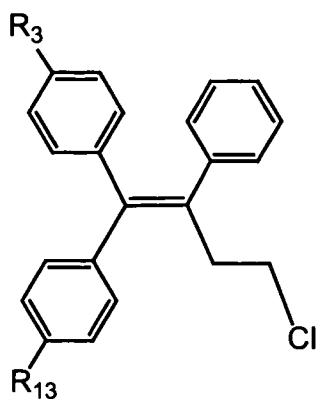
wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

or a salt thereof.

8. The compound of any one of claims 1-7 wherein X is halogen or OR_{33} , or a salt thereof.

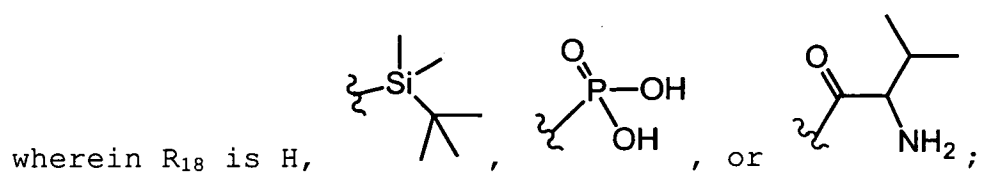
9. The compound of claim 8 wherein X is halogen, or a salt thereof.

10. The compound of claim 1 having the structure



wherein

R_{13} is H or $-OR_{18}$,

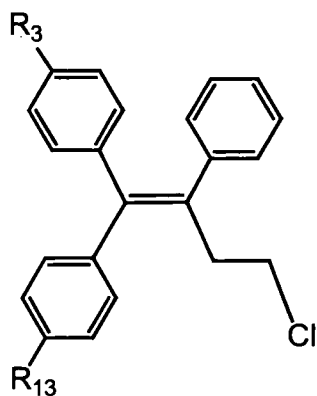


R_3 is Br, $-\text{CH}=\text{CH}-\text{CO}_2R_{32}$, or $-\text{OSO}_2\text{CF}_3$,

wherein R_{32} is H or t-butyl,

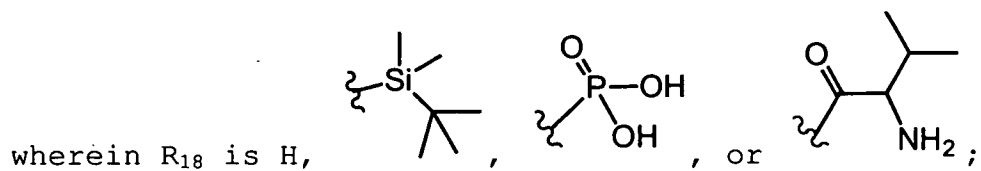
or a salt thereof.

11. The compound of claim 10 having the structure



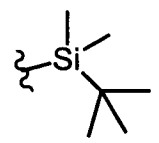
wherein

R_{13} is H or $-OR_{18}$,

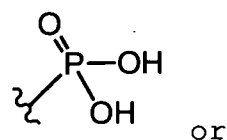


R_3 is $-\text{CH}=\text{CH}-\text{CO}_2R_{32}$,
 wherein R_{32} is H or t-butyl,
 or a salt thereof.

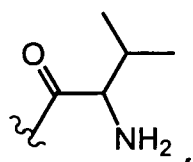
12. The compound of claim 11 wherein R_{18} is H or
 or a salt thereof.



13. The compound of claim 11 wherein R_{18} is

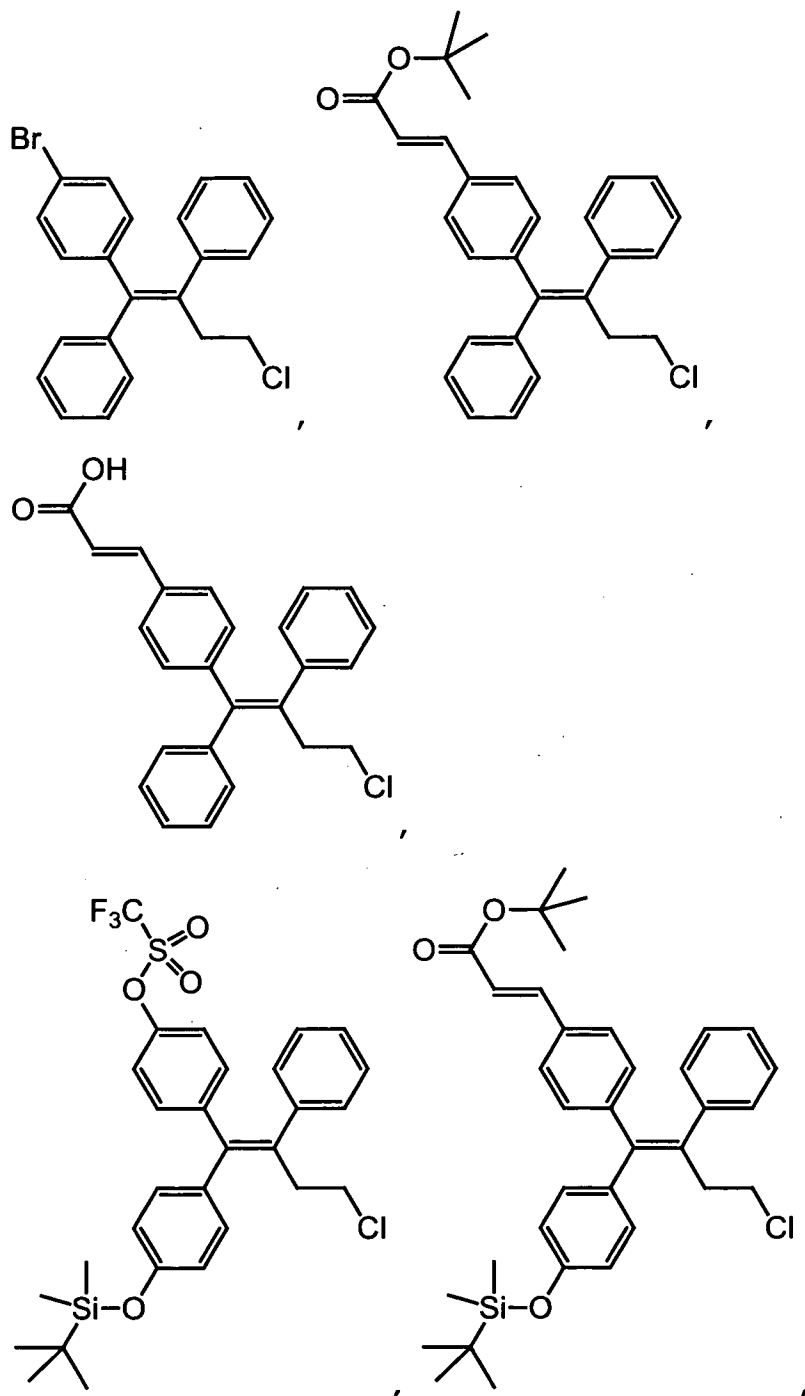


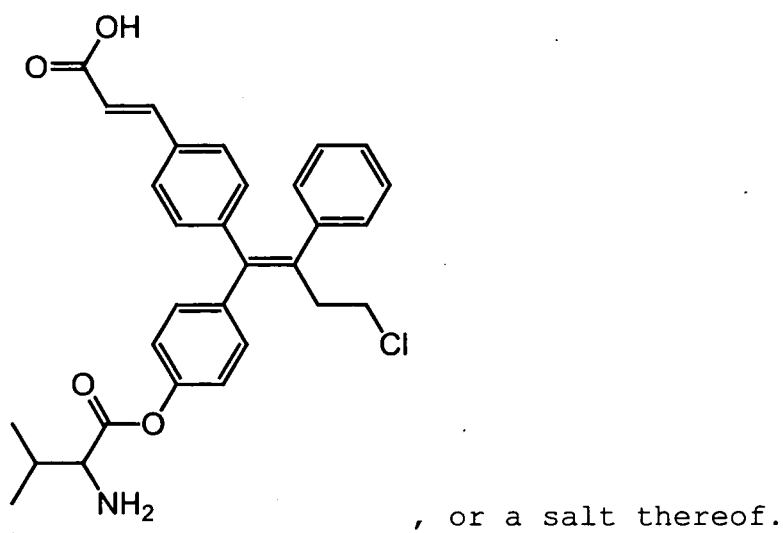
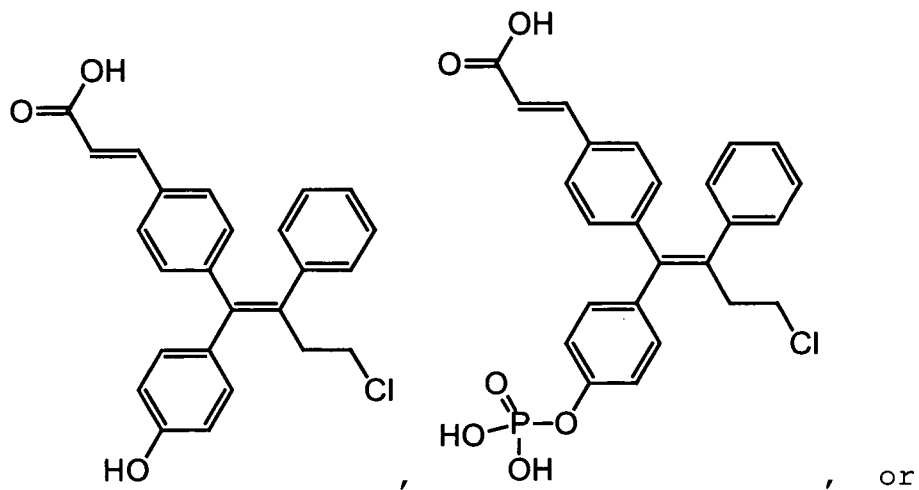
or



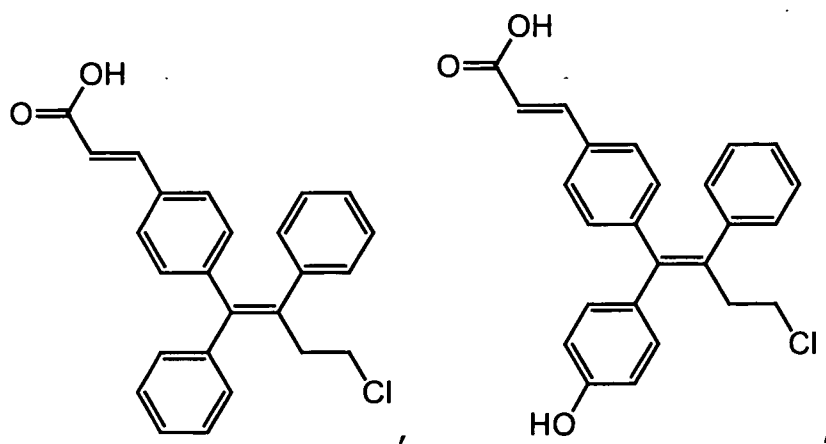
or a salt thereof.

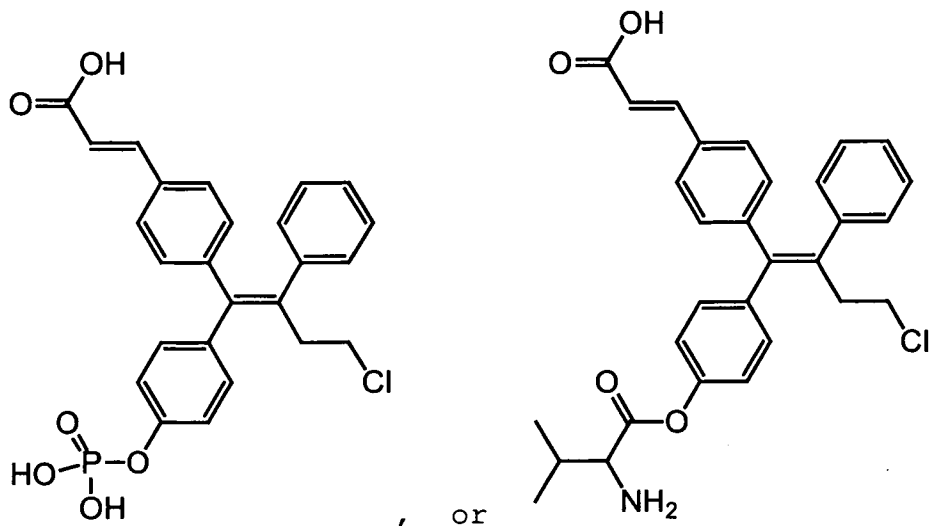
14. The compound of claim 1 having the structure





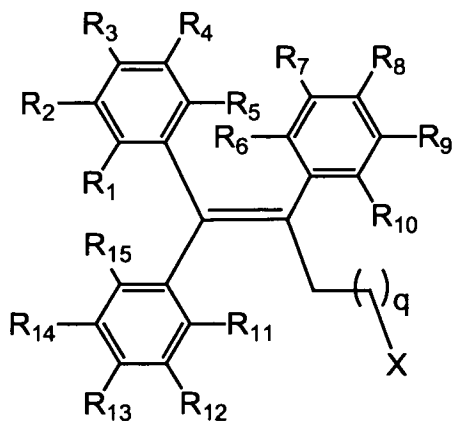
15. The compound of claim 14 having the structure





or a salt thereof.

16. A process for preparing a compound having the structure

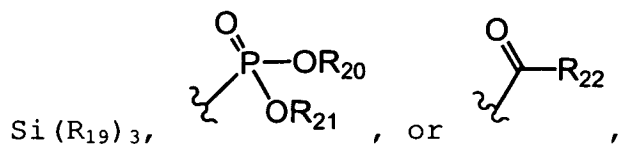


wherein

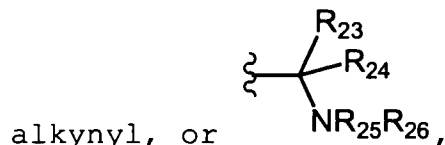
R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



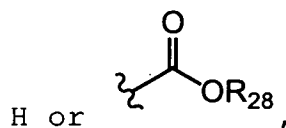
wherein each occurrence of R_{19} is, independently, H, C_{1-4} alkyl, or aryl; and
 wherein R_{20} and R_{21} are each, independently, H, C_{1-5} alkyl, C_{2-5} alkenyl, or C_{2-5} alkynyl; and
 wherein R_{22} is H, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5}



wherein R_{23} and R_{24} are each, independently, H, C_{1-5} alkyl, C_{2-5} alkenyl, C_{2-5} alkynyl, -
 $(CH_2)_{1-4}-R_{27}$,

wherein R_{27} is $-CO_2H$, $-CONH_2$, $-NH_2$, -
 SH , $-SCH_3$, $-OH$, aryl, or heteroaryl;
 and

wherein R_{25} and R_{26} are each, independently,



wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_3 is Br, I, $-(CR_{29}R_{30})_2-R_{31}$, $-CR_{29}=CR_{30}-R_{31}$, $-C\equiv C-R_{31}$, $-OSO_2H$,
 $-OSO_2R_{31}$,

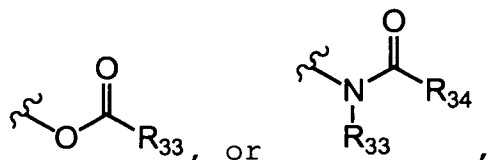
wherein R_{29} and R_{30} are each, independently, H, C_{1-10}
 alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl,
 aryl, heteroaryl, heterocyclyl, $-CO_2R_{32}$, or $-(CH_2)_{1-6}-$
 CO_2R_{32} ,

wherein R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or
 C_{2-10} alkynyl; and

q is an integer from 1 to 5;

X is H, halogen, -CN, -NO₂, -OR₃₃, -SR₃₃, -OSO₂R₃₃, -NR₃₃R₃₄,

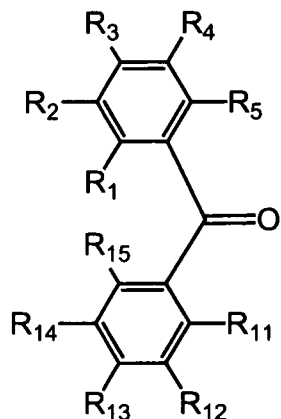


wherein R₃₃ and R₃₄ are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

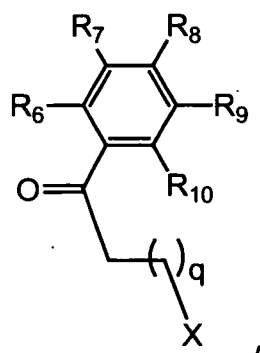
wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

comprising:

contacting a compound having the structure



with a compound having the structure



wherein

R₁, R₂, R₄, R₅, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₃, R₁₄, and R₁₅ are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

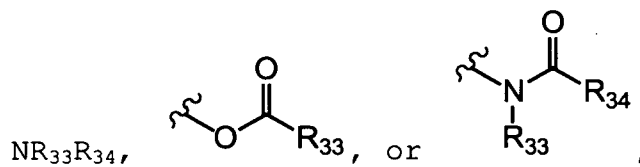
wherein R_{16} and R_{17} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;
 R_{18} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or $Si(R_{19})_3$,

wherein each occurrence of R_{19} is, independently, H, C_{1-4} alkyl, or aryl;

R_3 is Br, I, $-OSO_2H$, or $-OSO_2R_{31}$,
 wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, or heterocyclyl; and

q is an integer from 1 to 5;

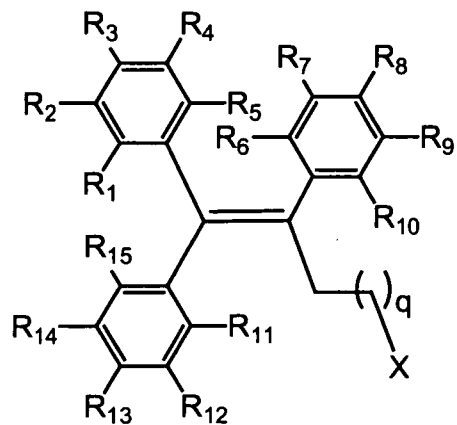
X is H, halogen, $-CN$, $-NO_2$, $-OR_{33}$, $-SR_{33}$, $-OSO_2R_{33}$, -



wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

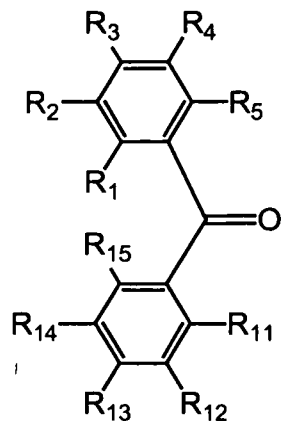
wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

in the presence of a titanium reagent and a reducing agent so as to form a product having the structure

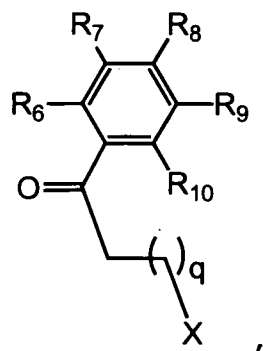


so as to thereby prepare the compound.

17. The process of claim 16 comprising:
contacting a compound having the structure



with a compound having the structure



wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} ,
and R_{15} are each, independently, H, halogen, -CN, -
 NO_2 , C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-\text{CO}_2\text{R}_{16}$, -
 $\text{CONR}_{16}\text{R}_{17}$, $-\text{SR}_{16}$, $-\text{NR}_{16}\text{R}_{17}$, $-\text{SO}_2\text{R}_{16}$, or $-\text{OR}_{18}$,

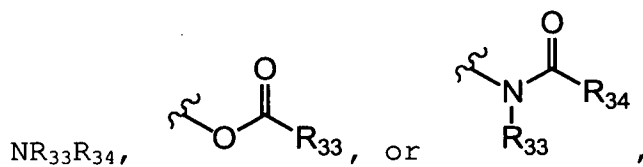
wherein R_{16} and R_{17} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;
 R_{18} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or $Si(R_{19})_3$,

wherein each occurrence of R_{19} is, independently, H, C_{1-4} alkyl, or aryl;

R_3 is Br, I, $-OSO_2H$, or $-OSO_2R_{31}$,
 wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, or heterocyclyl; and

q is an integer from 1 to 5;

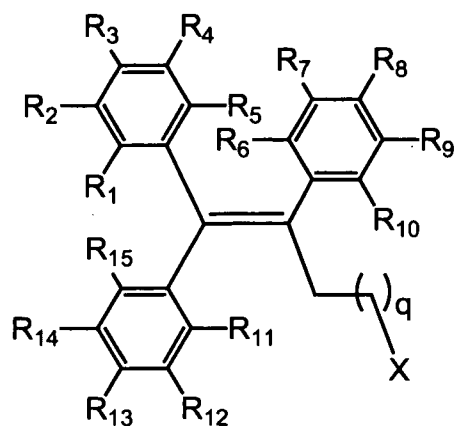
X is halogen, $-CN$, $-NO_2$, $-OR_{33}$, $-SR_{33}$, $-OSO_2R_{33}$, -



wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

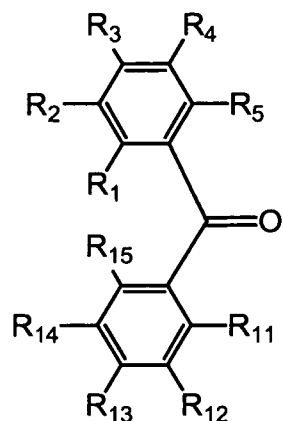
wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

in the presence of a titanium reagent and a reducing agent so as to form a product having the structure

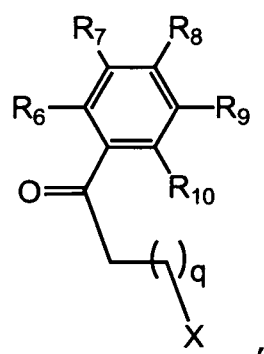


so as to thereby prepare the compound.

18. The process of claim 16 comprising:
contacting a compound having the structure



with a compound having the structure



wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} ,
and R_{15} are each, independently, H, halogen, -CN, -
 NO_2 , C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, $-\text{CO}_2\text{R}_{16}$, -
 $\text{CONR}_{16}\text{R}_{17}$, $-\text{SR}_{16}$, $-\text{NR}_{16}\text{R}_{17}$, $-\text{SO}_2\text{R}_{16}$, or $-\text{OR}_{18}$,

wherein R_{16} and R_{17} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl;
 R_{18} is H, C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, or $Si(R_{19})_3$,

wherein each occurrence of R_{19} is, independently, H, C_{1-4} alkyl, or aryl;

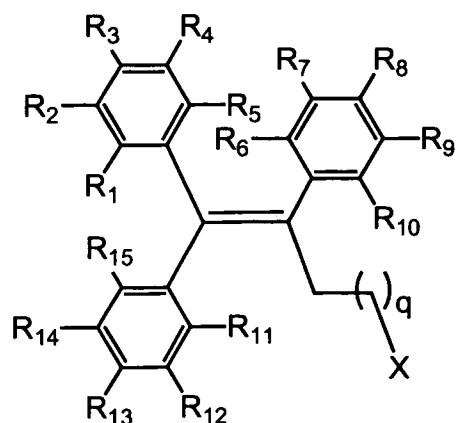
R_3 is Br, I, $-OSO_2H$, or $-OSO_2R_{31}$,
 wherein R_{31} is C_{1-10} alkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, aryl, heteroaryl, or heterocyclyl; and

q is an integer from 1 to 5;

X is H; and

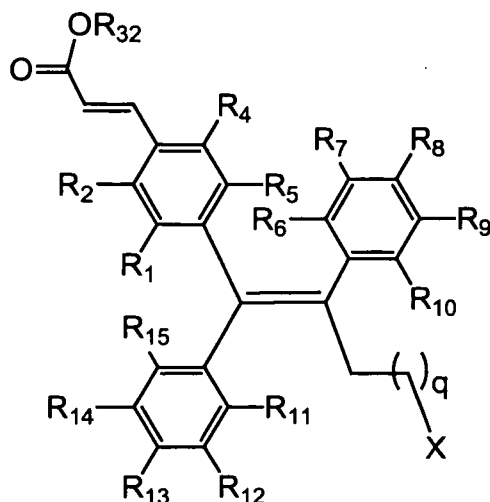
wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

in the presence of a titanium reagent and a reducing agent so as to form a product having the structure



so as to thereby prepare the compound.

19. A process of preparing a compound having the structure

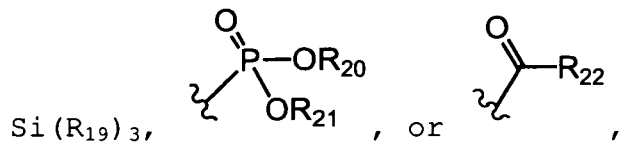


wherein

R_1 , R_2 , R_4 , R_5 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

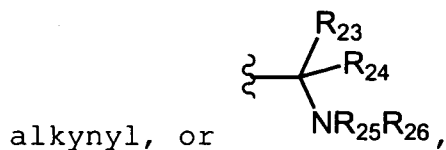
R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl,



wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl; and

wherein R_{20} and R_{21} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, or C₂₋₅ alkynyl; and

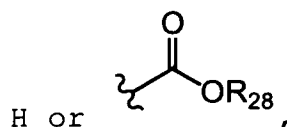
wherein R_{22} is H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅



wherein R_{23} and R_{24} are each, independently, H, C₁₋₅ alkyl, C₂₋₅ alkenyl, C₂₋₅ alkynyl, -
(CH₂)₁₋₄-R₂₇,

wherein R_{27} is $-\text{CO}_2\text{H}$, $-\text{CONH}_2$, $-\text{NH}_2$, $-\text{SH}$, $-\text{SCH}_3$, $-\text{OH}$, aryl, or heteroaryl;
and

wherein R_{25} and R_{26} are each, independently,

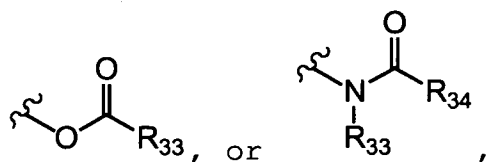


wherein R_{28} is C_{1-10} alkyl or C_{2-10} alkenyl;

R_{32} is H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

q is an integer from 1 to 5;

X is H, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}_{33}$, $-\text{SR}_{33}$, $-\text{OSO}_2\text{R}_{33}$, $-\text{NR}_{33}\text{R}_{34}$,

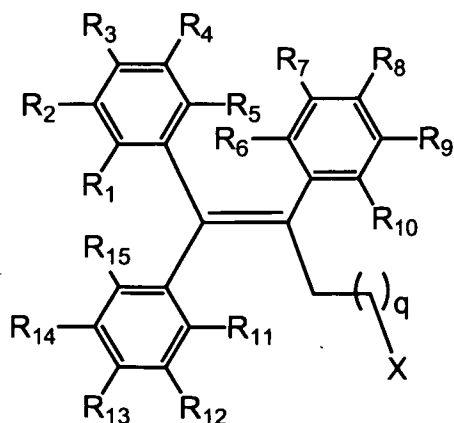


wherein R_{33} and R_{34} are each, independently, H, C_{1-10} alkyl, C_{2-10} alkenyl, or C_{2-10} alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

comprising:

contacting a compound having the structure



wherein

$R_1, R_2, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}$, and R_{15} are each, independently, H, halogen, -CN, -NO₂, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, -CO₂R₁₆, -CONR₁₆R₁₇, -SR₁₆, -NR₁₆R₁₇, -SO₂R₁₆, or -OR₁₈,

wherein R_{16} and R_{17} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl;

R_{18} is H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, or Si(R₁₉)₃,

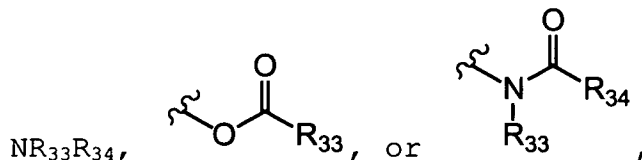
wherein each occurrence of R_{19} is, independently, H, C₁₋₄ alkyl, or aryl;

R_3 is Br, I, or -OSO₂R₃₁,

wherein R_{31} is C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, C₂₋₁₀ alkynyl, aryl, heteroaryl, or heterocyclyl; and

q is an integer from 1 to 5;

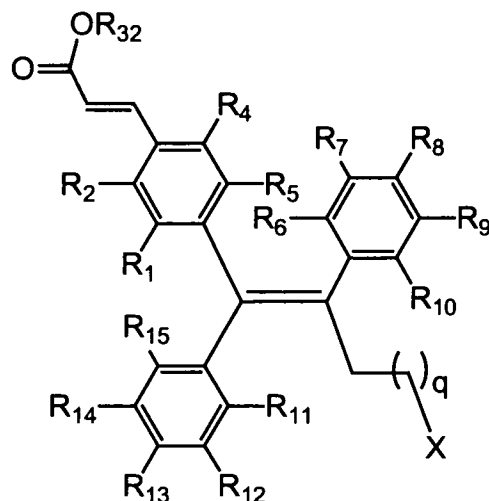
X is H, halogen, -CN, -NO₂, -OR₃₃, -SR₃₃, -OSO₂R₃₃, -



wherein R_{33} and R_{34} are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl; and

wherein each occurrence of alkyl, alkenyl, and alkynyl is substituted or unsubstituted, branched or unbranched;

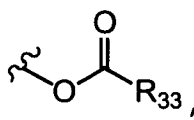
with CH₂=CH₂-CO₂R₃₂, wherein R_{32} is C₁₋₁₀ alkyl, in the presence of a palladium catalyst so as to form a product having the structure

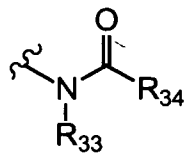


so as to thereby prepare the compound.

20. The process of claim 19 wherein X is H.

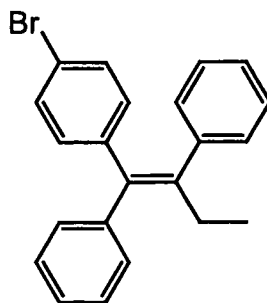
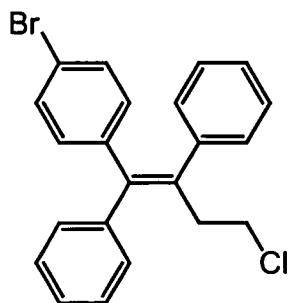
21. The process of claim 19 wherein X is halogen, -CN, -

NO₂, -OR₃₃, -SR₃₃, -OSO₂R₃₃, -NR₃₃R₃₄, , or

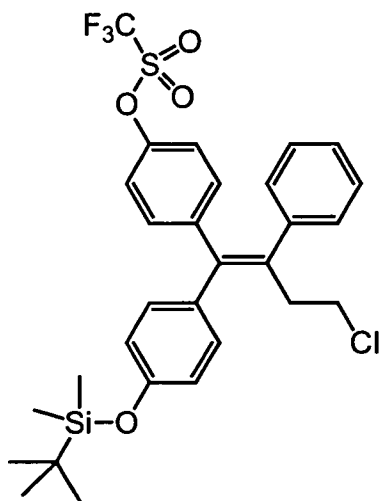


wherein R₃₃ and R₃₄ are each, independently, H, C₁₋₁₀ alkyl, C₂₋₁₀ alkenyl, or C₂₋₁₀ alkynyl.

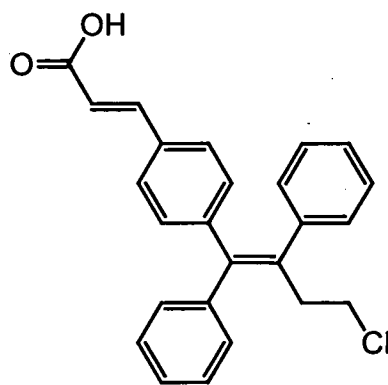
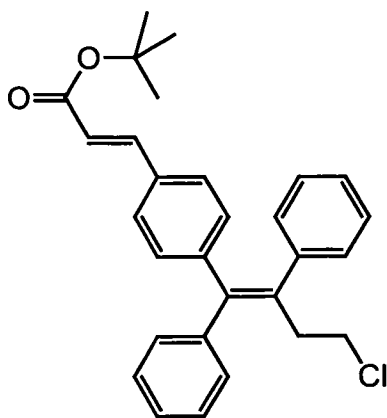
22. The process of claim 16 wherein the compound prepared has the structure

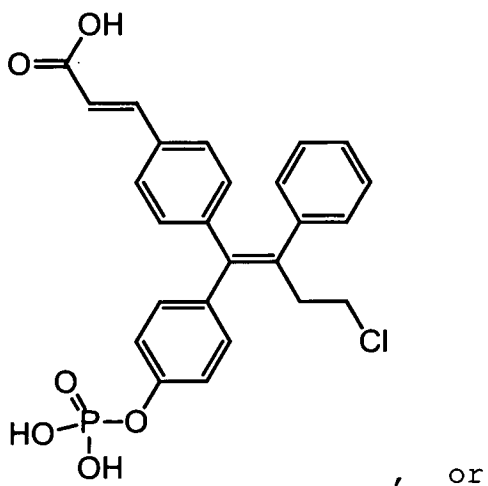
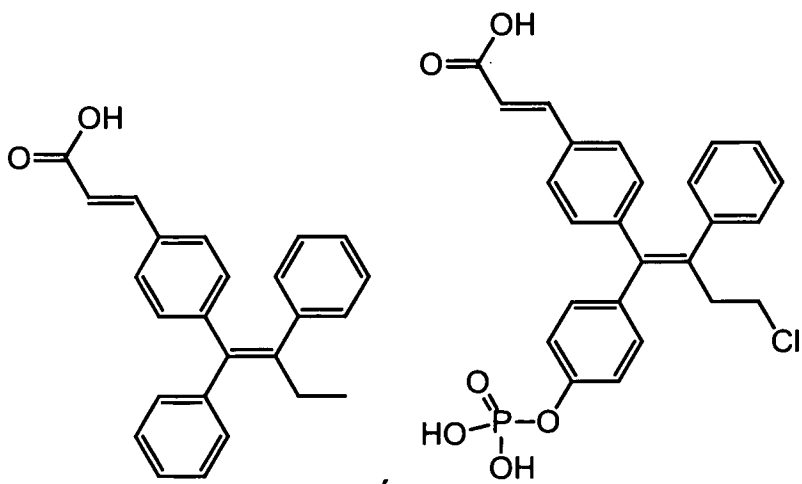
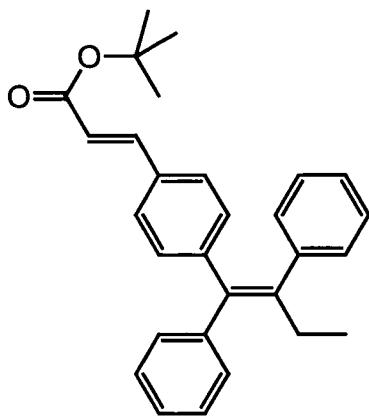
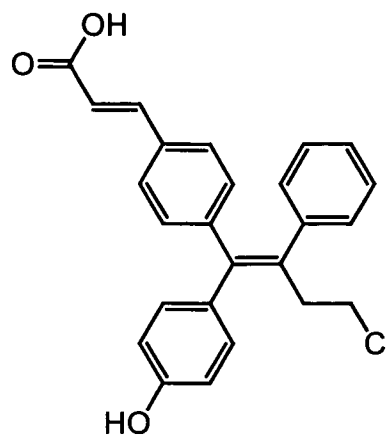
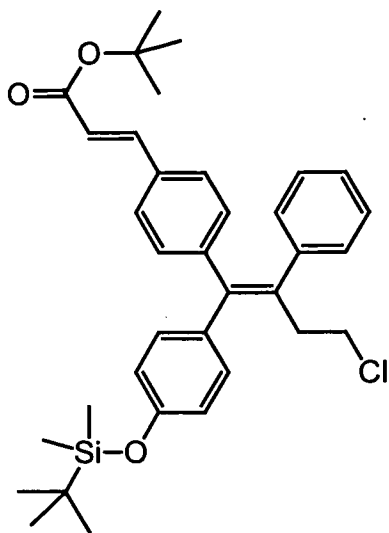


or

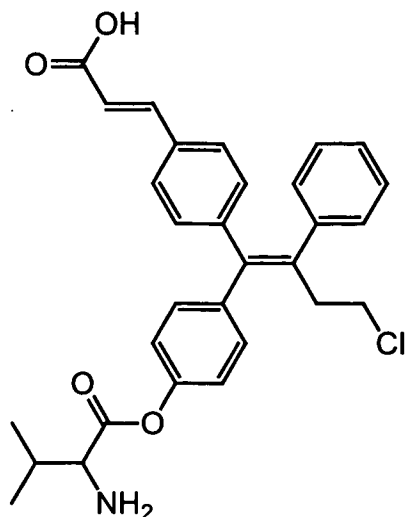


23. The process of claim 19 wherein the compound prepared has the structure





, or



24. A pharmaceutical composition comprising a compound of any one of claims 1-15, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

25. A method of inhibiting tumor proliferation in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-15, or a salt thereof, so as to inhibit tumor proliferation.

26. The method of claim 25 wherein the tumor is an estrogen-induced tumor.

27. The method of claim 25 or 26 wherein the tumor is an ER-positive tumor.

28. The method of claim 25 or 26 wherein the tumor is an ER-negative tumor.

29. A method of inhibiting and/or reducing the loss of bone mineral density in a mammal comprising administering to the mammal a therapeutically effective amount of a

compound of any one of claims 1-15, or a salt thereof, so as to inhibit and/or reduce loss of bone mineral density.

30. A method of delaying tumor formation in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-15, or a salt thereof, so as to delay tumor formation.

31. A method of prophylaxis against tumor formation in a mammal comprising administering to the mammal a therapeutically effective amount of a compound of any one of claims 1-15, or a salt thereof, so as to provide prophylaxis against tumor formation.

32. The compound of any one of claims 1-15 for use in inhibiting tumor proliferation in a mammal.

33. The compound of any one of claims 1-15 for use in inhibiting and/or reducing the loss of bone mineral density in a mammal.

34. The compound of any one of claims 1-15 for use in delaying tumor formation in a mammal.

35. The compound of any one of claims 1-15 for use in prophylaxis against tumor formation in a mammal.

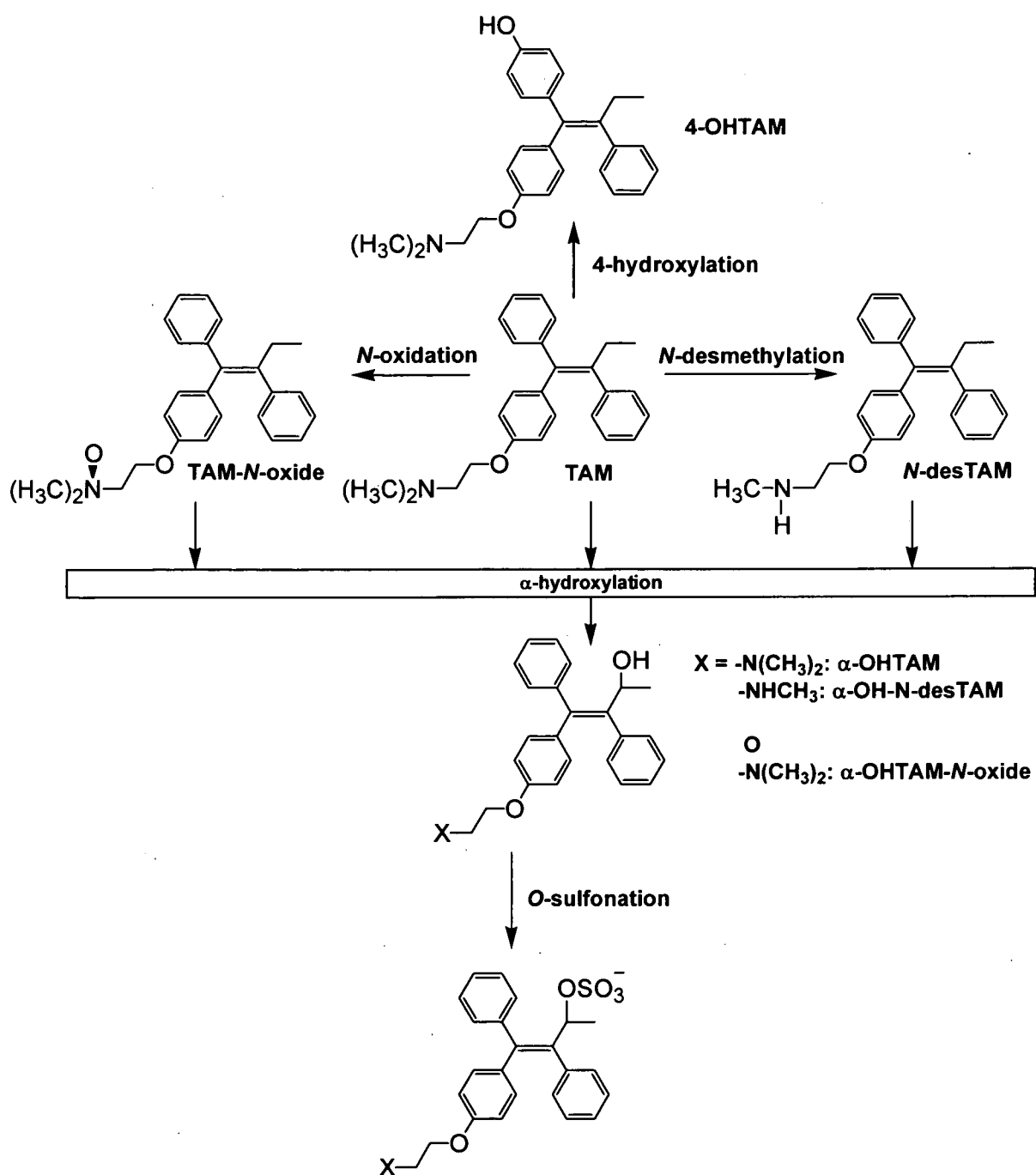


Figure 1a.

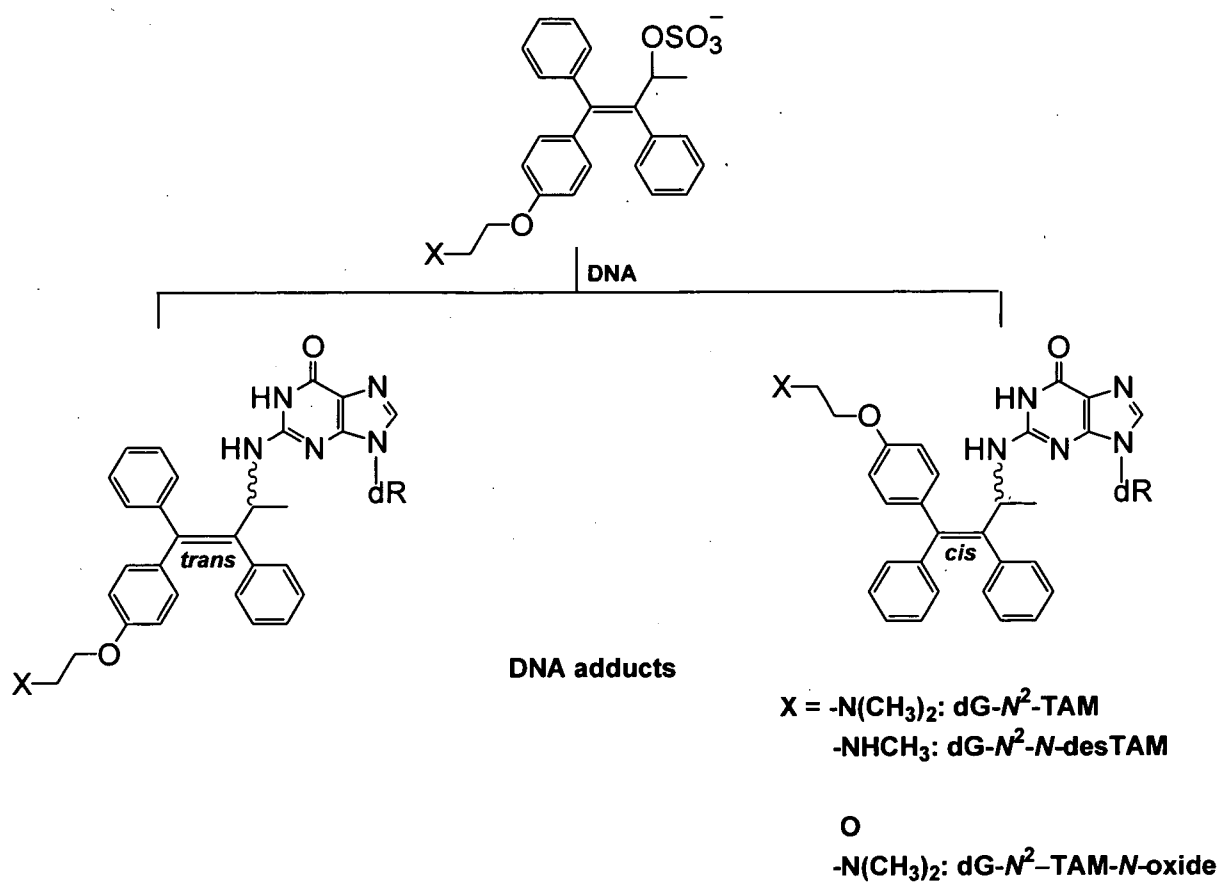
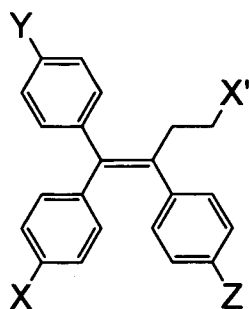


Figure 1b.



TAM:	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = H	X' = H	Z = H
4-OHTAM:	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = OH	X' = H	Z = H
TOR:	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = H	X' = Cl	Z = H
4-OHTOR:	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = OH	X' = Cl	Z = H
GW 5638	X = CH=CHCOOH	Y = H	X' = H	Z = H
GW7604:	X = CH=CHCOOH	Y = OH	X' = H	Z = H
Idoxifene:	X = OCH ₂ CH ₂ N(CH ₂) ₄	Y = I	X' = H	Z = H
Ospemifene:	X = OCH ₂ CH ₂ OH	Y = H	X' = Cl	Z = H
TAT-59 :	X = OCH ₂ CH ₂ N(CH ₃) ₂	Y = OPO ₃ H ₂	X' = H	Z = CH(CH ₃) ₂

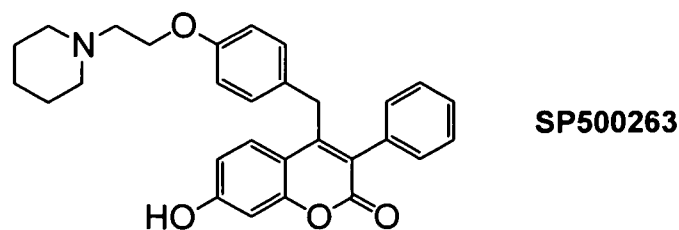
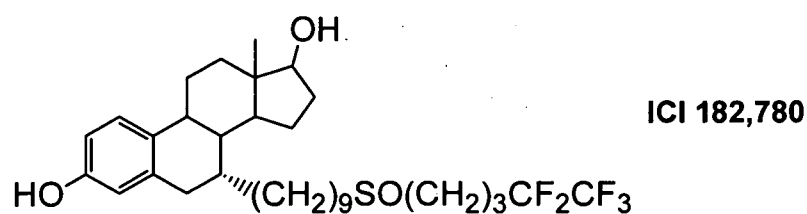
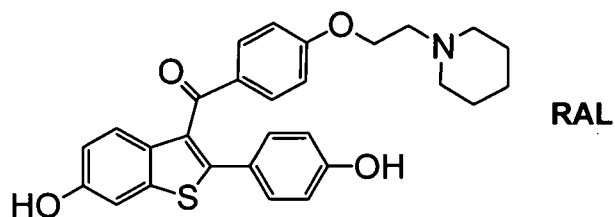


Figure 2.

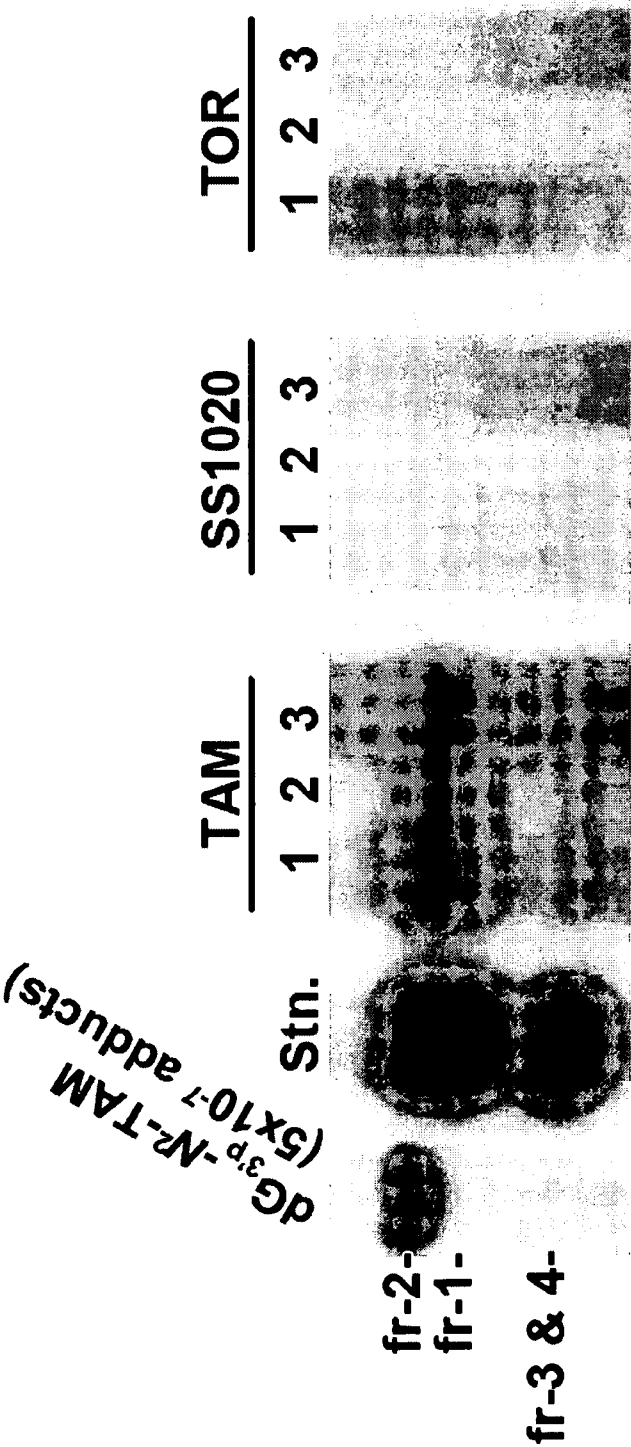


Figure 3.

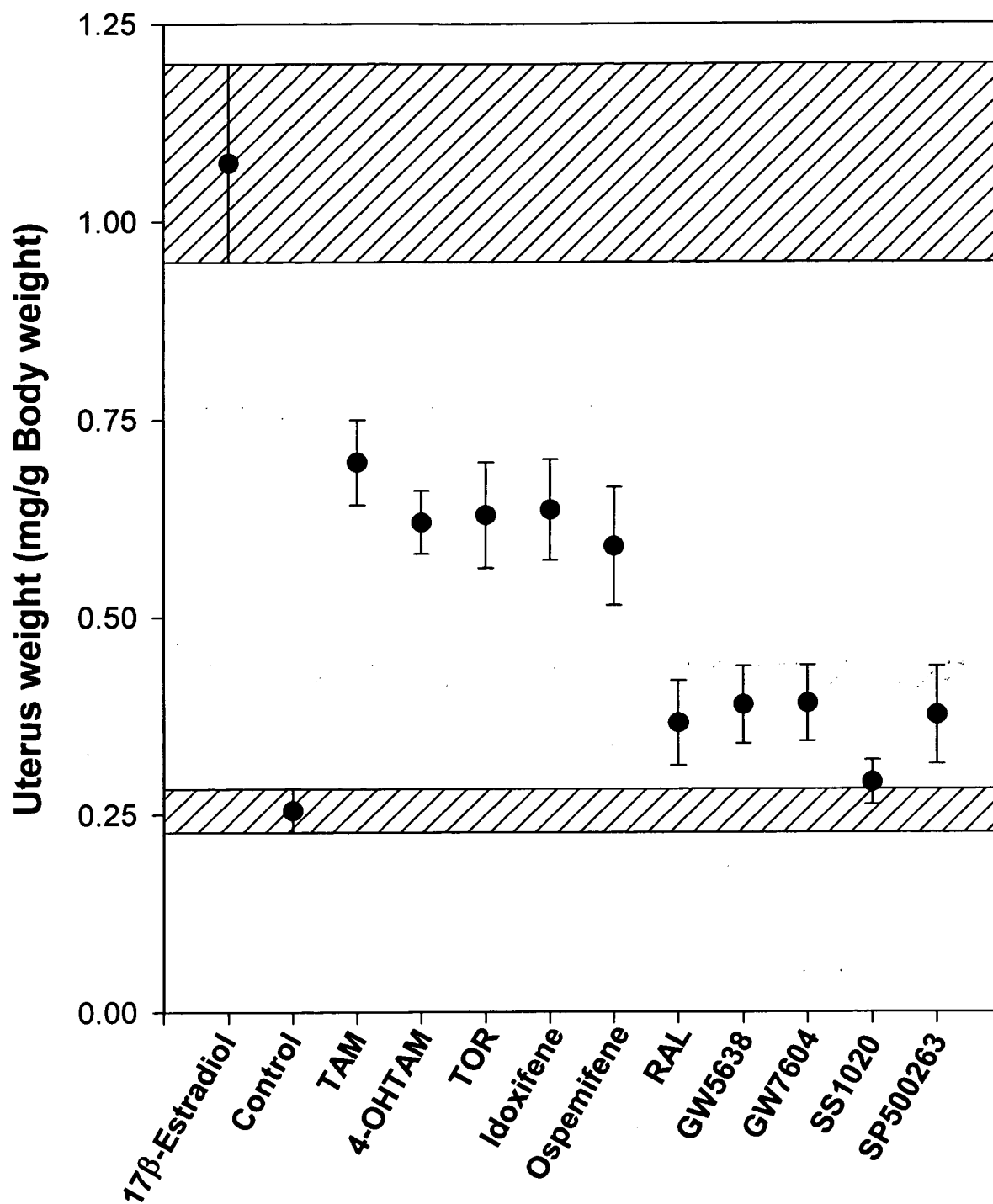


Figure 4.

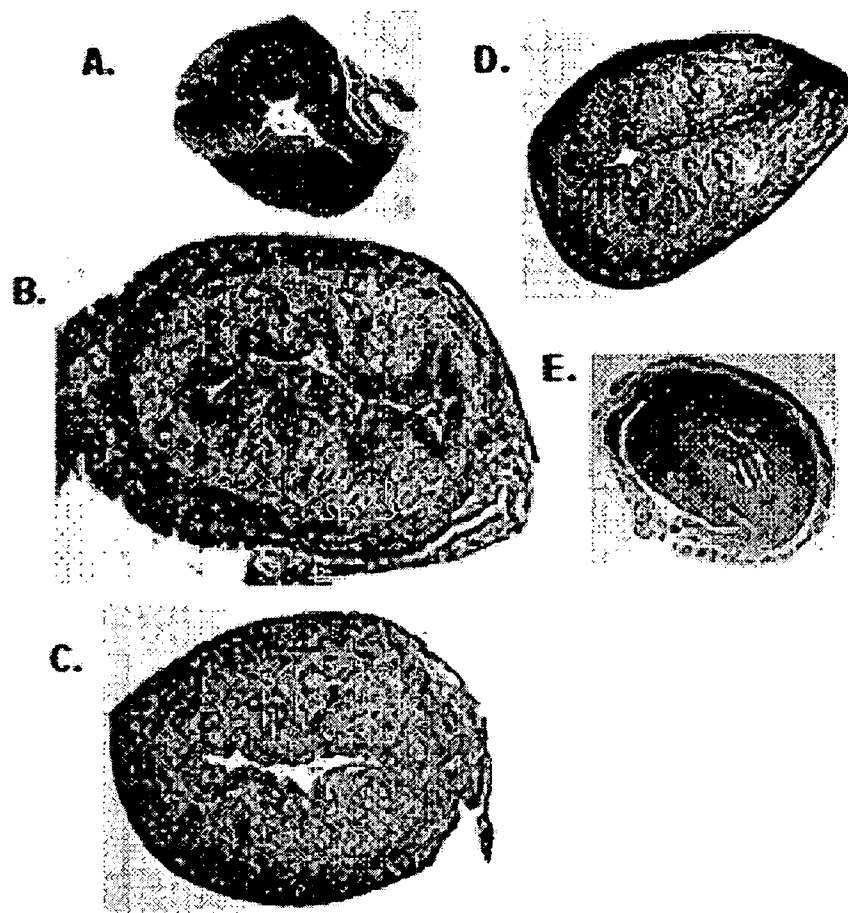


Figure 5.

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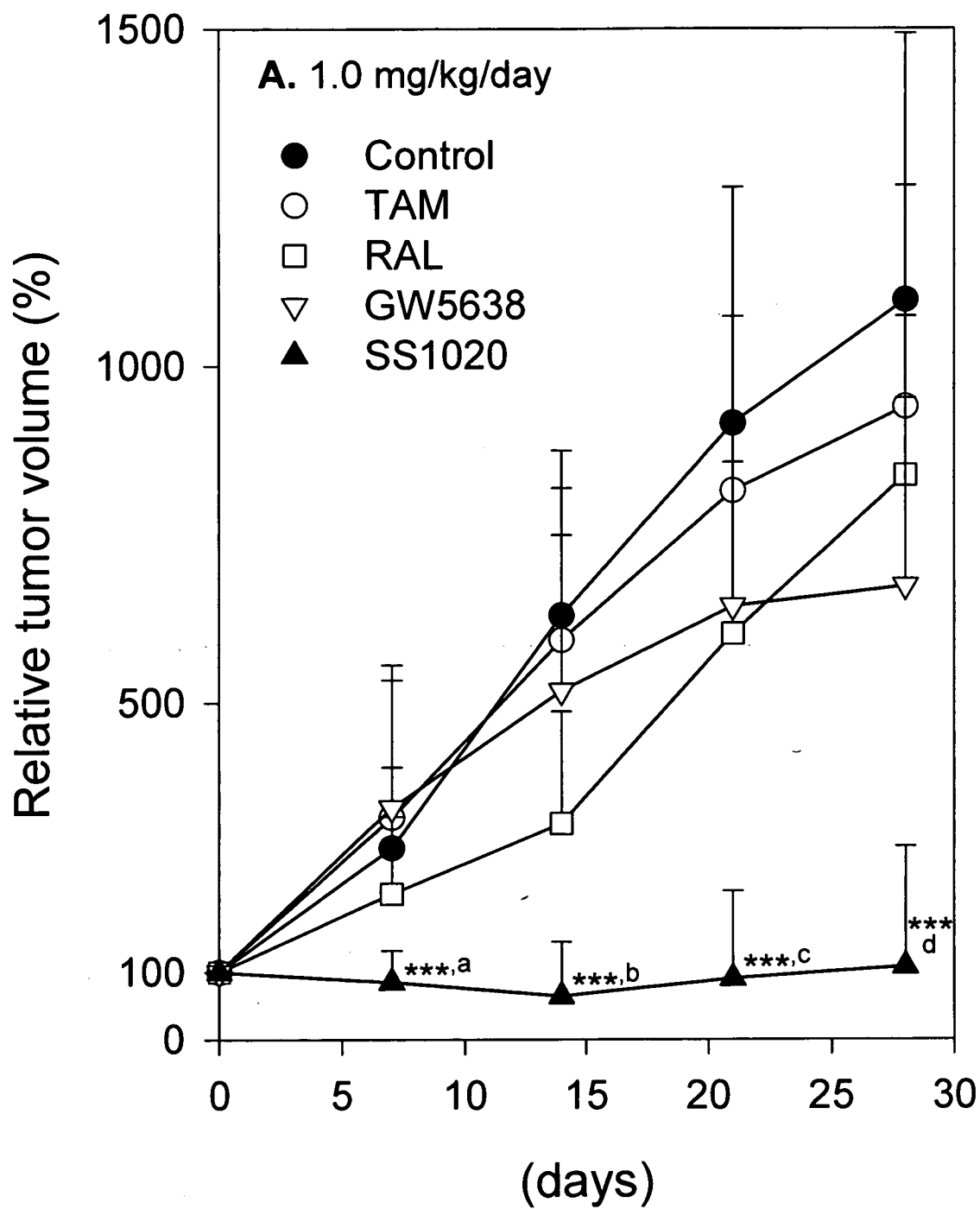


Figure 6a.

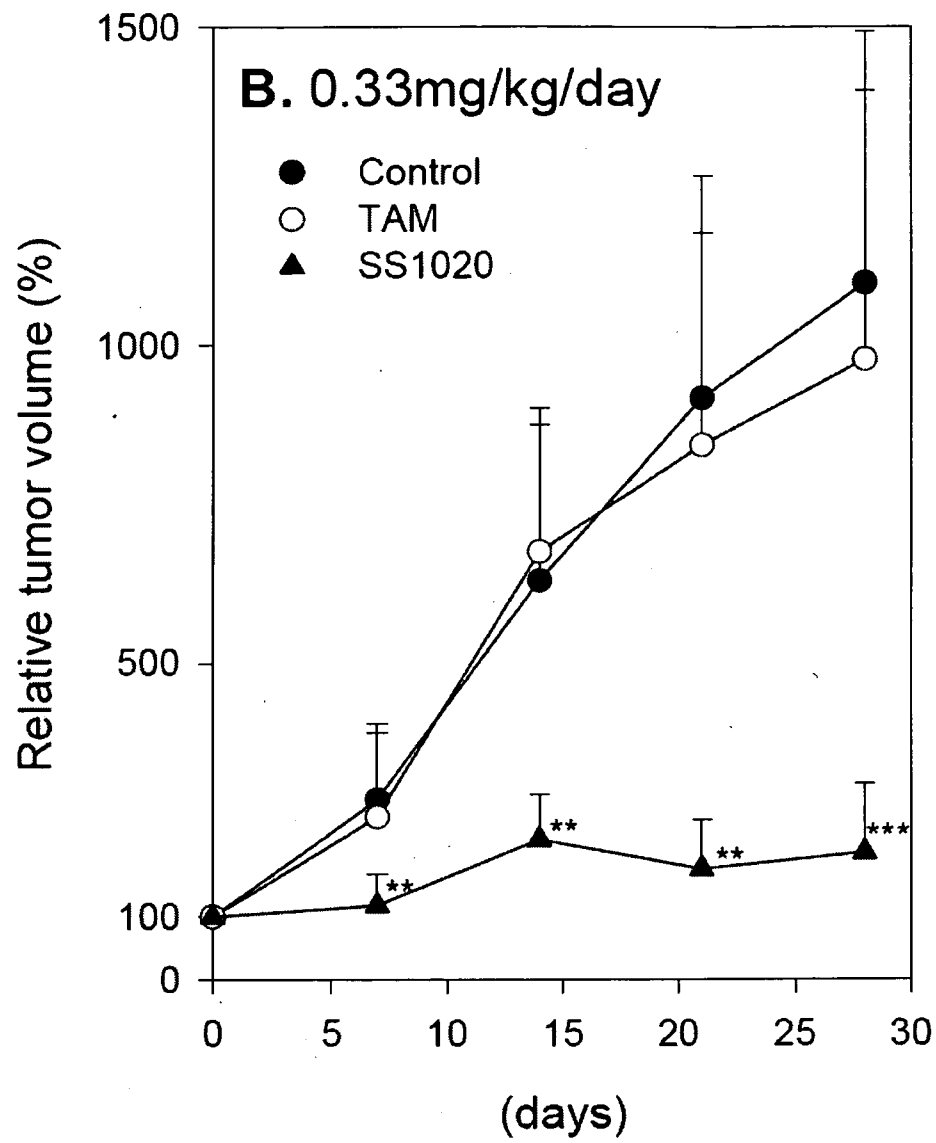


Figure 6b.

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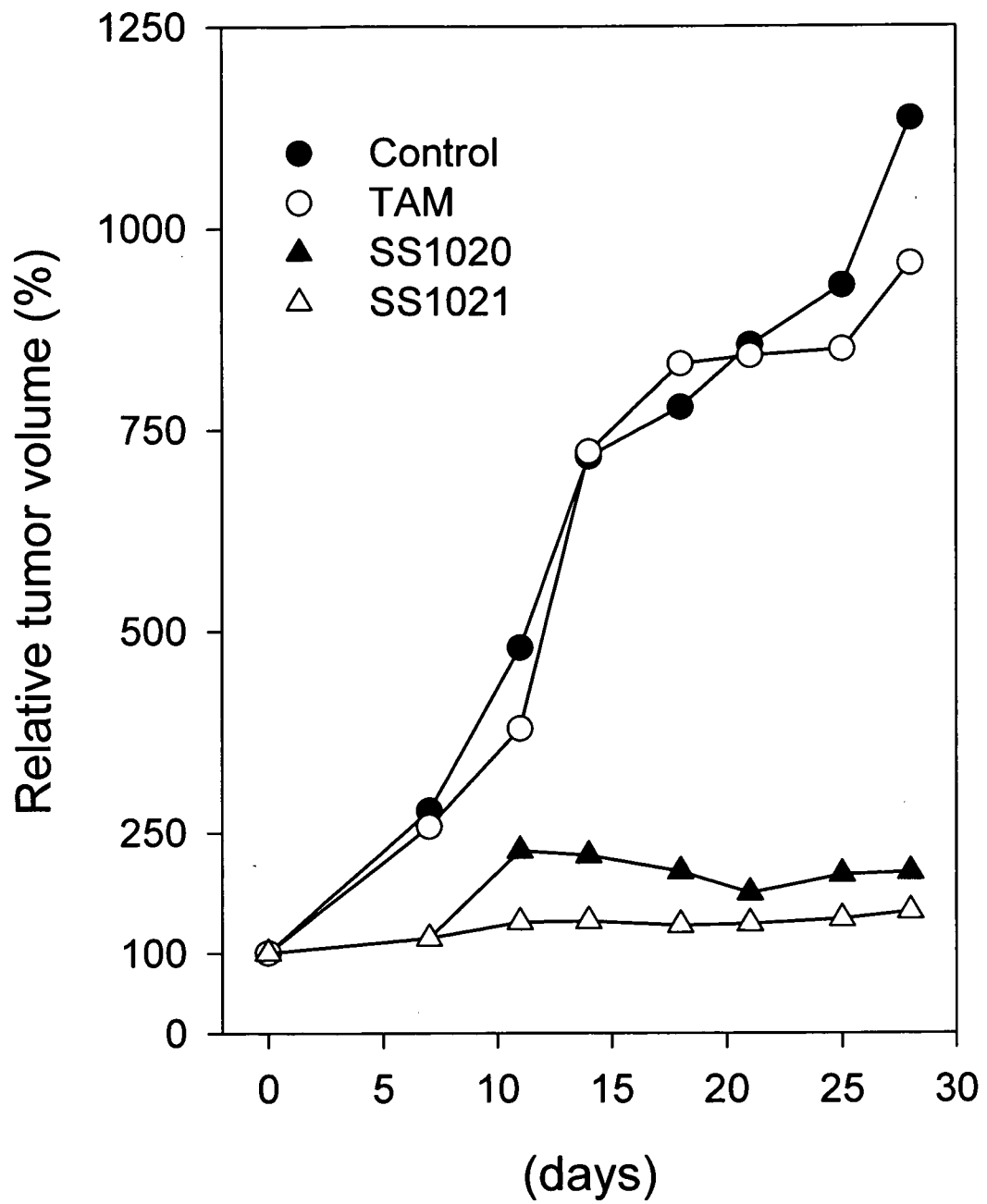


Figure 7.

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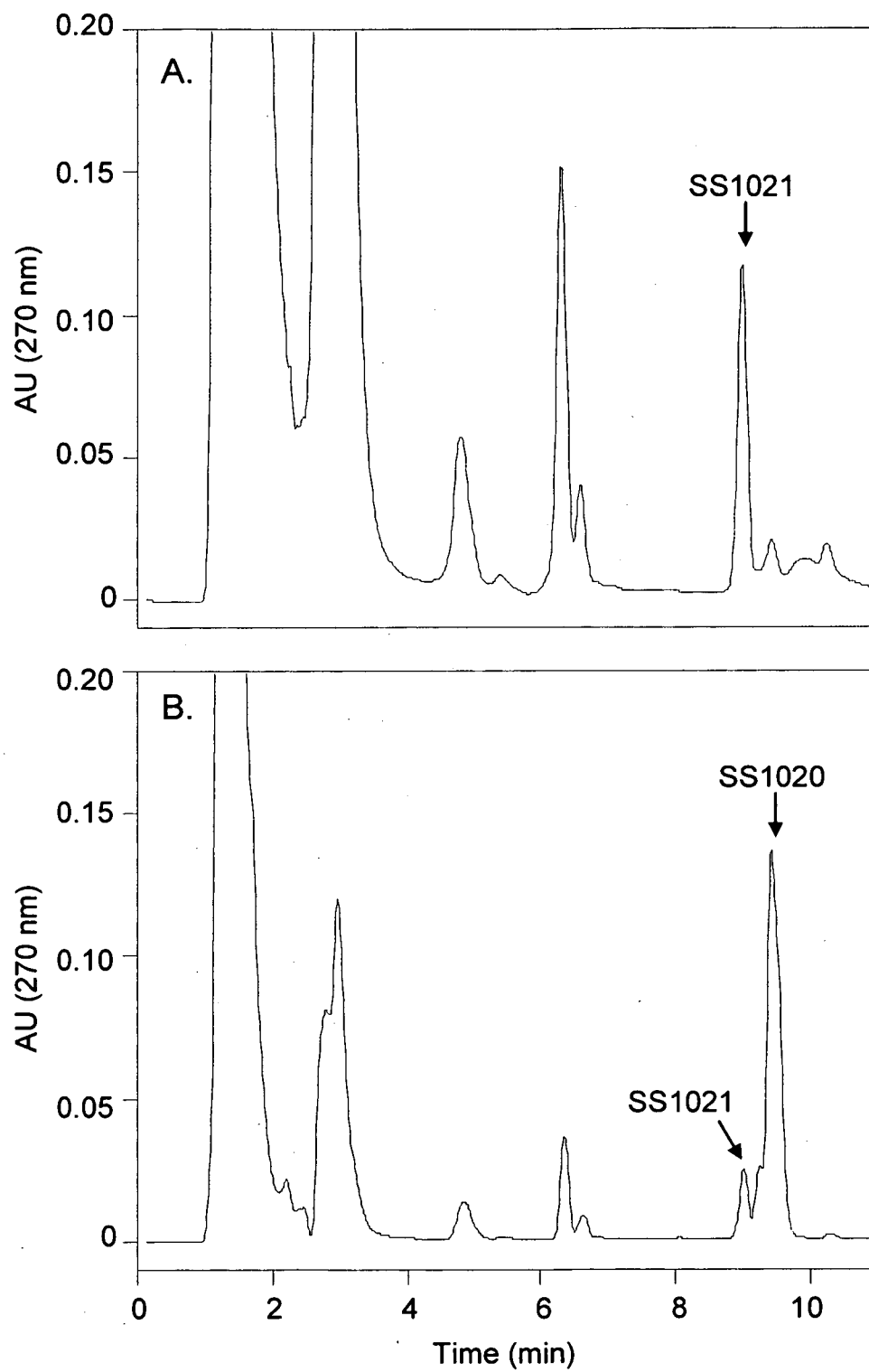


Figure 8.

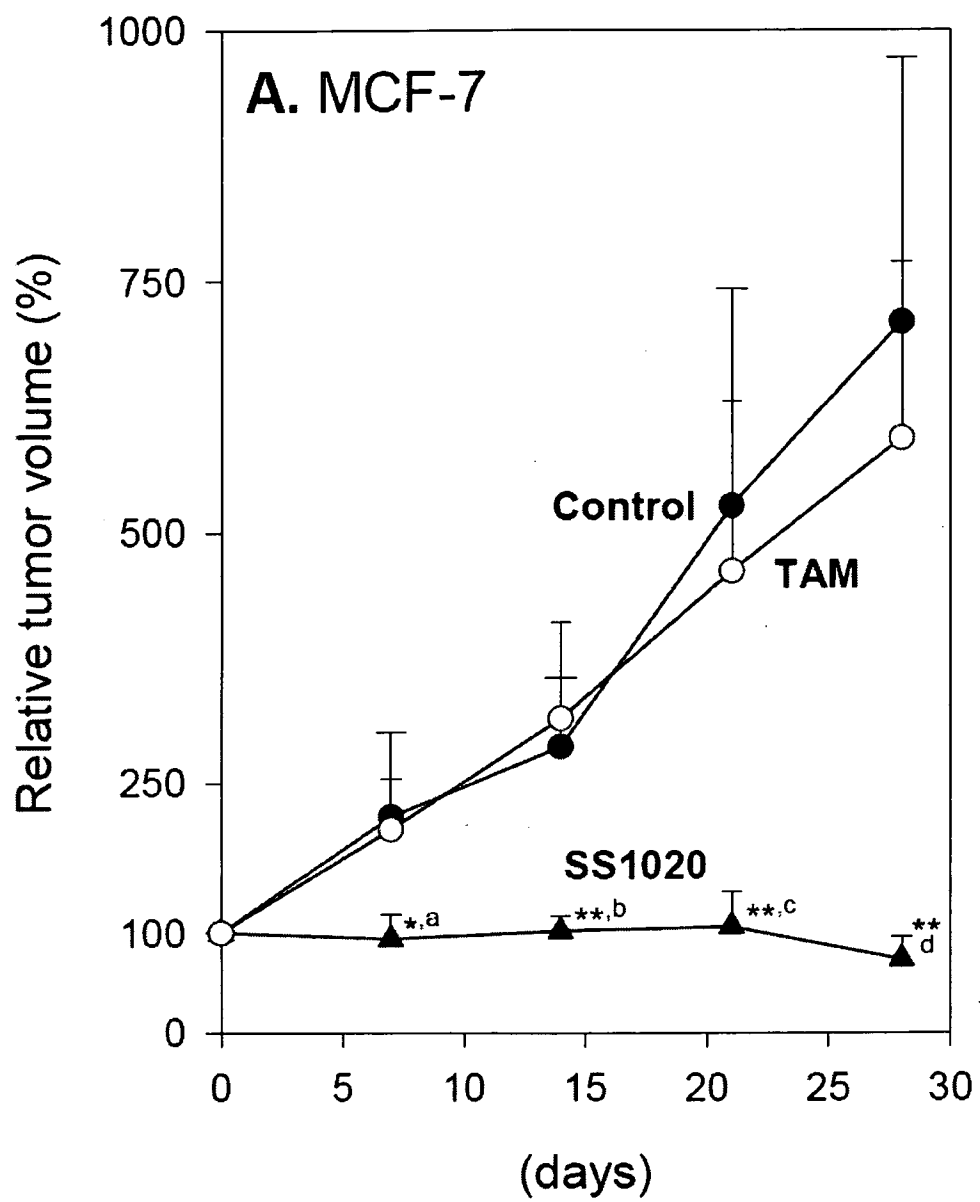


Figure 9a.

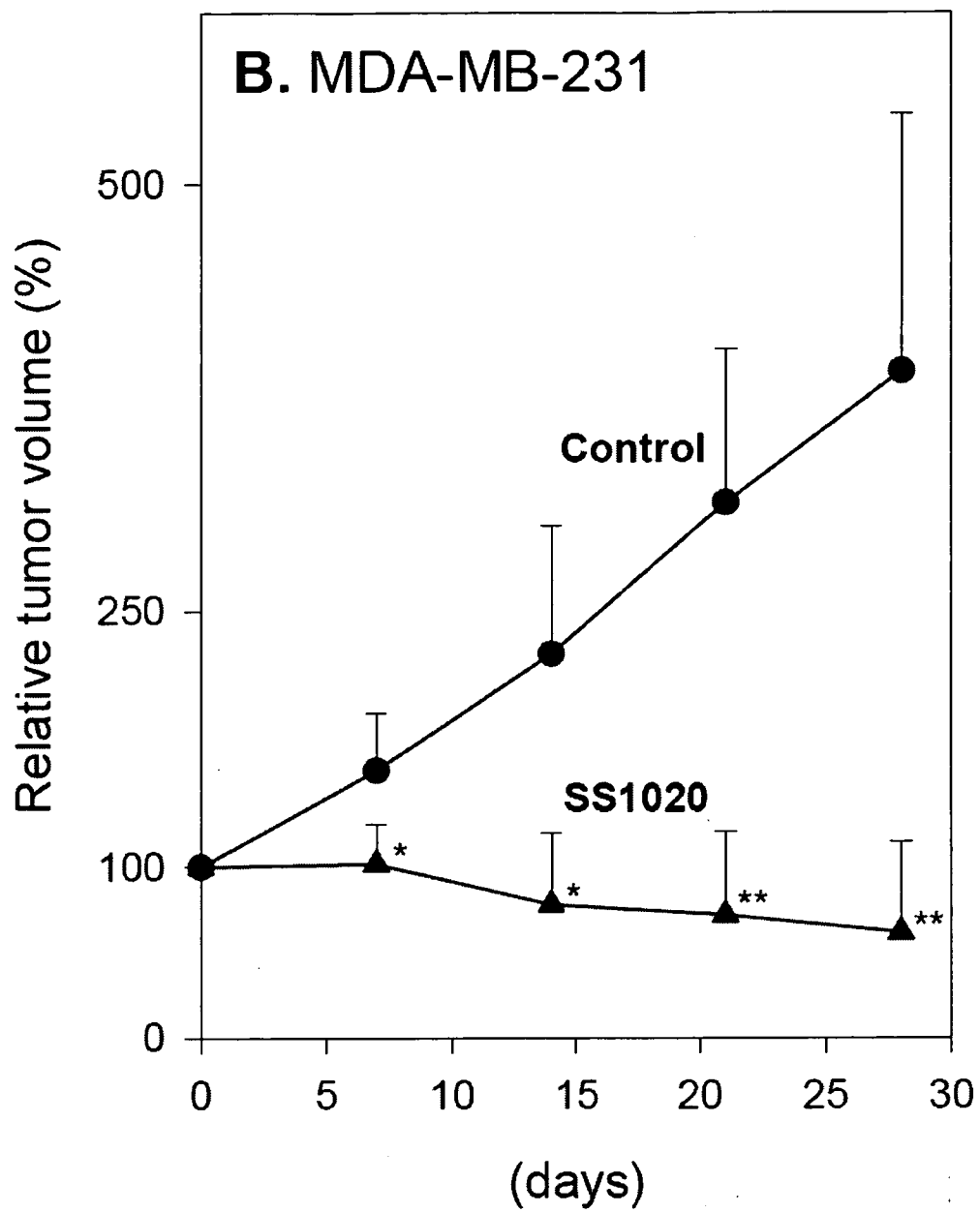
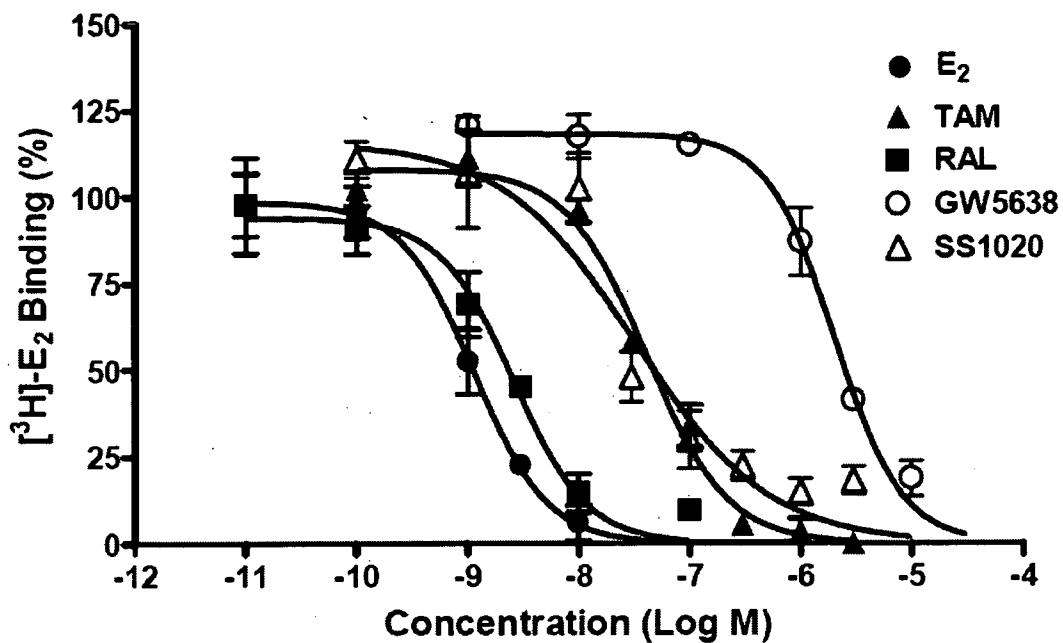


Figure 9b.



Competitor	ER α	
	IC_{50} (nM)	RBA ^a
E_2	1.13	100
TAM	41.4	2.73
4-OHTAM	0.88	128
RAL	2.57	44.0
GW5638	2040	0.06
GW7604	27.4	4.13
SS1020	32.6	3.47

^a Relative binding affinity

Figure 10.

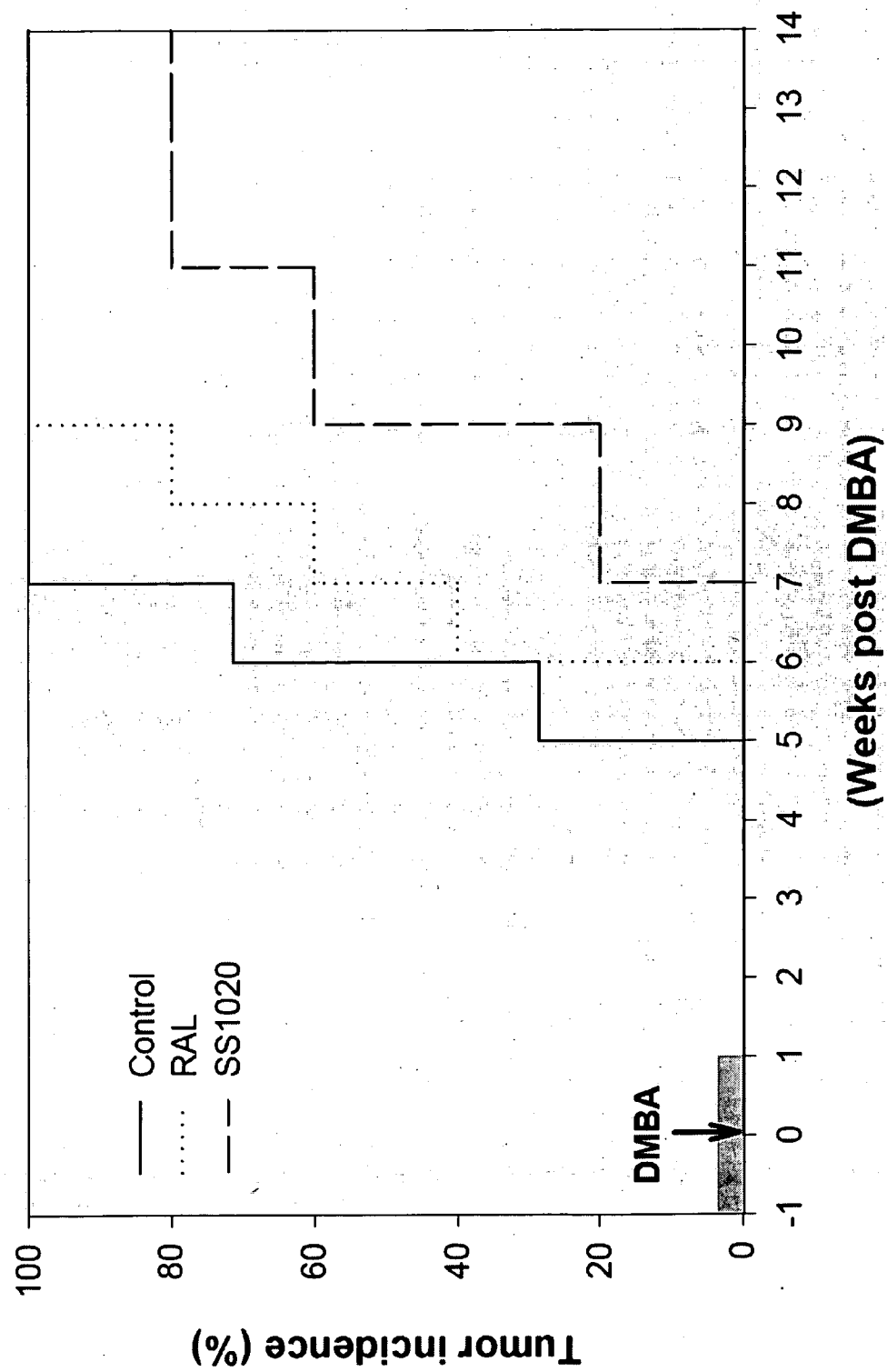


Figure 11.

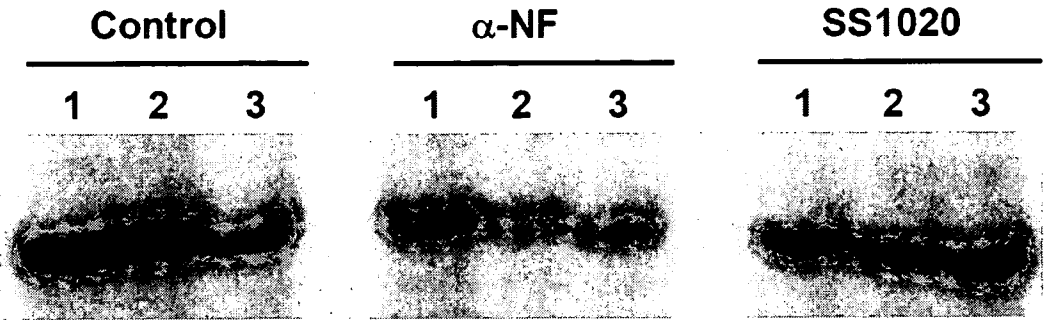


Figure 12.

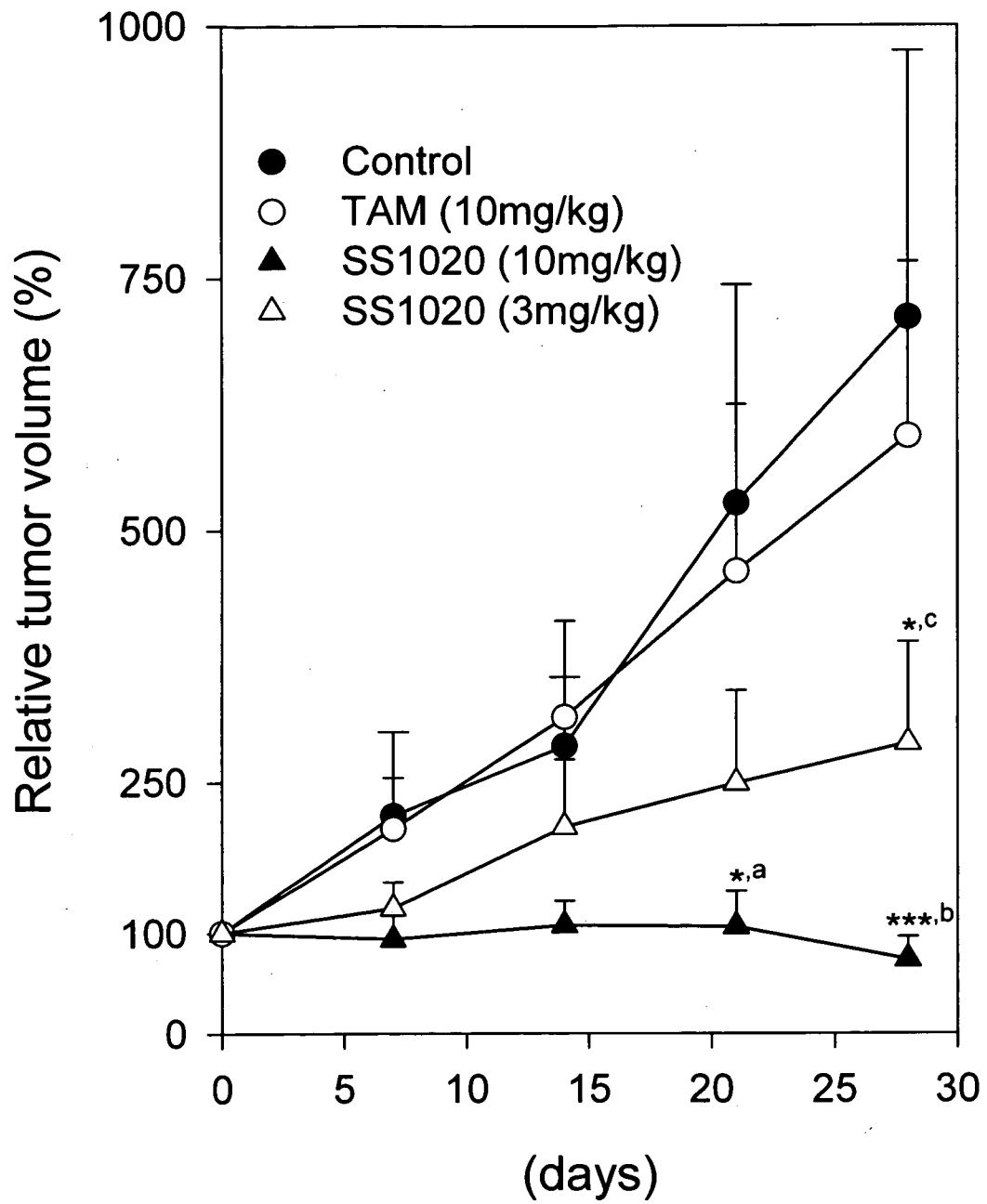


Figure 13.

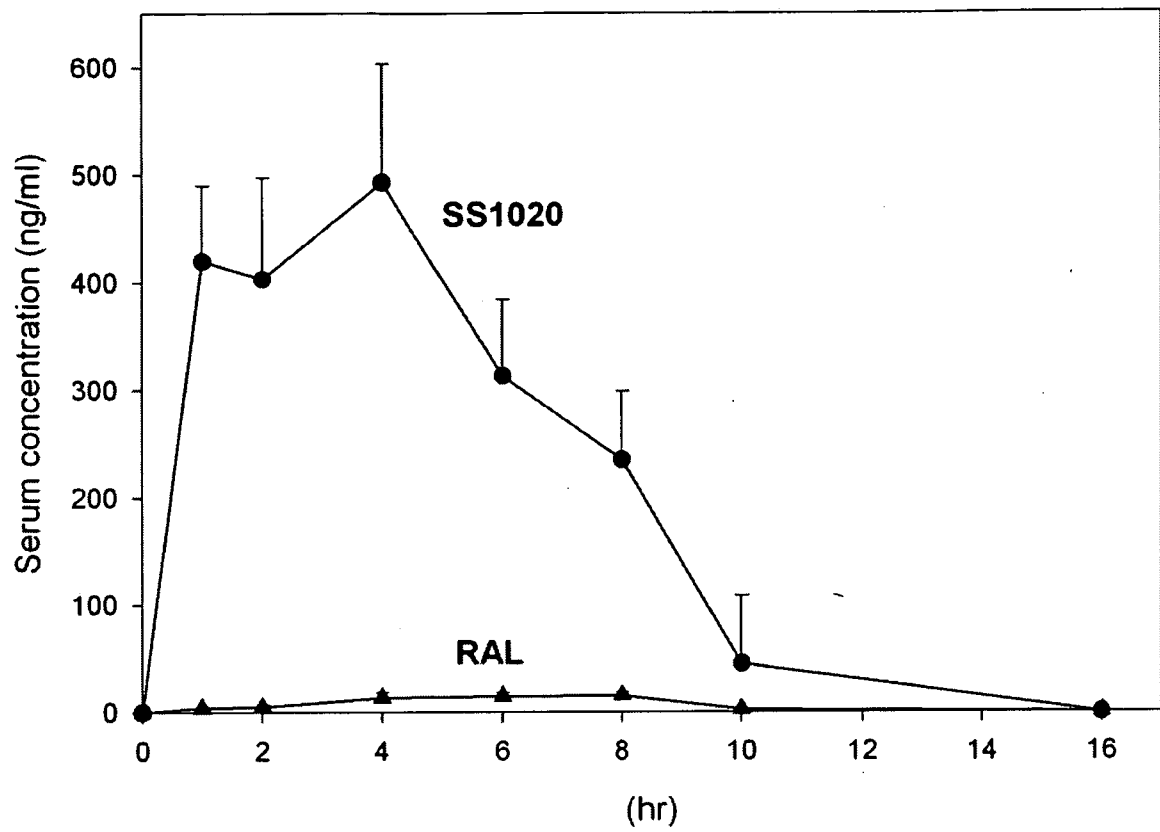


Figure 14.

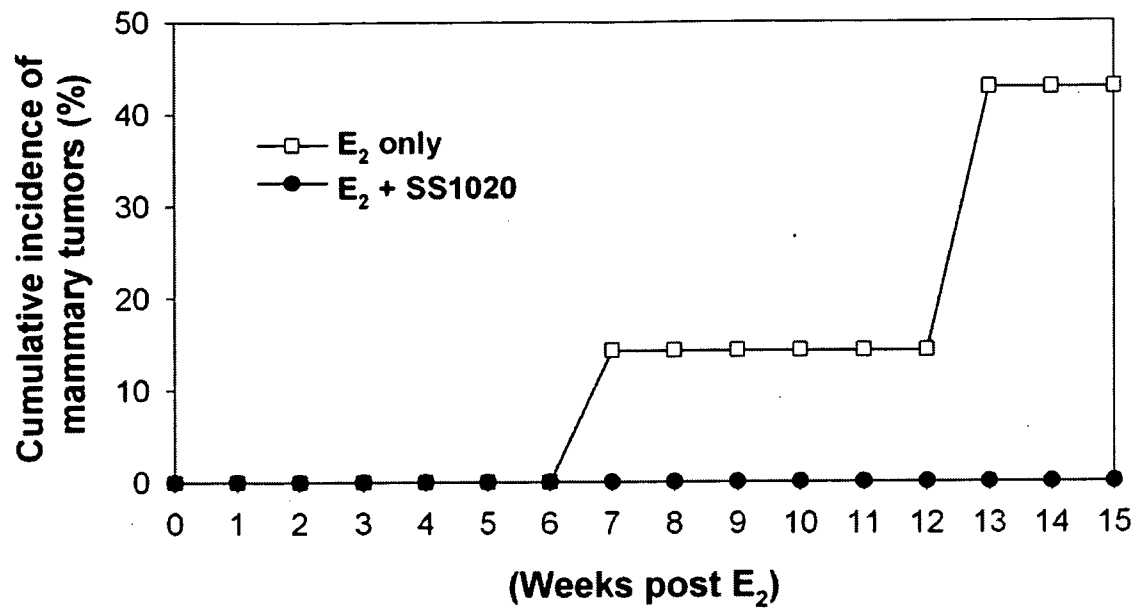


Figure 15.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/00755

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 33/02; A61K 31/135 (2010.01)
USPC - 514/651

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 514/651

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 435/7.23; 514/658 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Electronic Database Searched: PubWEST (PGPB,USPT,USOC,EPAB,JPAB), Google. Search Terms Used Tamoxifen, synthesis, preparation, manufacture, titanium or reducing agent, breast cancer therapy, antiestrogen

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Gauthier et al. New Highly Stereoselective Synthesis of (Z)-4-Hydroxytamoxifen and (Z)-4-Hydroxytoremifene via McMurry Reaction. J. Org. Chem., 1996, Vol 61, pp 3890-3893; pg 3890	1-23
Y	US 5,192,525 A (Yang et al.) 09 March 1993 (09.03.1993) especially col 2, ln 30-42	1-18, 22
Y	US 5,189,212 A (Ruenitz) 23 February 1993 (23.02.1993) col 3, ln 18-32	7, 11-13, 15, 19-21, 23
A	Itami. Diversity-Oriented Synthesis of Tamoxifen-type Tetra substituted Olefins. J Am Chem Soc, 2003, Vol 125, pp 14670-14671; retrived from http://ccc.chem.pitt.edu/wipl/Current%20Literature/gil_2.pdf on 14 April 2010; entire document	1-23

☐ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

14 April 2010 (14.04.2010)

Date of mailing of the international search report

23 APR 2010

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-3201

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 10/00755

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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

3. ☒ Claims Nos.: 24-35
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.