# INDOLINE DERIVATIVES AS PROGESTERONE ANTAGONISTS

## Field of the Invention

This invention relates to compounds which are antagonists of the progesterone receptor, their preparation and utility.

## Background of the Invention

Intracellular receptors (IR) form a class of structurally related gene regulators known as "ligand dependent transcription factors" (R. M. Evans, *Science*, 240, 889, 1988). The steroid receptor family is a subset of the IR family, including progesterone receptor (PR), estrogen receptor (ER), androgen receptor (AR), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR).

The natural hormone, or ligand, for the PR is the steroid progesterone, but synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, have been made which also serve as ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex binds to specific gene promoters present in the cell's DNA. Once bound to the DNA the complex modulates the production of mRNA and protein encoded by that gene.

A compound that binds to an IR and mimics the action of the natural hormone is termed an agonist, whilst a compound which inhibits the effect of the hormone is an antagonist.

PR antagonists may used in contraception. In this context they may be administered alone (Ulmann, et al, *Ann. N.Y. Acad. Sci.*, 261, 248, 1995), in combination with a PR agonist (Kekkonen, et al, *Fertility and Sterility*, 60, 610, 1993) or in combination with a partial ER antagonist such as tamoxifen (WO 96/19997 A1 July 4, 1996).

PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz, et al, Horm. Cancer, 283, pub: Birkhaeuser, Boston, Mass.,

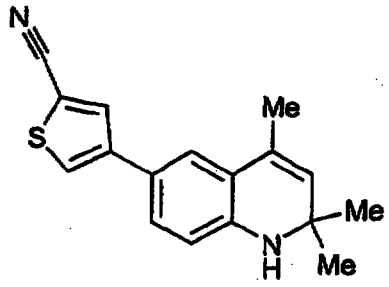
ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions such as fibroids (Murphy, et al, *J. Clin. Endo. Metab.*, 76, 513, 1993) and endometriosis (Kettel, et al, *Fertility and Sterility*, 56, 402, 1991).

PR antagonists may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (U.S. Patent No. 5,719,136).

PR antagonists, such as mifepristone and onapristone, have been shown to be effective in a model of hormone dependent prostate cancer, which may indicate their utility in the treatment of this condition in men (Michna, et al, *Ann. N.Y. Acad. Sci., 761, 224, 1995).*

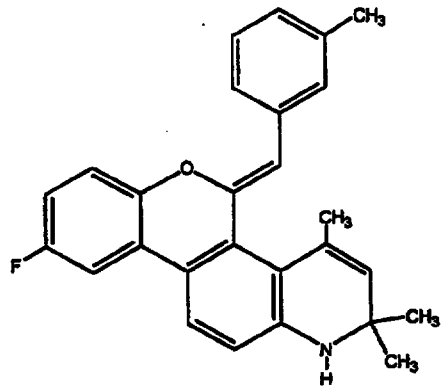
The compounds of this invention have been shown to act as competitive inhibitors of progesterone binding to the PR and act as antagonists in functional models, either/or *in-vitro* and *in-vivo*. These compounds may be used for contraception, in the treatment of fibroids, endometriosis, breast, uterine, ovarian and prostate cancer, and post menopausal hormone replacement therapy.

Described by Jones, *et al,* (U.S. Patent No. 5,688,810) is the PR antagonist dihydroquinoline A.



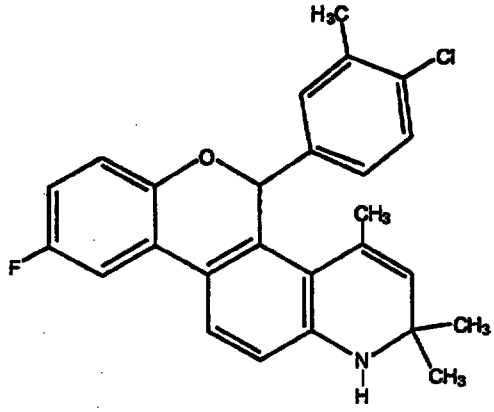

A

Jones, *et al*, described the enol ether B (U.S. Patent No. 5,693,646) as a PR ligand.



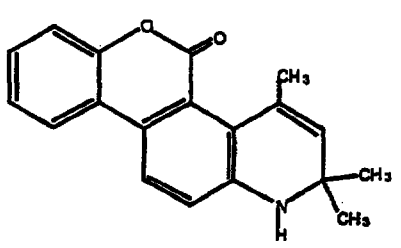

**B**

Jones, *et al*, described compound **C** (U.S. Patent No. 5,696,127) as a PR ligand.

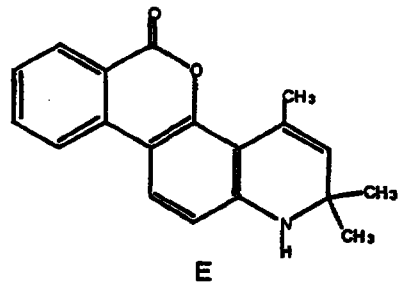



**C**

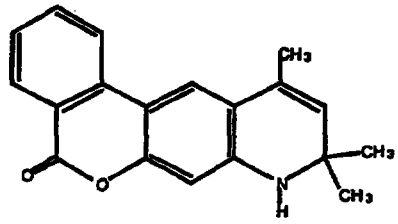
Zhi, *et al*, described lactones **D**, **E** and **F** as PR antagonists (J. Med. Chem., 41, 291, 1998).



D

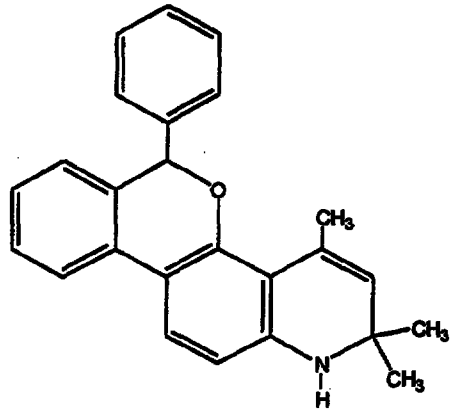


E



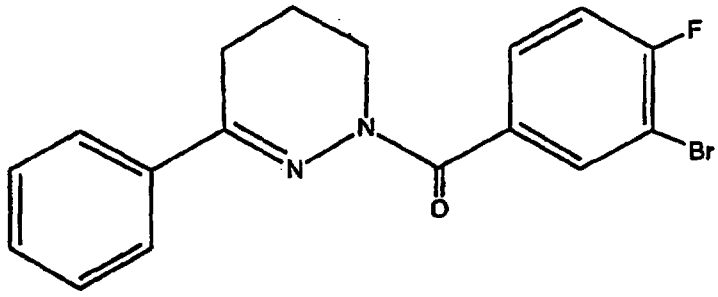
F

Zhi, *et al*, described the ether G as a PR antagonist (J. Med. Chem., 41, 291, 1998).



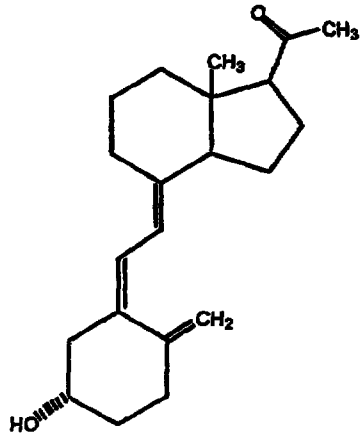
G

Combs, *et al.*, disclosed the amide H as a ligand for the PR (*J. Med. Chem.*, 38, 4880, 1995).



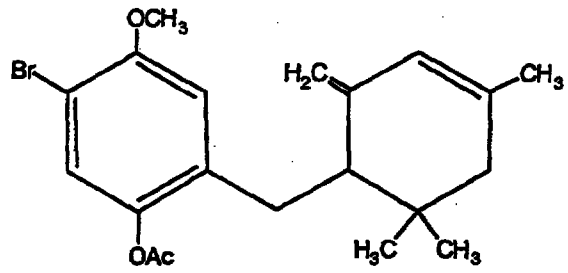

H

Perlman, *et. al.*, described the vitamin D analog I as a PR ligand (*Tet. Letters*, 35, 2295, 1994).



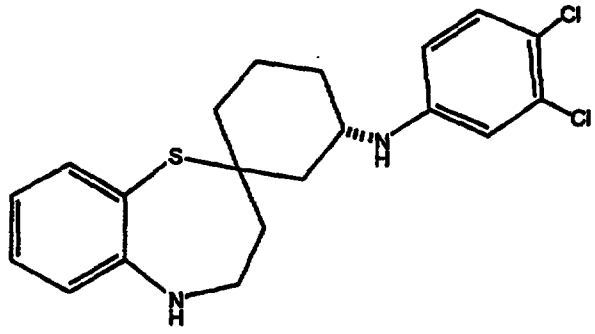

I

Hamann, *et al*, described the PR antagonist J (*Ann. N.Y. Acad. Sci.*, 761, 383, 1995).



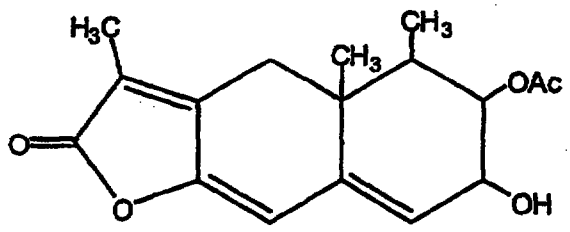

J

Chen, *et al*, described the PR antagonist K (Chen, et al, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997).



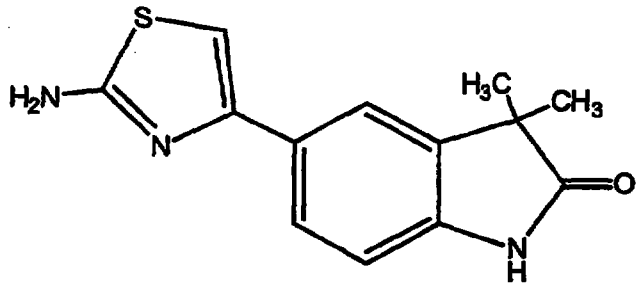

K

Kurihari, *et. al.*, described the PR ligand L (*J. Antibiotics*, 50, 360, 1997).



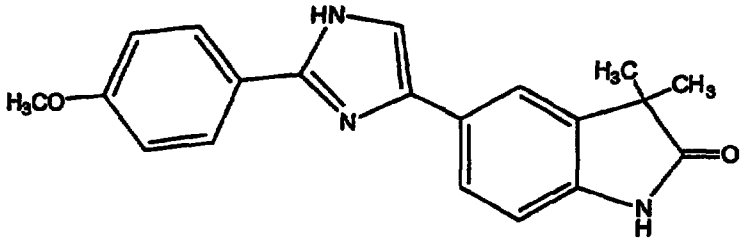

L

Kuhla, et al, disclosed the oxindole M as having cardiotonic activity (WO 86/03749).



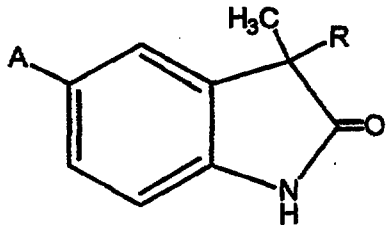
M

Weber, teaches the oxindole N for cardiovascular indications (WO 91/06545).



N

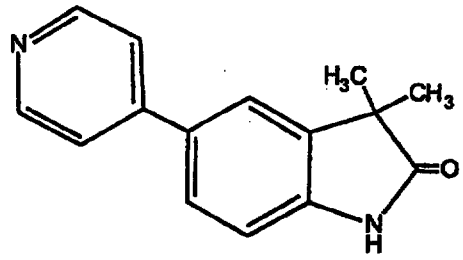
Fischer, et al, describe a preparation for making compounds which include the generic structure O (U.S. Patent No. 5,453,516).



O

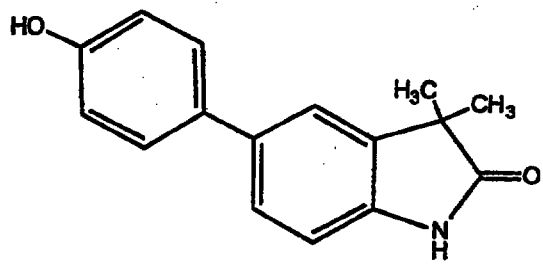
R = various

Singh, et al, described the PDE III inhibitor P (*J. Med. Chem.*, 37, 248, 1994).



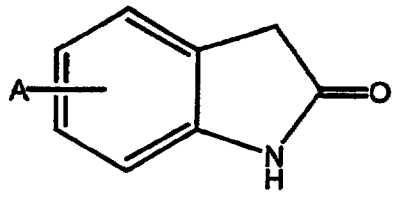
P

Andreani, et al, described the cytotoxic agent Q (*Acta. Pharn. Nord.*, 2, 407, 1990).



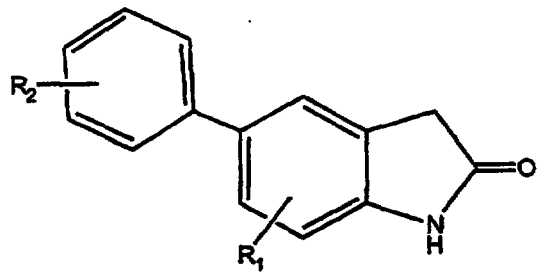
Q

Binder, et al, described structure R which is an intermediate for preparing COX II inhibitors (WO 97/13767).



R

Walsh described the oxindole S as an intermediate (U.S. Patent No. 4,440,785, U.S. Patent No. 4,670,566).

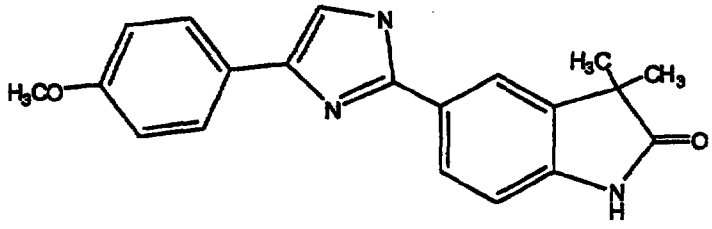


S

R1 = F, Cl, Br, alkyl, $NH_2$

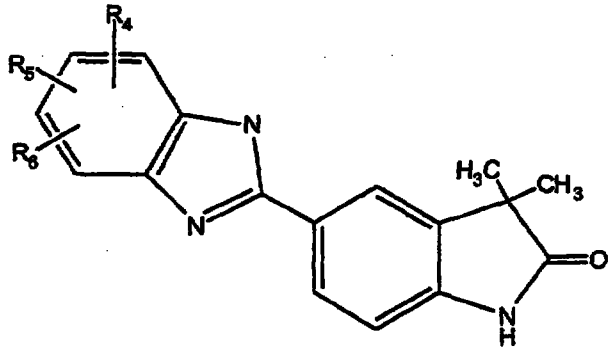
R2 = alkyl, alkoxy, F, Cl, NH2, $CF_3$

Bohm, et al, claim the oxindole T as cardiovascular agents (WO 91/06545).



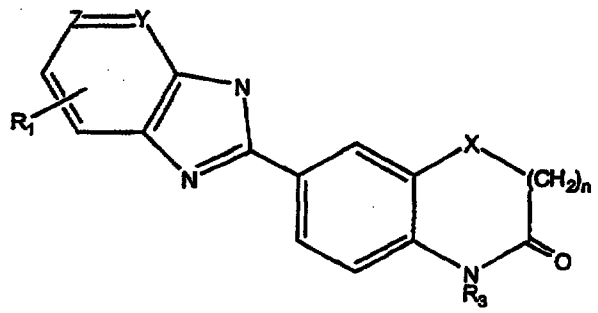
T

Bohm, et al, include the generic structure U (WO 91/04974).



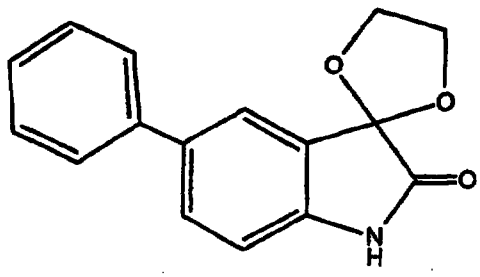
U

JP 63112584 A contains the generic structure V:



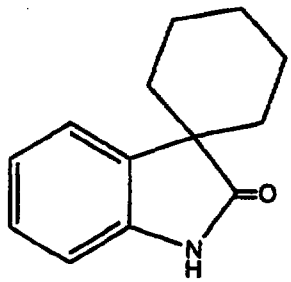
V

Boar, et al, described the dioxolane W as an intermediate for preparation of acetyl-cholinesterase inhibitors (WO 93/12085 A1).



W

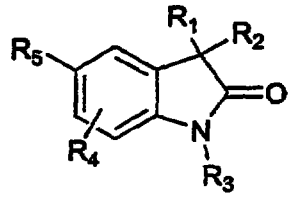
Kende, et al, described methodology for preparing 3,3-substituted oxindoles, e.g. X, that was utilized in the present invention (Synth. Commun., 12, 1, 1982).



X

**Description of the Invention.**

This invention comprises compounds of the Formula 1:



1

wherein:

$R_1$ and $R_2$ are chosen independently from H, alkyl, substituted alkyl; OH; O(alkyl); O(substituted alkyl); OAc; aryl; optionally substituted aryl; heteroaryl; optionally substituted heteroaryl; alkylaryl; alkylheteroaryl; 1-propynyl; or 3-propynyl;

or $R_1$ and $R_2$ are joined to form a ring comprising one of the following: $-CH_2(CH_2)_nCH_2-$; $-CH_2CH_2CMe_2CH_2CH_2-$; $-O(CH_2)_mCH_2-$; $O(CH_2)_pO$; $-CH_2CH_2OCH_2CH_2-$; or $-CH_2CH_2N(H \text{ or alkyl})CH_2CH_2-$;

or $R_1$ and $R_2$ comprise a double bond to $CMe_2$, C(cycloalkyl), O, or C(cyloether);

n is an integer from 0 to 5;

m is an integer from 1 to 4;

p is an integer from 1 to 4;

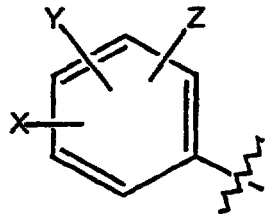
$R_3$ is selected from H, OH, $NH_2$, $C_1$ to $C_6$ alkyl, substituted $C_1$ to $C_6$ alkyl, $C_3$ to $C_6$ alkenyl, alkynyl or substituted alkynyl, or $COR^A$;

$R^A$ is selected from H, $C_1$ to $C_3$ alkyl, substituted $C_1$ to $C_3$ alkyl, $C_1$ to $C_3$ alkoxy, substituted $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ aminoalkyl, or substituted $C_1$ to $C_3$ aminoalkyl;

$R_4$ is selected from H, halogen, CN, $NH_2$, $C_1$ to $C_6$ alkyl, substituted $C_1$ to $C_6$ alkyl, $C_1$ to $C_6$ alkoxy, substituted $C_1$ to $C_6$ alkoxy, $C_1$ to $C_6$ aminoalkyl, or substituted $C_1$ to $C_6$ aminoalkyl;

$R^5$ is selected from the groups a), b) or c):

a) $R^5$ is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:




wherein:

X is selected from the group of halogen, OH, CN, $C_1$ to $C_3$ alkyl, substituted $C_1$ to $C_3$ alkyl, $C_1$ to $C_3$ alkoxy, substituted $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ thioalkyl, substituted $C_1$ to $C_3$ thioalkyl, S(O)alkyl, $S(O)_2$alkyl, $C_1$ to $C_3$ aminoalkyl, substituted $C_1$ to $C_3$ aminoalkyl, $NO_2$, $C_1$ to $C_3$ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, $COR^B$, $OCOR^B$, or $NR^CCOR^B$;

$R^B$ is H, $C_1$ to $C_3$ alkyl, substituted $C_1$ to $C_3$ alkyl, aryl, substituted aryl, $C_1$ to $C_3$ alkoxy, substituted $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ aminoalkyl, or substituted $C_1$ to $C_3$ aminoalkyl;

$R^C$ is H, $C_1$ to $C_3$ alkyl, or substituted $C_1$ to $C_3$ alkyl;

Y and Z are independently selected from H, halogen, CN, $NO_2$, $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ alkyl, or $C_1$ to $C_3$ thioalkyl;

or

b) $R^5$ is a five or six membered heterocyclic ring with 1, 2, or 3 heteroatoms selected from O, S, SO, $SO_2$ or $NR^6$ and containing one or two

independent substituents from the group of H, halogen, CN, $NO_2$ and $C_1$ to $C_3$ alkyl, $C_1$ to $C_2$ alkoxy, $C_1$ to $C_3$ aminoalkyl, $COR^D$, or $NR^ECOR^D$;

$R^D$ is H, $C_1$ to $C_3$ alkyl, substituted $C_1$ to $C_3$ alkyl, aryl, substituted aryl, $C_1$ to $C_3$ alkoxy, substituted $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ aminoalkyl, or substituted $C_1$ to $C_3$ aminoalkyl;

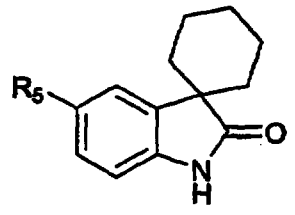
$R^E$ is H, $C_1$ to $C_3$ alkyl, or substituted $C_1$ to $C_3$ alkyl;

$R^6$ is H, or $C_1$ to $C_3$ alkyl; or

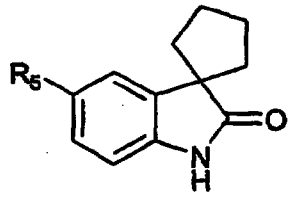
c) $R^5$ is an indol-4-yl, indol-7-yl or benzo-2-thiophene moiety, the moiety being optionally substituted by from 1 to 3 substituents selected from halogen, lower alkyl, CN, $NO_2$, lower alkoxy, or $CF_3$;

or a pharmaceutically acceptable salt thereof.

A preferred set of compounds of this invention is depicted by structure **2, 2a:**



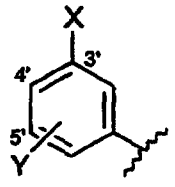

**2**




**2a**

wherein:

$R^5$ is a disubstituted benzene ring containing the substituents X and Y as shown below:

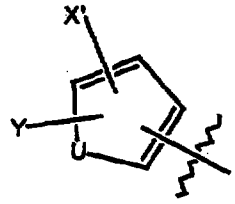


X is taken from the group of halogen, CN, $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ alkyl, $NO_2$, $C_1$ to $C_3$ perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms or $C_1$ to $C_3$ thioalkoxy;

Y is a substituent on the 4' or 5'position of the disubstituted benzene ring selected from the group of H, halogen, CN, $NO_2$, $C_1$ to $C_3$ alkoxy, $C_1$ to $C_4$ alkyl, or $C_1$ to $C_3$ thioalkyl;

or a pharmaceutically acceptable salt thereof.

Another preferred group of this invention comprises compounds of formulas 2 and 2a wherein $R^5$ is a five membered ring with the structure shown below:




U is O, S, or $NR^6$,

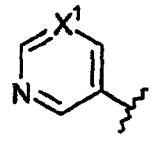
$R^6$ is H, or $C_1$ to $C_3$ alkyl, $C_1$ to $C_4$ $CO_2$alkyl,

X' is selected from the group of halogen, CN, $NO_2$, $C_1$ to $C_3$ alkyl or $C_1$ to $C_3$ alkoxy; with a proviso that, when X' is CN, U is not $NR^6$;

Y' is selected from H, F, CN, $NO_2$ or $C_1$ to $C_4$ alkyl;

or a pharmaceutically acceptable salt thereof.

Another preferred group of formulas 2 and 2a are those in which $R^5$ is a six membered ring with the structure shown




wherein :

$X^1$ is N or $CX^2$,

$X^2$ is halogen, CN or $NO_2$;

or pharmaceutically acceptable salt thereof

The compounds of this invention may contain an asymmetric carbon atom and some of the compounds of this invention may contain one or more asymmetric centers and may thus give rise to optical isomers and diastereomers. While shown without respect to stereochemistry in Formula 1 and 2 the present invention includes such optical isomers and diastereomers; as well as the racemic and resolved, enantiomerically pure R and S stereoisomers; as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof.

The term "alkyl" is used herein to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having 1 to 8 carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group with 1 or 2 carbon-carbon double bonds and containing 2 to 8 carbon atoms; "alkynyl" group is intended to cover both straight- and branched-chain alkyl group with at least 1 or 2 carbon-carbon triple bonds and containing 2 to 8 carbon atoms.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having one or more substituents from the group including halogen, CN, OH, $NO_2$, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

The term "aryl" is used herein to refers to an aromatic system which may be a single ring or multiple aromatic rings fused or linked together as such that at least one part of the fused or linked rings forms the conjugated aromatic system. The aryl groups include, but are not limited to, phenyl, naphthyl, biphenyl, anthryl, tetrohydronaphthyl, phenanthryl.

The term "substituted aryl" refers to aryl as just defined having 1 to 4 substituents from the group including halogen, CN, OH, $NO_2$, amino, alkyl,

cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "heterocyclic" is used herein to describe a stable 4- to 7-membered monocyclic or a stable multicyclic heterocyclic ring which is saturated, partially unsaturated, or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group including N, O, and S atoms. The N and S atoms may be oxidized. The heterocyclic ring also includes any multicyclic ring in which any of above defined heterocyclic rings is fused to an aryl ring. The heterocyclic ring may be attached at any heteroatom or carbon atom provided the resultant structure is chemically stable. Such heterocyclic groups include, but are not limited to, tetrahydrofuran, piperidinyl, piperazinyl, 2-oxopiperidinyl, azepinyl, pyrrolidinyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, isoxazolyl, morpholinyl, indolyl, quinolinyl, thienyl, furyl, benzofuranyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and isoquinolinyl.

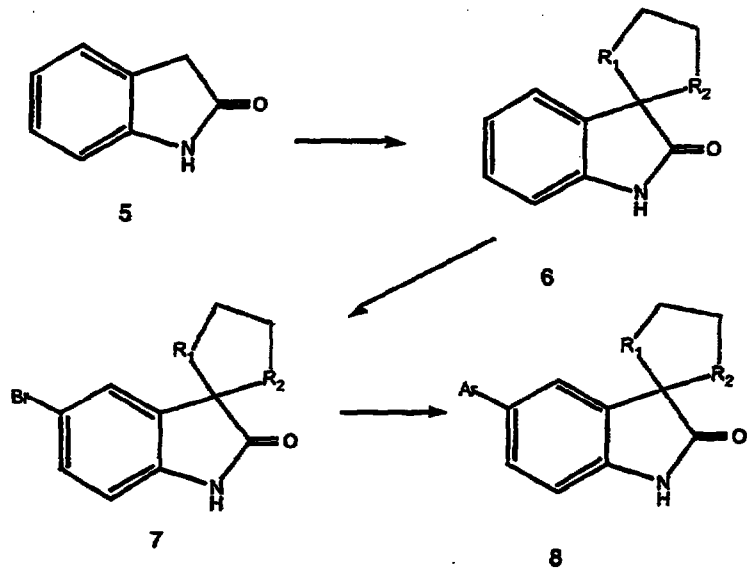
The term "substituted heterocyclic" is used herein to describe the heterocyclic just defined having 1 to 4 substituents selected from the group which includes halogen, CN, OH, $NO_2$, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

The term "thioalkyl" is used herein to refer to the SR group, where R is alkyl or substituted alkyl, containing 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms. The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl, containing 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms. The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl, as defined above. The term "alkylcarbonyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl, containing 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms. The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl, containing 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms. The term "aminoalkyl" refers to both

secondary and tertiary amines wherein the alkyl or substituted alkyl groups, containing 1 to 8 carbon atoms, preferably 1 to 6 carbon atoms, which may be either the same or different and the point of attachment is on the nitrogen atom. The term "halogen" refers to Cl, Br, F, or I.

The compounds of this invention may be prepared according to the methods described below.

Scheme 1

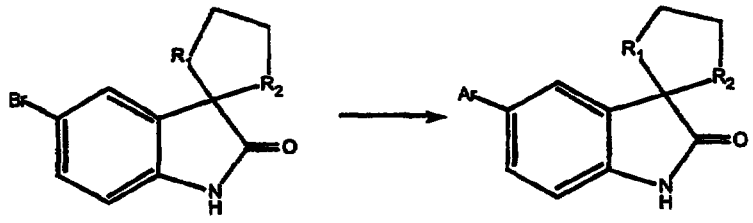



According to scheme 1, commercially available oxindole **5** is treated with mixture a strong organo-metallic base (e.g. butyl lithium, lithium diisopropylamide, potassium hexamethyldisilazide) in an inert solvent (e.g. THF, diethyl ether) under nitrogen at reduce temperature (ca. -20 °C) (Kende, et al, Synth. Commun., **12**, 1, 1982). The resulting di-anion is then treated with excess electrophile such as an alkyl halide, preferably the iodide. If $R_1$ and $R_2$ are to be joined such as the product **6** contains a spirocycle at position 3, then the electrophile should be bifunctional, i.e. a diiodide. Subsequent bromination of **6** proceeds smoothly with bromine in acetic acid (an organic co-solvent such as dichloromethane may be added as required) in the presence of sodium acetate, to afford the aryl bromide **7**. The bromide **7** is reacted with a palladium salt (e.g. tetrakis(triphenylphoshine)palladium(0)), in a suitable solvent (e.g. THF, dimethoxyethane, ethanol, toluene) at room temperature under an inert atmosphere (argon, nitrogen). The mixture is then treated with an arylboronic acid or boronic acid ester and a base (sodium carbonate, triethylamine, potassium

phosphate) in water or fluoride source (cesium fluoride) under anhydrous conditions. The required product 8 is then isolated and purified by standard means.

If $R_1$ and $R_2$ are different, then the intermediate 6 is prepared by reacting the dianion of 5 with one equivalent of the electrophile $R_1$-X (X = leaving group e.g. I). The resultant mono-alkylated compound may be then isolated and re-subjected to the reaction conditions using $R_2$-X, or alternatively used in-situ for the second alkylation with $R_2$-X. Alternatively if the desired product 8 is to contain $R_2$ = H, then the isolated mono-alkylated intermediate is taken though the subsequent steps.

Scheme 2



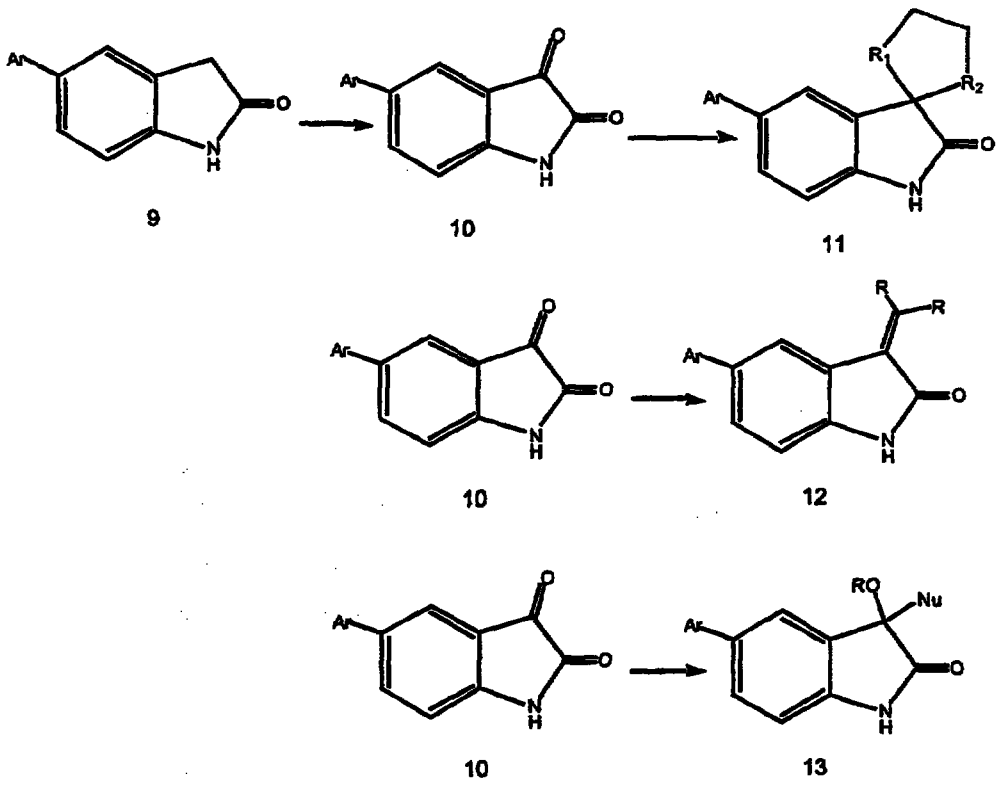

7 8

Other methodologies are also available for coupling the pendant aryl group, Ar, to the oxindole platform, for example reaction of compound 7 with an aryl stannane, aryl zinc, or aryl magnesium halide in the presence of a palladium or nickel catalyst (scheme 2). The required aryl-metallic species described above are formed through standard techniques.

Other functionalities can easily be installed into the 3-position of the indoline platform according to scheme 3. Oxidation of the unsubstituted indoline 9, preferably under neutral or acidic conditions (e.g. selenium dioxide in dry dioxane at reflux) affords the isatin 10. Compound 10 may be further functionalized to provide a ketal 11 by treatment with an alcohol and acid catalyst under dehydrating conditions. Alternatively reaction of 10 with a second ketone under suitable conditions (piperidine in toluene at reflux; or $TiCl_4$/Zn in THF at reflux) affords alkylidene derivatives 12. Reaction of the isatin 10 with a grignard reagent or organolithium

affords tertiary alcohols 13 (R = H). These alcohols may then be further functionalized by alkylation or acylation procedures.

Scheme 3

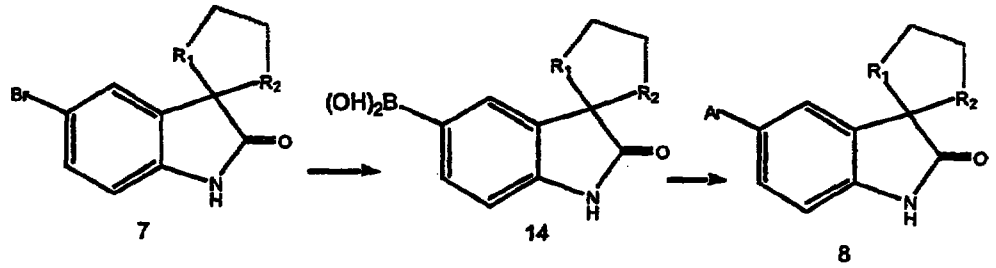



9 10 11

10 12

10 13

Scheme 4




7 14 8

Treatment of the bromide 7 in an anhydrous solvent (e.g. THF, $Et_2O$) with a strong base (sodium hydride preferred, sodium hexamethyldisilazide, potassium hydride) followed by reaction at reduced temperature (-50 to -20 °C) with n-butyllithium and *N,N,N,N'*-tetramethylethylenediamine followed after a suitable

period of time by a trialkylborate (trimethyl or triisopropylborate) gives after acidic work-up the boronic acid **14** (scheme 4). Compound **14** may then be reacted under palladium catalyzed conditions (tetrakis(triphenylphosphine)palladium(0), base ($NaHCO_3$, $Na_2CO_3$, $K_2CO_3$, triethylamine, CsF) solvent (toluene/EtOH/water, THF/water, dimethoxyethane/water, anhydrous dimethoxyethane) with an aryl bromide, aryl iodide, aryltrifluoromethane sulfonate of aryl fluorosulfonate, to provide the desired compounds **8**.

An alternative strategy would be to prepare an organo zinc or magnesium reagent from compound **7** and react it *in-situ* with an aryl bromide, aryl iodide, aryltrifluoromethane sulfonate of arylfluorosulfonate, under palladium catalyzed conditions to afford compound **8**. Such an organo zinc or magnesium species could be prepared by treatment of the bromide **7** in an anhydrous solvent (e.g. THF, $Et_2O$) with a strong base (sodium hydride preferred, sodium hexamethyldisilazide, potassium hydride) followed by reaction at reduced temperature (-50 to -20 °C) with n-butyllithium and *N,N,N',N'*-tetramethylethylenediamine followed after a suitable period of time by reaction with anhydrous zinc chloride or magnesium bromide.

The compounds of the present invention can be used in the form of salts derived from pharmaceutically or physiologically acceptable acids or bases. These salts include, but are not limited to, the following salts with inorganic acids such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and, as the case may be, such organic acids as acetic acid, oxalic acid, succinic acid, and maleic acid. Other salts include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium in the form of esters, carbamates and other conventional "pro-drug" forms, which, when administered in such form, convert to the active moiety *in vivo*.

This invention includes pharmaceutical compositions and treatments which comprise administering to a mammal a pharmaceutically effective amount of one or more compounds as described above as antagonists of the progesterone receptor.

The progesterone receptor antagonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of benign and malignant neoplastic disease. Specific uses of the compounds and pharmaceutical compositions of invention include the treatment and/or prevention of uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma and other hormone-dependent tumors. Additional uses of the present progesterone receptor antagonists include the synchronization of the estrus in livestock.

When the compounds are employed for the above utilities, they may be combined with one or more pharmaceutically acceptable carriers or excipients, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration and the severity of the condition being treated. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.5 to about 500 mg/kg of animal body weight, preferably given in divided doses two to four times a day, or in a sustained release form. For most large mammals, the total daily dosage is from about 1 to 100 mg, preferably from about 2 to 80 mg. Dosage forms suitable for internal use comprise from about 0.5 to 500 mg of the active compound in intimate admixture with a solid or liquid pharmaceutically acceptable

carrier. This dosage regimen may be adjusted to provide the optimal therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvents customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

The preferred pharmaceutical compositions from the standpoint of ease of preparation and administration are solid compositions, particularly tablets and hard-filled or liquid-filled capsules. Oral administration of the compounds is preferred.

These active compounds 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 hydroxypropylcellulose. 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 prevent 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 syringe ability exits. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can

be a solvent or dispersion medium containing, for example, water, ethanol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

The present invention may be further understood by the following non-limiting examples.

**EXAMPLE 1**

**5-(3-Nitro-phenyl)-1,3-dihydro-indol-2-one**

5-(Bromo)-1,3-dihydro-indol-2-one.

A solution of oxindole (2.0 g, 15.0 mmol) and sodium acetate (2.1 g, 25.5 mmol) in $CHCl_3$ (20 $cm^3$) was treated with bromine (2.4 g, 15.0 mmol) in $CHCl_3$ (10 $cm^3$). After 30 min. the mixture was allowed to warm to RT and stirred for 1h. The reaction mixture was diluted with EtOAc (500 $cm^3$) and poured into water. The aqueous layer was extracted with EtOAc (x 2), the combined organic layers were washed with water, sat. sodium hydrogen carbonate solution, brine, dried ($MgSO_4$), and evaporated to give the title compound (3.1 g, 14.6 mmol, 96 %) as an off-white solid which was used without further purification: m.p. 221-223 °C; $^1H$ NMR (DMSO-$d_6$) δ 3.51 (s, 2H), 6.76 (d, 1H, $J$ = 8.1 Hz), 7.33(dd, 1H, $J$ = 8.1, 1.7 Hz), 7.37 (s, 1H), 10.49 (br s, 1H); $^{13}C$ NMR (DMSO-$d_6$) δ 36.10 (t), 111.21 (d), 113.16 (s), 127.54 (d), 128.3 (s), 130.40 (d), 143.34 (s), 176.24 (s); MS (EI) *m/z* 211, 213 $(M)^+$.

5-bromo-2-indolinone (1.08 g, 5.09 mmol) and tetrakistriphenyl phosphine Pd (0) (0.273 g) were stirred under an atmosphere of nitrogen in ethylene glycol dimethyl ether (35 mL). After 15 minutes, 3-nitrophenyl boronic acid (1.70 g, 10.2 mmol) was added, followed by potassium carbonate (4.24 g, 30.7 mmol) in water (15 mL). The reaction was heated to reflux overnight, cooled to room temperature and then filtered. Saturated ammonium chloride was added. The water layer was extracted with ethyl acetate (3 X 20 mL). The combined organic layer was dried with $MgSO_4$, filtered, and solvent removed in vacuo. The product was purified by flash silica gel chromatography (3:2 hexane; ethyl acetate) to give 5-(3-Nitro-phenyl)-1, 3-dihydro-

indol-2-one (0.084 g, 65%), Mp = 269 °C; $^1$H NMR (DMSO) δ 10.5 (s, 1 H), 8.38-8.36 (m, 1 H) 8.17-8.14 (m, 1 H), 8.10-8.07 (m, 1 H), 7.75-7.60 (m, 3 H), 6.95 (d, 1 H, $J$ = 8.1 Hz), 3.57 (s, 2 H); IR (KBr) 3420, 3190, 1700 cm$^{-1}$; MS (EI) *m/z* 253 (M-H)$^-$; CHN calculated for $C_{14}H_{10}N_2O$: C, 66.14; H, 3.96; N, 11.02; Found: C, 64.59; H, 4.16; N, 9.43.

**EXAMPLE 2**

**3-methyl-5-(3-nitrophenyl)-1,3-dihydroindol-2-one**

5-bromo-3-methyl-indol-2-one

Under an atmosphere of nitrogen, bromine (0.96 g, 6.0 mmol) in acetic acid (5 cm$^3$) was added drop wise to a solution of 3-methyl-2-indolinone (0.8749 g, 6.0 mmol) (Kende, et al, Synth. Commun., 12, 1, 1982) and sodium acetate (0.50 g, 6.0 mmol) in acetic acid (10 cm$^3$). The reaction was stirred at room temperature for 3.5 h. Saturated sodium carbonate was added to quench the reaction. The water layer was extracted with EtOAc (x3), dried ($MgSO_4$), filtered, and evaporated to give the title compound (1.26 g, 93%), Mp = 119-120 °C; $^1$H NMR (DMSO) δ 1.32 (d, 3 H, $J$ = 7.66 Hz), 3.45 (q, 1 H, $J$ = 7.62 Hz), 6.77 (d, 1 H, $J$ = 8.23 Hz), 7.46 (s, 1 H), 7.36-7.33 (m, 1 H), 10.4 (s, 1 H); IR (KBr) 3200, 1725 cm$^{-1}$; MS (EI) *m/z* 224/226 (M-H)$^-$; CHN calculated for $C_9H_8BrNO$: C, 47.82; H, 3.57; N, 6.20; Found: C, 47.44; H, 3.42; N, 6.04.

5-Bromo-3-methyl-1,3-dihydro-indol-2-one (0.50 g, 2.22 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.15 g) were stirred under an atmosphere of nitrogen in dimethoxyethane (18 cm$^3$). After 15 min., 3-nitrophenyl boronic acid (0.74 g, 4.45 mmol) was added, followed by potassium carbonate (1.86 g, 13.5 mmol) in water (7 cm$^3$). The reaction was heated to reflux for 8 h and then stirred at room temperature overnight. Saturated ammonium chloride was added; and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc: hexane 1:2); eluted: 2:1 hexane; ethyl acetate, to give the title compound (0.30 g, 47 %), mp 200-203 °C; $^1$H NMR (DMSO-$d_6$) δ 1.41 (d, 3

H, $J$ = 7.61 Hz), 3.50 (q, 1 H, $J$ = 7.60 Hz), 6.96 (d, 1 H, $J$ = 8.08 Hz), 7.62 (d, 1 H, $J$ = 8.06 Hz), 7.75-7.70 (m, 2 H), 8.18-8.10 (m, 2 H), 8.41-8.39 (m, 1 H), 10.5 (s, 1 H); IR (KBr) 3450, 1700 $cm^{-1}$; MS (EI) *m/z* 267 (M-H); Anal. Calc. for $C_{15}H_{12}N_2O_3$ + $0.2C_4H_8O_2$: C, 66.61; H, 4.46; N, 9.83; Found: C, 66.26; H, 4.59; N, 10.06.

**EXAMPLE 3**

**5-(3-Methoxy-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one**

5-bromo-1,3-dihydro-3,3-dimethyl-2H-indol-2-one

3,3-dimethyl-indol-2-one (0.65 g, 4.03 mmol) and sodium acetate (0.33 g, 4.07 mmol) were stirred in acetic acid (5 $cm^3$) then bromine (0.66 g, 4.13 mmol) in acetic acid (5 $cm^3$) was added drop-wise to the reaction mixture. The reaction was stirred for 50 min., and then poured into water. The mixture was basified with sodium carbonate and then extracted with ethyl acetate (x3), dried ($MgSO_4$), filtered, and evaporated to the subtitled compound (0.89 g, 92%) $^1H$ NMR (DMSO-$d_6$) δ 1.21 (s, 6 H), 6.76 (d, 1 H, $J$ = 8.22 Hz), 7.29 (dd, 1 H, $J$ = 2.12 Hz, 8.23 Hz), 7.49 (d, 1 H, $J$ = 2.03 Hz), 10.4 (s, 1H).

5-bromo-1,3-dihydro-3,3-dimethyl-2H-indol-2-one (0.33 g, 1.38 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.094 g) were stirred under an atmosphere of nitrogen in dimethoxyethane (12 $cm^3$). After 15 minutes, 3-methoxyphenylboronic acid (0.42 g, 2.76 mmol) was added, followed by potassium carbonate (1.15 g, 8.34 mmol) in water (5 $cm^3$). The reaction was heated to reflux for 5 hours, and then cooled to room temperature. Saturated aqueous ammonium chloride and EtOAc were added and the mixture was filtered. The aqueous layer was extracted with EtOAc (x2), and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc: hexane 1:3) to afford the title compound (0.11g, 31%), mp = 157-158 °C; $^1H$ NMR (DMSO-$d_6$) δ 3.34 (s, 6 H), 3.82 (s, 3 H), 6.87 - 6.93 (m, 2 H), 7.20-7.15 (m, 2 H), 7.37-7.32 (m, 1 H), 7.49-7.46 (m, 1 H), 7.63 (d, 1 H, $J$ = 1.14 Hz), 10.4 (s, 1 H);

MS (EI) *m/z* 266 (M-H)$^-$; Anal. Calc. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24; Found: C, 76.02; H, 6.49; N, 5.02.

## EXAMPLE 4

**5-(3-Chloro-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one**

5-bromo-1,3-dihydro-3,3-dimethyl-2H-indol-2-one (0.98 g, 4.07 mol) and tetrakis(triphenylphosphine)palladium(0) (0.239 g) were stirred under an atmosphere of nitrogen in dimethoxyethane (35 cm$^3$). After 15 min., 3-chlorophenylboronic acid (1.27 g, 8.13 mol) was added, followed by potassium carbonate (3.40 g, 45 mmol) in water (15 cm$^3$). The reaction was heated to reflux for 2 hours and then stirred at room temperature overnight. The mixture was diluted with sat. ammonium chloride and extracted with EtOAc (x3). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc: hexane, 1:3) to afford the title compound (0.284 g, 25%): mp 188 -189 °C; $^1$H NMR (DMSO-$d_6$) δ 3.34 (s, 6 H), 6.93 (d, 1 H, $J$ = 8.04 Hz), 7.38-7.35 (m, 1 H), 7.53-7.43 (m, 2 H), 7.61 (d, 1 H, $J$ = 7.68 Hz), 7.70 (s, 2 H), 10.40 (s, 1 H); IR (KBr) 3420, 3150, 3050, 1700 cm$^{-1}$; MS (EI) *m/z* 270 (M-H)$^-$; Anal. Calc. for $C_{16}H_{14}ClNO$ + $0.1C_4H_8O_2$: C, 70.21; H, 5.32; N, 4.99; Found: C, 70.3; H, 5.44; N, 4.93.

## EXAMPLE 5

**3,3-Dimethyl-5-(3-nitro-phenyl)-1,3-dihydro-indol-2-one**

5-bromo-1,3-dihydro-3,3-dimethyl-2H-indol-2-one (1.02 g, 4.26 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.244 g) were stirred under an atmosphere of nitrogen in dimethoxyethane (35 cm$^3$). After 15 minutes, 3-nitrophenylboronic acid (1.43 g, 2.56 mmol) was added, followed by potassium carbonate (3.54 g, 2.56 mmol) in water (15 cm$^3$). The reaction was heated to reflux for 2 hours and then stirred at room temperature overnight. Saturated ammonium chloride and EtOAc were added and the mixture was filtered. The aqueous layer was extracted with ethyl acetate (x2), and then the combined organic layers were dried ($Na_2SO_4$), filtered, and

evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc: hexane, gradient elution) to afford the title compound (0.86 g, 67 %) mp 234 -235 °C; $^1$H NMR (DMSO-$d_6$) δ 3.33 (s, 6 H), 6.98 (d, 1 H, $J$ = 8.06 Hz), 7.61 (dd, 1H, $J$ = 1.85, 8.03 Hz), 7.73 (t, 1 H, $J$ = 7.98 Hz), 7.81 (d, 1 H, $J$ = 1.63 Hz), 8.11-8.18 (m, 2 H), 8.42-8.43 (m, 1H), 10.5 (s, 1 H); MS (EI) *m/z* 281; Anal. Calc. for $C_{16}H_{14}N_2O_3.0.2H_2O$: C, 67.51; H, 4.92; N, 9.37; Found: C, 67.48; H, 5.17; N, 9.48.

## EXAMPLE 6

### 5-(3-Chloro-phenyl)-3-ethyl-1.3-dihydro-indol-2-one

3-Ethyl-indol-2-one

A solution of oxindole (40 g, 0.3 mol) in dry THF (400 ml) under $N_2$ was cooled to -25 °C and treated drop wise with n-butyl lithium (2.5M in hexanes, 240 ml, 0.6 mol). To the resulting solution was added N,N,N',N'-tetramethylethylenediamine (90.4 ml, 0.6 mol). After 30 min. iodoethane (48 ml, 0.6 mol) was added and the reaction mixture was allowed to warm to RT and stirred over night. The reaction mixture was poured into aqueous $NH_4Cl$ solution, extracted with EtOAc (2x) and the combined organic layers were washed with dil. HCl, water, brine, dried ($MgSO_4$) and concentrated. The residual oil was triturated with hexane to afford the crude product (24.5 g, 51%). A sample (3 g) was recrystallized from EtOAc/hexane to obtain the subtitled compound (1.4 g), m.p. 100 – 101 °C; $^1$H-NMR (DMSO-$d_6$) δ 0.76 (t, 3H, $J$ = 7.5 Hz), 1.8 – 2.0 (m, 2H), 3.38 (t, 3H, $J$ = 5.7 Hz), 6.8 (dt, 1H, $J$ = 7.69, 0.45 Hz), 6.93 (dt, 1H, $J$ = 7.45, 1.10 Hz), 7.15 (m, 1H), 7.22 (m, 1H), 10.3 (s, 1H); MS (ESI) *m/z* 270 [M+H].

5-Bromo-3-ethyloxindole

A solution of 3-ethyloxindole (6.0 g, 40 mmol) and sodium acetate (4 g, 48 mmol) in acetic acid (100 ml) was treated with bromine (6.4 g, 40 mmol). After 30 min. the mixture was diluted with water and extracted with EtOAc (2x); the combined organic layers were washed with water, sat. sodium hydrogen carbonate solution, and brine, dried ($MgSO_4$) and evaporated to afford the crude product (9.2 g, 96%). A

sample was recrystallized from EtOAc/hexane to obtain the subtitled compound, m.p. 130 – 132 °C; $^1$H-NMR (DMSO-$d_6$) δ 0.74 (t, 3H, $J$ = 7.5 Hz), 1.8 – 2.0 (m, 2H), 3.45 (t, 1H, $J$ = 5.5 Hz,), 6.76 (d, 1H, $J$ = 8.35 Hz), 7.42 (m, 1H), 10.43 (s, 1H); MS (-ESI) *m/z* 238/240 (M-H).

A solution of 5-bromo-3-ethyl-oxindole (3.5 g, 14.6 mmol), 3-chlorophenylboronic acid (2.4 g, 15 mmol), potassium carbonate (4.5 g, 33 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.87 g, 0.75 mmol) in dimethoxyethane (160 ml), ethanol (40 ml), and water (40 ml) was heated to reflux to 6 hours. After cooling to RT, the mixture was diluted with water and extracted with EtOAc (3x). The combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc:hexane 1:3) to afford the title compound (0.46 g, 12%), m.p. 118 – 120 °C; $^1$H-NMR (DMSO-$d_6$) δ 0.78 (t, 3H, $J$ = 7.25 Hz) 1.8 – 2.02 (m, 2H), 3.47 (t, 1H, $J$ = 5.71 Hz), 6.89 (d, 3H, $J$ = 8.1 Hz), 7.35 (m, 1H), 7.44 (t, 1H, $J$ = 7.91 Hz), 7.51 (m, 1H), 7.58 (m, 2H), 7.67 (t, 1H, $J$ = 1.76 Hz), 10.5 (s, 1H); MS (-ESI) *m/z* 270 (M-H).

## EXAMPLE 7

### 5-(3-Chloro-phenyl)-3,3-diethyl-1,3-dihydro-indol-2-one

A solution of 3-ethylindol-2-one (16 g, 0.1 mol) in dry THF (200 ml) under $N_2$ was cooled to -25 °C and treated drop wise with n-butyllithium (2.5M in hexanes, 80 ml, 0.2 mol). To the resulting solution was added N,N,N',N'-tetramethylethylenediamine (30 ml, 0.2 mol). After 30 min. iodoethane (8 ml, 0.1 mol) was added and the reaction mixture was allowed to warm to RT and stirred over night. The reaction mixture was poured into an aqueous $NH_4Cl$ solution, extracted with EtOAc (2x) and the combined organic layers were washed with dil. HCl, water, brine, dried ($MgSO_4$) and concentrated. The residual oil was triturated with hexane to afford the title product (9 g, 45%), m.p. 156 – 159 °C; $^1$H NMR (DMSO-$d_6$) δ 10.44 (s,1H), 7.70 - 7.69 (t,1H), 7.62 - 7.59 (m, 1H), 7.58 (d,1H $J$=1.7Hz), 7.53-7.50 (m, 1H), 7.45 - 7.41 (t,1H), 7.36 - 7.35 (m,1H), 7.34 - 7.33 (m,1H), 6.91 - 6.89 (d,1H

$J$=8.2Hz), 1.87 - 1.80 (m,2H), 1.77 - 1.70 (m, 2H), 0.54 - 0.50 (t, 6H); MS (+ESI) m/z 190 (M+H).

5-Bromo-1,3-dihydro-3,3-diethyl-[2H]-indol-2-one

A solution of 3,3-diethylindol-2-one (8 g, 40 mmol) and sodium acetate (4 g, 48 mmol) in acetic acid (100 ml) was treated with bromine (6.4 g, 40 mmol). After 30 min. the mixture was diluted with water and extracted with EtOAc (2x); the combined organic layers were washed with water, sat. sodium hydrogen carbonate solution, then brine, dried ($MgSO_4$) and evaporated to afford the crude product (7.6 g, 75%). A sample was recrystallized from EtOAc/hexane to obtain the subtitled compound, m. p. 164 – 165 °C; $^1$H-NMR (DMSO-$d_6$) δ 10.45 (s, 1H), 7.41-7.40(d, 1H, $J$ = 2.2Hz), 7.34 - 7.31 (m, 1H), 6.78 - 6.76 (d, 1H $J$ = 8.2 Hz), 1.78-1.65 (m, 4H), 0.50 - 0.46 (m, 6H); MS (-ESI) m/z 266/268 (M-H).

A solution of 5-bromo-1,3-dihydro-3,3-diethyl-[2H]-indol-2-one (2.7 g, 10 mmol), 3-chlorophenylboronic acid (1.6 g, 10 mmol), potassium carbonate (4 g, 30 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.5 g, 0.4 mmol) in dimethoxyethane (100 ml), ethanol (25 ml), and water (25 ml) was heated to reflux for 6 hours. After cooling to RT, the mixture was diluted with water and extracted with EtOAc (2x). The combined organic extracts were washed with water, then brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc:hexane 1:3) to afford the title compound (0.8 g, 27%), m.p. 195 – 197 °C; $^1$H-NMR (DMSO-$d_6$) δ 7.70 (t, 1H, $J$ = 2 Hz), 7.62 - 7.60 (m, 1H), 7.58 (d, 1H, $J$ = 1.7 Hz), 7.52, (dd, 1H, $J$ = 8.1, 2 Hz), 7.43 (t, 1H, 7.9 Hz), 7.36 - 7.33 (m, 1H), 6.90 (d, 1H, $J$ = 8.1 Hz), 1.87 - 1.70 (m, 4H) and 0.52 (t, 6H, $J$ = 7.4 Hz); MS (+APCI) *m/z* 300/302 (M-H)

## EXAMPLE 8

5-(3-Chloro-phenyl)-3-methoxy-3-methyl-1,3-dihydro-indol-2-one

A solution of 5-bromoisatin (5.0 g, 22 mmol) in dry THF (50 cm$^3$) under $N_2$ was cooled to 0 °C and treated drop-wise with methyl magnesium bromide (3M in

diethylether, 14.7 $cm^3$, 44 mmol) and the mixture was allowed to warm up-to room temperature. The reaction was poured into sat. ammonium chloride solution, then extracted into EtOAc (x3). The combined organic layers were then washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was then purified by column chromatography ($SiO_2$, EtOAc: hexane, gradient elution) to afford 5-bromo-3-hydroxy-3-methyl-1,3-dihydro-indol-2-one (1.53 g, 6.32 mmol, 29%): $^1H$ NMR (DMSO-$d_6$) δ 1.38 (s, 3H), 5.99 (s, 1H), 6.77 (d, 1H, $J$ = 1.7 Hz), 7.38 (s, 1H, br); MS ((-) ESI) *m/z* 240/242 $(M)^-$.

5-bromo-3-hydroxy-3-methyl-1,3-dihydro-indol-2-one (1.0 g, 4.1 mmol) was dissolved in dry DMF (15 $cm^3$) cooled to 0 °C and treated with potassium *tert*-butoxide (1M in THF, 4.5 $cm^3$, 4.5 mmol). After 15 min. methyl-*p*-toluenesulfonate (0.93 g, 5 mmol) was added and the mixture was allowed to warm up-to room temperature. After 2h the mixture was poured into saturated ammonium chloride solution and extracted with EtOAc (x2), then the combined organic layers were washed with water, sodium hydroxide (1N, x2), water (x3), dried ($MgSO_4$) and evaporated. The residue was then purified by column chromatography ($SiO_2$, EtOAc: hexane, gradient elution) to afford 5-bromo-3-methoxy-3-methyl-1,3-dihydro-indol-2-one (0.56 g, 2.2 mmol, 53%): $^1H$ NMR ($CDCl_3$) δ 1.59 (s, 3H), 3.18 (s, 3H), 6.73 (d, 1H, $J$ = 8.2 Hz), 7.45 (dd, 1H, $J$ = 8.2, 2 Hz), 7.52 (d, 1H, $J$ = 2 Hz); MS (EI) *m/z* 225 $(M)^+$.

A solution of 5-bromo-3-methoxy-3-methyl-1,3-dihydro-indol-2-one (0.52 g, 2.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.1 mmol) was dissolved in dimethoxyethane (22 $cm^3$). After 15 min., 3-chlorophenylboronic acid (0.63 g, 4.1 mmol) and sodium carbonate (1.0 g) in water (10 $cm^3$) was added and the reaction was heated under reflux. After 2h the mixture was cooled, poured into water and extracted with EtOAc (x2), the combined organic extracts were washed with sodium hydroxide solution (1N, x2) water, brine, dried ($MgSO_4$) and evaporated. The residue was then purified by column chromatography ($SiO_2$, EtOAc: hexane, 5:1) to afford 5-(3-chloro-phenyl)-3-methoxy-3-methyl-1,3-dihydro-indol-2-one (0.17 g, 0.58

mmol, 29%): $^1$H NMR ($CDCl_3$) δ 1.65 (s, 3H), 2.91 (s, 1H), 3.24 (s, 3H), 6.92 (d, 1H, $J$ = 8.1 Hz), 7.26 - 7.38 (m, 2H), 7.43 - 7.46 (m, 1H), 7.52 - 7.55 (m, 1H), 7.62 (d, 1H, $J$ = 1.8 Hz); MS ((+) APCI) *m/z* 288 $(M + H)^+$.

## EXAMPLE 9

**5-(3-Chloro-phenyl)-3-methoxy-3-prop-1-ynyl-1,3-dihydro-indol-2-one**

To a solution of 5-bromoisatin (2.5 g, 11 mmol) in dry THF (100 $cm^3$) at -10 °C under a nitrogen atmosphere was added 1-propynylmagnesium bromide (0.5 M in THF, 47 $cm^3$, 23.5 mmol). After 1h, the mixture was poured into saturated ammonium chloride and extracted with EtOAc (x3), washed with brine, dried ($MgSO_4$) and evaporated to afford 5-bromo-3-hydroxy-3-prop-1-ynyl-1,3-dihydroindol-2-one (2.83 g, 10.6 mmol, 97%) which was used without further purification: ($CDCl_3$) δ 1.83 (s, 3H), 6.79 (d, 1H, $J$ = 8.0 Hz), 6.90 (s, 1H), 7.41 - 7.44 (m, 2H), 10.59 (s, 1H); MS ((-) ESI) *m/z* 264 $(M-H)^-$.

To a solution of 5-bromo-3-hydroxy-3-prop-1-ynyl-1,3-dihydroindol-2-one (1.0 g, 3.75 mmol) in dry DMF (15 $cm^3$) at 0 °C, was added potassium *tert*-butoxide (1M in THF, 4.1 $cm^3$, 4.1 mmol). After 15 min. methyl *p*-toluenesulfonate (0.85 g, 4.6 mmol) was added and the mixture was allowed to warm up to room temperature. After 16h the mixture was poured into saturated ammonium chloride, extracted with EtOAc (x3), washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc: hexane 1:3) to afford 5-bromo-3-methoxy-3-prop-1-ynyl-1,3-dihydroindol-2-one (0.62 g, 2.21 mmol, 59%): ($CDCl_3$) δ *inter alia* 1.87 (s, 3H), 3.19 (s, 3H), 3.35 (s, 1H), 6.72 (d, 1H, $J$ = 8.3 Hz), 7.48 (dd, 1H, $J$ = 8.3, 2 Hz), 7.63 (d, 1H, $J$ = 2 Hz): MS (EI) *m/z* 279 $(M)^+$.

5-bromo-3-methoxy-3-prop-1-ynyl-1,3-dihydroindol-2-one (0.56 g, 2.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.10 mmol ) were stirred at room temperature in dimethoxyethane (22 $cm^3$). After 15 min. 3-chlorophenylboronic acid (0.63 g, 4.0 mmol) and sodium carbonate (1.06 g, 10 mmol) in water (11 $cm^3$) were added and the mixture heated under reflux. After 16h, the mixture was cooled,

poured into water and extracted with EtOAc (x3). The combined organic layers were washed with sodium hydroxide (1N, x2), brine, dried ($MgSO_4$) and evaporated. The residue was subjected to column chromatography ($SiO_2$, EtOAc: hexane, gradient elution) and the product triturated with hexane to afford the title compound (0.095 g, 0.30 mmol, 15%) as a solid: mp. >190 °C (decomp.); ($CDCl_3$) δ 1.88 (s, 3H), 3.25 (s, 3H), 3.30 (s, 1H), 6.91 (d, 1H, $J$ = 8.1Hz), 7.29 - 7.39 (m, 2H), 7.44 - 7.47 (m, 1H), 7.54 - 7.57 (m, 2H), 7.74 (d, 1H, $J$ = 1.7 Hz); MS (EI) *m/z* 311 (M+).

## EXAMPLE 10

**5-(3-Chloro-phenyl)-1,3-dihydro-indol-2-one**

A solution of the 5-bromoxindole (0.5 g, 2.4 mmol) and tetrakis(triphenylphosphine) palladium (0.14 g, 0.12 mmol) in dimethoxyethane (10 $cm^3$) was stirred under $N_2$ for 20 min.. To this mixture was then added 3-chlorophenylboronic acid (0.44 g, 2.83 mmol) and sodium carbonate (0.75 g, 7.1 mmol) in water (4 $cm^3$). The solution was brought to reflux for 6 h then cooled to RT, poured into water and extracted with EtOAc (x 3). The combined organic extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, ethyl acetate: hexane 1:3) to afford the title compound (0.49 g, 2.0 mmol, 86 %) as a tan solid: m.p. 169-171 °C , $^1$H NMR (THF-$d_8$) δ 3.45 (s, 2H), 6.85 (d, 1H $J$ = 8.1 Hz), 7.25 (d, $J$ = 8.0 Hz, 1H), 7.35 (dd, $J$ = 7.8, 7.8 Hz, 1H), 7.43 (d, $J$ = 8.1 Hz, 1H), 7.49 (d, $J$ = 7.8 Hz, 1H), 7.50 (s, 1H), 7.59 (dd, $J$ = 1.78, 1.78 Hz, 1H), 9.5 (br s, 1H); $^{13}$C NMR (THF-$d_8$) δ 36.39 (t), 109.80, 123.97, 125.55, 127.19 (d), 127.68 (s), 130.89 (d), 133.73, 135.29, 144.23, 145.09, 176.45 (s); MS (EI) *m/z* 243, 245 $(M)^+$; Anal. ($C_{14}H_{10}ClNO$) C, H, N.

## EXAMPLE 11

**5'-(3-Chlorophenyl)spiro[1,3-dioxolane-2,3'-[3H] indol]-2'(1'H)-one**

**5-[3-Chloro-phenyl]-1H-indole-2,3-dione**

A solution of 5-(3-Chloro-phenyl)-1,3-dihydro-indol-2-one (10.0 g, 41 mmol) in dioxane (200 $cm^3$) and $SeO_2$ (22.8 g, 205 mmol) was brought to reflux for 2 h then cooled to RT and concentrated onto Florisil. The Florisil was washed (acetone:$CHCl_3$ 1:9) and the combined organic extracts were evaporated. The residue was purified by column chromatography ($SiO_2$, acetone:$CHCl_3$ 1:8) to afford the subtitled compound (8 g, 31 mmol, 76 %) as a tan solid: m.p. 256-258 °C , $^1H$ NMR (THF-$d_8$) δ 6.96 (d, $J$ = 8.8 Hz, 1H), 7.33 (d, $J$ = 8.1 Hz, 1H), 7.4 (dd, $J$ = 7.7, 7.7 Hz, 1H), 7.56 (d, $J$ = 7.7 Hz, 1H), 7.68 (dd, $J$ = 1.84, 1.84 Hz, 1H), 7.83-7.86 (m, 2H), 10.05 (br s, 1H); $^{13}C$ NMR (DMSO-$d_6$) δ 113.30 (d), 119.08 (s), 123.44, 125.57, 126.65, 127.92, 131.41 (d), 133.88, 134.47 (s), 137.25 (d), 141.51, 150.99, 160.15, 184.83 (s); MS (EI) *m/z* 256 $(M-H)^+$; Anal. ($C_{14}H_8ClNO_2$-0.1 $H_2O$) C, H, N.

A solution of the 5-[3-chloro-phenyl]-1H-indole-2,3-dione (0.5 g, 1.9 mmol) in toluene (30 $cm^3$) and ethylene glycol (1.1 $cm^3$ , 19.4 mmol) and pTsOH (0.04 g, 0.2 mmol) was brought to reflux with azeotropic removal of water for 12 h then cooled to RT. The reaction mixture was diluted with EtOAc (100 $cm^3$) and washed with water, sat. sodium hydrogen carbonate solution, brine, dried ($MgSO_4$), and evaporated to give an oily residue. The residue was purified by column chromatography ($SiO_2$, $CH_2Cl_2$) to afford the title compound (0.47 g, 1.6 mmol, 80 %) as a tan solid: m.p. 159-161 °C ; $^1H$ NMR (DMSO-$d_6$) δ 4.29-4.39 (M, 4H), 6.93 (d, $J$ = 8.6 Hz, 1H), 7.4 (d, $J$ = 8.1 Hz, 1H), 7.46 (dd, $J$ = 7.9, 7.9 Hz, 1H), 7.7 (d, $J$ = 7.7 Hz, 1H), 7.68-7.71 (m, 3H), 10.55 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$) δ 65.53 (t), 110.89, 123.25, 124.81 (d), 125.65 (s), 125.83, 126.79, 130.09, 130.61 (d), 132.96, 133.64, 141.53, 14267, 174.36 (s); MS (EI) *m/z* 301/303 $(M)^+$; Anal. ($C_{16}H_{12}ClNO_3$) C, H, N.

## EXAMPLE 12

**5'-(3-Chlorophenyl)spiro[1,3-dioxane-2,3'-[3H]indol]-2'(1'H)-one**

The title compound was prepared according to the procedure for example 11: m.p. 242-244 °C ; $^1H$ NMR (DMSO-$d_6$) δ 1.7 (M, 1H), 2.2 (M, 1H), 3.95 (m, 2H), 4.78 (t, 2H), 6.9 (d, $J$ = 7.9 Hz, 1H), 7.39 (d, $J$ = 7.9 Hz, 1H), 7.46 (dd, $J$ = 7.9, 7.9

Hz, 1H), 7.59-7.68 (m, 3H), 10.59 (br s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 25.19, 60.68 (t), 93.58 (s), 110.94, 122.93, 125.29, 126.29, 127.19 (d), 128.65 (s), 129.92, 131.07 (d), 133.16, 134.08, 141.61, 142.15, 173.29 (s); MS (EI) *m/z* 315/317 $(M)^+$; Anal. ($C_{17}H_{14}ClNO_3$) C, H, N.

**EXAMPLE 13**

**5'-(3-nitrophenyl)spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one**

Spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one

To a -25 °C solution of oxindole (2.0 g, 15.0 mmol) in 40 ($cm^3$) of anhydrous THF under $N_2$ was added *n*-butyllithium (1.6 M in hexanes, 19.7 $cm^3$, 31.5 mmol) drop-wise. To the resulting milky solution was added *N,N,N',N'*-tetramethylethylenediamine (4.75 $cm^3$, 31.5 mmol). After 30 min. a solution of 1,4-diiodobutane (21.9 g, 70.6 mmol) in THF (3 $cm^3$) was added and the reaction mixture was allowed to warm to RT and stirred for 14 h. The reaction mixture was poured into water, extracted with EtOAc (x 2), then the combined organic layers were washed with dil. HCl (pH 1), water (x 2), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc: hexane 1:4) to afford the subtitled compound (1.4 g, 7.5 mmol, 50%) as a tan solid: $^1$H NMR ($CDCl_3$) δ 1.8-2.2 (m, 8H), 6.94 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.01 (dd, *J* 7.5, 1.0 Hz, 1H), 7.14-7.25 (m, 2H), 9.30 (br s, 1H).

5-Bromo-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one

A solution of spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one (0.27 g, 1.4 mmol) and sodium acetate (0.12 g, 1.46 mmol) in acetic acid (10 $cm^3$) was treated with bromine (0.24 g, 1.51 mmol) in acetic acid (2 $cm^3$). After 30 min. the mixture was poured into sat. sodium hydrogen carbonate solution and extracted with EtOAc (x 2), the combined organic layers were washed with water, sat. sodium hydrogen carbonate solution, water, dried ($MgSO_4$), and evaporated to give the subtitled compound (0.37 g, 1.47 mmol, 96 %) as an off-white solid which was used without further purification: $^1$H NMR ($CDCl_3$) δ 1.8-2.27 (m, 8H), 6.79 (d, *J* = 8 Hz, 1H), 7.30-7.39 (m, 2H), 8.63 (br s, 1H).

A solution of 5-bromo-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one (0.3 g, 1.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.07 g, 0.06 mmol) in dimethoxyethane (8 $cm^3$) was stirred under $N_2$ for 20 min.. To this mixture was then added 3-nitrophenylboronic acid (0.23 g, 1.4 mmol) and sodium carbonate (0.36 g, 3.4 mmol) in water (3 $cm^3$). The solution was brought to reflux for 3 h then cooled to RT, poured into water and extracted with EtOAc (x 3). The combined organic extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, ethyl acetate: hexane 1:3) to afford the title compound (0.21 g, 0.68 mmol, 62%) as a yellow solid: m.p. 238-240 °C; $^1H$ NMR (DMSO-$d_6$) δ 1.89-1.99 (m, 8H), 6.96 (d, $J$ = 8.1 Hz, 1H), 7.58 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.66 (d, $J$ = 1.8 Hz, 1H), 7.71 (dd, $J$ = 8.0, 8.0 Hz, 1H), 8.13 (dd, $J$ = 7.0, 1.0 Hz, 2H), 8.4 (d, $J$ = 1.8 Hz, 1H), 10.42 ( br s, 1H); 13C NMR (dioxane-$d_8$) δ 26.31, 38.13 (t), 53.85 (s), 108.9, 121.15, 121.33, 126.23, 129.38, 132.11 (d), 132.6, 138.32, 141.84, 142.74, 149.14, 182.68 (s); MS (EI) *m/z* 308 $(M)^+$.

## EXAMPLE 14

**3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde**

Spiro[cyclohexane-1,3'-[3H]indol]-2'-(1'H)one

A solution of oxindole (25 g, 0.19 mol) in anhydrous tetrahydrofuran (800 $cm^3$) was cooled to -20°C, then *n*-butyllithium (2.5M in hexanes, 152 $cm^3$, 0.38 mol) was added slowly followed by *N,N,N',N'*-tetramethylethylenediamine (51 $cm^3$, 0.38 mol,). After 15 min. 1,5-*diiodopentane* (174 g, 0.54 mol) was added slowly and the mixture was allowed to warm to room temperature. After stirring for 16 h. saturated aqueous ammonium chloride solution (1L) and EtOAc (1L) were added. After 15 min. the layers were separated and the aqueous phase was extracted EtOAc (x2). The combined organic layers were extracted with hydrochloric acid (1N), then washed with brine (500 $cm^3$), dried ($MgSO_4$), and concentrated to obtain an oil. The oil was triturated with hexane (200 $cm^3$) and benzene (20 $cm^3$). The precipitate was collected and dried *in vacuo* to obtain the subtitled compound (26.3g, 69.6%) as colorless

crystals: mp 110-114°C; $^1$H NMR (DMSO-d6) δ 1.67 (m, 10H), 6.84 (d, 1H, $J$ = 8 Hz) 6.94 (t, 1H, $J$ = 8 Hz), 7.17 (t, 1H, $J$ = 8 Hz), 7.44 (d, 1H, $J$ = 8 Hz), 10.3 (s, 1H).

5'-Bromospiro[cyclohexane-1,3'-[3H] indol]-2'(1'H)-one

To a solution of spiro[cyclohexane-1,3'-[3H]indol]-2' (1'H)-one (17.6 g, 0.09 mol) in acetic acid (300 cm$^3$) was added sodium acetate (8.0 g, 0.1 mol) and bromine (14.6 g, 0.091 mol) with stirring. After 30 min. at room temperature, the reaction mixture was partitioned between water and EtOAc. The aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with water, dried ($MgSO_4$) and evaporated and the residue was triturated with hexane. The precipitate was collected, and dried *in vacuo* to obtain the subtitled compound (16.5g, 67%) as off-white crystals: mp 196 -199 °C; $^1$H NMR (DMSO-$d_6$) δ 1.62 (m, 10H), 6.8 (d, 1H, $J$ = 6.8 Hz), 7.36 (d, 1H, $J$ = 8.2, 1.8 Hz), 7.58 (dd, 1H, $J$ = 8.2, 1.8 Hz), 10.44 (s, 1H).

To a solution of 5'-bromospiro[cyclohexane-1,3'-[3H] indol]-2'(1'H)-one (1.00 g, 3.57 mmol) in dimethoxyethane (20 cm$^3$) was added tetrakis(triphenylphosphine)palladium (0.20 g, 0.17 mmol) under nitrogen. After 15 min. 3-formylphenylboronic acid (1.00 g, 6.93 g) was added followed by potassium carbonate (2.90 g, 21 mmol) in water (10 cm$^3$). After 20h at reflux, the mixture was cooled, poured into water and extracted with EtOAc (x3). The combined organic extract was washed with sat. brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc: hexane, gradient elution) to afford the title compound (0.66 g, 2.15 mmol, 60%) as a white solid, $^1$H NMR ($CDCl_3$) δ 1.65 – 1.85 (m, 6H), 1.86 - 2.08 (m, 4H), 7.22 (d, 1H, $J$ = 8 Hz), 7.48 (dd, 1H, $J$ = 8, 2 Hz), 7.61 (t, 1H, $J$ = 8 Hz), 7.66 (d, 1H, $J$ = 2 Hz), 7.81 - 7.88 ( m, 2H), 8.06 (t, 1H, $J$ = 2 Hz), 8.30 (s , 1H, br); MS ((+)ESI) *m/z* 306 $(M + H)^+$.

## EXAMPLE 15

### 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde oxime

To a solution of 3-(1',2'-dihydro-2'-oxospirocyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde (0.59 g, 1.95 mmol) in EtOH: $H_2O$ (10 $cm^3$, 8:2) was added hydroxylamine hydrochloride (0.17 g, 2.5 mmol) and sodium acetate (0.20 g, 2.5 mmol). After 20 min. the mixture was concentrated, water was added, and extracted with EtOAc (x2). The combined organic layers were washed with sat. sodium hydrogen carbonate solution, water, sat. brine, dried ($MgSO_4$) and evaporated to afford the title oxime (0.63 g, 1.95 mmol, 100%) which was used without further purification, $^1H$ NMR ($CDCl_3$) δ 1.60 - 1.84 (m, 6H), 1.85 - 2.00 (m, 4H), 6.86 (d, 1H, $J$ = 8 Hz), 7.36 (dd, 1H, $J$ = 8, 2 Hz), 7.43 - 7.50 (m, 1H), 7.57 - 7.67 (m, 2H), 7.85 (s, 1H, br), 8.25 (s, 1H), 8.68 (s, 1H, br), 8.94 (s, 1H, br); MS ((-)ESI) *m/z* 319 $(M - H)^-$.

## EXAMPLE 16

### 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl)benzaldehyde methyloxime ether

To a solution of 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde (0.24 g, 0.79 mmol), and sodium acetate (0.083 g, 1.00 mmol) in EtOH: water (5 $cm^3$, 8:2) was added methoxylamine hydrochloride (0.083 g, 1.00 mmol). After 30 min. the precipitate was isolated by filtration and washed with EtOH: water (8:2, x2), to afford the title compound (0.027 g, 0.08 mmol, 10%) as a white solid: mp 198 - 200 (decomp.): 1.58 - 2.07 (m, 10H), 4.00 (s, 3H), 6.98 (d, 1H, $J$ = 8 Hz), 7.42 - 7.49 (m, 2H), 7.53 - 7.58 (m, 2H), 7.64 (d, 1H, $J$ = 2 Hz), 7.75 (s, 1H), 8.07 (s, 1H, br), 8.15 (s, 1H); MS ((+)-ESI) m/z 335 $(M + H)^+$.

## EXAMPLE 17

### 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl)pyridine carbonitrile

A solution of 3-bromopyridine-5-carbonitrile (2.79 g, 15.26 mmol), hexamethylditin (5.00 g, 15.26 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.20 g, 0.17 mmol) in anhydrous dimethoxyethane (30 $cm^3$) under $N_2$ was heated

under reflux.. After 16 h the mixture was concentrated and purified by column chromatography ($SiO_2$, EtOAc: hexane 5:95) to afford 3-cyanopyridine-5-trimethylstannane (2.82 g, 10.55 mmol, 69%): $^1$H NMR ($CDCl_3$) δ 0.40 (s, 9H), 8.01 (m, 1H), 8.80 (m, 2H); MS ((+) APCI) m/z 269 $(M+H)^+$.

A solution of 5'-bromospiro[cyclohexane-1,3'-[3H] indol]-2'(1'H)-one (1.97 g, 7.05 mmol), 3-cyanopyridine-5-trimethylstannane (2.26 g, 8.46 mmol), bis(triphenylphosphine)palladium(II)chloride (0.33 g, 0.47 mmol) and lithium chloride (1.48 g, 35 mmol) in anhydrous toluene (30 $cm^3$) was heated under reflux. After 16h the mixture was cooled, partitioned between EtOAc and water, the aqueous layer was re-extracted with EtOAc (x 2), the combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated. The residue was subjected to column chromatography ($SiO_2$, EtOAc: hexane, 1:2) and then further purified by preparative LC (Primesphere C18, 10 micron, 50 x 250 mm, MeCN: $H_2O$ 1:1, 100 $cm_3$/min., RT 7.92 min.) to afford the title compound as white crystals (0.56 g, 1.84 mmol, 26%): mp. 232 - 234 °C, $^1$H NMR ($CDCl_3$) δ 1.68 - 1.89 (m, 6H), 1.93 - 2.13 (m, 4H), 7.12 (d, 1H, $J$ = 8 Hz), 7.49 (dd, 1H, $J$ = 8, 2 Hz), 7.66 (d, 1H, *2* Hz), 8.15 (t, 1H, $J$ = 2 Hz), 8.39 (s, 1H, br), 8.89 (d, 1H, $J$ = 2 Hz), 9.06 (d, 1H, $J$ = 2 Hz); MS ((+)-ESI) *m/z* 304 $(M+H)^+$.

## EXAMPLE 18

### 5'-(Pyrimidin-5-yl)-spiro[cyclohexane]-1,3'-[3H]indol-2'(1H)-one

To a solution of 5'-bromospiro [cyclohexane-1,3'-[3H]indol]-2'-(1'H)-one (11g, 0.04 mol) in dry tetrahydrofuran (200 $cm^3$) was added sodium hydride (60% dispersion in mineral oil, 1.6 g, 0.04 mol). After 30 min. stirring at room temperature, the mixture was cooled to -78°C and butyl lithium (1.7M in hexanes, 23.2 $cm^3$, 0.04 mol) was added slowly. After 30 min. di-*iso*-propylborate (25 $cm^3$, 0.11 mol) was added and the mixture was allowed to warm to room temperature. After 2 hrs. hydrochloric acid (1N, 500 $cm^3$) and ethylacetate (500 $cm^3$) were added. The aqueous phase was extracted with ethylacetate, then the combined organic layers were washed

with water, brine, dried ($MgSO_4$) and evaporated. The residue was triturated with hexane and the precipitate dried *in vacuo* to obtain (2'-oxo-2, 3-dihydrospiro[cyclohexane-1, 3'- [3H] indol] -5'-yl) boronic acid (8.3 g, 86%) as an off-white solid that was used without further purification. A sample that was further triturated with ethyl acetate had the following properties: mp. 255-260°C dec.; $^1H$ NMR (DMSO-d6) δ 1.50 (m, 2H), 1.73 (m, 8H), 6.82 (d, 1H, $J$ = 7.72 Hz) 7.66 (d, 1H, $J$ = 7.72 Hz) 7.91 (s, 3H, br), 10.36 (s, 1H);MS ((-)ESI) m/z 244 [M-H].

A stirred mixture of 5-bromopyrimidine (3.2g, 20 mmol) in toluene (20 $cm^3$), 2'-oxo-2,3-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'yl) boronic acid (0.49 g, 2.2 mmol) in ethanol (10 $cm^3$), potassium carbonate (0.28g, 2.0 mmol) in water (10 $cm^3$) and tetrakis (triphenylphosphine)palladium (0) (0.15 g, 0.13 mol) was heated overnight under reflux and in an atmosphere of nitrogen. The reaction mixture was treated with 20 mL of sodium bicarbonate solution and was then extracted with ethyl acetate (2x50mL). The combined organic phases were washed with saturated brine, dried ($MgSO_4$). Recrystallization from ethanol gave 0.13 g of pure product, mp 227 - 228 °C. IR (KBr) 1700 cm-1 $^1H$-NMR (DMSO-$d_6$) δ 10.48 (s, 1H), 9.13 (s,1H), 9.11 (s,2H), 7.86 (s, 1H) 7.63 (dd, 1H; $J$ = 1.5Hz and 8.1Hz), 6.98 (d, 1H $J$ = 8.1 Hz), 6.98 (d, 1H, $J$ = 8.1) 1.75 (m, 10); MS (ESI) *m/z* 278 (M-H).

## EXAMPLE 19

**5-(3-chlorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

Prepared according to the procedure for example 14: mp. 164-165 °C, $^1H$ NMR ($CDCl_3$) δ 1.60-1.78 (m, 6H), 1.81-1.99 (m, 4H), 7.04 (d, $J$ = 8.1 Hz, 1H), 7.22-7.47 (m, 4H), 7.53 (s, 1H), 7.61 (s, 1H), 9.28 (br s, 1H); $^{13}C$-NMR ($CDCl_3$) δ 20.17, 24.12, 31.92 (t), 47.22 (s), 109.21, 121.94, 124.06, 125.50, 125.79, 125.97, 126.38, 128.96 (d), 132.88, 133.59, 135.60, 139.14, 142.17, 182.89 (s); MS (EI) *m/z* 310, 312 $(M-H)^+$.

**EXAMPLE 20**

**5'-(3-Chloro-4-fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

Prepared according to the procedure for example 18: mp 188-189 °C; $^1$H-NMR ($CDCl_3$) δ 7.97 (s, 1H), 7.57 - 7.54 (m, 2H), 7.41 - 7.34 (m, 2H), 7.20 (t, 1H, *J* = 8.7 Hz), 9.96 (d, 1H, *J* = 8.1 Hz), 2.04 - 1.65 (m, 10H); MS ((+)APCI) *m/z* 330 $[M+H]^+$.

**EXAMPLE 21**

**5'-(3-Fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

Prepared according to the procedure for example 18: mp 171-172 °C; $^1$H-NMR ($CDCl_3$) δ 8.43 (s, 1H), 7.62 (d, 1H, *J* = 1.8 Hz), 7.42 (dt, 1H, *J* = 6.2, 2.0 Hz), 7.39 - 7.37 (m, 1 H), 7.33 (dt, 1H, *J* = 5.1, 1.3 Hz), 7.26 (dq, 1 H, *J* = 5.9, 2.1 Hz), 7.05 - 6.99 (m, 2H), 2.03 - 1.64 (m, 10H); MS ((+)APCI) *m/z* 296 $[M+H]^+$.

**EXAMPLE 22**

**5'-(3,5-Difluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

Prepared according to the procedure for example 18: mp 180-183 °C; $^1$H-NMR ($CDCl_3$) δ 8.35 (s, 1H), 7.59 (d, 1H, *J* = 2.0 Hz), 7.40 (dd, 1H, *J* = 6.2, 2.0 Hz), 7.10 - 7.03 (m, 2H), 6.99 (d, 1H, *J* = 8.1 Hz), 7.76 (tt, 1 H, *J* = 4.3, 2.3 Hz), 2.05 - 1.62 (m, 10H); MS ((+)APCI) *m/z* 314 $[M+H]^+$.

**EXAMPLE 23**

**5-(3,4-Difluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

Prepared according to the procedure for example 14: m.p. 187 – 189 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.5 – 2.0 (m, 10H), 6.9 (d, *J* = 8.13 Hz, 1H), 7.40 – 7.51 (m, 3H), 7.66 – 7.76 (m, 2H), 10.4 (s, 1H); MS (-ESI) *m/z* 312 $(M-H)^-$.

**EXAMPLE 24**

**5-[3-(Methylthio)phenyl]spiro [cyclo-hexane-1,3 -[3H] indol]-2(1H)-one**

Prepared according to the procedure for example 18: $^1$H NMR ($CDCl_3$) δ 1.62-2.06 (m, 10H), 2.54 (s, 3H), 6.96 (d, $J$ = 8.0 Hz , 1H), 7.2-7.5 (m, 5H), 7.62 (s, 1H), 7.75 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 16.37 (q), 21.62, 25.58, 33.37 (t), 48.67 (s), 110.55, 123.56, 124.36, 125.68, 126.94, 129.64 (d), 135.31, 136.91, 139.33, 140.27, 142.49, 184.29 (s); MS (EI) *m/z* 324 $(M+H)^+$.

**EXAMPLE 25**

**5'-[3-(Methysulfinylphenyl]spiro[cyclohexane-1,3' -[3H] indol]-2'(1'H)-one**

A solution of 5-[3-(Methylthio)phenyl]spiro[cyclo-hexane-1,3-[3H]indol]-2(1H)-one (0.15 g, 0.46 mmol) in methanol (6 $cm^3$) was treated with $NaIO_4$ (0.11 g, 0.51 mmol). The reaction was allowed to stir at RT overnight. The methanol was evaporated and the residue taken up in EtOAc (50 $cm^3$) and $H_2O$. The EtOAc layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, $CH_2Cl_2$:methanol, 8:2) to afford the title compound (0.11 g, 0.32 mmol, 70 %) as a white solid: m.p. 190-191 °C $^1$H NMR ($CDCl_3$) δ 1.65-2.05 (m, 10H), 2.80 (s, 3H), 7.02 (dd, $J$ = 8.0, 3.1 Hz , 1H), 7.46 (d, $J$ = 8.0 Hz , 1H), 7.52-7.75 (m, 4H), 7.0 (s, 1H), 8.7 (s, 1H); $^{13}$C NMR (DMSO-$d_6$) δ 21.59, 25.54, 33.44 (t), 44.38 (q), 48.46 (s), 110.53, 12.05, 123.31, 127.08, 129.94, 130.15 (d), 134.17, 137.2, 140.73, 143.27, 146.61, 183.71 (s); MS (EI) *m/z* 339 $(M)^+$.

**EXAMPLE 26**

**5-[3-(Methysulfonyl)phenyl]spiro[cyclohexane-1,3 -[3H] indol]-2(1H)-one**

A solution of the 5-[3-(Methylthio)phenyl]spiro[cyclo-hexane-1,3-[3H]-indol]-2(1H)-one (0.15 g, 0.46 mmol) in $CH_2Cl_2$ (2 $cm^3$) was added to a solution of

mCPBA (0.4 g, 2.3 mmol) in $CH_2Cl_2$ (5 $cm^3$) at RT. The reaction was allowed to stir overnight. The mixture was diluted with $CH_2Cl_2$ (50 $cm^3$) and washed with saturated bicarbonate solution, water, brine, dried ($MgSO_4$), and evaporated. The residue was crystallized (Hexane-EtOAc) to afford the title compound (0.132 g, 0.8 mmol, 80 %) as an off white solid: m.p. 240 °C; $^1H$ NMR ($CDCl_3$) δ 1.55-2.1 (m, 10H), 3.15 (s, 3H), 7.01 (d, $J$ = 8.1 Hz , 1H), 7.47 (dd, $J$ = 8.1, 1.5 Hz , 1H), 7.6-7.7 (m, 2H), 7.82-7.97 (m, 3H), 8.12 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$) δ 21.54, 25.50, 33.45 (t), 44.97 (q), 48.44 (s), 110.60, 123.28, 125.92, 127.20, 128.52, 130.31 (d), 132.46, 133.65, 137.34, 140.70, 141.53, 143.25, 183.63 (s); MS (EI) *m/z* 356 $(M+H)^+$.

## EXAMPLE 27

**5'-(3-Chloro-5-fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

Prepared according to the procedure for example 18: mp 178-180 °C; $^1H$-NMR ($CDCl_3$) δ 8.50 (s, 1H), 7.57 (d, 1H, $J$ = 1.8 Hz), 7.39 (dd, 1H, $J$ = 6.2, 1.9 Hz), 7.33 - 7.32 (m, 1 H), 7.15 (dq, 1H, $J$ = 5.7, 1.7, 0.7 Hz), 7.06 (dq, 1 H, $J$ = 4.2, 1.9, 0.4 Hz), 7.00 (d, 1H, $J$ = 8.1 Hz), 2.05 - 1.64 (m, 10H); MS ((-)ESI) $[M-H]^-$ @ m/z 328.

## EXAMPLE 28

**5-(3-Bromo-5-fluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

Prepared according to the procedure for example 18: mp. 194 - 196 °C; $^1H$ NMR ($CDCl_3$) δ 1.66 - 2.04 (m, 10H), 7.00 (d, 1H, $J$ = 8.0 Hz), 7.17 - 7.28 (m, 2H), 7.41 (dd, 1H, $J$ = 8, 1.8 Hz), 7.49 (t, 1H, $J$ = 1.4 Hz), 7.58 (d, 1H, $J$ = 1.5 Hz) and 8.24 (s, 1H, br); MS ((+)-EI) *m/z* 373/375 $[M^+]$.

## EXAMPLE 29

**5'-(3-Fluoro-5-methylphenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

A solution of 3-fluoro-5-methoxybenzene trifluoromethanesulfonate (1.6 g, 5.8 mmol) and tetrakis- (triphenylphosphene)-palladium(0) (0.33 g, 286 mmol) in

dimethoxyethane (50 mL) was stirred under $N_2$ for 20 minutes. To this mixture was then added lithium bromide (1.5 g, 172 mmol). This solution was stirred under $N_2$ for 10 minutes. To this mixture was then added (2'-oxo-2, 3-dihydrospiro[cyclohexane-1, 3'- [3H] indol] -5'-yl) boronic acid (1.3 g, 5.7 mmol) and sodium carbonate (1.2 g, 11.5 mmol) in distilled water (5 mL). The solution was brought to reflux for 6 hours, cooled to room temperature, poured into distilled water and extracted with EtOAc (x 3). The combined organic extracts were washed with 2N NaOH, water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc:Hexane 2:5) to afford the title compound (0.6 g, 32%) as an off-white solid: mp 180-182 °C; $^1$H-NMR ($CDCl_3$) δ 8.21 (s, 1H), 7.60 (d, 1H, $J$ = 1.8 Hz), 7.41 (dd, 1H, $J$ = 6.2, 1.9 Hz), 6.97 (d, 1H, $J$ = 7.9 Hz), 6.88 - 6.86 (m, 1H), 6.84 (t, 1H, $J$ = 1.8 Hz), 6.59 (dt, 1H, $J$ = 6.2, 2.2 Hz), 3.86 (s, 3H), 2.00 - 1.62 (m, 10H); MS ((-ESI) $[M-H]^-$ @ m/z 324.

## EXAMPLE 30

**5'-(3-Nitrophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

Prepared according to the procedure for example 14: mp. 196-198 °C, $^1$H NMR ($CDCl_3$) δ 1.67 - 1.81 (m, 6H), 1.82 - 2.05 (m, 4H), 7.04 (d, 1H, $J$ = 8 Hz), 7.48 (dd, 1H, $J$ = 8 and 1 Hz), 7.59 (d, 1H, $J$ = 8 Hz), 7.63 - 7.65 (m, 1H), 7.87 - 7.90 (m, 1H), 8.16 - 8.20 (m, 1H), 8.38 (s, br, 1H), 8.41 (t, 1H, $J$ = 2 Hz); MS ((-)ESI) *m/z* 321 $(M-H)^-$.

## EXAMPLE 31

**3-(1,2-Dihydro-2-oxospiro[cyclohexyane-1,3-[3H]indol]-5-yl)aniline**

A solution of 5'-(3-Nitrophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one (3.6g, 11mmol) in methanol (150ml) was shaken with 10% palladium on charcoal (1g) under a hydrogen atmosphere at 40 psi. The catalyst was filtered off and the solution was concentrated to obtain a residue. The residue was dissolved in ether and ethanolic hydrochloric acid was added. The solid thus obtained was recrystallized

from methanol/ether to obtain the title compound (1.7g, 47%): m.p. 275-278°C; $^1$H-NMR (DMSO-$d_6$) δ 1.5-2.0 (m, 10H), 6.98 (d, $J$ = 8.05Hz, 1H), 7.26 (d, $J$ = 7.90 Hz, 1H), 7.45-7.62 (m, 4H), 7.67 (d, $J$ = 8.3 Hz, 1H), 9.0-11.0 (s, 2H, br), 10.5 (s, 1H), MS ((+)APC1) m/z 293 (M+H).

**EXAMPLE 32**

**5-(3-Fluoro-5-nitrophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

Prepared according to the procedure for example 18: mp. 191-193 °C; $^1$H NMR ($CDCl_3$) δ 1.66 - 2.07 (m, 10H), 7.07 (d, 1H, $J$ = 8 Hz), 7.49 (dd, 1H, $J$ = 8, 1.8 Hz), 7.59 - 7.64 (m, 2H), 7.89 (dt, 1H, $J$ = 8.1, 2.1 Hz), 8.25 (s, 1H) and 8.54 (s, 1H); MS ((+)-APCI) *m/z* 341 $[M+H]^+$.

**EXAMPLE 33**

**5'-(3-Hydroxyphenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

Prepared according to the procedure for example 18: mp. 213 - 216 °C; $^1$H NMR ($CDCl_3$) δ 1.60-1.96 (m, 10H), 6.78 - 6.82 (m, 1H), 6.94 (d, 1H, $J$ = 8 Hz), 7.01 - 7.04 (m, 2H), 7.23 (t, 1H, $J$ = 7.7 Hz), 7.38 (d, 1H, $J$ = 8 Hz), 7.61 (s, 1H), 8.91 (s, 1H) and 9.73 (s, 1H, br); MS ((+)-APCI) *m/z* 294 $[M+H]^+$.

**EXAMPLE 34**

**4-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-2-thiophenecarbonitrile**

3-(Trimethylstannyl)-2-thiophenecarbonitrile

A solution of 3-bromo-2-thiophenecarbonitrile (0.8 g, 4.3 mmol), tetrakis(triphenylphosphine)palladium(0) (0.25 g, 0.2 mmol) and hexamethylditin (1.4 g, 4.3 mmol) in dimethoxyethane (5 $cm^3$) was heated under reflux for 14 hours then cooled to room temperature. The reaction mixture was absorbed onto florisil and purified by column chromatography ($SiO_2$, methylene chloride: hexane 1:9) to afford

the title compound (1.04 g, 3.8 mmol, 90%) as a clear viscous oil: $^1$H NMR ($CDCl_3$) δ 0.35 (s, 9H), 7.56 (d, $J$ = 0.9 Hz, 1H), 7.66 (d, $J$ = 0.9 Hz, 1H).

A solution of the 5'-bromospiro[cyclohexane-1,3'-[3H] indol]-2'(1'H)-one (0.53 g, 1.9 mmol), dichlorobis(triphenylphosphine) palladium(II) (0.1 g, 0.14 mmol) and triphenylarsine (0.14 g, 0.47 mmol) in dimethoxyethane (8 $cm^3$) was stirred under $N_2$ for 20 min.. To this mixture was then added 3-(trimethylstannyl)-2-thiophenecarbonitrile (0.64 g, 2.35 mmol). The solution was brought to reflux for 32 h. After cooling to room temperature the reaction mixture was absorbed onto florisil and purified by column chromatography ($SiO_2$, ethyl acetate: hexane 2:3) to afford the title compound (0.43 g, 1.39 mmol, 74%) as an off white solid: $^1$H NMR ($CDCl_3$) δ 1.56-2.1 (m, 10H), 6.97 (d, $J$ = 8.0 Hz, 1H), 7.39 (dd, $J$ = 8.03, 1.45 Hz, 1H), 7.57 (d, $J$ = 1.45 Hz, 1H), 7.59 (d, $J$ = 1.4 Hz, 1H), 7.84 (d, $J$ = 1.4 Hz, 1H), 8.32 (br s, 1H); 13C-NMR ($CDCl_3$) δ 22.07, 26.56, 34.4 (t), 48.13 (s), 110.18 (d), 111.3, 114.75 (s), 122.92, 126.76 (d), 128.44 (s), 137.55 (d), 138.11, 142.71, 144.49, 182.13 (s); MS (EI) *m/z* 307 (M-H)+.

## EXAMPLE 35

## 5-(2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'yl-2-thiophenecarbonitrile

5-Bromo-2-thiophenecarbonitrile. A mixture of 5-bromo-2-thiophenecarboxaldehyde (96.0g, 500 mmol), hydroxylamine hydrochloride (111.9 g, 500 mmol), pyridine (500 mL), and ethanol (500 mL) was heated under nitrogen at reflux for two hours. The reaction mixture was cooled to ambient temperature and concentrated *in vacuo* to give an oil. The crude product was triturated twice with ice water and the solid obtained was collected on a filter. A mixture of a portion of the above solid (44.31 g, 215 mmol), copper (II) acetate monohydrate (4.2 g, 21 mmol) in acetonitrile (1.4L) was heated at reflux for three hours. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed with 5% aqueous sulfuric acid (2X30 mL), water (2X30 mL), brine (20 mL), and dried

($MgSO_4$). The solvent was removed *in vacuo* and the residue was dissolved in a minimum amount of chloroform (1L) and allowed to crystallize. The crystal obtained was collected on a filter and the filtrate was concentrated and purified by a chromatography (silica gel, chloroform) to give the subtitled compound as an off-white solid (31.5g combined, 58%).: IR (film) $cm^{-1}$ 2200; $^1$H-NMR ($CDCl_3$) δ 7.39-7.38 (d, 1H, $J$ = 4. 1 Hz), 7.10 (d, 1H, $J$ = 4.0 Hz); MS (EI) *m/z* 187 ($M^+$, 98%) 189($M^+$, 100%).

The title compound was prepared according to the procedure for example 18 using 5-bromo-2-thiophenecarbonitrile and (2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'-yl) boronic acid: mp. 225-228°C; $^1$H NMR (DMSO-$d_6$) δ 1.63 (m, 8H), 1.90 (m, 2H) 6.91 (d, 1H, $J$ = 8.13 Hz), 7.55 (dd, 1H, $J$ = 8.13 , 1.76Hz), 7.60 (d, 1H, $J$ = 4.17 Hz), 7.75 (d, 1H, $J$ = 1.76 Hz), 7.93 (d, 1H, $J$ = 4.17 Hz), 10.51 (s, 1H); MS ((+)APC1) *m/z* 309 $[M + H]^+$.

## EXAMPLE 36

**4-Methyl-5-(2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol-5'-yl)-2-thiophene carbonitrile**

Prepared according to the procedure for example 18: m.p. 200-203°C; $^1$H NMR (DMSO-$d_6$) δ 1.63 (m, 8H), 1.87 (m, 2H), 2.27 (s, 3H), 6.95 (d, 1H, $J$ = 8.13 Hz), 7.34 (dd, 1H, $J$ = 8.13, 1.98 Hz) 7.54 (d, 1H, $J$ = 1.98 Hz), 7.82 (s, 1H) 10.50 (s, 1H); MS ((+)APC1) *m/z* 323 $[M + H]^+$.

## EXAMPLE 37

**4-Ethyl-5-(2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-2-thiophenecarbonitrile**

Prepared according to the procedure for example 18: mp 214 - 217 °C. $^1$H NMR (DMSO-$d_6$) δ 10.55 (s, 1H), 7.95 (s, 1H), 7.51 (s, 1H), 7.33 - 7.30 (m, 1H), 6.98 - 6.96 (d, 2H $J$ = 8.0 Hz), 2.67 - 2.62 (m, 2H), 1.89 - 1.86 (m, 2H), 1.69 - 1.55 (m,

8H), 1.20 - 1.15 (t, 3H); MS ((+)APCI) *m/z* 337 $[M+H]^+$. Anal.Calc. For $C_{20}H_{20}N_2OS.1/2\ H_2O$: C, 69.54;H, 6.13 ; N, 8.11. Found: C, 69.51 ;H, 6.06; N, 7.57.

**EXAMPLE 38**

**5-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-thiophene-3-carbonitrile**

Prepared according to the procedure for example 18: m.p. 188 – 190 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.5 – 2.0 (m, 10H), 6.89 (d, $J$ = 7.91 Hz, 1H), 7.49 (dd, $J$ = 7.91, 1.98 Hz, 1H), 7.75 (d, $J$ = 1.76 Hz, 1H), 7.86 (d, $J$ = 1.32 Hz, 1H), 8.44 (d, $J$ = 1.32 Hz, 1H); MS (-ESI) *m/z* 307 (M-H).

**EXAMPLE 39**

**2-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-thiophene-2-carbonitrile**

Prepared according to the procedure for example 18: m.p. 207 – 9 °C; $^1$H-NMR (DMSO-$d_6$) δ 1.4 – 2.0 (m, 10H), 7.0 (d, $J$ = 8.13 Hz, 1H), 7.48 (d, $J$ = 5.27 Hz, 1H), 7.54 (dd, $J$ = 8.13 Hz, 1.98 Hz, 1H), 7.71 (d, $J$ = 5.49 Hz, 1H), 7.85 (d, $J$ = 1.76 Hz, 1H), 10.6 (s, 1H); MS (-ESI) *m/z* 307 (M-H).

**EXAMPLE 40**

**5-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-3-furancarbonitrile**

Prepared according to the procedure for example 18: m.p. 243 – 245 °C. $^1$H-NMR (DMSO-$d_6$) δ 10.48 (s, 1H), 8.62 (d, 1H $J$ = 0.7 Hz), 7.76 (d, 1H $J$ = 1.5 Hz), 7.58 -7.55 (dd, 1H), 7.33 (d, 1H $J$ = 0.7 Hz), 6.92 - 6.90 (d, 1H $J$ = 8.1 Hz), 1.87 - 1.83 (m, 2H), 1.73 - 1.53 (m, 8H). MS ((+)EI) *m/z* 292 (M+).

**EXAMPLE 41**

**5-(5-Chloro-2-thienyl)spiro[cyclohexane-1,3-[3H] indol]-2(1H)-one**

Prepared according to the procedure for example 18: m.p. 191-192°C; $^1$H NMR ($CDCl_3$) δ 1.6-2.1 (m, 10H), 6.85-6.95 (m, 2H), 6.98 (d, $J$ = 4.0 Hz, 1H), 7.36 (dd, $J$ = 7.5, 1.6 Hz, 1H), 7.53 (d, $J$ = 0.9 Hz, 1H), 7.80 (br s, 1H),; $^{13}$C-NMR (THF-$d_8$) δ 21.35, 25.33, 33.12 (*t*), 48.32 (s), 110.40, 121.66, 121.96, 125.44, 127.25 (d), 128.17, 128.43, 136.92, 140.20, 143.43, 183.72 (s); MS (EI) *m/z* 318 $(M+H)^+$.

**EXAMPLE 42**

**5-(5-Acetyl-2-thienyl)spiro[cyclohexane-1,3-[3H] indol]-2(1H)-one**

Prepared according to the procedure for example 18: m.p. 195-196 °C , $^1$H NMR ($CDCl_3$) δ 1.6-2.1 (m, 10H), 2.58 (s, 3H), 6.95 (d, $J$ = 8.1 Hz , 1H), 7.25 (d, $J$ = 4.0 Hz, 1H), 7.54 (dd, $J$ = 8.1, 1.7 Hz, 1H), 7.66 (d, $J$ = 4.0 Hz, 1H), 7.7 (d, $J$ = 1.7 Hz, 1H), 7.9 (br s, 1H),; $^{13}$C NMR ($CDCl_3$) δ 22.24, 26.19 (t), 27.59 (q), 33.99 (t), 49.02 (s), 111.39, 123.45, 124.12, 127.02 (d), 128.59 (s), 134.79 (d), 137.92, 142.23, 143.41, 154.47, 184.51, 191.76 (s); MS (EI) *m/z* 326 $(M+H)^+$.

**EXAMPLE 43**

**5-(2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'yl-2-nitro-thiophene**

Prepared according to the procedure for example 11: mp. 242 °C (decomp.); $^1$H NMR (DMSO-$d_6$) δ 1.62 - 1.67 (m, 6H), 1.90 - 1.99 (m, 2H), 6.94 (d, 1H, $J$ = 8.1 Hz), 7.64 (d, 1H, $J$ = 4.5 Hz), 7.67 (dd, 1H, $J$ = 8.2, 1.8 Hz), 7.86 (d, 1H, $J$ = 1.5 Hz), 8.15 (d, 1H, $J$ = 4.5 Hz), 10.62 (s, 1H); MS (EI) *m/z* 328 $(M)^-$.

**EXAMPLE 44**

**5'-(5-Nitro-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

2-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester

To a solution of 5'-bromo-spiro[cyclohexane-1,3'-indolin]-2'-one (3.4 g, 12 mmol) in 1,2-DME (100 mL) under a nitrogen atmosphere was added

tetrakis(triphenylphospine)palladium(0) (70 mg, 5 mol%). After 15 min, 2-borono-1H-pyrrole-1-carboxylic acid, 1-tert butyl ester (1.3 eq, 3.31 g, 15.6 mmol) and a solution of $K_2CO_3$ (2.3 eq, 3.83 g, 27.6 mmol) in water (5 mL) were added sequentially. The solution was heated to 80 °C for 3 h and allowed to cool. The reaction mixture was poured into water (200 mL) and extracted with EtOAc (2 x 100 mL). The organic layers were combined, washed with brine (150 mL) and dried over $MgSO_4$. The solution was filtered, concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (eluting with 30% EtOAc/hexane) to give subtitled compound: (3.4 g, 76%) as a white powder, mp 177 °C. $^1H$ NMR ($CDCl_3$; 300 MHz) δ 1.38 (s, 9 H), 1.59-1.93 (m, 10 H), 6.18 (m, 1 H), 6.23 ('t', 1H, 3 Hz), 6.91 (d, 1 H, *J*=8 Hz), 7.21 (d, 1 H, *J*=8 Hz), 7.34 (m, 1 H), 7.44 (s, 1 H), 8.33 (br s, 1 H, $D_2O$ex). MS ((+)-APCI) *m/z* 367 [$(M+H)^+$]. Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 71.7; H, 7.16; N, 7.5.

2-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-nitro-1H-pyrrole-1-carboxylic acid, tert-butyl carbamate.

To a solution of 2-(1',2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester (72 mg, 0.2 mmol) in MeCN (5 mL) at room temperature was added silver nitrate (1.05 eq, 35 mg, 0.2 mmol). After 5 min, acetyl chloride (1.0 eq, 15 mg, 0.2 mmol) in MeCN (5 mL) was added and the solution was allowed to stir for 16h. Dichloromethane (10 mL) was added, and the solution was filtered through celite and washed sequentially with water, sat. $NaHCO_3$, water and brine (10 mL of each). The solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluting with 40% EtOAc/hexane) to give the subtitled compound (56 mg, 70%) as a yellow oil which crystallized from acetone/hexane, mp 163 °C (dec).

2-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-nitro-1H-pyrrole-1-carboxylic acid, tert-butyl ester (0.31 g, 0.85 mmol) was placed in a 5 mL round bottomed flask stoppered with a rubber septum and equipped with nitrogen inlet and a needle to allow gaseous outflow. A vigorous flow of nitrogen was

maintained as the flask was placed in an oil bath and heated to 200 °C. After 5 min at this temperature, the flask was removed from the oil bath and allowed to cool. The black residue was washed into a larger flask with acetone and adsorbed onto a small amount of silica gel. Purification by flash column chromatography on silica gel (eluting with 40% EtOAc/hexane) gave the title carbamate (0.20 g, 85%) as a yellow oil which crystallized from acetone/hexane, mp 278 °C (dec). $^1$H NMR (DMSO-$d_6$; 300 MHz) δ 1.55-1.87 (m, 10H), 6.80 (d, 1H, *J*=4 Hz), 6.91 (d, 1H, *J*=8 Hz), 7.27 (d, 1H, *J*=4 Hz), 7.77 (dd, 1H, *J*=8, 1 Hz), 8.04 (d, 1H, *J*=1 Hz), 10.51 (s, 1 H), 13.21 (br s, 1 H). MS ((+)-APCI) *m/z* 312 [(M+H)$^+$]. Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.5; N, 13.5. Found: C, 65.57; H, 5.54; N, 13.44.

## EXAMPLE 45

**5'-(5-Nitro-1-methyl-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

**5'-(1-Methyl-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

A mixture of 5'-(1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one (0.46 g, 1.7 mmol) and potassium carbonate (5 eq, 1.18 g, 8.6 mmol) in DMF (2 mL) at room temperature was treated with a solution of iodomethane (3 eq, 0.32 g, 5.1 mmol) in DMF (1 mL). The solution was stirred 16 h at room temperature, then poured into water (10 mL). EtOAC (15 mL) was added, the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 100 mL). The organic layers were combined, washed with brine (15 mL) and dried over $MgSO_4$. The solution was filtered, concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (eluting with 40% EtOAc/hexane) to give the subtitled compound (0.44 g, 76%) as a white powder, mp 148-9 °C. $^1$H NMR (DMSO-$d_6$; 400 MHz) δ 1.50-1.62 (m, 3 H), 1.62-1.82 (m, 5 H), 1.83-1.94 (m, 2 H), 3.11 (s, 3 H), 6.08 (m, 1H), 6.42 (m, 1 H), 6.79 (m, 1 H), 6.97 (d, 1 H, *J*=8.1 Hz), 7.51 (dd, 1 H, *J*=8.1, 1.8 Hz), 7.70 (d. 1 H, *J*=1.7 Hz), 11.20 (br s, 1 H). Anal. Calcd for $C_{18}H_{20}N_2O_1$: C, 77.11; H, 7.19; N, 9.98. Found: C, 76.44; H, 7.21; N, 9.96.

A mixture of 5'-(1-methyl-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one (0.36 g, 1.3 mmol) and silver nitrate (1.1 eq, 0.24 g, 1.4 mmol) in acetonitrile (10 mL) at room temperature was treated with acetyl chloride (1.1 eq, 0.1 mL, 1.4 mmol). The mixture was stirred 1 h at this temperature and then dichloromethane (30 mL) was added and the mixture was filtered through celite. The organic phase was washed sequentially with water (20 mL), sat. aq. $NaHCO_3$ (20 mL), and brine (20 mL). The solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluting with 40% EtOAc/hexane) to give the title compound (21 mg, 5%) as a yellow powder, mp 210 °C. $^1H$ NMR (DMSO-$d_6$; 300 MHz) δ 1.55-1.97 (m, 10H), 3.15 (s, 3H), 6.77 (dd, 1H, *J*=4.2, 2.3 Hz), 7.05 (d, 1H, *J*=8.2 Hz), 7.21 (dd, 1H, *J*=4.2, 2.3 Hz), 7.83 (dd, 1H, *J*=1.8, 8.2 Hz), 8.0 (d, 1H, *J*=1.8 Hz), 13.0 (br s, 1 H). MS ((+)-APCI) *m/z* 326 [(M+H)$^+$]. Anal. Calcd for $C_{18}H_{19}N_3O_3$: C, 65.45; H, 5.89; N, 12.91. Found: C, 64.66; H, 5.76; N, 12.52.

## EXAMPLE 46

**5'-(1H-Indol-4-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

Prepared according to the procedure for example 18: mp 211-213 °C; $^1H$-NMR ($CDCl_3$) δ 8.32 (s, 1H), 7.84 (s, 1H), 7.81 (d, 1H, J = 1.8 Hz), 7.55 (dd, 1 H, J = 6.2, 1.8 Hz), 7.40 (dt, 1H, J = 6.2, 1.0 Hz), 7.29 - 7.28 (m, 1H), 7.27 (t, 1H, J = 3.1 Hz), 7.18 (dd, 1H, J = 6.4, 0.9 Hz), 7.00 (dd, 1H, J = 7.5, 0.4 Hz), 6.72 - 6.71 (m, 1H), 2.00 - 1.59 (m, 10H); MS ((+)APCI) [M+H]$^+$ @ m/z 317.

## EXAMPLE 47

**3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzonitrile**

A solution of 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl)benzaldehyde oxime (0.48 g, 1.49 mmol) in chloroform (10 cm$^3$) was treated with selenium dioxide (0.38 g, 3.50 mmol) and heated under reflux. After 16 h, the mixture was concentrated and the residue purified by column chromatography ($SiO_2$,

EtOAc: hexane 1:4) and the product re-crystallized from EtOAc-hexane to afford the title compound (0.161 g, 0.53 mmol, 35%) as a white solid: mp. 190 - 191 °C; $^1$H NMR ($CDCl_3$) δ 1.59 - 1.87 (m, 6H), 1.88 - 2.09 (m, 4H), 7.03 (d, 1H, $J$ = 8 Hz), 7.42 (dd, 1H, $J$ = 8, 2 Hz), 7.54 (t, 1H, $J$ = 8 Hz), 7.58 - 7.65 (m, 2H), 7.78 (dt, 1H, $J$ = 7, 2 Hz), 7.83 (m, 1H), 8.26 (s, 1H, br); MS ((+) ESI) *m/z* 303 $(M + H)^+$.

**EXAMPLE 48**

**3-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-5-fluorobenzonitrile**

To a solution of 3,5-dibromofluorobenzene in diethyl ether (100 cm$^3$) at -78 °C was added *n*-butyl lithium (2.5 M, 8 cm$^3$, 20 mmol) dropwise. After 30 min. the mixture was treated with DMF (20 cm3) in diethyl ether (10 cm3) and stirring was continued at -78 °C. After 30 min. the mixture was quenched with dilute HCl aq., separated and the aqueous layer was extracted with EtOAc. The combined organic layers were combined, washed with water, brine, dried ($MgSO_4$) and evaporated to give 3-fluoro-5-bromobenzaldehyde (4.0 g, 19.7 mmol, 100%) as an oil: $^1$H NMR ($CDCl_3$) δ *inter alia* 7.50 - 7.53 (m, 2H), 7.82 (s, 1H) and 9.93 (m, 1H); MS (EI) *m/z* 202, 204 [M$^+$].

To a solution of the last cited compound (4.0 g, 19.7 mmol) in ethanol:water (8:2, 50 cm$^3$), was added sodium acetate (1.72 g, 21 mmol) and hydroxylamine hydrochloride (1.45 g, 21 mmol), and the mixture was heated under reflux. After 30 min., the mixture was cooled, evaporated and the residue partitioned between water and EtOAc. The aqueous layer was re-extracted with EtOAc and the combined organic layers were washed with water, saturated sodium hydrogen carbonate solution, brine, dried ($MgSO_4$) and evaporated to give 3-fluoro-5-bromobenzaldehyde oxime (3.76 g, 17.24 mmol, 87%) which was used without further purification: $^1$H NMR ($CDCl_3$) δ 7.24 - 7.27 (m, 2H), 7.50 (s, 1H), 7.68 (s, 1H) and 8.04 (s, 1H); MS (EI) *m/z* 217 [M$^+$].

The above oxime (3.76 g, 17.24 mmol) and copper (II) acetate (370 mg) were dissolved in acetonitrile (100 cm$^3$) under nitrogen and heated under reflux. After 5h,

the mixture was evaporated, the residue taken into EtOAc, washed with sulfuric acid (1N), water, brine, dried ($MgSO_4$) and evaporated to give 3-fluoro-5-bromobenzonitrile (3.08 g, 15.39 mmol, 89%) which was used without further purification.

The above bromide (3.0 g, 15 mmol) and tetrakis(triphenylphosphine)palladium (0) (0.86 g, 0.75 mmol) were dissolved in dimethoxyethane (130 $cm^3$) under nitrogen. After 15 min. (2'-oxo-2, 3-dihydrospiro[cyclohexane-1, 3'- [3H] indol] -5'-yl) boronic acid (2.82 g, 11.5 mmol) and sodium carbonate (3.1 g, 29.3 mmol) dissolved in water (40 $cm^3$) were added, and the mixture heated under reflux. After 8h the mixture was cooled, poured into water and extracted with EtOAc (x3). The combined organic layers were then washed with water, dried ($MgSO_4$) and evaporated. The residue was then purified by column chromatography (EtOAc: hexane, gradient elution), and the product recrystallized from methanol to give 3-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-5-fluorobenzonitrile (1.78 g, 5.55 mmol, 48%): mp 199 - 205 °C; $^1H$ NMR ($CDCl_3$) δ 1.64 -2.03 (m, 10H), 7.03 (d, 1H, $J$ = 8 Hz), 7.31 (dt, 1H, $J$ = 7.7 and 1.6 Hz), 7.41 (dd, 1H, $J$ = 8, 1.7 Hz), 7.49 (dt, 1H, $J$ = 9.6, 2 Hz), 7.58 (d, 1H, $J$ = 2 Hz), 7.64 (s, 1H) and 8.37 (s, 1H): MS (EI) *m/z* 320 [$M^+$].

## EXAMPLE 49

**3-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-4-fluorobenzonitrile**

Prepared according to the procedure for example 18: m.p. 205 – 206 °C. $^1H$ NMR (DMSO-$d_6$) δ 10.47 (s,1H), 8.08 - 8.06 (dd, 1H), 7.89 - 7.85 (m, 1H), 7.65 (s, 1H), 7.54 -7.49 (m, 1H), 7.43 - 7.40 (tt, 1H), 6.95 - 6.93 (d, 1H $J$ = 7.9 Hz), 1.97 - 1.83 (m, 2H), 1.69 - 1.55 (m, 8H); MS (EI) *m/z* 320 ($M^+$)

## EXAMPLE 50

**3-(1'-Diethoxymethyl-1', 2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluorobenzonitrile**

A solution of 3-(1', 2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluorobenzonitrile (1.0 eq, 0.27 g, 0.84 mmol) in triethylorthoformate (2 mL, 12 mmol) was heated to 150 °C for 1 h. The reaction mixture was allowed to cool, the excess triethylorthoformate was removed *in vacuo*, and the residue was purified by flash column chromatography on silica gel (eluting with 10% EtOAc/hexane) to give the title compound (0.2 g, 56%) as a white powder, mp 146 °C. $^1$H NMR (DMSO-$d_6$; 400 MHz) δ 1.13 (t, 6 H, *J*= 7 Hz), 1.60-1.96 (m, 10 H), 3.48 (m, 2 H), 3.66 (m, 2 H), 6.17 (s, 1H), 7.35 (d, 1 H, *J*= 8.3 Hz), 7.68 (dd, 1 H, *J*= 2.0, 8.3 Hz), 7.77 (ddd, 1 H, *J*= 1.3, 2.4 Hz), 7.89 (d, 1 H, *J*= 2.0 Hz), 7.92 (dt, 1 H, *J*= 2.4, 10.5 Hz)8.08 (dd, 1H, *J*= 1.3, 2.9 Hz). MS ((+)-EI) *m/z* 422 [M$^+$]. Anal. Calcd for $C_{25}H_{27}FN_2O_3$: C, 71.07; H, 6.44; N, 6.63. Found: C, 70.75; H, 6.48; N, 6.52.

## EXAMPLE 51

**3-(7'-Bromo-1', 2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluoro-benzonitrile**

A mixture of 3-(1',2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluorobenzonitrile (0.40 g, 1.23 mmol) and potassium acetate (0.13 g, 1.3 mmol) in glacial acetic acid (3 mL) at room temperature was treated with a solution of bromine (1.05 eq, 0.21 g, 1.3 mmol) in a glacial acetic acid (3 mL). After stirring for 1 h the mixture was poured onto ice (20 g). The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 10 mL). The organic layers were combined, washed sequentially with 10% aqueous sodium thiosulfate (20 mL), water (2 x 10 mL), saturated sodium bicarbonate (10 mL) and brine (15 mL) and dried over $MgSO_4$. The solution was filtered, concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (eluting with 30% EtOAc/hexane) to give the title compound (0.21 g, 43%) as an oil which crystallized upon addition of 10% EtOAc/hexanes, mp 217 °C. $^1$H NMR ($CDCl_3$; 300 MHz) δ 1.56-2.04 (m, 10 H), 7.33 (dddd, 1 H, *J*= 1.25, 2.3, 3.6 and 9.0 Hz), 7.45 (m, 1 H), 7.47 (m, 2 H), 7.54 (m, 1H),

7.60 (m, 1 H). MS ((–)-ESI) *m/z* 399 [M⁻]. Anal. Calcd for $C_{20}H_{16}BrFN_2O_1$: C, 60.17; H, 4.04; N, 7.02. Found: C, 60.03; H, 4.08; N, 6.83.

## EXAMPLE 52

**3-(7'-Nitro-1', 2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluoro-benzonitrile**

A mixture of 3-(1',2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluorobenzonitrile (0.19 g, 0.6 mmol) and silver nitrate 0.11 g, 0.6 mmol) in trifluoroacetic acid (5 mL) was stirred 1 h at room temperature and then poured onto ice (20 g). Ether (15 mL) was added, the layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined and washed sequentially with water (2 × 20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine (15 mL) and dried over $MgSO_4$. The solution was filtered, concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (eluting with 20% EtOAc/hexane) to give the title compound (0.2 g, 94%) as a white powder, mp 196 °C. $^1$H NMR (DMSO-$d_6$; 400 MHz) δ 1.46-1.58 (m, 1 H), 1.62-1.77 (m, 5 H), 1.83 (m, 2 H), 1.92-2.20 (m, 2 H), 7.85 (dddd, 1H, *J*= 1.3, 2.4, 3.7 and 8.6 Hz), 8.12 (dddd, 1 H, *J*= 1.8, 2.4, 4.2 and 10.5 Hz), 8.23 (m, 2 H), 8.36 (d, 1 H, *J*= 2.0 Hz), 11.17 (bs, 1 H). MS ((–)-APCI) *m/z* 365 [M⁻]. Anal. Calcd for $C_{20}H_{16}FN_3O_3$: C, 65.75; H, 4.41; N, 11.5. Found: C, 65.4; H, 4.54; N, 11.3.

## EXAMPLE 53

**3-(7'-Amino-1', 2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluoro-benzonitrile**

To a solution of 3-(7'-nitro-1', 2'-dihydro-2'-oxospiro-[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluorobenzonitrile (1.0 eq, 0.16 g, 0.4 mmol) in glacial acetic acid (4 mL) at room temperature was added a solution of tin (II) chloride dihydrate (0.25 g, 1.1 mmol) in hydrochloric acid (2 mL). The yellow mixture was boiled for 30 min at which point the yellow color disappeared. After cooling to room temperature, 1N HCl

(10 mL) and ether (20 mL) were added. The layers were separated and the aqueous phase was extracted with ether (2 × 20 mL). The organic layers were combined, washed sequentially with water (2 × 20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL). The solution was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (eluting with 40% EtOAc/hexane) to give the title compound (70 mg, 50%) as an oil which crystallized upon addition of 10% EtOAc/hexanes, mp 241-3 °C. $^1$H NMR (DMSO-$d_6$; 400 MHz) δ 1.50-1.75 (m, 8H), 1.82-1.95(m, 2H), 4.98 (s, 2H), 6.90 (d, 1H, *J*= 1.8 Hz), 7.09 (d, 1H, *J*= 1.5 Hz), 7.75 (m, 2H), 7.90 ('s', 1H), 9.96 (bs, 1H). MS ((+)-APCI) *m/z* 336 [(M+H)$^+$]. Anal. Calcd for $C_{20}H_{18}FN_3O$: C, 71.63; H, 5.41; N, 12.18. Found: C, 71.16; H, 5.58; N, 12.18.

## EXAMPLE 54

**5-(3-cyano-4-fluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

Prepared according to the procedure for example 18: mp. 239-242 °C; $^1$H NMR ($CDCl_3$) δ 1.64 - 1.82 (m, 6H), 1.88 - 2.04 (m, 2H), 7.00 (d, 1H, *J* = 8 Hz), 7.29 - 7.31 (m, 1H), 7.36 (dd, 1H, *J* = 8.8, 2 Hz), 7.54 (d, 1H, *J* = 1.5 Hz), 7.73 - 7.78 (m, 2H) and 8.19 (s, 1H, br); MS ((+)-APCI) *m/z* 321 [M+H]$^+$.

## EXAMPLE 55

**5'-(3-Chlorophenyl)spiro[4,4-dimethylcyclohexane-1',3'-[3H]indol]-2'(1'H)-one**

A solution of 3,3-dimethylglutaric anhydride in dry THF (60 cm$^3$) was added over 30 min. to lithium aluminum hydride in dry THF (300 cm$^3$) under nitrogen at 0°C. The mixture was then brought gradually up-to reflux. After 3 h, the mixture was cooled, treated with water (3.3 cm$^3$), sodium hydroxide solution (15%, 3.3 cm$^3$) and water (9.9 cm$^3$). The mixture was then filtered, the precipitate extracted with EtOAc (x3), and the combined organics evaporated to afford 3,3-dimethyl-1,5-pentanediol (quantitative yield); $^1$H NMR ($CDCl_3$) δ 0.95 (s, 6H), 1.57 (t, 4H, *J* = 6.3 Hz), 3.75 (t, 4H, *J* = 6.3 Hz).

A solution of 3,3-dimethyl-1,5-pentanediol (8.4 g, 63.5 mmol) in dry pyridine (180 $cm^3$) was cooled to 0 °C under nitrogen and treated over 5h with a solution of *p*-toluenesulfonyl chloride (26.7 g, 140 mmol) in dry pyridine (100 $cm^3$). The mixture was then allowed to warm up to room temperature. After 16 h, the mixture was poured into ice/water and extracted with EtOAc (x3). The combined organics were washed with dil. HCl (30%), saturated sodium hydrogen carbonate, brine, dried ($MgSO_4$) and evaporated to afford 1,5-bis-(3,3-dimethylpentane)-*p*-toluenesulfonate (19.8 g, 45 mmol) which was used without further purification: $^1H$ NMR ($CDCl_3$) δ *inter alia* 0.85 (s, 6H), 1.56. (t, 4H, $J$ = 7.0 Hz), 2.45 (s, 6H), 4.02 (t, 4H, $J$ = 7.0 Hz), 7.35 (d, 4H, $J$ = 8.0 Hz), 7.77 (d, 4H, $J$ = 8.0 Hz); MS ((+) APCI) m/z 441 $(M + H)^+$.

A solution of 1,5-bis-(3,3-dimethylpentane)-*p*-toluenesulfonate (53.0 g, 120 mmol) and sodium iodide (72.0 g, 480 mmol) was dissolved with stirring in dry acetone (500 $cm^3$). After 16 h at reflux the mixture was cooled, poured into water and extracted with diethylether (x3). The combined organic extracts were washed with water, dried ($MgSO_4$), and evaporated to afford 3,3-dimethyl-1,5-diiodopentane (41.3 g, 117 mmol) as a yellow oil that was used without further purification: $^1H$ NMR ($CDCl_3$) δ *inter alia* 0.90 (s, 6H), 1.87 - 1.91 (m, 4H), 3.09 -3.15 (m, 4H).

A solution of oxindole (2.0 g, 15 mmol) dissolved in dry THF (50 $cm^3$) under nitrogen was cooled to -60 °C and treated with *n*-butyllithium (2.5 M in hexanes, 15 $cm^3$, 37.5 mmol) followed by *N,N,N'N'*-tetramethylethylenediamine (5.66 g, 37.5 mmol). After 20 min. 3,3-dimethyl-1,5-diiodopentane (15.8 g, 45 mmol) in dry THF (10 $cm^3$) was added and the mixture was allowed to warm up to room temperature. After 16 h, the mixture was poured into water, extracted with EtOAc (x3), washed with water, dilute HCl (10%), water, brine, dried ($MgSO_4$) and evaporated. The residue was then subjected to column chromatography ($SiO_2$, EtOAc: hexane, 1:6) to afford spiro[4,4-dimethylcyclohexane-1',3'-[3H]indol]-2'(1'H)-one (0.37 g, 1.62 mmol, 11%): $^1H$ NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.10 (s, 3H), 1.23 - 1.30 (m, 2H), 1.54 - 1.68 (m, 4H), 1.94 - 2.04 (m, 2H), 6.94 (d, 1H, $J$ = 7.7 Hz), 7.01 (t, 1H, $J$ = 7.6 Hz),

7.20 (t, 1H, $J$ = 7.7 Hz), 7.42 (d, 1H, $J$ = 7.4 Hz), 8.76 (s, 1H, br); MS (EI) *m/z* 229 $(M)^+$.

To a solution of the last cited compound (0.37 g, 1.62 mmol) and sodium acetate (0.14 g, 1.7 mmol) in acetic acid (5 $cm^3$) was added bromine (0.27 g, 1.7 mmol) in acetic acid (2 $cm^3$). After 30 min. the mixture was poured into sodium hydroxide solution (2N) and extracted with dichloromethane (x2). The organic extracts were washed with water, dried ($MgSO_4$) and evaporated to afford 5'-bromospiro[4,4-dimethylcyclohexane-1',3'-[3H]indol]-2'(1'H)-one (0.435 g, 1.41 mmol, 87%) which was used without further purification: $^1H$ NMR ($CDCl_3$) δ 1.08 (s, 3H), 1.49 - 1.64 (m, 4H), 1.69 - 1.74 (m, 2H), 1.89 - 1.98 (m, 2H), 6.77 (d, 1H, $J$ = 8.2 Hz), 7.33 (dd, 1H, $J$ = 8.2, 1.8 Hz), 7.48 (d, 1H, $J$ = 1.7 Hz), 7.71 (s, 1H, br); MS ((+)APCI) *m/z* 308 $(M + H)^+$.

The last cited compound (0.56 g, 1.81 mmol) and tetrakis(triphenylphosphine) palladium(0) (0.1 g, 0.08 mmol) were dissolved in dimethoxyethane (20 $cm^3$) under nitrogen. After 20 min. 3-chlorophenylboronic acid (0.57 g, 3.64 mmol) and sodium carbonate (0.97 g, 9.15 mmol) were added and the mixture heated under reflux. After 16h the mixture was cooled, poured into water and extracted with EtOAc (x2). The combined organic layers were washed with sodium hydroxide (2N), water, brine, dried ($MgSO_4$) and evaporated. The residue was then subjected to column chromatography ($SiO_2$, EtOAc: hexanes, 1:5) to afford the title compound which was triturated with hexane to give a solid (0.26 g, 0.77 mmol, 43%): mp. 184 - 185 °C; $^1H$ NMR ($CDCl_3$) δ 1.11 (s, 6H), 1.57 - 1.80 (m, 6H), 1.45 - 2.03 (m, 2H), 6.98 (d, 1H, $J$ = 8.0 Hz), 7.29 - 7.44 (m, 4H), 5.52 - 7.55 (m, 2H), 8.12 (s, 1H, br); MS ((+)APCI) m/z 340 $(M+H)^+$.

## EXAMPLE 56

**5'-(3-Nitrophenyl)spiro[4,4-dimethylcyclohexane-1',3'-[3H]indol]-2'(1'H)-one**

To a solution of 5'-bromospiro[4,4-dimethylcyclohexane-1',3'-[3H]indol]-2'(1'H)-one (0.29 g, 0.95 mmol) in dimethoxyethane (15 $cm^3$) was added tetrakis

(triphenylphosphine)palladium(0) (0.053 g, 0.046 mmol). After 20 min. 3-nitrophenylboronic acid (0.32 g, 1.9 mmol) and sodium carbonate (0.5 g, 4.75 mmol) in water (7.5 $cm^3$) and the mixture heated under reflux. After 16 h, the mixture was cooled, poured into water and extracted with EtOAc (x2). The combined organic layers were washed with sodium hydroxide solution (2N), water, brine, dried ($MgSO_4$) and evaporated. The residue was then subjected to column chromatography ($SiO_2$, EtOAc: hexanes, gradient elution), then the product was triturated with hexane to afford the title compound (0.12 g, 0.35 mmol, 37%) as a yellow solid: mp. 230 - 231 °C; $^1H$ NMR ($CDCl_3$) δ 1.18 - 1.24 (m, 6H), 1.57 - 1.86 (m, 6H), 1.94 - 2.03 (m, 2H), 7.03 (d, 1H, $J$ = 8.0 Hz), 7.48 (d, 1H, $J$ = 8.0 Hz), 7.59 - 7.64 (m, 2H), 7.87 (d, 1H, $J$ = 7.7 Hz), 8.06 (s, 1H, br), 8.19 (d, 1H, $J$ = 7.7 Hz), 8.40 (s, 1H); MS ((+)APCI) *m/z* 351 $(M+H)^+$.

## EXAMPLE 57

**2,3,5,6-Tetrahydro-5-(3-nitrophenyl)spiro[3H-indole-3,4-[4H]pyran]- 2(1H)-one**

To a solution of sodium iodide (64 g, 0.43 mol) in acetone under $N_2$ was added 2-bromoethyl ether (20 g, 0.086 mol), causing a white solid to precipitate. After 16 h the mixture was filtered and the filtrate concentrated. Dichloromethane was added to the residue which was filtered, the cake further washed with dichloromethane, the combined organic layers were dried ($MgSO_4$) and evaporated to give 2-iodoethyl ether (26.61 g, 0.0816 mol, 95%) as a colorless oil: $^1H$ NMR ($CDCl_3$) δ 3.26 (t, 2H, $J$ = 7 Hz), 3.78 (t, 2H, $J$ = 7 Hz).

A solution of oxindole (5.00 g, 37.5 mmol) in anhydrous THF under $N_2$ was cooled to -20 °C. *n*-butyllithium (2.5 M in hexanes, 30 $cm^3$, 75.1 mmol) was added drop-wise followed by *N,N,N'N'*-tetramethylethylenediamine (11.4 $cm^3$). After 20 min. a solution of 2-iodoethyl ether (36 g, 112 mmol) in anhydrous THF (20 $cm^3$) was added slowly. The mixture was allowed to warm to room temperature, then after 16 h was brought to reflux. After 5 h the mixture was cooled then poured into water, extracted with EtOAc (x 2), the combined organic layers were washed with dil. HCl

(pH 1), water (x 2), dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography ($SiO_2$, acetone: hexane 1:5) to afford the title compound (0.78 g, 3.82 mmol, 10%) as a white solid: $^1H$ NMR ($CDCl_3$) δ 1.84 - 1.95 (m, 4H), 3.91 - 3.96 (m, 2H), 4.21 - 4.27 (m, 2H), 6.89 - 6.92 (m, 1H), 7.06 (t, 1H, $J$ = 7, 1 Hz), 7.22 (t , 1H, $J$ = 7, 1 Hz), 7.35 - 7.38 (m, 1H).

A solution of the above product (0.78 g, 3.82 mmol) and sodium acetate (0.32 g, 4.02 mmol) in acetic acid (10 $cm^3$) was treated with bromine (0.64 g, 4.02 mmol) in acetic acid (2 $cm^3$). After 30 min. the mixture was poured into sat. sodium hydrogen carbonate solution and extracted with EtOAc (x 2) washed with water, sat. sodium hydrogen carbonate solution, water, dried ($MgSO_4$), and evaporated to give the title compound (0.59 g, 2 mmol, 54%) as an off-white solid which was used without further purification: $^1H$ NMR ($CDCl_3$) δ 1.83 - 2.00 (m, 4H), 3.91 - 4.03 (m, 2H), 4.22 - 4.32 (m, 2H), 6.86 (d, 1H, $J$ = 7 Hz), 7.38 - 7.45 (m, 1H), 7.52 (d, 1H, $J$ = 1 Hz), 8.36 (s, 1H, br); MS ((+)ESI) *m/z* 282 $(M+H)^+$.

A solution of the above product (0.58 g, 2.04 mmol) and tetrakis(triphenylphosphine)palladium (0.11 g, 0.09 mmol) in dimethoxyethane (16 $cm^3$) was stirred under $N_2$ for 20 min.. To this mixture was then added 3-nitrophenylboronic acid (0.63 g, 4.06 mmol) and potassium carbonate (1.68 g) in water (7 $cm^3$). After 3 h at reflux the mixture was cooled, poured into water and extracted EtOAc (x 3). The combined organic extracts were washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was then subjected to column chromatography ($SiO_2$, EtOAc: hexane, 1:2) to provide the title compound (0.19 g, 0.58 mmol, 28 %). A sample which was further purified by preparative LC (Primesphere C18, 10 micron, 50 x 250 mm, MeCN: $H_2O$ 46:54, 100 $cm^3$/min., RT 7.57 min.) had the following properties: mp >250 oC, $^1H$ NMR (acetone-$d_6$) δ 1.78 – 1.88 (m, 2H), 1.92 - 2.01 (m, 2H), 3.85 - 3.94 (m, 2H), 4.12 - 4.23 (2H), 7.08 - 7.13 (m, 1H), 7.62 - 7.69 (m, 1H), 7.70 - 7.79 (m, 1H), 7.92 - 7.97 (m, 1H), 8.13 - 8.23 (m, 2H), 8.45 - 8.51 (m, 1H), 9.55 (s, 1H, br); MS (EI) *m/z* 341 $(M)^+$.

**EXAMPLE 58**

**5'-(5-Chloro-3-methylbenzo[b]thien-2-yl)spiro [cyclo-hexane-1,3'-[3H] indol]-2'(1'H)-one**

A solution of the 2-bromo-5-chloro-3-methylbenzo[b]-thiophene (0.28 g, 1.1 mmol) and tetrakis-(triphenylphosphine) palladium (0.13 g, 0.1 mmol) in dimethoxyethane (8 $cm^3$) was stirred under $N_2$ for 20 min.. To this mixture was then added (2'-oxo-2, 3-dihydrospiro[cyclohexane-1, 3'- [3H] indol] -5'-yl) boronic acid (0.32 g, 1.3 mmol) and sodium carbonate (0.35 g, 3.3 mmol) in water (4 $cm^3$). The solution was brought to reflux for 12 h then cooled to RT, poured into water and extracted with EtOAc (3 x 50 $cm^3$). The combined organic extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, $CH_2Cl_2$) to afford the title compound (0.18 g, 0.47 mmol, 45 %) as a white solid: m.p. 256-258 °C , $^1H$ NMR (DMSO-$d_6$) δ 1.47-1.97 (m, 10H), 2.42 (s, 3H), 6.99 (d, $J$ = 8.0 Hz , 1H), 7.39 (d, $J$ = 1.6 Hz, 1H), 7.42 (d, $J$ = 1.2 Hz, 1H), 7.6 (s, 1H), 7.85 (d, $J$ = 1.9 Hz, 1H), 7.99 (d, $J$ = 8.5 Hz, 1H), 10.53 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$) δ 12.84 (q), 20.96, 25.08, 32.88 (t), 47.23 (s), 109.98, 121.99, 124.25, 124.71, 125.01 (d), 126.47, 126.59, 129.17, 130.01, 136.51, 140.42, 141.79, 142.76, 181.74 (s); MS (EI) *m/z* 380 $(M-H)^+$.

**EXAMPLE 59**

**5-(3-Fluoro-4-nitrophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

The title compound was prepared from (2'-oxo-2,3-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)boronic acid (3.2 g, 12.5 mmol) and 4-bromo-2-fluoro-nitrobenzene (3 g, 13.6 mmol) as described for example 18 (0.7 g, 16%) as a yellow solid: mp. 213-215 °C; 1H NMR (DMSO-d6) δ 1.5 - 1.8 (m, 8H), 1.8 - 2.0 (m, 2H), 6.96 (d, 1H, $J$ = 8.13 Hz), 7.68 (dd, 1H, $J$ = 8.13, 1.76 Hz), 7.74 (dd, 1 H, $J$ = 8.68, 1.76 Hz), 7.86 (d, 1H, $J$ = 1.98 Hz), 7.92 (dd, 1H, $J$ = 13.4, 1.76 Hz), 8.18 (t, 1H, $J$ = 8.46 Hz) and 10.52 (s, 1H); MS (EI) *m/z* = 340 ($M^+$).

## EXAMPLE 60

**4-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-2- furancarbonitrile**

A solution of 3-bromo-5-cyano-furan (0.75 g, 4.4 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.4 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (1.6 g, 6.5 mmol) and sodium acetate (1.4 g, 13.1 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.45 g, 36%) as an off-white solid. mp: 240 - 242 °C; $^1$H NMR (DMSO-$d_6$) δ 10.4 (s, 1H), 8.5 (s, 1H), 8.2 (s, 1H), 7.7 (s, 1H), 7.5 (dd, 1H, J = 1.5 6.5 Hz), 6.9 (d, 1H, J = 8.0 Hz), 2.0 - 1.6 (m, 10H); MS (EI) $M^+$ @ m/z 292.

## EXAMPLE 61

**5-[4-Fluoro-3-(trifluoromethyl)phenyl]spiro[cyclohexane-1,3- [3H]indol]-2(1H)-one**

The title compound was prepared from (2'-oxo-2,3-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)boronic acid (2.5 g, 10 mmol) and 5-bromo-2-fluoro-trifluoromethylbenzene (2 g, 8 mmol) as described for example 18, to afford the title compound (0.87 g, 30%) as a solid: mp. 222 °C; $^1$H NMR (DMSO-$d_6$) δ 1.5 - 1.8 (m, 8 H), 1.8 - 2.0 (m, 2 H), 6.92 (d, 1 H, $J$ = 8.13 Hz), 7.51 (dd, 1 H, $J$ = 8.13, 1.76 Hz), 7.55 (dd, 1 H, $J$ = 10.54, 9.01 Hz) 7.72 (d, 1 H, $J$ = 1.76 Hz), 7.90 (dd, 1 H, $J$ = 7.03, 2.20 Hz), 7.98 (m, 1 H) and 10.39 (s, 1 H); MS (EI) *m/z* 363 ($M^+$).

## EXAMPLE 62

**5-[4-Fluoro-3-nitrophenyl]spiro[cyclohexane-1,3- [3H]indol]-2(1H)-one**

The title compound was prepared from (2'-oxo-2,3-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)boronic acid (2.8 g, 11 mmol) and 5-bromo-2-fluoro-nitrobenzene (2.7 g, 12.2 mmol) as described for example 18, to afford the title compound (2.5 g, 66%) as a solid: mp. 243-245 °C; $^1$H NMR (DMSO-$d_6$) δ 1.8 - 2.0 (m, 2H), 1.5 - 1.8 (m, 8H), 6.94 (d, 1H, $J$ = 8.13 Hz), 7.55 (dd, 1H, $J$ = 8.01, 1.87 Hz), 7.63 (dd, $J$ = 10.98, 8.79 Hz), 8.07 (m, 1H), 8.30 (dd, 1H, $J$ = 7.14, 2.53 Hz) and 10.43 (s, 1H); MS (ESI (neg)) *m/z* 339 (M-H)$^-$.

## EXAMPLE 63

**5'-(4-Cyano-3-fluorophenyl)-spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one**

A solution of 4-cyano-3-fluoro-bromobenzene (0.76 g, 3.8 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.3 g) in ethylene glycol dimethyl ether (15 cm$^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (1.4 g, 5.7 mmol) and sodium acetate (1.2 g, 11.4 mmol) in water (5 cm$^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.45 g, 37%) as an off-white solid. mp: 258 - 260 °C; $^1$H NMR (DMSO-$d_6$) δ 8.8 (s, 1H), 7.7 - 7.6 (m, 2 H), 7.5 (td, 2H, J = 0.9. 1.5, 5.7 Hz), 7.4 (dd, 1H, J = 1.5, 8.8 Hz), 7.0 (d, 1H, J = 8.1 Hz), 2.0 - 1.6 (m, 10H); MS (-)APCI [M-H]$^-$ @ m/z 319.

## EXAMPLE 64

**2-fluoro-4-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde oxime**

A solution of 3-fluoro-4-bromobenzaldehyde oxime (0.5 g, 2.2 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (10 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (0.8 g, 3.3 mmol) and sodium acetate (0.7 g, 6.5 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.25 g, 34%) as an off-white solid. mp: 240 - 242 °C; $^1H$ NMR (DMSO-$d_6$) δ 11.6 (s, 1H), 10.4 (s, 1H), 8.2 (s, 1H), 7.8 - 7.7 (m, 2H), 7.6 - 7.5 (m, 3H), 6.9 (d, 1H, J = 8.1 Hz), 2. 0 -1.6 (m, 10H); MS (EI) $M^+$ @ m/z 338.

## EXAMPLE 65

**5-(2'-oxo-2',3'-dihydrospiro[cyclopentane-1,3'-[3H]indol]-5'yl-2-nitrothiophene**

A solution of 2-bromo-5-nitrothiophene (0.6 g, 2.9 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (1.0 g, 4.3 mmol) and sodium acetate (1.0 g, 10.0 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.87 g, 96%) as a yellow solid. mp: 264 - 266 °C; $^1H$ NMR (DMSO-$d_6$) δ 10.6 (s, 1H), 8.1 (d, 1H, J = 4.5 Hz), 7.7 (d, 1H, J = 1.8 Hz) 7.6 (m, 2H), 6.9 (d, 1H, J = 8.1 Hz), 2. 0 -1.9 (m, 8H); MS (EI) $M^+$ @ m/z 314.

## EXAMPLE 66

**5-(3-Chloro-4-fluoro-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one**

A solution of 5-bromo-3,3-dimethyl-1,3-dihydro-indol-2-one (0.35 g, 1.46 mmol) and tetrakis(triphenylphosphine) palladium (0.13 g, 0.11 mmol) in dimethoxyethane (10 cm3) was stirred under $N_2$ for 20 min.. To this mixture was then added 3-chloro-4-fluorobenzene boronic acid (0.26 g, 1.49 mmol) and potassium carbonate (0.62 g, 4.5 mmol) in water (5 cm3). The solution was brought to reflux for 16 h then cooled to RT, poured into saturated ammonium chloride and extracted with EtOAc (x 3). The combined organic extracts were dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, ethyl acetate: hexane 1:3) to afford the title compound (0.124 g, 0.43 mmol, 30%) as a white solid: m.p. 206.5-207.8 °C, $^1$H NMR (DMSO-$d_6$) δ 1.3 (s, 6H), 6.93 (d, $J$ = 8.1 Hz, 1H), 7.45 (dd, $J$ = 8.9, 8.9 Hz, 1H), 7.5 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.6 (ddd, $J$ = 8.9, 7.1, 2.2 Hz, 1H), 7.7 (d, $J$ = 1.8 Hz, 1H), 7.8 (dd, $J$ = 7.1, 2.2 Hz, 1H), 10.5 (s, 1H); MS (EI) *m/z* 289/291 $(M)^+$.

## EXAMPLE 67

**3-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-benzonitrile**

(2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid

To a solution of 5'-bromo-3,3-dimethyl-[1,3'-[3H]indol]-2'-(1'H)-one (3.5 g, 14.6 mmol) in dry tetrahydrofuran (60 $cm^3$) was added of sodium hydride (60% dispersion in mineral oil, 0.59 g, 14.6 mmol). After 30 min. stirring at room temperature, the mixture was cooled to -78°C and *n*-butyl lithium (2.5 M in hexanes, 5.9 $cm^3$, 14.6 mmol) was added slowly. After 30 min. tri-isopropyl borate (9 $cm^3$, 38.9 mmol) was added and the mixture was allowed to warm to room temperature. After 8 hrs. hydrochloric acid (1N, 200 $cm^3$) and ethylacetate (200 $cm^3$)was added and the mixture stirred for 20 min. The aqueous phase was extracted with ethylacetate, then the combined organic layers were washed with water, brine, dried ($Na_2SO_4$) and evaporated. The residue was triturated with hexane and the precipitate dried *in vacuo*

to obtain (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid (1.8 g, 8.8 mmol, 60%) as a yellow-white solid that was used without further purification. $^1$H NMR (DMSO-$d_6$) δ 1.23 (s, 6H), 6.81 (d, $J$ = 7.8 Hz, 1H) 7.63 (d, $J$ = 7.8 Hz, 1H) 7.66 (s, 1H), 7.84 (s, 2H) 8.69 (s, 1H).

A solution of 3-bromobenzonitrile (0.30 g, 1.65 mmol) and tetrakis(triphenylphosphine) palladium (0.13 g, 0.11mmol) in dimethoxyethane (10 cm3) was stirred under $N_2$ for 20 min.. To this mixture was then added the (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid, (0.41 g, 2.0 mmol) and potassium carbonate (0.86 g, 6.2 mmol) in water (5 cm3). The solution was brought to reflux for 16 h then cooled to room temperature, poured into saturated ammonium chloride and extracted with EtOAc (x 3). The combined organic extracts were dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, ethyl acetate: hexane 1:2.5) to afford the title compound (0.22 g, 0.68 mmol, 51%) as a white solid: m.p. 200.2-202.0 °C, $^1$H NMR (DMSO-$d_6$) δ 1.32 (s, 6H), 6.96 (d, $J$ = 8.1 Hz, 1H), 7.58 (dd, $J$ = 8.1, 1.8, 1H), 7.63 (dd, $J$ = 7.8, 7.8 Hz, 1H), 7.75-7.78 (m, 2H), 7.98 (d, $J$ = 8.0 Hz, 1H), 8.15 (s, 1H), 10.49 (s, 1H); MS (EI) m/z 263 (M+H)+.

## EXAMPLE 68

**2-fluoro-3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde oxime**

A solution of 3-bromo-2-fluorobenzoic acid (0.219 g, 1 mmol) in dry methanol (5 ml) under nitrogen was treated with trimethylorthoformate (0.22 ml, 2 mmol) and p-toluenesulfonic acid (catalytic amount), and then heated under reflux. After 16 h, the mixture was evaporated and the residue partitioned between water and $Et_2O$. The organic layer was washed with sat. sodium hydrogen carbonate solution, water, brine, dried ($MgSO_4$) and evaporated to give methyl 3-bromo-2-fluorobenzoate

(0.195 g, 0.84 mmol, 84%): $^1$H NMR ($CDCl_3$) δ 7.90 - 7.85 (m, 1H), 7.71 - 7.65 (m, 1H), 7.10 (dt, 1H, $J$ = 8.0, 1.0 Hz) and 3.94 (s, 3H): MS (EI) 232 ($M^+$).

A solution of the last cited compound (3.077 g, 13.2 mmol) in dry toluene (80 ml) at -78 °C under nitrogen was treated with di-iso-butylaluminum hydride in toluene (1M, 15.7 ml, 15.7 mmol). After 1 h at -78 °C, the mixture was quenched with aqueous HCl (3M, 16 ml). The mixture was warmed to room temperature (RT), partitioned between EtOAc/$H_2O$, the aqueous layer was re-extracted with EtOAc, and the combined organic layers were washed with water, dried ($MgSO_4$) and evaporated to afford 3-bromo-2-fluorobenzaldehyde (2.63 g, 12.9 mmol, 98%), which was used without further purification: $^1$H NMR ($CDCl_3$) δ 10.35 (s, 1H), 7.82 (m, 2H), 7.18 (t, 7.8 Hz).

A mixture of the last cited compound (2.63 g, 12.9 mmol), hydroxylamine hydrochloride (1.0g, 14 mmol) and potassium acetate (1.37 g, 14 mmol) was placed in ethanol/$H_2O$ (60 ml, 8:2) and the mixture was heated under reflux. After 30 min. the mixture was cooled, evaporated and partitioned between EtOAc and water. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give afford 3-bromo-2-fluorobenzaldoxime which was used without further characterization.

The title compound was prepared from 3-bromo-2-fluorobenzaldoxime (0.40 g, 1.83 mmol) and (spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid as described in example 18, to afford the product (0.094 g, 0.27 mmol, 15% yield) as a white solid: mp. 213 - 217 °C; $^1$H NMR ($CDCl_3$) δ 10.95 (s, 1H), 9.65 (s, 1H), 8.41 (s, 1H), 7.76 (t, 1H, $J$ = 7.1 Hz), 7.59 (s, 1H), 7.43 - 7.33 (m, 3H), 7.19 (t, 1H, $J$ = 7.7 Hz), 6.98 (d, 1H, J = 8 Hz) and 1.91 - 1.60 (m, 10H); MS ((+) ESI) *m/z* = 339 $[M+H]^+$.

## EXAMPLE 69

## 5-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-4-methyl thiophene-2-carbonitrile

5-Bromo-4-methyl-2-thiophene carboxaldehyde. To a solution of diethylamine (28g, 0.383 mol) in anhydrous THF (400 mL) was added at -40 °C under nitrogen a solution of *n*-BuLi (2.5 M, 153 mL, 0.383 mol) in hexane. After addition, the solution was stirred at -40 °C under nitrogen for 30 minutes, cooled to -78 °C and treated dropwise with a solution of 2-bromo-3-methylthiophene (45g, 0.254 mol) in anhydrous THF (450 mL). The reaction solution was stirred at -78 °C for 30 minutes and treated with anhydrous DMF (100 mL). The mixture was allowed to warm to ambient temperature and was quenched with 1N aqueous hydrochloride solution (1L). The solution was extracted with ethyl acetate(3x450 mL). The extracts were washed with water, brine and dried ($MgSO_4$). After removal of solvent *in vacuo*, the subtitled compound was obtained as a white solid (46g, 88.3%). A sample of the product was crystallized from hexane: mp 63-65 °C; IR (KBr) 1654 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ 9.75 (s, 1H), 7.45 (s, 1H), 2.26 (s, 3H); MS (EI) *m/z* 204/206 ($M^+$). Anal. Calc. For $C_6H_5BrOS$: C, 35.14; H, 2.46. Found: C, 35.00; H, 2.44.

5-Bromo-4-methyl-2-thiophenecarbonitrile. Prepared from 5-bromo-4-methyl-2-thiophene carboxaldehyde using the procedure of Example 35. White solid: mp 40-42 °C; IR (KBr) 2200 $cm^{-1}$; $^1$H-NMR ($CDCl_3$) δ 7.29 (s, 1H), 2.21 (s, 3H). MS (EI) *m/z* 201/203 ($M^+$, 98%/100%); Anal. Calc. For $C_6H_4BrNS$: C, 35.66; H, 1.99; N, 6.93. Found: C, 36.00; H, 2.14; N, 6.76.

Prepared according to the procedure for example 18 using (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid (357 mg, 1.7 mmol) and 5-bromo-4-methylthiophene-2-carbonitrile (295 mg, 1.5 mmol) to afford the title compound (227 mg, 0.8 mmol, 55 %) as a white solid: mp. 192.3-193 °C , $^1$H NMR (DMSO-$d_6$) δ 1.29 (s, 6H), 2.29 (s, 3H), 6.97 (d, $J$ = 8.0 Hz, 1H), 7.34 (dd, $J$ = 8.0, 1.8 Hz, 1H), 7.49 (d, $J$ = 1.7 Hz, 1H), 7.84 (s, 1H), 10.57 (s, 1H); MS (EI) *m/z* 282 $(m)^+$.

## EXAMPLE 70

**5-(3-Chloro-5-fluoro-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one,**

Prepared according to the procedure for example 18 for using (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid (345 mg, 1.7 mmol) and 1-bromo-3-chloro-5-fluorobenzene (295 mg, 1.4 mmol) to afford the title compound (245 mg, 0.85 mmol, 60 %) as a white solid: mp. 205.9-206.8 °C . $^1$H NMR (DMSO-$d_6$) δ 1.31 (s, 6H), 6.93 (d, J = 8.1 Hz), 7.35 (d, J = 8.6 Hz, 1H), 7.5-7.6 (m, 2H), 7.6 (s, 1H), 7.78 (d, J = 1.4 Hz, 1H), 10.49 (s, 1H); MS (EI) *m/z* 290 $(M+H)^+$.

## EXAMPLE 71

**5-(3-Fluoro-5-nitro-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one,**

Prepared according to the procedure for example 18 using (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid (272 mg, 1.3 mmol) and 1-fluoro-3-iodo-5-nitrobenzene (299 mg, 1.1 mmol) to afford the title compound (192 mg, 0.64 mmol, 57 %) as a yellow solid: mp. 231.2-232.7 °C , $^1$H NMR (DMSO-$d_6$) δ 1.33 (s, 6H), 6.97 (d, *J* = 8.1 Hz, 1H), 7.67 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.88 (d, *J* = 1.6 Hz, 1H), 8.0-8.1 (m, 2H), 8.32 (s,1H), 10.55 (s, 1H);MS (ESI) *m/z* 301 $(M+H)^+$.

## EXAMPLE 72

**4-(3,3-Dimethyl-2-oxo-2.3-dihydro-1H-indol-5-yl)-furan-2-carbonitrile**

Prepared according to the procedure for example 18 using (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid (354 mg, 1.7 mmol) and 4-bromo-furan-2-carbonitrile (200 mg, 1.2 mmol) to afford the title compound (76 mg, 0.3 mmol, 26 %) as a white solid: mp.199.6-201.4 °C , $^1$H NMR (DMSO-$d_6$) δ 1.28 (s, 6H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.65 (d, *J* = 1.5 Hz, 1H), 8.1 (s, 1H), 8.5 (s, 1H), 10.46 (s, 1H); MS (ESI) *m/z* 251 $(M-H)^-$.

## EXAMPLE 73

**4-Methyl-5-(2'-oxo-2',3'-dihydrospiro[cyclopentane-1,3'-[3H]indol-5'-yl)-2-thiophene carbonitrile**

(Spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid

To a solution of 5-bromo-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one (13.1 g, 53 mmol) in anhydrous THF (300 $cm^3$) under $N_2$, was added sodium hydride (60% in mineral oil, 2.1 g, 53 mmol). After 30 minutes, the reaction mixture was cooled to -78 °C and butyl lithium (2.5 M in hexanes, 22 $cm^3$, 53 mmol) was added slowly. After 30 minutes, tris-*iso*-propylborate (34 $cm^3$, 146 mmol) was added, and the reaction mixture was slowly brought to room temperature, and stirred for 14 hours. The reaction mixture was poured into 1N HCl and extracted with EtOAc (x 3). The organic layers were collected and washed with 1N HCl, water, dried ($MgSO_4$) and evaporated to give the subtitled compound (7.8 g, 64%) as a tan solid which was used without further purification. $^1$H NMR (DMSO-$d_6$) δ 10.3 (s, 1H), 7.9 (s, 1H), 7.7 - 7.6 (m, 2H), 6.8 (d, 1H, J = 7.7 Hz), 3.4 (s, 1H), 2.0 - 1.7 (m, 8H); MS (FI-POS) m/z @ 231.

A solution of 2-bromo-5-cyano-3-methylthiophene (0.63 g, 3.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was added (spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (1.0 g, 4.7 mmol) and sodium carbonate (1.0 g, 9.4 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.6 g, 62%) as a pale-yellow solid. mp: 135 - 136 °C; 1H NMR (DMSO-$d_6$) δ 10.5 (s, 1H), 7.8 (s, 1H), 7.4 - 7.3 (m, 2H), 7.0 (d, 1H, J = 8.0 Hz), 2.3 (s, 3H), 2.0 - 1.8 (m, 8H); MS $[M-H]^-$ = 307.

## EXAMPLE 74

**5'-(4-Cyano-3-fluorophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one**

A solution of 4-cyano-3-fluoro-bromobenzene (0.63 g, 3.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (1.0 g, 4.7 mmol) and sodium carbonate (1.0 g, 9.4 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.35 g, 36%) as a yellow solid. mp: dec. @ 235 °C; $^1H$ NMR (DMSO-$d_6$) δ 10.5 (s, 1H), 7.9 (t, 1 H, J = 7.6 Hz), 7.9 (dd, 1H, J = 1.4, 10.2 Hz), 7.3 (td, 2H, J = 1.6, 6.5 Hz), 7.6 (dd, 1H, J = 1.9, 6.3 Hz), 6.9 (d, 1H, J = 8.1 Hz), 2.0 - 1.9 (m, 8H); MS $[M-H]^-$ = 305.

## EXAMPLE 75

**5'-(3-cyano-4-fluorophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one**

A solution of 3-cyano-4-fluoro-bromobenzene (0.63 g, 3.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (1.0 g, 4.7 mmol) and sodium acetate (1.0 g, 9.4 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.10 g, 10%) as white crystals. mp: 264 - 266 °C; $^1H$ NMR (DMSO-$d_6$) δ 10.4 (s, 1H), 8.3 (dd, 1 H, J = 2.4, 3.7 Hz), 8.1 - 8.0 (m, 1H), 7.6 - 7.5 (m, 2H), 7.5 (dd, 1H, J = 1.9, 6.3 Hz), 6.9 (d, 1H, J = 8.1 Hz), 2.0 - 1.9 (m, 8H); MS $[M-H]^-$ = 305.

## EXAMPLE 76

**5'-(3-Chloro-4-fluorophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one**

A solution of 3-chloro-4-fluoro-bromobenzene (0.4 $cm^3$, 0.66 g, 3.1 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (1.0 g, 4.7 mmol) and sodium carbonate (1.0 g, 9.4 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.65 g, 66%) as a pale-yellow solid. mp: 202 - 204 °C; $^1H$ NMR (DMSO-$d_6$) δ 10.4 (s, 1H), 7.9 (dd, 1H, J = 2.3, 4.9 Hz), 7.7 - 7.6 (m, 1H), 7.6 (d, 1H, J = 1.5 Hz), 7.5 (s, 1H), 7.4 (d, 1H, J = 1.8 Hz), 6.9 (d, 1H, J = 8.0 Hz), 2.0 - 1.9 (m, 8H); MS $[M-H]^-$ = 314.

## EXAMPLE 77

**5'-(3-Cyanophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one**

A solution of 3-bromobenzonitrile (0.5 g, 2.6 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (0.9 g, 3.9 mmol) and sodium carbonate (0.8 g, 7.8 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.30 g, 40%) as an off-white solid. mp: 217 -219 °C; $^1H$ NMR (DMSO-$d_6$) δ 10.4 (s, 1H), 8.2 (s, 1H),

8.0 (d, 1H, J = 8.1 Hz), 7.8 (d, 1H, J = 7.7 Hz), 7.6 (m, 2H), 7.5 (dd, 1H, J = 1.8, 6.3 Hz), 6.9 (d, 1H, J = 8.1 Hz), 2.0 - 1.9 (m, 8H); MS $[M-H]^-$ = 287.

## EXAMPLE 78

**5-(1,2-Dihydro-2-oxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-2-thiophenecarbonitrile**

A solution of 2-bromo-5-cyanothiophene (0.5 g, 2.6 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (0.9 g, 3.9 mmol) and sodium carbonate (0.8 g, 7.8 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.3 g, 40%) as a yellow solid. mp: 248 °C; $^1H$ NMR (DMSO-$d_6$) δ 10.4 (s, 1H), 8.5 (d, 1H, J = 1.4 Hz), 8.3 (d, 1H, J = 1.4 Hz), 7.6 (s, 1H), 7.5 (dd, 1H, J = 1.7, 6.4 Hz), 6.9 (d, 1H, J = 8.1 Hz), 2.0 - 1.8 (m, 8H); MS $[M-H]^-$ = 293.

## EXAMPLE 79

**5-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-furan-2-carbonitrile**

A solution of 5-cyano-2-bromofuran (0.5 g, 2.6 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (0.9 g, 3.9 mmol) and sodium carbonate (0.8 g, 7.8 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column

chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.35 g, 49%) as an off-white solid. mp: 193 - 194 °C; $^1$H NMR (DMSO-$d_6$) δ 10.6 (s, 1H), 7.7 (d, 2H, J = 3.3 Hz), 7.6 (dd, 1H, J = 1.6, 6.6 Hz), 7.1 (d, 1H, J = 3.8 Hz), 6.9 (d, 1H, J = 8.1 Hz), 2.0 - 1.8 (m, 8H); MS $[M-H]^-$ = 277.

**EXAMPLE 80**

**5'-(3-Cyano-5-fluorophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one**

A solution of 3-cyano-5-fluoro-bromobenzene (0.5 g, 2.6 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 $cm^3$) was stirred under $N_2$ for 20 minutes. To this mixture was then added (spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one-5-yl) boronic acid (0.9 g, 3.9 mmol) and sodium carbonate (0.8 g, 7.8 mmol) in water (5 $cm^3$). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (x 3). The combined extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, EtOAc, hexane) to afford the title compound (0.35 g, 44%) as white needles. mp: 235 - 237 °C; $^1$H NMR (DMSO-$d_6$) δ 10.5 (s, 1H), 8.1 (s, 1H), 8.0 (dt, 1H, J = 1.7, 2.0, 7.0 Hz), 7.8 - 7.7 (m, 2H), 7.6 (dd, 1H, J = 1.8, 6.4 Hz), 6.9 (d, 1H, J = 8.1 Hz), 2.0 - 1.9 (m, 8H); MS (EI) $M^+$ @ m/z 306.

**EXAMPLE 81**

**3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl)phenylacetonitrile**

Prepared from 3-bromophenylacetonitrile and 2'-oxo-2',3,-dihydrospiro [cyclohexane-1,3'-[3H]indol]-5'-yl)boronic acid according to the procedure for example 18 to afford the title compound as a white powder; mp. 190 - 193°C; $^1$H-NMR (DMSO-$d_6$) δ 10.42 (s, 1H), 7.67 (d, 1H, *J* = 1.39Hz), 7.58 (d, 2H *J* = 6.87 Hz), 7.46 (m, 2H), 7.31 (d, 1H *J* = 7.6 Hz), 6.94 (d, 1H, *J* = 8.05 ) 4.10 (s, 2H) 2.04 - 1.50 (m, 10H); MS *m/z* 316(M+.). Anal. Calc. For $C_{21}H_{20}N_2O_2$ 0.2 H20: C,78.82, H, 6.42, N, 8.75. Found: C, 78.73, H,6.44, N, 8.52.

## EXAMPLE 82

**3-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-fluoro-benzonitrile**

Prepared according to the procedure for example 18 using (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid (640 mg, 3.1 mmol) and 5-bromo-3-cyano-fluorobenzene (423 mg, 21.2 mmol) to afford the title compound (261 mg, 0.93 mmol, 44 %) as a yellow solid: mp. 231.2-232.3 °C , $^1$H NMR (DMSO-$d_6$) δ 1.32 (s, 6H), 6.95 (d, $J$ = 8.0 Hz, 1H), 7.64 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.76 (d, $J$ = 8.4 Hz, 1H), 7.85 (d, $J$ = 1.6 Hz, 1H), 7.93 (d, $J$ = 8.6 Hz, 1H), 8.07 (s, 1H), 10.52 (s, 1H); MS (EI) *m/z* 280 $(M)^+$.

## EXAMPLE 83

**3,3-Dimethyl-5-(5-nitro-thiophene-2-yl)-1,3-dihydro-indol-2-one,**

Prepared according to the procedure for example 18 using (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid (384 mg, 1.9 mmol) and 2-bromo-5-nitrothiophene (300 mg, 1.4 mmol) to afford the title compound (270 mg, 0.9 mmol, 65 %) as a yellow brown solid: mp. 223-225 °C , $^1$H NMR ($CDCl_3$) δ 1.5 (s, 6H), 6.99 (d, $J$ = 8.1 Hz, 1H), 7.18 (d, J = 4.3 Hz, 1H), 7.44 d, J = 1.7 Hz, 1H), 7.51 (dd, $J$ = 8.1, 1.9 Hz, 1H), 7.91 (d, $J$ = 4.3 Hz, 1H), 8.07 (br s, 1H); MS (EI) *m/z* 288 $(M)^+$.

## EXAMPLE 84

**2-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-pyrrole-1-carboxylic acid tert-butyl ester**

Prepared according to the procedure for example 18 using 5'-bromo-3,3-dimethyl-[1,3'-[3H]indol]-2'-(1'H)-one (1.24 g, 5.2 mmol) and N-BOC-pyrrole-2-boronic acid (1.5 g, 5.93 mmol) to afford the title compound (506 mg, 1.5 mmol, 30 %) as off-white solid: mp. 168.4-170.2 °C , $^1$H NMR (DMSO-$d_6$) δ 1.26 (s, 6H), 1.28 (s, 9H), 6.1 (dd, $J$ = 3.2, 1.8 Hz, 1H), 6.2 (dd, $J$ = 3.2, 3.2 Hz, 1H), 6.8 (d, $J$ = 7.9 Hz,

1H), 7.1 (dd, $J$ = 7.9, 1.6 Hz, 1H), 7.2 (d, $J$ = 1.6 Hz, 1H), 7.3 (dd, $J$ = 3.2, 1.8 Hz, 1H), 10.4 (s, 1H); MS (APCI) *m/z* 327 (M+H)+.

**EXAMPLE 85**

**2-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-2-nitro-pyrrole**

To a solution of 2-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-pyrrole-1-carboxylic acid tert-butyl ester (0.90 g, 2.8 mmol) in acetonitrile (anhydrous, 40 mL) at -15 °C was added silver nitrate (0.49 g,, 2.9 mmol) followed by acetyl chloride (0.21 mL, 2.95 mmol). The reaction was allowed to warm to room temperature and stirred 16 h. Dichloromethane (250 mL) was added to the reaction mixture; filtered through celite and washed with water, saturated sodium bicarbonate, water then brine dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification via flash column chromatography on silica gel (2:3 ethyl acetate/hexane) gave 2-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-2-nitro-pyrrole-1-carboxylic acid tert-butyl ester as a yellow solid: $^1$H NMR ($CDCl_3$) δ 1.43 (s, 6H), 1.48 (s, 9H), 6.3 (d, $J$ = 4.1 Hz, 1H), 7.0 (d, $J$ = 8.0 Hz, 1H), 7.2 (d, $J$ = 4.1 Hz, 1H), 7.34 (d, $J$ = 1.7 Hz, 1H), 7.4 (dd, $J$ = 8.0, 1.7 Hz, 1H), 8.2 (s, 1H).

2-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-2-nitro-pyrrole-1-carboxylic acid tert-butyl ester, was placed in a 50 mL round bottomed flask under nitrogen. A vigorous flow of nitrogen was maintained as the flask was placed in an oil bath and heated to 160 °C . After 10 min at this temperature, the flask was removed from the oil bath and allowed to cool. The black residue was washed into a larger flask with acetone and adsorbed onto a small amount of florisil. Purification by flash column chromatography on silica gel (1:2 EtOAc:hexane) to afford the title compound (76 mg, 15 %) which was triturated from ether/ hexane to provide a greenish-yellow solid, mp 293.9-294.2 °C (dec). $^1$H NMR (DMSO-$d_6$) δ 1.3 (s, 6H), 6.77 (d, $J$ = 4.3 Hz, 1H), 6.91 (d, $J$ = 8.1 HZ, 1H), 7.26 (d, $J$ = 4.3 Hz, 1H), 7.78 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.96 (d, $J$ = 1.8 Hz, 1H), 10.55 (s, 1H), 13.12 (s, 1H); MS (ESI) *m/z* 270 (M-H)$^-$.

**EXAMPLE 86**

**5-(3,3-Dimethyl-2-oxo-2.3-dihydro-1H-indol-5-yl)-thiophene-2-carbonitrile**

Prepared according to the procedure for example 18 using (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid (570 mg, 2.8 mmol) and 5-bromo-thiophene-2-carbonitrile (350 mg, 1.9 mmol) to afford the title compound (299 mg, 1.1 mmol, 60 %) as an off-white solid: mp. 255-256 °C , $^1$H NMR ($CDCl_3$) δ $^1$H NMR ($CDCl_3$) δ 1.46 (s, 6H), 6.97 (d, $J$ = 8.1 Hz, 1H), 7.21 (d, $J$ = 3.9 Hz, 1H), 7.39 (d, $J$ = 1.3 Hz, 1H), 7.47 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.58 (d, $J$ = 3.9 Hz, 1H), 8.14 (s, 1H); MS (EI) *m/z* 268 $(M)^+$.

**EXAMPLE 87**

**3-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-2-fluoro-benzonitrile**

Prepared according to the procedure for example 18 using (2'-oxo-[2, 3-dihydro-3,3-dimethyl -1, 3'- [3H] indol] -5'-yl) boronic acid (300 mg, 1.5 mmol) and 4-bromo-2-fluoro-benzonitrile (240 mg, 1.2 mmol) to afford the title compound (185 mg, 0.66 mmol, 55 %) as an off white solid: mp. 270-272 °C , $^1$H NMR (DMSO-$d_6$) δ 1.31 (s, 6H), 6.96 (d, $J$ = 8.1 Hz, 1H), 7.67 (dd, $J$ = 8.1, 1.8 Hz, 1H), 7.74 (dd, $J$ = 8.2, 1.5 Hz, 1H), 7.85 (s, 1H), 7.89 (d, $J$ = 1.3 Hz, 1H), 7.96 (dd, J = 7.5, 7.5, 1H), 10.56 (s, 1H); MS (ESI) *m/z* 279 $(M-H)^-$.

**EXAMPLE 88 - Pharmacology**

The biological activity for the compounds of the current invention was evaluated in the in-vitro and in-vivo assays described below. In-vitro potencies lie in the range 0.01 nM - 10,000 nM, and in-vivo potencies in the range 1 μg/kg to 100 mg/kg.

**A. In-vitro biology**

The in-vitro biology is determined by (1) competitive Radioligand Binding: using the A-form of the human progesterone receptor with progesterone as the radioligand; (2) co-transfection assay, which provides functional activity expressed as agonist EC50 and Antagonist IC50 values; (3) a T47D cell proliferation, which is a further functional assay which also provides agonist and antagonist data; and (4) T47D cell alkaline phosphatase assay, which is a further functional assay which also provides agonist and antagonist data.

1. hPR Binding assay - This assay is carried out in accordance with: Pathirana, C.; Stein, R.B.; Berger, T.S.; Fenical, W.; Ianiro, T.; Mais, D.E.; Torres, A.; Glodman, M.E., *Nonsteroidal human progesterone receptor modulators from the marine alga* cymoplia barbata, J. Steroid Biochem. Mol. Biol., 1992, 41, 733-738.

2. PRE-luciferase assay in CV-1 cells

The object of this assay is to determine a compound's progestational or antiprogestational potency based on its effect on PRE-luciferase reporter activity in CV-1 cells co-transfected with human PR and PRE-luciferase plasmids. The materials methods used in the assay are as follows.

a. Medium: The growth medium was as follows: DMEM (BioWhittaker) containing 10% (v/v) fetal bovine serum (heat inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL). The experimental medium was as follows: DMEM (BioWhittaker), phenol red-free, containing 10% (v/v) charcoal-stripped fetal bovine serum (heat-inactivated), 0.1 mM MEM non-essential amino acids, 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Cell culture, transfection, treatment, and luciferase assay

Stock CV-1 cells are maintained in growth medium. Co-transfection is done using $1.2x10^7$ cells, 5 mg pLEM plasmid with hPR-B inserted

at SphI and BamHI sites, 10 mg pGL3 plasmid with two PREs upstream of the luciferase sequence, and 50 mg sonicated calf thymus DNA as carrier DNA in 250 ml. Electroporation is carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II. After electroporation, cells are resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 µl. Following overnight incubation, the medium is changed to experimental medium. Cells are then treated with reference or test compounds in experimental medium. Compounds are tested for antiprogestational activity in the presence of 3 nM progesterone. Twenty-four hr. after treatment, the medium is discarded, cells are washed three times with D-PBS (GIBCO, BRL). Fifty µl of cell lysis buffer (Promega, Madison, WI) is added to each well and the plates are shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase activity is measured using luciferase reagents from Promega.

c. Analysis of Results:

Each treatment consists of at least 4 replicates. Log transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. $EC_{50}$ or $IC_{50}$ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear response analyses.

d. Reference Compounds:

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the $EC_{50}$ or $IC_{50}$ values are calculated.

**Table 1. Estimated $EC_{50}$, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies**

| | | EC50 | | 95% CI | |
|---|---|---|---|---|---|
| Compound | Exp. | (nM) | SE | lower | upper |
| Progesterone | 1 | 0.616 | 0.026 | 0.509 | 0.746 |

| | | | | | |
|---|---|---|---|---|---|
| | 2 | 0.402 | 0.019 | 0.323 | 0.501 |
| | 3 | 0.486 | 0.028 | 0.371 | 0.637 |
| Trimegestone | 1 | 0.0075 | 0.0002 | 0.0066 | 0.0085 |
| | 2 | 0.0081 | 0.0003 | 0.0070 | 0.0094 |
| | 3 | 0.0067 | 0.0003 | 0.0055 | 0.0082 |

**Table 2. Estimated $IC_{50}$, standard error (SE), and 95% confident interval (CI) for the antiprogestin, RU486 from three individual studies**

| | | IC 50 | | 95% CI | |
|---|---|---|---|---|---|
| Compound | Exp. | (nM) | SE | lower | upper |
| RU486 | 1 | 0.028 | 0.002 | 0.019 | 0.042 |
| | 2 | 0.037 | 0.002 | 0.029 | 0.048 |
| | 3 | 0.019 | 0.001 | 0.013 | 0.027 |

Progestational activity: Compounds that increase PRE-luciferase activity significantly ($p<0.05$) compared to vehicle control are considered active.

Antiprogestational activity: Compounds that decrease 3 nM progesterone induced PRE-luciferase activity significantly ($p<0.05$)

$EC_{50}$: Concentration of a compound that gives half-maximal increase PRE-luciferase activity (default-nM) with SE.

$IC_{50}$: Concentration of a compound that gives half-maximal decrease in 3 nM progesterone induced PRE-luciferase activity (default-nM) with SE.

3. T47D cell proliferation assay

The objective of this assay is the determination of progestational and antiprogestational potency by using a cell proliferation assay in T47D cells. A compound's effect on DNA synthesis in T47D cells is measured. The materials and methods used in this assay are as follows.

a. Growth medium: DMEM:F12 (1:1) (GIBCO, BRL) supplemented with 10% (v/v) fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Treatment medium: Minimum Essential Medium (MEM) (#51200-038GIBCO, BRL) phenol red-free supplemented with 0.5% charcoal stripped fetal bovine serum, 100U/ml penicillin, 200 mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

c. Cell culture

Stock T47 D cells are maintained in growth medium. For BrdU incorporation assay, cells are plated in 96-well plates (Falcon, Becton Dickinson Labware) at 10,000 cells/well in growth medium. After overnight incubation, the medium is changed to treatment medium and cells are cultured for an additional 24 hr before treatment. Stock compounds are dissolved in appropriate vehicle (100% ethanol or 50% ethanol/50% DMSO), subsequently diluted in treatment medium and added to the cells. Progestin and antiprogestin reference compounds are run in full dose-response curves. The final concentration of vehicle is 0.1%. In control wells, cells receive vehicle only. Antiprogestins are tested in the presence of 0.03 nM trimegestone, the reference progestin agonist. Twenty-four hours after treatment, the medium is discarded and cells are labeled with 10 mM BrdU (Amersham Life Science, Arlington Heights, IL) in treatment medium for 4 hr.

d. Cell Proliferation Assay

At the end of BrdU labeling, the medium is removed and BrdU incorporation is measured using a cell proliferation ELISA kit (#RPN 250, Amersham Life Science) according to manufacturer's instructions. Briefly, cells are fixed in an ethanol containing fixative for 30 min, followed by incubation in a blocking buffer for 30 min to reduce background. Peroxidase-labeled anti-BrdU antibody is added to the wells and incubated for 60 min. The cells are rinsed three times with PBS and incubated with 3,3'5,5'-tetramethylbenzidine (TMB) substrate for 10-20 min

depending upon the potency of tested compounds. Then 25 µl of 1 M sulfuric acid is added to each well to stop color reaction and optical density is read in a plate reader at 450 nm within 5 min.

e. Analysis of Results:

Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. $EC_{50}$ or $IC_{50}$ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

f. Reference Compounds:

Trimegestone and medroxyprogesterone acetate (MPA) are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose-response curves and the $EC_{50}$ or $IC_{50}$ values are calculated.

**Table 3. Estimated $EC_{50}$, standard error (SE), and 95% confidence intervals (CI) for individual studies**

| | | $EC_{50}$ | | 95% CI | |
|---|---|---|---|---|---|
| Compound | Exp | (nM) | SE | lower | upper |
| Trimegestone | 1 | 0.017 | 0.003 | 0.007 | 0.040 |
| | 2 | 0.014 | 0.001 | 0.011 | 0.017 |
| | 3 | 0.019 | 0.001 | 0.016 | 0.024 |
| MPA | 1 | 0.019 | 0.001 | 0.013 | 0.027 |
| | 2 | 0.017 | 0.001 | 0.011 | 0.024 |

**Table 4. Estimated $IC_{50}$, standard error, and 95% confident interval for the antiprogestin. RU486**

| Compound | Exp | $IC_{50}$ (nM) | SE | 95% CI lower | 95% CI upper |
|---|---|---|---|---|---|
| RU486 | 1 | 0.011 | 0.001 | 0.008 | 0.014 |
| | 2 | 0.016 | 0.001 | 0.014 | 0.020 |
| | 3 | 0.018 | 0.001 | 0.014 | 0.022 |

$EC_{50}$: Concentration of a compound that gives half-maximal increase in BrdU incorporation with SE; $IC_{50}$: Concentration of a compound that gives half-maximal decrease in 0.1 trimegestone induced BrdU incorporation with SE

4. T47D cell alkaline phosphatase assay

The purpose of this assay is to identify progestins or antiprogestins by determining a compound's effect on alkaline phosphatase activity in T47D cells. The materials and methods used in this assay are as follows.

a. Culture medium: DMEM:F12 (1:1) (GIBCO, BRL) supplemented with 5% (v/v) charcoal stripped fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100 µg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

b. Alkaline phosphatase assay buffer:

I. 0.1 M Tris-HCl, pH 9.8, containing 0.2% Triton X-100

II. 0.1 M Tris-HCl, pH 9.8 containing 4 mM p-nitrophenyl phosphate (Sigma).

c. Cell Culture and Treatment:

Frozen T47D cells were thawed in a 37°C water bath and diluted to 280,000 cells/ml in culture medium. To each well in a 96-well plate (Falcon, Becton Dickinson Labware), 180 µl of diluted cell suspension was added. Twenty µl of reference or test compounds diluted in the culture medium was then added to each well. When testing for progestin antagonist activity, reference antiprogestins or test compounds were added in the presence of 1 nM progesterone. The cells were incubated at 37°C in a 5% $CO_2$/humidified atmosphere for 24 hr.

d. Alkaline Phosphatase Enzyme Assay:

At the end of treatment, the medium was removed from the plate and fifty µl of assay buffer I was added to each well. The plates were shaken in a titer plate shaker for 15 min. Then 150 µl of assay buffer II was added to each well. Optical density measurements were taken at 5 min intervals for 30 min at a test wavelength of 405 nM.

e. Analysis of Results: Analysis of dose-response data

For reference and test compounds, a dose response curve is generated for dose (X-axis) vs. the rate of enzyme reaction (slope) (Y-axis). Square root-transformed data are used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting is used to downweight the effects of outliers. $EC_{50}$ or $IC_{50}$ values are calculated from the retransformed values. JMP software (SAS Institute, Inc.) is used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

f. Reference Compounds:

Progesterone and trimegestone are reference progestins and RU486 is the reference antiprogestin. All reference compounds are run in full dose response curves and the $EC_{50}$ or $IC_{50}$ values are calculated.

**Table 5. Estimated $EC_{50}$, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three independent experiments**

| Compound | Exp. | EC50 (nM) | SE | 95% CI lower | 95% CI upper |
|---|---|---|---|---|---|
| Progesterone | 1 | 0.839 | 0.030 | 0.706 | 0.996 |
| | 2 | 0.639 | 0.006 | 0.611 | 0.669 |
| | 3 | 1.286 | 0.029 | 1.158 | 1.429 |
| Trimegestone | 1 | 0.084 | 0.002 | 0.076 | 0.091 |

| | | | | | |
|---|---|---|---|---|---|
| | 2 | 0.076 | 0.001 | 0.072 | 0.080 |
| | 3 | 0.160 | 0.004 | 0.141 | 0.181 |

**Table 6. Estimated $IC_{50}$, standard error, and 95% confident interval for the reference antiprogestin RU486 from three independent experiments**

| Compound | Exp | IC 50 (nM) | SE | 95% CI lower | upper |
|---|---|---|---|---|---|
| RU486 | 1 | 0.103 | 0.002 | 0.092 | 0.115 |
| | 2 | 0.120 | 0.001 | 0.115 | 0.126 |
| | 3 | 0.094 | 0.007 | 0.066 | 0.134 |

**B. In-vivo Biology**

The primary in-vivo assay is the rat decidualization model which may be used to determine progestational effects of both agonists and antagonists. The secondary in-vivo assay is the rat ovulation inhibition model which is under development and hence the protocol is un-available.

1. Rat decidualization assay The objective of this procedure is used to evaluate the effect of progestins and antiprogestins on rat uterine decidualization and compare the relative potencies of various test compounds. The materials and methods used in this assay are as follows.

a. Methods: Test compounds are dissolved in 100% ethanol and mixed with corn oil (vehicle). Stock solutions of the test compounds in oil (Mazola™) are then prepared by heating (~80 °C) the mixture to evaporate ethanol. Test compounds are subsequently diluted with 100% corn oil or 10% ethanol in corn oil prior to the treatment of animals. No difference in decidual response was found when these two vehicles were compared.

b. Animals (RACUC protocol #5002)

Ovariectomized mature female Sprague-Dawley rats (~60-day old and 230g) are obtained from Taconic (Taconic Farms, NY) following surgery. Ovariectomy is performed at least 10 days prior to treatment to reduce circulating sex steroids. Animals are housed under 12 hr light/dark cycle and given standard rat chow and water ad libitum.

c. Treatment

Rats are weighed and randomly assigned to groups of 4 or 5 before treatment. Test compounds in 0.2 ml vehicle are administered by subcutaneous injection in the nape of the neck or by gavage using 0.5 ml. The animals are treated once daily for seven days. For testing antiprogestins, animals are given the test compounds and a $EC_{50}$ dose of progesterone (5.6 mg/kg) during the first three days of treatment. Following decidual stimulation, animals continue to receive progesterone until necropsy four days later.

d. Dosing

Doses are prepared based upon mg/kg mean group body weight. In all studies, a control group receiving vehicle is included. Determination of dose-response curves is carried out using doses with half log increases (e.g. 0.1, 0.3, 1.0, 3.0 mg/kg...).

e. Decidual induction

Approximately 24 hr after the third injection, decidualization is induced in one of the uterine horns by scratching the antimesometrial luminal epithelium with a blunt 21 G needle. The contralateral horn is not scratched and serves as an unstimulated control. Approximately 24 hr following the final treatment, rats are sacrificed by $CO_2$ asphyxiation and body weight measured. Uteri are removed and trimmed of fat. Decidualized (D-horn) and control (C-horn) uterine horns are weighed separately.

f. Analysis of Results:

The increase in weight of the decidualized uterine horn is calculated by D-horn/C-horn and logarithmic transformation is used to maximize

normality and homogeneity of variance. The Huber M-estimator is used to down weight the outlying transformed observations for both dose-response curve fitting and one-way analysis of variance. JMP software (SAS Institute, Inc.) is used for both one-way ANOVA and non-linear dose-response analyses.

g. Reference Compounds:

All progestin reference compounds were run in full dose-response curves and the $EC_{50}$ for uterine wet weight were calculated.

**Table 7. Estimated $EC_{50}$, standard error (SE), and 95% confidence intervals for individual studies**

| | | $EC_{50}$ | | 95% CI | |
|---|---|---|---|---|---|
| Compound | Exp | (mg/kg, s.c.) | SE | lower | upper |
| Progesterone | 1 | 5.50 | 0.77 | 4.21 | 7.20 |
| | 2 | 6.21 | 1.12 | 4.41 | 8.76 |
| 3-Ketodesogestrel | 1 | 0.11 | 0.02 | 0.07 | 0.16 |
| | 2 | 0.10 | 0.05 | 0.11 | 0.25 |
| | 3 | 0.06 | 0.03 | 0.03 | 0.14 |
| Levonorgestrel | 1 | 0.08 | 0.03 | 0.04 | 0.16 |
| | 2 | 0.12 | 0.02 | 0.09 | 0.17 |
| | 3 | 0.09 | 0.02 | 0.06 | 0.13 |
| | 4 | 0.09 | 0.02 | 0.06 | 0.14 |
| MPA | 1 | 0.42 | 0.03 | 0.29 | 0.60 |
| | 2 | 0.39 | 0.05 | 0.22 | 0.67 |
| | 3 | 0.39 | 0.04 | 0.25 | 0.61 |

**Table 8. Estimated average $EC_{50}$, standard error, and 95% confidence intervals for dose-response curves of 3 reference compounds**

| | EC50 | | 95% CI | |
|---|---|---|---|---|
| Compound | (mg/kg, s.c.) | SE | lower | upper |
| Progesterone | 5.62 | 0.62 | 4.55 | 7.00 |
| 3-Ketodesogestrel | 0.10 | 0.02 | 0.07 | 0.14 |
| Levonorgestrel | 0.10 | 0.01 | 0.08 | 0.12 |

**Table 9. Estimated $IC_{50}$, standard error, and 95% confident interval for the antiprogestin, RU 486**

| | | $IC_{50}$ | | 95% CI | |
|---|---|---|---|---|---|
| Compound | Exp. | (mg/kg, p.o.) | SE | lower | upper |
| RU 486 | 1 | 0.21 | 0.07 | 0.05 | 0.96 |
| | 2 | 0.14 | 0.02 | 0.08 | 0.27 |

Concentration: Compound concentration in assay(default-mg/kg body weight)

Route of administration: Route the compound is administered to the animals

Body weight: Mean total animal body weight (default-kg)

D-horn: Wet weight of decidualized uterine horn (default-mg)

C-horn: Wet weight of control uterine horn (default-mg)

Decidual response: [(D-C)/C]x100%

Progestational activity: Compounds that induce decidualization significantly ($p<0.05$) compared to vehicle control are considered active

Antiprogestational activity: Compounds that decrease $EC_{50}$ progesterone induced decidualization significantly ($p<0.05$)

$EC_{50}$ for uterine weight: Concentration of compound that gives half-maximal increase in decidual response (default-mg/kg)

$IC_{50}$ for uterine weight: Concentration of compound that gives half-maximal decrease in $EC_{50}$ progesterone induced decidual response (default-mg/kg)

**Data for Representative Compounds**

| Example # | Ki/nM | CV-1 IC50/nM | Decid. IC50 mg/kg |
|---|---|---|---|
| 34 | 19 | 14 | 50% @ 10 |
| 35 | 22 | 19 | 50% @ 10 |
| 80 | | | 70% # 3 |
| 77 | | | 60% @ 3 |
| 44 | 123 | 20 | 50% @ 3 |
| 73 | | | 50% @ 3 |
| 36 | 4.8 | 9 | 50% @ 10 |
| 32 | 9 | 1 | 60% @ 10 |
| 47 | 18 | 7 | 50% @ 10 |

**EXAMPLE 89**

**4-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-2-fluorobenzeneacetonitrile**

Prepared from 4-bromo-2-fluorophenylacetonitrile and (2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'-yl) boronic acid according to the procedure for example 18 to afford the title compound as a white solid; mp. 180-183 °C; $^1$H-NMR (DMSO-$d_6$) δ 10.4 (s, 1H), 7.7 (s, 1H), 7.6-7.7 (m. 4H) 6.9 (d, 1H, J = 8.1 Hz), 4.1(s, 2H),1.9 (m, 2H), 1.7 - 1.6 (m, 8H). MS (APCI (-)) m/z 333 $[M-H]^-$Anal. calc. for $C_{21}H_{19}FN_2O$. 0.5 $H_2O$: C, 73.49, H, 5.87, N, 8.20. Found: C, 73.55, H, 5.50, N, 7.36.

## EXAMPLE 90

**5-(3-Fluoro-4-methoxyphenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

Prepared from 4-bromo-2-fluoroanisole and (2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'-yl) boronic acid according to the procedure for example 18 to afford the title compound as a white solid, mp. 178 – 180 °C; $^1$H-NMR (DMSO - d6) δ 10.4 (s, 1H), 7.65 (d, 1H, J = 1.1 Hz), 7.5 - 7.4 (m, 3H), 7.2(t, 1H, *J* = 8.9 Hz), 6.9 (d, 1H, J = 8 Hz), 3.9(s, 3H), 1.9 (m, 2H) 1.7 - 1.6 (m, 8H); MS (APCI (-)) m/z 324 [M-H]$^-$; Anal. Calc. For $C_{20}H_{20}FNO_2$. : C, 73.83, H, 6.20, N, 4.30. Found: C, 73.55, H, 6.23, N, 4.40.

## EXAMPLE 91

**5-(3-Chlorophenyl)spiro[cyclobutane-1,3-[3H]indole]-2(1H)-one**

5-Bromospiro[cyclobutane-1,3-[3H]indol]-2(1H)-one. To a stirred solution of spiro[cyclobutane-1,3'-[3*H*]indol]-2'(1'*H*)-one (*J. Med. Chem.* 1987, 824-9) (1.0 g, 6 mmol) in glacial acetic acid (10 mL) was added dropwise at room temperature a solution of bromine (0.30 mL, 6 mmol) in glacial acetic acid (6 mL). After stirring for 10 min, anhydrous sodium acetate (0.47 g, 6 mmol) was added and the solution was concentrated *in vacuo*. The residue was dissolved in ethyl ether (50 mL) and washed sequentially with water (50 mL), aqueous saturated sodium bicarbonate solution (50 mL), water (50 mL) and brine (30 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. Crystallization from ethyl ether yielded the product as a white fluffy solid (1.1 g, 73%), mp 235-7 °C; $^1$H NMR (DMSO-*d*$_6$, 300 MHz) δ 2.15-2.41 (m, 6 H), 6.74 (d, 1 H, *J* = 8.2 Hz), 7.33 (dd, 1 H, *J* = 2, 8.2 Hz), 7.75 (d, 1 H, *J* = 2 Hz), 10.36 (bs, 1 H); MS (EI) *m/z* 251 [M$^+$]; Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.41; H, 4.00; N, 5.56. Found: C, 51.98; H, 4.24; N, 5.42.

To a solution of 5-bromospiro[cyclobutane-1,3-[3H]indol]-2(1H)-one (0.6 g, 2 mmol) in ethylene glycol dimethyl ether (50 mL) under a nitrogen atmosphere was added tetrakis(triphenylphosphine)palladium(0) (140 mg, 0.1 mmol). To the solution

was added sequentially 3-chlorophenyl boronic acid (0.48 g, 3 mmol) and potassium carbonate (0.76 g, 5 mmol) in water (5 mL). The mixture was heated to 80 °C for 3 h and allowed to cool. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with brine (50 mL) and dried over magnesium sulfate. The solution was filtered, concentrated *in vacuo*, and the residue was purified by HPLC (Zorbax PRO, C18, 10u, 15A, 50 X 250mm; 35% Water/65% AcCN; 254NM; AMB. temp.) to give the title compound (200 mg, 35%) as a white powder, mp 199.5-201 °C. $^1$H NMR (DMSO-*d*$_6$, 300 MHz) δ 2.21-2.28 (m, 2 H), 2.40-2.45 (m, 4 H), 6.87 (d, 1 H, *J* = 8.1 Hz), 7.37 ('d', 1 H), 7.44-7.52 (m, 2 H), 7.65 (bd, 1 H, *J* = 7.8 Hz), 7.76 (bs, 1 H), 7.92 (bs, 1 H), 10.35 (s, 1 H). MS (EI) *m/z* 283 [M$^+$]. Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found: C, 70.75; H, 5.07; N, 4.68.

## EXAMPLE 92

**5-(3-Chlorophenyl)spiro[cyclopropane-1,3-[3H]indole]-2(1H)-one**

To 5-(3-chloro-phenyl)-1,3-dihydro-indol-2-one (1.2 g, 5 mmol) in tetrahydrofuran (25 mL, anhydrous) at -20 °C was added slowly n-butyllithium (2.5 M solution in hexanes, 3.93 mL, 9.8 mmol), followed by *N,N,N',N'*-tetramethylethylenediamine (1.48 mL, 9.8 mmol). After 15 min, 1,2-dibromoethane (1.27 mL, 15 mmol) was added slowly and the mixture was allowed to reach room temperature. After 5 days, saturated aqueous ammonium chloride solution (50 mL) and ethyl acetate (50 mL) were added. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 mL). The organic layers were combined, washed with 1 N HCl (25 mL) and brine (25 mL), and dried over magnesium sulfate. The solution was filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (40% ethyl acetate/hexane) on a pad of silica gel to give the product (40 mg) as white crystals, mp 212-214 °C; $^1$H NMR ($CDCl_3$, 300 MHz) δ 1.59-1.63 (m, 2 H), 1.80-1.84 (m, 2 H), 7.00-7.03 (m, 2 H), 7.28-7.42 (m, 4 H), 7.51 ('t', 1 H), 7.85 (bs, 1 H). MS (EI) *m/z* 269 [M$^+$]. Anal.

Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 70.78; H, 4.88; N, 5.10.

**EXAMPLE 93**

**2-Nitro-5-(1,2-dihydro-2-oxospiro[cyclobutane-1,3-[3H]indol]-5-yl)-1H-pyrrole-1-carboxylic acid, *tert*-butyl ester**

1-t-Butoxycarbonylpyrrole-2-boronic acid. To 1-tert-butyl pyrrolecarboxylate (Aldrich, 25 g, 0.15 mol, 1.0 eq) in THF at -78 °C (anhydrous, 250 mL) was added LDA (2 *M* solution in heptane/THF/ethylbenzene, 82 mL, 1.1 eq). After stirring for 30 min at -78 °C, trimethylborate (85 mL, 0.750 mol, 5.0 eq) was added. After stirring at -78 °C for 1 h, the dry ice bath was removed and the reaction was allowed to come to room temperature overnight. HCl (0.25 N, 200 mL) was added to the reaction and the THF was removed *in vacuo*. The aqueous layer was extracted with ethyl ether (3 x 300 mL). The combined ether layers were washed with water (2 x 200 mL), then with brine (200 mL), and dried over magnesium sulfate. The solution was filtered and concentrated *in vacuo*. When the product began to crystallize on the rotary, the flask was removed and allowed to stand. The crystals were filtered and washed with ice-cold ethyl ether to give the product (14 g, 44%) as a white solid. Several crystallizations of filtrate from cold ether gave more product (4.5 g, 14 %).

5-(1,2-dihydro-2-oxospiro[cyclobutane-1,3-[3H]indol]-5-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester. To a solution of 5-Bromospiro[cyclobutane-1,3-[3H]indol]-2(1H)-one (WAY-163202) (0.6 g, 2.4 mmol) in ethylene glycol dimethyl ether (50 mL) under a nitrogen atmosphere was added tetrakis(triphenylphosphine)palladium(0) (140 mg, 0.1 mmol). To the solution was added sequentially 1-t-butoxycarbonylpyrrole-2-boronic acid (0.65 g, 3.1 mmol) and potassium carbonate (0.75 g, 5.4 mmol) in water (5 mL). The mixture was heated to 80 °C for 3 h and allowed to cool. The reaction mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with brine (50 mL) and dried over magnesium sulfate. The

solution was filtered, concentrated *in vacuo*, and the residue was purified by flash column chromatography to give the product (0.7 g, 86%) as a tan powder, mp 163-165 °C. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ1.3 (s, 9 H), 2.16 – 2.49m, 6 H), 6.19 (dd, 1 H, $J$ = 1.8, 3.2 Hz), 6.24 (t, 1 H, $J$ = 3.3 Hz), 6.76 (d, 1 H, $J$ = 8.1 Hz), 7.09 (dd, 1 H, $J$ = 1.8, 8.0 Hz), 7.30 (dd, 1 H, $J$ = 1.8, 3.3), 7.48 (d, 1 H, $J$ = 1.8 Hz), 10.24 (s, 1 H). MS (APCI) *m/z* 339 $[M+H]^+$. Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 69.51; H, 6.38; N, 7.69.

To a solution of 5-(1,2-dihydro-2-oxospiro[cyclobutane-1,3-[3H]indol]-5-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester (0.97 g, 2.9 mmol) in acetonitrile (50 mL) and dichloromethane (5 mL) at -20 °C was added silver nitrate (0.51 g, 3.0 mmol). After 20 min, acetyl chloride (0.20 mL, 2.9 mmol) in acetonitrile (3 mL) was added and the solution was allowed to come to room temperature. After 24 h, the reaction mixture was diluted with dichloromethane (100 mL) and filtered through celite. The filtrate was poured into water (100 mL) and the layers were separated. The organic layer was washed with brine (50 mL) and dried over magnesium sulfate. The solution was filtered, concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (40% ethyl acetate/hexane) to give the title compound (415 mg, 37%) as a yellow powder, mp 265 °C (dec.). $^1$H NMR (DMSO-$d_6$; 400 MHz) δ 1.45 (s, 9 H), 2.17 – 2.48 (m, 6 H), 6.60 (d, 1 H, $J$ = 4.2 Hz), 6.90 (d, 1 H, $J$ = 8.1 Hz), 7.35 (dd, 1 H, $J$ = 2.0, 8.1 Hz), 7.46 (d, 1 H, $J$ = 4.2 Hz), 7.70 ('d', 1 H, $J$ = 1.8 Hz), 10.50 (s, 1 H). MS (ESI) *m/z* 382 $[M - H]^-$. Anal. Calcd for $C_{20}H_{21}N_3O_5$: C, 62.65; H, 5.52; N, 10.96. Found: C, 62.58; H, 5.60; N, 10.91.

## EXAMPLE 94

**Nitro-5-(1,2-dihydro-2-oxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester**

To a solution of 5-(1,2-dihydro-2-oxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester (1.5 g, 4.0 mmol) in acetonitrile (50 mL) and dichloromethane (5 mL) at -20 °C was added silver nitrate (0.76 g, 4.5

mmol). After 20 min, acetyl chloride (0.30 mL, 4.0 mmol) in acetonitrile (3 mL) was added and the solution was allowed to come to room temperature. After 24 h, the reaction mixture was diluted with dichloromethane (100 mL) and filtered through celite. The filtrate was poured into water (100 mL) and the layers were separated. The organic layer was washed with brine (50 mL) and dried over magnesium sulfate. The solution was filtered, concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (40% ethyl acetate/hexane) to give the title compound (650 mg, 41%) as a yellow powder, mp 150 - 153 °C. $^1$H NMR (DMSO-$d_6$; 400 MHz) δ 1.42 (s, 9 H), 1.77-2.00 (m, 8 H), 6.55 (d, 1 H, $J$ = 4.2 Hz), 6.93 (d, 1 H, $J$ = 8.0 Hz), 7.33 (dd, 1 H, $J$ = 1.7, 8.0 Hz), 7.37 ('d', 1 H, $J$ = 1.7 Hz), 7.43 (d, 1 H, $J$ = 4.2 Hz), 10.53 (s, 1 H). MS ((-) APCI) *m/z* 396 [M - H]$^-$. Anal. Calcd for $C_{21}H_{23}N_3O_5$: C, 63.47; H, 5.83; N, 10.57. Found: C, 62.95; H, 5.52; N, 10.32.

## EXAMPLE 95

5-(5-Nitro-1H-pyrrol-2-yl)spiro[cyclobutane-1,3-[3H]indol]-2(1H)-one

2-Nitro-5-(1,2-dihydro-2-oxospiro[cyclobutane-1,3-[3H]indol]-5-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester (350 mg, 0.91 mmol) was placed in a 25 mL round bottomed flask stoppered with a rubber septum and equipped with nitrogen inlet and a needle to allow gaseous outflow. A vigorous flow of nitrogen was maintained as the flask was placed in an oil bath and heated to 150 °C. After 20 min at this temperature, the flask was removed from the oil bath and allowed to cool. The residue was dissolved in acetone and was purified by flash column chromatography (40% ethyl acetate/hexane) on a pad of silica gel. Further purification by HPLC gave the title compound (100 mg, 39%) as a bright yellow powder, mp 250 °C (dec.); $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 2.18 – 2.48 (m, 6 H), 6.77 (dd, 1 H, $J$ = 2.4, 4.4 Hz), 6.83 (d, 1 H, $J$ = 8.1 Hz), 7.25 (dd, 1 H, $J$ = 2.4, 4.3 Hz), 7.73 (dd, 1 H, $J$ = 2.0, 8.1 Hz), 8.23 ('d', 1 H, $J$ = 1.8 Hz), 10.41 (bs, 1 H), 13.13 (s, 1 H); MS (ESI) *m/z* 282 [M-H]. Anal. Calcd. For $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.63; N, 14.83. Found: C, 62.59; H, 4.58; N, 14.28.

## EXAMPLE 96

**5-(5-Nitro-1H-pyrrol-2-yl)spiro[cyclopentane-1,3-[3H]indol]-2(1H)-one**

2-Nitro-5-(1,2-dihydro-2-oxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester (580 mg, 1.5 mmol) was placed in a 25 mL round bottomed flask stoppered with a rubber septum and equipped with nitrogen inlet and a needle to allow gaseous outflow. A vigorous flow of nitrogen was maintained as the flask was placed in an oil bath and heated to 150 °C. After 20 min at this temperature, the flask was removed from the oil bath and allowed to cool. The residue was dissolved in acetone and was purified by flash column chromatography (40% ethyl acetate/hexane) on a pad of silica gel. Further purification by HPLC gave the title compound (300 mg, 67%) as a yellow powder, mp 275 °C (dec.). $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 1.78-2.07 (m, 8 H), 6.77 (dd, 1 H, $J$ = 2.4, 4.2 Hz), 6.86 (d, 1 H, $J$ = 8.2 Hz), 7.24 (dd, 1 H, $J$ = 2.4, 4.2 Hz), 7.71 (dd, 1 H, $J$ = 1.8, 8.2 Hz), 7.87 ('d', 1 H, $J$ = 1.8 Hz), 10.47 (bs, 1 H), 13.12 (s, 1 H). MS (ESI) *m/z* 296 $[M-H]^-$. Anal. Calcd. For $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 63.82; H, 5.20; N, 13.73.

## EXAMPLE 97

**5-(1,2-dihydro-2-oxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester**

A solution of 5'-Bromospiro[cyclopentane-1,3'-[3H]indol]-2'(1H)-one (2.0 g, 7.5 mmol) and tetrakis(triphenylphosphine)palladium(0) (430 mg, 0.3 mmol) in ethylene glycol dimethyl ether (50 mL) was stirred under a flow of nitrogen for 15 min. To the solution was added sequentially 1-t-butoxycarbonylpyrrole-2-boronic acid (2.1 g, 9.7 mmol) and potassium carbonate (2.4 g, 17 mmol) in water (10 mL). The mixture was heated to 80 °C for 3 h and allowed to cool. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The organic layers were combined, washed with brine (30 mL) and dried over magnesium sulfate. The solution was filtered and concentrated *in vacuo*. Crystallization from

20% ethyl acetate/hexane gave the product (2.2 g, 83%) as a white powder, mp 179-180.5 °C. $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 1.30 (s, 9H), 1.75-1.98 (m, 8 H), 6.16 (dd, 1 H, $J$ = 1.8, 3.3 Hz), 6.22 ('t', 1 H, $J$ = 3.3, 3.3 Hz), 6.79 (d, 1 H, $J$ = 7.9 Hz), 7.08 (dd, 1 H, $J$ = 1.8, 7.9 Hz), 7.14 ('d', 1 H, $J$ = 1.5 Hz), 7.28 (dd, $J$ = 1.9, 3.3 Hz),10.30 (s, 1 H); MS (EI) *m/z* 352 [M$^+$]; Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.08; H, 6.83; N, 7.74.

To a solution of 5-(1,2-dihydro-2-oxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-1H-pyrrole-1-carboxylic acid, tert-butyl ester (WAY-163755) (2.2 g, 6.0 mmol) in THF (anhydrous, 25 mL) was added at -78 °C chlorosulfonyl isocyanate (0.63 mL, 7.0 mmol). After 90 min, dimethylformamide (11 mL, 140 mmol) was added and the reaction was allowed to warm to room temperature. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification via flash column chromatography on silica gel (30% ethyl acetate/hexane) gave the title compound (1.7 g, 75%) as white crystals, mp 167-9 °C; $^1$H NMR (DMSO-$d_6$, 400 MHz) δ 1.34 (s, 9H), 1.75-1.98 (m, 8 H), 6.39 (d, 1 H, $J$ = 3.7 Hz), 6.84 (d, 1 H, $J$ = 7.9 Hz), 7.17 (dd, 1 H, $J$ = 1.8, 7.9 Hz), 7.28 ('t', 2 H), 10.41 (s, 1 H); MS (ESI) *m/z* 376 [M-H]$^-$. Anal. Calcd. for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 69.67; H, 6.38; N, 11.04.

## EXAMPLE 98

## 5-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-4-propyl- 2-thiophenecarbonitrile

The title compound was prepared in a manner similar to example 69 from 5-bromo-4-n-propyl thiophene-2-carbonitrile ( 1.17 g, 5 mmol ), ( 1,2-dihydro-2-oxospiro[cyclohexane-1,3-[3H] indol)-5-boronic acid ( 1.24 g, 5 mmol ), tetrakis(triphenylphosphine) palladium, potassium carbonate ( 2.75 g,21 mmol), water (10 mL ), and dimethoxyethane (50 mL) heated at reflux over night, to afford the title compound (0.7 g, 40%): m.p.168-171 °C; $^1$H NMR ( DMSO-$d_6$) δ 10.56 (

s,1H ), 7.93 ( s, 1H ) 7.52-7.51 (d, 1H, $J$ = 1.5 Hz), 7.33 - 7.29 (dd, 1H, $J$ = 1.6 Hz), 7.00-6.96 (d, 1H, $J$ = 8.0 Hz), 2.62-2.57 (t, 2H), 1.86 (m, 2H), 1.70-1.56 (m, 11 H), 0.88-0.84 (t, H); MS m/z (APCI (+)) 351 $[M+H]^+$. IR (KBr) 1620, 1700, 2200 $cm^{-1}$; Anal. Calc. For $C_{21}H_{22}N_2OS \cdot 1/2\ H_2O$: C, 70.2; H, 6.39; N, 7.79. Found. C, 70.67; H,6.34; N,7.62.

**EXAMPLE 99**

**5-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)4-n-butyl-2-thiophenecarbonitrile**

The title compound was prepared in a manner similar to example 69 from 5-bromo-4-n-butyl thiophenecarbonitrile[1] (1.24 g, 5.1 mmol), (1,2-dihydro -2-oxospiro[cyclohexane-1,3-[3H] indol)-5-boronic acid (1.24 g, 5.05 mmol), tetrakis(triphenylphosphine) palladium (0.25 g), potassium carbonate (2.75 g, 21 mmol), water (10 mL),and dimethoxyethane (50 mL) heated at reflux for 5 hours to afford the title compound (1 g, 54%), m.p.130-132° C. $^1H$ NMR ( DMSO-$d_6$ ) δ 10.56 (s, 1H), 7.92 (s, 1H) , 7.52-7.51 (d, 1H, $J$ = 1.2 Hz ), 7.32-7.29 (dd, 1H, $J$ = 1.5 Hz), 6.98 - 6.96 (d, 1H, $J$ = 8.0 Hz), 2.64 - 2.59 (t, 2H), 1.99 - 1.86 (m, 2H), 1.70 - 1.50 (m, 11 H), 1.32 - 1.22 (m, 2H) , 0.86 - 0.82 (t, 3H ); MS (APCI (+)) *m/z* 365 $[M+H]^+$; IR (KBr) 1620,1700;2200 $cm^{-1}$; Anal. Calc. For $C_{22}H_{24}N_2OS \cdot 1/4\ H_2O$. C, 71.61; H, 6.69; N, 7.59. Found: C, 71.13; H, 6.61; N, 6.91.

**EXAMPLE 100**

**5-(3-Chlorophenyl)-4-methylspiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

To a -25 °C solution of 4-methyl-2-oxindole (3.0 g, 20.2 mmol) (Tett, 1966, 22 ,10, 3337-43) in of anhydrous THF (100 mL) under $N_2$ is added *N,N,N',N'*-tetramethylethylenediamine (8.0 mL, 51.0 mmol) followed by dropwise addition of *n*-butyl lithium (10.0 M in hexanes, 5.1 mL, 51.0 mmol). After 30 min. a solution of 1,5-diiopentane (9.2 mL, 61.0 mmol) in 3 (mL) of THF was added and the reaction mixture was allowed to warm to RT and stir for 14 h. The reaction mixture was

poured into water, extracted with EtOAc (x 2), the combined organic layers were washed with dil. HCl (pH 1), water (x 2), dried (MgSO4) and evaporated. The residue was purified by column chromatography ($SiO_2$, ethyl acetate: hexane 1:4) to afford the product (3.2 g, 15 mmol, 74%) as a tan solid: $^1$H NMR ($CDCl_3$) δ 1.2-1.45 (m, 1H), 1.55-1.75 (m, 4H), 1.85-1.95 (d, $J$ = 13 Hz, 1H), 2.05-2.35 (m, 4H), 2.47 (s, 3H), 6.72 (dd, $J$ = 8.1, 1.0 Hz, 1H), 6.95 (dd, $J$ = 8.1, 8.0 Hz, 1H), 7.32 (dd, $J$ = 8.0, 1.0 Hz, 1H), 8.6 (br s, 1H).

5-Bromo-4-methylspiro[cyclohexane-1,3 -[3H]indol]-2 (1 H)-one. A solution of the above oxindole (0.44 g, 2.0 mmol) in $CHCl_3$ (10 mL) with sodium acetate (0.28 g, 3.4 mmol) is cooled to 0 °C and treated with bromine (0.11 mL, 2.0 mmol) in $CHCl_3$ (4 mL). After 30 min. the mixture is warmed to RT and stirred an additional hour. The reaction mixture is poured into sat. sodium hydrogen carbonate solution and extracted with EtOAc (x 2), the combined organic layers were washed with water, sat. sodium hydrogen carbonate solution, water, dried (MgSO4), and evaporated to give an off-white solid which was purified by column chromatography ($SiO_2$, ethyl acetate: hexane 2:4) to afford (0.2 g, 0.7 mmol, 35 %) of the product: $^1$H NMR ($CDCl_3$) δ 1.2-1.45 (m, 1H), 1.55-1.75 (m, 4H), 1.85-1.95 (d, $J$ = 13 Hz, 1H), 2.05-2.35 (m, 4H), 2.47 (s, 3H), 6.62 (d, $J$ = 8.0 Hz, 1H), 7.4 (d, $J$ = 8.0, Hz, 1H), 8.47 (br s, 1H).

5-(3-chlorophenyl)-4-methylspiro[cyclohexane-1,3-[3H]indol]-2(1H)-one. A solution of the above 5-bromo-4-methyl-oxindole (0.1 g, 0.34 mmol) and tetrakis(triphenylphosphine) palladium (0.05 g, 0.04 mmol) in dimethoxyethane (10 mL) was stirred under $N_2$ for 20 min.. To this mixture was then added 3-chlorophenylboronic acid (0.065 g, 0.41 mmol) and sodium carbonate (0.1 g, 1.0 mmol) in water (3 mL). The solution was brought to reflux for 6 h then cooled to RT, poured into water and extracted with EtOAc (x 3). The combined organic extracts were washed with water, brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography ($SiO_2$, ethyl acetate: hexane 1:3) to afford the subtitled compound (0.077 g, 0.2 mmol, 70%) as a yellow solid: m.p. 164-165

°C; $^1$H NMR ($CDCl_3$) δ 1.25-1.4 (m, 1H), 1.6-1.7 (m, 3H), 1.78 (d, *J* = 12.0 Hz, 2H), ), 1.9 (d, *J* = 13.0 Hz, 1H), 2.1-2.35 (m, 3H), 2.49 (s, 3H), 6.75 (d, *J* = 7.9 Hz, 1H), 7.1 (d, *J* = 7.9, Hz, 1H), 7.15-7.18 (m, 1H), 7.26-7.35 (m, 3H), 7.88 (br s, 1H);13C-NMR ($CDCl_3$) □ 16.71 (q), 20.7, 25.5, 29.9 (t), 48.5 (s), 107.1, 127.0, 128.0, 129.4, 129.5, 130 (d), 132.2, 133.0, 134.0, 136.6, 140.1, 144, 182.6 (s); MS (EI) *m/z* 326, (M+H)+ w/1 Cl.

## EXAMPLE 101

**5-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-1H-3-nitropyrrole-2-carbonitrile**

To a solution of *tert*-butyl 2-cyano-5-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-1H-pyrrole-1-carboxylate (0.11 g, 2.6 mmol) in TFA (5 mL) at 0 °C was added silver nitrate (1.1 eq, 49 mg, 2.86 mmol). After 5 min the reaction was poured onto ice, DCM (5 mL) was added and the layers were separated. The aqueous layer was extracted with DCM (3 x 5 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 40% ethyl acetate/hexane to 5-(1,2-dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-1H-3-nitropyrrole-2-carbonitrile (20 mg, 21%) as a white solid. $^1$H NMR (400 MHz, *d6*-DMSO) δ1.4 – 1.9 (10H, m), 6.94 (d, 1H, *J*=8.1Hz), 7.47 (dd, 1H, *J*=8.1, 1.75Hz), 7.73 (s, 1H), 7.75 (d, 1H, *J*=1.75Hz), 10.6 (s, 1H), 13.4 (s, 1H). M/*z* (ES) 335 $(M-H)^-$. Anal. calcd for C18H16N4O3, C, 64.3, H, 4.79, N, 16.7. Found, C, 62.2, H, 5.20, N, 15.1.

## EXAMPLE 102

**5-(2-Nitro-1H-pyrrol-3-yl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one.**

According to a procedure described in *J. Med. Chem.* **1983**, *26*, p.800, succinic anhydride (2.0 g, 20 mmol) and spiro[cyclohexane-1,3-[3H]indol]-2(1H)-

one (4.03 g, 20 mmol) gave 4-oxo-4-(1,2-dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)butanoic acid (100%). $^1$H NMR ($d_6$-DMSO, 300 MHz) δ 1.5 – 2.0 (m, 10H), 2.56 (t, 1H, *J*=6Hz), 3.20 (t, 1H, *J*=6Hz), 6.95 (d, 1H, *J*=8.1Hz), 7.91 (d, 1H, *J*=8.1Hz), 8.0 (s, 1H), 10.7 (s, 1H), 12.1 (s, 1H). MS (EI) *m/z* 300 $(M-H)^-$.

According to a procedure described in *J. Org. Chem.* 1984, p.3840 4-oxo-4-(1,2-dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)butanoic acid (5.64 g, 18 mmol) and thallium nitrate gave dimethyl-2-(1,2-dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)succinate (7.95 g, 18 mmol) as a white powder (71%). $^1$H NMR ($d_6$-DMSO, 300 MHz) δ 1.44-1.84 (m, 1H), 2.68 (dd, 1H, *J*=4.97, 16.9Hz), 3.06 (dd, 1H, *J*=16.9, 10.5Hz), 3.5 (s, 6H), 4.03 (dd, 1H, *J*=4.9, 10.5Hz), 6.78 (d, 1H, *J*=7.9 Hz), 7.07 (d, 1H, *J*=7.9 Hz), 7.39 (s, 1H), 10.31 (s, 1H). MS (EI) *m/z* 346 $(M+H)^+$.

To a solution of dimethyl-2-(1,2-dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)succinate (2.0g, 6.0 mmol) in THF (30 mL) was added $LiBH_4$ (2.5 eq, 0.33 g, 15 mmol). The solution was refluxed for 1.5h, cooled and quenched by the careful addition of 1N HCl. The aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$ and purified by flash column chromatography on silica gel eluting with 5% MeOH/ethyl acetate to give of 2-(1,2-dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)butan-1,4-diol (78 g, 47%) as a white solid. $^1$H NMR (300 MHz, $d_6$-DMSO) δ 1.53 - 1.60 (m, 1H), 1.72 (m, 2H), 1.93 (m, 7H), 2.69 (m, 1H), 3.26 (m, 2H), 3.46 (t, 2H, *J*=5.8Hz), 4.35 (t, 1H, *J*=5.2Hz), 4.55 (t, 1H, *J*=5.2Hz), 6.70 (d, 1H, *J*=7.8Hz), 6.94 (d, 1H, *J*=7.8Hz), 7.03 (s, 1H), 10.2 (s, 1H). M/z (ES) 276 $(M+H)^+$. Anal. calcd for C16H21NO3, C, 96.79, H, 7.69, N, 5.09. Found, C, 70.02, H, 7.64, N, 5.02.

Oxalyl chloride (4 eq, 1.0 mL, 11 mmol) in DCM (40 mL) at -78 °C was treated with DMSO (8 eq, 1.62 mL, 22 mmol). After 2 min a solution of 2-(1,2-dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)butan-1,4-diol (1 eq, 0.78 g, 2.9 mmol) in DMSO:DCM (1:3, 5 mL) was added followed 15 min later by addition of triethylamine (18 eq, 7.2 mL, 52 mmol). The solution was removed from the cooling bath and allowed to reach room temperature. The solution was filtered through

celite, concentrated in vacuo and redissolved in MeOH (10 mL). A large excess of ammonium acetate was added and the solution was heated to 60 °C for 1h then stored in a refrigerator for 16h. The solution was partitioned between DCM and water. The layers were separated and the aqueous layer was extracted with DCM (3 x 10 mL) and the combined organic layer was washed with brine, dried over $MgSO_4$ and purified by flash column chromatography on silica gel eluting with 60% ethyl acetate/hexane to give 5-(1H-pyrrol-3-yl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one (0.12 g, 19%) as a white solid. $^1$H NMR (300 MHz, $d_6$-DMSO) δ1.79 - 1.83 (m, 2H), 1.95 (m, 6H), 6.37 (s, 1H), 6.73 (m, 2H), 7.13 (s, 1H), 7.29 (d, 1H, *J*=8Hz), 10.17 (s, 1H), 10.83 (s, 1H). M/z (ES) 253 $(M+H)^+$.

To a solution of give 5-(1H-pyrrol-3-yl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one (45 mg, 0.17 mmol) in DCM:MeCN (1:1, 5 mL) at -40 °C sequentially was added silver nitrate (1.1 eq, 32 mg, 0.19 mmol) and a solution of acetyl chloride (1.1 eq, .01 mL, 0.19 mmol) in MeCN (0.5 mL). After 1h the cooling bath was removed and the reaction was allowed to stir for 16h. DCM (20 mL) was added and the suspension was filtered through celite, washed sequentially with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 40% ethyl acetate/hexane to give 5-(2-nitro-1H-pyrrol-3-yl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one (20 mg, 40%) as a yellow powder. $^1$H NMR (300 MHz, $d_6$-DMSO) δ1.63 – 1.95 (m, 10*J*), 6.44 (t, 1H, *J*=2.69Hz), 6.97 (d, 1H, *J*=8.1Hz), 7.22 (t, 1H, *J*=2.9Hz), 7.44 (dd, 1H, *J*=8.1, 1.7Hz), 7.79 (d, 1H, *J*=1.4Hz), 9.39 (s, 1H), 11.85 (s, 1H). M/z 310 $(M-H)^-$.

## EXAMPLE 103

**5-(4-Chlorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

The title compound was prepared from CAT-817819 (1.9 g, 7.8 mmol ) and 4-bromochlorobenzene (1.0 g, 5.2 mmol) according to the method for Example 18 to afford the product (0.68 g, 42%) as an off white solid: mp. 226 – 229 °C; $^1$H NMR

(DMSO-$d_6$) δ 10.41 (br s, 1H), 7.68 – 7.63 (m, 3H), 7.49 – 7.46 (m, 3H), 6.93 (d, 1H, $J$ = 8.0 Hz), 1.99 – 1.82 (m, 2H), 1.76 – 1.51 (m, 8H); MS (EI) *m/z* 311/313 $[M]^+$; C19H18ClON requires C, 73.19; H, 5.82; N, 4.49; Found C, 73.13; H, 5.68; N, 4.40.

**EXAMPLE 104**

**5-(2-Chlorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one**

The title compound was prepared from CAT-817819 (1.9 g, 7.8 mmol ) and 2-bromochlorobenzene (1.0 g, 5.2 mmol) according to the method for Example 18 to afford the title compound (0.68 g, 42%) as an off white solid: mp. 174 – 175 °C; $^1$H NMR (DMSO-$d_6$) δ 10.43 (br s, 1H), 7.56 – 7.52 (m, 2H), 7.43 – 7.33 (m, 3H), 7.25 (dd, 1H, $J$ = 8.0 and 1.7 Hz), 6.93 (d, 1H, $J$ = 8.0 Hz), 1.92 – 1.79 (m, 2H) and 1.77 – 1.43 (M, 8H); MS (EI) *m/z* 311/313 $[M]^+$; Anal. Calc. For $C_{19}H_{18}ClON$: C, 73.19; H, 5.82; N, 4.49; Found C, 73.10; H, 5.86; N, 4.30.

**EXAMPLE 105**

**5-(1,2-Dihydro-2-oxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-2-furancarbonitrile**

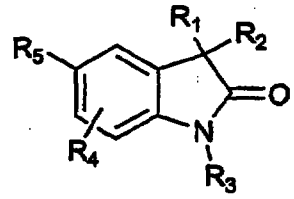
The title compound was prepared from CAT-830083 (0.9 g, 3.9 mmol ) and 5-cyano-furancarbonitrile (0.5 g, 2.6 mmol) according to the method for Example 18 to afford the title compound (0.35, 49%) as an off white solid: mp. 193 – 194 °C; $^1$H NMR (DMSO-$d_6$) δ 10.55 (br s, 1H), 7.69 – 7.63 (m, 3H), 7.15 (d, 1H, $J$ = 3.8 Hz), 6.92 (d, 1H, $J$ = 8.1 Hz), 2.00 – 1.83 (m, 8H); MS (ESI (-)) m/z 277 $[M-H]^-$. Anal. Calc. For $C_{17}H_{14}N_2O_2$: C, 73.73; H, 5.07; N, 10.07; Found C, 73.01; H, 4.98; N, 9.69.

All publications cited in this specification are incorporated herein by reference herein. While the invention has been described with reference to a particularly preferred embodiment, it will be appreciated that modifications can be

made without departing from the spirit of the invention. Such modifications are intended to fall within the scope of the appended claims.

**What is Claimed:**

1. A compound of the Formula 1:




1

wherein:

$R_1$ and $R_2$ are chosen independently from H, alkyl, substituted alkyl; OH; O(alkyl); O(substituted alkyl); OAc; aryl; optionally substituted aryl; heteroaryl; optionally substituted heteroaryl; alkylaryl; alkylheteroaryl; 1-propynyl; or 3-propynyl;

or $R_1$ and $R_2$ are joined to form a ring comprising one of the following: $-CH_2(CH_2)nCH_2-$; $-CH_2CH_2CMe_2CH_2CH_2-$; $-O(CH_2)mCH_2-$; $O(CH_2)pO$; $-CH_2CH_2OCH_2CH_2-$; or $-CH_2CH_2N(H \text{ or alkyl})CH_2CH_2-$;

or $R_1$ and $R_2$ comprise a double bond to $CMe_2$, C(cycloalkyl), O, or C(cyloether);

n is an integer from 0 to 5;

m is an integer from 1 to 4;

p is an integer from 1 to 4;

$R_3$ is selected from H, OH, $NH_2$, $C_1$ to $C_6$ alkyl, substituted $C_1$ to $C_6$ alkyl, $C_3$ to $C_6$ alkenyl, alkynyl or substituted alkynyl, or $COR^A$;

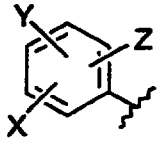
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$R^A$ is selected from H, $C_1$ to $C_3$ alkyl, substituted $C_1$ to $C_3$ alkyl, $C_1$ to $C_3$ alkoxy, substituted $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ aminoalkyl, or substituted $C_1$ to $C_3$ aminoalkyl;

$R_4$ is selected from H, halogen, CN, $NH_2$, $C_1$ to $C_6$ alkyl, substituted $C_1$ to $C_6$ alkyl, $C_1$ to $C_6$ alkoxy, substituted $C_1$ to $C_6$ alkoxy, $C_1$ to $C_6$ aminoalkyl, or substituted $C_1$ to $C_6$ aminoalkyl;

$R^5$ is selected from the groups a), b) or c):

a) $R^5$ is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:




wherein:

X is selected from the group of halogen, OH, CN, $C_1$ to $C_3$ alkyl, substituted $C_1$ to $C_3$ alkyl, $C_1$ to $C_3$ alkoxy, substituted $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ thioalkyl, substituted $C_1$ to $C_3$ thioalkyl, S(O)alkyl, $S(O)_2$alkyl, $C_1$ to $C_3$ aminoalkyl, substituted $C_1$ to $C_3$ aminoalkyl, $NO_2$, $C_1$ to $C_3$ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, $COR^B$, $OCOR^B$, or $NR^CCOR^B$;

$R^B$ is H, $C_1$ to $C_3$ alkyl, substituted $C_1$ to $C_3$ alkyl, aryl, substituted aryl, $C_1$ to $C_3$ alkoxy, substituted $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ aminoalkyl, or substituted $C_1$ to $C_3$ aminoalkyl;

$R^C$ is H, $C_1$ to $C_3$ alkyl, or substituted $C_1$ to $C_3$ alkyl;

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Y and Z are independently selected from H, halogen, CN, $NO_2$, $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ alkyl, or $C_1$ to $C_3$ thioalkyl;

or

b) $R^5$ is a five or six membered heterocyclic ring with 1, 2, or 3 heteroatoms selected from O, S, SO, $SO_2$ or $NR^6$ and containing one or two independent substituents from the group of H, halogen, CN, $NO_2$ and $C_1$ to $C_3$ alkyl, $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ aminoalkyl, $COR^D$, or $NR^ECOR^D$;

$R^D$ is H, $C_1$ to $C_3$ alkyl, substituted $C_1$ to $C_3$ alkyl, aryl, substituted aryl, $C_1$ to $C_3$ alkoxy, substituted $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ aminoalkyl, or substituted $C_1$ to $C_3$ aminoalkyl;

$R^E$ is H, $C_1$ to $C_3$ alkyl, or substituted $C_1$ to $C_3$ alkyl;

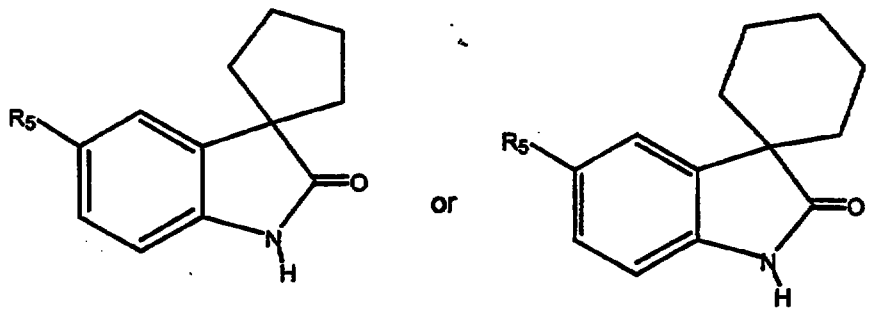
$R^6$ is H, or $C_1$ to $C_3$ alkyl; or

c) $R^5$ is an indol-4-yl, indol-7-yl or benzo-2-thiophene moiety, the moiety being optionally substituted by from 1 to 3 substituents selected from halogen, lower alkyl, CN, $NO_2$, lower alkoxy, or $CF_3$;

or a pharmaceutically acceptable salt thereof.

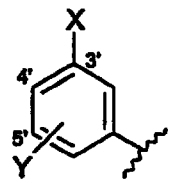
2. A compound of Claim 1 having the structure:

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wherein:

$R^5$ is a disubstituted benzene ring containing the substituents X and Y as shown below:



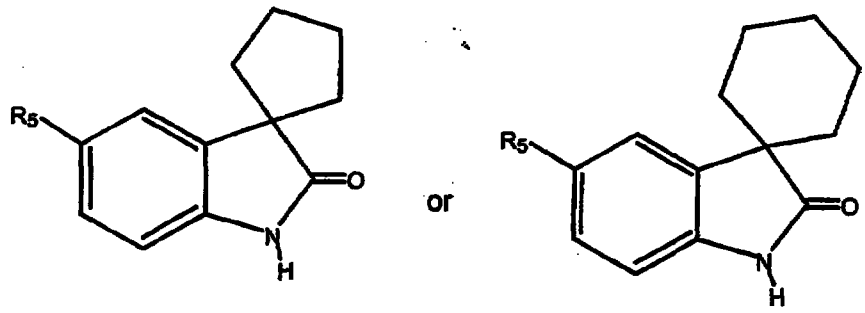
X is taken from the group of halogen, CN, $C_1$ to $C_3$ alkoxy, $C_1$ to $C_3$ alkyl, $NO_2$, $C_1$ to $C_3$ perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms or $C_1$ to $C_3$ thioalkoxy; and

Y is a substituent on the 4' or 5'position of the disubstituted benzene ring selected from the group of H, halogen, CN, $NO_2$, $C_1$ to $C_3$ alkoxy, $C_1$ to $C_4$ alkyl, or $C_1$ to $C_3$ thioalkyl;

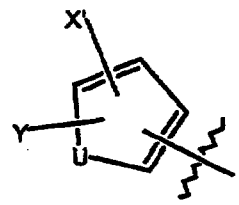
or a pharmaceutically acceptable salt thereof.

3. A compound of Claim 1 having the structure:

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wherein $R^5$ is a five membered ring with the structure:



U is O, S, or $NR^6$,

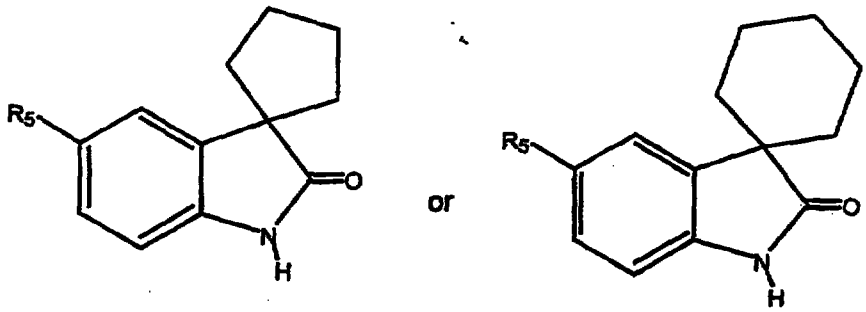
$R^6$ is H, or $C_1$ to $C_3$ alkyl, $C_1$ to $C_4$ $CO_2$alkyl,

X' is selected from the group of halogen, CN, $NO_2$, $C_1$ to $C_3$ alkyl or $C_1$ to $C_3$ alkoxy; with the proviso that when X' is CN, U is not $NR^6$;

Y' is selected from H, F, CN, $NO_2$ or $C_1$ to $C_4$ alkyl;
or a pharmaceutically acceptable salt thereof.

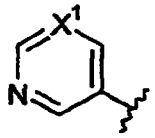
4. A compound of Claim 1 having the structure:

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wherein:

$R^5$ is a six membered ring with the structure shown



wherein :

$X^1$ is N or $CX^2$,

$X^2$ is halogen, CN or $NO_2$;

or pharmaceutically acceptable salt thereof

5. A compound of Claim 1 which is selected from the group of

i) 5-(3-Nitro-phenyl)-1,3-dihydro-indol-2-one;

ii) 3-methyl-5-(3-nitrophenyl)-1,3-dihydroindol-2-one;

iii) 5-(3-Methoxy-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one;

iv) 5-(3-Chloro-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one;

v) 3,3-Dimethyl-5-(3-nitro-phenyl)-1,3-dihydro-indol-2-one;

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vi) 5-(3-Chloro-phenyl)-3-ethyl-1,3-dihydro-indol-2-one;

vii) 5-(3-Chloro-phenyl)-3,3-diethyl-1,3-dihydro-indol-2-3,3-Diethyl-indol-2-one;

vii) 5-(3-Chloro-phenyl)-3-methoxy-3-methyl-1,3-dihydro-indol-2-one;

viii) 5-(3-Chloro-phenyl)-3-methoxy-3-prop-1-ynyl-1,3-dihydro-indol-2-one; or

ix) 5-(3-Chloro-phenyl)-1,3-dihydro-indol-2-one;

or a pharmaceutically acceptable salt thereof.

6. A compound of Claim 1 which is selected from the group of:

i) 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde;

ii) 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde oxime;

iii) 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl)benzaldehyde methyloxime ether;

iv) 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl)pyridine carbonitrile;

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v) 3-(1,2-Dihydro-2-oxospiro[cyclohexyane-1,3-[3H]indol]-5-yl)aniline;

vi) 4-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-2-thiophenecarbonitrile;

vii) 5-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-thiophene-3-carbonitrile;

viii) 2-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-thiophene-2-carbonitrile; or

ix) 5-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-3-furancarbonitrile;

or a pharmaceutically acceptable salt thereof.

7. A compound of Claim 1 which is selected from the group of:

i) 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzonitrile;

ii) 3-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-5-fluorobenzonitrile;

iii) 3-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-4-fluorobenzonitrile;

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iv) 3-(1'-Diethoxymethyl-1', 2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluorobenzonitrile;

v) 3-(7'-Bromo-1', 2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluoro-benzonitrile;

vi) 3-(7'-Nitro-1', 2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluoro-benzonitrile;

vii) 3-(7'-Amino-1', 2'-dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-5-fluoro-benzonitrile;

viii) 4-(1,2-Dihydro-2-oxospiro[cyclohexane-1,3-[3H]indol]-5-yl)-2-furancarbonitrile;

ix) 2-fluoro-4-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde oxime; or

x) 3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl)phenylacetonitrile;

or a pharmaceutically acceptable salt thereof.

8. A compound of Claim 1 which is selected from the group of:

i) 5-(3-chlorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one;

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ii) 5'-(3-Chloro-4-fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

iii) 5'-(3-Fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

iv) 5'-(3,5-Difluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

v) 5-(3,4-Difluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one;

vi) 5-[3-(Methylthio)phenyl]spiro [cyclohexane-1,3 -[3H] indol]-2(1H)-one;

vii) 5'-[3-(Methysulfinylphenyl]spiro[cyclohexane-1,3' -[3H] indol]-2'(1'H)-one;

viii) 5-[3-(Methysulfonyl)phenyl]spiro[cyclohexane-1,3 -[3H] indol]-2(1H)-one;

ix) 5'-(3-Chloro-5-fluorophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

x) 5'-(5-Nitro-1H-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one; or

xi) 5-(3-Fluoro-4-nitrophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one;

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or a pharmaceutically acceptable salt thereof.

9. A compound of Claim 1 which is selected from the group of:

i) 5-(3-Bromo-5-fluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one;

ii) 5'-(3-Fluoro-5-methylphenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

iii) 5'-(3-Nitrophenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

iv) 5-(3-Fluoro-5-nitrophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one;

v) 5'-(3-Hydroxyphenyl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

vi) 5-[4-Fluoro-3-nitrophenyl]spiro[cyclohexane-1,3- [3H]indol]-2(1H)-one;

vii) 5-(3-cyano-4-fluorophenyl)spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one;

viii) 5'-(4-Cyano-3-fluorophenyl)-spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

ix) 2,3,5,6-Tetrahydro-5-(3-nitrophenyl)spiro[3H-indole-3,4-[4H]pyran]-2(1H)-one;

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x) 5'-(Pyrimidin-5-yl)-spiro[cyclohexane]-1,3'-[3H]indol-2'(1H)-one;

xi) 5'-(1H-Indol-4-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

xii) 5-(5-Chloro-2-thienyl)spiro[cyclohexane-1,3-[3H] indol]-2(1H)-one;

xiii) 5-(5-Acetyl-2-thienyl)spiro[cyclohexane-1,3-[3H] indol]-2(1H)-one; or

xiv) 5'-(5-Nitro-1-methyl-pyrrol-2-yl)spiro[cyclohexane-1,3'-[3H]indol]-2'(1'H)-one;

or a pharmaceutically acceptable salt thereof.

10. A compound of Claim 1 which is selected from:

i) 5-(2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'yl-2-thiophenecarbonitrile;

ii) 4-Methyl-5-(2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol-5'-yl)-2-thiophene carbonitrile;

iii) 4-Ethyl-5-(2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'-yl)-2-thiophenecarbonitrile;

iv) 5-(2'-oxo-2',3'-dihydrospiro[cyclohexane-1,3'-[3H]indol]-5'yl-2-nitro-thiophene;

v) 5'-(3-Chlorophenyl)spiro[4,4-dimethylcyclohexane-1',3'-[3H]indol]-2'(1'H)-one;

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vi) 5'-(3-Nitrophenyl)spiro[4,4-dimethylcyclohexane-1',3'-[3H]indol]-2'(1'H)-one;

vii) 2-fluoro-3-(1',2'-Dihydro-2'-oxospiro[cyclohexane-1,3'-[3H]indol-5'-yl) benzaldehyde oxime;

viii) 5'-(5-Chloro-3-methylbenzo[b]thien-2-yl)spiro [cyclohexane-1,3'-[3H] indol]-2'(1'H)-one; or

ix) 5-[4-Fluoro-3-(trifluoromethyl)phenyl]spiro[cyclohexane-1,3-[3H]indol]-2(1H)-one;

or a pharmaceutically acceptable salt thereof.

11. A compound of Claim 1 which is selected from:

i) 5'-(4-Cyano-3-fluorophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one;

ii) 5'-(3-cyano-4-fluorophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one;

iii) 5'-(3-Chloro-4-fluorophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one;

iv) 5'-(3-Cyanophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one ;

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v) 4-(1,2-Dihydro-2-oxospiro[cyclopentane-1,3-[3H]indol]-5-yl)-2-thiophenecarbonitrile;

vi) 5'-(3-Cyano-5-fluorophenyl)-spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one;

vii) 4-Methyl-5-(2'-oxo-2',3'-dihydrospiro[cyclopentane-1,3'-[3H]indol-5'-yl)-2-thiophene carbonitrile;

viii) 5-(2'-oxo-2',3'-dihydrospiro[cyclopentane-1,3'-[3H]indol]-5'yl-2-nitrothiophene; or

ix) 5'-(3-nitrophenyl)spiro[cyclopentane-1,3'-[3H]indol]-2'(1'H)-one;

or a pharmaceutically acceptable salt thereof.

12. A compound of Claim 1 which is selected from:

i) 5-(3-Chloro-4-fluoro-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one;

ii) 3-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-benzonitrile;

iii) 5-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-4-methyl thiophene-2-carbonitrile;

iv) 5-(3-Chloro-5-fluoro-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one;

v) 5-(3-Fluoro-5-nitro-phenyl)-3,3-dimethyl-1,3-dihydro-indol-2-one;

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vi) 4-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-furan-2-carbonitrile;

vii) 5-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-furan-2-carbonitrile;

viii) 3-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-5-fluoro-benzonitrile;

ix) 2-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-2-nitro-pyrrole;

x) 5-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-thiophene-2-carbonitrile;

xi) 3-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-2-fluoro-benzonitrile;

xii) 2-(3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indol-5-yl)-pyrrole-1-carboxylic acid tert-butyl ester; or

xiii) 3,3-Dimethyl-5-(5-nitro-thiophene-2-yl)-1,3-dihydro-indol-2-one;

or a pharmaceutically acceptable salt thereof.

13. A compound of Claim 1 which is selected from:

i) 5'-(3-Chlorophenyl)spiro[1,3-dioxolane-2,3'-[3H] indol]-2'(1'H)-one;

or

ii) 5'-(3-Chlorophenyl)spiro[1,3-dioxane-2,3'-[3H]indol]-2'(1'H)-one;

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or a pharmaceutically acceptable salt thereof.

14. A pharmaceutical composition comprising a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

15. A method of inducing contraception in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

16. A method of treating or preventing benign or malignant neoplastic disease, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of Claim 1, or a pharmaceutically acceptable salt thereof.

17. The method of Claim 16 wherein the benign or malignant neoplastic disease is selected from uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma or other hormone-dependent tumors.

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