SUBSTITUTED PHENYL NAPHTHALENES AS ESTROGENIC AGENTS

BACKGROUND OF THE INVENTION

This invention relates to substituted phenyl naphthalenes, which are useful as estrogenic agents.

The pleiotropic effects of estrogens in mammalian tissues have been well documented, and it is now appreciated that estrogens affect many organ systems [Mendelsohn and Karas, New England Journal of Medicine 340: 1801-1811 (1999), Epperson, et al., Psychosomatic Medicine 61: 676-697 (1999), Crandall, Journal of Womens Health & Gender Based Medicine 8: 1155-1166 (1999), Monk and Brodaty, Dementia & Geriatric Cognitive Disorders 11: 1-10 (2000), Hurn and Macrae, Journal of Cerebral Blood Flow & Metabolism 20: 631-652 (2000), Calvin, Maturitas 34: 195-210 (2000), Finking, et al., Zeitschrift fur Kardiologie 89: 442-453 (2000), Brincat, Maturitas 35: 107-117 (2000), Al-Azzawi, Postgraduate Medical Journal 77: 292-304 (2001)]. Estrogens can exert effects on tissues in several ways, and the most well characterized mechanism of action is their interaction with estrogen receptors leading to alterations in gene transcription. Estrogen receptors are ligand-activated transcription factors and belong to the nuclear hormone receptor superfamily. Other members of this family include the progesterone, androgen, glucocorticoid and mineralocorticoid receptors. Upon binding ligand, these receptors dimerize and can activate gene transcription either by directly binding to specific sequences on DNA (known as response elements) or by interacting with other transcription factors (such as AP1), which in turn bind directly to specific DNA sequences [Moggs and Orphanides, EMBO Reports 2: 775-781 (2001), Hall, et al., Journal of Biological Chemistry 276: 36869-36872 (2001), McDonnell, Principles Of Molecular Regulation. p351-361(2000)]. A class of "coregulatory" proteins can also interact with the ligand-bound receptor and further modulate its transcriptional activity [McKenna, et al., Endocrine Reviews 20: 321-344 (1999)]. It has also been shown that estrogen receptors can suppress NFκB-mediated transcription in both a ligand-dependent and independent manner [Quaedackers, et al., Endocrinology 142: 1156-1166 (2001), Bhat, et al., Journal of Steroid Biochemistry & Molecular Biology 67: 233-240 (1998), Pelzer, et al., Biochemical & Biophysical Research Communications 286: 1153-7 (2001)].

Estrogen receptors can also be activated by phosphorylation. This phosphorylation is mediated by growth factors such as EGF and causes changes in gene transcription in the absence of ligand [Moggs and Orphanides, EMBO Reports 2: 775-781 (2001), Hall, et al., Journal of Biological Chemistry 276: 36869-36872 (2001)].

A less well-characterized means by which estrogens can affect cells is through a so-called membrane receptor. The existence of such a receptor is controversial, but it has been well documented that estrogens can elicit very rapid non-genomic responses from cells. The molecular entity responsible for transducing these effects has not been definitively isolated, but there is evidence to suggest it is at least related to the nuclear forms of the estrogen receptors [Levin, Journal of Applied Physiology 91: 1860-1867 (2001), Levin, Trends in Endocrinology & Metabolism 10: 374-377 (1999)].

Two estrogen receptors have been discovered to date. The first estrogen receptor was cloned about 15 years ago and is now referred to as ERα [Green, et al., Nature 320: 134-9 (1986)]. The second form of the estrogen receptor was found comparatively recently and is called ERβ [Kuiper, et al., Proceedings of the National Academy of Sciences of the United States of America 93: 5925-5930 (1996)]. Early work on ERβ focused on defining its affinity for a variety of ligands and indeed, some differences with ERα were seen. The tissue distribution of ERβ has been well mapped in the rodent and it is not coincident with ERα. Tissues such as the mouse and rat uterus express predominantly ERα, whereas the mouse and rat lung express predominantly ERβ [Couse, et al., Endocrinology 138: 4613-4621 (1997), Kuiper, et al., Endocrinology 138: 863-870 (1997)]. Even within the same organ, the distribution of ERα and ERβ can be compartmentalized. For example, in the mouse ovary, ERβ is highly expressed in the granulosa cells and ERα is restricted to the thecal and stromal cells [Sar and Welsch, Endocrinology 140: 963-971 (1999), Fitzpatrick, et al., Endocrinology 140: 2581-2591 (1999)]. However, there are examples where the receptors are coexpressed and there is evidence from in vitro studies that ERα and ERβ can form heterodimers [Cowley, et al., Journal of Biological Chemistry 272: 19858-19862 (1997)].

A large number of compounds have been described that either mimic or block the activity of 17β-estradiol. Compounds having roughly the same biological effects

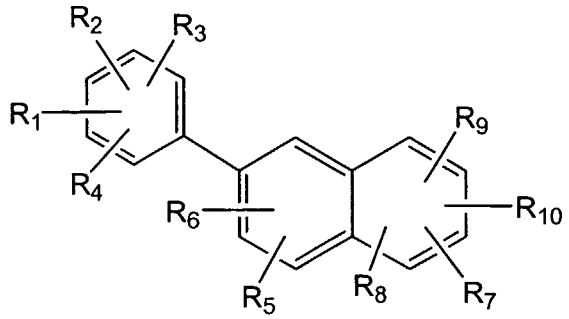
as 17β-estradiol, the most potent endogenous estrogen, are referred to as "estrogen receptor agonists". Those which, when given in combination with 17β-estradiol, block its effects are called "estrogen receptor antagonists". In reality there is a continuum between estrogen receptor agonist and estrogen receptor antagonist activity and indeed some compounds behave as estrogen receptor agonists in some tissues and estrogen receptor antagonists in others. These compounds with mixed activity are called selective estrogen receptor modulators (SERMS) and are therapeutically useful agents (e.g. EVISTA) [McDonnell, Journal of the Society for Gynecologic Investigation 7: S10-S15 (2000), Goldstein, et al., Human Reproduction Update 6: 212-224 (2000)]. The precise reason why the same compound can have cell-specific effects has not been elucidated, but the differences in receptor conformation and/or in the milieu of coregulatory proteins have been suggested.

It has been known for some time that estrogen receptors adopt different conformations when binding ligands. However, the consequence and subtlety of these changes has been only recently revealed. The three dimensional structures of ERα and ERβ have been solved by co-crystallization with various ligands and clearly show the repositioning of helix 12 in the presence of an estrogen receptor antagonist which sterically hinders the protein sequences required for receptor-coregulatory protein interaction [Pike, et al., Embo 18: 4608-4618 (1999), Shiau, et al., Cell 95: 927-937 (1998)]. In addition, the technique of phage display has been used to identify peptides that interact with estrogen receptors in the presence of different ligands [Paige, et al., Proceedings of the National Academy of Sciences of the United States of America 96: 3999-4004 (1999)]. For example, a peptide was identified that distinguished between ERα bound to the full estrogen receptor agonists 17β-estradiol and diethylstilbesterol. A different peptide was shown to distinguish between clomiphene bound to ERα and ERβ. These data indicate that each ligand potentially places the receptor in a unique and unpredictable conformation that is likely to have distinct biological activities.

As mentioned above, estrogens affect a panoply of biological processes. In addition, where gender differences have been described (e.g. disease frequencies, responses to challenge, etc), it is possible that the explanation involves the difference in estrogen levels between males and females.

DESCRIPTION OF THE INVENTION

This invention provides estrogenic compound of formula I having the structure,



I

wherein

R_1, R_2, R_3, and R_4 are each, independently, selected from hydrogen, hydroxyl, alkyl of 1-6 carbon atoms, alkoxy of 1-6 carbon atoms, or halogen;

R_5, R_6, R_7, R_8, R_9, and R_{10}, are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, halogen, alkoxy of 1-6 carbon atoms, -CN, -CHO, phenyl, or a 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S; wherein the alkyl or alkenyl moieties of R_5, R_6, R_7, R_8, R_9, or R_{10} may be optionally substituted with hydroxyl, -CN, halogen, trifluoroalkyl, trifluoroalkoxy, $-NO_2$, or phenyl; wherein the phenyl moiety of R_5, R_6, R_7, R_8, R_9, or R_{10} may be optionally mono-, di-, or tri-subsitituted with alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, halogen, hydroxyl, alkoxy of 1-6 carbon atoms, -CN, $-NO_2$, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl group, thio, alkylthio of 1-6 carbon atoms, alkylsulfinyl of 1-6 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, alkoxycarbonyl of 2-7 carbon atoms, alkylcarbonyl of 2-7 carbon atoms, or benzoyl;

with the proviso that at least one of R_1, R_2, R_3, R_4, R_7, R_8, R_9, or R_{10} is hydroxyl,

or a pharmaceutically acceptable salt thereof.

Pharmaceutically acceptable salts can be formed from organic and inorganic acids, for example, acetic, propionic, lactic, citric, tartaric, succinic, fumaric, maleic, malonic, mandelic, malic, phthalic, hydrochloric, hydrobromic, phosphoric, nitric, sulfuric, methanesulfonic, naphthalenesulfonic, benzenesulfonic, toluenesulfonic,

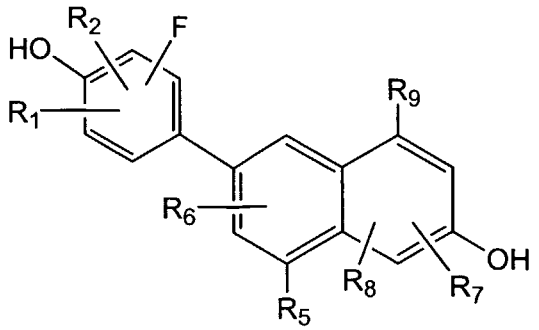
camphorsulfonic, and similarly known acceptable aids when a compound of this invention contains a basic moiety. Salts may also be formed from organic and inorganic bases, such as alkali metal salts (for example, sodium, lithium, or potassium) alkaline earth metal salts, ammonium salts, alkylammonium salts containing 1-6 carbon atoms or dialkylammonium salts containing 1-6 carbon atoms in each alkyl group, and trialkylammonium salts containing 1-6 carbon atoms in each alkyl group, when a compound of this invention contains an acidic moiety.

The terms alkyl and alkenyl include both branched and straight chain moieties ,eg of 1-6 and 2-7 carbon atoms respectively. Examples include methyl, ethyl, propyl, butyl, isopropyl, sec-butyl, tert-butyl, vinyl, allyl, 1-methyl vinyl, and the like. When alkyl or alkenyl moieties are substituted, they may typically be mono-, di-, tri- or persubstituted. Examples for a halogen substituent include 1-bromovinyl, 1-fluorovinyl, 1,2-difluorovinyl, 2,2-difluorovinyl, 1,2,2-trifluorovinyl, 1,2-dibromo ethane, 1,2-difluoro-ethane, 1-fluoro-2-bromo ethane, CF_2CF_3, $CF_2CF_2CF_3$, and the like. The term halogen includes bromine, chlorine, fluorine, and iodine.

Preferred 5-6 membered heterocyclic rings include furan, thiophene, pyrrole, isopyrrole, pyrazole, imidazole, triazole, dithiole, oxathiole, isoxazole, oxazole, thiazole, isothiazolem oxadiazole, furazan, oxatriazole, dioxazole, oxathiazole, tetrazole, pyran, pyridine, pyridazine, pyrimidine, pyrazine, triazine, oxazine, oxathiazine, or oxadiazine. It is more preferred that the heterocyclic ring is furan, thiophene, or pyridine.

As used in accordance with this invention, the term "providing," with respect to providing a compound or substance covered by this invention, means either directly administering such a compound or substance, or administering a prodrug, derivative, or analog which will form the effective amount of the compound or substance within the body.

Of the compounds of this invention, it is preferred that the compound of formula I has the structure



I

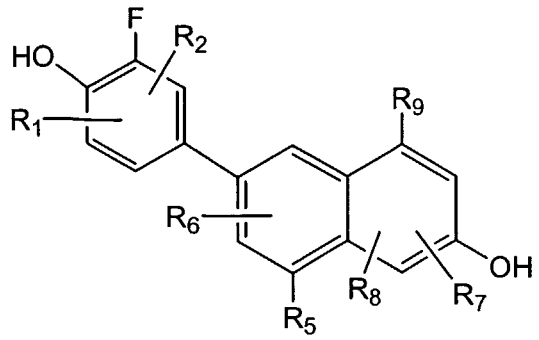
wherein

R_1 and R_2 are each, independently, selected from hydrogen, hydroxyl, alkyl of 1-6 carbon atoms, alkenyl, of 2-7 carbon atoms, and alkynyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, or halogen;

R_5, R_6, R_7, R_8, and R_9 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, halogen, alkoxy of 1-6 carbon atoms, -CN, -CHO, trifluoromethyl, phenylalkyl of 7-12 carbon atoms, phenyl, or a 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S; wherein the alkyl or alkenyl moieties of R_5, R_6, R_7, R_8, or R_9 may be optionally substituted with hydroxyl, -CN, halogen, trifluoroalkyl, trifluoroalkoxy, $-NO_2$, or phenyl; wherein the phenyl moiety of R_5, R_6, R_7, R_8, R_9, or R_{10} may be optionally mono-, di-, or tri-subsitituted with alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, halogen, hydroxyl, alkoxy of 1-6 carbon atoms, halogen, -CN, $-NO_2$, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl group, thio, alkylthio of 1-6 carbon atoms, alkylsulfinyl of 1-6 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, alkoxycarbonyl of 2-7 carbon atoms, alkylcarbonyl of 2-7 carbon atoms, or benzoyl;

with the proviso that at least one of R_5 or R_9 is not hydrogen, or a pharmaceutically acceptable salt thereof.

It is more preferred that the compound of formula I has the structure



and still more preferred that the 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S is furan, thiophene, or pyridine. It is yet more preferred that R_5, R_6, R_7, R_8, and R_9 are each, independently, hydrogen, halogen, -CN, or alkynyl of 2-7 carbon atoms.

Examples of R_1 and R_2 are each independently selected from hydrogen and fluorine.

R_5, R_6, R_7, R_8, and R_9 may each be for example, independently, hydrogen, halogen, -CN, or alkynyl of 2-7 carbon atoms.

R_5 may be for example selected from hydrogen, fluorine or cyano.

R_9 may be selected from hydrogen, fluorine or cyano.

R_6, R_7, and R_8 may each independently be hydrogen.

The 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S is for example furan, thiophene, or pyridine.

Examples of compounds of this invention including structure (I) above are:
8-fluoro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-8-fluoro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol;
3-(3-fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile;
3-(3,5-difluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile;
6-(3-fluoro-4-hydroxyphenyl)-2-naphthol;

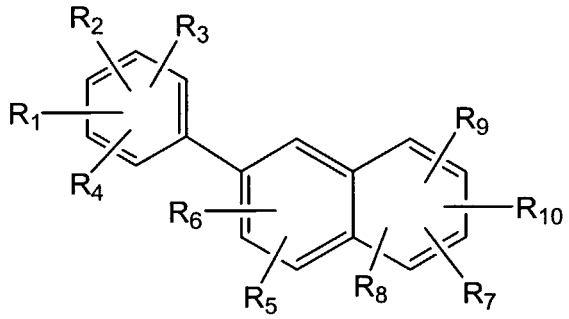
1-chloro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(2-fluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(2,5-difluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(2,6-difluoro-4-hydroxyphenyl)-2-naphthol;
6-(2,5-difluoro-4-hydroxyphenyl)-2-naphthol;
6-(3,5-difluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(3,5-difluoro-4-hydroxyphenyl)-2-naphthol;
6-(2,6-difluoro-4-hydroxyphenyl)-2-naphthol; or
8-chloro-3-(3-fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile;
7-(4-hydroxyphenyl)-2-naphthol;
7-(3-hydroxyphenyl)-2-naphthol;
6-(4-hydroxyphenyl)-1-naphthol;
6-phenyl-2-naphthol;
6-(3-hydroxyphenyl)-2-naphthol;
6-(3-chlorophenyl)-2-naphthol;
2-fluoro-4-(2-naphthyl)phenol ;
6-(3-chloro-4-hydroxyphenol)-2-naphthol;
1-chloro-6-phenyl-2-naphthol;
1-bromo-6-(4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(4-hydroxyphenyl)-2-naphthol;
1-fluoro-6-(4-hydroxyphenyl)-2-naphthol;
2-hydroxy-6-(4-hydroxyphenyl)-1-naphthonitrile;
6-(4-hydroxyphenyl)-1-phenyl-2-naphthol;
6-(4-hydroxyphenyl)-1-methyl-2-naphthol;
1-chloro-6-(3-chloro-4-hydroxyphenyl)-2-naphthol;
6-(4-hydroxyphenyl)-1-nitro-2-naphthol;
1-chloro-6-(4-hydroxy-2-methylphenyl)-2-naphthol;
6-(4-hydroxy-2-methylphenyl)-2-naphthol;
6-(4-hydroxy-2-methoxyphenyl)-2-naphthol;
6-(2-chloro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(2-chloro-4-hydroxyphenyl)-2-naphthol;
6-(2-fluoro-4-hydroxyphenyl)-2-naphthol;
8-fluoro-6-(4-hydroxyphenyl)-2-naphthol;
1-chloro-8-fluoro-6-(4-hydroxyphenyl)-2-naphthol;

8-chloro-6-(4-hydroxyphenyl)-2-naphthol;
1,5-dichloro-8-fluoro-6-(4-hydroxyphenyl)-2-naphthol;
2-chloro-4-(2-naphthyl)phenol;
3-bromo-8-chloro-6-(4-hydroxyphenyl)-2-naphthol;
1,8-dichloro-6-(4-hydroxyphenyl)-2-naphthol;
3-bromo-1,8-dichloro-6-(4-hydroxyphenyl)-2-naphthol;
7-hydroxy-3-(4-hydroxyphenyl)-1-naphthonitrile;
8-chloro-3-(4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile;
8-bromo-7-hydroxy-3-(4-hydroxyphenyl)-1-naphthonitrile;

or a pharmaceutically acceptable salt thereof.

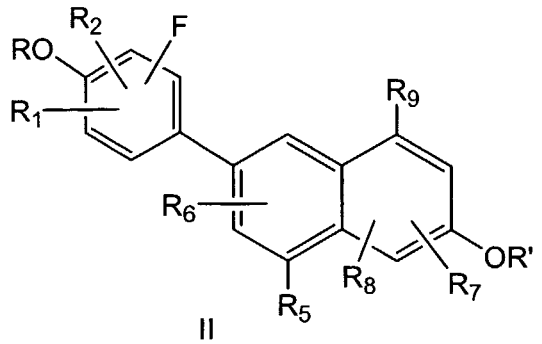
Also provided are processes for preparing compounds of the invention including those ofstructure (I) above. Accordingly this invention provides a process for preparing a naphthyl compound as defined herein above, including structure (I) above, which comprises one of the following:

a) de-alkylating or de-aralkylating a compound of formula



I

wherein R_1-R_{10} are as defined above providing at least one of R_1, R_2, R_3, R_4, R_7, R_8, R_9, or R_{10} is alkoxy or aralkyloxy to give a corresponding compound of formula I wherein at least one of R_1, R_2, R_3, R_4, R_7, R_8, R_9, or R_{10} is hydroxy;
{e.g., de-alkylating or de-aralkylating a compound of formula:

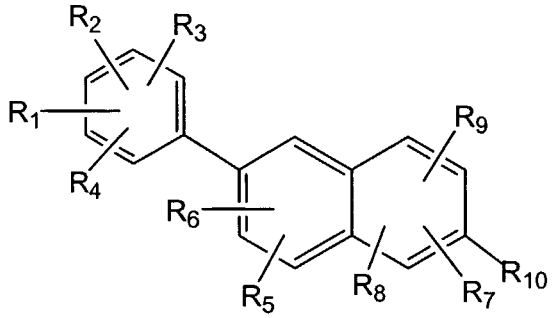


II

wherein at least one of R and R' is alkyl (eg of 1-6 carbons) or aralkyl (eg of 7-12 carbons) to give a corresponding compound of formula (I)};

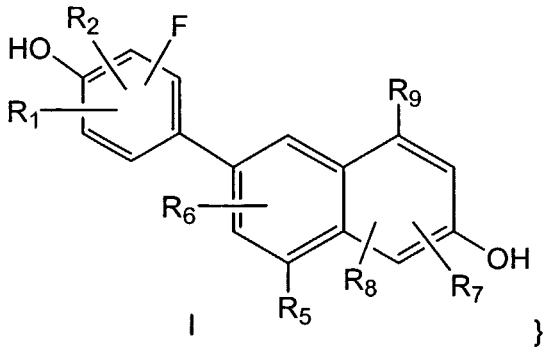
or

b) halogenating a compound of formula I



I

wherein R_{10} is hydroxy; {such as a compound of formula:



I }

to give a corresponding 1-halonaphthol;

or

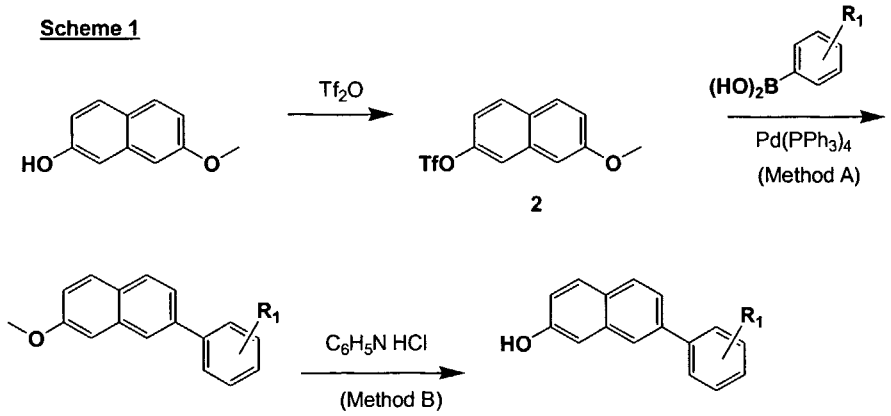
c) converting a basic compound of formula I to a salt thereof or vice versa.

In any of the reactions described herein any reactive group or site may be protected prior to the reaction and the protecting group removed thereafter.

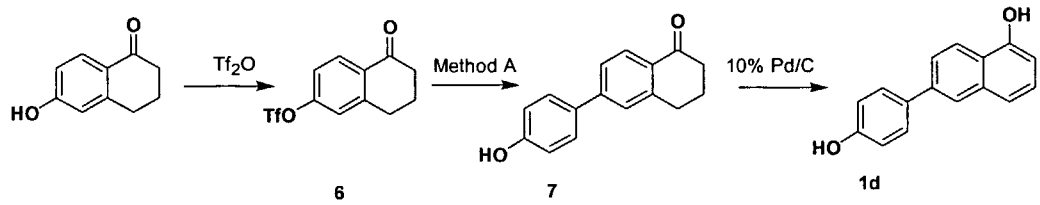
The reagents used in the preparation of the compounds of this invention can be either commercially obtained or can be prepared by standard procedures described in the literature.

The preparation of several representative examples of this invention are described in the following Schemes 1-15.

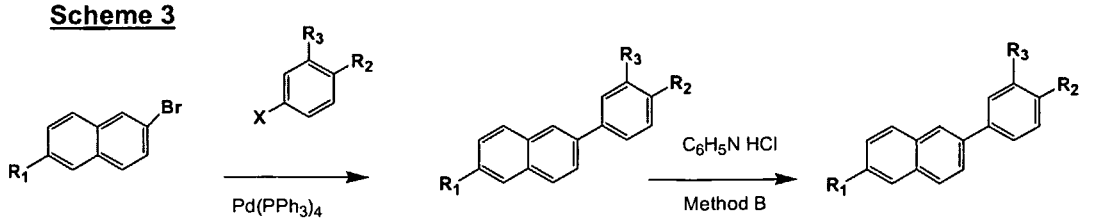
Scheme 1



Scheme 2



Scheme 3

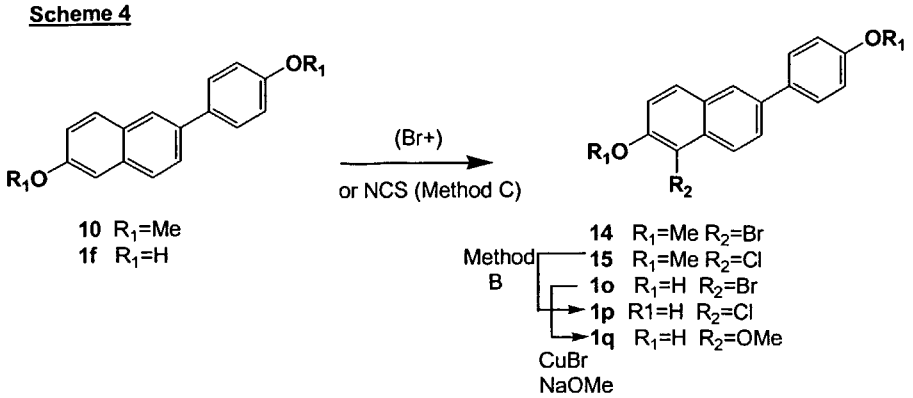


8 R_1=OMe
9 R_1=H

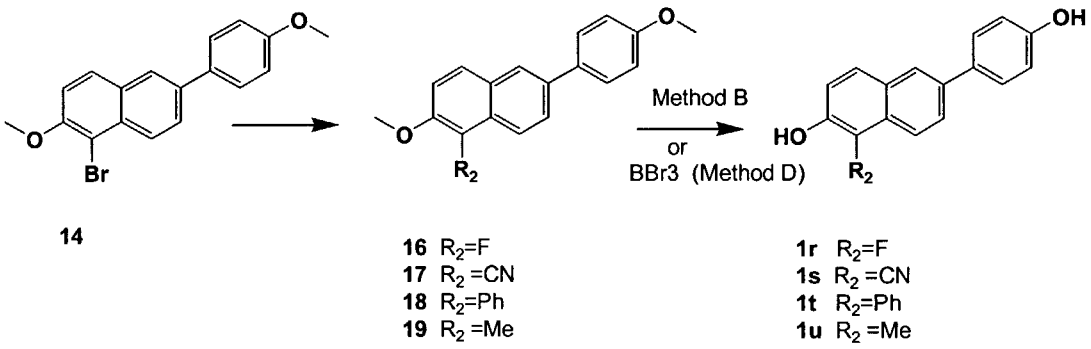
10 R_1 =OMe R_2 = OMe R_3=H
11 R_1 =H R_2 = OMe R_3=H
12 R_1 =OMe R_2 = H R_3= H
13 R_1 =OMe R_2 = H R_3=OMe
1i R_1 =OH, R_2 = H R_3=Cl

1e R_1 = OH, R_2 = OH R_3=H
1f R_1 = H R_2 = OH R_3=H
1g R_1 = OH, R_2 = H R_3=H
1h R_1 = OH, R_2 = H R_3=OH

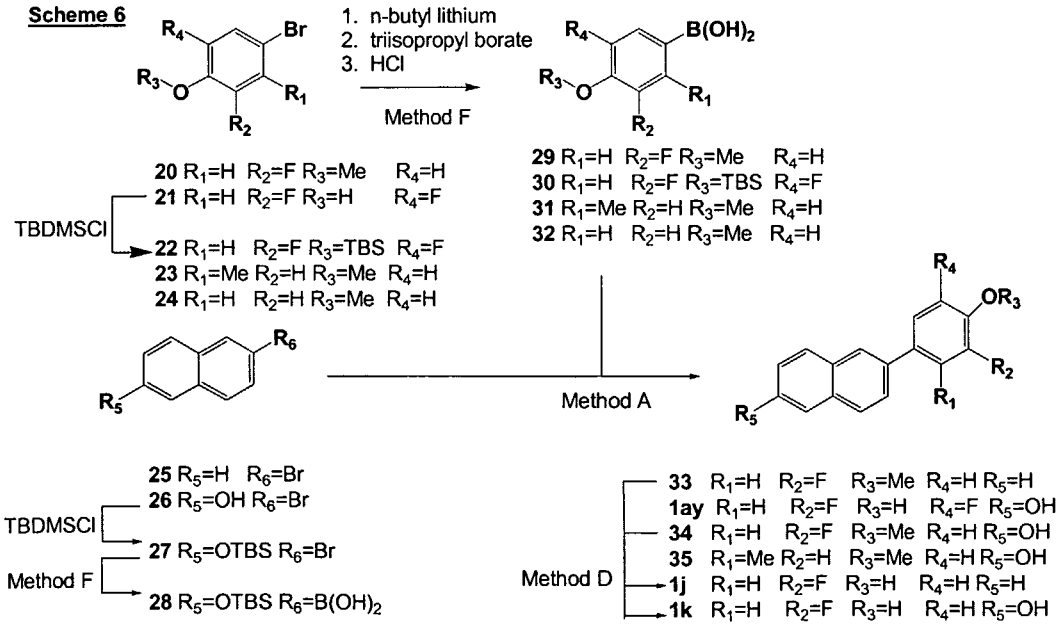
Scheme 4



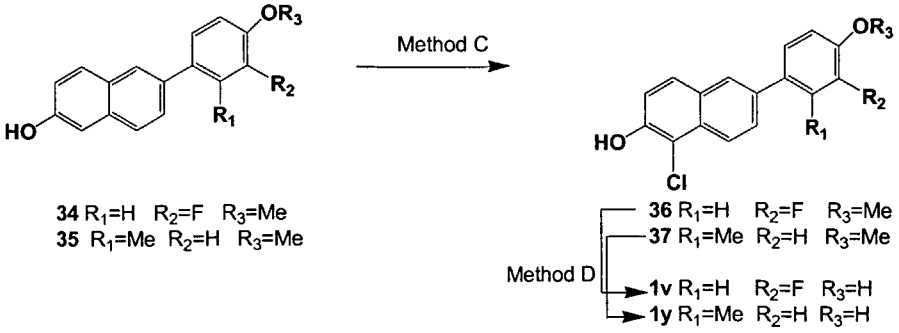
Scheme 5



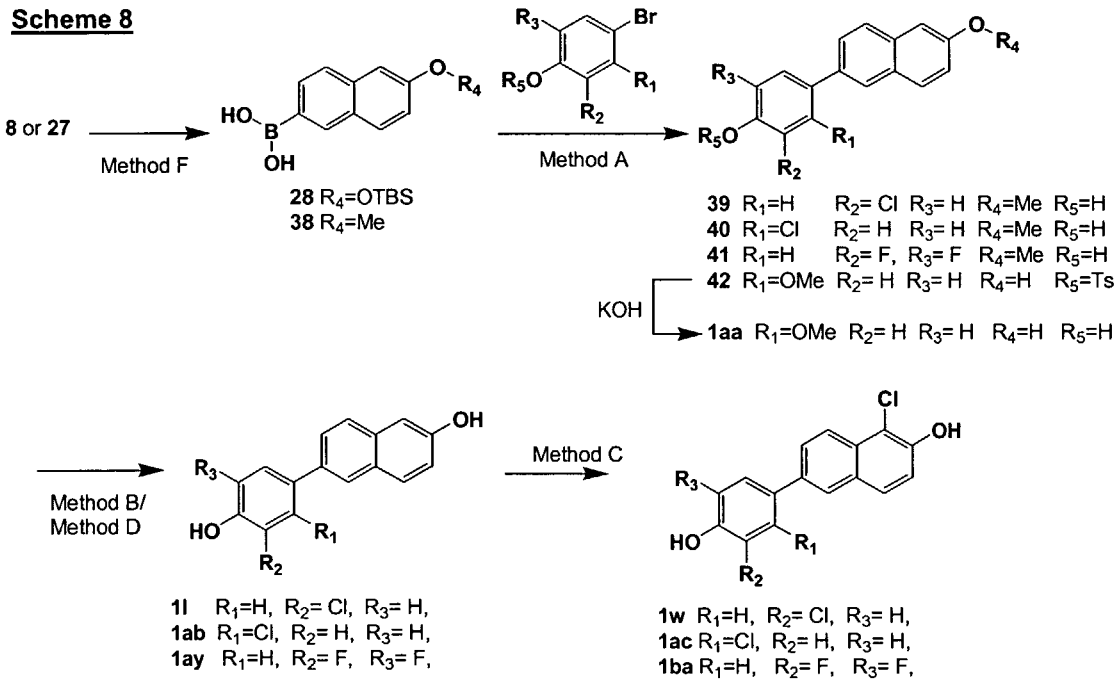
Scheme 6



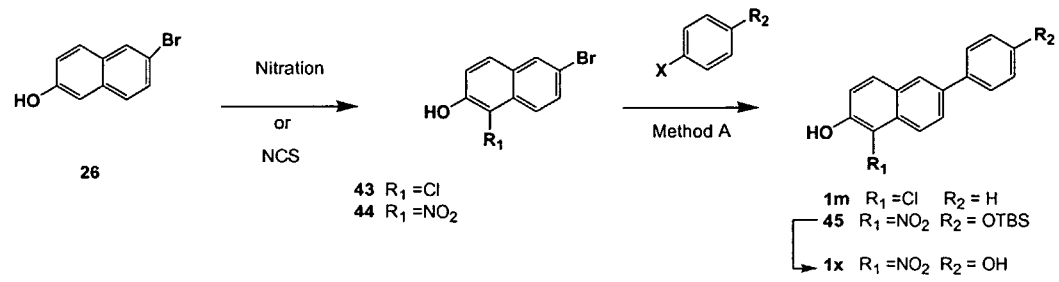
Scheme 7



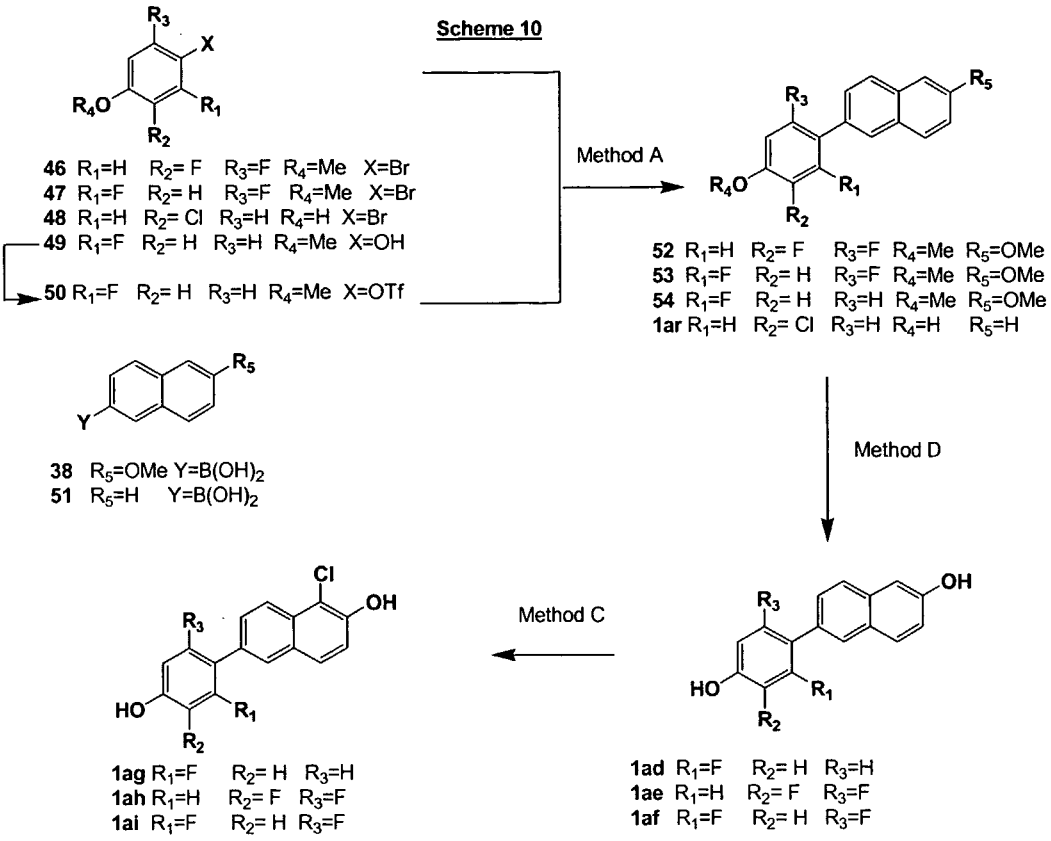
Scheme 8



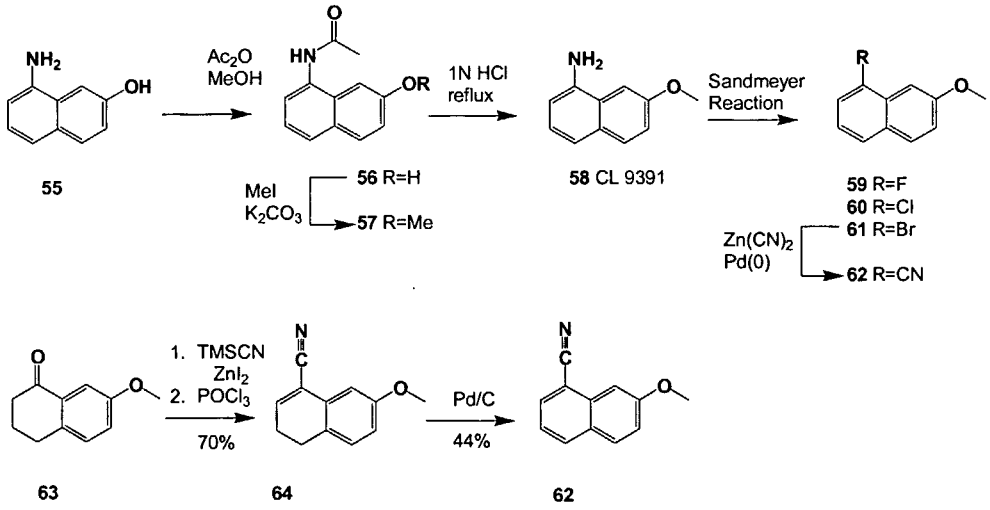
Scheme 9



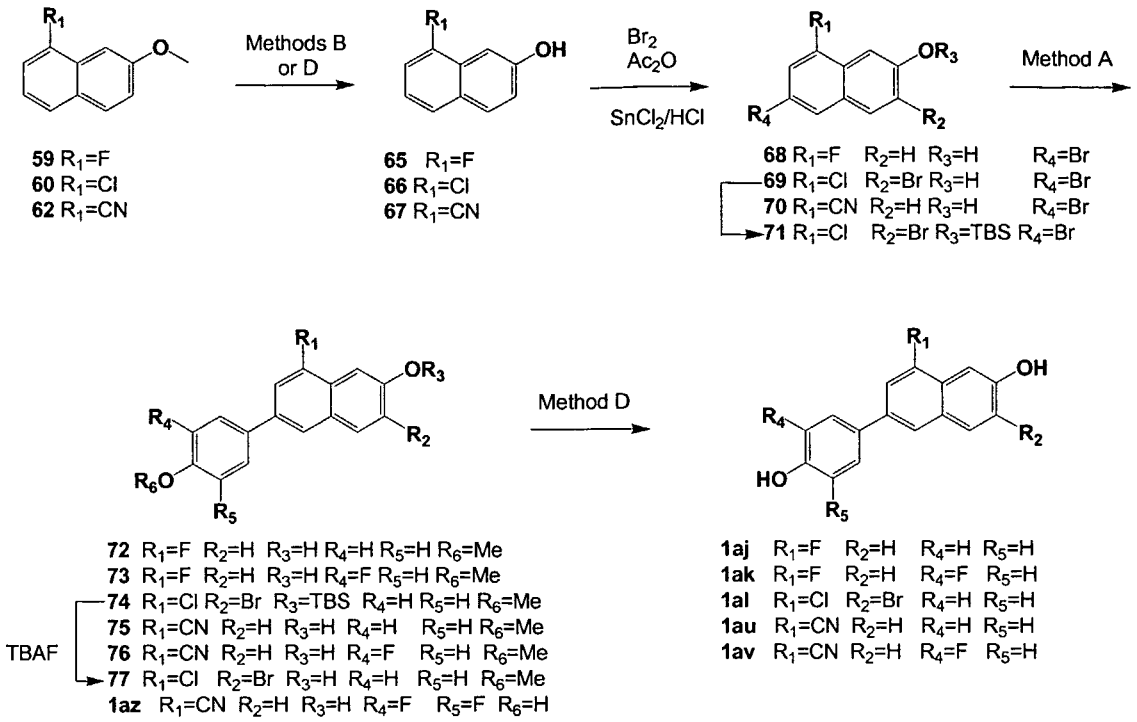
Scheme 10



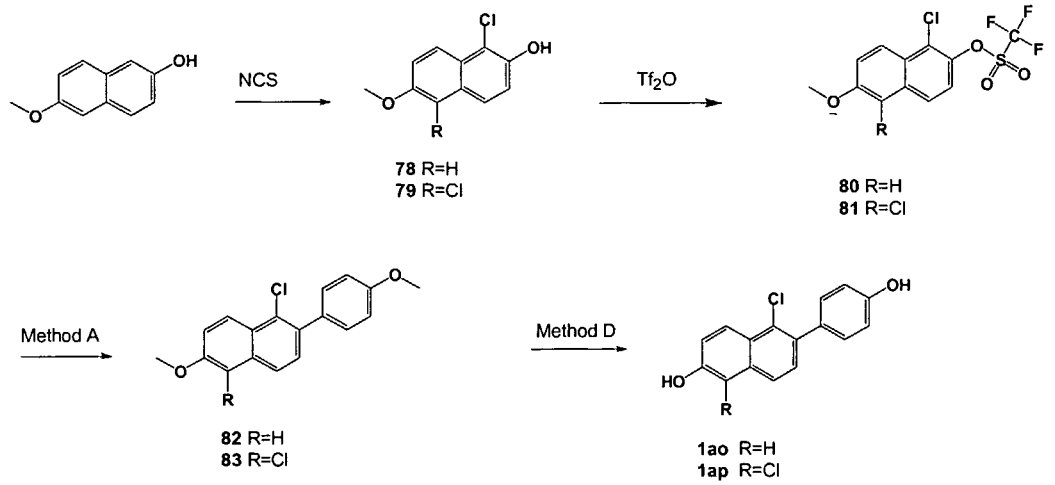
Scheme 11

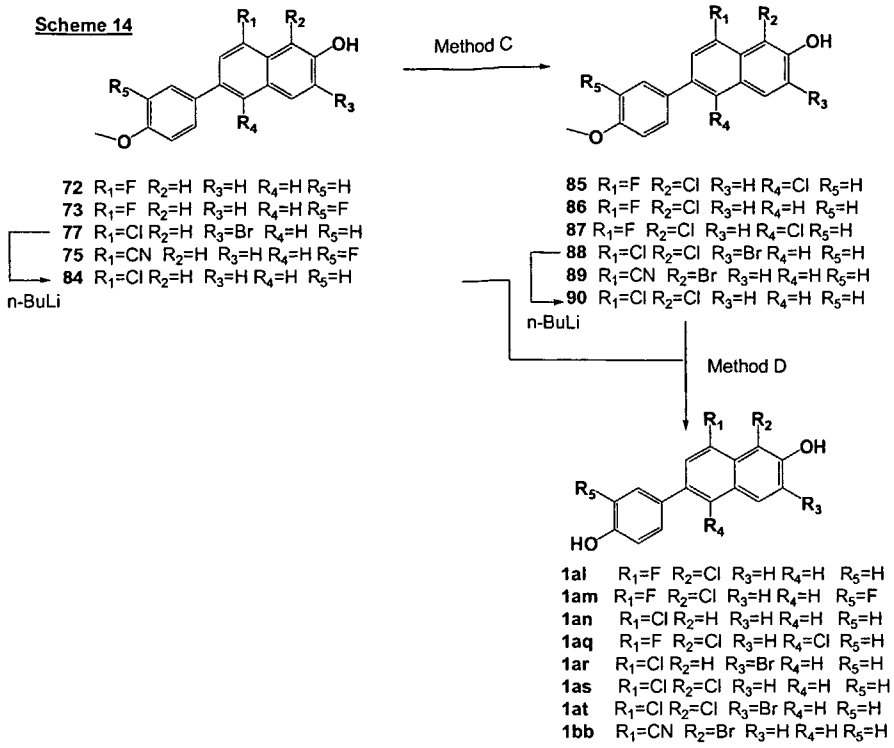


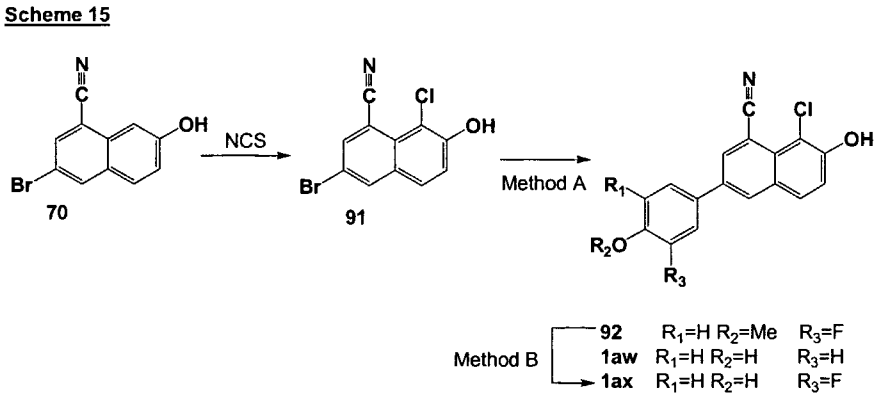
Scheme 12



Scheme 13







Standard pharmacological test procedures are readily available to determine the activity profile of a given test compound. The following briefly summarizes several representative test procedures and may include data for representative compounds of the invention. All assays, except the radioligand binding assay, can be used to detect estrogen receptor agonist or antagonist activity of compounds. In general, estrogen receptor agonist activity is measured by comparing the activity of the compound to a

reference estrogen (e.g. 17β-estradiol, 17α-ethinyl,17β-estradiol, estrone, diethylstilbesterol etc). Estrogen receptor antagonist activity is generally measured by co-treating the test compound with the reference estrogen and comparing the result to that obtained with the reference estrogen alone. Standard pharmacological test procedures for SERMs are also provided in US Patents 4,418,068 and 5,998,402 which are hereby incorporated by reference.

Evaluation of binding affinities to ERα and ERβ

Representative examples of the invention were evaluated for their ability to compete with 17β-estradiol for both ERα and ERβ in a conventional radioligand binding assay. This test procedure provides the methodology for one to determine the relative binding affinities for the ERα or ERβ recptors. The procedure used is briefly described below.

Preparation of receptor extracts for characterization of binding selectivity. The ligand binding domains, conveniently defined here as all sequence downstream of the DNA binding domain, were obtained by PCR using full length cDNA as templates and primers that contained appropriate restriction sites for subcloning while maintaining the appropriate reading frame for expression. These templates contained amino acids M_{250}-V_{595} of human ERα [Green, et al., Nature 320: 134-9 (1986)] and M_{214}-Q_{530} of human ERβ [Ogawa, et al., Biochemical & Biophysical Research Communications 243: 122-6 (1998)]. Human ERβ was cloned into pET15b (Novagen, Madison WI) as a Nco1-BamH1 fragment bearing a C-terminal Flag tag. Human ERα was cloned as for human ERβ except that an N-terminal His tag was added. The sequences of all constructs used were verified by complete sequencing of both strands.

BL21(DE3) cells were used to express the human proteins. Typically a 10 mL overnight culture was used to inoculate a 1 L culture of LB medium containing 100 μg/mL of ampicillin. After incubation overnight at 37°C, IPTG was added to a final concentration of 1 mM and incubation proceeded at 25°C for 2 hours. Cells were harvested by centrifugation (1500 x *g*) , and the pellets washed with and resuspended in 100 mL of 50 mM Tris-Cl (pH 7.4), 150 mM NaCl. Cells were lysed by passing twice through a French press at 12000 psi. The lysate was clarified by centrifugation at 12,000 x *g* for 30 minutes at 4 °C and stored at –70°C.

Evaluation of extracts for specific [^{3}H]-estradiol binding. Dulbecco's phosphate buffered saline (Gibco, 1x final concentration) supplemented with 1 mM EDTA was used as the assay buffer. To optimize the amount of receptor to use in the assay, [^{3}H]-17β-estradiol (New England Nuclear; final concentration = 2 nM) ± 0.6 μM diethlystilbestrol and 100 μL of various dilutions of the E. coli lysate were added to each well of a high binding masked microtiter plate (EG&G Wallac). The final assay volume was 120 μL and the concentration of DMSO was ≤ 1%. After incubation at room temperature for 5-18 hours, unbound material was aspirated and the plate washed three times with approximately 300 μL of assay buffer. After washing, 135 μL of scintillation cocktail (Optiphase Supermix, EG&G Wallac) was added to the wells, and the plate was sealed and agitated for at least 5 minutes to mix scintillant with residual wash buffer. Bound radioactivity was evaluated by liquid scintillation counting (EG&G Wallac Microbeta Plus).

After determining the dilution of each receptor preparation that provided maximum specific binding, the assay was further optimized by estimating the IC_{50} of unlabelled 17β-estradiol using various dilutions of the receptor preparation. A final working dilution for each receptor preparation was chosen for which the IC_{50} of unlabelled 17β-estradiol was 2-4 nM.

Ligand binding competition test procedure. Test compounds were initially solubilized in DMSO and the final concentration of DMSO in the binding assay was ≤1%. Eight dilutions of each test compound were used as an unlabelled competitor for [^{3}H]-17β-estradiol. Typically, a set of compound dilutions would be tested simultaneously on human ERα and ERβ. The results were plotted as measured DPM vs. concentration of test compound. For dose-response curve fitting, a four parameter logistic model on the transformed, weighted data was fit and the IC_{50} was defined as the concentration of compound decreasing maximum [^{3}H]-estradiol binding by 50%.

Binding affinities for ERα and ERβ (as measured by IC_{50}) for representative examples of the invention are shown in Table (1).

Table 1: ER binding affinities of representative compounds of the invention

Example	ER-β IC_{50} (nM)	ER-α IC_{50} (nM)
1a	0.054	0.280
1b	0.570	3.140
1c	0.527	3.405
1d	0.006	0.022
1e	0.0175	0.180
1f	0.245	0.638
1g	0.374	1.345
1h	0.030	0.230
1i	0.519	1.360
1j	0.242	2.120
1k	0.006	0.092
1l	0.011	0.107
1m	0.468	1.785
1n	1.360	3.070
1o	0.0127	0.266
1p	0.0025	0.091
1q	0.114	0.884
1r	0.007	0.077
1s	0.081	1.402
1t	0.657	1.720
1u	0.017	0.282
1v	0.004	0.143
1w	0.032	0.356
1x	0.206	0.802
1y	0.013	0.140
1z	0.0095	0.039
1aa	0.027	0.074
1ab	0.001	0.006
1ac	0.0032	0.0032
1ad	0.0020	0.024

Table 1: ER binding affinities of representative compounds of the invention		
1ae	0.0027	0.018
1af	0.002	0.008
1ag	0.0012	0.058
1ah	0.011	0.131
1ai	0.0025	0.038
1aj	0.0016	0.022
1ak	0.0015	0.021
1al	0.0011	0.040
1am	0.0025	0.125
1an	0.0035	0.029
1ao	0.0016	0.012
1ap	0.002	0.029
1aq	0.002	0.017
1ar	0.004	0.052
1as	0.0085	0.043
1at	0.010	0.160
1au	0.0023	0.105
1av	0.0028	0.208
1aw	0.006	0.109
1ax	0.011	0.299
1ay	0.0084	0.092
1az	0.058	0.548
1ba	0.011	0.519
1bb	0.0095	0.095

The results obtained in the standard pharmacologic test procedure described above demonstrate that the compounds of this invention bind both subtypes of the estrogen receptor. The IC_{50}s are generally lower for ERβ, indicating these compounds are preferentially ERβ selective ligands, but are still considered active at ERα. Compounds of this invention will exhibit a range of activity based, at least partially, on their receptor affinity selectivity profiles. Since the compounds of the

invention bind ER-β with higher affinity than ER-α, they will be useful in treating or inhibiting diseases that can be modulated via ER-β. Additionally, since each receptor ligand complex is unique and thus its interaction with various coregulatory proteins is unique, compounds of this invention will display different and unpredictable activities depending on cellular context. For example, in some cell-types, it is possible for a compound to behave as an estrogen receptor agonist while in other tissues, an estrogen receptor antagonist. Compounds with such activity have sometimes been referred to as SERMs (Selective Estrogen Receptor Modulators). Unlike many estrogens, however, many of the SERMs do not cause increases in uterine wet weight. These compounds are antiestrogenic in the uterus and can completely antagonize the trophic effects of estrogen receptor agonists in uterine tissue. These compounds, however, act as estrogen receptor agonists in the bone, cardiovascular, and central nervous systems. Due to this tissue selective nature of these compounds, they are useful in treating or inhibiting in a mammal disease states or syndromes which are caused or associated with an estrogen deficiency (in certain tissues such as bone or cardiovascular) or an excess of estrogen (in the uterus or mammary glands). In addition, compounds of this invention also have the potential to behave as estrogen receptor agonists on one receptor type while behaving as estrogen receptor antagonists on the other. For example, it has been demonstrated that compounds can be antagonize the action of 17β-estradiol via ERβ while exhibiting estrogen receptor agonist activity with ERα [Sun, et al., Endocrinology 140: 800-804 (1999)]. Such ERSAA (Estrogen Receptor Selective Agonist Antagonist) activity provides for pharmacologically distinct estrogenic activity within this series of compounds

Regulation of metallothionein-II mRNA

Estrogens acting through ERβ, but not ERα can upregulate metallothionein II mRNA levels in Saos-2 cells as described by Harris [Endocrinology 142: 645-652 (2001)]. Results from this test procedure can be combined with results from the test procedure described below (ERE reporter test procedure) to generate a selectivity profile for compounds of this invention (see also WO 00/37681). Data for representative compounds of the invention are shown in Table (2).

Table 2: Regulation of metallothionein-II mRNA in Saos-2 cells	
Example 1e	17.0
Example 1l	5.5
Example 1o	5.7
Example 1p	6.0
Example 1s	4.9

Evaluation of test compound using an ERE-reporter test procedure in MCF-7 breast cancer cells

Stock solutions of test compounds (usually 0.1 M) are prepared in DMSO and then diluted 10 to 100-fold with DMSO to make working solutions of 1 or 10 mM. The DMSO stocks are stored at either 4°C (0.1 M) or –20°C (< 0.1M). MCF-7 cells are passaged twice a week with growth medium [D-MEM/F-12 medium containing 10% (v/v) heat-inactivated fetal bovine serum, 1% (v/v) Penicillin-Streptomycin, and 2 mM glutaMax-1]. The cells are maintained in vented flasks at 37°C inside a 5% CO_2/95% humidified air incubator. One day prior to treatment, the cells are plated with growth medium at 25,000 cells/well into 96 well plates and incubated at 37 °C overnight.

The cells are infected for 2 hr at 37°C with 50 μl/well of a 1:10 dilution of adenovirus 5-ERE-tk-luciferase in experimental medium [phenol red-free D-MEM/F-12 medium containing 10% (v/v) heat-inactived charcoal-stripped fetal bovine serum, 1% (v/v) Penicillin-Streptomycin, 2 mM glutaMax-1, 1 mM sodium pyruvate]. The wells are then washed once with 150 μl of experimental medium. Finally, the cells are treated for 24 hr at 37 °C in replicates of 8 wells/treatment with 150 μl/well of vehicle (≤ 0.1% v/v DMSO) or compound that is diluted ≥ 1000-fold into experimental medium.

Initial screening of test compounds is done at a single dose of 1 μM that is tested alone (estrogen receptor agonist mode) or in combination with 0.1 nM 17β-estradiol (EC_{80}; estrogen receptor antagonist mode). Each 96 well plate also includes a vehicle control group (0.1% v/v DMSO) and an estrogen receptor agonist control group (either 0.1 or 1 nM 17β-estradiol). Dose-response experiments are performed in either the estrogen receptor agonist and/or estrogen receptor antagonist modes on active compounds in log increases from 10^{-14} to 10^{-5} M. From these dose-response curves, EC_{50} and IC_{50} values, respectively, are generated. The final well

in each treatment group contains 5 μl of 3 x 10^{-5} M ICI-182,780 (10^{-6} M final concentration) as an estrogen receptor antagonist control.

After treatment, the cells are lysed on a shaker for 15 min with 25 μl/well of 1X cell culture lysis reagent (Promega Corporation). The cell lysates (20 μl) are transferred to a 96 well luminometer plate, and luciferase activity is measured in a MicroLumat LB 96 P luminometer (EG & G Berthold) using 100 μl/well of luciferase substrate (Promega Corporation). Prior to the injection of substrate, a 1 second background measurement is made for each well. Following the injection of substrate, luciferase activity is measured for 10 seconds after a 1 second delay. The data are transferred from the luminometer to a Macintosh personal computer and analyzed using the JMP software (SAS Institute); this program subtracts the background reading from the luciferase measurement for each well and then determines the mean and standard deviation of each treatment.

The luciferase data are transformed by logarithms, and the Huber M-estimator is used to down-weight the outlying transformed observations. The JMP software is used to analyze the transformed and weighted data for one-way ANOVA (Dunnett's test). The compound treatments are compared to the vehicle control results in the estrogen receptor agonist mode, or the positive estrogen receptor agonist control results (0.1 nM 17β-estradiol) in the estrogen receptor antagonist mode. For the initial single dose experiment, if the compound treatment results are significantly different from the appropriate control ($p<0.05$), then the results are reported as the percent relative to the 17β-estradiol control [i.e., ((compound - vehicle control)/(17β-estradiol control - vehicle control)) x 100]. The JMP software is also used to determine the EC_{50} and/or IC_{50} values from the non-linear dose-response curves.

Evaluation of uterotrophic activity

Uterotrophic activity of a test compound can be measured according to the following standard pharmacological test procedures.

Procedure 1: Sexually immature (18 days of age) Sprague-Dawley rats were obtained from Taconic and provided unrestricted access to a casein-based diet (Purina Mills 5K96C) and water. On day 19, 20 and 21 the rats were dosed subcutaneously with 17α-ethinyl-17β-estradiol (0.06 μg/rat/day), test compound or vehicle (50% DMSO/50% Dulbecco's PBS). To assess estrogen receptor antagonist,

compounds were coadministered with 17α-ethinyl-17β-estradiol (0.06 μg/rat/day). There were six rats/group and they were euthanized approximately 24 hours after the last injection by CO_2 asphyxiation and pneumothorax. Uteri were removed and weighed after trimming associated fat and expressing any internal fluid. A tissue sample can also be snap frozen for analysis of gene expression (e.g. complement factor 3 mRNA). Results obtained from representative compounds of the invention are shown in Table (3).

Table 3: Evaluation of selected compounds in a rat uterotrophic Test Procedure.

Compound	mean uterine weight (mg) ± SEM
Vehicle	21.4 ± 1.6
17α-ethinyl-17β-estradiol (0.06μg/rat/day)	85.5 ± 3.1
Example 1av (2mg/rat/day)	23.3 ± 1.3
Example 1av (2mg/rat/day) + 17α-ethinyl-17β-estradiol (0.06μg/rat/day)	81.9 ± 4.2

Procedure 2: Sexually immature (18 days of age) 129 SvE mice were obtained from Taconic and provided unrestricted access to a casein-based diet (Purina Mills 5K96C) and water. On day 22, 23, 24 and 25 the mice were dosed subcutaneously with compound or vehicle (corn oil). There were six mice/group and they are euthanized approximately 6 hours after the last injection by CO_2 asphyxiation and pneumothorax. Uteri were removed and weighed after trimming associated fat and expressing any internal fluid. The following results (Table (4)) were obtained for representative compounds from the invention.

Table 4: Evaluation of selected compounds in a mouse uterotrophic Test Procedure.

Compound	mean uterine weight (mg) ± SEM
Vehicle	10.3 ± 0.8
17β-estradiol (50mg/kg/day)	45.3 ± 1.9
Example 1av (50mg/kg/day)	12.6 ± 0.8

Evaluation of osteoporosis and lipid modulation (cardioprotection)

Female Sprague-Dawley rats, ovariectomized or sham operated, are obtained 1 day after surgery from Taconic Farms (weight range 240 - 275 g). They are housed 3 or 4 rats/cage in a room on a 12/12 (light/dark) schedule and provided with food (Purina 5K96C rat chow) and water ad libitum. Treatment for all studies begin 1 day after arrival and rats are dosed 7 days per week as indicated for 6 weeks. A group of age matched sham operated rats not receiving any treatment serve as an intact, estrogen replete control group for each study.

All test compounds are prepared in a vehicle of 50% DMSO (JT Baker, Phillipsburg, NJ) / 1x Dulbecco's phosphate saline (GibcoBRL, Grand Island, NY) at defined concentrations so that the treatment volume is 0.1 mL/100 g body weight. 17β–estradiol is dissolved in corn oil (20 μg/mL) and delivered subcutaneously, 0.1 mL/rat. All dosages are adjusted at three week intervals according to group mean body weight measurements, and given subcutaneously.

Five weeks after the initiation of treatment and one week prior to the termination of the study, each rat is evaluated for bone mineral density (BMD). The total and trabecular density of the proximal tibia are evaluated in anesthetized rats using an XCT-960M (pQCT; Stratec Medizintechnik, Pforzheim, Germany). The measurements are performed as follows: Fifteen minutes prior to scanning, each rat is anesthetized with an intraperitoneal injection of 45 mg/kg ketamine, 8.5 mg/kg xylazine, and 1.5 mg/kg acepromazine.

The right hind limb is passed through a polycarbonate tube with a diameter of 25 mm and taped to an acrylic frame with the ankle joint at a 90° angle and the knee joint at 180°. The polycarbonate tube is affixed to a sliding platform that maintains it perpendicular to the aperture of the pQCT. The platform is adjusted so that the distal end of the femur and the proximal end of the tibia is in the scanning field. A two dimensional scout view is run for a length of 10 mm and a line resolution of 0.2 mm. After the scout view is displayed on the monitor, the proximal end of the tibia is located. The pQCT scan is initiated 3.4 mm distal from this point. The pQCT scan is 1 mm thick, has a voxel (three dimensional pixel) size of 0.140 mm, and consists of 145 projections through the slice.

After the pQCT scan is completed, the image is displayed on the monitor. A region of interest including the tibia but excluding the fibula is outlined. The soft tissue is mathematically removed using an iterative algorithm. The density of the remaining

bone (total density) is reported in mg/cm^3. The outer 55% of the bone is mathematically peeled away in a concentric spiral. The density of the remaining bone (Trabecular density) is reported in mg/cm^3.

One week after BMD evaluation the rats are euthanized by CO_2 asphyxiation and pneumothorax, and blood is collected for cholesterol determination. The uteri are also removed and the weighed after trimming associated fat and expressing any luminal fluid. Total cholesterol is determined using a Boehringer-Mannheim Hitachi 911 clinical analyzer using the Cholesterol/HP kit. Statistics were compared using one-way analysis of variance with Dunnet's test.

Evaluation of antioxidant activity

Porcine aortas are obtained from an abattoir, washed, transported in chilled PBS, and aortic endothelial cells are harvested. To harvest the cells, the intercostal vessels of the aorta are tied off and one end of the aorta clamped. Fresh, sterile filtered, 0.2% collagenase (Sigma Type I) is placed in the vessel and the other end of the vessel then clamped to form a closed system. The aorta is incubated at 37 °C for 15-20 minutes, after which the collagenase solution is collected and centrifuged for 5 minutes at 2000 x g. Each pellet is suspended in 7 mL of endothelial cell culture medium consisting of phenol red free DMEM/Ham's F12 media supplemented with charcoal stripped FBS (5%), NuSerum (5%), L-glutamine (4 mM), penicillin-streptomycin (1000 U/ml, 100 μg/ml) and gentamycin (75 μg/ml), seeded in 100 mm petri dish and incubated at 37 °C in 5%CO_2. After 20 minutes, the cells are rinsed with PBS and fresh medium added, this was repeated again at 24 hours. The cells are confluent after approximately 1 week. The endothelial cells are routinely fed twice a week and, when confluent, trypsinized and seeded at a 1:7 ratio. Cell mediated oxidation of 12.5 μg/mL LDL is allowed to proceed in the presence of the compound to be evaluated (5 μM) for 4 hours at 37 °C. Results are expressed as the percent inhibition of the oxidative process as measured by the TBARS (thiobarbituric acid reactive substances) method for analysis of free aldehydes [Yagi, Biochemical Medicine 15: 212-6 (1976)].

Progesterone receptor mRNA regulation standard pharmacological test procedure

This test procedure can be used to evaluate the estrogenic or antiestrogenic activity of compounds from this invention [Shughrue, et al., Endocrinology 138: 5476-

5484 (1997)]. Data for representative compounds of the invention are shown in Table (5).

Table 5. Effect of representative compounds of the invention on regulation of progesterone mRNA in the preoptic area of the rat brain	
Compound	Progesterone receptor mRNA (arbitrary units; mean ± stdev)
Vehicle	55.4 ± 9.4
17β-estradiol (30μg/kg)	557.1 ± 80.6
Example 1av (10mg/kg)	33.7 ± 20.6

Rat Hot Flush Test Procedure

The effect of test compounds on hot flushes can be evaluated in a standard pharmacological test procedure which measures the ability of a test compound to blunt the increase in tail skin temperature which occurs as morphine-addicted rats are acutely withdrawn from the drug using naloxone [Merchenthaler, et al., Maturitas 30: 307-16 (1998)]. It can also be used to detect estrogen receptor antagonist activity by co-dosing test compound with the reference estrogen.

Evaluation of vasomotor function in isolated rat aortic rings

Sprague-Dawley rats (240-260 grams) are divided into 4 groups:
1. Normal non-ovariectomized (intact)
2. Ovariectomized (ovex) vehicle treated
3. Ovariectomized 17β–estradiol treated (1 mg/kg/day)
4. Ovariectomized animals treated with test compound (various doses)

Animals are ovariectomized approximately 3 weeks prior to treatment. Each animal receives either 17-β estradiol sulfate (1 mg/kg/day) or test compound suspended in distilled, deionized water with 1% tween-80 by gastric gavage. Vehicle treated animals received an appropriate volume of the vehicle used in the drug treated groups.

Animals are euthanized by CO_2 inhalation and exsanguination. Thoracic aortae are rapidly removed and placed in 37°C physiological solution with the following composition (mM): NaCl (54.7), KCl (5.0), $NaHCO_3$ (25.0), $MgCl_2$ $2H_2O$ (2.5), D-glucose (11.8) and $CaCl_2$ (0.2) gassed with CO_2-O_2, 95%/5% for a final pH of 7.4. The advantitia is removed from the outer surface and the vessel is cut into 2-3

mm wide rings. Rings are suspended in a 10 mL tissue bath with one end attached to the bottom of the bath and the other to a force transducer. A resting tension of 1 gram is placed on the rings. Rings are equilibrated for 1 hour, signals are acquired and analyzed.

After equilibration, the rings are exposed to increasing concentrations of phenylephrine (10^{-8} to 10^{-4} M) and the tension recorded. Baths are then rinsed 3 times with fresh buffer. After washout, 200 mM L-NAME is added to the tissue bath and equilibrated for 30 minutes. The phenylephrine concentration response curve is then repeated.

Evaluation of cardioprotective activity

Apolipoprotein E-deficient C57/B1J (apo E KO) mice are obtained from Taconic Farms. All animal procedures are performed under strict compliance to IACUC guidelines. Ovariectomized female apo E KO mice, 4-7 weeks of age, are housed in shoe-box cages and were allowed free access to food and water. The animals are randomized by weight into groups (n=12-15 mice per group). The animals are dosed with test compounds or estrogen (17β-estradiol sulfate at 1 mg/kg/day) in the diet using a Precise-dosing Protocol, where the amount of diet consumed is measured weekly, and the dose adjusted accordingly, based on animal weight. The diet used is a Western-style diet (57U5) that is prepared by Purina and contains 0.50% cholesterol, 20% lard and 25 IU/KG Vitamin E. The animals are dosed/fed using this paradigm for a period of 12 weeks. Control animals are fed the Western-style diet and receive no compound. At the end of the study period, the animals are euthanized and plasma samples obtained. The hearts are perfused in situ, first with saline and then with neutral buffered 10% formalin solution.

For the determination of plasma lipids and lipoproteins, total cholesterol and triglycerides are determined using enzymatic methods with commercially available kits from Boehringer Mannheim and Wako Biochemicals, respectively and analyzed using the Boehringer Mannheim Hitachii 911 Analyzer. Separation and quantification of plasma lipoproteins were performed using FPLC size fractionation. Briefly, 50-100 mL of serum is filtered and injected into Superose 12 and Superose 6 columns connected in series and eluted at a constant flow rate with 1 mM sodium EDTA and 0.15 M NaCl. Areas of each curve representing VLDL, LDL and HDL are integrated using Waters Millennium™ software, and each lipoprotein fraction is quantified by multiplying the

Total Cholesterol value by the relative percent area of each respective chromatogram peak.

For the quantification of aortic atherosclerosis, the aortas are carefully isolated and placed in formalin fixative for 48-72 hours before handling. Atherosclerotic lesions are identified using Oil Red O staining. The vessels are briefly destained, and then imaged using a Nikon SMU800 microscope fitted with a Sony 3CCD video camera system in concert with IMAQ Configuration Utility (National Instrument) as the image capturing software. The lesions are quantified en face along the aortic arch using a custom threshold utility software package (Coleman Technologies). Automated lesion assessment is performed on the vessels using the threshold function of the program, specifically on the region contained within the aortic arch from the proximal edge of the brachio-cephalic trunk to the distal edge of the left subclavian artery. Aortic atherosclerosis data are expressed as percent lesion involvement strictly within this defined luminal area.

Evaluation of cognition enhancement

Ovariectomized rats (n=50) are habituated to an 8-arm radial arm maze for 10-min periods on each of 5 consecutive days. Animals are water-deprived prior to habituation and testing. A 100 µL aliquot of water placed at the ends of each arm serves as reinforcement. Acquisition of a win-shift task in the radial arm maze is accomplished by allowing the animal to have access to one baited arm. After drinking, the animal exits the arm and re-enters the central compartment, where it now has access to the previously visited arm or to a novel arm. A correct response is recorded when the animal chooses to enter a novel arm. Each animal is given 5 trials per day for 3 days. After the last acquisition trial, the animals are assigned to one of the following 4 groups:

1. Negative controls: injected with 10% DMSO/ sesame oil vehicle once daily for 6 days (1 mL/kg, SC)
2. Positive controls: injected with 17β-estradiol benzoate for 2 days and tested 4 days after the second injection (17β-estradiol benzoate at 10 µg/0.1 mL per rat)
3. Estradiol: 17β-estradiol will be injected daily for 6 days (20 µg/kg, SC)
4. Test compound: injected daily for 6 days (doses vary).

All injections will begin after testing on the last day of acquisition. The last injection for groups 1, 3, and 4 will take place 2 hours before testing for working memory.

The test for working memory is a delayed non-matching-to-sample task (DNMS) utilizing delays of 15, 30, or 60 seconds. This task is a variation of the acquisition task in which the rat is placed in the central arena and allowed to enter one arm as before. A second arm is opened once the rat traverses halfway down the first arm, and again the rat is required to choose this arm. When it has traveled halfway down this second arm, both doors are closed and the delay is instituted. Once the delay has expired, both of the original two doors, and a third novel door, are opened simultaneously. A correct response is recorded when the animal travels halfway down the third, novel arm. An incorrect response is recorded when the animal travels halfway down either the first or second arms. Each animal will receive 5 trials at each of the three delay intervals for a total of 15 trials per subject.

Evaluation of effect on pleurisy

The ability to reduce the symptoms of experimentally-induced pleurisy in rats can be evaluated according to the procedure of Cuzzocrea [Endocrinology 141: 1455-63 (2000)].

Evaluation of protection against glutamate-induced cytotoxicity (neuroprotection)

The neuroprotective activity of compounds of this invention can be evaluated in an in vitro standard pharmacological test procedure using glutamate challenge [Zaulyanov, et al., Cellular & Molecular Neurobiology 19: 705-18 (1999); Prokai, et al., Journal of Medicinal Chemistry 44: 110-4 (2001)].

Evaluation in the Mammary End Bud Test Procedure

Estrogens are required for full ductal elongation and branching of the mammary ducts, and the subsequent development of lobulo-alveolar end buds under the influence of progesterone. In this test procedure, the mammotrophic activity of selected compounds of the invention was evaluated according to the following standard pharmacological test procedure. Twenty-eight day old Sprague-Dawley rats (Taconic Farms, Germantown, NY) were ovariectomized and rested for nine days. Animals were housed under a 12-hour light/dark cycle and fed a casein-based Purina Laboratory Rodent Diet 5K96 (Purina, Richmond, IN) and allowed free access to water. Rats were then dosed subcutaneously for six days with vehicle (50% DMSO

(JT Baker, Phillipsburg, NJ) / 50% 1x Dulbecco's Phosphate buffered saline (GibcoBRL, Grand Island, NY), 17β-estradiol (0.1 mg/kg) or test compound (20 mg/kg). For the final three days, rats were also dosed subcutaneously with progesterone (30 mg/kg). On the seventh day, rats were euthanised and a mammary fat pad excised. This fat pad was analyzed for casein kinase II mRNA as a marker of end bud proliferation. Casein kinase II mRNA was anlayzed by real-time RT-PCR. Briefly, RNA was isolated following Trizol (GibcoBRL, Grand Island, NY) according to the manufacture's directions, Samples were treated with DNAse I using DNA-free kit (Ambion), and casein kinase II mRNA levels were measured by real-time RT-PCR using the Taqman Gold procedure (PE Applied Biosystems). A total of 50 ng of RNA was analyzed in triplicate using casein kinase II specific primer pair (5' primer, CACACGGATGGCGCATACT; 3' primer, CTCGGGATGCACCATGAAG) and customized probe (TAMRA-CGGCACTGGTTTCCCTCACATGCT-FAM). Casein kinase II mRNA levels were normalized to 18s ribosomal RNA contained within each sample reaction using primers and probe supplied by PE Applied Biosystems. The following results were obtained for representative compounds of the invention (Table (6)).

Table 6: Evaluation of compounds in a rat mammotrophic assay

Compound	Casein kinase II mRNA/18S rRNA (mean ± SEM)
Vehicle	2.66 ± 0.13
Progesterone (30mg/kg) + 17β-estradiol (0.1mg/kg)	39.0 ± 5.4
Progesterone (30mg/kg) + Example 1av (20mg/kg)	1.06 ± 0.17

Evaluation in the HLA Rat Standard Pharmacological Test Procedure for inflammatory bowel disease

Compounds of the invention can be evaluated in the HLA rat standard pharmacological test procedure that emulates inflammatory bowel disease in humans. The following briefly describes the procedure used and results obtained. Male HLA-B27 rats (8-10 weeks old) were obtained from Taconic and provided unrestricted access to food (PMI Lab diet 5001) and water. Rats were dosed orally each day for 46 days with either vehicle (2% tween-80/0.5% mentylcellulose) or Example 1av (10mg/kg). Stool quality was observed daily and graded according to the following

scale: Diarrhea = 3; soft stool = 2; normal stool = 1. At the end of the study, serum was collected and stored at –70°C. A section of colon was prepared for histological analysis and an additional segment was analyzed for myeloperoxidase activity. The following results were obtained (Table (7)) and show that stool character normalized within 21 days of administration of Example 1av.

Table 7: Stool scores from HLA rats treated orally with vehicle or Example 1av for 46 days. Value reported is the group's average score for the first 26 days of dosing.

Day	Vehicle	Example 1av
1	2.75	2.75
2	3	2.5
3	3	2.25
4	3	2.5
5	3	2.25
6	3	2.5
7	3	2.5
8	3	2
9	3	2
10	3	1.5
11	3	1.5
12	3	1.5
13	3	1.75
14	3	1.75
15	3	1.5
16	3	1.5
17	3	1.25
18	3	1.25
19	3	1.25
20	3	1.25
21	3	1.25
22	3	1
23	3	1
24	3	1
25	3	1

3= diarrhea; 2= soft stool; 1=normal stool

For histological analysis, colonic tissue was immersed in 10% neutral buffered formalin. Each specimen of colon was separated into four samples for evaluation. The formalin-fixed tissues were processed in a Tissue Tek vacuum infiltration processor (Miles, Inc; West Haven, Connecticut) for paraffin embedding. The samples were sectioned at 5 µm and then stained with hematoxylin and eosin (H&E) for blinded histologic evaluations using a scale modified after Boughton-Smith. After the scores were completed the samples were unblinded, and data were tabulated and analyzed by ANOVA linear modeling with multiple mean comparisons. Sections of colonic tissue were evaluated for several disease indicators and given relative scores.

As shown in Table (8) Example 1av is effective in reducing several measurements of tissue injury.

Table 8: Histological scoring of disease severity in the HLA-B27 rat model after oral dosing for 46 days with vehicle or Example 1av.

Group	Ulceration (0-2)	Inflammation (0-3)	Lesion depth (0-2)	Fibrosis (0-2)	Total score
Vehicle	1.19 ± 0.69	2.38 ± 0.32	1.0 ± 0.54	0.94 ± 0.75	5.50 ± 2.1
Example 1av	0.44 ± 0.43	1.13 ± 0.43*	0.38 ± 0.43	0.07 ± 0.13*	2.00 ± 1.14*

* sig < vehicle

Evaluation in two models of arthritis

Lewis rat assay of adjuvant-induced arthritis. Sixty, female, 12 weeks old, Lewis rats are housed according to standard facility operating procedures. They receive a standard regimen of food and water ad libitum. Each animal is identified by a cage card indicating the project group and animal number. Each rat number is marked by indelible ink marker on the tail. At least 10-21 days before study they are anesthetized and ovariectomized by standard aseptic surgical techniques.

Freund's Adjuvant-Complete (Sigma Immuno Chemicals, St. Louis, MO) is used to induce arthritis, each mL containing 1 mg Mycobacterium tuberculosis heat killed and dried, 0.85 mL mineral oil and 0.15 mL mannide monooleate Lot No. 084H8800.

The following are examples of two test procedures. Inhibition test procedure: Thirty rats are injected intradermally with 0.1 mL of Freund's Adjuvant-Complete at the base of the tail. The animals are randomized to groups of six rats each., Each day, the groups receive vehicle (50% DMSO (JT Baker, Phillipsburg, NJ) / 1x Dulbecco's phosphate saline (GibcoBRL, Grand Island, NY)) or test compound (administered subcutaneously). All rats began treatment on Day 1. Data for Example 1av is shown in Table (9).

Treatment test procedure: Thirty rats are injected intradermally with 0.1 mL of Freund's Adjuvant-Complete at the base of the tail. The animals are randomized to four groups, each group containing six rats. Each day, the groups receive vehicle (50% DMSO (JT Baker, Phillipsburg, NJ) / 1x Dulbecco's phosphate saline (GibcoBRL, Grand Island, NY)) or test compound (administered subcutaneously). All rats began treatment on Day 8 after adjuvant injection. Data for Example 1av is shown in Tables (10), (11) and (12).

Statistical analysis was performed using Abacus Concepts Super ANOVA. (Abacus Concepts, Inc., Berkeley, CA). All of the parameters of interest were subjected to Analysis of Variance with Duncan's new multiple range post hoc testing between groups. Data are expressed throughout as mean ± standard deviation (SD), and differences were deemed significant if $p<0.05$.

The degree of arthritis severity is monitored daily in terms of the following disease indices: Hindpaw erythema, hindpaw swelling, tenderness of the joints, and movements and posture. An integer scale of 0 to 3 is used to quantify the level of erythema (0= normal paw, 1= mild erythema, 2= moderate erythema, 3= severe erythema) and swelling (0=normal paw, 1=mild swelling, 2= moderate swelling, 3= severe swelling of the hind paw). The maximal score per day is 12.

At the end of the study the rats are euthanized with CO_2, hindlimbs removed at necropsy and fixed in 10% buffered formalin, and the tarsal joints decalcified and embedded in paraffin. Histologic sections are stained with Hematoxylin and Eosin or Saffranin O - Fast Green stain.

Slides are coded so that the examiner is blinded to the treatment groups. Synovial tissue from tarsal joints is evaluated based on synovial hyperplasia, inflammatory cell infiltration, and pannus formation [Poole and Coombs, International Archives of Allergy & Applied Immunology 54: 97-113 (1977)] as outlined below.

Category	Grade
1. Synovial lining cells	
a. No change	0
b. Cells enlarged, slightly thickened	1
c. Cells enlarged, increase in numbers, moderately thickened. No villus present	2
d. Cells enlarged, thickened. Villlus present	3
2. Fibroplasia	
a. No change	0
b. Fibroplasia present under lining cells	1
c. Small areas of areolar tissue replaced by fibrous tissue	2
d. Replacement of areolar tissue by fibrous tissue	3
3. Inflammatory cells	
a. Occasionally seen, scattered throughout selection	0
b. Cells present in small numbers in or just under lining cell layer and/or around blood vessels.	1
c. Small focal collection of cells may be present	2
d. Large numbers of cells present in capsule and in or under lining cell layers. Large foci often seen.	3
4. Pannus	
a. Not detectable	0
b. Detectable	1

In addition, articular cartilage and bone is evaluated using Mankin's histological grading system [Mankin, et al., Journal of Bone & Joint Surgery - American Volume 53: 523-37 (1971)] as shown below.

Category	Grade
1. Structure	
a. Normal	0
b. Surface irregularity	1
c. Pannus and surface irregularity	2
d. Clefts to transitional zone	3
e. Clefts to radial zone	4
f. Clefts to calcified zone	5
g. Complete disorganization	6
2. Cells	
a. Normal	0
b. Diffuse hypercellularity	1
c. Cloning	2
d. Hypocellularity	3
3. Safranin-O staining	
a. Normal	0
b. Slight reduction	1
c. Modest reduction	2
d. Severe reduction	3
e. No dye noted	4
4. Tidemark integrity	
a. Intact	0
b. Crossed by blood vessels	1

Table 9: Evaluation of joint inflammation of Lewis rats: Inhibition protocol

Day	Vehicle	Example 1av
1	0.00	0.00
2	0.00	0.00
3	4.50	2.66
4	5.50	1.83
5	9.33	2.66
6	10.50	2.16
7	10.60	2.00
8	11.00	1.66
9	11.50	2.00
10	11.33	2.00
11	10.83	1.66
12	10.83	1.66
13	11.00	2.16
14	11.00	2.00
15	11.00	2.00
16	11.00	1.00
17	10.50	1.33

Table 10: Evaluation of joint inflammation of Lewis rats: Treatment protocol		
Day	Vehicle	Example 1av
1	10.83	11.33
2	11.00	10.83
3	10.83	9.33
4	11.33	8.00
5	11.50	5.83
6	11.50	3.33
7	11.50	3.00
8	11.50	2.50
9	11.00	2.50
10	11.00	2.50
11	10.66	2.50
12	10.66	2.50
13	10.50	2.50
14	9.83	2.50
15	8.10	2.00
16	7.35	1.33
17	6.50	1.00

Table 11: Histological scoring of synovitis in the tarsal joints of Lewis rats (mean ± SD): Treatment protocol					
Group	Synovial Structure (0-3)	Fibroplasia (0-3)	Inflammatory Cells (0-3)	Pannus (0-1)	Total Synovitis Score (0-10)
Vehicle	2.58 ± 0.38	1.75 ± 0.42	2.92 ± 0.20	1.00 ± 0.89	8.25 ± 1.57
Example 1av 10mg/kg	1.58 ± 0.38*	0.75 ± 0.42*	1.25 ± 0.42*	0.33 ± 0.61*	3.83 ± 0.93*
* sig < vehicle					

Table 12: Histological scoring of cartilage change (Mankin scores) in the tarsal joints of Lewis rats (mean ± SD): Treatment protocol					
Group	Cartilage Structure (0-6)	Cartilage Cells (0-3)	Saffranin-O/ Fast Green Staining (0-4)	Tidemark Integrity (0-1)	Total Mankin Score (0-14)
Vehicle	2.83 ± 0.26	2.58 ± 0.38	2.50 ± 0.32	0	7.92 ± 0.74
Example 1av 10mg/kg	1.83 ± 0.68*	0.75 ± 0.42*	1.25 ± 0.52*	0	3.83 ± 1.21*
* sig < vehicle					

Evaluation in the HLA-B27 Rat model of arthritis. Compounds of the invention can be evaluated in the HLA-B27 rat standard pharmacological test procedure which emulates arthritis in humans. The following briefly describes the procedure used and results obtained. Male HLA-B27 rats were obtained from Taconic and provided unrestricted access to a food (PMI Lab diet 5001) and water. Joint scores and histology are evaluated as described above for the Lewis rat model of adjuvant-induced arthritis. Rats (8-10 weeks old) were dosed orally once per day for forty-six days with either vehilce (2% Tween-80/0.5% methylcellulose) or Example 1av (10mg/kg) There were 4 rats in each group and the last dose was administered two hours before euthanasia. As shown in Table (13), joint inflammation was reduced by treatment with Example 1av. The synovitis and Mankin scores (Table (14)) were also reduced, but were not statistically different than those of vehicle-treated rats.

Table 13: Evaluation of joint inflammation from HLA rats treated orally for 46 days with Example 1av

Day	Vehicle	Example 1av (10mg/kg)
29	2.5	0.5
30	6	0.5
31	5	0.5
32	6.75	1
33	8	1.75
34	8	1.5
35	8	1
36	6	1.75
37	7.5	1.75
38	6.5	1.5
39	7.5	0.75
40	7.5	0.75
41	6.5	0.5
42	6.5	1.5
43	6	1.25
44	6.75	1.75
45	5.5	1.25
46	6	0.75

Table 14: Evaluation of joint histology from HLA rats treated orally for 46 days with Example 1av		
Compound	Synovitis score (mean ± SD)	Mankin score (mean ± SD)
Vehicle	7.6 ± 3.1	6.5 ± 1.2
Example 1av (10mg/kg)	5.0 ± 2.5	4.5 ± 1.8

Evaluation in in vivo models of carcinogeneisis

The ability of compounds of this invention to treat and inhibit various malignancies or hyperprolific disorders can be evaluated in standard pharmacological test procedures that are readily available in the literature, and include the following two procedures.

Breast cancer. Athymic nu/nu (nude) mice are obtained ovariectomized from Charles River Laboratories (Wilmington, MA). One day prior to tumor cell injection, animals are implanted with time-release pellets containing 0.36-1.7 mg 17β-estradiol (60 or 90 day release, Innovative Research of America, Sarasota, FL) or a placebo. The pellet is introduced subcutaneously into the intrascapular region using a 10-gauge precision trochar. Subsequently, mice are injected subcutaneously into the breast tissue with either $1x10^7$ MCF-7 cells or $1x10^7$ BG-1 cells. The cells are mixed with an equal volume of matrigel, a basement membrane matrix preparation to enhance tumor establishment. Test compounds can be evaluated either by dosing one day after tumor cell implantation (inhibition regimen) or after tumors have reached a certain size (treatment regimen). Compounds are administered either intraperitoneally or orally in a vehicle of 1% tween-80 in saline each day. Tumor size is evaluated every three or seven days.

Colon cancer. The ability to treat or inhibit colon cancer can be evaluated in the test procedure of Smirnoff [Oncology Research 11: 255-64 (1999)].

Evaluation of neuroprotection in two in vivo test procedures

Transient global ischemia in the Mongolian gerbil. The effect of test compounds on preventing or treating brain injury in response to oxygen deprivation/reperfusion can be measured using the following test procedure.

Female Mongolian gerbils (60-80 g; Charles River Laboratories, Kingston, NY) are housed in the Wyeth-Ayerst animal care facility (AAALAC certified) with a 12-hour light, 12-hour dark photoperiod and free access to tap water and a low-estrogen

casein diet (Purina; Richmond, IN). After acclimation (3-5 days), gerbils are anesthetized with isoflurane (2-3% mixture with O_2), ovariectomized (Day 0). Beginning the following morning (Day 1), gerbils are treated subcutaneously each day with either vehicle (10% ETOH/corn oil), 17β-estradiol (1 mg/kg, sc) or an experimental compound.. On Day 6, gerbils (n=4-5/group) are anesthetized with isoflurane, the common carotid arteries visualized via a mid-line neck incision and both arteries simultaneously occluded for 5 minutes with non-traumatic micro aneurysm clips. After occlusion, the clips are removed to allow cerebral reperfusion and the neck incision closed with wound clips. All animals are fasted overnight prior to the global ischemia surgery, a step that facilitates consistent ischemic injury. On Day 12, gerbils are exposed to a lethal dose of CO_2, and the brains frozen on dry ice and stored at -80°C. The animal protocols used for these studies are reviewed and approved by the Radnor/Collegeville Animal Care and Use Committee (RACUC/CACUC) at Wyeth-Ayerst Research.

The degree of neuronal protection is evaluated by in situ hybridization analysis of neurogranin mRNA. Briefly, 20 μm coronal cryostat sections are collected on gelatin-coated slides, dried and stored at -80°C. At the time of processing, the desiccated slide boxes are warmed to room temperature, the slides postfixed in 4% paraformaldehyde, treated with acetic anhydride and then delipidated and dehydrated with chloroform and ethanol. Processed section-mounted slides are then hybridized with 200 μl ($6x10^6$ DPM/ slide) of an antisense or sense (control) riboprobe for Neurogranin (^{35}S-UTP-labeled NG-241; bases 99-340). in a 50% formamide hybridization mix and incubated overnight at 55°C in a humidified slide chamber without coverslipping. The following morning, the slides are collected in racks, immersed in 2xSSC (0.3 M NaCl, 0.03 M sodium citrate; pH 7.0) / 10 mM DTT, treated with RNase A (20 μg/ml) and washed (2 x 30 min) at 67°C in 0.1x SSC to remove nonspecific label. After dehydration, the slides are opposed to BioMax (BMR-1; Kodak) X-ray film overnight.

The level of neurogranin hybridization signal is used to quantitatively assess the degree of neuronal loss in the CA1 region after injury and to evaluate the efficacy of 17β-estradiol and experimental compounds. Neurogranin mRNA is selected for these studies because it is highly expressed in the hippocampal neurons including CA1, but absent in glia and other cell types present in this brain region. Therefore,

measurement of the amount of neurogranin mRNA present represents surviving neurons. Relative optical density measurements of neurogranin hybridization signal are obtained from film autoradiograms with a computer based image analysis system (C-Imaging Inc., Pittsburgh, PA). The results from 6 sections (40 μm apart) per animal are averaged and statistically evaluated. Numerical values are reported as the mean ± SEM. One-way analysis of variance is used to test for differences in the level of neurogranin mRNA and all statements of non-difference in the results section imply that $p>0.05$.

Middle cerebral artery occlusion in mice. Neuroprotection can be evaluated according to the test procedures described by Dubal [see, Dubal, et al., Proceedings of the National Academy of Sciences of the United States of America 98: 1952-1957 (2001), Dubal, et al., Journal of Neuroscience 19: 6385-6393 (1999)].

Ovulation inhibition standard pharmacological test procedure

The test procedure is used to determine whether test compounds can inhibit or change the timing of ovulation. It can also be used to determine the number of oocytes ovulated [Lundeen, et al., J Steroid Biochem Mol Biol 78: 137-143 (2001)].

Based on the results obtained in the standard pharmacological test procedures, the compounds of this invention are estrogen receptor modulators useful in the treatment or inhibition of conditions, disorders, or disease states that are at least partially mediated by an estrogen deficiency or excess, or which may be treated or inhibited through the use of an estrogenic agent. The compounds of this invention are particularly useful in treating a peri-menopausal, menopausal, or postmenopausal patient in which the levels of endogenous estrogens produced are greatly diminished. Menopause is generally defined as the last natural menstrual period and is characterized by the cessation of ovarian function, leading to the substantial diminution of circulating estrogen in the bloodstream. As used herein, menopause also includes conditions of decreased estrogen production that may be surgically, chemically, or be caused by a disease state which leads to premature diminution or cessation of ovarian function.

The compounds of this invention are also useful in inhibiting or treating other effects of estrogen deprivation including, hot flushes, vaginal or vulvar atrophy,

atrophic vaginitis, vaginal dryness, pruritus, dyspareunia, dysuria, frequent urination, urinary incontinence, urinary tract infections. Other reproductive tract uses include the treatment or inhibition of dysfunctional uterine bleeding. The compounds are also useful in treating or inhibiting endometriosis.

The compounds of this invention are also active in the brain and are therefore useful for inhibiting or treating Alzheimer's disease, cognitive decline, decreased libido, senile dementia, neurodegenerative disorders, depression, anxiety, insomnia, schizophrenia, and infertility. The compounds of this invention are also useful in treating or inhibiting benign or malignant abnormal tissue growth including, glomerulosclerosis, prostatic hypertrophy, uterine leiomyomas, breast cancer, scleroderma, fibromatosis, endometrial cancer, polycystic ovary syndrome, endometrial polyps, benign breast disease, adenomyosis, ovarian cancer, melanoma, prostate cancer, cancers of the colon, CNS cancers, such as glioma or astioblastomia.

The compounds of this invention are cardioprotective and are antioxidants, and are useful in lowering cholesterol, triglycerides, Lp(a), and LDL levels; inhibiting or treating hypercholesteremia, hyperlipidemia, cardiovascular disease, atherosclerosis, peripheral vascular disease, restenosis, and vasospasm, and inhibiting vascular wall damage from cellular events leading toward immune mediated vascular damage.
The compounds of this invention are also useful in treating disorders associated with inflammation or autoimmune diseases, including inflammatory bowel disease (Crohn's disease, ulcerative colitis, indeterminate colitis), arthritis (rheumatoid arthritis, spondyloarthropathies, osteoarthritis), pleurisy, ischemia/reperfusion injury (e.g. stroke, transplant rejection, myocardial infarction, etc.), asthma, giant cell arteritis, prostatitis interstitial cystitis, uveitis, psoriasis, multiple sclerosis, systemic lupus erythematosus and sepsis.

The compounds of this invention are also useful in treating or inhibiting ocular disorders including cataracts, uveitis, and macular degeneration and in treating skin conditions such as aging, alopecia, and acne.

The compounds of this invention are also useful in treating or inhibiting metabolic disorders such as type-II diabetes, of lipid metabolism, appetite (e.g. anorexia nervosa and bulimia).

Compounds in this invention are also useful in treating or inhibiting bleeding disorders such as hereditary hemorrhagic telangiectasia, dysfunctional uterine bleeding, and combating hemorrhagic shock.

The compounds of this invention are useful in disease states where amenorrhea is advantageous, such as leukemia, endometrial ablations, chronic renal or hepatic disease or coagulation diseases or disorders.

The compounds of this invention can be used as a contraceptive agent, particularly when combined with a progestin.

When administered for the treatment or inhibition of a particular disease state or disorder, it is understood that the effective dosage may vary depending upon the particular compound utilized, the mode of administration, the condition, and severity thereof, of the condition being treated, as well as the various physical factors related to the individual being treated. Effective administration of the compounds of this invention may be given at an oral dose of from about 0.1 mg/day to about 1,000 mg/day. Preferably, administration will be from about 10 mg/day to about 600 mg/day, more preferably from about 50 mg/day to about 600 mg/day, in a single dose or in two or more divided doses. The projected daily dosages are expected to vary with route of administration.

Such doses may be administered in any manner useful in directing the active compounds herein to the recipient's bloodstream, including orally, via implants, parentally (including intravenous, intraperitoneal, intraarticularly and subcutaneous injections), rectally, intranasally, topically, ocularly (via eye drops), vaginally, and transdermally.

Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions or solutions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods

and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surface modifying agents (including surfactants), suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Preferred surface modifying agents include nonionic and anionic surface modifying agents. Representative examples of surface modifying agents include, but are not limited to, poloxamer 188, benzalkonium chloride, calcium stearate, cetostearl alcohol, cetomacrogol emulsifying wax, sorbitan esters, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, magnesium aluminum silicate, and triethanolamine. Oral formulations herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s). The oral formulation may also consist of administering the active ingredient in water or a fruit juice, containing appropriate solubilizers or emulsifiers as needed.

In some cases it may be desirable to administer the compounds directly to the airways in the form of an aerosol.

The compounds of this invention may also be administered parenterally or intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to inhibit the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

For the purposes of this disclosure, transdermal administrations are understood to include all administrations across the surface of the body and the inner linings of bodily passages including epithelial and mucosal tissues. Such administrations may be carried out using the present compounds, or pharmaceutically acceptable salts thereof, in lotions, creams, foams, patches, suspensions, solutions, and suppositories (rectal and vaginal).

Transdermal administration may be accomplished through the use of a transdermal patch containing the active compound and a carrier that is inert to the active compound, is non toxic to the skin, and allows delivery of the agent for systemic absorption into the blood stream via the skin. The carrier may take any number of forms such as creams and ointments, pastes, gels, and occlusive devices. The creams and ointments may be viscous liquid or semisolid emulsions of either the oil-in-water or water-in-oil type. Pastes comprised of absorptive powders dispersed in petroleum or hydrophilic petroleum containing the active ingredient may also be suitable. A variety of occlusive devices may be used to release the active ingredient into the blood stream such as a semi-permeable membrane covering a reservoir containing the active ingredient with or without a carrier, or a matrix containing the active ingredient. Other occlusive devices are known in the literature.

Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppository's melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

The preparation of representative examples of this invention is described below.

Synthesis of Compounds in Scheme 1

INTERMEDIATE 2

7-Methoxy-2-naphthyl trifluoromethanesulfonate

To a solution of 7-methoxy-2-naphthol (4.75 g, 27.27 mmol) and pyridine (3.5 mL, 44 mmol) in 200 mL of dichloromethane at 0°C was added trifluoromethane-sulfonic anhydride (10.0 g, 35 mmol). The solution was allowed to slowly warm to room temperature and stirred overnight. The solution was cooled to 0°C and stirred

with ice water to decompose excess anhydride. The mixture was made slightly basic by the addition of saturated sodium bicarbonate solution. The resulting layers were separated and the aqueous layer was extracted with dichloromethane (2x 250 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered, and evaporation of the solvent yielded a red oil which was purified by silica chromatography (5% ethyl acetate-hexanes) to yield 8.08 g (97%) of the title compound as a clear, colorless oil. ^{1}H NMR (DMSO-d_6) δ 3.92 (3H, s), 7.30 (1H, dd, *J* = 2.58 Hz, *J* = 8.93 Hz), 7.42 (1H, dd, *J* = 2.59 Hz, *J* = 8.93 Hz), 7.52 (1H, d, *J* = 2.38 Hz), 7.96 (1H, d, *J* = 9.12 Hz), 8.00 (1H, d, *J* = 2.38 Hz), 8.06 (1H, d, *J* = 8.73 Hz); MS (EI)*m/z*306($M^{\cdot}$)$^+$.

Anal. for $C_{12}H_9F_3O_4S$

Calc'd: C: 47.06 H: 2.96

Found: C: 46.62 H: 2.84

INTERMEDIATE 3

2-Methoxy-7-(4-methoxyphenyl)naphthalene

Method A

A mixture of 7-methoxy-2-naphthyl trifluoromethanesulfonate (3.15 g, 10.3 mmol), 4-methoxy-phenylboronic acid (2.2 g, 14 mmol) sodium carbonate (10 mL of 2N aqueous solution), tetrakis(triphenylphosphine)palladium (0.59 g, 0.05 mmol), and 100 mL ethylene glycol dimethyl ether were heated to reflux for 8 hr. The mixture was cooled to room temperature and poured into 100 mL of 1N NaOH, The mixture was extracted with ethyl acetate (3x 250 mL), washed with brine (2x100 mL), dried over magnesium sulfate, filtered, evaporation of the solvent and purification by silica chromatography (5%-10% ethyl acetate-hexanes) yielded 2.17 g (79 %) of the title compound as a white solid: mp 154 °C; ^{1}H NMR ($CDCl_3$): δ 3.87 (3H, s), 3.94 (3H, s), 7.02 (2H, d, *J* = 8.72 Hz), 7.13 (1H, dd, *J* = 2.54 Hz, *J* = 9.09 Hz), 7.18 (1H, d, *J* = 2.55 Hz), 7.56 (1H, dd, *J* = 1.82 Hz, *J* = 8.36 Hz), 7.65 (2H, d, *J* = 8.72 Hz), 7.74 (1H, d, *J* = 9.09 Hz), 7.81 (1H, d, *J* = 8.36 Hz), 7.89 (1H, d, *J* = 1.09 Hz);

MS (EI) *m/z* 264 ($M^{\cdot}$).

Anal. for $C_{18}H_{16}O_2$:

Calc'd: C: 81.79 H: 6.10

Found: C: 81.78 H: 6.17

INTERMEDIATE 4

2-Methoxy-7-(3-methoxyphenyl)naphthalene

The title compound was prepared by reacting 7-methoxy-2-naphthyl trifluoromethanesulfonate (2.20 g, 7.18 mmol) with 3-methoxyphenylboronic acid (1.20 g, 7.90 (mmol) according to method A above to yield a white solid: mp 58-59°C; ^{1}H NMR ($CDCl_3$): δ 3.89 (3H, s), 3.93 (3H, s), 6.91 – 6.94 (1H, m), 7.15 (1H, dd, *J* = 2.42 Hz, *J* = 8.83 Hz), 7.19 1H, d, *J* = 2.27 Hz), 7.23 – 7.25 (1H, m), 7.28 – 7.31 (1H, m), 7.37- 7.42 (1H, m), 7.59 (1H, dd, *J* = 1.56 Hz, *J* = 8.46 Hz), 7.75 (1H, d, *J* = 8.84 Hz), 7.83 (1H, d, *J* = 8.45 Hz), 7.94 (s1H, s); MS (ESI) *m/z* 265 $(M+H)^-$.

Anal.for $C_{18}H_{16}O_2$:

Calc'd C: 81.79 H: 6.10

Found: C: 81.61 H: 5.99

INTERMEDIATE 5

2-Methoxy-7-phenylnaphthalene

The title compound was prepared by reacting 7-methoxy-2-naphthyl trifluoromethanesulfonate (3.01 g, 9.83 mmol) with phenylboronic acid (1.4 g, 12 mmol) according to method A to yield 1.95 g (85 %) of a white solid mp 62-64 °C; ^{1}H NMR ($CDCl_3$) δ 3.95 (3H, s), 7.15 (1H, dd, *J* = 2.56 Hz, *J* = 8.79 Hz), 7.20 (1H, d, *J* = 2.56 Hz), 7.36 – 7.39 (1H, m), 7.46 – 7.50 (2H, m), 7.60 (1H, dd, *J* = 1.83 Hz, *J* = 8.42 Hz), 7.70 – 7.73 (2H, m), 7.76 (1H, d, *J* = 8.79 Hz), 7.84 (1H, d, *J* = 8.42 Hz), 7.94 (1H, d, *J* = 1.46 Hz); MS (EI) *m/z* 234 $(M^{\cdot})^+$.

Anal. for $C_{17}H_{14}O \cdot 0.1\,H_2O$:

Calc'd C: 86.48 H: 6.06

Found: C: 86.29 H: 6.04

EXAMPLE 1a

7-(4-Hydroxyphenyl)-2-naphthol

Method B

2-Methoxy-7-(4-methoxy-phenyl)naphthalene (1.02 g, 3.86 mmol) was added to of pyridinium HCl (10 g) at 190°C. The solution was stirred for 3 hr at 190°C and cooled to room temperature and stirred with 200 mL of 1N HCl. The resulting suspension was filtered and dissolved ethyl acetate (500 mL). The combined organic

layers were washed with water (200 mL), dried over magnesium sulfate, filtered, the solvent removed under vacuum, and the product purified by silica chromatography (40% ethyl acetate-hexanes to yield 0.36 g (39%) of a white solid: mp 210°C; ^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, *J* = 8.58 Hz), 7.05 (1H, dd, *J* = 2.42 Hz, *J* = 8.77 Hz), 7.17 (1H, d, *J* = 2.24 Hz), 7.52 (1H, dd, *J* = 1.68 Hz, *J* = 8.40 Hz), 7.61 (2H, d, *J* = 8.58 Hz), 7.74 (1H, d, *J* = 8.58 Hz), 7.79 (1H, d, *J* = 8.58 Hz), 7.86 (1H, d, *J* = 1.12 Hz), 9.60 (1H, bs), 9.72 (1H, bs); MS (ESI) *m/z* 235 $(M-H)^-$.

Anal. for $C_{16}H_{12}O_2$:

Calc'd :C: 81.34 H: 5.12

Found: C: 81.23 H: 5.09

EXAMPLE 1b

7-(3-Hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 2-methoxy-7-(3-methoxyphenyl)-naphthalene (0.52 g, 1.97 mmol) with pyridinium HCl (8 g) at 190°C according to Method B to yield 0.13 g (28%) of a white solid: mp 163-165°C; ^{1}H NMR (DMSO-d_6): δ 6.78 – 6. 80 (1H, m), 7.08 (1H, dd, *J* = 2.56 Hz, *J* = 8.54 Hz), 7.13 – 7.14 (1H, m), 7.17 – 7.20 (2H, m), 7.27 – 7.30 (1H, m), 7.51 (1H, dd, *J* = 2.14 Hz, *J* = 8.54 Hz), 7.70 (1H, d, *J* = 8.97 Hz), 7.83 (1H, d, *J* = 8.54 Hz), 7.90 (1H, d, *J* = 1.28 Hz), 9.55 (1H, s), 9.78 (1H, s); MS (ESI) *m/z* 235 $(M-H)^-$.

Anal. for $C_{16}H_{12}O_2$:

Calc'd :C: 81.34 H:5.12

Found: C: 80.96 H:5.07 .

EXAMPLE 1c

7-Phenyl-2-naphthol

The title compound was prepared by reacting 2-methoxy-7-phenylnaphthalene (0.53 g, 2.26 mmol) with pyridinium HCl (10g) at 190°C according to method B to yield 0.36 g (72%) of a white solid: mp 142-143°C; ^{1}H NMR (DMSO-d_6): δ 7.10 (1H, dd, *J* = 2.75 Hz, *J* = 8.70 Hz), 7.23 (1H, d, *J* = 2.29 Hz), 7.37 – 7.40 (1H, m), 7.48 – 7.51 (2H, m), 7.58 (1H, dd, *J* = 1.83 Hz, 8.70 Hz), 7.78 – 7.90 (3H, m), 7.86 (1H, d, *J* = 8.24 Hz), 7.99 (1H, d, *J* = 0.92 Hz) 9.81 (1H, s); MS (ESI) *m/z* 219 $(M-H)^-$.

Anal. for $C_{16}H_{12}O \cdot 0.1\ H_2O$:
Calc'd C:86.66 H:5.47
Found: C:86.72 H:5.62

Synthesis of Compounds in Scheme 2

INTERMEDIATE 6

6-(trifluoromethanesulfonate)-1-tetralone

In a 500 mL flask 6-hydroxy-1-tetralone (4.8 g, 29.6 mmol) was azeotroped with xylenes and dissolved in anhydrous CH_2Cl_2 (220 mL). The solution was then cooled to 0°C and anhydrous pyridine (3.35 mL, 41.4 mmol) was added followed by triflic anhydride (10.0 g, 35.5 mmol). After 0.5 h at 0°C the reaction was quenched with sat. bicarbonate and washed with water. The organic layer was passed through a silica plug and concentrated to 8.39 g (96%) product as a pale yellow oil: ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.07 (2H, m), 2.65 (2H, t, *J* = 6.5 Hz), 3.03 (2H, t, *J* = 6.0 Hz), 7.47 (1H, dd, *J* = 8.7 Hz, 2.3 Hz), 7.57 (1H, d, *J* = 1.9 Hz), 8.03 (1H, d, *J* = 8.7 Hz).

INTERMEDIATE 7

6-(4-Hydroxyphenyl)-1-tetralone

4-{[Tert-butyl(dimethyl)silyl]oxy}phenylboronic acid. In a 500 mL flask was added (4-bromophenoxy)-tert-butyldimethylsilane (15.0 g, 52.2 mmol), and anhydrous THF (125 mL). The mixture was cooled to –78°C and n-butyllithium (25 mL of 2.5 M solution in hexanes, 62.7 mmol) was slowly added via syringe. After stirring for 0.5h triisopropyl borate (60 mL, 261 mmol) was added and the solution was stirred for 1.5 h at –78 °C and then allowed to warm to ambient temperature. Then ice cold 2 N HCl (150 mL) was added and the mixture was stirred for 10 minutes. The mixture was then extracted with ethyl acetate (3x), dried over Na_2SO_4, and concentrated to approximately 50 mL under reduced pressure. Hexanes were added to the concentrate induced crystallization (3 crops) which was then collected by filtration and then dried under vacuum to give 12.36 g (89%) of an off-white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.19 (6H, s), 0.95 (9H, s), 6.80 (2H, d, *J* = 8.1 Hz), 7.67 (2H, d, *J* = 8.1 Hz).

In a 500 mL flask was added 6-(trifluoromethanesulfonate)-1-tetralone (5.0 g, 17.0 mmol), 4-{[*tert*-butyl(dimethyl)silyl]oxy}phenylboronic acid (5.45 g, 20.4 mmol, prepared from above), sodium carbonate (4.56 g as 2 N aqueous, 42.5 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.98 g, 0.85 mmol) in DME (200 mL) was brought to reflux for 12 h. The reaction was allowed to cool, extracted with ethyl acetate (3x), and concentrated to a solid. The solids were washed with hexanes and dried under vacuum to 3.68 g product (92%) as a brown solid. mp 208-210°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.06 (2H, m), 2.60 (2H, t, *J* = 6.5 Hz), 2.99 (2H, t, *J* = 5.9 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 7.57 (4H, m), 7.86 (1H, d, *J* = 8.7 Hz), 9.74 (1H, s); MS *m/z* 237 (M – H$^+$);

Anal. for $C_{16}H_{14}O_2$:

Calc'd: C: 80.65 H: 5.92

Found: C: 79.04 H: 5.60

EXAMPLE 1d

6-(4-Hydroxyphenyl)-1-naphthol

To a 25 mL flask was added 6-(4-hydroxyphenyl)-1-tetralone (500 mg, 2.12 mmol), palladium on carbon (510 mg) and *p*-cymene (15 mL). The mixture was heated to reflux for 24 h, cooled, filtered through celite and extracted with 1 M NaOH (2 x 25 mL). The aqueous layer was then acidified, extracted with ether (3x), and passed through a silica plug. Concentration under reduced pressure afforded 260 mg (53%) product as a brown solid: mp above 200 °C (dec.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.82 (1H, d, *J* = 7.5 Hz), 6.87 (2H, d, *J* = 8.1 Hz), 7.29 (1H, t, *J* = 7.5 Hz), 7.38 (1H, d, *J* = 7.5 Hz), 7.63 (2H, d, *J* = 8.2 Hz), 7.70 (1H, d, *J* = 8.5 Hz), 7.99 (1H, s) 8.14 (1H, d, *J* = 8.5 Hz), 9.59 (1H, s), 10.09 (1H, s); MS *m/z* 235 (M – H$^+$).

Anal. for $C_{16}H_{12}O_2$:

Calc'd: C: 81.34 H: 5.12

Found: C: 81.22 H: 5.30

Synthesis of Compounds in Scheme 3

INTERMEDIATE 10

2-Methoxy-6-(4-methoxyphenyl)naphthalene

To a mixture of 2-bromo-6-methoxynaphthalene (23.79 g, 100.3 mmol) and tetrakis(triphenylphosphine)palladium (5.8 g, 5 mmol) was added a solution of 4-methoxyphenylmagnesium bromide in THF (400 mL of 0.5 N solution, 200 mmol). The stirred solution was heated to reflux for 3 hr, cooled to RT, and stirred into 200 mL of 1N HCl. The mixture was extracted with dichloromethane and filtered through a short silica plug with dichloromethane. The solvent was removed to yield a crude yellow solid which was further purified by silica chromatography (20-50% ethyl acetate-hexanes) to yield 25.68 g (97 %) of the title compound as a white solid: mp 190 °C; ^{1}H NMR ($CDCl_3$): δ 3.86 (3H, s), 3.93 (3H, s), 7.01 (2H, d, *J* = 8.57 Hz), 7.14-7.18 (2H, m), 7.63 (2H, d, *J* = 8.50 Hz), 7.67 (1H, dd, *J* = 1.68 Hz, *J* = 8.73 Hz), 7.76 – 7.80 (2H, m), 7.91 (1H, d, *J* = 0.94 Hz); MS (ESI) *m/z* 265 $(M+H)^+$.

Anal. for $C_{18}H_{16}O_2$:

Calc'd: C: 81.79 H: 6.10

Found: C: 82.04 H: 6.17

INTERMEDIATE 11

2-(4-Methoxyphenyl)naphthalene

The title compound was prepared by reacting 2-bromonaphthalene (3.04 g, 14.7 mmol) with 4-methoxyphenylmagnesium bromide according to method used to prepared intermediate 10 to yield 2.89 g (89 %) of a white solid: mp 114°C; ^{1}H NMR ($CDCl_3$): δ 3.86 (3H, s), 7.01 (2H, d, *J* = 9.06 Hz), 7.43 – 7.50 (2H, m), 7.65 (2H, d, *J* = 8.73 Hz), 7.71 (1H, dd, *J* = 1.84 Hz, *J* = 8.56 Hz), 7.83 – 7.89 (3H, m), 7.98 (1H, d, *J* = 0.67 Hz); MS (EI) *m/z* 234 $(M^{\cdot})^+$.

Anal. for $C_{17}H_{14}O$:

Calc'd: C: 87.15 H: 6.02

Found: C: 86.75 H: 6.14

INTERMEDIATE 12

2-Methoxy-6-phenylnaphthalene

The title compound was prepared by reacting 2-bromo-6-methoxynaphthalene (1.97 g, 8.31 mmol) with phenylmagnesium bromide according to the method used to prepare intermedite 10 to yield 1.59 g (82 %) of a white solid: mp 122-126°C; ^{1}H NMR ($CDCl_3$): δ 3.94 (3H, s), 7.16 – 7.18 (2H, m), 7.34 – 7.37 (1H, m), 7.46 – 7.49 (2H, m), 7.69 – 7.72 (2H, m), 7.78 – 7.82 (2H, m), 7.97 (1H, s);

MS (EI) *m/z* 234.2 $(M^{\cdot})^+$.

Anal. for $C_{17}H_{14}O$:

Calc'd: C: 87.15 H: 6.02

Found: C: 86.79 H: 6.14

INTERMEDIATE 13

2-Methoxy-6-(3-methoxyphenyl)naphthalene

The title compound was prepared by reacting 6-methoxy-2-bromonaphthalene (3.09 g, 13.0 mmol) with 3-methoxyphenylboronic acid (2.18 g, 14.3 mmol according to method A to yield 1.18 g (34%) of a white solid: mp 80 °C; ^{1}H NMR ($CDCl_3$):δ 3.88 (3H, s), 3.92(3H, s), 6.90 (1H, dd, *J* = 2.17 Hz, *J* = 7.76 Hz), 7.14 – 7.18 (2H, m), 7.22 – 7.24 (1H, m), 7.28 (1H, d, *J* = 7.45 Hz), 7.36 – 7.39, (1H, m), 7.70 (1H, dd, *J* = 1.86 Hz, *J* = 8.70 Hz), 7.77 – 7.80 (2H, m), 7.96 (1H, d, *J* = 1.24 Hz); MS (ESI) *m/z* 265 $(M+H)^+$.

Anal. for $C_{18}H_{16}O_2$:

Calc'd: C: 81.79 H: 6.10

Found: C: 81.61 H: 6.47

EXAMPLE 1i

6-(3-Chlorophenyl)-2-naphthol

A mixture of 6-bromo-2-naphthol (1.78 g, 8.0 mmol), 2-chlorophenylboronic acid (1.5 g, 9.6 mmol), sodium carbonate (2.11 g as 2 N aqueous, 20.0 mmol), and tetrakis(triphenylphosphine)palladium(0) (550 mg, 0.48 mmol) in DME (95 mL) was were reacted according to Method A. Column chromatography (30% ethyl acetate-hexanes) produced 520 mg (26%) of product as a tan solid: mp 116-118 °C; ^{1}H NMR

(300 MHz, DMSO-d_6) δ 7.13 (2H, m), 7.42 (1H, td, *J* = 7.9 Hz, 0.9 Hz), 7.51 (1H, t, *J* = 7.6 Hz), 7.80 (5H, m), 8.16 (1H, s), 9.88 (1H, s);

MS *m/z* 253/255 (Cl pattern) (M – H^+);

Anal. for $C_{16}H_{11}ClO$:

Calc'd: C: 75.45 H: 4.35

Found: C: 75.20 H: 4.34

EXAMPLE 1e

6-(4-Hydroxyphenyl)-2-naphthol

2-Methoxy-6-(4-methoxyphenyl)naphthalene (5.61g, 21.2 mmol) was added to pyridinium HCl (30 g) at 190°C according to Method B to afford 4.88 g (98%) of a white solid: mp > 220 (discolors above 200°C); ^{1}H NMR (DMSO-d_6): δ 6.87 (2H, d, *J* = 8.54 Hz), 7.08 (1H, dd, *J* = 2.34 Hz, *J* = 8.76 Hz), 7.11 (1H, d, *J* = 2.14 Hz), 7.58 (2H, d, *J* = 8.54 Hz), 7.65 (1H, dd, *J* = 1.92 Hz, *J* = 8.76 Hz), 7.71 (1H, d, *J* = 8.54 Hz), 7.79 (1H, d, *J* = 8.97 Hz), 7.95 (1H, s), 9.56 (1H, bs), 9.70 (1H, bs); MS (ESI) *m/z* 235 $(M-H)^-$.

Anal. for $C_{16}H_{12}O_2$:

Calc'd: C: 81.34 H: 5.12

Found: C: 81.05 H: 5.18

EXAMPLE 1f

4-(2-Naphthyl)phenol

The title compound was prepared by reacting 2-(4-methoxyphenyl)-naphthalene (1.01 g, 4.31 mmol) with 10 g of pyridinium HCl at 190°C according to method B to yield 0.84 g (89%) of a white solid: mp 148°C; ^{1}H NMR (DMSO-d_6): δ 6.92 (2H, d, *J* = 8.71 Hz), 7.46 – 7.53 (2H, m), 7.66 (2H, d, *J* = 8.71 Hz), 7.79 (1H, dd, *J* = 1.78 Hz, *J* = 8.51 Hz), 7.90 (*1H, d, J* = 8.31 Hz), 7.95 (2H, d, *J* = 8.31 Hz), 8.11 (1H, d, *J* = 1.19 Hz), 9.65 (1H, s); MS (ESI) *m/z* 219 $(M-H)^-$.

Anal. for $C_{16}H_{12}O_2$:

Calc'd: C: 87.25 H: 5.49

Found: C: 87.31 H: 5.86

EXAMPLE 1g

6-Phenyl-2-naphthol

The title compound was prepared by reacting 2-methoxy-6-phenylnaphthalene (0.54 g, 2.30 mmol) with of pyridinium HCl (10 g) at 190°C according to method B to yield 0.32 g (63%) of a light pink solid: mp 169-170 °C; ^{1}H NMR (DMSO-d_6): δ 7.12 (1H, dd, *J* = 2.56 Hz, *J* = 8.54 Hz), 7.16 (1H, d, *J* = 2.56 Hz), 7.35 – 7.38 (1H, m), 7.47 – 7.50 (2H, m), 7.73 (1H, dd, *J* = 1.71 Hz, *J* = 8.54 Hz), 7.76 – 7.79 (3H, m), 7.85 (1H, d, *J* = 8.54 Hz), 8.08 (1H, d, *J* = 1.28 Hz), 9.82 (1H, s); MS (ESI) *m/z* 219 $(M-H)^-$.

Anal. for $C_{16}H_{12}O$:

Calc'd: C: 87.25 H:5.49

Found: C: 87.05 H:5.55

EXAMPLE 1h

6-(3-Hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 2-methoxy-6-(3-methoxyphenyl)-naphthalene (0.51 g, 1.90 mmol) with pyridinium HCl (6 g) at 190°C according to method B to yield 0.21 g (47%) of an off white solid: mp 192-194°C; ^{1}H NMR (DMSO-d_6): δ 6.75 – 6.78 (1H, m), 7.10 – 7.14 (3H, m), 7.16 – 7.18 (1H, m), 7.65 (1H, dd, *J* = 1.79 Hz, *J* = 8.57 Hz), 7.75 (1H, d, *J* = 8.77 Hz), 7.84 (1H, d, *J* = 8.77 Hz), 8.01 (1H, d, *J* = 1.59 Hz), 9.51 (1H, s), 9.78, (1H, s); MS (ESI) *m/z* 235 $(M-H)^-$.

Anal. for $C_{16}H_{12}O_2$:

Calc'd: C: 81.34 H: 5.12

Found: C: 80.94 H: 5.09

Synthesis of Compounds in Scheme 4

INTERMEDIATE 14

1-Bromo-2-methoxy-6-(4-methoxyphenyl)naphthalene

To a mixture of 2-methoxy-6-(4-methoxyphenyl)naphthalene (9.68 g, 36.6 mmol) and glacial acetic acid (150 mL) was slowly added a solution of bromine (5.85g, 36.6 mmol) in glacial acetic acid (20 mL). The mixture was stirred for 1 hour and the resulting suspension was poured into water (200 mL) and the solid product

was collected by filtration. The solid was triturated first with water and then with ethyl acetate to yield 11.25 g (90%) of the title compound as a white solid: mp 172-174°C; ^{1}H NMR ($CDCl_3$): δ 3.88 (3H, s), 4.05 (3H, s), 7.04 (2H, d, *J* = 8.56 Hz), 7.30 (1H, d, *J* = 9.01 Hz), 7.67 (2H, d, *J* = 8.65 Hz), 7.81 (1H, dd, *J* = 1.61 Hz, *J* = 8.84 Hz), 7.87 (1H, d, *J* = 9.04 Hz), 7.94 (1H, d, *J* = 1.47 Hz), 8.27 (1H, d, *J* = 8.92 Hz); MS (EI) *m/z* 343 $(M^{\cdot})^+$.

Anal. for $C_{18}H_{15}BrO_2$:

Calc'd: C: 62.99 H: 4.41

Found: C: 62.66 H: 4.57

INTERMEDIATE 15

1-Chloro-2-methoxy-6-(4-methoxyphenyl)naphthalene

Method C

A suspension of 2-methoxy-6-(4-methoxyphenyl)naphthalene (0.51 g, 1.93 mmol) and NCS (0.28 g, 2.13 mmol) in acetonitrile (20 mL) was heated to reflux for 3 hr. The resulting solution was cooled to room temperature and the resulting solid was collected by filtration and rinsed with acetonitrile to yield 0.41 g (72%) of the title compound as a white solid: mp 158-164 °C; 1H NMR ($CDCl_3$): δ 3.87 (3H, s), 4.05 (3H, s), 7.03 (2H, d, *J* = 8.62 Hz), 7.32 (1H, d, *J* = 9.02 Hz), 7.65 (2H, d, *J* = 8.55 Hz), 7.82 (2H, d, *J* = 9.01 Hz), 7.95 (1H, d, *J* = 1.36 Hz), 8.27 (1H, d, *J* = 8.81 Hz); MS (EI) *m/z* 298 $(M^{\cdot})^+$.

Anal. for $C_{18}H_{15}ClO_2$:

Calc'd: C: 72.36 H: 5.06

Found: C: 72.06 H: 4.89

EXAMPLE 1o

1-Bromo-6-(4-hydroxyphenyl)-2-naphthol

To a solution of 6-(4-hydroxyphenyl)-2-naphthol (4.02 g, 17.0 mmol) in acetonitrile (150 mL) at 0°C was added NBS (3.03 g, 17.0 mmol). The reaction was stirred at 0°C for 3 hr and then poured into water (200 mL) and extracted with ethyl acetate (3x300 mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered, evaporation of the solvent, and purification by silica column chromatography (20% ethyl acetate – hexanes) yielded 5.33 g (100 %) of the title compound as a tan solid. The title compound was further purified by reverse

phase HPLC to yield a white solid: mp 208-210 °C; ^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, *J* = 8.47 Hz), 7.28 (1H, d, *J* = 8.80 Hz), 7.63 (2H, d, *J* = 8.50 Hz), 7.85 (2H, d, *J* = 8.84 Hz), 8.02 – 8.06 (2H, m), 9.60 (1H, s), 10.54 (1H, s);
MS (ESI) *m/z* 313/315 $(M-H)^-$.
Anal. for $C_{16}H_{11}BrO_2$:
Calc'd: C: 60.98 H: 3.52
Found: C: 60.63 H: 3.46

EXAMPLE 1p

1-Chloro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 1-chloro-2-methoxy-6-(4-methoxyphenyl)naphthalene (0.32 g, 1.07 mmol) with pyridinium HCl (7g) at 190°C according to method B to yield 0.12 g (41%) of an off white solid: mp 222-224°C (dec.); ^{1}H NMR (DMSO-d_6): δ 6.88 (2H, d, *J* = 8.46 Hz), 7.29 (1H, d, *J* = 8.88 Hz), 7.63 (2H, d, *J* = 8.50 Hz), 7.81 – 7.88 (2H, m), 8.02 – 8.08 (2H, m), 9.59 (1H, s), 10.43(1H, s); MS (ESI) *m/z* 269/271$(M-H)^-$.
Anal. for $C_{16}H_{11}ClO_2$: :
Calc'd: C: 70.99 H:4.10
Found: C: 70.59 H:4.12

EXAMPLE 1q

6-(4-Hydroxyphenyl)-1-methoxy-2-naphthol

A mixture of 1-bromo-6-(4-hydroxyphenyl)-2-naphthol (0.41 g, 1.30 mmoles), CuBr (0.19 g, 0.13 mmoles), sodium methoxide (3 ml of 4.4 N in methanol), and DMF (6 ml) was heated to reflux for 3 hours. The reaction mixture was cooled to room temperature, poured into HCl (50 ml of 1N aqueous solution), and extracted with ethyl acetate (3x100 ml). The combined organic layers were washed with sodium bicarbonate solution, dried over sodium sulfate, filtered, stripped of solvent, and purified by silica column chromatgraphy (40% ethyl acetate – hexanes) to yield 0.31 g (89 %) of the title compound as a white solid: mp 204-206°C; ^{1}H NMR (DMSO-d_6): δ 6.88 (2H, d, *J* = 8.47 Hz), 7.19 (1H, d, *J* = 8.81 Hz), 7.57 – 7.60 (3H, m), 7.71 (1H, dd, *J* = 1.41 Hz, *J* = 8.78 Hz), 7.94 – 7.98 (2H, m), 9.54 (2H, s);
MS *m/z* $(M-H)^-$ = 265;

Anal. for $C_{17}H_{14}O_3$:

Calc'd: C:76.68 H:5.30

Found: C:76.46 H:5.13

Synthesis of Compounds in Scheme 5

INTERMEDIATE 16

2-Methoxy-6-(4-methoxyphenyl)-1-fluoronaphthalene

To a solution of 2-methoxy-6-(4-methoxyphenyl)-1-bromonaphthalene (1.28 g, 3.72 mmol) in THF (25 mL) at –78°C was slowly added n-butyl lithium (1.9 mL of 2.5 N in hexanes). The resulting solution was stirred at –78°C for thirty minutes and a solution of N-fluorobenzenesulfonimide (1.40 g, 4.5 mmol) in THF (10 mL) was added. After 2 additional hr at – 78°C, the reaction was warmed to room temperature, poured in water, and extracted with ethyl acetate (2x250mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered, evaporation of the solvent, and purification by silica chromatography (5% THF – hexanes) yielded 0.66 g (63 %) of a white solid: mp 150-155°C; ^{1}H NMR ($CDCl_3$): δ 3.88 (3H, s), 4.04 (3H, s), 7.02 (2H, d, *J* = 8.69 Hz), 7.28 – 7.34 (1H, m), 7.62 – 7.67 (3H, m), 7.74 (1H, dd, *J* = 1.60 Hz, *J* = 8.79 Hz), 7.93 (1H, s), 8.09 (1H, d, *J* = 8.77 Hz).

Anal. for $C_{18}H_{15}O_2F$:

Calc'd: C: 76.58 H: 5.36

Found: C: 75.78 H: 5.95

INTERMEDIATE 17

2-Methoxy-6-(4-methoxyphenyl)-1-naphthonitrile

A mixture of 1-bromo-2-methoxy-6-(4-methoxyphenyl)naphthalene (0.76 g, 2.21 g), CuCN (0.24 g, 2.66 mmol) and DMF (10 mL) was stirred at 120°C for 4 hr. The reaction mixture was cooled to room temperature, slurried with ethyl acetate, filtered through silica, and evaporation of the solvent, and purification by silica column chromatography (20% ethyl acetate – hexanes) yielded 0.19 g (30%) of the title compound as a pale yellow solid: mp 182-185°C; ^{1}H NMR ($CDCl_3$): δ 3.88 (3H, s), 4.09 (3H, s), 7.03 (2H, d, *J* = 8.73 Hz), 7.29 (1H, d, *J* = 9.12 Hz), 7.63 (2H, d, *J* =

8.73 Hz), 7.88 (1H, dd, J = 1.98 Hz, J = 8.73 Hz), 7.97 (1H, d, J = 1.98 Hz), 8.09 (1H, d, J = 9.12 Hz), 8.14 (1H, d, J = 8.73 Hz).

Anal. for $C_{19}H_{15}O_2N$:

Calc'd: C: 78.87 H: 5.23 N: 4.84

Found: C: 79.06 H: 7.27 N: 2.91

INTERMEDIATE 18

2-Methoxy-6-(4-methoxyphenyl)-1-phenylnaphthalene

To a mixture of 2-methoxy-6-(4-methoxyphenyl)-1-bromonaphthalene (0.80 g, 2.33 mmol) and tetrakis(triphenylphosphine)palladium (0.13 g, 0.12 mmol) in THF (10 mL) was added phenylmagnesiumbromide (2.2 mL of 3 N in ether). The reaction mixture was stirred at reflux overnight, cooled to room temperature, poured into 1 N HCl (100 mL), and extracted with ethyl acetate (3x200 mL). The combined organic layers were washed with sodium bicarbonate solution, dried over magnesium sulfate, filtered, evaportation of the solvent, and purification by silica column chromatography (10% ethyl acetate–hexanes) yielded 0.42 g (53 %) of a gray solid: mp 157-160 °C; ^{1}H NMR ($CDCl_3$): δ 3.85 (3H, s), 3.87 (3H, s), 7.01 (2H, d, J = 8.64 Hz), 7.38 – 7.46 (4H, m), 7.49 – 7.57 (4H, m), 7.64 (2H, d, J = 8.64 Hz), 7.92 (1H, d, J = 9.05 Hz), 7.97 (1H, s); MS (ESI) m/z 341 $(M+H)^+$.

Anal. for $C_{24}H_{20}O_2 \cdot 0.5\ H_2O$:

Calc'd: C: 82.50 H: 6.06

Found: C: 82.60 H: 5.66

INTERMEDIATE 19

2-Methoxy-6-(4-methoxyphenyl)-1-methylnaphthalene

To a solution of 2-methoxy-6-(4-methoxyphenyl)-1-bromonaphthalene in THF (25 mL) at 0°C was slowly added n-butyl lithium (2 mL of 2.5N) and TMEDA (0.60 g, 5.13 mmol, freshly distilled from KOH). After thirty minutes at 0°C iodomethane (7.3 g, 51.3 mmol, passed through basic alumina) was added and the stirring solution was allowed to warm to room temperature overnight. The reaction was poured into water (100 mL) and extracted with ethyl acetate (3x200 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered, evaporation of the solvent, and purification by silica column chromatography (5% THF–hexanes) yielded

0.63 g (88%) of a white solid: mp 136-138°C; ^{1}H NMR ($CDCl_3$): δ 3.87 (3H, s), 3.96 (3H, s), 7.02 (2H, d, *J* = 8.74 Hz), 7.29 (1H, d, *J* = 9.01 Hz), 7.60 –7.80 (4H, m), 7.95 (1H, d, *J* = 1.76 Hz), 8.00 (1H, d, *J* = 8.86 Hz); MS (ESI) *m/z* 279 $(M+H)^+$.

Anal. for $C_{19}H_{18}O_2 \cdot 0.3\ H_2O$:

Calc'd: C: 80.43 H: 6.61

Found: C: 80.20 H: 6.33

EXAMPLE 1r

1-Fluoro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 2-methoxy-6-(4-methoxyphenyl)-1-fluoronaphthalene (0.250 g, 0.886 mmol) with boron tribromide (2.7 mL of 1 N solution, 2.7 mmol) according to method D to yield 0.13 g (15%) of a white solid: mp 219-224°C; ^{1}H NMR (DMSO-d_6): δ (6.89 (2H, d, *J* = 8.49 Hz), 7.22 – 7.28 (1H, m), 7.61 (2H, d, *J* = 8.53 Hz), 7.65 (1H, d, *J* = 9.12 Hz), 7.79 (1H, d, *J* = 8.77 Hz), 7.92 (1H, d, *J* = 8.73 Hz), 8.05 (1H, s), 9.63 (1H, bs), 10.00 (1H, bs); MS (ESI) *m/z* 253 $(M-H)^-$.

Anal. for $C_{16}H_{11}FO_2$: :

Calc'd: C: 75.58 H: 4.36

Found: C: 75.13 H: 4.40

EXAMPLE 1s

2-Hydroxy-6-(4-hydroxyphenyl)-1-naphthonitrile

The title compound was prepared by reacting 2-methoxy-6-(4-methoxyphenyl)-1-naphthonitrile (0.115 g, 0.397 mmol) with pyridinium HCl (4g) at 190°C according to method D to yield 0.025 g (24%) of a tan solid: mp > 220°C; ^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, *J* = 8.37 Hz), 7.28 (1H, d, *J* = 9.07 Hz), 7.63 (2H, d, *J* = 8.42 Hz), 7.88 – 7.98 (2H, m), 8.12 – 8.16 (2H, m), 9.63 (1H, s), 11.65 (1H, bs); MS (ESI) *m/z* 260 $(M-H)^-$

Anal. for $C_{17}H_{11}NO_2 \cdot 0.4\ H_2O$:

Calc'd: C: 76.05 H: 4.43 N: 5.22

Found: C: 76.09 H: 4.25 N: 4.83.

EXAMPLE 1t

6-(4-Hydroxyphenyl)-1-phenyl-2-naphthol

Method D

To a mixture of 2-methoxy-6-(4-methoxyphenyl)-1-phenylnaphthalene (0.36 g, 1.06 mmol) in CH_2Cl_2 (25 mL) at 0 ° C was slowly added boron tribromide (3.2 mL of 1N in CH_2Cl_2). The mixture was allowed to warm slowly to room temperature and was stirred overnight. The resulting solution was poured into water (100 mL) and extracted with ethyl acetate (3x150 mL). The combined organic layers were washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, evaporation of thesolvent, and purification by silica column chromatography (25% ethyl acetate–hexanes) followed by preparative reverse-phase HPLC and drying under vacuum at 105 ° C yielded 0.14 g (42%) of the title compound as a white solid: mp 142-146 °C; ^{1}H NMR (DMSO-d_6): δ 6.86 (2H, d, *J* = 8.50 Hz), 7.26 – 7.42 (5H, m), 7.48 – 7.61 (5H, m), 7.84 (1H, d, *J* = 8.96 Hz), 8.02 (1H, d, *J* = 1.46 Hz), 9.52 (2H, s); MS (ESI) *m/z* 311 $(M-H)^-$.

Anal. for $C_{22}H_{16}O_2 \cdot 0.1\ H_2O$: :

Calc'd: C: 84.11 H: 5.20

Found: C: 83.90 H: 5.15

EXAMPLE 1u

6-(4-Hydroxyphenyl)-1-methyl-2-naphthol

The title compound was prepared by reacting 2-methoxy-6-(4-methoxyphenyl)-1-methylnaphthalene (0.35 g, 1.26 mmol) with boron tribromide 3.8 mL of 1 N solution, 3.8 mmol) according to method D to yield 0.15 g (48 %) of a white solid: mp > 170°C (dec.); ^{1}H NMR (DMSO-d_6): δ 2.42 (3H, s), 6.87 (2H,k d, *J* = 8.33 Hz), 7.15 (1H, d, *J* = 8.81 Hz), 7.59 (2H, d, *J* = 8.35 Hz), 7.65 (1H, d, *J* = 8.93 Hz), 7.71 (1H, dd, *J* = 1.24 Hz, *J* = 8.90 Hz), 7.88 (1H, d, *J* = 8.87 Hz), 7.95 (1H, s), 9.49 (1H, s), 9.52 (1H, s); MS (ESI) 249 *m/z* $(M-H)^-$.

Anal. for $C_{17}H_{14}O_2$:

Calc'd: C:81.58 H:5.64

Found: C:81.15 H:5.58

Synthesis of Compounds in Scheme 6

INTERMEDIATE 27

***Tert*-butyl[(6-bromo-2-naphthyl)oxy]dimethylsilane**

Method E

To a solution of 6-bromo-2-naphthol (13.68 g, 61.33 mmol) and TBDMS-Cl (11.09 g, 73.6 mmol) in DMF (50 mL) was added imidazole (10.2 g, 150 mmol). The solution was stirred for 3 hr, mixed with sodium bicarbonate solution (250 mL), and extracted with 50% ethyl acetate–hexanes (3x 250 mL). The combined organic layers were washed with water, dried over magnesium sulfate, filtered and evaporation of the solvent yielded a tan oil which was dried under vacuum to yield 19.92 g (97 %) of the title compound as a white solid:

^{1}H NMR ($CDCl_3$): δ 0.24 (6H, s), 1.01 (9H, s), 7.08 (1H, dd, *J* = 2.26 Hz, *J* = 8.81 Hz), 7.14 (1H, d, *J* = 2.15 Hz), 7.46 (1H, dd, *J* = 1.80 Hz, *J* = 8.77 Hz), 7.54 (1H, d, *J* = 8.77 Hz), 7.61 (1H, d, *J* = 8.81 Hz), 7.90 (1H, s); MS (EI) *m/z* 336/338 $(M^{\cdot})^+$.

Anal. for $C_{16}H_{21}BrO_1Si \cdot 0.25\ H_2O$:

Calc'd: C: 56.97 H: 6.27

Found: C: 56.81 H: 6.43

INTERMEDIATE 22

***Tert*-butyl(4-bromo-2,6-difluoro-phenyloxy)dimethylsilane**

The title compound was prepared by reacting 4-bromo-2,6-difluoro-phenol (10.54 g, 50.4 mmol) with TBDMS-Cl (9.88 g, 150.7 mmol) according to method E to yield 14.61 g (90%) of a clear, colorless, oil: ^{1}H NMR ($CDCl_3$) δ 0.17 (6H, s), 0.99 (9H, s), 7.02 (H, d, *J* = 7.13 Hz).

INTERMEDIATE 28

***Tert*-butyl[(2-(6-naphthyl boronic acid)oxy]dimethylsilane**

Method F

To a solution of *tert*-butyl[(6-bromo-2-naphthyl)oxy]dimethylsilane (19.18 g, 56.9 mmol) in THF (200 mL) at –78 °C was slowly added n-butyl lithium (25 mL of 2.5 N solution in hexanes). The solution was stirred for thirty minutes and triisopropyl borate (53.5 g, 285 mmol) was added. The solution was stirred for 1 hour at –78 °C and then allowed to warm to room temperature overnight. The solution was then

cooled to 0 °C and stirred with HCl (200 mL of 1N solution) for 10 minutes. The mixture was extracted with ethyl acetate (3x 250 mL). The combined organic layers were concentrated to a volume of 25 mL. Crystallization was induced with hexanes, and the solid product was collected by filtration and dried under vacuum to yield 13.5 g (79%) of the title compound as an off white solid:

^{1}H NMR (DMSO-d_6): δ 0.25 (6H, s), 0.99 (9H, s), 7.10 (1H, dd, *J* = 2.56 Hz, *J* = 8.97 Hz), 7.26 (1H, d, *J* = 2.56 Hz), 7.73 (1H, d, *J* = 8.54 Hz), 7.82 (1H, dd, *J* = 1.07 Hz, *J* = 8.33 Hz), 7.83 (1H, d, *J* = 8.97 Hz), 8.30 (1H, s); MS (ESI) *m/z* 303 $(M+H)^+$.

Anal. for $C_{16}H_{23}BO_3Si$:

Calc'd: C: 63.58 H: 7.67

Found: C: 46.97 H: 6.78

INTERMEDIATE 29

3-Fluoro-4-methoxyphenylboronic acid

The title compound was prepared by reacting 4-bromo-2-fluoroanisole (10g, 0.049 mol) with n-butyl lithium (23.4 mL of 2.5 M solution in hexane, 0.059 mol) followed by triisopropyl borate (45.2 mL, 36.9 g, 0.196 mol) according to method F to yield 7.1 g (85.2 %) of a white solid: MS (ESI) *m/z* 169 $(M-H)^-$: ^{1}H NMR (DMSO-d_6): δ 3.84 (3H, s), 7.10 – 7.16 (1H, m), 7.51 – 7.60 (2H, m).

INTERMEDIATE 30

3,5-Difluoro-4-*tert*-butyldimethylsilyoxyboronic acid

The title compound was prepared by reacting *tert*-butyl(4-bromo-2,6-difluoro-phenyloxy)dimethylsilane (12.98 g, 40.19 mmol) with n-butyl lithium (27.6 mL of 1.6N solution, 44.2 mmol) followed by triisopropyl borate (37.8 g, 200 mmol) according to method F to yield 4.38 g (38%) of a white solid: ^{1}H NMR (DMSO-d_6): δ 0.25 (6H, s), 1.06 (9H, s), 7.54 (2H, d, *J* = 7.93 Hz).

INTERMEDIATE 31

4-Methoxy-2-methylphenylboronic acid

The title compound was prepared by reacting 4-bromo-3-methylanisole (10g, 0.050 mol) with n-butyl lithium (24 mL of 2.5 M solution in hexane, 0.055 mol) followed

by triisopropyl borate (57.7 mL, 47.02 g, 0.25 mol) according to method F to yield 5.7 g (69 %) of a white solid: MS (ESI) *m/z* 313 $(2M-H_2O-H)^-$.

INTERMEDIATE 33

2-(3-Fluoro-4-methoxyphenyl)naphthalene

The title compound was prepared by reacting 2-bromonaphthalene (0.31 g, 1.50 mmol) with 3-fluoro-4-methoxyphenylboronic acid (0.31 g, 1.80 mmol) according to method A to yield 0.30 g (79%) of a white solid: mp 108-110 °C; ^{1}H NMR ($CDCl_3$): δ (3.96, 3H, s), 7.04 – 7.10 (1H, m), 7.43 – 7.52 (4H, m), 7.68 (1H, dd, *J* = 1.81 Hz, *J* = 8.57 Hz), 7.84 – 7.92 (3H, m), 7.97 (1H, d, *J* = 1.05 Hz).

Anal. for $C_{17}H_{13}FO$: :

Calc'd: C: 80.93 H: 5.19

Found: C: 81.01 H: 4.78

EXAMPLE 1ay

6-(3,5-Difluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-bromo-2-naphthol (0.165 g, 0.74 mmol) with 3,5-difluoro-4-*tert*-butyldimethylsilyoxyboronic acid (0.25 g, 0.87 mmol) according to method A to yield 0.14 g (70%) of a tan solid. This material was further purified by preparative reverse phase HPLC to yield the title compound as a white solid: mp 216-220 °C; ^{1}H NMR (DMSO-d_6): δ 7.09 – 7.13 (2h, m), 7.50 (2H, d, *J* = 10.00 Hz), 7.73 (2H, s), 7.78 (1H, d, *J* = 8.58 Hz), 8.10 (1H, s), 9.83 (1H, s), 10.28 91H, s); MS (ESI) *m/z* 271 $(M-H)^-$.

Anal. for $C_{16}H_{10}F_2O_2 \cdot 0.25\ H_2O$:

Calc'd: C: 69.44 H: 3.82

Found: C: 69.70 H: 3.63

INTERMEDIATE 34

6-(3-Fluoro-4-methoxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-bromo-2-naphthol (3.2 g, 18.8 mmol) with 3-fluoro-4-methoxyphenylboronic acid (3.5 g, 15.7 mmol) according to method A to yield 3.3 g (78 %) of white solid: mp 174-176°C; ^{1}H NMR (DMDO-d_6): δ 3.89 (3H, s), 7.11 (1H, dd, *J* = 8.79 Hz, *J* = 1.95 Hz), 7.13 (1H, s), 7.26 (1H, *J* = 8.79

Hz), 7.57 (1H, d, J = 8.79 Hz), 7.66 (1H, dd, J = 13.18 Hz, J = 1.95 Hz), 7.71 (1H, dd, J = 8.79 Hz, J = 1.46 Hz), 7.75 (1H, d, J = 8.79 Hz), 7.82 (1H, d, J = 8.79 Hz), 8.07 (1H, s), 9.81 (1H, s); MS (ESI) *m/z* 267 $(M-H)^-$.

Anal. for $C_{17}H_{13}FO_2$:

Calc'd: C: 76.11 H: 4.88

Found: C: 76.03 H: 4.78

INTERMEDIATE 35

6-(4-Methoxy-2-methylphenyl)-2-naphthol

The title compound was prepared by reacting 6-bromo-2-naphthol (1.8 g, 5.4 mmol) with 4-methoxy-3-methylphenylboronic acid (1.74 g, 7.0 mmol) according to method A to yield 1.56 g (73 %) of yellowish solid: mp 124-126°C; ^{1}H NMR (DMDO-d_6): δ 2.25(3H,s), 3.78 (3H, s), 6.85 (1H, dd, J = 8.35 Hz, J = 2.56 Hz), 6.90 (1H, d, J = 2.37 Hz), 7.09 (1H, dd, J = 8.75 Hz, J = 2.25 Hz), 7.13 (1H, s), 7.20 (1H, d, J = 8.33 Hz), 7.35 (1H, dd, J = 8.39 Hz, J = 1.37 Hz), 7.67 (1H,s), 7.70 (1H, d, J = 8.53 Hz), 7.78 (1H, d, J = 8.78 Hz), 9.74 (1H, s); MS (ESI) *m/z* 263 $(M-H)^-$.

Anal. for $C_{18}H_{16}O_2$:

Calc'd: C: 81.79 H: 6.10

Found: C: 81.43 H: 6.01

EXAMPLE 1j

2-Fluoro-4-(2-naphthyl)phenol

The title compound was prepared by reacting 2-(3-fluoro-4-methoxyphenyl)-naphthalene (0.22 g, 0.87 mmol) with boron tribromide (1.75 mL of 1N solution, 1.75 mmol) according to method D to yield 0.13 g (63%) of a white solid: mp 110-112 °C; ^{1}H NMR (DMSO-d_6): δ 7.05 – 7.11 (1H, m), 7.47 – 7.54 (3H, m), 7.65 (1H, dd, J = 2.20 Hz, J = 12.92 Hz), 7.82 (1H, dd, J = 1.80 Hz, J = 8.62), 7.90 – 7.98 (3H, m), 8.17 (1H, bs), 10.07 (1H, bs); MS (ESI) *m/z* 237 $(M-H)^-$.

Anal. for $C_{16}H_{11}FO$:

Calc'd: C: 80.66 H: 4.65

Found: C: 80.31 H: 4.29

EXAMPLE 1k

6-(3-Fluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-(3-fluoro-4-methoxyphenyl)-2-naphthol (600 mg, 2.24 mmol) with boron tribromide (6.27 mL of 1.0 M solution in CH_2Cl_2, 6.27 mmol) according to method D to yield 385 mg (68 %) of a yellowish solid: mp 216-219 °C; ^{1}H NMR (DMDO-d_6): δ 7.03-7.13 (3H, m), 7.43 (1H, dd, *J* = 8.37 Hz, *J* = 1.77 Hz), 7.58 (1H, dd, *J* = 12.92 Hz, *J* = 2.13 Hz), 7.68 (1H, dd, *J* = 8.68 Hz, *J* = 1.61 Hz), 7.74 (1H, d, *J* = 8.68 Hz), 8.03 (1H, s), 9.79 (1H, s), 9.98 (1H, s); MS (ESI) *m/z* 253 $(M-H)^-$.

Anal. for $C_{16}H_{11}FO_2 \cdot 0.13H_2O$:

Calc'd: C:74.89 H:4.42

Found: C:74.86 H:4.33

Synthesis of Compounds in Scheme 7

INTERMEDIATE 36

1-Chloro-6-(3-fluoro-4-methoxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-(3-fluoro-4-methoxylphenyl)-2-naphthol (1 g, 3.73 mmol) and NCS (748 mg, 5.60 mmol) in THF (35 mL) according to method A to yield 780 mg (69 %) of brown solid: mp 137-139 °C; ^{1}H NMR (DMDO-d_6): δ 3.89 (3H, s), 7.26-7.33 (2H, m), 7.61 (1H, d, *J* = 8.63 Hz), 7.71 (1H, dd, *J* = 13.08 Hz, *J* = 2.16 Hz), 7.84 (1H, d, *J* = 8.93 Hz), 7.92 (1H, dd, *J* = 8.92 Hz, *J* = 1.80 Hz), 8.06 (1H, d, *J* = 8.86 Hz), 8.19 (1H, d, *J* = 1.55 Hz), 10.52 (1H, s); MS (ESI) *m/z* 301/303$(M-H)^-$.

Anal. for $C_{16}H_{11}ClO$:

Calc'd: C: 67.45 H: 4.00

Found: C: 67.35 H: 3.78

INTERMEDIATE 37

1-Chloro-6-(4-methoxy-2-methylphenyl)-2-naphthol

The title compound was prepared by reacting 6-(4-methoxy-2-methylphenyl)-2-naphthol (800 mg, 3.03 mmol) and NCS (485 mg, 3.61mmol) in THF (30 mL) according to method A to yield 640 mg (71 %) of yellow solid: ^{1}H NMR (DMDO-d_6): δ 2.26 (3H, s), 3.79 (3H, s), 6.86 (1H, dd, *J* = 8.36 Hz, *J* =2.63 Hz), 6.91 (1H, d, *J* =

2.51 Hz), 7.22 (1H, d, J = 8.34 Hz), 7.31 (1H, d, J = 8.89 Hz), 7.56 (1H, dd, J = 8.71 Hz, J = 1.71 Hz), 7.79-7.83(2H, m), 8.04 (1H, J = 8.91 Hz), 10.46 (1H, s); ^{13}C NMR (DMDO-d_6): δ 20.54, 55.07, 111.48, 112.21, 115.71, 118.73, 121.94, 127.92, 128.15, 128.35, 129.34, 130.12. 130.87, 133.26, 136.14, 136.36, 150.99, 158.49; MS (ESI) *m/z* 297/299 $(M-H)^-$.

Anal. for $C_{18}H_{15}ClO_2$:

Calc'd: C: 72.36 H: 5.06

Found: C: 72.02 H: 5.03

EXAMPLE 1v

1-Chloro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 1-chloro-6-(3-fluoro-4-methoxy-phenyl)-2-naphthol (420 mg, 1.39 mmol) with boron tribromide (3.9 mL of 1.0 M solution in CH_2Cl_2, 3.89 mmol) according to method D to yield 330 mg (82 %) of a yellowish solid: mp 195-198 °C; ^{1}H NMR (DMDO-d_6): δ 7.08 (1H, t, J = 8.86 Hz), 7.32 (1H, d, J = 8.89 Hz), 7.47 (1H, dd, J = 8.42 Hz, J = 1.52 Hz), 7.63 (1H, dd, J = 12.88 Hz, J = 1.98 Hz), 7.83 (1H, d, J = 8.95 Hz), 7.88 (1H, dd, J = 8.93 Hz, J = 1.61 Hz), 8.05 (1H, d, 8.86 Hz), 8.15 (1H, d, J = 1.25 Hz), 10.05 (1H, s), 10.50 (1H, s); MS (ESI) *m/z* 287/289 $(M-H)^-$.

Anal. for $C_{16}H_{10}ClFO_2$:

Calc'd: C: 66.56 H: 3.49

Found: C: 66.37 H: 3.65

EXAMPLE 1y

1-Chloro-6-(4-hydroxy-2-methylphenyl)-2-naphthol

The title compound was prepared by reacting 1-chloro-6-(4-methoxy-2-methylphenyl)-2-naphthol (400 mg, 1.41 mmol) with boron tribromide (4.0 mL of 1.0 M solution in CH_2Cl_2, 4.0 mmol) according to method D to yield 310 mg (77 %) of a yellowish solid: mp 216-218 °C; ^{1}H NMR (DMDO-d_6): δ 2.20 (1H, s), 6.68 (1H, dd, J = 8.19 Hz, J = 2.42 Hz), 6.72 (1H, d, J = 2.13 Hz), 7.10 (1H, d, J = 8.16 Hz), 7.29 (1H, d, J = 8.89 Hz), 7.29 (1H, d, J = 8.89 Hz), 7.53 (1H, dd, J = 8.78 Hz, J = 1.62 Hz), 7.76 (1H, d, J = 1.38 Hz), 7.80 (1H, d, J = 8.94 Hz), 8.02 (1H, d, J = 8.72 Hz), 9.4 (1H, s), 10.43 (1H, s); ^{13} NMR (DMDO-d_6): δ 20.47, 112.20, 112.99, 117.00, 118.66,

121.85, 127.83, 128.09, 128.38, 129.47, 130.00, 130.88, 131.65, 136.09, 136.51, 150.88, 156.62; MS (ESI) *m/z* 283/285(M-H)$^-$.

Anal. for $C_{18}H_{15}ClO_2$:

Calc'd: C: 71.71 H: 4.60

Found: C: 71.30 H: 4.66

Synthesis of Compounds in Scheme 8

INTERMEDIATE 38

6-Methoxy-2-naphthalenyl)boronic acid

In a 500 mL flask was added 2-bromo-6-methoxynaphthalene (8.02 g, 33.8 mmol), anhydrous THF (125 mL), and a few crystals of 1,10-phenanthroline as an indicator. The mixture was cooled to –78°C and sec-butyllithium (56 mL of 1.3 N solution in hexanes, 72.8 mmol) was slowly added via syringe. After stirring for 0.5 h triisopropyl borate (47 mL, 203.7 mmol) was added and the solution was stirred for 1 h at –78°C and then allowed to warm to ambient temperature. Then ice cold 2 N HCl (100 mL) was added and the mixture was stirred for 5 minutes after which more 2 N HCl (100 mL) was added and stirred for another 5 minutes. The mixture was then extracted with ethyl acetate (3x), dried over $MgSO_4$, and concentrated to near dryness. Hexanes added to the concentrate induced crystallization which was then collected by filtration and then dried under vacuum to give 7.01 g (~100%) of a light orange powder. ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.88 (3H, s), 7.15 (1H, dd, *J* = 8.9 Hz, 2.7 Hz), 7.29 (1H, d, *J* = 2.5 Hz), 7.75 (1H, d, *J* = 8.3 Hz), 7.83 (2H, appt), 8.30 (1H, s); MS (EI) *m/z* 202.17(M$^+$).

INTERMEDIATE 39

2-Chloro-4-(6-methoxy-2-naphthyl)phenol

A mixture of 4-bromo-2-chlorophenol (730 mg, 3.5 mmol), (6-methoxy-2-naphthalenyl)boronic acid (780 mg, 3.85 mmol), sodium carbonate (930 mg as 2 N aqueous, 8.8 mmol), and tetrakis(triphenylphosphine)palladium(0) (203 mg, 0.18 mmol) in DME (45 mL) was brought to reflux for 12 h. The reaction was then cooled, extracted with ethyl acetate (3x), dried over Na_2SO_4 and concentrated. Column chromatography (30% EtOAc/hexanes) produced 360 mg (30%) of product as a white solid. mp 129-130°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.88 (3H, s), 7.08 (1H, d, *J* =

8.2 Hz), 7.17 (1H, dd, *J* = 8.6 Hz, 2.1 Hz), 7.34 (1H, d, *J* = 2.1 Hz), 7.59 (1H, dd, *J* = 8.6 Hz, 2.1 Hz), 7.75 (2H, m), 7.87 (1H, d, *J* = 8.8 Hz), 7.88 (1H, d, *J* = 8.6), 8.09 (1H, s), 10.34 (1H, s); MS *m/z* 283/285(Cl pattern) ($M - H^+$);

Anal. for $C_{17}H_{13}ClO_2$: :

Calc'd: C: 71.71 H: 4.60

Found: C: 71.68 H: 4.72

INTERMEDIATE 40

3-Chloro-4-(6-methoxy-2-naphthyl)phenol

The title compound was prepared by reacting 4-bromo-3-chlorophenol (3.8 g, 18.3 mmol) with I12372-104 (4.81g, 23.8 mmol) according to method A to yield 5.09 g (98 %) of white solid: mp 139-142 °C; ^{1}H NMR (DMSO-d_6): δ 3.89 (3H,s), 6.87 (1H, dd, *J* = 8.39 Hz, *J* = 2.45 Hz), 6.98 (1H, *J* = 2.40 Hz), 7.19 (1H, dd, *J* = 8.98 Hz, *J* = 2.46 Hz), 7.32 (1H, d, *J* = 8.39 Hz), 7.35 (1H, d, *J* = 2.38 Hz), 7.50 (1H, dd, *J* = 8.47 Hz, *J* = 1.73 Hz), 7.83-7.88 (3H, m), 10.04 (1H, s); MS (ESI) *m/z* 283/285 $(M-H)^-$.

Anal. for $C_{16}H_{11}ClO$: :

Calc'd: C: 71.71 H: 4.60

Found: C: 71.50 H: 4.62

INTERMEDIATE 41

2,6-Difluoro-4-(6-methoxy-2-naphthyl)phenol

The title compound was prepared by reacting 4-bromo-2,6-difluorophenol (3.5 g, 16.8 mmol) with intermediate 38 (4.2 g, 20.2 mmol) according to method A to yield 1.1 g (23 %) of white solid: mp 188-190 °C; ^{1}H NMR (DMSO-d_6): δ 3.89 (3H, s), 7.19 (1H, dd, *J* = 8.92 Hz, *J* = 2.52 Hz), 7.34 (1H, *J* = 2.41 Hz), 7.48-7.59 (2H, m), 7.80 (1H, dd, *J* = 8.61 Hz, *J* = 1.76 Hz), 7.88 (1H, d, *J* = 8.65 Hz), 8.17 (1H, d, *J* = 1.25 Hz), 10.31 (1H, s); MS (ESI) *m/z* 285 $(M-H)^-$.

Anal. for $C_{17}H_{12}F_2O_2$: :

Calc'd: C: 71.32 H: 4.23

Found: C: 71.10 H: 4.17

INTERMEDIATE 42

4-(6-Hydroxy-2-naphthyl)-3-methoxyphenyl 4-methylbenzenesulfonate

4-Bromo-3-methoxyphenyl 4-methylbenzenesulfonate

A mixture of 4-bromo-resorcinol (4.92 g, 26.0 mmol), p-toluenesulfonic chloride (5.95 g, 31.2 mmol), potassium carbonate (23 g, 167 mmol), and acetone (300 mL) was refluxed for 16 hr. Iodomethane (9.89 g, 70 mmol) was added and the mixture was refluxed for an additional 12 hr. The mixture was cooled to room temperature and ether (200 mL) was added and the suspension was filtered. The filtrate was stripped of solvent and purified on a silica column (10% ethyl acetate – hexanes) to yield 6.49 g (70 %) of the title compound as a white solid.

^{1}H NMR ($CDCl_3$): δ 2.45 (3H, s), 3.78 (3H, s), 6.40 (1H, dd, *J* = 2.45 Hz, *J* = 8.60 Hz), 6.59 (1H, d, *J* = 2.48 Hz), 7.33 (2H, d, *J* = 8.30 Hz), 7.40 (1H, d, *J* = 8.69 Hz), 7.71 (2H, d, *J* = 8.23 Hz); MS (ESI) *m/z* 355/357 $(M-H)^-$

Anal. for $C_{14}H_{13}BrO_4S$:

Calc'd: C: 47.07 H: 3.67

Found: C: 47.14 H: 3.57

The title compound was prepared by reacting 4-bromo-3-methoxyphenyl 4-methylbenzenesulfonate (3.07 g, 8.60 mmol) and *tert*-butyl[(2-(6-naphthyl boronic acid)oxy]dimethylsilane (2.86 g, 9.46 mmol) according to method A to yield 2.15 g (53%) of an orange solid): ^{1}H NMR ($CDCl_3$): δ 2.44 (3H, s), 3.65 (3H, s), 6.69 (1H, dd, *J* = 2.10 Hz, *J* = 8.29 Hz), 6.74 (1H, d, *J* = 2.10 Hz), 7.06 – 7.11 (2H, m), 7.36 (1H, d, *J* = 8.27 Hz), 7.45 69 (1H, dd, *J* = 1.32 Hz, *J* = 8.57 Hz), 7.51 (1H, d, *J* = 8.28 Hz), 7.67 (1H, d, *J* = 8.61 Hz), 7.77 (1H, d, *J* = 8.80 Hz), 7.80 – 7.85 (3H, m), 9.78 (1H, s); MS (ESI) *m/z* 419 $(M-H)^-$.

Anal. for $C_{24}H_{20}O_5S \cdot 0.25\ H_2O$:

Calc'd: C: 67.82 H: 4.86

Found: C: 67.75 H: 4.56

EXAMPLE 1aa

6-(4-Hydroxy-2-methoxyphenyl)-2-naphthol

A solution of 4-(6-hydroxy-2-naphthyl)-3-methoxyphenyl 4-methylbenzenesulfonate (1.74 g, 4.05 mmol), potassium hydroxide (5 g), water (85 mL), and ethanol

(85 mL) was stirred at 90°C for 2 hr. The reaction was cooled to room temperature and concentrated to 50% volume, neutralized with acetic acid, and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, evaporation of the solvent, and purification by silica column (25 % ethyl acetate – hexanes) yielded 1.01 g (94 %) of the title compound as a tan solid. A sample was further purified by preparative reverse phase HPLC to yield a tan solid: mp 152-154°C; ^{1}H NMR (DMSO-d_6): δ 3.72 (3H, s), 6.46 (1H, dd, *J* = 1.52 Hz, *J* = 8.20 Hz), 6.52 (1H, d, *J* = 1.77 Hz), 7.04 – 7.09 (2H, m), 7.16 (1H, d, *J* = 8.23 Hz), 7.47 (1H, d, *J* = 8.50 Hz), 7.63 (1H, d, *J* = 8.57 Hz), 7.72 – 7.75 (2H, m), 9.56 (1H, bs), 9.68 (1H, bs); MS (ESI) *m/z* 265 $(M-H)^-$.

Anal. for $C_{17}H_{14}O_3$:

Calc'd: C: 76.68 H: 5.30

Found: C: 76.68 H: 5.30

EXAMPLE 1l

6-(3-Chloro-4-hydroxyphenol)-2-naphthol

A mixture of 2-chloro-4-(6-methoxy-2-naphthyl)phenol (192 mg, 0.71 mmol) and pyridine hydrochloride (3 g, 26 mmol) was heated to 200°C for 1 h while stirring. After allowing the mixture to cool, water was added to dissolve the solid and the aqueous layer was extracted with ether (3x). The ether layers were combined, dried over Na_2SO_4 and passed through a silica plug. Evaporation under reduced pressure afforded 180 mg (98%) of product as a tan colored solid. mp 176-177°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.09 (3H, m), 7.57 (1H, dd, *J* = 7.6 Hz, 1.5 Hz), 7.70 (3H, m), 7.82 (1H, d, *J* = 8.6 Hz), 8.02 (1H, s), 9.77 (1H, s), 10.28 (1H, s); MS *m/z* 269/271(Cl pattern) $(M - H^+)$;

Anal. for $C_{16}H_{11}ClO_2$:

Calc'd: C: 70.99 H: 4.10

Found: C: 70.64 H: 4.16

EXAMPLE 1ab

6-(2-Chloro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 3-chloro-4-(6-methoxy-2-naphthyl)phenol (2.4g, 8.43 mmol) with boron tribromide (21.9 mL of 1.0 M solution in

CH_2Cl_2, 21.9 mmol) according to method D to yield 2.1 g (92 %) of a yellowish solid: mp 209-210°C; ^{1}H NMR (DMDO-d_6): δ 6.86 (1H, dd, *J* = 8.42 Hz, *J* = 2.45 Hz), 6.97 (1H, d, 2.41 Hz), 7.11 (1H, dd, *J* = 8.78 Hz, *J* = 2.35 Hz), 7.16 (1H, d, *J* = 2.15 Hz), 7.30 (1H, d, *J* = 8.40 Hz), 7.42 (1H, dd, *J* = 8.51 Hz, *J* = 1.71 Hz), 7.71 (1H, d, *J* = 8.59 Hz), 7.76 (1H, s), 7.80 (1H, d, *J* = 8.82 Hz), 9.82 (1H, s), 10.01 (1H,s); ^{13}C NMR (DMDO-d_6): δ 108.45,114.79, 116.21, 118.90, 125.53, 127.43, 127.77, 127.92, 129.56, 130.70, 131.73, 132.34, 133.18, 133.52, 155.56, 157.46; MS (ESI) *m/z* 269/271 $(M-H)^-$.

Anal. for $C_{16}H_{11}ClO_2$:

Calc'd: C: 70.99 H: 4.10

Found: C: 70.68 H: 4.09

EXAMPLE 1w

1-Chloro-6-(3-chloro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-(3-chloro-4-hydroxyphenyl)-2-naphthol (500 mg, 1.85 mmol) and NCS (346 mg, 2.59 mmol) in THF (37 mL) according to method A to yield 380 mg (68 %) of yellowish solid: mp 174-175°C; ^{1}H NMR (DMDO-d_6): δ 7.09 (1H, d, 8.47 Hz), 7.31 (1H, d, *J* = 8.89 Hz), 7.60 (1H, dd, *J* = 8.20 Hz, *J* = 2.26 Hz), 7.78 (1H, d, *J* = 2.22 Hz), 7.84 (1H, d, *J* = 8.99 Hz), 7.88 (1H, dd, *J* = 9.00 Hz, *J* = 1.80 Hz), 8.05 (1H, d, *J* = 8.86 Hz), 8.14 (1H, d, *J* = 1.60 Hz), 10.37 (1H, s), 10.49 (1H, s);MS (ESI) *m/z* 303/305/307 $(M-H)^-$.

Anal. for $C_{16}H_{10}Cl_2O_2$:

Calc'd: C: 62.98 H: 3.30

Found: C: 62.65 H: 3.21

EXAMPLE 1ac

1-Chloro-6-(2-chloro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-(2-chloro-4-hydroxyphenyl)-2-naphthol (500 mg, 1.85 mmol) and NCS (321 mg, 2.40 mmol) in THF (40 mL) according to method C to yield 435 mg (77 %) of yellowish solid: mp 224-226 °C; ^{1}H NMR (DMDO-d_6): δ 6.86 (1H, dd, *J* = 8.42 Hz, *J* = 2.41 Hz), 6.96 (1H, d, *J* = 2.44 Hz), 7.30 (1H, d, *J* = 3.19 Hz), 7.33 (1H, d, *J* = 2.65 Hz), 7.62 (1H, dd, *J* = 8.81 Hz, *J* = 1.71 Hz), 7.83 (1H, d, *J* = 8.93 Hz), 7.86 (1H, d, *J* = 1.54 Hz), 8.04 (1H, *J* = 8.76 Hz),

10.04 (1H, s), 10.51 (1H, s); ^{13}C NMR (DMDO-d_6): δ 112.24, 114.84, 116.26, 118.79, 121.84, 128.16, 128.24, 128.35, 129.27, 130.03, 130.40, 131.73, 132.38, 133.98, 151.24, 157.70; MS (ESI) *m/z* 303/305/307 $(M-H)^-$.

Anal. for $C_{16}H_{10}Cl_2O_2$:

Calc'd: C: 62.98 H: 3.30

Found: C: 62.69 H: 3.36

EXAMPLE 1ba

1-Chloro-6-(3,5-difluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-(3,5-difluoro-4-hydroxyphenyl)-2-naphthol (300 mg, 1.10 mmol) and NCS (155 mg, 1.16 mmol) in THF (30 mL) according to method C to yield 264 mg (78 %) of grey solid: mp 209-210°C; ^1H NMR (DMSO-d_6): δ 7.32 (1H, d, *J* = 8.89 Hz), 7.50-7.61 (2H, m), 7.83 (1H, d, *J* = 8.96 Hz), 7.92 (1H, dd. *J* = 8.94 Hz, *J* = 1.59 Hz), 8.05 (1H, d, *J* = 8.88 Hz), 8.22 (1H, d, *J* = 1.19 Hz), 10.36 (1H, s), 10.54 (1H, s); MS (ESI) *m/z* 305/307 $(M-H)^-$.

Anal. for $C_{16}H_9ClF_2O_2$:

Calc'd: C: 62.66 H: 2.96

Found: C: 62.58 H: 3.09

Synthesis of Compounds in Scheme 9

INTERMEDIATE 43

6-Bromo-1-chloro-naphthalen-2-ol

The title compound was prepared by reacting 6-bromo-2-naphthol (3 g, 13.4 mmol) and NCS (2.47 g, 18.5 mmol) in THF (50 mL) according to method C to yield 2.2 g (64%) of yellow solid: ^1H NMR (DMDO-d_6): δ 7.34 (1H, d, *J* = 8.87 Hz), 7.69 (1H, dd, *J* = 1.75 Hz, *J* = 6.09 Hz), 7.79 (1H, d, *J* = 8.96 Hz), 7.96 (1H, d, *J* = 9.03 Hz), 8.17 (1H, d, *J* = 1.75 Hz), 10.68(1H, s); MS (ESI) *m/z* 255/257/259 $(M-H)^-$.

EXAMPLE 1m

1-Chloro-6-phenyl-2-naphthol

The title compound was prepared by reacting 6-bromo-1-chloro-naphthalen-2-ol (300 mg, 1.17 mmol) with phenylboronic acid (170.7 mg, 1.40 mmol) according to method A to yield 240 mg (81 %) of white solid: mp 135-137°C; ^1H NMR (DMDO-d_6):

δ 7.33 (1H, d, *J* = 8.85 Hz), 7.39 (1H, td , *J* = 7.25 Hz, *J* = 0.75 Hz), 7.51 (2H, t, *J* = 7.59 Hz), 7.80 (2H, d, *J* =7.63 Hz), 7.88 (1H, d, *J* = 8.96 Hz), 7.93 (1H, dd, *J* = 8.85 Hz, *J* = 1.19 Hz), 8.10(1H, d, *J* = 8.84 Hz), 8.20 (1H, s), 10.53 (1H, s); MS (ESI) *m/z* 253/255 $(M-H)^-$.

Anal. for $C_{16}H_{11}ClO$:

Calc'd: C: 75.45 H: 4.35

Found: C: 75.16 H: 4.17

INTERMEDIATE 44

6-Bromo-1-nitro-2-naphthol

4-Nitro-4-methyl-2,3,5,6-tetrabromo-2,5-cyclohexadien-1-one (2.53 g, 4.95 mmol, purity: 82.6 %) was added to 6-bromo-2-naphthol (1g, 4.5 mmol) in 40 mL of dry ether. The reaction was allowed to react for 1.5 hr at room temperature. The solid was filtered to give 2,3,5,6-tetrabromo-4-methyl-phenol (144 mg). The solution was then evaporated under vacuum. The crude mixture was dissolved in ethyl acetate and washed with water. The organic layer was dried over anhydrous Na_2SO_4 and filtered and the solvent removed under vacuum. 2,3,5,6-tetrabromo-4-methyl-phenol (1.2 g) was separated by recrystallization of the crude product with ethyl acetate - hexane. The mother liquid was concentrated onto Florosil and purified on a silica column (15 % -20 % ethyl acetate- hexane) to yield 0.731 g (61 %) of the title compound as a yellow solid: mp 111-113 °C; ^1H NMR (DMDO-d_6): δ 7.39 (1H, d, *J* = 9.07 Hz), 7.54 (1H, d, *J* = 9.05 Hz), 7.75 (1H, dd, *J* = 9.05 Hz, *J* = 1.70 Hz), 8.03 (1H, d, *J* = 9.14 Hz), 8.29 (1H, d, *J* = 1.84 Hz), 11.65 (1H, s); MS (ESI) *m/z* 266/268 $(M-H)^-$; IR 1350 cm^{-1}, 1490 cm^{-1}.

Anal. for $C_{10}H_6BrNO_3 \cdot 0.18\ H_2O$:

Calc'd: C: 44.27 H: 2.36 N: 5.16

Found: C: 44.24 H: 2.14 N: 4.76.

INTERMEDIATE 45

6-[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-1-nitro-2-naphthol

The title compound was prepared by reacting 6-bromo-1-nitro-2-naphthol (560 mg, 2.1 mmol) with 4-*tert*-butyl-dimethylsilyoxyboronic acid (688 mg, 2.73 mmol) according to method A to yield 347 mg (42 %) of yellowish solid: ^1H NMR (DMDO-d_6):

δ 0.23 (6H, s), 0.98 (9H, s), 6.99(2H, d, *J* = 8.47 Hz), 7.35 (1H, d, *J* = 9.05 Hz), 7.64 (1H, d, *J* = 8.86Hz), 7.70 (2H, d, *J* = 8.51 Hz), 7.94 (1H, dd, *J* = 6.62 Hz, *J* = 1.25 Hz), 8.08 (1H, d, *J* = 9.16 Hz), 8.22(1H, s), 11.45 (1H, s); MS (ESI) *m/z* 394 $(M-H)^-$.

EXAMPLE 1x

6-(4-Hydroxyphenyl)-1-nitro-2-naphthol

To a solution of 6-[4-(tert-Butyl-dimethyl-silanyloxy)-phenyl]-1-nitro-2-naphthol (302 mg, 0.764 mmol) in THF (12mL) was added TBAF (0.92 mL, 0.917 mmol, 1.0 M solution in THF). The solution was stirred for 10 minutes at room temperature, poured in water. The mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried anhydrous Na_2SO_4, filtered, evaporation of the solvent, and purification on a silica column (20% - 40% ethyl acetate-hexane) yielded 130 mg (61%) of a orange solid. An analytical sample was further purified by recrystallization with ethyl acetate-hexane to yield the title compound as a orange solid: : mp 199-201°C; ^{1}H NMR (DMDO-d_6): δ 6.89(2H, d, *J* = 8.51 Hz), 7.33 (1H, d, *J* = 9.05 Hz), 7.62 (1H, d, *J* = 8.94 Hz), 7.63(2H, d, 8.48 Hz), 7.91 (1H, dd, *J* = 8.87 Hz, *J* = 1.59 Hz), 8.06 (1H, d, 9.18 Hz), 8.17 (1H, d, *J* = 1.31 Hz), 9.64(1H, s), 11.40 (1H,s); MS (ESI) *m/z* 280 $(M-H)^-$.

Anal. for $C_{16}H_{11}NO_4$:

Calc'd: C: 68.32 H: 3.94 N: 4.98

Found: C: 67.91 H: 4.06 N: 4.60

Synthesis of Compounds in Scheme 10

INTERMEDIATE 52

2-(2,5-Difluoro-4-methoxyphenyl)-6-methoxynaphthalene

The title compound was prepared by reacting 4-bromo-2,5-difluoroanisole (4.06 g, 18.3 mmol) with intermediate 38 (4.81 g, 23.8 mmol) according to method A to yield 5.18 g (94.2 %) of white solid: mp 153-155 °C; ^{1}H NMR (DMSO-d_6): δ 3.90 (3H, s), 3.91 (3H, s), 7.20 (1H, dd, *J* = 8.94 Hz, *J* = 2.50 Hz), 7.28 (1H, dd, *J* = 12.38 Hz, *J* = 7.47 Hz), 7.36 (1H, d, *J* = 2.42 Hz), 7.56 (1H, dd, *J* = 12.17 Hz, *J* = 7.53 Hz), 7.62-7.66 (1H, m), 7.89 (2 H, d, *J* = 8.67 Hz), 8.02 (1H, s); MS (ESI) *m/z* 301 $(M-H)^+$; HRMS: calcd for $C_{18}H_{14}F_2O_2$, 300.0962; found (CI (ISOBUTANE)), 300.0953

Anal. for $C_{18}H_{14}F_2O_2$:

Calc'd: C: 71.99 H: 4.70

Found: C: 73.00 H: 4.62

5

INTERMEDIATE 53

2-(2,6-Difluoro-4-methoxyphenyl)-6-methoxynaphthalene

The title compound was prepared by reacting 4-bromo-3,5-difluoroanisole (4.06 g, 18.3 mmol) with intermediate 38 (4.43 g, 22.0 mmol) according to method A to yield 3.4 g (62 %) of white solid: mp 130-132 °C; ^{1}H NMR (acetone-d_6): δ 3.91 (3H,

10 s), 3.94 (3H, s), 6.72-6.80 (2H, m), 7.20 (1H, dd, *J* = 8.97 Hz, *J* = 2.54 Hz), 7.35 (1H, d, *J* = 2.48 Hz), 7.48-7.52 (1H, m), 7.85-7.90 (3H, m); MS (ESI) *m/z* 301 $(M-H)^+$.

Anal. for $C_{18}H_{14}F_2O_2$:

Calc'd: C: 71.99 H: 4.70

Found: C: 71.67 H: 4.81

15

INTERMEDIATE 50

Trifluoro-methanesulfonic acid 2-fluoro-4-methoxy-phenyl ester

2-Fluoro-4-methoxy-phenol

A mixture of 4-bromo-2-fluorophenol (8 g, 41.9 mmol), CuBr (6.0 g, 41.9

20 mmol), sodium methoxide (95.8 mL of 4.4 M in methanol), and DMF (200 mL) were heated at 150°C for 4 hr. The reaction mixture was cooled to room temperature, poured into HCl (419 mL of 2N aqueous solution), filtered through celite and then extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution, dried over sodium sulfate, filtered, evaporation of the solvent,

25 and purification by silica column chromatography (5% -15 % ethyl acetate – hexane) yielded 5.63 g (95 %) of the title compound as a yellowish oil: ^{1}H NMR (DMDO-d_6): δ 3.67 (3H,s), 6.55 (1H, m), 6.78 (1H, dd, *J* = 12.97 Hz, *J* = 2.95 Hz), 6.85 (1H, dd, *J* = 10.14 Hz, *J* = 8.87 Hz), 9.24 (1H, s) 3.67 (3H,s)

30 The title compound was prepared by reacting 2-fluoro-4-methoxy-phenol (2.8 g, 19.7 mmol) with trifluoromethanesulfonic anhydride (4.31 mL, 7.23 g, 25.6 mmol) according to method B to yield 3.86 g (68%) of a clear yellow oil. ^{1}H NMR

(DMSO-d_6): δ 3.82 (3H, s), 6.89-6.94 (1H, m), 7.24 (1H, dd, J = 12.49 Hz, J = 2.98 Hz), 7.61 (1H, t, J = 9.09 Hz).

INTERMEDIATE 54

2-(2-Fluoro-4-methoxyphenyl)-6-methoxynaphthalene

The title compound was prepared by reacting trifluoro-methanesulfonic acid 2-fluoro-4-methoxy-phenyl ester (3.86 g, 14.0 mmol) with intermediate 38 (2.97 g, 14.8 mmol) according to method A to yield 2.27 g (58 %) of white solid: mp 104-106°C; ^{1}H NMR (DMSO-d_6): δ 3.83 (3H, s), 3.89 (3H, s), 6.92 (1H, dd, J = 8.46 Hz, J = 2.64 Hz), 6.98 (1H, dd, J = 12.92, J = 2.48 Hz), 7.19 (1H, dd, J = 8.94 Hz, J = 2.46 Hz), 7.35 (1H, J = 2.38 Hz), 7.53-7.63 (2H, m), 7.90 (2H, d, J = 8.72 Hz), 7.97 (1H, s); MS (ESI) m/z 283 ($M+H^+$).

Anal. for $C_{18}H_{15}FO_2$:

Calc'd: C: 76.58 H: 5.36

Found: C: 76.30 H: 5.23

EXAMPLE 1ar

2-Chloro-4-(2-naphthyl)phenol

A mixture of 4-bromo-2-chlorophenol (1.45 g, 6.98 mmol), 2-naphthalene-boronic acid (1.0 g, 5.81 mmol), sodium carbonate (1.54 g as 2 N aqueous, 14.53 mmol), and tetrakis(triphenylphosphine)palladium(0) (340 mg, 0.3 mmol) in DME (70 mL) was brought to reflux for 6 h according to Method A. The reaction was then cooled, extracted with ethyl acetate (3x), dried over Na_2SO_4 and concentrated. Column chromatography (30% ethyl acetate-hexanes) produced 610 mg (34%) of product as a white solid. An analytical sample was prepared by reverse phase HPLC (CH_3CN/H_2O, 0.1% TFA). mp 99.5 - 100.0°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.10 (1H, d, *J* = 8.4 Hz), 7.52 (2H, m), 7.63 (1H, dd, *J* = 8.5 Hz, 2.0 Hz), 7.81 (2H, m), 7.95 (3H, m), 8.17 (1H, s), 10.40 (1H, s); MS *m/z* 253/255 (Cl pattern) ($M - H^+$);

Anal. for $C_{16}H_{11}ClO$:

Calc'd: C: 75.45 H: 4.35

Found: C: 75.24 H: 4.34

EXAMPLE 1z

6-(4-Hydroxy-2-methylphenyl)-2-naphthol

The title compound was prepared by reacting 6-(4-methoxy-2-methylphenyl)-2-naphthol (420 mg, 1.59 mmol) with boron tribromide (4.53 mL of 1.0 M solution in CH_2Cl_2, 4.53 mmol) according to method D to yield 400 mg (quantitative yield) of a yellowish solid: mp 191-193°C; ^{1}H NMR (DMDO-d_6): δ 6.68 (1H, dd, *J* = 8.41 Hz, *J* = 2.21 Hz), 6.72 (1H, d, *J* = 2.21 Hz), 7.07-7.11 (2H, m), 7.14 (1H, d, *J* = 2.21 Hz), 7.33 (1H, dd, *J* = 8.41 Hz, *J* = 2.21 Hz), 7.64 (1H, d, *J* = 0.885 Hz), 7.68 (1H, d, *J* = 8.41 Hz), 7.77 (1H, d, *J* = 9.29 Hz), 9.33 (1H, s), 9.69 (1H, s); ^{13}C NMR (DMDO-d_6): δ 108.34, 112.82, 116.84, 118.68, 125.47, 127.13, 127.56, 128.02, 129.26, 130.71, 132.26, 133.02, 135.63, 135.90, 155.11, 156.31; MS (ESI) *m/z* 249 $(M-H)^-$.

Anal. for $C_{17}H_{14}O_2$:

Calc'd: C: 81.58 H: 5.64

Found: C: 81.36 H: 5.53

EXAMPLE 1ad

6-(2-Fluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by 2-(2-fluoro-4-methoxyphenyl)-6-methoxy-naphthalene (1.12 g, 3.97 mmol) with boron tribromide (23.8 mL of 1.0 M solution in CH_2Cl_2, 23.8 mmol) according to method D to yield 0.92 g (91 %) of a white solid: mp 208-209°C; ^{1}H NMR (DMSO-d_6): δ 6.66-6.75 (2H, m), 7.08-7.13 (2H, m), 7.41 (1H, dd, *J* = 9.37 Hz, *J* = 8.57 Hz), 7.49-7.53 (1H, m), 7.72 (1H, d, *J* = 8.64 Hz), 7.80 (1H, d, *J* = 8.76 Hz), 7.86 (1H, s), 9.79 (1H, s), 10.01 (1H, s); MS (ESI) *m/z* 255 $(M+H)^+$, MS (ESI) *m/z* 253 $(M-H)^-$.

Anal. for $C_{16}H_{11}FO_2 \cdot 0.15\ H_2O$:

Calc'd: C: 74.79 H: 4.43

Found: C: 74.79 H: 4.23

EXAMPLE 1ae

6-(2,5-Difluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by 2-(2,5-difluoro-4-methoxyphenyl)-6-methoxynaphthalene (1.5 g, 5.0 mmol) with boron tribromide (25 mL of 1.0 M solution in CH_2Cl_2, 25 mmol) according to method D to yield 1.28 g (94 %) of a yellowish solid: mp 217-219 °C; ^{1}H NMR (DMSO-d_6): δ 6.90 (1H, dd, *J* = 11.87 Hz, *J* = 7.51 Hz), 7.10-

7.15 (2H, m), 7.45 (1H, dd, J = 11.87, J = 7.61 Hz), 7.53-7.55 (1H, m), 7.74 (1H, d, J = 8.65 Hz), 7.92 (1H, s), 9.85 (1H, s), 10.50 (1H, s); MS (ESI) *m/z* 271 $(M-H)^-$.

Anal. for $C_{16}H_{10}F_2O_2$:

Calc'd: C: 70.59 H: 3.70

Found: C: 70.35 H: 3.65

EXAMPLE 1af

6-(2,6-Difluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 2-(2,6-difluoro-4-methoxyphenyl)-6-methoxynaphthalene (1.5 g, 5.0 mmol) with boron tribromide (25 mL of 1.0 M solution in CH_2Cl_2, 25 mmol) according to method D to yield 1.35 g (99 %) of a yellowish solid: mp > 240 °C; ^{1}H NMR (DMSO-d_6): δ 6.55-6.63 (2H, m), 7.11 (1H, dd, J = 8.76 Hz, J = 2.34 Hz), 7.15 (1h, d, J = 2.05 Hz), 7.36 (1H, dd, J = 8.58 Hz, J = 1.34 Hz), 7.39 (1H, d, J = 8.83 Hz), 7.79 (1H, s), 7.80 (1H, d, J = 8.74 Hz), 9.85 (1H, s), 10.48 (1H, s); MS (ESI) *m/z* 271 $(M-H)^-$; MS (ESI) *m/z* 543 $(2M-H)^-$.

Anal for $C_{16}H_{10}F_2O_2$:

Calc'd: C: 70.59 H: 3.70

Found: C: 70.19 H: 3.58

EXAMPLE 1ag

1-Chloro-6-(2-fluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-(2-fluoro-4-hydroxyphenyl)-2-naphthol (300 mg, 1.18 mmol) and NCS (191 mg, 1.43 mmol) in THF (30 mL) according to method C to yield 170 mg (50 %) of yellowish solid: mp 179-180 °C; ^{1}H NMR (DMSO-d_6): δ 6.73 (1H, dd, J = 12.69 Hz, J = 2.44 Hz), 6.75 (1H, dd, J = 8.30 Hz, J = 2.44 Hz), 7.31 (1H, d, J = 8.79 Hz), 7.45 (1H, t, J = 9.28 Hz), 7.70-7.72 (1H, m), 7.83 (1H, d, J = 8.79 Hz), 7.97 (1H, s), 8.06 (1H, d, J = 7.79 Hz), 10.06 (1H, s), 10.48 (1H, s); MS (ESI) *m/z* 287/289 $(M-H)^-$.

Anal. for $C_{16}H_{10}ClFO_2$:

Calc'd: C: 66.56 H: 3.49

Found: C: 66.45 H: 3.52

EXAMPLE 1ah

1-Chloro-6-(2,5-difluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-(2,5-difluoro-4-hydroxyphenyl)-2-naphthol (500 mg, 1.84 mmol) and NCS (295 mg, 2.21 mmol) in THF (37 mL) according to method Cto yield 370 mg (66 %) of yellowish solid: mp 203-204 °C; ^{1}H NMR (DMSO-d_6): δ 6.90 (1H, dd, *J* = 11.90 Hz, *J* = 7.50 Hz), 7.32 (1H, d, *J* = 8.88 Hz), 7.49 (1H, dd, *J* = 11.87 Hz, *J* = 7.60 Hz), 7.72-7.76 (1H, m), 7.84 (1H, d, *J* = 8.97 Hz), 8.03 (1H, s), 8.06 (1H, d, 8.87 Hz), 10.58 (2H, s); MS (ESI) *m/z* 305/307 $(M-H)^-$; HRMS calcd for $C_{16}H_9ClF_2O_2$ 306.02591, observed 305.01863 $(M-H)^-$.

Anal. for $C_{16}H_9ClF_2O_2 \cdot 0.4\ H_2O$:

Calc'd: C: 61.22 H: 3.15

Found: C: 61.29 H: 3.17

EXAMPLE 1ai

1-Chloro-6-(2,6-difluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-(2,6-difluoro-4-hydroxyphenyl)-2-naphthol (510 mg, 1.86 mmol) and NCS (301 mg, 2.25 mmol) in THF (30 mL) according to Method C to yield 440 mg (77 %) of yellowish solid: mp 213-214 °C; ^{1}H NMR (acetone-d_6): δ 6.71-6.78 (2H, m), 7.47 (1H, d, *J* = 8.85 Hz), 7.76 (1H, dd, *J* = 8.12 Hz, *J* = 1.52 Hz), 7.97 (1H, d, *J* = 8.90 Hz), 8.04 (1H, s), 8.29 (1H, d, *J* = 8.80 Hz), 9.26 (1H, s), 9.60 (1H, s); MS (ESI) *m/z* 305/307 $(M-H)^-$; HRMS: calcd for $C_{16}H_9ClF_2O_2$, 306.0259; found (ESI-), 306.01991

Anal. for $C_{16}H_9ClF_2O_2 \cdot 0.25\ H_2O$:

Calc'd: C: 61.75 H: 3.08

Found: C: 61.75 H: 2.90

Synthesis of Compounds in Scheme 11

Intermediate 56

N-(7-hydroxynaphthyl)acetamide

To a solution of 8-amino-2-naphthol (149.1 g, 0.937 mol) in methanol (1L) was added acetic anhydride (93 mL, 0.984 mol). The reaction was refluxed for 90 minutes and cooled to room temperature. The solvent was removed and the residue was filtered through a plug of silica with ethyl acetate. The solvent was removed to yield

175.8 g (93%) of the title compound as a dark purple solid. An analytical sample was further purified by reverse phase preparative HPLC to yield a pink solid: mp 161-162°C; ^{1}H NMR (DMSO-d_6):δ 2.15 (3H, s), 7.09 (1H, dd, *J* = 1.95 Hz, *J* = 8.79 Hz), 7.20 – 7.26 (2H, m), 7.49 (1H, d, *J* = 7.31 Hz), 7.63 (1H, d, *J* = 8.11 Hz), 7.77 (1H, d, *J* = 8.81 Hz), 9.76 (1H, s), 9.79 (1H, s); MS (ESI) *m/z* 202 $(M+H)^+$.

Anal. for $C_{12}H_{11}NO_2$:

Calc'd: C: 71.63 H: 5.51 N: 6.96

Found: C: 71.21 H: 5.45 N: 6.89

INTERMEDIATE 57

N-(7-methoxynaphthyl)acetamide

To a mixture of N-(7-hydroxynaphthyl)acetamide (175.4 g, 0.872 mol), potassium carbonate (301 g, 2.18 mol), and acetone (1 l) was added iodomethane (270 mL, 4.36 mol). The reaction mixture was refluxed for 6 hr, cooled to room temperature, and the solvent removed. The residue was filtered through silica with ethyl acetate and triturated with ethyl acetate to yield 161.6 g (86%) of a gray solid. An analytical sample was further purified by preparative reverse phase HPLC to yield the title compound as a white solid: mp 154-155°C; ^{1}H NMR (DMSO-d_6): δ 2.19 (3H, s), 3.90 (3H, s), 7.19 (1H, dd, *J* = 2.39 Hz, *J* = 8.94 Hz), 7.29 – 7.34 (2H, m), 7.39 (1H, d, *J* = 1.86 Hz), 7.75 – 7.68 (2H, m), 7.87 (1H, d, *J* = 8.96 Hz), 9.82 (1H, s); MS (ESI) *m/z* 216 $(M+H)^+$.

Anal. for $C_{13}H_{13}NO_2$:

Calc'd: C: 72.54 H: 6.09 N: 6.51

Found: C: 72.24 H: 6.43 N: 6.52.

INTERMEDIATE 58

7-Methoxynaphthylamine

A mixture of N-(7-methoxynaphthyl)acetamide (160.6 g, 0.747 mol) and HCl (1.5 l of 1N solution) was refluxed for 5 hr. The cooled reaction was neutralized with solid sodium bicarbonate and extracted with dichloromethane until UV clear. The combined organic layers were filtered through silica and evaporation of the solvent yielded 89.5 g (69%) of a brown solid. An analytical sample was prepared by preparative HPLC to yield the title compound as a white solid: mp 134-136°C; ^{1}H

NMR ($CDCl_3$): δ 3.94 (3H, s), 4.01 (2H, bs), 6.80 (1H, d, *J* = 7.26 Hz), 7.05 (1H, d, *J* = 2.20 Hz), 7.12 – 7.19 (2H, m), 7.28 (1H, d, *J* = 8.17 Hz), 7.71 (1H, d, *J* = 8.93 Hz); MS (ESI) *m/z* 174 $(M+H)^+$.

Anal. for $C_{11}H_{11}NO \cdot CF_3CO_2H$:

Calc'd: C: 54.55 H: 3.87 N: 4.89

Found: C: 54.39 H: 4.28 N: 4.78.

INTERMEDIATE 59

1-Fluoro-7-methoxynaphthalene

To a mixture of 7-methoxynaphthylamine (10.94 g, 63.24 mmol), HCl (15.8 mL of 12 N solution, 190 mmol), and water (50 mL) cooled to 10°C was added a solution of sodium nitrite (4.58 g, 66.40 mmol) in water (25 mL) over ten minutes. The solution was stirred for 30 minutes and combined with fluoroboric acid (100 mL). The resulting green solid was collected by filtration, washed first with water, then with ethanol, and then with ether to yield a yellow solid [15.48 g (90%) of the uncharacterized diazonium fluoroborate salt intermediate]. This yellow solid was combined with xylenes (250 mL) and refluxed for 1 hour. The solvent was removed and the residue was partitioned between ethyl acetate and sodium bicarbonate solution. The organic layer was dried over sodium sulfate, filtered, evaporation of the solvent, and purification on silica (hexanes) yielded the title compound as a light yellow liquid. ^1H NMR ($CDCl_3$): δ 3.94 (3H, s), 7.10 – 7.28 (3H, m), 7.34 (1H, d, *J* = 2.50 Hz), 7.55 (1H, d, *J* = 8.12 Hz), 7.75 (1H, dd, *J* = 1.69 Hz, *J* = 9.00 Hz); MS (EI) *m/z* 176 $(M^{\cdot})^+$.

Anal. for $C_{11}H_9FO$:

Calc'd: C: 74.99 H: 5.15

Found: C: 74.84 H: 5.14

INTERMEDIATE 60

8-Chloro-2-methoxynaphthalene

$CuCl_2$ (4.6 g, 24.6 mmol) and t-butyl nitrite (4.46 g, 43.3 mmol) were added to acetonitrile (125 mL) at 0°C. To this mixture was slowly added a solution of 7-methoxynaphthylamine (4.99 g, 28.8 mmol) in acetonitrile (25 mL). The reaction was allowed to warm to room temperature , stirred with HCl (400 mL of 2N solution) and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed

with 2N HCl, dried over sodium sulfate, filtered, evaporation of the solvent, and purification on a silica column (hexanes) yielded 2.27 g (41%) of an orange liquid. An analytical sample was further purified by reverse phase preparative HPLC to yield the title compound as a yellow solid: mp 32-34°C; ^{1}H NMR ($CDCl_3$): δ 3.98 (3H, s), 7.20 (1H, dd, *J* = 2.52 Hz, *J* = 8.96 Hz), 7.22 – 7.27 (1H, m), 7.52 (1H, d, *J* = 2.47 Hz), 7.55 (1h, d, *J* = 7.47 Hz), 7.69 (1H, d, *J* = 8.15 Hz), 7.75 (1H, d, *J* = 8.95 Hz); MS *m/z* 191/193 $(M-H)^-$.

Anal. for $C_{11}H_9ClO$:

Calc'd: C: 68.58 H: 4.71

Found: C: 68.35 H: 4.85

INTERMEDIATE 61

1-Bromo-7-methoxy-naphthalene

To a solution of $CuBr_2$ (15.7 g, 70.3 mmol) and TBN (9.05 g, 87.9 mmol) in acetonitrile (250 mL) at 0 °C was slowly added a solution of 2-methoxynaphthylamine (10.14 g, 58.6 mmol) in acetonitrile (60 mL). The dark solution was stirred at 0°C for 2.5 hr, concentrated onto silica, and purified on a silica column to yield 4.03 g (29%) of a white solid . An analytical sample was further purified by preparative reverse phase HPLC to yield the title compound as a white solid: mp 54-58°C; ^{1}H NMR ($CDCl_3$): δ 3.97 (3H, s), 7.15 – 7.21 (2H, m), 7.50 (1H, d, *J* = 2.42 Hz), 7.71 – 7.76 (3H, m); MS (EI) *m/z* 236 $(M^{\cdot})^+$.

Anal. for $C_{11}H_9BrO$:

Calc'd: C: 55.72 H: 3.83

Found: C: 55.58 H: 3.60

INTERMEDIATE 62

7-Methoxy-1-naphthonitrile

A mixture of 1-bromo-7-methoxy-naphthalene (3.26 g, 13.8 mmol), $Zn(CN)_2$ (2.26 g, 19.2 mmol), and tetrakis(triphenylphosphine)palladium (1.6 g, 1.4 mmol) in DMF (50 mL) was stirred at 120 °C for 15 hr. The cooled reaction mixture was poured into 200 mL 1N NH_4Cl solution and extracted with ethyl acetate (3x 350 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, evaporation of the solvent, and purification on a silica column (10% ethyl acetate – hexanes)lyielded 1.28 g (51%) of the title compound as a white solid: mp 62-66 °C;

^{1}H NMR (DMSO-d_6): δ 4.00 (3H, s), 7.25 (1H, dd, *J* = 2.48 Hz, *J* = 8.96 Hz), 7.36 – 7.47 (1H, m), 7.47 (1H, d, *J* = 2.39 Hz), 7.81 (1H, d, *J* = 9.00 Hz), 7.88 (1H, dd, *J* = 0.81 Hz, *J* = 7.23 Hz), 8.00 (1H, d, *J* = 8.21 Hz); MS (EI) *m/z* 183 $(M^{\cdot})^+$;

Anal. for $C_{12}H_9NO$:

Calc'd: C: 78.67 H: 4.95 N: 7.65

Found: C: 78.83 H: 4.60 N: 6.80.

INTERMEDIATE 64

7-Methoxy-3, 4-dihydronaphthalene-1-carbonitrile

To a mixture of 7-methoxy-1-tetralone (39.65 g, 0.23 mol), zinc iodide (1.73 g, 5.4 mmol), and benzene (100 mLs) was added trimethylsilylcyanide (25.0 g. 0.25 mol). The mixture was stirred overnight at room temperature. Pyridine (350 mL) was added and phosphorous oxychloride (100 mL) was then added dropwise, with a slight temperature increase.. The mixture was heated to reflux and held for 6 hr. TLC showed one mid-Rf spot for the desired product. The mixture was stirred overnight at room temperature. The mixture was carefully poured onto ice/hydrochloric acid (about 1.5 liter of 10% HCl). The total volume was 2 liters. This mixture was extracted with ethyl acetate (3 x 500 mLs), the organics combined and washed with water (2 x 500 mLs) and then brine (500 mLs). The ethyl acetate was dried over magnesium sulfate and evaporated off provide a liquid which on standing solidified. This crude solid was slurried in hexane and filtered to give 31.3 g (74%) of a tan solid. Some of this material was purified by silica gel chromatography (10% ethyl acetate-hexanes) to provide a solid: mp 47-49 ° C; ^{1}H NMR (DMSO-d_6): δ 2.44-2.50 (2H, m), 2.72 (2H, t, *J*=8.4 Hz), 6.81 (1 H, d, *J*=2.6 Hz), 6.90 (1H, dd, *J* = 2.9 Hz, *J* = 8.2 Hz), 7.17-7.19 (2H, m); MS *m/z* 168 ([M-H]-);

Anal. for $C_{12}H_{11}NO$:

Calc'd: C: 77.81 H: 5.99 N: 7.56

Found: C: 77.71 H: 5.69 N: 7.50

INTERMEDIATE 62

7-Methoxy-1-cyanonaphthalene

To a mixture of 7-methoxy-3, 4-dihydronaphthalene-1-carbonitrile (9.95 g, 53.1 mmol) in p-cymene (100 mLs) was added 10 % Pd/C (5 g), the reaction mixture was

stirred and heated to 150°C overnight. The mixture was cooled and the catalyst removed by filtering through filter aid. The p-cymene was removed on the rotovap with the vacuum pump, giving a liquid which solidified on standing. The solid was slurried in hexane, filtered and dried to afford a white solid (4.3 g, 44 %). A portion was purified further by silica gel (10% ethyl acetate-hexanes) to produce a white solid: mp 77-78°C; ^{1}H NMR (DMSO-d_6): δ 3.97 (3H, s), 7.36 (1H, s), 7.39 (1 H, d, *J*=2.5 Hz), 7.52 (1H, t, *J* = 7.4 Hz), 8.04-8.13 (2H, m), 8.24 (1H, d, *J*=8.2 Hz).

Anal. for $C_{12}H_9NO$:

Calc'd: C: 78.67 H: 4.95 N: 7.51

Found: C: 78.47 H: 4.73 N: 7.51

Synthesis of Compounds in Scheme 12

INTERMEDIATE 65

8-Fluoro-2-naphthol

The title compound was prepared by reacting 1-fluoro-7-methoxynaphthalene (7.99 g, 45.34 mmol) with boron tribromide (68 mL of 1N solution, 68 mmol) according to method D to yield 3.99 g (54 %) of a red solid. An analytical sample was prepared by preparative reverse phase HPLC to yield a white solid: mp 89-92°C; ^{1}H NMR (DMSO-d_6): δ 7.16 (1H, dd, *J* = 2.42 Hz, *J* = 8.90 Hz), 7.21 – 7.25 (3H, m), 7.62 – 7.65 (1H, m), 7.85 (1H, dd, *J* = 1.72 Hz, *J* = 8.87 Hz), 10.08 (1H, s); MS (ESI) *m/z* 161$(M-H)^-$.

Anal. for $C_{10}H_7FO$:

Calc'd: C: 74.07 H: 4.35

Found: C: 73.90 H: 4.30

INTERMEDIATE 66

8-Chloro-2-naphthol

The title compound was prepared by reacting 8-chloro-2-methoxynaphthalene (10.25 g, 53.4 mmol) with boron tribromide (67 mL of 1N solution, 67 mmol) according to method D to yield 8.76 g (92%) of a yellow solid. An analytical sample was further purified by reverse phase preparative HPLC to yield the title compound as a white solid: mp 95-100 °C; ^{1}H NMR (DMSO-d_6): δ 7.18 (1H, dd, *J* = 2.37 Hz, *J* = 8.85 Hz),

7.23 – 7.28 (1H, m), 7.41 (1H, d, J = 2.28 Hz), 7.59 (1H, d, J = 7.37 Hz), 7.81 (1H, d, J = 8.15 Hz), 7.87 (1H, d, J = 8.86 Hz), 10.17 (1H, s); MS *m/z* 177/179 $(M-H)^-$.

Anal. for $C_{10}H_7ClO$:

Calc'd: C: 67.24 H: 3.95

Found: C: 66.99 H: 4.06

INTERMEDIATE 67

7-Hydroxy-1-naphthonitrile

The title compound was prepared by reacting 7-methoxy-1-naphthonitrile (1.19 g, 6.50 mmol) with pyridinium HCl (9 g) according to method D to yield 0.88 g (80%) of a white solid: mp 184-188°C; ^{1}H NMR (DMSO-d_6): δ 7.25 (1H, dd, J = 2.30 Hz, J = 8.88 Hz), 7.38 (1H, d, J = 2.20 Hz), 7.39 – 7.44 (1H, m), 7.98 (1H, d, J = 8.91 Hz), 8.04 (1H, d, J = 7.14 Hz), 8.17 (1H, d, J = 8.19 Hz), 10.48 (1H, s); MS (ESI) *m/z* 170 ([M+H]+); MS (ESI) *m/z* 168 $(M-H)^-$.

Anal. for $C_{11}H_7NO$:

Calc'd: C: 78.09 H: 4.17 N: 8.28

Found: C: 77.99 H: 3.99 N: 8.47.

INTERMEDIATE 68

6-Bromo-8-fluoro-2-naphthol

To a solution of 8-fluoro-2-naphthol (3.24 g, 20.0 mmol) in glacial acetic acid (30 mL) was slowly added a solution of bromine (7.35 g, 46.0 mmol) in glacial acetic acid (30 mL). The solution was stirred at 100°C for 1 hour. The reaction was cooled to room temperature, poured into water (50 mL) and extracted with ethyl acetate (3x 150 mL). The combined organic layers were washed with sodium bicarbonate solution, dried over sodium sulfate, filtered, evaporation of the solvent, and purified on a silica column (2.5% ethyl acetate – hexanes) to yield 3.96 g (12.4 mmol, 62%) of the intermediate 1,6-dibromo-8-fluoro-2-naphthol as a yellow solid. This solid was combined with $SnCl_2$ (7.0 g, 31 mmol), glacial acetic acid (35 mL) and HCl (35 mL of 12 N) and heated to 100°C for 1 hour. The resulting solution was cooled to room temperature, poured into water (100 mL), and extracted with ethyl acetate (3x 200 mL). The combined organic layers were washed with water, dried over sodium sulfate, filtered, stripped of solvent, and purified on silica 2.5% ethyl acetate –

hexanes) to yield 1.97 g (41%) of the title compound as a white solid: mp 124-126°C; ^{1}H NMR (DMSO-d_6): δ 7.20 (1H, s), 7.23 (1H, d, *J* = 2.39 Hz), 7.48 (1H, dd, *J* = 1.78 Hz, *J* = 10.52 Hz), 7.84 – 7.88 (1H, m), 7.94 (1H, d, *J* = 0.79 Hz), 10.28 (1H, s);
MS (ESI) *m/z* 239/241 $(M-H)^-$.
Anal. for $C_{10}H_6BrFO$:
Calc'd: C: 49.83 H: 2.51
Found: C: 49.86 H: 2.46

INTERMEDIATE 69

3,6-Dibromo-8-chloro-2-naphthol

To a solution of 8-chloro-2-naphthol (4.92 g, 27.6 mmol) in glacial acetic acid (40 mL) was slowly added a solution of bromine (9.7 g, 60.7 mmol) in glacial acetic acid (40 mL). The solution was stirred at 100°C for 1 hour, cooled to room temperature, poured into water (250 mL), and extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate, dried with sodium sulfate, filtered, stripped of solvent, and purified on a silica column (20 % ethyl acetate – hexanes) to yield 4.61 g (50%) of a yellow solid. An analytical sample was further purified by reverse phase preparative HPLC to yield the title compound as a white solid: mp 156-158 °C; ^{1}H NMR (DMSO-d_6): δ 7.57 (1H, s), 7.82 (1H, d, *J* = 1.89 Hz), 8.11 (1H, d, *J* = 1.69 Hz), 8.31 (1H, s), 11.30 (1H, bs);
MS (ESI) *m/z* 333/335/337 $(M-H)^-$.
Anal. for $C_{10}H_5Br_2ClO$:
Calc'd: C: 35.70 H: 1.50
Found: C: 35.74 H: 1.44

INTERMEDIATE 70

3-Bromo-7-hydroxy-1-naphthonitrile

To a mixture of 7-hydroxy-1-naphthonitrile (26.03 g, 154.0 mmol) and glacial acetic acid (400 mL) was added bromine (51.8 g, 323 mmol). The mixture was stirred at 100 °C for 6 hr. HCl (400 mL of 12 N solution) and $SnCl_2$ (69 g, 308 mmol) were added and the mixture was stirred at 100°C for 1 hour. The resulting solution was cooled to room temperature and poured into water (1 l). The resulting yellow precipitate was collected by filtration, dried under vacuum, and triturated with ethyl

acetate to yield 14.68 g (38 %) of the title compound as an off-white solid. An analytical sample was prepared by preparative reverse phase HPLC to yield the title compound as a white solid: mp 222-224 °C; ^{1}H NMR (DMSO-d_6): δ 7.28 – 7.35 (2H, m), 7.97 (1H, d, *J* = 8.73 Hz), 8.26 (1H, s), 8.47 (1H, s), 10.65 (1H, s); MS (ESI) *m/z* 246/247 $(M-H)^-$.

Anal. for $C_{11}H_6BrNO$:

Calc'd: C: 53.26 H: 2.44 N: 5.65

Found: C: 52.81 H: 2.70 N: 4.82.

INTERMEDIATE 71

***tert*-Butyl[(3,6-dibromo-8-chloro-2-naphthyl)oxy]dimethylsilane**

The title compound was prepared by reacting 3,6-dibromo-8-chloro-2-naphthol (3.00 g, 8.92 mmol) with TBDMS-Cl (1.75g, 150.7 mmol) according to method F to yield 3.36 g (84%) of a white solid: mp 58-64°C; ^{1}H NMR ($CDCl_3$): δ 0.34 (6H, s), 1.08 (9H, s), 7.57 (1H, s), 7.62 (1H, d, *J* = 1.72 Hz), 7.75 (1H, d, *J* = 1.24 Hz), 7.97 (1H, s); MS (ESI) *m/z* 333/335/337 $(M-H)^-$.

Anal. for $C_{16}H_{19}Br_2ClOSi$:

Calc'd: C: 42.64 H: 4.25

Found: C: 42.73 H: 4.08

INTERMEDIATE 72

8-Fluoro-6-(4-methoxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-bromo-8-fluoro-2-naphthol (0.39 g, 1.62 mmol) with 4-methoxyphenyl boronic acid (0.34 g, 2.27 mmol) according to method A to yield 0.35 g (81 %) of a white solid: mp 150-151°C; ^{1}H NMR (DMSO-d_6): δ 3.81 (3H, s), 7.05 (2H, d, *J* = 8.75 Hz), 7.16 – 7.20 (2H, m), 7.57 (1H, dd, *J* = 1.21 Hz, *J* = 12.76 Hz), 7.74 (2H, d, *J* = 8.74 Hz), 7.89 – 7.92 (2H, m), 10.10 (1H, s); MS (ESI) *m/z* 269 $(M-H)^+$.

Anal. for $C_{17}H_{13}FO_2 \cdot 0.1\ H_2O$:

Calc'd: C: 75.60 H: 4.93

Found: C: 75.30 H: 4.57

INTERMEDIATE 73

8-Fluoro-6-(3-fluoro-4-methoxyphenyl)-2-naphthol

The title compound was prepared by reacting 6-bromo-8-fluoro-2-naphthol (0.66 g, 2.74 mmol) with 3-fluoro-4-methoxyphenyl boronic acid (0.56 g, 3.3 mmol) according to method A to yield 0.67 g (85 %) of a white solid: mp 138-140 °C; ^{1}H NMR (DMSO-d_6): δ 3.90 (3H, s), 7.17 – 7.30 (3H, m), 7.60 – 7.65 (2H, m), 7.71 (1H, dd, , *J* = 2.19 Hz), , *J* = 13.14 Hz), 7.90 (1H, d, , *J* = 8.37 Hz), 7.99 (1H, bs), 10.15 (1H, bs); MS (ESI) *m/z* 285 $(M-H)^-$.

Anal. for $C_{17}H_{12}F_2O_2$:

Calc'd: C: 71.32 H: 4.23

Found: C: 71.09 H: 4.15

INTERMEDIATE 74

tert-Butyl[(3-bromo-8-chloro-(4-methoxyphenyl)-2-naphthyl)oxy]dimethylsilane

A solution of *tert*-butyl[(3,6-dibromo-8-chloro-2-naphthyl)oxy]dimethylsilane (1.95 g, 4.32 mmol), 4-methoxyphenylmagnesium bromide (13.8 mL of 0.5 N solution, 6.9 mmol), and tetrakis(triphenylphosphine)palladium (0.25 g, 0.21 mmol) in THF (10 mL) were stirred at reflux for 8 hr. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (3x150 mL). The combined organic layers were washed with water, dried with sodium sulfate, filtered, evaporation of the solvent, and purified on a silica column (5% ethyl acetate – hexanes) to yield 1.42 g (69%) of the title compound as a white solid: ^{1}H NMR ($CDCl_3$): δ 0.36 (6H, s), 1.10 (9H, s), 3.87 (3H, s), 7.01 (2H, d, *J* = 8.78 Hz), 7.33(1H,d, *J* = 1.36 Hz), 7.58 (2H, d, *J* = 8.75 Hz), 7.73 (1H, s), 7.78 (1H, d, *J* = 1.62 Hz), 8.10 (1H, s).

INTERMEDIATE 75

7-Hydroxy-3-(4-methoxyphenyl)-1-naphthonitrile

The title compound was prepared by reacting 3-bromo-7-hydroxy-1-naphthonitrile (0.249 g, 1.00 mmol) with 4-methoxyphenylboronic acid (0.21 g, 1.4 mmol) according to Method A to yield 0.19 (69%) of a light yellow solid: mp 226°C; ^{1}H NMR (DMSO-d_6): δ 3.82 (3H, s), 7.07 (2H, d, *J* = 8.82 Hz), 7.26 (1H, dd, *J* = 2.32 Hz, *J* = 8.90 Hz), 7.37 (1H, d, *J* = 2.27 Hz), 7.80 (2H, d, *J* = 8.80 Hz), 8.02 (1H, d, *J* = 8.96

Hz), 8.37 (1H, d, J = 1.85 Hz), 8.44 (1H, d, J = 1.43 Hz), 10.48 (1H, bs); MS (ESI) m/z 274 $(M-H)^-$.

Anal. for $C_{18}H_{13}NO_2 \cdot 0.1\ H_2O$:

Calc'd: C: 78.02 H: 4.80 N: 5.05

Found: C: 77.73 H: 4.65 N: 4.92.

INTERMEDIATE 76

3-(3-Fluoro-4-methoxyphenyl)-7-hydroxy-1-naphthonitrile

The title compound was prepared by reacting 3-bromo-7-hydroxy-1-naphthonitrile (0.208 g, 0.839 mmol) with 3-fluoro-4-methoxyphenylboronic acid (0.18 g, 1.1 mmol) according to method A to yield 0.16 (65%) of a light yellow solid. An analytical sample was prepared by preparative reverse phase HPLC to yield the title compound as a white solid: mp 214-216 °C; ^{1}H NMR (DMSO-d_6): δ 3.90 (3H, s), 7.23-7.32 (2H, m), 7.37 (1H, d, J = 2.24 Hz), 7.65 – 7.70 (1H, m), 7.79 (1H, dd, J = 2.22 Hz, J = 13.10 Hz), 8.03 (1H, d, J = 8.96 Hz), 8.41 (1H, d, J = 1.86 Hz), 8.50 (1H, d, J = 1.43 Hz), 10.55 (1H, s); MS (ESI) m/z 292 $(M-H)^-$.

Anal. for $C_{18}H_{12}FNO_2 \cdot 0.1\ H_2O$:

Calc'd:C: 73.26 H: 4.17 N: 4.75

Found: C: 72.91 H: 4.01 N: 4.60.

INTERMEDIATE 77

3-Bromo-8-chloro-6-(4-methoxyphenyl)-2-naphthol

Method I

To a solution of *tert*-butyl[(3-bromo-8-chloro-(4-methoxyphenyl)-2-naphthyl)-oxy]dimethylsilane (0.50 g, 1.06 mmol) in THF (20 mL) was added TBAF (5 mL of 1N solution in THF, 55 mmol). The solution was stirred for one hour at room temperature, evaporation of the solvent, taken up in water (50 mL), and extracted with ethyl acetate (3x150 mL). The combined organic layers were washed with water, dried with sodium sulfate, filtered, stripped of solvent, and purified on a silica column (10% ethyl acetate – hexanes) to yield 0.34 g (88%) of a white solid. An analytical sample was further prepared by reverse phase preparative HPLC to yield the title compound as a white solid: mp 138-139°C; ^{1}H NMR (DMSO-d_6): δ 3.82 (3H, s), 7.06 (2H, d, J = 8.76 Hz), 7.58 91H, s), 7.73 (2H, d, J = 8.73 Hz), 7.94 (1H, d, J = 1.56 Hz), 8.07 (H, bs), 8.34 (1H, s), 11.05 (1H, s); MS (ESI) m/z 361/363/365 $(M-H)^-$.

Anal. for $C_{17}H_{12}BrClO_2 \cdot 0.6\ H_2O$:

Calc'd:C: 54.53 H: 3.55

Found: C: 54.30 H: 3.11

EXAMPLE 1az

3-(3,5-Difluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile

The title compound was prepared by reacting 3-bromo-7-hydroxy-1-naphthonitrile (0.124 g, 0.50 mmol) with 2,5-difluoro-4-*tert*-butyldimethylsilyloxyphenylboronic acid (0.17 g, 0.59 mmol) according to method A to yield 0.090 g (61%) of a yellow solid. An analytical sample was prepared by preparative reverse phase HPLC to yield the title compound as a light yellow solid: mp 300-304°C(d); ^{1}H NMR (DMSO-d_6): δ 7.27 91H, dd, *J* = 2.26 Hz, *J* = 8.88 Hz), 7.36 (1H, d, *J* = 2.12 Hz), 7.63 – 7.66 (2H, m), 8.00 (1H, d, *J* = 8.95 Hz), 8.43 (1H, d, *J* = 1.77 Hz), 8.52 (1H, s), 10.44 (1H, s), 10.54 (1H, s); MS (ESI) *m/z* 296 $(M-H)^-$.

Anal. for $C_{17}H_9F_2NO_2 \cdot 0.3\ H_2O$:

Calc'd:C: 67.46 H: 3.20 N: 4.63

Found: C: 67.18 H: 2.89 N: 4.55.

EXAMPLE 1aj

8-Fluoro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 8-fluoro-6-(4-methoxyphenyl)-2-naphthol (0.10 g, 0.37 mmol) with boron tribromide (0.56 mL of 1N solution, 0.56 mmol) according to method D to yield 0.10 g (quantitative) of a white solid: mp 236-238°C; ^{1}H NMR (DMSO-d_6): δ 6.87 (2H, d, *J* = 8.57 Hz), 7.14 – 7.18 (2H, m), 7.52 (1H, dd, *J* = 1.18 Hz, *J* = 12.78 Hz), 7.61 (2H, d, *J* = 8.59 Hz, 7.86 – 7.89 (2H, m), 9.61 (1H, bs), 10.05 (1H, bs); MS (ESI) *m/z* 253 $(M-H)^-$.

Anal. for $C_{16}H_{11}FO_2 \cdot 0.1\ H_2O$:

Calc'd: C: 75.06 H: 4.41

Found: C: 75.01 H: 4.11

EXAMPLE 1ak

8-Fluoro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 8-fluoro-6-(3-fluoro-4-methoxyphenyl)-2-naphthol (0.10 g, 0.35 mmol) with boron tribromide (0.7 mL of 1N solution, 0.7 mmol) according to method D to yield 0.020 g (21%) of a white solid: mp 218-220 °C d; ^{1}H NMR (DMSO-d_6): δ 7.01 – 7.07 (1H, m), 7.16 – 7.19 (2H, m), 7.46 (1H, dd, , *J* = 1.74 Hz, , *J* = 8.40 Hz), 7.56 – 7.65 (2H, m), 7.88 (1H, d, , *J* = 8.31 Hz), 7.93 (1H, bs), 10.04 (1H, s), 10.11 (1H, s); MS (ESI) *m/z* 271 $(M-H)^-$.

Anal. for $C_{16}H_{10}F_2O_2 \cdot 0.25\ H_2O$

Calc'd: C: 69.44 H: 3.82

Found: C: 69.13 H: 3.45

EXAMPLE 1au

7-Hydroxy-3-(4-hydroxyphenyl)-1-naphthonitrile

The title compound was prepared by reacting 7-hydroxy-3-(4-methoxyphenyl)-1-naphthonitrile (0.14 g, 0.51 mmol) with pyridinium HCl (3 g) according to method B to yield 0.10 g (75%) of a white solid: mp 254-257°C; ^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, *J* = 8.53 Hz), 7.25 (1H, dd, *J* = 2.15 Hz, *J* = 8.88 Hz), 7.36 (1H, d, *J* = 1.86 Hz), 7.67 (2H, d, *J* = 8.55 Hz), 8.00 (1H, d, *J* = 8.94 Hz), 8.31 – 8.38 (2H, m), 9.70 (1H, bs), 10.44 (1H, bs); MS (ESI) *m/z* 260 $(M-H)^-$.

Anal. for $C_{17}H_{11}NO_2 \cdot 0.25\ H_2O$

Calc'd:C: 76.83 H: 4.36 N: 5.27

Found: C: 76.85 H: 4.31 N: 5.10.

EXAMPLE 1av

3-(3-Fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile

The title compound was prepared by reacting 7-hydroxy-3-(3-fluoro-4-methoxyphenyl)-1-naphthonitrile (0.12 g, 0.41 mmol) with pyridinium HCl (3 g) according to method B to yield 0.085g (74%) of a white solid: mp 265-269 °C;^{1}H NMR (DMSO-d_6): δ 7.04 – 7.09 (1H, m), 7.26 (1H, dd, *J* = 2.31 Hz, *J* = 8.88 Hz), 7.36 (1H, d, *J* = 2.19 Hz), 6.52 (1H, d, *J* = 2.19 Hz), 6.52 (1H, dd, *J* = 1.76 Hz, *J* = 8.40 Hz),

6.71 (1H, dd, J = 2.22 Hz, J = 12.88 Hz), 8.01 (1H, d, J = 8.97 Hz), 8.37 (1H, d, J = 1.83 Hz), 8.45 (1H, d, J = 1.41 Hz), 10.33 (2H, bs); MS (ESI) *m/z* 278 $(M-H)^-$.

Anal. for $C_{17}H_{10}FNO_2$:

Calc'd: C: 73.11 H: 3.61 N: 5.02

Found: C: 72.75 H: 3.45 N: 4.82.

Synthesis of Compounds in Scheme 13

INTERMEDIATE 78 and INTERMEDIATE 79

1-Chloro-6-methoxy-2-naphthol and 1,5-Dichloro-6-methoxy-2-naphthol

A mixture of 6-methoxy-2-naphthol (5.43 g, 31.17 mmol), NCS (4.58 g, 34.3 mmol), and acetonitrile (150 mL) was stirred overnight at room temperature according to Method A. The solvent was removed and the resulting brown solid residue was taken up in ethyl acetate (500 mL), washed with water, dried over sodium sulfate, evaporation of solvent, and purification on a silica column (20% ethyl acetate – hexanes) yielded a white solid. This solid was further purified by reverse phase preparative HPLC to yield 3.91 g (60%) of intermediate 78 as a white solid: mp 104-105 °C; ^{1}H NMR (DMSO-d_6): δ 3.85 (3H, s), 7.22 – 7.26 (2H, m), 7.31 (1H, d, J = 2.42 Hz), 7.68 (1H, d, J = 8.91 Hz), 7.93 (1H, d, J = 9.17 Hz); MS (ESI) *m/z* 207/209 $(M-H)^-$.

Anal. for $C_{11}H_9ClO_2$:

Calc'd: C: 63.32 H: 4.35

Found: C: 63.21 H: 4.50

The HPLC separation also yielded 0.83 g (3.43 mmol) of intermediate 79 as a white solid: mp 152-158 °C; ^{1}H NMR (DMSO-d_6): δ3.97 (3H, s), 7.41 (1H, d, J = 9.22 Hz), 7.63 (1H, d, J = 9.17 Hz), 7.97 (1H, d, J = 9.23 Hz), 8.04 (1H, d, J = 9.34 Hz), 10.51 (1H, s); MS (ESI) *m/z* 241/243 $(M-H)^-$.

Anal. for $C_{11}H_8Cl_2O_2$:

Calc'd: C: 54.35 H: 3.32

Found: C: 54.13 H: 3.21

INTERMEDIATE 80

1-Chloro-6-methoxy-2-naphthyl trifluoromethanesulfonate

The title compound was prepared by reacting 1-chloro-6-methoxy-2-naphthol (0.70 g, 3.36 mmol) with trifluoromethanesulfonic anhydride (1.23 g, 4.4 mmol) according to intermediate 6 to yield 1.02 g (89%) of a white solid: mp 60-61 °C; ^{1}H NMR ($CDCl_3$): δ 3.95 (3H, s), 7.17 (1H, d, *J* = 2.48 Hz), 7.35 (1H, dd, *J* = 2.50 Hz, *J* = 9.30 Hz), 7.39 (1H, d, *J* = 9.06 Hz), 7.71 (1H, d, *J* = 9.11 Hz), 8.21 (1H, d, *J* = 9.28 Hz); MS (EI) *m/z* 340/342 $(M^{\cdot})^+$.

Anal. for $C_{12}H_8ClF_3O_4S$

Calc'd:C: 42.30 H: 2.37

Found: C: 42.20 H: 2.37

INTERMEDIATE 81

1,5-Dichloro-6-methoxy-2-naphthyl trifluoromethanesulfonate

The title compound was prepared by reacting 1,5-dichloro-6-methoxy-2-naphthol (0.27 g, 1.11 mmol) with trifluoromethanesulfonic anhydride (0.41 g, 1.44 mmol) according to intermediate 6 to yield 0.37 g (89%) of a white solid: mp 73-78°C; ^{1}H NMR ($CDCl_3$): δ 4.08 (3H, s), 7.48 – 7.52 (2H, m), 8.24 – 8.30 (2H, m); MS (EI) *m/z* 374/376/378 $(M^{\cdot})^+$.

Anal. for $C_{12}H_7Cl_2F_3O_4S$:

Calc'd: C: 38.42 H: 1.88

Found: C: 38.65 H: 1.90

INTERMEDIATE 82

1-Chloro-6-methoxy-2-(4-methoxyphenyl)naphthalene

The title compound was prepared by reacting 1-chloro-6-methoxy-2-naphthyl trifluoromethanesulfonate (0.95 g, 2.79 mmol) with 4-methoxyphenyl boronic acid (0.59 g, 3.9 mmol) according to method A to yield 0.71 g (85 %) of a white solid: mp 126-128 °C; ^{1}H NMR ($CDCl_3$): δ 3.88 (3H, s), 3.95 (3H, s), 7.01 (2H, d, *J* = 8.60 Hz), 7.16 (1H, d, *J* = 2.49 Hz), 7.27 (1H, dd, *J* = 1.97 Hz, *J* = 8.99 Hz), 7.41 (1H, d, *J* = 8.45 Hz), 7.46 (2H, d, *J* = 8.61 Hz), 7.68 (1H, d, *J* = 8.48 Hz), 8.28 (1H, d, *J* = 9.27 Hz); MS (ESI) *m/z* 299/301 $(M+H)^+$.

Anal. for $C_{18}H_{15}ClO_2 \cdot 0.25\ H_2O$

Calc'd: C: 71.29 H: 5.15

Found: C: 70.84 H: 4.80

INTERMEDIATE 83

1,5-Dichloro-2-methoxy-6-(4-methoxyphenyl)naphthalene

The title compound was prepared by 1,5-dichloro-6-methoxy-2-naphthyl trifluoromethanesulfonate (0.32 g, 0.85 mmol) with 4-methoxyphenyl boronic acid (0.18 g, 1.2 mmol) according to method A to yield 0.27 g (95 %) of a white solid mp 146-149 °C; ^{1}H NMR ($CDCl_3$): δ 3.88 (3H, s), 4.07 (3H, s), 7.02 (2H, d, *J* = 8.73 Hz), 7.41 (1H, d, *J* = 9.52 Hz), 7.46 (2H, d, *J* = 8.83 Hz), 7.53 (1H, d, *J* = 8.73 Hz), 8.19 (1H, d, *J* = 8.73 Hz), 8.36 (1H, d, *J* = 9.12 Hz);

Anal. for $C_{18}H_{14}Cl_2O_2$:

Cald'd: C: 64.88 H: 4.23

Found: C: 64.63 H: 4.28

EXAMPLE 1ao

5-Chloro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 1-chloro-6-methoxy-2-(4-methoxyphenyl)naphthalene (0.65 g, 2.18 mmol) with boron tribromide (6.5 mL of 1N solution) according to method D to yield 0.44 g (75 %) of a white solid: mp > 220°C; ^{1}H NMR (DMSO-d_6): δ 6.86 (2H, d, *J* = 8.33 Hz), 7.23 – 7.28 (2H, m), 7.30 (2H, d, *J* = 8.32 Hz), 7.37 (1H, d, *J* = 8.51 Hz), 7.72 (1H, d, *J* = 8.55 Hz), 8.13 (1H, d, *J* = 9.07 Hz); MS (ESI) *m/z* 269/271$(M-H)^-$.

Anal. for $C_{16}H_{11}ClO_2 \cdot 0.1\ H_2O$

Calc'd: C: 70.52 H: 4.14

Found: C: 70.52 H: 4.05

EXAMPLE 1ap

1,5-Dichloro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 1,5-dichloro-2-methoxy-6-(4-methoxyphenyl)naphthalene (0.15 g, 0.45 mmol) with boron tribromide (1.4 mL of 1N solution) according to method D to yield 0.10 g (73 %) of a white solid: mp 204-206°C;

^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, *J* = 8.47 Hz), 7.33 (2H, d, *J* = 8.45 Hz), 7.46 (1H, d, *J* = 9.26 Hz), 7.56 (1H, d, *J* = 8.80 Hz), 8.06 (1H, d, *J* = 8.81 Hz), 8.17 (1H, d, *J* = 9.28 Hz), 9.68 (1H, bs), 10.84 (1H, bs); MS (ESI) *m/z* 303/305/307(M-H)$^-$.

Anal. for $C_{16}H_{10}Cl_2O_2$

Calc'd: C: 62.98 H: 3.30

Found: C: 62.78 H: 3.28

Synthesis of Compounds in Scheme 14

INTERMEDIATE 84

8-Chloro-6-(4-methoxyphenyl)-2-naphthol

To a solution of 3-bromo-8-chloro-6-(4-methoxyphenyl)-2-naphthol (0.254 g, 0.698 mmol) in THF (25 mL) at –78°C was slowly added t-butyl lithium (1.65 mL of 1.7N solution, 2.8 mmol). The resulting solution was stirred for twenty minutes at -78°C and 2.5 mL of water was added and the mixture was warmed to room temperature slowly with stirring. The reaction was poured into 50 mL of water and extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with water, dried with sodium sulfate, filtered, evaporated off the of solvent, and purified on a silica column (10% ethyl acetate – hexanes) to yield 0.15 g (88%) of a yellow solid. An analytical sample was further prepared by reverse phase preparative HPLC to yield the title compound as a light yellow solid: mp 116-118°C; ^{1}H NMR (DMSO-d_6): δ 3.81 (3H, s), 7.05 (2H, d, *J* = 8.75 Hz), 7.19 (1H, dd, *J* = 2.34 Hz, *J* = 8.84 Hz), 7.40 (1H, d, *J* = 2.25 Hz), 7.74 (2H, d, *J* = 8.73 Hz), 7.89 (1H, d, *J* = 1.65 Hz), 7.92 (1H, d, *J* = 8.93 Hz), 8.07 (1H, s), 10.19 (1H, s);

MS (ESI) *m/z* 283/285 (M-H)$^-$.

Anal. for $C_{17}H_{13}ClO_2 \cdot 0.1\ H_2O$:

Calc'd: C: 71.26 H 4.64

Found: C: 71.18 H: 4.43 N

INTERMEDIATE 85

1-Chloro-8-fluoro-6-(3-fluoro-4-methoxyphenyl)-2-naphthol

The title compound was prepared by reacting 8-fluoro-6-(3-fluoro-4-methoxy-phenyl)-2-naphthol (0.30 g, 1.05 mmol) and NCS (0.17 g, 1.26 mmol) according to method C to yield 0.21 g (62%) of a light orange solid: mp 126-128°C; ^{1}H NMR

(DMSO-d_6): δ 3.90 (3H, s), 7.25 – 7.31 (1H, m), 7.35 (1H, d, , *J* = 8.91 Hz), 7.64 – 7.67 (1H, m), 7.70 – 7.78 (2H, m), 7.87 (1H, dd, , *J* = 1.58 Hz, , *J* = 9.04 Hz), 10.68 (1H, s); MS (ESI) *m/z* 319/321 $(M-H)^-$.

Anal. for $C_{17}H_{11}ClF_2O_2$:

Calc'd: C: 63.66 H: 3.46

Found: C: 63.23 H: 3.39

INTERMEDIATE 86

1-Chloro-8-fluoro-6-(4-methoxyphenyl)-2-naphthol

A solution of 8-fluoro-6-(4-methoxyphenyl)-2-naphthol (0.17 g, 0.63 mmol) and NCS (0.10 g, 0.76 mmol) in THF (20 mL) were stirred under nitrogen at room temperature overnight according to Method C. The solution was concentrated onto Florosil and purified on a silica column (20% ethyl acetate – hexanes) to yield 0.16 g (84%) of the title compound as a yellow solid. An analytical sample was further prepared by preparative reverse phase HPLC to yield a light yellow solid: mp 120-124°C; ^{1}H NMR (DMSO-d_6): δ 3.82 (3H, s), 7.06 (2H, d, , *J* = 8.80 Hz), 7.34 (1H, d, *J* = 8.91 Hz), 7.67 (1H, dd, *J* = 1.69 Hz, , *J* = 15.48 Hz), 7.78 (2H, d, *J* = 8.78 Hz), 8.01 (1H, d, *J* = 1.54 Hz), 10.62 (1H, s); MS (ESI) *m/z* 301/303 $(M-H)^-$.

Anal. for $C_{17}H_{12}ClFO_2$

Calc'd: C: 67.45 H: 4.00

Found: C: 67.23 H: 3.65

INTERMEDIATE 87

1,5-Dichloro-8-fluoro-6-(4-methoxyphenyl)-2-naphthol

The title compound was prepared by reacting 8-fluoro-6-(4-methoxyphenyl)-2-naphthol (0.24 g, 0.90 mmol) and NCS (0.22 g, 1.6 mmol) in acetonitrile (20 mL) according to method C to yield 0.22 g (73%) of a yellow solid: ^{1}H NMR (DMSO-d_6): δ 3.82 (3H, s), 7.06 (2H, d, *J* = 8.69 Hz), 7.39 (1H, d, *J* = 14.34 Hz), 7.47 (2H, d, *J* = 8.68 Hz), 7.53 (1H, d, *J* = 9.36 Hz), 8.22 (1H, dd, *J* = 1.65 Hz, *J* = 9.32 Hz), 11.01 (1H, s); MS (ESI) *m/z* 335/337 $(M-H)^-$.

INTERMEDIATE 88

3-Bromo-1,8-dichloro-6-(4-methoxyphenyl)-2-naphthol

The title compound was prepared by reacting 3-bromo-8-chloro-6-(4-methoxyphenyl)-2-naphthol (0.69 g, 1.90 mmol) and NCS (0.31 g, 2.3 mmol) in THF (25 mL) according to method C to yield 0.61 g (81%) of a yellow solid. An analytical sample was further prepared by reverse phase preparative HPLC to yield the title compound as a white solid: mp 176-178°C (dec.); ^{1}H NMR (DMSO-d_6): δ 3.82 (3H, s), 7.08 (2H, d, *J* = 8.77 Hz), 7.77 (2H, d, *J* = 8.75 Hz), 8.00 (1H, d, *J* = 1.84 Hz), 8.19 (1H, d, *J* = 1.84 Hz), 8.39 (1H, s), 10.53 (1H, bs); MS (ESI) *m/z* 395/397/399 $(M-H)^-$.

Anal. for $C_{17}H_{11}BrCl_2O_2$

Calc'd:C: 51.29 H: 2.79

Found: C: 51.37 H: 2.62

INTERMEDIATE 89

8-Bromo-7-hydroxy-3-(4-methoxyphenyl)-1-naphthonitrile

The title compound was prepared by reacting 7-hydroxy-3-(4-methoxyphenyl)-1-naphthonitrile (0.160 g, 0.58 mmol) with NBS (0.12 g, 0.70 mmol) in THF (10 mL) according to method C to yield 0.080 g (39%) of a yellow solid: mp 145-146 °C; ^{1}H NMR (DMSO-d_6): δ 3.83 (3H, s), 7.08 (2H, d, *J* = 8.79 Hz), 7.42 (1H, d, *J* = 8.79 Hz), 7.84 (2H, d, *J* = 8.79 Hz), 8.04 (1H, d, *J* = 8.79 Hz), 8.42 (1H, d, *J* = 1.95 Hz), 8.53 (1H, d, *J* = 1.95 Hz), 11.21 (1H, s); MS (ESI) *m/z* 354/356 $(M+H^+$; MS (ESI) *m/z* 352/354 $(M-H)^-$.

Anal. for $C_{18}H_{12}BrNO_2 \cdot 0.25\ H_2O$

Calc'd: C: 60.27 H: 3.51 N: 3.90

Found: C: 60.27 H: 3.51 N: 3.46.

INTERMEDIATE 90

1,8-Dichloro-6-(4-methoxyphenyl)-2-naphthol

The title compound was prepared by reacting 3-bromo-1,8-dichloro-6-(4-methoxyphenyl)-2-naphthol (0.30 g, 0.754 mmol) with t-butyl lithium (1.75 mL of 1.7N solution, 3.0 mmol) and quenching with water according to the method use to prepare intermediate 84 to yield 0.19 g (79%) of a yellow solid. An analytical sample was further prepared by reverse phase preparative HPLC to yield the title compound as a

light yellow solid: mp 132-134 °C; ^{1}H NMR (DMSO-d_6): δ 3.82 (3H, s), 7.06 (2H, d, *J* = 8.77 Hz), 7.37 (1H, d, *J* = 8.90 Hz), 7.77 (2H, d, *J* = 8.75 Hz), 7.89 – 7.93 (2H, m), 8.15 (1H, d, *J* = 1.85 Hz), 10.68 (1H, s); MS (ESI) *m/z* 317/319/321 $(M-H)^-$.
Anal. for $C_{17}H_{12}Cl_2O_2$

Calc'd: C: 63.97 H: 3.79

Found: C: 63.57 H: 3.65

EXAMPLE 1al

1-Chloro-8-fluoro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 1-chloro-8-fluoro-6-(4-methoxy-phenyl)-2-naphthol (0.14 g, 0.46 mmol) with boron tribromide (0.69 mL of 1N solution, 0.69 mmol) according to method D to yield 0.050 g (38%) of a white solid mp 174-176°C; ^{1}H NMR (DMSO-d_6): δ 6.88 (2H, d, *J* = 8.62 Hz), 7.33 (1H, d, *J* = 8.92 Hz), 7.60 – 7.67 (3H, m), 7.86 (1H, dd, , *J* = 1.43 Hz, *J* = 9.02 Hz), 7.95 (1H, d, *J* = 1.37 Hz), 9.68 (1H, s), 10.59 (1H, s); MS (ESI) *m/z* 287/289 $(M-H)^-$.
Anal.for $C_{16}H_{10}ClFO_2 \cdot 0.25\ H_2O$

Calc'd:C: 65.54 H: 3.61

Found: C: 65.52 H: 3.19

EXAMPLE 1am

1-Chloro-8-fluoro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 1-chloro-8-fluoro-6-(3-fluoro-4-methoxyphenyl)-2-naphthol (0.13 g, 0.41 mmol) with boron tribromide (0.8 mL of 1N solution, 0.8 mmol) according to method D to yield 0.070 g (56%) of a white solid mp 198-200 °C; ^{1}H NMR (DMSO-d_6): δ 7.03 – 7.09 (1H, m) 7.34 (1H, d, *J* = 8.92 Hz), 7.49 – 7.52 (1H, m), 7.68 (2H, d, , *J* = 15.0 Hz), 7.85 – 7.88 (1H, m), 8.02 (1H, d, *J* = 0.70 Hz), 10.13 (1H, s), 10.66 (1H, s); MS (ESI) *m/z* 305/307 $(M-H)^-$.
Anal. for $C_{16}H_9ClF_2O_2$

Calc'd: C: 62.66 H: 2.96

Found: C: 62.27 H: 2.90

EXAMPLE 1an

8-Chloro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 8-chloro-6-(4-methoxyphenyl)-2-naphthol (0.10 g, 0.35 mmol) with boron tribromide (0.9 mL of 1N solution, 0.9 mmol) according to method D to yield 0.080 g (85%) of product which was further purified by reverse phase preparative HPLC to yield the title compound as a white solid: mp 204-206 °C; ^{1}H NMR (DMSO-d_6): δ 6.87 (2H, d, *J* = 8.61 Hz), 7.17 (1H, dd, *J* = 2.34 Hz, *J* = 8.83 Hz), 7.38 (1H, d, *J* = 2.26 Hz), 7.62 (2H, d, *J* = 8.59 Hz), 7.85 (1H, d, *J* = 1.64 Hz), 7.90 (1H, d, *J* = 8.92 Hz), 8.01 (1H, bs), 9.62 (1H, s), 10.14 (1H, s); MS (ESI) *m/z* 269/(M-H)$^-$.

Anal. for $C_{16}H_{11}ClO_2 \cdot 0.25\ H_2O$

Calc'd: C: 70.99 H: 4.10

Found: C: 69.95 H: 3.89

EXAMPLE 1aq

1,5-Dichloro-8-fluoro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 1,5-dichloro-8-fluoro-6-(4-methoxyphenyl)-2-naphthol (0.15 g, 0.445 mmol) with boron tribromide (0.67 mL of 1N solution, 0.67 mmol) according to method D to yield 0.12 g (83%) of a light yellow solid mp 206-216°C; ^{1}H NMR (DMSO-d_6): δ 6.88 (2H, d, *J* = 8.55 Hz), 7.34 – 7.39 (3H, m), 7.51 (1H, d, *J* = 9.34 Hz), 8.21 (1H, dd, *J* = 1.66 Hz, *J* = 9.34 Hz), 9.74 (1H, bs), 10.99 (1H, bs); MS (ESI) *m/z* 321/323/326 (M-H)$^-$.

Anal. for $C_{16}H_9Cl_2FO_2 \cdot 0.1\ H_2O$

Calc'd: C: 59.13 H: 2.85

Found: C: 58.88 H: 2.85

EXAMPLE 1ar

3-Bromo-8-chloro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 3-bromo-8-chloro-6-(4-methoxyphenyl)-2-naphthol (0.24 g, 0.66 mmol) with boron tribromide (1.6 mL of 1N solution, 1.6 mmol) according to method D to yield 0.14 g (61%) of a yellow oil. The product was further purified by reverse phase preparative HPLC to yield the title

compound as a white solid: mp 188-190°C; ^{1}H NMR (DMSO-d_6): δ 6.88 (1H, d, *J* = 8.60 Hz), 7.57 (1H, s), 7.71 (2H, d, *J* = 8.61 Hz), 7.89 (1H, d, *J* = 1.60 Hz), 8.02 (1H, s), 8.31 (1H, s), 9.67 (1H, s), 11.01 (1H, s); MS (ESI) *m/z* 347/349/351 $(M-H)^-$.
Anal. for $C_{16}H_{10}BrClO_2$:
Calc'd: C: 54.97 H: 2.88
Found: C: 54.68 H: 2.82

EXAMPLE 1as

1,8-Dichloro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 1,8-dichloro-6-(4-methoxyphenyl)-2-naphthol (0.12 g, 0.38 mmol) with boron tribromide (0.75 mL of 1N solution, 0.75 mmol) according to method D to yield 0.10 (86%) of which was further purified by reverse phase preparative HPLC to yield the title compound as a white solid: mp 172-174°C (dec.); ^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, *J* = 8.54 Hz), 7.36 (1H, d, *J* = 8.90 Hz), 7.65 (2H, d, *J* = 8.56 Hz), 7.88 – 7.91 (2H, m), 8.10 (1H, d, *J* = 1.63 Hz), 9.69 (1H, s), 10.64 (1H, s); MS (ESI) *m/z* 303/305/307 $(M-H)^-$.
Anal. for $C_{16}H_{10}Cl_2O_2 \cdot 0.25\ H_2O$
Calc'd: C: 62.98 H: 3.30
Found: C: 61.80 H: 3.08

EXAMPLE 1at

3-Bromo-1,8-dichloro-6-(4-hydroxyphenyl)-2-naphthol

The title compound was prepared by reacting 3-bromo-1,8-dichloro-6-(4-methoxyphenyl)-2-naphthol (0.18 g, 0.45 mmol) with boron tribromide (0.9 mL of 1N solution, 0.9 mmol) according to method D to yield 0.12 g (69%) of a light brown solid. The product was further purified by reverse phase preparative HPLC to yield the title compound as a white solid: mp 184-188°C; ^{1}H NMR (DMSO-d_6): δ 6.89 (2H, d, *J* = 8.59 Hz), 7.65 (2H, d, *J* = 8.61 Hz), 7.95 (1H, d, *J* = 1.78 Hz), 8.13 (1H, d, *J* = 1.75 Hz), 8.37 (1H, s), 9.74 (1H, s), 10.50 (1H, s); MS (ESI) *m/z* 381/383/385 $(M-H)^-$.
Anal. for $C_{16}H_9BrCl_2O_2 \cdot 0.25\ H_2O$
Calc'd: C: 50.04 H: 2.36
Found: C: 49.10 H: 2.14

EXAMPLE 1bb

8-Bromo-7-hydroxy-3-(4-hydroxyphenyl)-1-naphthonitrile

The title compound was prepared by reacting 8-bromo-7-hydroxy-3-(4-methoxyphenyl)-1-naphthonitrile (0.13 g, 0.37 mmol) with boron tribromide (1.1 mL of 1N solution, 1.1 mmol) according to method D to yield 0.050 g (40%) of an off white solid: mp 204-208 °C(d);^{1}H NMR (DMSO-d_6): δ 6.90 (2H, d, *J* = 8.30 Hz), 7.41 (1H, d, *J* = 8.79 Hz), 7.72 (2H, d, *J* = 8.79 Hz), 8.02 (1H, d, *J* = 9.23 Hz), 8.37 (1H, d, *J* = 1.95 Hz), 8.47 (1H, d, *J* = 2.44 Hz), 9.72 (1H, s), 11.16 (1H, s);
MS (ESI) *m/z* 338/340 (M-H).
Anal. for $C_{17}H_{10}BrNO_2$

Calc'd: C: 60.02 H: 2.96 N: 4.12

Found: C: 59.84 H: 3.18 N: 3.83.

Synthesis of Compounds in Scheme 15

INTERMEDIATE 91

3-Bromo-8-chloro-7-hydroxy-1-naphthonitrile

To a mixture of 8-chloro-7-hydroxy-1-naphthonitrile (0.127 g, 0.63 mmol) and glacial acetic acid (1 mL) in a pressure tube was added a solution of bromine (0.24 g, 1.5 mmol) in glacial acetic acid (2 mL). The tube was sealed and the mixture was stirred at 100 °C overnight. The reaction was cooled, poured into water (50 mL), and extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with sodium bicarbonate solution, dried over sodium sulfate, filtered, stripped of solvent, and purified on a silica column (20% ethyl acetate – hexanes) to yield 0.10 g (56%) of the title compound as a yellow solid. An analytical sample was prepared by preparative reverse phase HPLC to yield the title compound as a white solid: mp 148-150 °C; ^{1}H NMR (DMSO-d_6): δ 7.47 (1H, d, *J* = 8.98 Hz), 7.95 (1H, d, *J* = 9.02 Hz), 8.32 (1H, d, *J* = 2.08 Hz), 8.55 (1H, d, *J* = 2.08 Hz), 11.33 (1H, s); MS (ESI) *m/z* 280/282/284 $(M-H)^-$.
Anal. for $C_{11}H_5BrClNO \cdot 0.25\ H_2O$:

Calc'd: C: 46.03 H: 1.93 N: 4.88

Found: C: 45.92 H: 1.75 N: 4.78.

IINTERMEDIATE 91

3-Bromo-8-chloro-7-hydroxy-1-naphthonitrile

The title compound was prepared by reacting 3-bromo-7-hydroxy-1-naphthonitrile (0.32 g, 1.28 mmol) with NCS (0.24 g, 1.8 mmol) in THF (25 mL) at 45°C for 3 hr according to method C to yield 0.30 g (83%) of a yellow solid. An analytical sample was prepared by preparative reverse phase HPLC to yield the title compound as a white solid: mp 148-150°C; ^{1}H NMR (DMSO-d_6): δ 7.47 (1H, d, *J* = 8.98 Hz), 7.95 (1H, d, *J* = 9.02 Hz), 8.32 (1H, d, *J* = 2.08 Hz), 8.55 (1H, d, *J* = 2.08 Hz), 11.33 (1H, s); MS (ESI) *m/z* 280/282/284 $(M-H)^-$

Anal. for $C_{11}H_5BrClNO \cdot 0.25\ H_2O$:

Calc'd: C: 46.03 H: 1.93 N: 4.88

Found: C: 45.92 H: 1.75 N: 4.78.

INTERMEDIATE 92

8-Chloro-3-(3-fluoro-4-methoxyphenyl)-7-hydroxy-1-naphthonitrile

The title compound was prepared by reacting 3-bromo-8-chloro-7-hydroxy-1-naphthonitrile (0.20 g, 0.71 mmol) with 3-fluoro-4-methoxyphenylboronic acid (0.17 g, 1.0 mmol) according to Method A to yield 0.14 (60%) of a yellow solid: mp 198-200°C;^{1}H NMR (DMSO-d_6): δ 3.91 (3H, s), 7.27 – 7.33 (1H, m), 7.45 (1H, d, *J* = 8.93 Hz), 7.71 – 7.74 (1H, m), 7.85 (1H, dd, *J* = 2.23 Hz, *J* = 13.09 Hz), 8.00 (1H, d, *J* = 9.08 Hz), 8.48 (1H, d, *J* = 1.97 Hz), 8.57 (1H, d, *J* = 1.95 Hz), 11.18 (1H, s); MS (ESI) *m/z* 326/328 $(M-H)^-$.

Anal. for $C_{18}H_{11}ClFNO_2$

Calc'd: C: 65.97 H: 3.38 N: 4.27

Found: C: 65.76 H: 3.36 N: 4.11.

EXAMPLE 1aw

8-Chloro-3-(4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile

The title compound was prepared by reacting 3-bromo-8-chloro-7-hydroxy-1-naphthonitrile (0.10 g, 0.37 mmol) with 4-*tert*-butyldimethylsilyloxyphenylboronic acid (0.13 g, 0.52 mmol) according to Method A to yield 0.036 g (33%) of a white solid: mp 254-256 °C; ^{1}H NMR (DMSO-d_6): δ 6.90 (2H, d, *J* = 8.64 Hz), 7.43 (1H, d, *J* = 8.95

Hz), 7.72 (2H, d, J = 8.64 Hz), 7.99 (1H, d, J = 8.97 Hz), 8.38 (1H, d, J = 1.95 Hz), 8.47 (1H, d, J = 1.92 Hz), 9.73 (1H, s), 11.08 (1H, s); MS (ESI) *m/z* 294/296 $(M-H)^-$.

Anal. for $C_{17}H_{10}ClNO_2$

Calc'd: C: 69.05 H: 3.41 N: 4.74

Found: C: 69.01 H: 3.63 N: 4.31.

EXAMPLE 1ax

8-Chloro-3-(3-fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile

The title compound was prepared by reacting 8-chloro-3-(3-fluoro-4-methoxyphenyl)-7-hydroxy-1-naphthonitrile (0.042 g, 0.13 mmol) with pyridinium HCl (1.8 g) according to method D to yield 0.033 g (78%) of a tan solid. This material was further purified by preparative reverse phase HPLC to yield the title compound as a white solid: mp 246-252 °C; ^{1}H NMR (DMSO-d_6): δ 7.04 – 7.10 (1H, m), 7.44 91H, d, J = 8.94 Hz), 7.56 (1H, dd, J = 1.66 Hz, J = 8.37 Hz), 7.76 (1H, dd, J = 2.20 Hz, J = 12.88 Hz), 7.99 (1H, d, J = 9.09 Hz), 8.43 (1H, d, J = 1.98 Hz), 8.52 (1H, d, J = 1.94 Hz), 10.19 (1H, bs), 11.05 (1H, bs); MS (ESI) *m/z* 312/314 $(M-H)^-$.

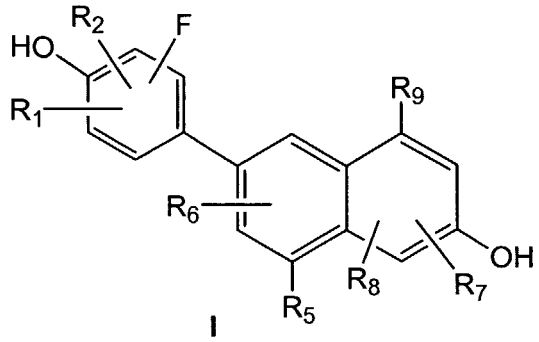
Anal. for $C_{17}H_9ClFNO_2 \cdot 0.25\ H_2O$:

Calc'd: C: 64.16 H: 3.01 N: 4.40

Found: C: 63.75 H: 2.84 N: 4.20.

CLAIMS

1. A compound of formula I having the structure



I

wherein

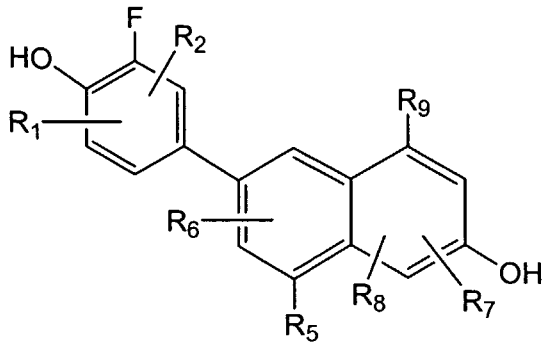
R_1 and R_2 are each, independently, selected from hydrogen, hydroxyl, alkyl of 1-6 carbon atoms, alkenyl, of 2-7 carbon atoms, and alkynyl of 2-7 carbon atoms, alkoxy of 1-6 carbon atoms, or halogen;

R_5, R_6, R_7, R_8, and R_9 are each, independently, hydrogen, alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, alkynyl of 2-7 carbon atoms, halogen, alkoxy of 1-6 carbon atoms, -CN, -CHO, trifluoromethyl, phenylalkyl of 7-12 carbon atoms, phenyl, or a 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S; wherein the alkyl or alkenyl moieties of R_5, R_6, R_7, R_8, or R_9 may be optionally substituted with hydroxyl, -CN, halogen, trifluoroalkyl, trifluoroalkoxy, $-NO_2$, or phenyl; wherein the phenyl moiety of R_5, R_6, R_7, R_8, R_9, or R_{10} may be optionally mono-, di-, or tri-subsitituted with alkyl of 1-6 carbon atoms, alkenyl of 2-7 carbon atoms, halogen, hydroxyl, alkoxy of 1-6 carbon atoms, halogen, -CN, $-NO_2$, amino, alkylamino of 1-6 carbon atoms, dialkylamino of 1-6 carbon atoms per alkyl group, thio, alkylthio of 1-6 carbon atoms, alkylsulfinyl of 1-6 carbon atoms, alkylsulfonyl of 1-6 carbon atoms, alkoxycarbonyl of 2-7 carbon atoms, alkylcarbonyl of 2-7 carbon atoms, or benzoyl;

with the proviso that at least one of R_5 or R_9 is not hydrogen,

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1 having the structure



or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or claim 2 wherein R_1 and R_2 are each independently selected from hydrogen and fluorine.

4. A compound of according to any one of claims 1 to 3 wherein R_5, R_6, R_7, R_8, and R_9 are each, independently, hydrogen, halogen, -CN, or alkynyl of 2-7 carbon atoms.

5. A compound according to any one of claims 1 to 4 wherein R_5 is selected from hydrogen, fluorine or cyano.

6. A compound according to any one of claims 1 to 5 wherein R_9 is selected from hydrogen, fluorine or cyano.

7. A compound according to any one of claims 1 to 6 wherein R_6, R_7, and R_8 are hydrogen.

8. A compound according to any one of claims 1 to 7 wherein the 5 or 6-membered heterocyclic ring having 1 to 4 heteroatoms selected from O, N or S is furan, thiophene, or pyridine.

9. A compound according to claim 1 which is 8-fluoro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 1 which is 1-chloro-8-fluoro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol or a pharmaceutically acceptable salt thereof.

11. A compound according to claim 1 which is 3-(3-fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile or a pharmaceutically acceptable salt thereof.

12. A compound according to claim 1 which is 3-(3,5-difluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile or a pharmaceutically acceptable salt thereof.

13. A naphthol compound which is one of the following:
6-(3-fluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(3-fluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(2-fluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(2,5-difluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(2,6-difluoro-4-hydroxyphenyl)-2-naphthol;
6-(2,5-difluoro-4-hydroxyphenyl)-2-naphthol;
6-(3,5-difluoro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(3,5-difluoro-4-hydroxyphenyl)-2-naphthol;
6-(2,6-difluoro-4-hydroxyphenyl)-2-naphthol; or
8-chloro-3-(3-fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile;
or a pharmaceutically acceptable salt thereof.

14. A compound which is one of the following:
7-(4-hydroxyphenyl)-2-naphthol;
7-(3-hydroxyphenyl)-2-naphthol;
6-(4-hydroxyphenyl)-1-naphthol;
6-phenyl-2-naphthol;
6-(3-hydroxyphenyl)-2-naphthol;
6-(3-chlorophenyl)-2-naphthol;
2-fluoro-4-(2-naphthyl)phenol ;
6-(3-chloro-4-hydroxyphenol)-2-naphthol;
1-chloro-6-phenyl-2-naphthol;
1-bromo-6-(4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(4-hydroxyphenyl)-2-naphthol;

1-fluoro-6-(4-hydroxyphenyl)-2-naphthol;
2-hydroxy-6-(4-hydroxyphenyl)-1-naphthonitrile;
6-(4-hydroxyphenyl)-1-phenyl-2-naphthol;
6-(4-hydroxyphenyl)-1-methyl-2-naphthol;
1-chloro-6-(3-chloro-4-hydroxyphenyl)-2-naphthol;
6-(4-hydroxyphenyl)-1-nitro-2-naphthol;
1-chloro-6-(4-hydroxy-2-methylphenyl)-2-naphthol;
6-(4-hydroxy-2-methylphenyl)-2-naphthol;
6-(4-hydroxy-2-methoxyphenyl)-2-naphthol;
6-(2-chloro-4-hydroxyphenyl)-2-naphthol;
1-chloro-6-(2-chloro-4-hydroxyphenyl)-2-naphthol;
6-(2-fluoro-4-hydroxyphenyl)-2-naphthol;
8-fluoro-6-(4-hydroxyphenyl)-2-naphthol;
1-chloro-8-fluoro-6-(4-hydroxyphenyl)-2-naphthol;
8-chloro-6-(4-hydroxyphenyl)-2-naphthol;
1,5-dichloro-8-fluoro-6-(4-hydroxyphenyl)-2-naphthol;
2-chloro-4-(2-naphthyl)phenol;
3-bromo-8-chloro-6-(4-hydroxyphenyl)-2-naphthol;
1,8-dichloro-6-(4-hydroxyphenyl)-2-naphthol;
3-bromo-1,8-dichloro-6-(4-hydroxyphenyl)-2-naphthol;
7-hydroxy-3-(4-hydroxyphenyl)-1-naphthonitrile;
8-chloro-3-(4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile;
8-bromo-7-hydroxy-3-(4-hydroxyphenyl)-1-naphthonitrile

or a pharmaceutically acceptable salt thereof.

15. A method of treating or inhibiting prostatitis or interstitial cystitis in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

16. A method of treating or inhibiting inflammatory bowel disease, Crohn's disease, ulcerative proctitis, or colitis in a mammal in need thereof which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

17. A method of treating or inhibiting prostatic hypertrophy, uterine leiomyomas, breast cancer, endometrial cancer, polycystic ovary syndrome, endometrial polyps, benign breast disease, adenomyosis, ovarian cancer, melanoma, prostrate cancer, colon cancer, glioma or astioblastomia in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

18. A method of lowering cholesterol, triglycerides, Lp(a), or LDL levels; inhibiting or treating hypercholesteremia; hyperlipidemia; cardiovascular disease; atherosclerosis; hypertension; peripheral vascular disease; restenosis, or vasospasm; or inhibiting vascular wall damage from cellular events leading toward immune mediated vascular damage in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

19. A method of providing cognition enhancement or neuroprotection; or treating or inhibiting senile dementias, Alzheimer's disease, cognitive decline, stroke, anxiety, or neurodegenerative disorders in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

20. A method of treating or inhibiting free radical induced disease states in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

21. A method of treating or inhibiting vaginal or vulvar atrophy; atrophic vaginitis; vaginal dryness; pruritus; dyspareunia; dysuria; frequent urination; urinary incontinence; urinary tract infections in a mammal in need thereof which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

22. A method of treating or inhibiting vasomotor symptoms in a mammal in need thereof which comprises providing to said mammal an effective amount of a

compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

23. A method of inhibiting conception in a mammal in need thereof which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

24. A method of treating or inhibiting arthritis in a mammal in need thereof which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

25. The method according to claim 24 wherein the arthritis is rheumatoid arthritis, osteoarthritis, or spondyloarthropathies.

26. A method of treating or inhibiting joint swelling or erosion; or treating or inhibiting joint damage secondary to arthroscopic or surgical procedures in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

27. A method of treating or inhibiting psoriasis or dermatitis in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

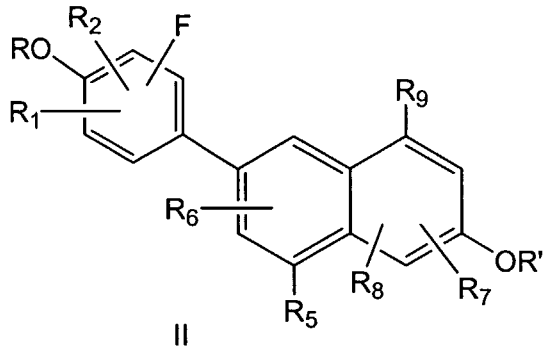
28. A method of treating or inhibiting ischemia, reperfusion injury, asthma, pleurisy, multiple sclerosis, systemic lupus erythematosis, uveitis, sepsis, hemmorhagic shock, macular degeneration or type II diabetes in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

29. A method of treating or inhibiting endometriosis in a mammal in need thereof, which comprises providing to said mammal an effective amount of a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof.

30. A pharmaceutical composition which comprises a compound as claimed in any one of claims 1 to 14 or a pharmaceutically acceptable salt thereof, and a pharmaceutical carrier.

31. A process for preparing a naphthyl compound according to any one of claims 1 to 14 which comprises one of the following:

a) de-alkylating or de-aralkylating an compound of formula

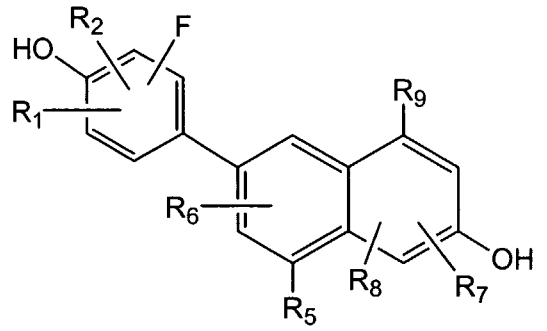


II

wherein R_1, R_2 and R_{5-9} are as defined above and R and R' are independently selected from hydrogen, alkyl or aralkyl providing at least one of R and R' is alkyl (eg of 1-6 carbons) or aralkyl (eg of 7-12 carbons) to give a corresponding compound of formula (I);

or

b) halogenating a compound of formula I



I }

wherein R_1, R_2 and R_{5-9} are as defined above and to give a corresponding 1-halonaphthol;

or

c) converting a basic compound as claimed in any one of claims 1 to 14 to a salt thereof or vice versa.