

**CYCLOCARBAMATE DERIVATIVES AS PROGESTERONE RECEPTOR
MODULATORS**

Field of the Invention

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

Background of the Invention

10 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).

15 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
20 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.

25 PR antagonists may be 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).



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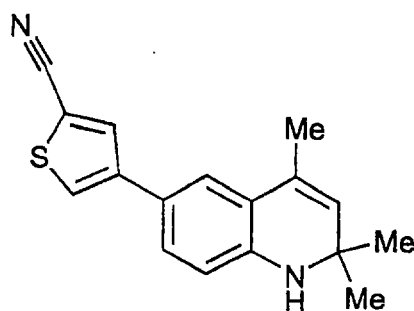
PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz, et al, *Horm. Cancer*, 283, pub: Birkhaeuser, Boston, Mass., ed. Vedeckis) as well as uterine and ovarian cancers. PR antagonists may also be useful for the treatment of non-malignant chronic conditions 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 (US 5719136).

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).

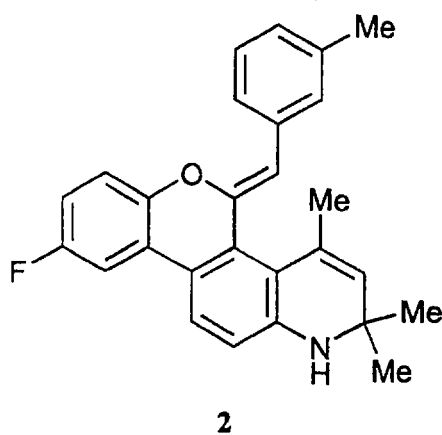
The compounds of this invention have been shown to act as competitive inhibitors of progesterone binding to the PR and act as antagonists in functional models, either/or *in-vitro* and *in-vivo*. These compounds may be used for contraception, in the treatment of fibroids, endometriosis, breast, uterine,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

Compounds of the prior art are described by Jones, *et al*, (U.S. Patent No. 5,688,810) is the PR antagonist dihydroquinoline 1.

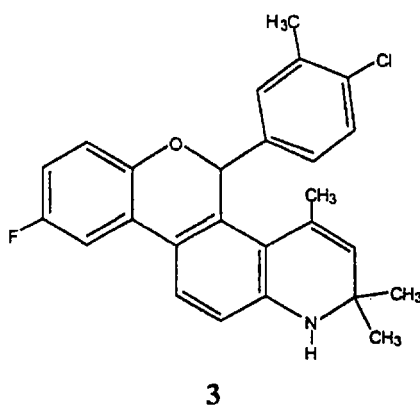


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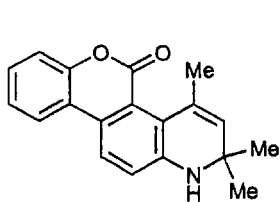
Jones, *et al*, described the enol ether **2** (U.S. Patent No. 5,693,646) as a PR ligand.



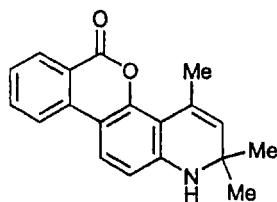
Jones, *et al*, described compound **3** (U.S. Patent No. 5,696,127) as a PR ligand.



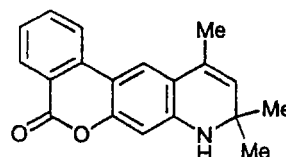
Zhi, *et al*, described lactones **4**, **5** and **6** as PR antagonists (J. Med. Chem., 41, 291, 1998).



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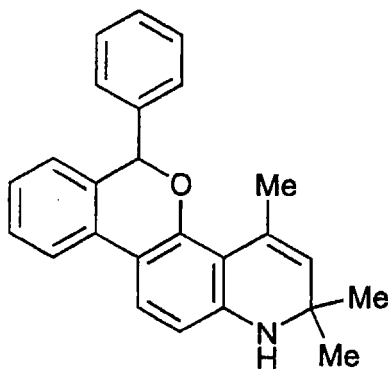


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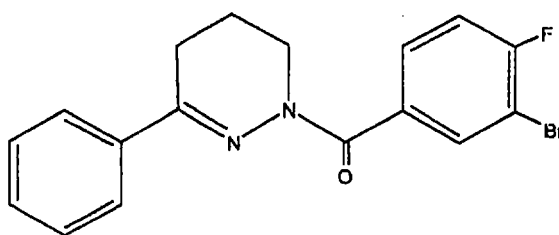
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Zhi, *et al.*, described the ether 7 as a PR antagonist (*J. Med. Chem.*, **41**, 291,
5 1998).



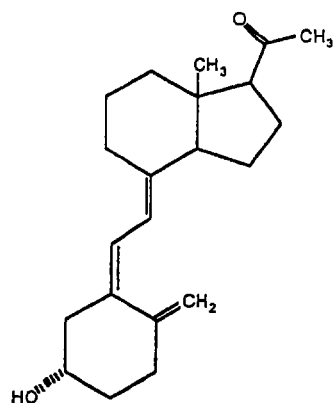
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Combs, *et al.*, disclosed the amide 8 as a ligand for the PR (*J. Med. Chem.*, **38**,
10 4880, 1995).



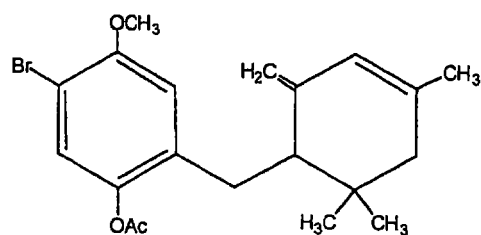
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15 Perlman, *et al.*, described the vitamin D analog 9 as a PR ligand (*Tet. Letters*,
35, 2295, 1994).



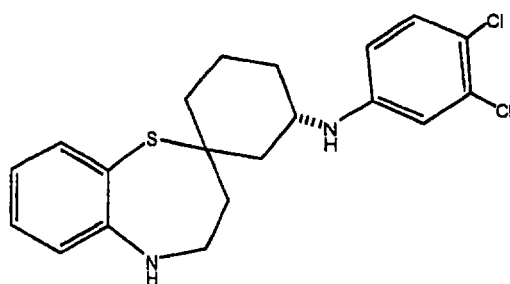
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Hamann, *et al*, described the PR antagonist 10 (*Ann. N.Y. Acad. Sci.*, **761**, 383,
5 1995).



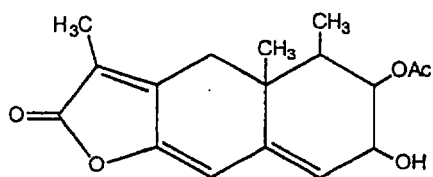
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Chen, *et al*, described the PR antagonist 11 (Chen, *et al*, POI-37, 16th Int.
10 Cong. Het. Chem., Montana, 1997).



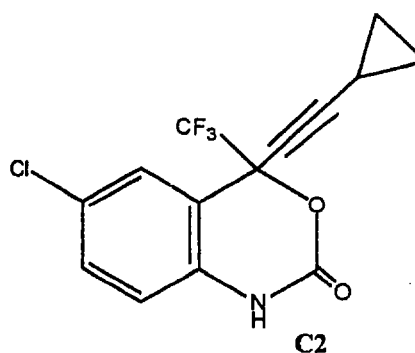
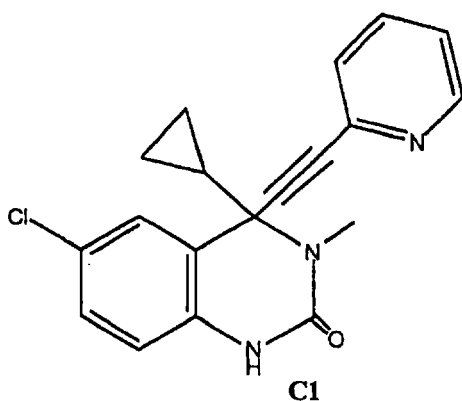
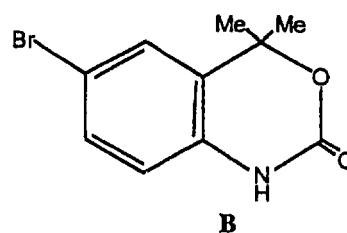
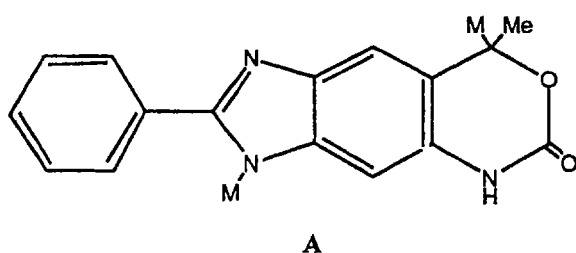
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Kurihari, *et. al.*, described the PR ligand 12 (*J. Antibiotics*, **50**, 360, 1997).



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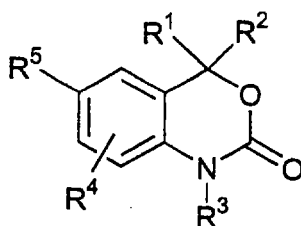
- 5 Narr et al. (German Patent, DE 3633861, CA 109:22973) claimed that imidazobenzoxazinones, e.g. **A**, as cardotonics; Benzoxazin-2-ones, such as brofoxine (**B**), being active as an anxiolytic was reported by Hartmann et al. (*Proc. West. Pharmacol. Soc.* 21, 51-55 (1978)); More recently, a number of patents (e.g. Young et al. WO95/20389; Christ et al. WO98/14436) claimed quinazolin-2-ones and benzoxazin-2-ones such as compound **C1** and **C2** as inhibitors of HIV reverse transcriptase.



The compounds in the present invention contain a pendent aromatic substituent. The aromatic substituents proved to be critical for the resultant compounds being active as progesterone receptor modulators and have broad structural diversity which may consist of aryl, substituted aryl, heteroaryl or substituted heteroaryl group.

Description of the Invention

This invention provides compounds of Formula (I):



I

10 wherein:

R¹ and R² are independent substituents selected from the group of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or R¹ and R² are fused to form:

- an optionally substituted 3 to 8 membered spirocyclic alkyl ring;
- an optionally substituted 3 to 8 membered spirocyclic alkenyl; or
- an optionally substituted 3 to 8 membered heterocyclic ring containing one to three heteroatoms from the group including O, S and N; the spirocyclic rings of a), b) and c) being optionally substituted by from 1 to 4 groups selected from fluorine, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to C₆ thioalkyl, -CF₃, -OH, -CN, NH₂, -NH(C₁ to C₆ alkyl), or -N(C₁ to C₆ alkyl)₂;

R^A 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;

5 R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

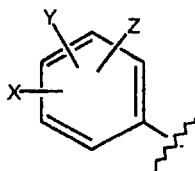
R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, COR^C ;

R^C 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^4 is H, halogen, CN, NO_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, alkynyl, or substituted alkynyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, amino, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^5 is selected from a) or b)

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



wherein:

X is taken from the group including halogen, CN, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 thioalkoxy, substituted C_1 to C_3 thioalkoxy, amino, 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^D , $OCOR^D$, or $NR^E COR^D$;

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;

5 Y and Z are independent substituents taken from the group including H, halogen, CN, NO_2 , amino, aminoalkyl, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkoxy; or

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

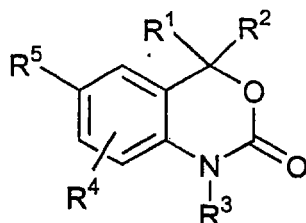
R^F is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

15 R^G 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 pharmaceutically acceptable salt thereof.

Preferred compounds of this invention include those of Formula I



I

20 wherein:

R^1 is H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A , or $NR^B COR^A$;

R² is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;

or

- 5 R¹ and R² are fused to form spirocyclic alkyl as a 3 to 8 membered spirocyclic ring, substituted spirocyclic alkyl constructed by fusing R¹ and R² to form a 3 to 8 membered spirocyclic ring, spirocyclic alkenyl constructed by fusing R¹ and R² to form a 3 to 8 membered spirocyclic ring, substituted spirocyclic alkenyl constructed by fusing R¹ and R² to form a 3 to 8 membered spirocyclic ring, spirocyclic alkyl
10 constructed by fusing R¹ and R² to form a 3 to 8 membered spirocyclic ring and containing one to three heteroatoms from the group including O, S and N; substituted spirocyclic alkyl constructed by fusing R¹ and R² to form a 3 to 8 membered spirocyclic ring and containing one to three heteroatoms from the group including O, S and N; the spirocyclic rings made by fusing R¹ and R² being optionally substituted
15 by from 1 to 4 groups selected from fluorine, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to C₆ thioalkyl, -CF₃, -OH, -CN, NH₂, -NH(C₁ to C₆ alkyl), or -N(C₁ to C₆ alkyl)₂;

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

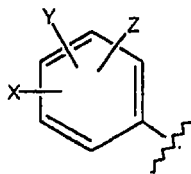
- 20 R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, or substituted alkynyl, COR^C;

- R^C is H, C₁ to C₄ alkyl, substituted C₁ to C₄ alkyl, aryl, substituted aryl, C₁ to C₄ alkoxy, substituted C₁ to C₄ alkoxy, C₁ to C₄ aminoalkyl, or substituted C₁ to C₄
25 aminoalkyl;

R⁴ is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆ aminoalkyl;

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



X is taken from the group including halogen, 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 thioalkoxy, substituted C_1 to C_3 thioalkoxy, amino, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D , $OCOR^D$, or $NR^E COR^D$;

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;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkoxy;

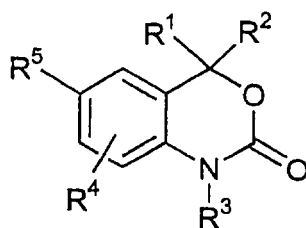
or

R^5 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO_2 or NR^6 and containing one or two independent substituents from the group including H, halogen, CN, NO_2 , amino, and C_1 to C_3 alkyl, or C_1 to C_3 alkoxy;

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

or pharmaceutically acceptable salt thereof.

Other preferred compounds are those of Formula I



I

wherein:

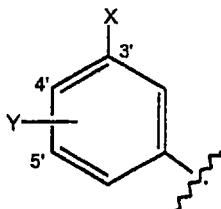
$R^1 = R^2$ and are selected from the group which includes C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, spirocyclic alkyl constructed by fusing R^1 and R^2 to form a
5 3 to 6 membered spirocyclic ring;

R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, or substituted C_1 to C_6 alkyl, COR^C ;

R^C is H, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy;

10 R^4 is H, halogen, CN, NO_2 , C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, or substituted C_1 to C_3 alkoxy;

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

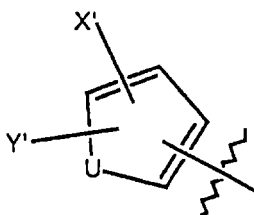


15 X is taken from the group including halogen, CN, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, C_1 to C_3 thioalkoxy;

Y is a substituent from the group including H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_4 alkyl, C_1 to C_3 thioalkoxy;

20 or

R^5 is a five membered ring with the structure



U is O, S, or NR⁶,

R⁶ is H, or C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

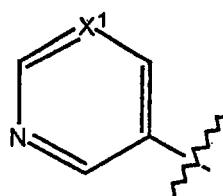
X' is from the group including halogen, CN, NO₂, or C₁ to C₃ alkyl and C₁ to

5 C₃ alkoxy, provided that when U is NR⁶, then X' is not CN;

Y' is from the group including H and C₁ to C₄ alkyl;

or

R⁵ is a six membered ring with the structure:

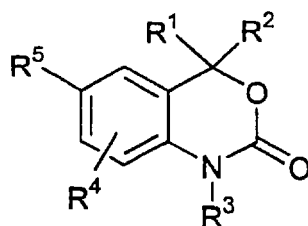


10 X¹ is N or CX²;

X² is halogen, CN, alkoxy, or NO₂;

or pharmaceutically acceptable salt thereof

Further preferred compounds are those of Formula I



I

15 wherein:

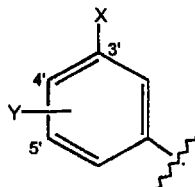
R¹ = R² and are selected from the group which includes CH₃ and spirocyclic alkyl constructed by fusing R¹ and R² to form a 6 membered spirocyclic ring

R³ is H, OH, NH₂, CH₃, substituted methyl, or COR^c;

R^c is H, C_1 to C_3 alkyl, or C_1 to C_4 alkoxy;

R^4 is H, halogen, NO_2 , CN, or C_1 to C_3 alkyl;

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



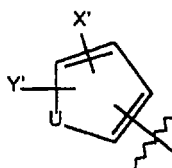
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X is taken from the group including halogen, CN, methoxy, NO_2 , or 2-thiazole;

Y is H or F;

10 or

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



U is O, S, or NH,

X' is halogen, CN, or NO_2 , provided that when U is NR^6 , X' is not CN;

15

Y' is H or C_1 to C_4 alkyl

and pharmaceutically acceptable salts.

20

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 I, 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 one to eight carbon atoms, preferably one to six carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group with at least one carbon-carbon double bond and two to eight carbon atoms, preferably two to six carbon atoms; "alkynyl" group is intended to cover both straight- and branched-chain alkyl group with at least one carbon-carbon triple bond and two to eight carbon atoms, preferably two to six carbon atoms.

The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having from one to three substituents selected from the group including halogen, CN, OH, NO₂, 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 refer 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 not limited to phenyl, naphthyl, biphenyl, anthryl, tetrahydronaphthyl, phenanthryl.

The term "substituted aryl" refers to aryl as just defined having one to four substituents from the group including halogen, CN, OH, NO₂, 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, for example, 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 one to four substituents selected from the group which includes halogen, CN, OH, NO₂, amino, alkyl, substituted alkyl, cycloalkyl, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio. The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl. The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl. The term "alkylcarbonyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl. The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl. The term "aminoalkyl" refers to both secondary and tertiary amines wherein the alkyl or substituted alkyl groups, containing one to eight carbon atoms, which may be either 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 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 comprising one or more compounds of this invention and a pharmaceutically acceptable carrier or excipient. The invention also includes methods of treatment which comprise administering to a mammal a pharmaceutically effective amount of one or more compounds as described
5 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
10 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,
20 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
25 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.

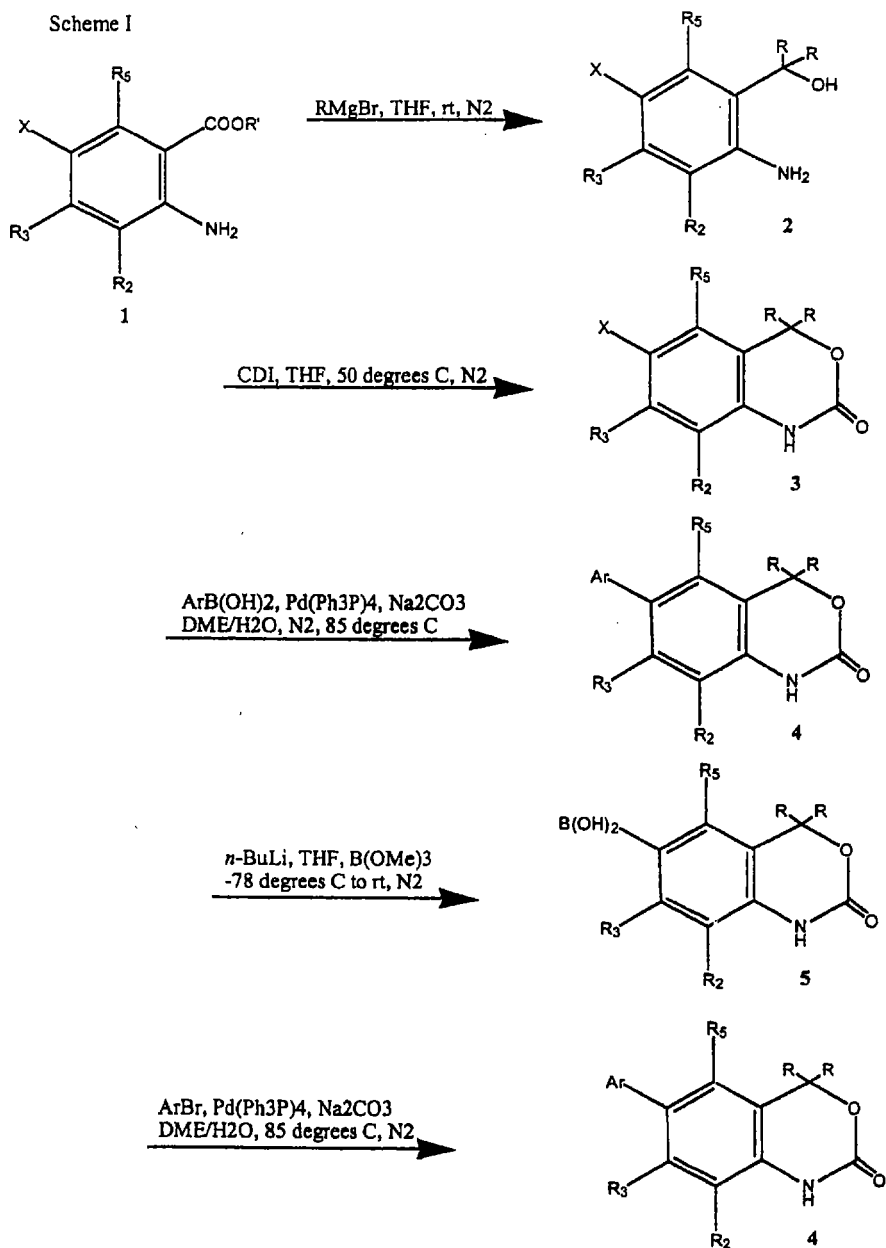
10 These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic 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. Adjuvants 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.

20 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.

25 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 exists. It must be stable under
5 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.

10 The compounds of this invention can be prepared following the Schemes illustrated below:

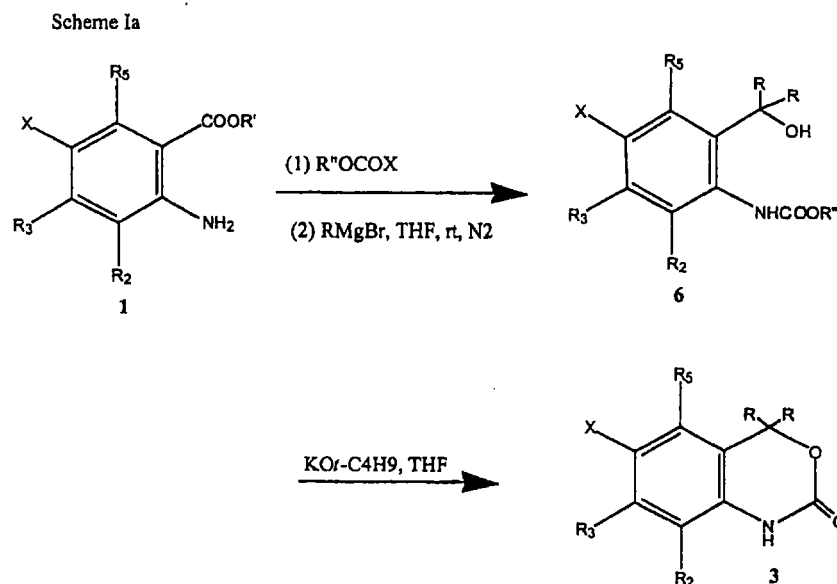


As demonstrated in Scheme I, the compounds of this invention are generally prepared by employing the suitable coupling reaction as a final step. An appropriately substituted ortho-amino benzoic acid or its derivatives such as ethyl ester ($\text{X} = \text{Br, I, Cl}$), or a latent coupling precursor such as alkoxy group which can be converted into

OTf group suitable in the coupling reaction.) was treated with a suitable organo metallic reagent, e.g. Grignard reagent, in appropriate nonprotic solvents which include but not limited to THF or ether to give ortho-amino carbinol 2 under an inert atmosphere such as argon or nitrogen at -78 °C to room temperature. Ring closure of carbinol 2 to yield benzoxazin-2-ones 3 is commonly effected by a condensing agent such as carbonyldiimidazole, phosgene, dimethylcarbonate, or diethylcarbonate in a suitable nonprotic solvent such as THF at temperatures ranging from room temperature to 65 °C. The arylation of benzoxazin-2-ones 3 to yield 4 can be effected by various coupling reactions including Suzuki, Stille reactions. These reactions are commonly performed in the presence of transition metallic catalyst, e.g., palladium or nickel complex often with phosphino ligands, e.g., Ph_3P , 1,1'-bis(diphenylphosphino)ferrocene, 1,2-bis(diphenylphosphino)ethane or palladium salt such as palladium acetate. Under this catalytic condition, an appropriately substituted nucleophilic reagent, e.g., aryl boronic acid, arylstannane, or aryl zinc compound, is coupled with benzoxazinones 3 to give 4. If a base is needed in the reaction, the commonly used bases include but not limited to sodium bicarbonate, sodium carbonate, potassium phosphate, barium carbonate, potassium acetate, or cesium fluoride. The most commonly used solvents in these reactions include benzene, DMF, isopropanol, toluene, ethanol, DME, ether, acetone or a mixture of any one of these solvent and water. The coupling reaction is generally executed under an inert atmosphere such as nitrogen or argon at temperatures ranging from room temperature to the boiling point of the solvent or solvent system or mixture.

Benzoxazinones 3 can be converted into a nucleophile such as boronic acid which can be coupled with an appropriate electrophile, e.g., aryl bromide or aryl iodide, to yield 4 employing the coupling reaction condition as described above. The transformation of 3 into 5 can be effected by treating 3 with an organo metallic reagent, e.g., *n*-BuLi, in a nonprotic solvent such as THF or ether followed by quenching the reaction solution with a suitable electrophile such as trimethyl borate,

triisopropyl borate, bishexalkyl tin reagent, or zinc chloride at temperatures ranging from -78 °C to reflux temperature under an inert atmosphere such as argon or nitrogen.



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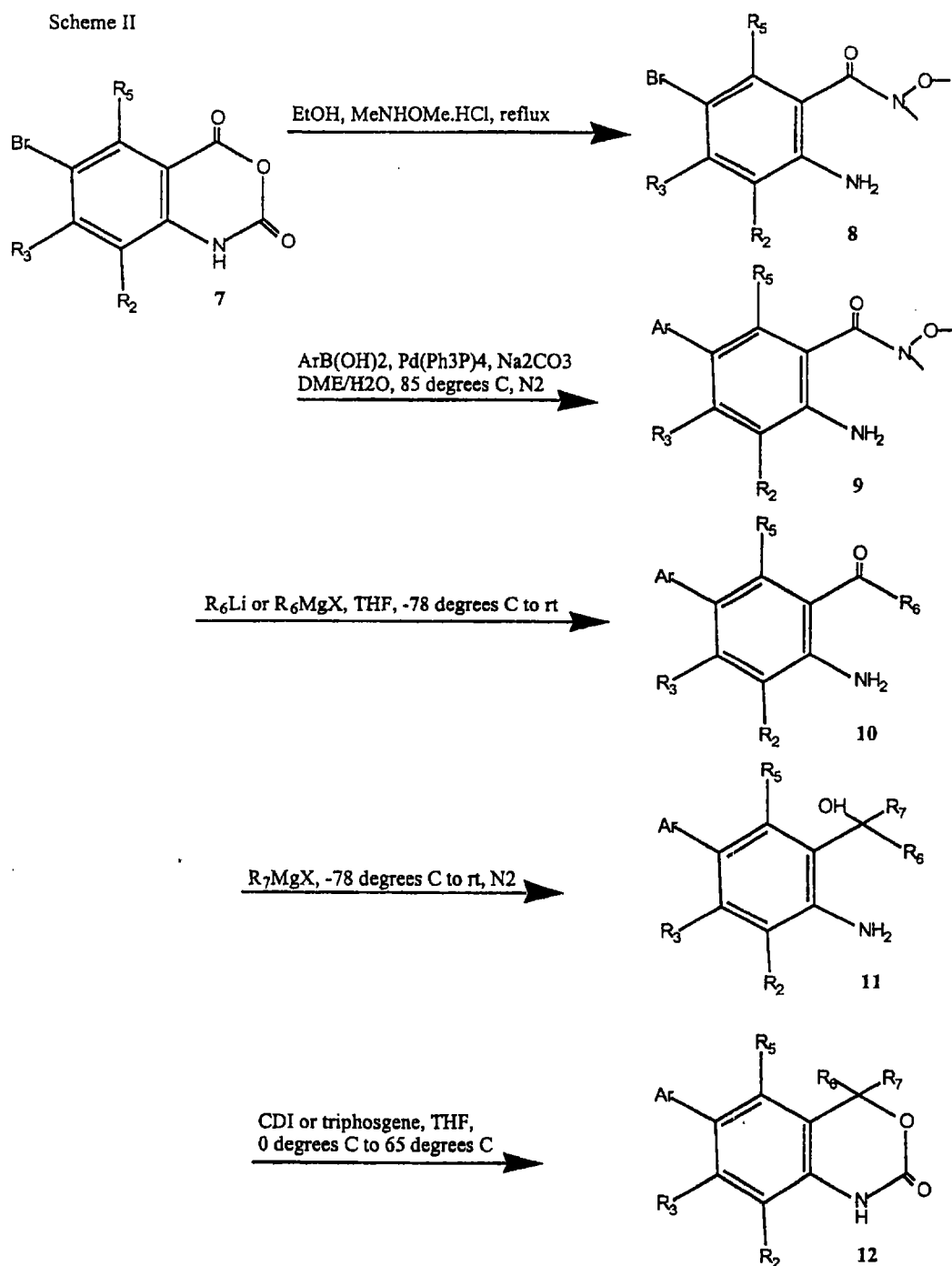
Scheme Ia illustrates an alternative approach leading to the benzoxazinones 3. Thus, an appropriate aniline 1 is protected with a suitable alkoxy carbonyl protective group including but not limited to allyloxy carbonyl, *t*-butoxy carbonyl, benzyloxy carbonyl, ethoxy carbonyl, or methoxy carbonyl in a suitable solvent such as THF, acetonitrile, with or without presence of a base either as a catalyst or as an acid scavenger. The protected aniline is then treated with a suitable organo metallic reagent such as organo lithium agent or Grignard reagent in the same fashion as to prepare compound 2 to give the carbinol 6. The treatment of 6 with a suitable base such as potassium *t*-butoxide, *n*-butyl lithium, potassium hydroxide in an appropriate solvent such as toluene, THF, alcohol under an inert atmosphere such as nitrogen or argon at the temperature ranging from room temperature to the boiling point of the relevant solvent to afford benzoxazinones 3.

10

15

Scheme II describes the procedures to prepare benzoxazinones bearing two different substituents at position-4. The Weinreb amide 8 can be prepared from an appropriately substituted isatoic anhydride 7 when treated with *N*-, *O*-dimethylhydroxyl-amine hydrochloride salt in a protic solvent such as ethanol, isopropanol at reflux under an inert atmosphere such as argon or nitrogen. Coupling of amide 8 with an aryl electrophile such as aryl boronic acid or arylstannane to give 9 can be effected by employing a typical coupling reaction such as Suzuki, Stille coupling procedure in a similar fashion as described for the preparation of benzoxazinones 4. Treatment of Weinreb amide 9 with organo metallic compounds, e.g., alkyllithium, alkynyllithium, aryllithium, or their Grignard counterpart in a nonprotic solvent such as THF or ether under an inert atmosphere such as argon or nitrogen at -78 ° to room temperature affords amino ketone 10. Conversion of ketone 10 to carbinol 11 can be effected by treatment of 10 with an organo metallic reagent such as alkyl, alkynyl, or aryl Grignard compound in a nonprotic solvent such as THF or ether under an inert atmosphere such as argon or nitrogen at -78 °C to room temperature. Conversion of ketone 10 to carbinol 11 can also be effected by reduction of ketone group of 10 to the carbinol moiety of 11 using an appropriate reducing reagent such as lithium aluminum hydride, sodium borohydride in a suitable solvent such as THF, ether, or anhydrous alcohol under an inert atmosphere in the temperature ranging from 0 °C to the boiling point of the solvent. Ring closure of carbinol 11 to produce the compounds of this invention can be accomplished with condensing agents such as carbonyldiimidazole, phosgene, dimethylcarbonate, or diethylcarbonate in a suitable nonprotic solvent such as THF at temperatures ranging from room temperature to 65 °C.

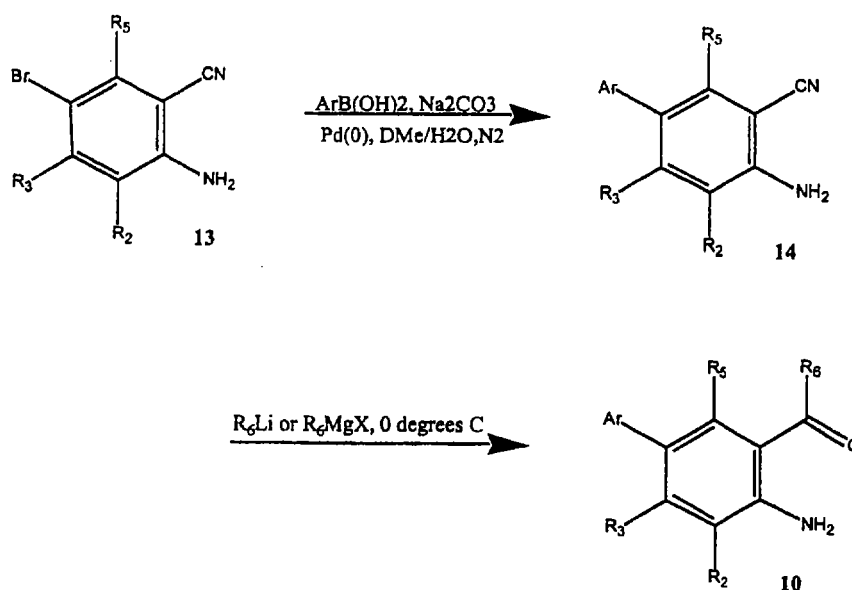
Scheme II



Alternatively, ortho-amino ketone 10 can be prepared by treatment of ortho-amino benzonitrile 14 with an organo metallic compound such as organo lithium reagent or Grignard reagent in a suitable solvent such as THF or ether under an inert

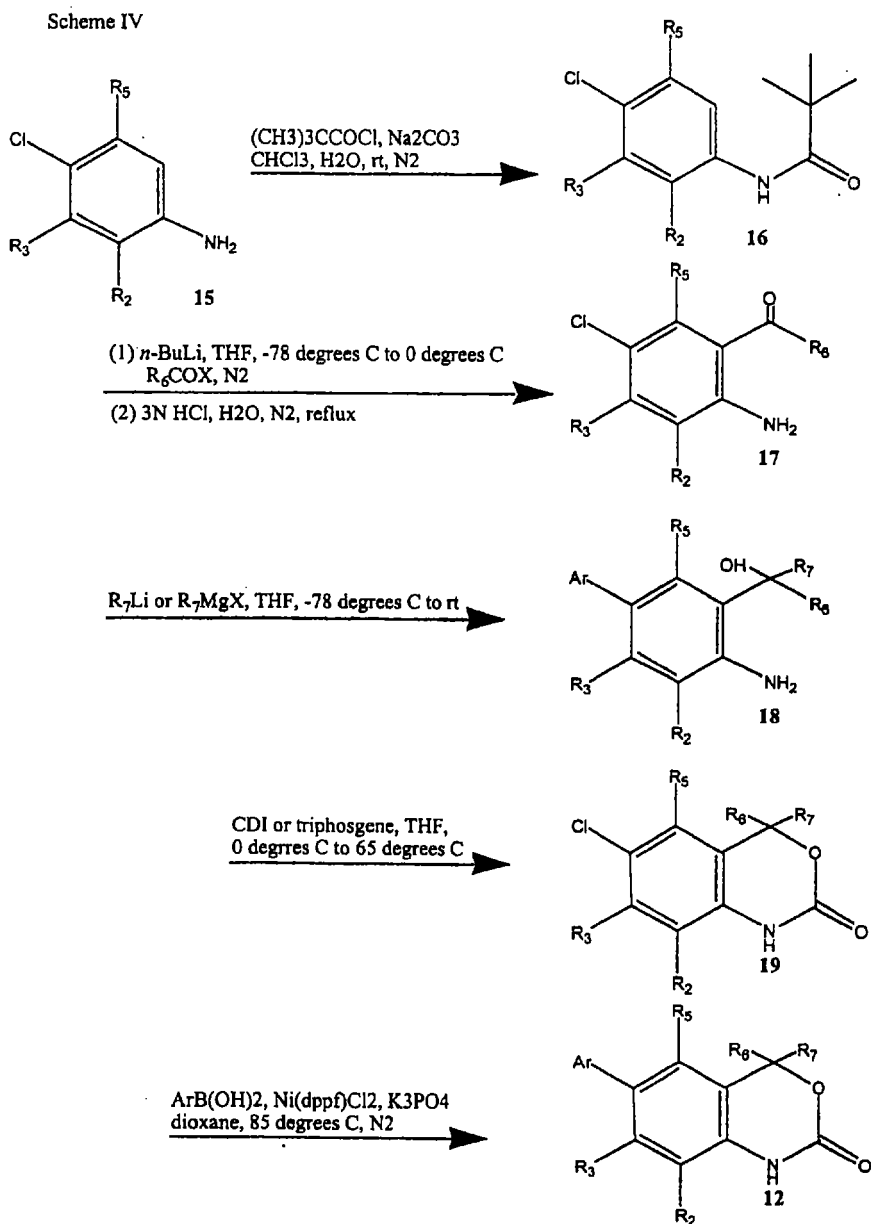
atmosphere such as argon or nitrogen at temperatures ranging from -78 °C to room temperature as illustrated in Scheme III. Benzonitrile 14 can be readily prepared from an appropriately substituted benzonitrile such as bromobenzonitrile 13 using a suitable coupling reaction such as Stille or Suzuki protocol carried out in a similar fashion as described for the preparation of the Weinreb amide 9.

Scheme III



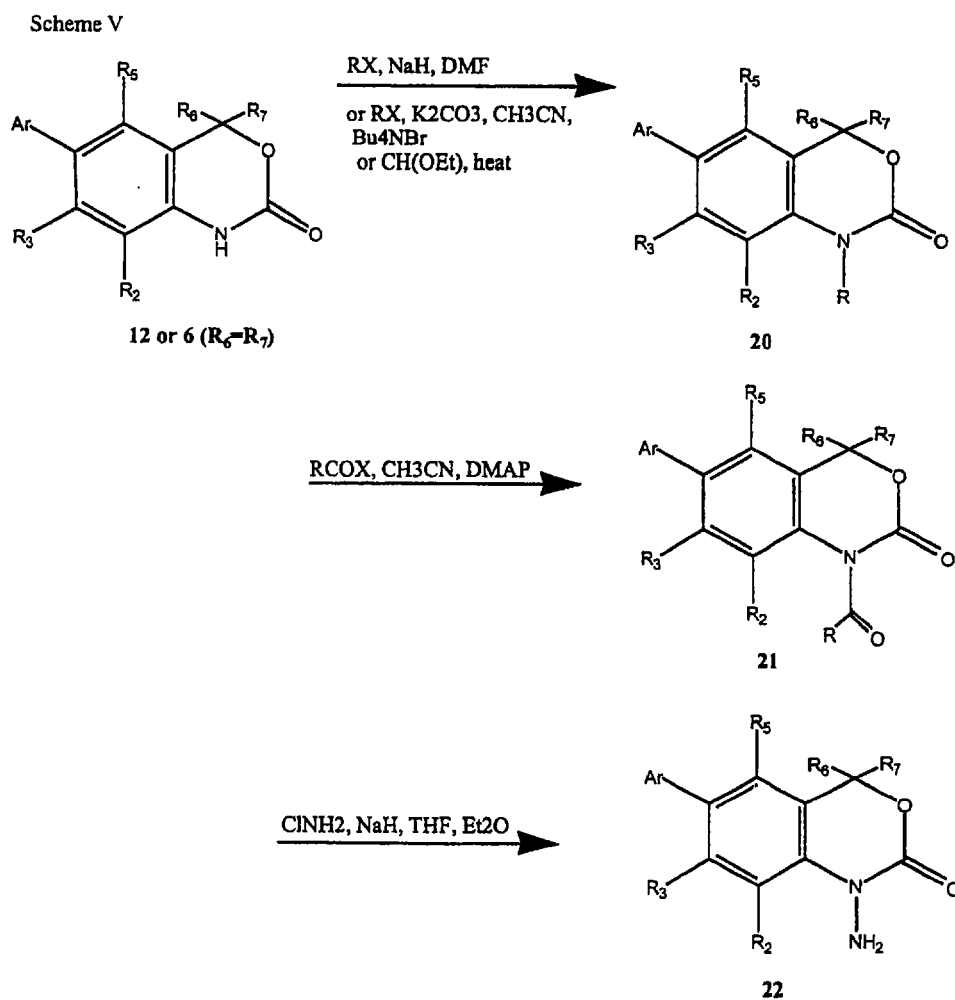
Scheme IV depicts an approach to prepare benzoxazinones with a low perfluoroalkyl substituent at position-4, e.g. R_6 is trifluoromethyl group. An appropriately substituted chloroaniline 15 was protected with a suitable protective reagent such as pivaloyl chloride or di-*tert*-butyl pyrocarbonate to give protected aniline 16 in a suitable solvent such as acetonitrile, acetone, THF, methylene chloride, or a mixture of solvent such as methylene chloride and water under an inert atmosphere such as argon or nitrogen at temperatures ranging from 0 °C to 70 °C. A suitable base such as sodium carbonate, sodium bicarbonate, or potassium carbonate may be needed when the reaction produces an acid as a side-product such as

hydrochloride. Treatment of 16 with an appropriate alkylolithium such as *n*-butyllithium or *s*-butyllithium followed by reaction with a low perfluorocarboxy derivatives, e.g., trifluoroacetyl chloride, 1-(trifluoroacetyl)-imidazole, or ethyl trifluoroacetate in a nonprotic solvent such as ether or THF under an inert atmosphere
5 such as argon or nitrogen at -78 °C to ambient temperature gives the protective ortho-amino ketones. Subsequent removal of the protecting group can be effected by reaction of protected amino ketones with a suitable acid such as TFA, 3N aqueous hydrochloride solution in a suitable solvent such as methylene chloride or water at 0 °C to boiling point of the solvent to afford ortho-amino ketone 17. The preparation of
10 6-chlorobenzoxazinones 19 from 17 can be accomplished in the same fashion as described for the synthesis of benzoxazinone 12 from ketone 10. Coupling of 19 with an aryl group to yield the compounds of this invention, 12 as shown in scheme IV can be effected by a nickel complex catalyzed coupling reaction. The palladium catalysts proved not to be an efficient catalyst in this coupling process. The coupling reaction
15 of 19 with an appropriate aryl boronic acid can be accomplished in the presence of a suitable base such as potassium phosphate and a catalyst of nickel (0 or II) complex, e.g. a nickel complex of dppe, dppf, or triphenylphosphine. The most commonly used solvents in the reaction include dioxane or THF. The coupling reaction is generally executed under an inert atmosphere such as nitrogen or argon at temperatures ranging
20 from ambient temperature to 95 °C.



As illustrated in Scheme V, the compounds **6** or **12** can be further derivatized at position-1 *via* numerous approaches leading to a variety of novel cyclocarbamate derivatives including 1-alkyl, 1-substituted alkyl, 1-carbonyl, 1-substituted carbonyl, 1-carboxy, substituted 1-carboxy derivatives. For examples, alkyl or substituted alkyl derivatives **20** can be formed by treatment of carbamate **12** or **6** with a suitable base

such as sodium hydride in suitable solvent such as DMF under an inert atmosphere such as argon or nitrogen followed by addition of an appropriate electrophile such as alkyl or substituted alkyl bromide, iodide, or triflate. Such a transformation of **12** or **6** at position-1 can also be effected using biphasic conditions as indicated in scheme V in which alkylation is executed using a biphasic catalyst such as tributylammonium bromide in a suitable solvent such as acetonitrile. Another example of this type of modification includes, but is not limited to, the one depicted in scheme V where heating **12** or **6** with triethyl orthoformate affords 1-substituted derivatives of compound **12** or **6**.



The acylation or carboxylation of the compound 12 or 6 at position-1 to give compound 21 can be readily effected by treatment of 12 or 6 with a suitable acylating or carboxylating reagent such as di-*t*-butyl dicarbonate in the presence of a suitable basic catalyst such as DMAP in a suitable solvent such as acetonitrile under an inert atmosphere such as argon or nitrogen. The amination of position-1 of compound 12 or 6 to give 22 can be accomplished using a suitable aminating reagent such as chloroamine in the presence of a suitable base, such as sodium hydride, in a suitable solvent, such as THF or diethyl ether, following literature procedures (Metlesics et al. *J. Org. Chem.* 30, 1311(1965).)

10

EXAMPLE 1

2-(2-Amino-5-bromophenyl)propan-2-ol

A solution of 2-amino-5-bromobenzoic acid (10g, 46 mmol) in dry THF (200 mL) was treated at -78 °C under nitrogen with a solution of methylmagnesium bromide in ether (3.0 M, 90 mL, 270 mmol). The reaction mixture was slowly warmed to ambient temperature, kept stirring for 48 hours under nitrogen and then poured into a cold 0.5 N aqueous hydrochloride solution (300 mL). The mixture was neutralized with aqueous 1 N sodium hydroxide solution and ethyl acetate (300 mL) was added. The organic layer was separated and aqueous layer was extracted with ethyl acetate (3x100 mL). The combined organic layers were washed with brine and dried (MgSO₄). After removal of solvent *in vacuo*, the residue was purified by a silica gel flash chromatography (hexane:ethyl acetate/3:2) to give 2-(2-amino-5-bromophenyl)propan-2-ol as off-white solid (6g, 57%): mp 62-63 °C; ¹H-NMR (CDCl₃) δ 7.19 (d, 1H, *J* = 2.3 Hz), 7.12 (dd, 1H, *J* = 8.4, 2.3 Hz), 6.51 (d, 1H, *J* = 8.4 Hz), 4.70 (s, 2H), 1.82 (s, 1H), 1.65 (s, 6H).

25

EXAMPLE 2

6-Bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

To a solution of 2-(2-amino-5-bromophenyl)propan-2-ol (18g, 78 mmol) in dry THF (150 mL) was added 1,1'-carbonyldiimidazole (15.5g, 94 mmol) under nitrogen. The reaction solution was heated at 50 °C overnight. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (100 mL). The solution was washed with 1N aqueous hydrochloride solution (2x40 mL), brine (20 mL), and dried with MgSO₄. After removal of solvent *in vacuo*, 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one was obtained as a white solid (20 g, 100%): mp 199-200 °C; ¹H-NMR (DMSO-d₆) δ 10.32 (s, 1H, D₂O exchangeable), 7.48 (d, 1H, *J* = 2.1 Hz), 7.43 (dd, 1H, *J* = 8.5, 2.1 Hz), 6.84 (d, 1H, *J* = 8.4 Hz), 1.61 (s, 6H).

EXAMPLE 3

6-Iodo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

The product was prepared, from 2-amino-5-iodobenzoic acid following the procedures of Example 1 and 2, as a white solid: mp 196-197 °C; ¹H-NMR (DMSO-d₆) δ 10.30 (s, 1H, D₂O exchangeable), 7.58 (m, 2H), 6.71 (d, 1H, *J* = 8.4 Hz), 1.58 (s, 6H). MS (EI) *m/z* 326 ([M+Na]⁺, 100%). Anal. Calc. For C₁₀H₁₀INO₂: C, 39.63, H, 3.33, N, 4.62. Found: C, 39.25, H, 3.24, N, 4.49.

EXAMPLE 4

(1,4-Dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid

To a solution of 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (2g, 7.8 mmol) in anhydrous THF (60 mL) was added a solution of *n*-BuLi in hexane (10 M, 2.4 mL, 24 mmol) at -78 °C under nitrogen. After stirring at -78 °C for 30 minutes, a slurry was obtained and treated with triisopropyl borate (6.5 mL, 28 mmol). The reaction medium was slowly warmed to ambient temperature and quenched with 1N aqueous hydrochloric acid solution (60 mL). Ethyl acetate (100 mL) was added and organic layer was separated, and aqueous layer was extracted with ethyl acetate (3x60 mL). The combined organic layer was washed with brine and

dried with MgSO_4 . The solvent was removed *in vacuo* and the residue was purified by a silica gel flash chromatography (ethyl acetate:hexane/2:1) to afford (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid as a white solid (1.4g, 81%): mp 249-250 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 10.21 (s, 1H, D_2O exchangeable), 7.90-7.95 (br s, 2H, D_2O exchangeable), 7.67 (m, 2H), 6.79 (d, 1H, $J = 7.8$ Hz), 1.61 (s, 6H); MS (ESI) m/z 222 ($[\text{M}+\text{H}]^+$, 87%).

EXAMPLE 5

6-(3-Chlorophenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one

10

(Procedure A)

A mixture of 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (1.5g, 5.9 mmol), 3-chlorophenyl boronic acid (1.83g, 11.7 mmol), tetrakis(triphenylphosphine)-palladium (0) (0.35g, 0.3 mmol), and sodium carbonate (2.48g, 23.4 mmol) in a mixture of DME and water (40 mL/10 mL) was degassed to remove the oxygen and then heated at 85 °C under a blanket of nitrogen for 3 hours. The reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous ammonium chloride solution (20 mL). Ethyl acetate (50 mL) was added and organic layer was separated. The aqueous layer was extracted with ethyl acetate (3x15 mL). The combined organic layers were washed with brine and dried with MgSO_4 . The solvent was removed *in vacuo* and the residue was purified by a silica gel flash chromatography (hexane:ethyl acetate/2:1) to afford 6-(3-chlorophenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one as a yellowish solid (1.4g, 82%): mp 158-159 °C; $^1\text{H-NMR}$ (DMSO-d_6) δ 10.31 (s, 1H, D_2O exchangeable), 7.75 (s, 1H), 7.61 (m, 3H), 7.46 (t, 1H, $J = 7.9$ Hz), 7.39 (dd, 1H, $J = 7.0, 1.1$ Hz), 6.96 (d, 1H, $J = 8.6$ Hz), 1.68 (s, 6H); Anal. Calc. For $\text{C}_{16}\text{H}_{14}\text{ClNO}_2 \cdot 0.1 \text{H}_2\text{O}$: C, 66.37, H, 4.94, N, 4.84. Found: C, 66.14, H, 4.61, N, 4.71.

EXAMPLE 6

6-(3-Methoxy-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-

oxazin-2-one

Prepared according to Procedure A from 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one and 3-methoxyphenyl boronic acid. Yellow solid: mp 164-165 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.56 (m, 2H), 7.36 (t, 1 H, *J* = 7.89 Hz), 7.20 (m, 2H), 6.96 (d, 1H, *J* = 8.88 Hz), 6.91 (dd, 1H, *J* = 8.13, 2.35 Hz), 3.8 (s, 3H), 1.7 (s, 6H); MS (ESI) *m/z* 284 ([M+H]⁺, 30%); Anal. Calc. For C₁₇H₁₇NO₃: C, 72.07, H, 6.05, N, 4.94. Found: C, 70.58, H, 5.73, N, 4.67

EXAMPLE 7

10 **6-(2-Chloro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one**

Prepared according to Procedure A from 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one and 2-chlorophenyl boronic acid. White solid: mp 181-182 °C; MS (ESI) *m/z* 288 ([M+H]⁺, 70%); Anal. Calc. For C₁₆H₁₄ClNO₂: C, 66.79, H, 4.90, N, 4.87. Found: C, 66.78, H, 4.82, N, 4.55

15

EXAMPLE 8

6-(4-Chloro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

Prepared according to Procedure A from 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one and 4-chlorophenyl boronic acid. White solid: mp 255-257 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.7 (d, 2H, *J* = 8.52 Hz), 7.55 (m, 2H), 7.5 (d, 2H, *J* = 8.52 Hz), 6.96 (d, 1H, *J* = 8.52 Hz), 1.7 (s, 6H); MS (ESI) *m/z* 288 ([M+H]⁺, 70%); Anal. Calc. For C₁₆H₁₄ClNO₂: C, 66.79, H, 4.90, N, 4.87. Found: C, 66.34, H, 4.76, N, 4.75

25

EXAMPLE 9

6-(3-Chloro-phenyl)-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

To a solution of 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanone (see example 35, 0.15g, 0.61 mmol) in anhydrous methanol was added sodium borohydride (0.07g,

- 1.03 mmol) at room temperature (rt) under nitrogen. After 15 minutes, the reaction mixture was treated with ice-water. Ethyl acetate (30 mL) was then added, the organic layer was separated, and aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic layers were washed with brine (10 mL) and dried over
5 MgSO₄. After removal of solvent, the residue obtained was crystallized from toluene to afford 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanol as a white solid (0.087g, 58%): ¹H-NMR (DMSO-d₆) δ 7.55 (t, 1H, *J* = 1.4 Hz), 7.50 (d, 1H, *J* = 7.8 Hz), 7.44 (d, 1H, *J* = 2.1 Hz), 7.39 (t, 1H, *J* = 8.2 Hz), 7.31-7.21 (m, 2H), 6.68 (d, 1H, *J* = 8.1 Hz), 5.25 (s, 2H), 5.20 (m, 1H), 4.83 (m, 1H), 1.35 (d, 3H, *J* = 8.8 Hz); MS (EI) *m/z* 247 (M⁺).
- 10 A mixture of 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanol (0.03 g, 0.13 mmol) and triphosgene (0.01 g, 0.04 mmol) in dry THF (3 mL) was stirred under a blanket of nitrogen for 10 minutes. The solvent was removed to give 6-(3-chloro-phenyl)-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one as a white solid (0.031 g, 91%): mp 155-156 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.72 (m, 1H), 7.62 (m, 2H), 7.56
15 (m, 1H), 7.47 (t, 1H, *J* = 8.00 Hz), 7.39 (d, 1H, *J* = 8.0 Hz), 6.98 (d, 1H, *J* = 8.0 Hz), 5.50 (q, 1H, *J* = 6.82 Hz), 1.6 (d, 3H, *J* = 6.82 Hz); MS (APCI) *m/z* 274 ([M+H]⁺, 100%).

EXAMPLE 10

20 **6-(3-Chloro-phenyl)-4-ethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one**

- Prepared according to the procedure of Example 9 from 1-(4-amino-3'-chloro-biphenyl-3-yl)-propanol and triphosgene. White solid: mp 146-148 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.70 (m, 1H), 7.60 (m, 3H), 7.47 (t, 1H, *J* = 8.22 Hz), 7.39 (d, 1H, *J* = 8.28 Hz), 6.97 (d, 1H, *J* = 8.22 Hz), 5.4 (t, 1H, *J* = 10.9 Hz), 1.9 (m, 2H),
25 0.97 (t, 3H, *J* = 7.68 Hz); MS (ESI) *m/z* 286 ([M-H]⁺, 100%)

EXAMPLE 11

6-(3-Chloro-phenyl)-4-phenyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from 1-(4-amino-3'-chloro-biphenyl-3-yl)-benzyl alcohol and triphosgene according to the procedure of Example 9. Off-white solid: mp 177-178 °C; ¹H-NMR (DMSO-d₆) δ 10.5 (s, 1H), 7.68 (dd, 1H, *J* = 8.7, 1.7 Hz), 7.62 (t, 1H, *J* = 1.74 Hz), 7.54-7.5 (m, 1H), 7.48-7.34 (m, 8H), 7.04 (d, 1H, *J* = 8.7 Hz), 6.6 (s, 1H);
5 MS (ESI) *m/z* 336 ([M+H]⁺, 30%).

EXAMPLE 12

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile

(Procedure B)

10 A mixture of (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid (2.22g, 10 mmol), 3-bromobenzonitrile (2.18g, 12 mmol), tetrakis(triphenylphosphine)palladium (0) (0.6g, 0.52 mmol), and sodium carbonate (2.2g, 21 mmol) in a mixture of DME and water (70 mL/15 mL) was degassed to remove the oxygen and then heated at 85 °C under a blanket of nitrogen for 3 hours.
15 The reaction mixture was cooled to ambient temperature and quenched with a saturated aqueous ammonium chloride solution (20 mL). Ethyl acetate (100 mL) was added and organic layer was separated. The aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with brine and dried with MgSO₄. The solvent was removed *in vacuo* and the residue was purified by a
20 silica gel flash chromatography (hexane:ethyl acetate/1:1) to give 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile as an off-white solid (0.7g, 25%): mp 236-237 °C; ¹H-NMR (DMSO-d₆) δ 10.34 (s, 1H, D₂O exchangeable), 8.21 (s, 1H), 8.02 (d, 1H, *J* = 8.1 Hz), 7.79 (d, 1H, *J* = 7.7 Hz), 7.60-7.70 (m, 3H), 6.98 (d, 1H, *J* = 8.2 Hz), 1.71 (s, 6H); Anal. Calc. For C₁₇H₁₄N₂O₂·0.1
25 H₂O: C, 72.89, H, 5.11, N, 10.00. Found: C, 72.75, H, 5.05, N, 9.65.

EXAMPLE 13

4,4-Dimethyl-6-(3-nitrophenyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one

Prepared from 6-iodo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one and 3-nitrophenyl boronic acid according to Procedure A. Yellowish solid: mp 244-245 °C; ¹H-NMR (DMSO-d₆) δ 10.38 (s, 1H, D₂O exchangeable), 8.47 (s, 1H), 8.14-8.20 (m, 2H), 7.70-7.76 (m, 3H), 7.01 (d, 1H, *J* = 8.1 Hz), 1.68 (s, 6H); MS (EI) *m/z* 297([M-H]⁺, 100%). Anal. Calc. For C₁₆H₁₄N₂O₄: C, 64.42, H, 4.73, N, 9.39. Found: C, 63.93, H, 4.91, N, 8.71.

10

EXAMPLE 14

6-(3-Bromo-5-fluorophenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 1,3-dibromo-5-fluorobenzene following Procedure B. White solid: mp 182-183 °C; ¹H-NMR (DMSO-d₆) δ 10.36 (s, 1H, D₂O exchangeable), 7.78 (s, 1H), 7.58-7.65 (m, 3H), 7.49 (dd, 1H, *J* = 8.3, 1.8 Hz), 6.96 (d, 1H, *J* = 8.5 Hz), 1.69 (s, 6H); ¹⁹F-NMR (DMSO-d₆) δ -112.46 (m, 1F); MS (CI) *m/z* 352 ([M+H]⁺, 78%), 350 ([M+H]⁺, 75%). Anal. Calc. For C₁₆H₁₃BrFNO₂: C, 54.88, H, 3.74, N, 4.00. Found: C, 54.83, H, 3.82, N, 3.95.

20

EXAMPLE 15

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluorobenzonitrile

A mixture of 6-(3-bromo-5-fluorophenyl)-4,4-dimethyl-2H-benz[d][1,3]oxazin-2-one (1g, 2.8 mmol), zinc cyanide (0.2g, 1.7 mmol), and tetrakis(triphenylphosphine)-palladium (0) (0.2g, 0.17 mmol) in dry DMF (20 mL) was degassed to remove oxygen and then was heated at 85 °C under a blanket of nitrogen for 6.5 hours. The reaction solution was cooled to room temperature and poured onto a cold saturated aqueous ammonium chloride solution (100 mL). The white precipitate appeared and was collected on a filter. The white solid was washed

with the distilled water (3x20 mL) and dissolved in a mixture of ethyl acetate (10 mL) and methanol (10 mL). The solution was applied on a pad of silica gel and eluted with a mixture of ethyl acetate and hexane (1:1). After evaporation, 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluorobenzonitrile was obtained as a white solid (0.7g, 84%): mp 253-254 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H, D₂O exchangeable), 8.13 (s, 1H), 7.92 (m, 1H), 7.82 (m, 1H), 7.73 (m, 2H), 6.98 (d, 1H, *J* = 8.2 Hz), 1.68 (s, 6H); ¹⁹F-NMR (DMSO-d₆) δ -112.25 (m, 1F); MS (EI) *m/z* 296 (M⁺, 65%); Anal. Calc. For C₁₇H₁₃FN₂O₂: C, 68.91, H, 4.42, N, 9.45. Found: C, 68.85, H, 4.58, N, 9.14.

10

EXAMPLE 16

5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-nicotinonitrile

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 3-bromo-5-cyanopyridine according to Procedure B. Off-white solid: mp 290-291 °C; ¹H-NMR (DMSO-d₆) δ 10.41 (s, 1H, D₂O exchangeable), 9.21 (d, 1H, *J* = 2.2 Hz), 8.97 (d, 1H, *J* = 1.7 Hz), 8.68 (t, 1H, *J* = 2.1 Hz), 7.76 (m, 2H), 7.01 (d, 1H, *J* = 8.2 Hz), 1.70 (s, 6H); MS (ESI) *m/z* 278(M-H, 96%). Anal. Calc. For C₁₆H₁₃N₃O₂·0.2 H₂O: C, 67.94, H, 4.77, N, 14.85. Found: C, 68.04, H, 4.70, N, 14.58.

20

EXAMPLE 17

4-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-2-carbonitrile

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 4-bromo-2-thiophenecarbonitrile according to Procedure B. Yellowish solid: mp 230-231 °C (decomposed); ¹H-NMR (CDCl₃) δ 8.32 (s, 1H, D₂O exchangeable), 7.83 (d, 1H, *J* = 1.5 Hz), 7.61 (d, 1H, *J* = 1.4 Hz), 7.43 (dd, 1H, *J* = 8.2, 1.9 Hz), 7.29 (d, 1H, *J* = 1.8 Hz), 6.85 (d, 1H, *J* = 8.2 Hz), 1.78 (s, 6H); MS (EI)

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m/z 283(M-H, 100%). Anal. Calc. For $C_{15}H_{12}N_2O_2S \cdot 0.2 H_2O$: C, 62.57, H, 4.34, N, 9.73. Found: C, 62.48, H, 4.31, N, 9.64.

EXAMPLE 18

5

5-Bromo-2-thiophenecarbonitrile

A mixture of 5-bromo-2-thiophenecarboxaldehyde (96.0g, 500 mmol), hydroxylamine hydrochloride (111.9g, 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
10 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 (44.31g, 215 mmol), copper (II) acetate monohydrate (4.2g, 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
15 (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 title compound as an off-white solid (31.5g combined, 58%). IR (film) cm^{-1} 2200.
20 1H -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%).

EXAMPLE 19

5-Bromo-4-methyl-2-thiophene carboxaldehyde

25

To a solution of diethylamine (28g, 0.383 mol) in anhydrous THF (400 mL) was added a solution of *n*-BuLi (2.5 M, 153 mL, 0.383 mol) in hexane. The solution was then stirred at $-40^\circ C$ under nitrogen for 30 minutes, cooled to $-78^\circ C$ 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 $-78^\circ C$ 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 product was extracted with ethyl acetate (3x450 mL). The extracts were washed with water, brine and dried (MgSO₄). After removal of solvent *in vacuo*, the title 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. ¹H-NMR (CDCl₃) δ 9.75 (s, 1H), 7.45 (s, 1H), 2.26 (s, 3H); MS (EI) *m/z* 204/206 (M⁺). Anal. Calc. For C₆H₅BrOS: C, 35.14; H, 2.46. Found: C, 35.00; H, 2.44.

10

EXAMPLE 20

5-Bromo-4-methyl-2-thiophenecarbonitrile

Prepared from 5-bromo-4-methyl-2-thiophene carboxaldehyde using the procedure of Example 18. White solid: mp 40-42 °C; IR (KBr) 2200 cm⁻¹; ¹H-NMR (CDCl₃) δ 7.29 (s, 1H), 2.21 (s, 3H). MS (EI) *m/z* 201/203 (M⁺, 98%/100%); Anal. Calc. For C₆H₄BrNS: C, 35.66; H, 1.99; N, 6.93. Found: C, 36.00; H, 2.14; N, 6.76.

15

EXAMPLE 21

5-(4,4-Dimethyl-2-oxo-1, 4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-2-carbonitrile

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Prepared according to Procedure B from 5-bromo-2-thiophenecarbonitrile and (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid. Off-white solid: mp 264-266 °C. ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.97 (d, 1H, *J* = 7.9 Hz), 7.60-7.66 (m, 3H), 6.96 (d, 1H, *J* = 8.1 Hz), 1.65 (s, 6H). MS (APCI) *m/z* 285 (M+H)⁺, 302 (M+NH₄)⁺. Anal. Calc. For C₁₅H₁₂N₂O₂S: C, 63.36; H, 4.25; N, 9.85. Found: C, 63.01; H, 4.36; N, 9.39.

25

EXAMPLE 22

5-(4, 4-Dimethyl-2-oxo-1, 4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-methyl-thiophene-2-carbonitrile

Prepared according to Procedure B from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 5-bromo-4-methyl-2-thiophenecarbonitrile.

- 5 Off-white solid: mp 195-200 °C. ¹H-NMR (DMSO-d₆) δ 10.2 (s, 1H), 8.32 (s, 1H), 7.41-7.44 (m, 2H), 7.01 (d, 1H, *J* = 8.8 Hz), 2.28 (s, 3H), 1.64 (s, 6H); MS (APCI) *m/z* 299 [M+H]⁺. Anal. Calc. For C₁₆H₁₄N₂O₂S; C, 64.41; H, 4.75; N, 8.89. Found: C, 64.64; H, 4.62; N, 9.39.

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EXAMPLE 23

4-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-furan-2-carbonitrile

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 4-bromo-2-furancarbonitrile according to Procedure B. Off-white

- 15 solid: mp 255-256 °C. ¹H-NMR (DMSO-d₆) δ 10.32 (s, 1H, D₂O exchangeable), 8.57 (s, 1H), 8.15 (s, 1H), 7.61 (s, 1H), 7.55 (dd, 1H, *J* = 8.3, 1.5 Hz), 6.92 (d, 1H, *J* = 8.2 Hz), 1.65 (s, 6H); MS (ESI) *m/z* 269(M+H, 72%). Anal. Calc. For C₁₅H₁₂N₂O₃; C, 67.16, H, 4.51, N, 10.44. Found: C, 67.14, H, 4.59, N, 10.07.

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EXAMPLE 24

4,4-Diethyl-6-(3-nitrophenyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one

Prepared from 4,4-diethyl-6-iodo-1,4-dihydrobenzo[d][1,3]oxazin-2-one and 3-nitrophenyl boronic acid according to Procedure A. Off-white solid: mp 193-194

- 25 °C. ¹H-NMR (CDCl₃) δ 9.19 (s, 1H, D₂O exchangeable), 8.38 (t, 1H, *J* = 1.9 Hz), 8.20 (m, 1H), 7.83 (m, 1H), 7.61 (t, 1H, *J* = 8.0 Hz), 7.50 (dd, 1H, *J* = 8.2, 2.0 Hz), 7.23 (d, 1H, *J* = 1.7 Hz), 6.99 (d, 1H, *J* = 8.3 Hz), 2.09 (q, 4H, *J* = 7.4 Hz), 0.96 (t, 6H, *J* = 8.3 Hz); MS (EI) *m/z* 325 ([M-H]⁺, 100%). Anal. Calc. For C₁₈H₁₈N₂O₄·0.3 H₂O: C, 65.17, H, 5.65, N, 8.44. Found: C, 65.31, H, 5.60, N, 8.10.

EXAMPLE 25

6-(3-Chlorophenyl)-4,4-diethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one

Prepared from 4,4-diethyl-6-iodo-1,4-dihydrobenzo[d][1,3]oxazin-2-one and 3-chlorophenyl boronic acid according to Procedure A. White solid: mp 150-151 °C.

5 ¹H-NMR (CDCl₃) δ 8.52 (s, 1H, D₂O exchangeable), 7.50 (s, 1H), 7.31-7.44 (m, 4H), 7.16 (d, 1H, *J* = 1.5 Hz), 6.89 (d, 1H, *J* = 8.2 Hz), 2.03 (m, 4H), 0.94 (t, 6H, *J* = 7.4 Hz); MS (EI) *m/z* 315(M⁺, 53%). Anal. Calc. For C₁₈H₁₈ClNO₂: C, 68.46, H, 5.75, N, 4.44. Found: C, 68.16, H, 5.81, N, 4.32.

10

EXAMPLE 26

1-(2-Amino-5-bromo-phenyl) cyclohexanol

Prepared according to the procedure of Example 1 from 2-amino-5-bromobenzoic acid and the Grignard reagent prepared from 1,5-dibromopentane. A clear oil: ¹H-NMR (DMSO-d₆) δ 7.07 (d, 1H, *J* = 2.3 Hz), 7.03 (dd, 1H, *J* = 8.4, 2.4 Hz), 6.55 (d, 1H, *J* = 8.6 Hz), 5.49 (s, 2H, D₂O exchangeable), 5.00 (s, 1H, D₂O exchangeable), 2.01 (d, 2H, *J* = 1.8 Hz), 1.66-1.77 (m, 2H), 1.44-1.61 (m, 4H), 1.16-1.34 (m, 2H). MS (ESI) *m/z* 270/272 ([M+H]⁺, 98%/100%).

15

EXAMPLE 27

6-Bromo-spiro[4H-3, 1-benzoxazine-4, 1'-cyclohexane-2-(1H)-one

Prepared from 1-(2-amino-5-bromo-phenyl) cyclohexanol and carbonyl diimidazole according to the procedure of Example 2. Off-white solid: mp 208-210 °C. ¹H-NMR (DMSO-d₆) δ 10.26 (s, 1H), 7.45 (d, 1H, *J* = 2.2 Hz), 7.39 (dd, 1H, *J* = 8.2, 2.2 Hz), 6.81 (d, 1H, *J* = 8.3 Hz), 1.90-1.97 (m, 2H), 1.80-1.85 (m, 5H), 1.25-1.35 (m, 1H); MS (APCI) *m/z* 296 ([M+H]⁺, 68%)

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EXAMPLE 28

Spiro-(4, 1'-cyclohexane-1, 4-dihydro-2-oxo-2H-3, 1-benzoxazin-6-yl) boronic acid

Prepared according to the procedure of Example 4 from 6-bromo-spiro[4H-3, 1-benzoxazine-4, 1'-cyclohexane-2-(1H)-one. Off-white solid: mp 223-225 °C. ¹H-NMR (DMSO-d₆) δ 10.17 (s, 1H, D₂O exchangeable), 7.92 (s, 2H, D₂O exchangeable), 7.67 (s, 1H), 7.63 (dd, 1H, *J* = 8.0, 1.1 Hz), 6.81 (d, 1H, *J* = 7.9 Hz), 1.96(s, 1H), 1.93 (s, 1H), 1.57-1.88 (m, 7H), 1.24-1.34 (m, 1H); MS (ESI) *m/z* 262 (M+H)⁺.

EXAMPLE 29

6-(3-Chlorophenyl)-spiro[4H-3, 1-benzoxazine-4, 1'-cyclohexane-2-(1H)-one

Prepared according to Procedure A from 6-bromo-spiro[4H-3,1-benzoxazine-4,1'-cyclohexane]-2(1H)-one and 3-chlorophenyl boronic acid. Off-white solid: mp 165-168 °C. ¹H-NMR (DMSO-d₆) δ 10.25 (s, 1H), 7.74 (t, 1H, *J* = 1.9 Hz), 7.50-7.67 (m, 3H), 7.42-7.49 (m, 1H), 7.35-7.38 (m 1H), 6.93-6.95 (d, 1H, *J* = 4.2 Hz), 1.91-1.98 (m, 4H), 1.64-1.76 (m, 3H), 1.60 (m, 2H), 1.29-1.39 (m, 1H); MS (APCI) *m/z* 328 ([M+H]⁺, 80%)

EXAMPLE 30

6-Bromo-spiro-[4H-3, 1-benzoxazine-4, 1'-cyclopentane-2-(1H)-one

Prepared according to the procedure of Example 26 and 27 from 2-amino-5-bromobenzoic acid and the Grignard reagent prepared from 1,4-dibromobutane. Off-white solid: mp 180-185 °C. ¹H-NMR (DMSO-d₆) δ 10.29 (s, 1H, D₂O exchangeable), 7.45 (d, 1H, *J* = 2.2 Hz), 7.41 (dd, 1H, *J* = 8.1, 2.1 Hz), 6.82 (d, 1H, *J* = 8.0 Hz), 1.96-2.09 (m, 4H), 1.76-1.87 (m, 4H); MS (EI) *m/z* 281 (M⁺, 98%). Anal. Calc. For C₁₂H₁₂BrNO₂: C 51.08; H, 4.29; N, 4.96. Found: C, 50.53; H, 4.21; N, 4.85

EXAMPLE 31

6-(3-Chlorophenyl)-spiro-[4H-3, 1-benzoxazine-4, 1'-cyclopentane]-2(1H)-one

Prepared from 6-bromo-spiro-[4H-3, 1-benzoxazine-4, 1'-cyclopentane-2-(1H)-one and 3-chlorophenyl boronic acid according to Procedure A. Off-white solid:

mp 140-145 °C. ¹H-NMR (DMSO-d₆) δ 10.27 (s, 1H), 7.75 (t, 1H, *J* = 1.8 Hz), 7.53-7.63 (m, 3H), 7.44 (t, 1H, *J* = 7.9 Hz), 7.36 (m, 1H), 6.95 (d, 1H, *J* = 8.6 Hz), 2.09-2.15 (m, 4H), 1.81-1.89 (m, 4H). MS (ESI) *m/z* 314 [M+H]⁺. Anal. Calc. For C₁₈H₁₆ClNO₂: C, 68.90; H, 5.14; N, 4.46. Found: C, 60.94; H, 4.94; N, 3.78.

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EXAMPLE 32

6-(3-Nitrophenyl)-spiro[4H-3,1-benzoxazine-4,1'-cyclohexan]-2(1H)-one

Prepared from 6-bromo-spiro[4H-3,1-benzoxazine-4,1'-cyclohexane]-2(1H)-one and 3-nitrophenyl boronic acid according to Procedure A. Off-white solid: mp 245-246 °C. ¹H-NMR (CDCl₃) δ 8.39 (t, 1H, *J* = 1.9 Hz), 8.20 (dd, 1H, *J* = 8.2, 1.4 Hz), 8.11 (s, 1H, D₂O exchangeable), 7.86 (d, 1H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 8.1 Hz), 7.50 (dd, 1H, *J* = 8.2, 1.9 Hz), 7.39 (d, 1H, *J* = 1.8 Hz), 6.93 (d, 1H, *J* = 8.2 Hz), 2.25 (d, 2H, *J* = 12.7 Hz), 1.60-1.99 (m, 7H), 1.31-1.42 (m, 1H); MS (EI) *m/z* 337 ([M-H]⁺, 100%). Anal. Calc. For C₁₉H₁₈N₂O₄·0.35H₂O: C, 66.21, H, 5.47, N, 8.13. Found: C, 66.22, H, 5.43, N, 7.86.

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EXAMPLE 33

2-Amino-5-bromo-N-methoxy-N-methylbenzamide

To a mixture of *N*, *O*-dimethylhydroxylamine hydrochloride (9.42g, 96 mmol) and triethyl amine (13.5 mL, 96 mmol) in ethanol and water (100 mL/10 mL) was added a solution of 5-bromoisatoic anhydride (20g, 74 mmol) in ethanol and water (100 mL/10 mL) at ambient temperature under nitrogen. The reaction mixture was heated at reflux for 3 hours. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate (100 mL), washed with 1N aqueous sodium hydroxide solution (2x 20 mL), brine (30 mL), and dried with MgSO₄. After removal of the solvent, the residue was purified by a silica gel flash chromatography (hexane:ethyl acetate/3:2) to give 2-amino-5-bromo-N-methoxy-N-methylbenzamide as an off-white solid (13g, 68%): mp 80-81 °C; ¹H-NMR (CDCl₃) δ 7.49 (d, 1H, *J* = 2.1 Hz), 7.26

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(dd, 1H, $J = 8.3, 2.0$ Hz), 6.59 (d, 1H, $J = 8.4$ Hz), 4.69 (br, 2H), 3.58 (s, 3H), 3.34 (s, 3H); Anal. Calc. For $C_9H_{11}BrN_2O_2$: C, 41.72, H, 4.28, N, 10.81. Found: C, 41.99, H, 4.16, N, 10.82.

EXAMPLE 34

5

4-Amino-3'-chloro-biphenyl-3-carbonitrile

Prepared from 2-amino-5-bromobenzonitrile and 3-chlorophenyl boronic acid according to procedure A. Off-white solid: mp 118-119 °C; 1H -NMR (DMSO- d_6) δ 7.80 (d, 1H, $J = 2.3$ Hz), 7.65-7.72 (m, 2H), 7.57 (d, 1H, $J = 8.0$ Hz), 7.42 (t, 1H, $J = 7.9$ Hz), 7.31 (m, 1H), 6.87 (d, 1H, $J = 8.7$ Hz), 6.29 (br, 2H); Anal. Calc. For $C_{13}H_9ClN_2$: C, 68.28, H, 3.97, N, 12.25. Found: C, 67.68, H, 4.06, N, 11.89.

EXAMPLE 35

1-(4-Amino-3'-chloro-biphenyl-3-yl)-ethanone

A mixture of 2-amino-5-bromo-*N*-methoxy-*N*-methylbenzamide (7.78g, 30 mmol), 3-chlorophenyl boronic acid (5.63g, 36 mmol), tetrakis(triphenylphosphine)palladium (0) (1.73g, 1.5 mmol), and sodium carbonate (7.63g, 72 mmol) in a mixture of DME and water (150 mL/30 mL) was degassed to remove the oxygen and heated at 85 °C under nitrogen for 3 hours. The reaction mixture was cooled to room temperature and treated with brine (30 mL) and ethyl acetate (100 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. After removal of solvent, the residue was purified by a flash chromatography (silica gel, hexane:ethyl acetate/1:1) to give 5-(3-chlorophenyl)-*N*-methoxy-*N*-methylbenzamide as a brown oil (5g, 57%). To a solution of this benzamide (5g, 17.2 mmol) in anhydrous THF was added in a dropwise fashion a solution of methyllithium in ether (1.4M, 28.6 mL, 40 mL) at -78 °C under nitrogen. After stirring for 30 minutes, the reaction mixture was treated with a saturated aqueous ammonium chloride solution (50 mL) at -78 °C. Ethyl acetate (100 mL) was added, organic layer was separated, and aqueous layer was extracted with ethyl

acetate (3x20 mL). The combined organic layers were washed (brine) and dried (MgSO₄). After removal of solvent, the residue was purified by a flash chromatography (silica gel, hexane:ethyl acetate/2:1) to afford 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanone as a yellow solid (2g, 47%): mp 89-90 °C; ¹H-NMR (CDCl₃) δ 7.89 (d, 1H, *J* = 2.0 Hz), 7.51 (m, 2H), 7.25-7.40 (m, 3H), 6.73 (d, 1H, *J* = 8.6 Hz), 6.38 (br, 2H), 2.65 (s, 3H); MS (EI) *m/z* 268([M+Na]⁺, 60%); Anal. Calc. For C₁₄H₁₂ClNO: C, 68.44, H, 4.92, N, 5.70. Found: C, 68.40, H, 4.89, N, 5.61.

EXAMPLE 36

10 4-Allyl-6-(3-chlorophenyl)-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (Procedure C)

To a solution of 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanone (0.2g, 0.82 mmol) in anhydrous THF (10 mL) was added a solution of allylmagnesium bromide in ether (1.0 M, 3 mL, 3 mmol) at 0 °C under nitrogen. The reaction solution was slowly warmed to ambient temperature and stirred under nitrogen for 1 hour. A saturated aqueous ammonium chloride solution (10 mL) was added, followed by addition of ethyl acetate (50 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (3x10 mL). The combined organic layers were washed with brine and dried with MgSO₄. After removal of solvent, the residue was purified by flash chromatography (silica gel, hexane:ethyl acetate/3:1) to afford an amino carbinol intermediate which was used without further purification.

To a solution of above amino carbinol in anhydrous THF was added CDI (0.38g, 2.3 mmol) at ambient temperature under nitrogen. The reaction solution was heated at 55 °C for 12 hours and then cooled to room temperature. The solvent was removed *in vacuo* and the residue was purified by flash chromatography (silica gel, hexane:ethyl acetate/2:1) to yield 4-allyl-6-(3-chlorophenyl)-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one as a white solid (130 mg from two steps, 52%): mp 128-129 °C; ¹H-NMR (CDCl₃) δ 8.68 (s, 1H, D₂O exchangeable), 7.50 (s, 1H), 7.44 (dd, 1H, *J* = 8.2, 1.9 Hz), 7.31-7.40 (m, 3H), 7.25 (d, 1H, *J* = 1.6 Hz), 6.92 (d, 1H, *J* = 8.2

Hz), 5.70-5.85 (m, 1H), 5.17 (m, 2H), 2.76 (m, 2H), 1.79 (s, 3H); MS (ESI) m/z 314 ($[M+H]^+$, 40%); Anal. Calc. For $C_{18}H_{16}ClNO_2$: C, 68.90, H, 5.14, N, 4.46. Found: C, 68.90, H, 5.18, N, 4.43.

EXAMPLE 37

5 **6-(3-Chlorophenyl)-4-methyl-4-propyn-1-yl-1,4-dihydro-benzo[d][1,3]oxazin-2-one**

Prepared from 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanone and propynyl-magnesium bromide followed by treatment with CDI according to Procedure C. White solid: mp 184-185 °C; 1H -NMR ($CDCl_3$) δ 8.18 (s, 1H, D_2O exchangeable),
10 7.53 (t, 1H, $J = 1.7$ Hz), 7.49 (s, 1H), 7.31-7.48 (m, 4H), 6.92 (d, 1H, $J = 8.1$ Hz), 2.02 (s, 3H), 1.87 (s, 3H); MS (ESI) m/z 304 ($[M-H]^+$, 100%); Anal. Calc. For $C_{18}H_{14}ClNO_2$: C, 69.35, H, 4.53, N, 4.49. Found: C, 69.19, H, 4.37, N, 4.41.

EXAMPLE 38

15 **6-(3-Chlorophenyl)-4-ethynyl-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one**

Prepared from 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanone (0.2g, 0.82 mmol) and ethynylmagnesium bromide followed by treatment with CDI according to procedure C. Off-white solid: mp 185-186 °C; 1H -NMR ($CDCl_3$) δ 8.18 (s, 1H, D_2O exchangeable), 7.53 (t, 1H, $J = 1.7$ Hz), 7.49 (s, 1H), 7.31-7.48 (m, 4H), 6.92 (d, 1H, $J = 8.1$ Hz), 2.81 (s, 1H), 1.87 (s, 3H); MS (ESI) m/z 304 ($[M-H]^+$, 100%); Anal. Calc. For $C_{17}H_{12}ClNO_2$: C, 68.58, H, 4.06, N, 4.70. Found: C, 68.24, H, 3.94, N, 4.65.

EXAMPLE 39

25 **6-(3-Chlorophenyl)-4-methyl-4-phenyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one**

Prepared from 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanone (0.2g, 0.82 mmol) and phenylmagnesium bromide followed by treatment with CDI according to Procedure C. White solid: mp 179-180 °C; 1H -NMR ($CDCl_3$) δ 8.27 (s, 1H, D_2O exchangeable), 7.51-7.57 (m, 2H), 7.28-7.45 (m, 9H), 6.92 (d, 1H, $J = 8.4$ Hz), 2.12

(s, 3H); MS (ESI) m/z 348 ($[M-H]^+$, 100%); Anal. Calc. For $C_{21}H_{16}ClNO_2$: C, 72.10, H, 4.61, N, 4.00. Found: C, 71.72, H, 4.86, N, 3.91.

EXAMPLE 40

5 4-Benzyl-6-(3-chloro-phenyl)-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

A mixture of 1-(4-amino-3'-chloro-biphenyl-3-yl)-1-benzyl-ethanol (prepared using 1-(4-amino-3'-chloro-biphenyl-3-yl)-ethanone and benzylmagnesium bromide according to Procedure C, 0.14 g, 0.42 mmol) and triphosgene (0.04 g, 0.14 mmol) in dry THF (10 mL) was stirred under a blanket of nitrogen for 10 minutes. Upon completion of the reaction, the THF was removed and the residue purified via flash chromatography (silica gel, 35% ethyl acetate/hexane) to give 4-benzyl-6-(3-chloro-phenyl)-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (0.045 g, 30%) as an off-white solid: mp 187-188 °C; 1H -NMR (DMSO- d_6) δ 10.1 (s, 1H), 7.70 (t, 1H, $J = 2.3$ Hz), 7.6 (d, 1H, $J = 8.0$ Hz), 7.58-7.53 (m, 2H), 7.46 (t, 1H, $J = 8.0$ Hz), 7.38 (d, 1H, $J = 8.0$ Hz), 7.22-7.17 (m, 3H), 7.06-7.0 (m, 2H), 6.84 (d, 1H, $J = 9.14$ Hz), 3.24 (d, 1H, $J = 14.3$ Hz), 3.06 (d, 1H, $J = 14.3$ Hz), 1.68 (s, 3H); MS (ESI) m/z 364 ($[M+H]^+$, 100%); Anal. Calc. For $C_{22}H_{18}ClNO_2$: C, 72.63; H, 4.99; N, 3.85. Found: C, 71.82; H, 5.09; N, 3.58.

20

EXAMPLE 41

6-(3-Chloro-phenyl)-4-cyclopropyl-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

To a solution of cyclopropylmagnesium bromide in anhydrous THF (prepared using cyclopropyl bromide and magnesium metal, 70 mmol) at 52 °C was added under nitrogen 4-amino-3'-chloro-biphenyl-3-carbonitrile (5.2g, 22.7 mmol). The reaction mixture was stirred at 52 °C for 1 hour, cooled to rt, and quenched with 1N aqueous HCl solution (100 mL). Ethyl acetate (100 mL) was added and the aqueous layer was extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed and the residue

was purified *via* silica gel column (hexane:ethyl acetate/20:1) to give the (4-amino-3'-chloro-biphenyl-3-yl)-cyclopropyl-methanone: ¹H-NMR (hydrogen chloride salt, DMSO-d₆) δ 8.30 (d, 1H, *J* = 2.1 Hz), 7.76 (t, 1H, *J* = 1.7 Hz), 7.68-7.63 (m, 2H), 7.43 (t, 1H, *J* = 7.9 Hz), 7.32 (m, 1H), 6.88 (d, 1H, *J* = 8.7 Hz), 4.50 (bs, 3H), 3.07 (m, 1H), 0.98 (m, 4H); (MS ((+)ESI) *m/z* 272/274 (M⁺).

To a solution of (4-amino-3'-chloro-biphenyl-3-yl)-cyclopropyl-methanone (0.67g, 2.5 mmol) in anhydrous THF (10 mL) at -78 °C was added a solution of methylmagnesium bromide (3.0 M in diethyl ether, 2.5 mL, 7.5 mmol) under nitrogen. The reaction mixture was slowly warmed to rt, stirred under nitrogen for 12 hours, and quenched with a saturated aqueous ammonium chloride solution (40 mL). Ethyl acetate (50 mL) was added, the organic layer was separated, and dried (MgSO₄). After removal of the solvent, the residue was purified *via* silica gel chromatography (hexane:ethyl acetate/7:1) to afford 1-(4-amino-3'-chloro-biphenyl-3-yl)-1-cyclopropyl-ethanol as yellow oil: MS (EI) *m/z* 287/289 (M⁺).

The title compound was prepared from 1-(4-amino-3'-chloro-biphenyl-3-yl)-1-cyclopropyl-ethanol and 1,1'-carbonyldiimidazole according to Procedure C. Off-white solid: mp 158-159 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.74 (t, 1H, *J* = 1.71 Hz), 7.67-7.57 (m, 3H), 7.47 (t, 1H, *J* = 7.88 Hz), 7.39 (d, 1H, *J* = 8.1 Hz), 6.95 (d, 1H, *J* = 8.12 Hz), 1.7 (s, 3H), 1.45 (m, 1H), 0.48 (m, 2H), 0.28 (m, 2H); MS (APCI) *m/z* 314 ([M+H]⁺, 100%); Anal. Calc. For C₁₈H₁₆ClNO₂: C, 68.9; H, 5.14; N, 4.46. Found: C, 68.13; H, 5.01; N, 4.36.

EXAMPLE 42

6-(3-Chloro-phenyl)-4-cyclopropyl-4-propyn-1-yl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

1-(4-Amino-3'-chloro-biphenyl-3-yl)-1-cyclopropyl-1-propynyl-methanol was prepared from (4-amino-3'-chloro-biphenyl-3-yl)-cyclopropyl-methanone and propynylmagnesium bromide according to Example 41.

A mixture of 1-(4-amino-3'-chloro-biphenyl-3-yl)-1-cyclopropyl-1-propynyl-methanol (0.02 g, 0.064 mmol) and 1,1'-carbonyldiimidazole (0.016 g, 0.096 mmol) in dry THF (10 mL) was stirred under a blanket of nitrogen for 10 minutes. Upon completion of the reaction, the THF was removed and the residue purified *via* flash chromatography (silica gel, 40% ethyl acetate/hexane) to give 6-(3-chlorophenyl)-4-cyclopropyl-4-prop-1-ynyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (0.014 g, 56%) as a light yellow solid: mp 178-179 °C; ¹H-NMR (DMSO-d₆) δ 10.6 (s, 1H), 7.68 (m, 2H), 7.64 (bs, 1H), 7.59 (d, 1H, *J* = 7.72 Hz), 7.49 (t, 1H, *J* = 7.82 Hz), 7.42 (d, 1H, *J* = 7.95 Hz), 7.02 (d, 1H, *J* = 8.0 Hz), 1.86 (s, 3H), 1.66 (m, 1H), 0.82 (m, 1H), 0.66 (m, 3H); MS (ESI) *m/z* 336 ([M-H]⁺, 100%).

EXAMPLE 43

6-(3-Chloro-phenyl)-4,4-dicyclopropyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

(4-Amino-3'-chloro-biphenyl-3-yl)-dicyclopropyl-methanol (mp 90-92 °C; MS ((+)ESI) *m/z* 314 (M+H)⁺.) was prepared from (4-amino-3'-chloro-biphenyl-3-yl)-cyclopropyl-methanone and cyclopropylmagnesium bromide according to Example 41.

The title compound was prepared according to Example 41 from (4-amino-3'-chloro-biphenyl-3-yl)-dicyclopropyl-methanol and 1,1'-carbonyldiimidazole. Yellow solid: mp 198-200 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.72 (bs, 1H), 7.67 (bs, 1H), 7.62 (m, 2H), 7.48 (t, 1H, *J* = 7.88 Hz), 7.40 (d, 1H, *J* = 8.04 Hz), 6.94 (d, 1H, *J* = 8.27 Hz), 1.55 (m, 2H), 0.5 (m, 6H), 0.28 (m, 2H); MS (EI) *m/z* 339 (M⁺, 40%); Anal. Calc. For C₂₀H₁₈ClNO₂: C, 70.69; H, 5.34 N, 4.12. Found: C, 69.38; H, 5.07; N, 4.02.

EXAMPLE 44

6-(3-Chloro-phenyl)-4,4-dipropyn-1-yl-1,4-dihydrobenzo[d][1,3]oxazin-2-one

Following the procedure of Example 41, (4-amino-3'-chloro-biphenyl-3-yl)-propynyl-methanone (mp 112-114 °C; MS ((+) ESI) *m/z* 270/272 (M+H)⁺) was

treated with propynylmagnesium bromide to give (4-amino-3'-chloro-biphenyl-3-yl)-dipropynyl-methanol which was reacted with 1,1'-carbonyldiimidazole to afford the title compound. Yellow solid: mp 151 °C (decomposed); ¹H-NMR (DMSO-d₆) δ 10.8 (s, 1H), 7.71 (dd, 1H, *J* = 8.52, 1.94 Hz), 7.69 (m, 2H), 7.61 (d, 1H, *J* = 7.64 Hz), 7.50 (t, 1H, *J* = 7.85 Hz), 7.43 (d, 1H, *J* = 7.99 Hz), 7.06 (d, 1H, *J* = 8.23 Hz), 2.0 (s, 6H); MS (APCI) *m/z* 336 ([M+H]⁺, 20%).

EXAMPLE 45

10 6-(3-Bromo-5-fluorophenyl)-1,4,4-trimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one

To a solution of 6-(3-bromo-5-fluorophenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one (0.34g, 0.99 mmol) in dry DMF (10 mL) was added under nitrogen at room temperature sodium hydride (80 mg, 2.0 mmol) in one portion. The mixture was stirred at ambient temperature for 30 minutes, treated with iodomethane (1 mL, excess), and stirred for 2 hours. To the reaction mixture was added a cold saturated ammonium chloride solution (30 mL) and the white precipitate obtained was collected on a filter, washed with the distilled water to afford the title compound as a white solid (0.31g, 87%): mp 157-158 °C; ¹H-NMR (DMSO-d₆) δ 7.83 (s, 1H), 7.76 (dd, 1H, *J* = 8.5, 2.0 Hz), 7.67 (m, 2H), 7.53 (dt, 1H, *J* = 8.3, 1.9 Hz), 7.18 (d, 1H, *J* = 8.5 Hz), 3.33 (s, 3H), 1.67 (s, 6H); ¹⁹F-NMR (DMSO-d₆) δ -111.01 (m, 1F); MS (APCI) *m/z* 364 ([M+H]⁺, 96%), 366 ([M+H]⁺, 100%).

EXAMPLE 46

25 1-(2-Amino-5-chloro-phenyl)-2,2,2-trifluoro-ethanone
To a solution of *N*-(4-chlorophenyl)-2,2-dimethylpropanamide (6.7g, 30 mmol) in anhydrous THF (100 mL) under nitrogen at 0 °C was added a solution of *n*-BuLi (2.5M, 30 mL, 70 mmol) in hexane in a dropwise fashion. After addition, the solution was kept stirring at 0 °C for 40 minutes and treated with a solution of 1-(trifluoroacetyl)imidazole (9 mL, 78 mmol) in anhydrous THF (10 mL). The reaction

mixture was warmed to ambient temperature and kept for 18 hours. To the reaction solution was added a saturated aqueous ammonium chloride solution (50 mL) followed by addition of ethyl acetate (100 mL). The organic layer was separated and the solvent was removed *in vacuo*. The residue obtained was suspended in 3N aqueous hydrochloride solution (50 mL) and heated at reflux overnight. The reaction solution was cooled to room temperature and treated with a cold ammonium hydroxide solution to a pH above 8. The aqueous mixture was extracted with ethyl acetate (3x50 mL) and the organic layers were washed with brine and dried (MgSO₄). After removal of solvent, the residue was purified by a flash chromatography (silica gel, hexane:ethylacetate/4:1) to afford the title compound as a yellow solid (1g, 15%): mp 93-94 °C; ¹H-NMR (CDCl₃) δ 7.70 (m, 1H), 7.33 (dd, 1H, *J* = 9.0, 2.3 Hz), 6.70 (d, 1H, *J* = 9.1 Hz), 6.45 (bs, 2H); MS (ESI) *m/z* 222(M-H, 100%), 224(M-H, 33%).

EXAMPLE 47

15 6-Chloro-4-methyl-4-trifluoromethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from 1-(2-amino-5-chloro-phenyl)-2, 2, 2-trifluoro-ethanone by addition of methylmagnesium bromide followed by treatment of the resultant carbinol with 1,1'-carbonyldiimidazole according to the procedure of Example 2. White solid: mp 216-216 °C; ¹H-NMR (DMSO-d₆) δ 10.91 (bs, 1H, D₂O exchangeable), 7.64 (d, 1H, *J* = 1.6 Hz), 7.49 (dd, 1H, *J* = 8.6, 2.3 Hz), 6.95 (d, 1H, *J* = 8.6 Hz), 1.91 (s, 3H); ¹⁹F-NMR (DMSO-d₆) δ -82.0 (s, 1F); MS (EI) *m/z* 264 ([M-H]⁺, 100%), 266 ([M-H]⁺, 33%). Anal. Calc. For C₁₀H₇ClF₃NO₂: C, 45.22, H, 2.66, N, 5.27. Found: C, 45.32, H, 2.77, N, 4.83.

25 EXAMPLE 48

6-(3-Methoxyphenyl)-4-methyl-4-trifluoromethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

A mixture of 6-chloro-4-methyl-4-trifluoromethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one (0.2g, 0.75 mmol), 3-methoxyphenyl boronic acid (0.13g, 0.9 mmol),

potassium phosphate (0.23g, 1.1 mmol), and nickel (II) (diphenylphosphino)ferrocenyl dichloride (52 mg, 0.076 mmol) in anhydrous dioxane was subject to a blanket of nitrogen to remove oxygen and heated at 95 °C under nitrogen for 48 hours. Another portion of 3-methoxyphenyl boronic acid (0.13g, 0.9 mmol) and nickel (II) (diphenylphosphino)ferrocenyl dichloride (52 mg, 0.076 mmol) was added and the reaction solution was heated at 95 °C under nitrogen for 48 hours. The reaction solution was cooled to room temperature. Saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x20 mL). The combined organic layer was washed with brine and dried (MgSO₄). After removal of solvent, the residue was purified by a flash chromatography (silica gel, hexane:ethyl acetate/4:1) to afford the title compound as a white solid (50 mg, 20%): mp 178-179 °C; ¹H-NMR (DMSO-d₆) δ 10.85 (bs, 1H, D₂O exchangeable), 7.73 (m, 2H), 7.38 (t, 1H, *J* = 7.9 Hz), 7.23 (d, 1H, *J* = 7.7 Hz), 7.19 (d, 1H, *J* = 1.9 Hz), 7.02 (d, 1H, *J* = 8.2 Hz), 6.94 (dd, 1H, *J* = 8.2, 2.4 Hz), 3.88 (s, 3H), 1.98 (s, 3H); ¹⁹F-NMR (DMSO-d₆) □ -81.88 (s, 1F); Anal. Calc. For C₁₇H₁₄F₃NO₃: C, 60.54, H, 4.18, N, 4.15. Found: C, 60.58, H, 4.44, N, 4.19.

EXAMPLE 49

20 7-(3-Methoxy-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

A mixture of 7-chloro-4,4'-dimethylbenzoxazin-2-one (0.197 g, 0.93 mmol), 3-methoxyphenyl boronic acid (0.21 g, 1.4 mmol), Ni(dppf)Cl₂ (0.095 g, 0.14 mmol), and potassium phosphate (0.59 g, 2.79 mmol) in dioxane (10 mL) was subject to a blanket of nitrogen for 15 minutes at 50 °C and then was heated at 95 °C for 48 hours. The reaction mixture was cooled to room temperature and ethyl acetate (100 mL) was added. The organics were washed twice with aqueous ammonium chloride (30 mL), once with brine (30 mL), and dried over magnesium sulfate. The residue was purified *via* flash chromatography (silica gel, 40% ethyl acetate/hexane) to give 7-(3-methoxy-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (0.090 g, 35%) as a

clear oil. The oil was triturated with ether (25 ml) to furnish a white solid: mp 167-168 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.42-7.28 (m, 3H), 7.14 (d, 1 H, *J* = 8.11 Hz), 7.11 (bs, 2H), 6.96 (dd, 1H, *J* = 8.11 Hz), 3.56 (s, 3H), 1.52 (s, 6H); MS (EI) *m/z* 283 ([M+H]⁺, 90%); Anal. Calc. For C₁₇H₁₇NO₃: C, 72.07, H, 6.05, N, 4.94. Found:
5 C, 71.59, H, 6.08, N, 4.79.

EXAMPLE 50

6-(3-Acetyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

10 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)benzonitrile (0.25 g, 0.9 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. To this solution, methylmagnesium bromide (3.0 M in ether, 1.8 mL, 5.4 mmol) was added and the reaction mixture was heated to reflux under nitrogen. Upon completion of the reaction, the reaction mixture was quenched with 1 N aqueous HCl solution after
15 cooled to rt. The mixture was extracted with ethyl acetate (100 mL), dried over MgSO₄ and concentrated. Purification of the residue obtained *via* chromatography (silica gel, 50% ethyl acetate/ hexane) gave 6-(3-acetyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one as a white solid (0.031 g, 12%): mp 178-179 °C; ¹H-NMR (CDCl₃) δ 8.15 (t, 1H, *J* = 1.71 Hz), 8.04 (s, 1H), 7.95 (dt, 1H, *J* = 8.85, 1.13
20 Hz), 7.76 (dt, 1H, *J* = 7.90, 1.43 Hz), 7.57 (t, 1H, *J* = 7.72 Hz), 7.52 (dd, 1H, *J* = 8.28, 2.11 Hz), 7.39 (d, 1H, *J* = 1.81 Hz), 6.93 (d, 1H, *J* = 8.19 Hz), 2.69 (s, 3H), 1.81 (s, 6H); MS (EI) *m/z* 295 ([M+H]⁺, 40%)

EXAMPLE 51

25 6-(3-Benzoyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

Prepared from 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)benzonitrile and phenylmagnesium bromide according to the procedure of Example 50. A white solid: mp 156-157 °C; ¹H-NMR (DMSO-d₆) δ 10.33 (s, 1H), 8.0-7.96 (m,

2H), 7.80 (m, 2H), 7.73-7.56 (m, 7H), 6.99 (d, 1H, $J = 8.06$ Hz), 1.67 (s, 6H); MS (EI) m/z 357 ($[M+H]^+$, 40%); Anal. Calc. For $C_{23}H_{19}NO_3$: C, 77.29, H, 5.36, N, 3.92 Found: C, 75.7, H, 5.28, N, 3.86

5

EXAMPLE 52

4,4-Dimethyl-6-[3-(1H-tetrazol-5-yl)-phenyl]-1,4-dihydrobenzo[d][1,3]oxazin-2-one

A mixture of 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)benzonitrile (0.77 g, 2.8 mmol), trimethylsilyl azide (0.68 g, 5.6 mmol), and
10 dibutyl tin oxide (0.071 g, 0.28 mmol) in dioxane (20 mL) was heated at reflux under a blanket of nitrogen. Upon completion of the reaction, the dioxane was removed, the organics taken up in ethyl acetate (100 mL), and washed with $NaHCO_3$ (100 mL). The aqueous layer was acidified with 1 N aqueous HCl and extracted with ethyl acetate (100 mL). The organic layer was dried over $MgSO_4$, and concentrated.
15 Crystallization from ether (20 mL) gave 4,4-dimethyl-6-[3-(1H-tetrazol-5-yl)-phenyl]-1,4-dihydrobenzo[d][1,3]-oxazin-2-one as a light yellow solid (0.23 g, 26%): mp 238-240 °C; 1H -NMR ($DMSO-d_6$) δ 10.4 (s, 1H), 8.3 (bs, 1H), 8.02 (d, 1H, $J = 7.66$ Hz), 7.9 (d, 1H, $J = 7.91$ Hz), 7.72-7.65 (m, 3H), 7.03 (d, 1H, $J = 8.75$ Hz), 1.70 (s, 6H); MS (ESI) m/z 320 ($[M-H]^+$, 100%); Anal. Calc. For $C_{17}H_{15}N_5O_2$: C, 63.54, H, 4.71, N, 21.79. Found: C, 62.16, H, 4.67, N, 21.31.
20

EXAMPLE 53

4-(4,4-Dicyclopropyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-2-carbonitrile

25 (4, 4-Dicyclopropyl-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid was prepared from 2-amino-5-bromobenzoic acid according to Example 1, 2, and 4. A white solid: mp 240-242 °C; 1H -NMR ($DMSO-d_6$) δ 10.13 (s, 1H), 8.01 (s, 2H), 7.85 (s, 1H), 7.64 (d, 1H, $J = 7.9$ Hz), 6.77 (d, 1H, $J = 7.9$ Hz), 1.38 (m, 2H), 0.52 (m, 2H), 0.39 (m, 4H), 0.22 (m, 2H).

The title compound was prepared according to Procedure B from (4,4-dicyclopropyl-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 4-bromo-2-thiophene carbonitrile. A white solid: mp 244-245 °C; ¹H-NMR (DMSO-d₆) δ 10.25 (s, 1H), 8.49 (d, 1H, *J* = 0.87 Hz), 8.33 (s, 1H), 7.74 (d, 1H, *J* = 1.44 Hz), 7.67 (dd, 1H, *J* = 8.28, 1.54 Hz), 6.90 (d, 1H, *J* = 8.28 Hz), 1.53 (m, 2H), 0.59-0.41 (m, 6H), 0.31-0.24 (m, 2H); MS (ESI) *m/z* 335 ([M-H]⁺, 100%); Anal. Calc. For C₁₉H₁₆N₂O₂S: C, 67.84, H, 4.79, N, 8.33. Found: C, 64.92, H, 4.66, N, 7.71.

EXAMPLE 54

10 6-(3-Bromo-5-fluoro-phenyl)-4,4-dicyclopropyl-1,4-dihydrobenzo-[d][1,3]oxazin-2-one

Prepared according to Procedure B from (4,4-dicyclopropyl-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 1,3-dibromo-5-fluorobenzene. A white solid: mp 228-229 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.76-7.72 (m, 2H), 7.65 (dd, 1H, *J* = 8.32, 1.74 Hz), 7.60 (d, 1H, *J* = 10.36 Hz), 7.51 (d, 1H, *J* = 8.3 Hz), 6.93 (d, 1H, *J* = 8.31 Hz), 1.63-1.54 (m, 2H), 0.58-0.41 (m, 6H), 0.30-0.28 (m, 2H); MS (APCI) *m/z* 402/404 ([M-H]⁺, 100%); Anal. Calc. For C₂₀H₁₇BrFNO₂: C, 58.48, H, 4.17, N, 3.41. Found: C, 58.77, H, 4.23, N, 3.32.

20 EXAMPLE 55

3-(4, 4-Dicyclopropyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluorobenzonitrile

A mixture of 6-(3-bromo-5-fluoro-phenyl)-4,4-dicyclopropyl-1,4-dihydrobenzo-[d][1,3]oxazin-2-one (0.4 g, 1.0 mmol), Zn(CN)₂ (0.71 g, 0.61 mmol), and tetrakis(triphenylphosphine)-palladium (0) (0.07 g, 0.06 mmol) in DMF (20 mL) was subject to a blanket of nitrogen for 15 minutes at 50 °C and then was heated at 85 °C for 1 hour. After cooling to room temperature, the reaction mixture was poured into NH₄Cl (100 mL) and extracted with ethyl acetate (3x50 mL). The organic layers were washed with brine, dried over MgSO₄, and concentrated. The clear oil obtained was

trituated with ether (30 ml) to give a white solid. Recrystallization of the solid from ethyl acetate gave 3-(4,4-dicylopropyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluoro-benzonitrile (0.016 g, 4.6%): mp 250-252 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 8.12 (s, 1H), 7.97 (d, 1H, *J* = 10.54 Hz), 7.81-7.79 (m, 2H), 7.73 (dd, 1H, *J* = 8.3, 1.59 Hz), 6.94 (d, 1H, *J* = 8.34 Hz), 1.59 (m, 2H), 0.58-0.42 (m, 6H), 0.30-0.28 (m, 2H); MS (ESI) *m/z* 347 ([M-H]⁺, 100%); Anal. Calc. For C₂₁H₁₇FN₂O₂: C, 72.4, H, 4.92, N, 8.04 Found: C, 72.4, H, 4.74, N, 7.61

EXAMPLE 56

10 6-(3-Bromo-5-methyl-phenyl)-4,4-dimethyl-1,4-dihydrobenzo-[d][1,3]oxazin-2-one

Prepared from (4,4-dimethyl-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 3,5-dibromotoluene according to Procedure B. White solid: mp 231-233 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.66 (s, 1H), 7.58-7.56 (m, 2H), 7.50 (s, 1H), 7.37 (s, 1H), 6.95 (d, 1H, *J* = 8.67 Hz), 2.37 (s, 3H), 1.67 (s, 6H); MS (ESI) *m/z* 344/346 ([M-H]⁺, 100%); Anal. Calc. For C₁₇H₁₆BrNO₂: C, 58.98, H, 4.66, N, 4.05. Found: C, 58.82, H, 4.62, N, 3.94.

EXAMPLE 57

20 6-(3-Bromo-5-trifluoromethoxy-phenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]-oxazin-2-one

Prepared from (4, 4-dimethyl-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 1, 3-dibromo-5-trifluoromethoxybenzene according to Procedure B. White solid: mp 214-216 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.99 (s, 1H), 7.73 (s, 1H), 7.68-7.62 (m, 3H), 6.97 (d, 1H, *J* = 8.0 Hz), 1.68 (s, 6H); MS (ESI) *m/z* 414 ([M - H]⁺, 100%); Anal. Calc. For C₁₇H₁₃BrF₃NO₃: C, 49.06, H, 3.15, N, 3.37. Found: C, 49.16, H, 3.05, N, 3.30.

EXAMPLE 58

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-methyl-benzonitrile

Prepared from 6-(3-bromo-5-methyl-phenyl)-4,4-dimethyl-1,4-dihydrobenzo-
5 [d][1,3]oxazin-2-one according to the procedure of example 55. White solid: mp
256-258 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.99 (s, 1H), 7.86 (s, 1H), 7.67-7.62
(m, 3H), 6.97 (d, 1H, J = 8.11 Hz), 2.42 (s, 3H), 1.68 (s, 6H); MS (APCI) m/z 293
([M+H]⁺, 100%); Anal. Calc. For C₁₈H₁₆N₂O₂: C, 73.96, H, 5.52, N, 9.58. Found: C,
73.26, H, 5.46, N, 9.24.

10

EXAMPLE 59

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-trifluoromethoxy-benzonitrile

Prepared from 6-(3-bromo-5-trifluoromethoxy-phenyl)-4,4-dimethyl-1,4-
15 dihydrobenzo[d][1,3]oxazin-2-one according to the procedure of example 55. White
solid: mp 227-228 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 8.32 (s, 1H), 8.09 (s, 1H),
7.97 (s, 1H), 7.75-7.72 (m, 3H), 6.99(d, 1H, J = 8.11 Hz), 1.7 (s, 6H); MS (APCI) m/z
363 ([M+H]⁺, 80%); Anal. Calc. For C₁₈H₁₃F₃N₂O₃: C, 59.67, H, 3.62, N, 7.73.
Found: C, 59.63, H, 3.55, N, 7.58.

20

EXAMPLE 60

6-(3,5-difluoro-phenyl)-4,4-dimethyl-1,4-dihydrobenzo-[d][1,3]oxazin-2-one

Prepared according to procedure B from (4,4-dimethyl-1,4-dihydro-2-oxo-2H-
3,1-benzoxazin-6-yl)boronic acid and 1-bromo-3,5-difluorobenzene. A white solid:
25 mp 218-219 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.67-7.65 (m, 2H), 7.49 (d, 2H,
J = 7.73 Hz), 7.19 (t, 1H, J = 9.29 Hz), 6.96 (d, 1H, J = 8.88 Hz), 1.7 (s, 6H); MS
(APCI) m/z 290 ([M + H]⁺, 100%); Anal. Calc. For C₁₆H₁₃F₂NO₂: C, 66.43, H, 4.53,
N, 4.84. Found: C, 66.01, H, 4.46, N, 4.67.

EXAMPLE 61

6-(3,5-dichloro-phenyl)-4,4-dimethyl-1,4-dihydrobenzo-[d][1,3]oxazin-2-one

Prepared from 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one and 3,5-dichlorophenyl boronic acid according to Procedure A. A white solid: mp
5 245-246 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.77 (m, 2H), 7.67-7.64 (m, 2H), 7.56 (bs, 1H), 6.96 (d, 1H, *J* = 7.98 Hz), 1.7 (s, 6H); MS (EI) *m/z* 321 ([*M*+*H*]⁺, 40%); Anal. Calc. For C₁₆H₁₃Cl₂NO₂: C, 59.32, H, 4.11, N, 4.32. Found: C, 59.13, H, 4.29, N, 4.17.

10

EXAMPLE 62

6-(3,5-Bis-trifluoromethyl-phenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one

Prepared from 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one and bis-trifluoromethylphenyl boronic acid according to Procedure A. A white solid:
15 mp 258-260 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 8.35 (s, 2H), 8.05 (s, 1H), 7.79-7.76 (m, 2H), 7.01 (d, 1H, *J* = 8.01 Hz), 1.7 (s, 6H); MS (ESI) *m/z* 390 ([*M*+*H*]⁺, 20%); Anal. Calc. For C₁₈H₁₃F₆NO₂: C, 55.54, H, 3.37, N, 3.6. Found: C, 55.5, H, 3.54, N, 3.47.

20

EXAMPLE 63

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-methoxy-benzonitrile

A mixture of (4,4-dimethyl-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid (4.2 g, 19.0 mmol), 3-cyano-5-methoxyphenyltriflate (5.1 g, 19.0
25 mmol), tetrakis(triphenylphosphine)-palladium (0) (1.1 g, 0.95 mmol), sodium carbonate (4.0 g, 38.0 mmol), and lithium bromide (5 g, 57 mmol) in DME (50 mL) and water (25 mL) was subject to a blanket of nitrogen for 15 minutes at 50 °C and then was heated at 85 °C for 1 hour. The reaction was cooled to room temperature and ethyl acetate (100 mL) was added. The organic layers were washed twice with

aqueous ammonium chloride (100 mL) and once with brine (100 mL), dried over magnesium sulfate and concentrated. Purification via chromatography (silica gel, 40% ethyl acetate/ hexane) gave 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-methoxy-benzonitrile as a white solid (0.69 g, 53%): mp 254-255 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.84 (s, 1H), 7.67-7.61 (m, 2H), 7.55 (bs, 1H), 7.4 (bs 1H) 6.99 (d, 1H, *J* = 7.94 Hz), 3.88 (s, 3H), 1.67 (s, 6H,); MS (EI) *m/z* 308 ([M + H]⁺, 30%); Anal. Calc. For C₁₈H₁₆N₂O₃: C, 68.13, H, 5.40, N, 8.83. Found: C, 68.03, H, 5.22, N, 8.46.

10

EXAMPLE 64

6-(3-Fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

Prepared from 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one and 1-bromo-3-fluorobenzene according to Procedure A. A light yellow solid: mp 181-182 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.62-7.44 (m, 5H), 7.16 (t, 1H, *J* = 2.22 Hz), 6.97 (d, 1H, *J* = 8.83), 1.67 (s, 6H); MS (EI) *m/z* 271 ([M + H]⁺, 40%); Anal. Calc. For C₁₆H₁₄FNO₂: C, 69.91, H, 5.3, N, 5.1. Found: C, 70.0, H, 5.32, N, 4.92.

15

EXAMPLE 65

6-(3-Chloro-4-fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one and 1-bromo-3-chloro-4-fluorobenzene according to Procedure A. White solid: mp 211-212 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.92 (dd, 1H, *J* = 7.13, 2.19 Hz), 7.71-7.66 (m, 1H), 7.60-7.57 (m, 2H), 7.49 (t, 1H, *J* = 8.95 Hz), 6.96 (d, 1H, *J* = 8.01 Hz), 1.67 (s, 6H); MS (EI) *m/z* 305 ([M + H]⁺, 20%); Anal. Calc. For C₁₆H₁₃ClFNO₂: C, 62.86, H, 4.29, N, 4.58. Found: C, 62.52, H, 4.45, N, 4.42.

25

EXAMPLE 66

3-(1-Diethoxymethyl-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluoro-benzonitrile

A mixture of 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluoro-benzonitrile (0.25 g, 0.84 mmol) and triethylorthoformate (50 mL) was heated at 160 °C for 12 hours. The excess triethylorthoformate was removed in vacuo and purification via chromatography (silica gel, 20% ethyl acetate/hexane) gave 3-(1-diethoxymethyl-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluoro-benzonitrile (0.116 g, 33%) as a white solid: mp 123-124 °C; ¹H-NMR (DMSO-d₆) δ 7.97 (d, 1H, *J* = 8.68 Hz), 7.66 (bs, 1H), 7.53-7.44 (m, 2H), 7.35-7.32 (m, 2H), 6.65 (s, 1H), 3.88-3.78 (m, 2H), 3.73-3.61 (m, 2H), 1.77 (s, 6H), 1.27 (t, 6H, *J* = 7.05 Hz); MS (ESI) *m/z* 295 ([M - H]⁺, 100%, lower MW ion consistent with loss of diethyl acetal); Anal. Calc. For C₂₂H₂₃FN₂O₄: C, 66.32, H, 5.82, N, 7.03. Found: C, 65.89, H, 5.92, N, 6.66.

15

EXAMPLE 67

3-Fluoro-5-(1-methoxymethyl-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile

A solution of 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluorobenzonitrile (0.150 g, 0.51 mmol) in DMF (5 mL) was treated at rt with sodium hydride (0.061 g, 1.53 mmol). The mixture was stirred for 30 minutes and treated with chloromethyl methylether (0.062 g, 7.7 mmol). Upon completion of the reaction, the reaction mixture was quenched with water (25 mL) and extracted with ethyl acetate (3x30 mL), dried over MgSO₄, and concentrated. The residue was purified via chromatography (silica gel, 25% ethyl acetate/hexane) to give 3-fluoro-5-(1-methoxymethyl-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile as a white solid (0.11 g, 65%): mp 169-171 °C; ¹H-NMR (DMSO-d₆) δ 8.17 (bs, 1H), 8.03 (dt, 1H, *J* = 10.4, 2.13 Hz), 7.85-7.77 (m, 3H), 7.31 (d, 1H, *J* = 8.49 Hz), 5.33 (s, 2H), 3.35 (s, 3H), 1.7 (s, 6H); MS (APCI) *m/z* 341 ([M + H]⁺,

50%); Anal. Calc. For $C_{19}H_{17}FN_2O_3$: C, 65.32, H, 5.19, N, 8.02. Found: C, 64.92, H, 4.96, N, 7.73.

EXAMPLE 68

5 Phosphoric acid 6-(3-cyano-5-fluoro-phenyl)-4,4-dimethyl-4H-
 benzo[d][1,3]oxazin-2-yl ester diethyl ether

To a solution of 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluorobenzonitrile (0.25 g, 0.84 mmol) in DMF (5 mL) was added sodium hydride (60% in oil, 0.101 g, 2.53 mmol). After stirred for 30 minutes, the reaction
10 mixture was treated with diethyl chlorophosphate (0.22 mL, 1.52 mmol). Upon completion of the reaction, the reaction solution was quenched with water (25 mL) and the product extracted with ethyl acetate (2x50 mL), dried over $MgSO_4$, and concentrated. The residue was purified *via* chromatography (silica gel, 25% ethyl acetate/hexane) to give phosphoric acid 6-(3-cyano-5-fluoro-phenyl)-4,4-dimethyl-
15 4H-benzo[d][1,3]oxazin-2-yl ester diethyl ether as a white solid (0.064 g, 18%): mp 196-198 °C; 1H -NMR ($DMSO-d_6$) δ 8.19 (bs, 1H), 8.05 (d, 1H, $J = 10.4$ Hz), 7.9-7.8 (m, 3H), 7.51 (d, 1H, $J = 8.41$ Hz), 4.33-4.41 (m, 4H), 1.76 (s, 6H), 1.27 (t, 6H, $J = 7.05$ Hz); MS (APCI) m/z 433 ($[M + H]^+$, 80%); Anal. Calc. For $C_{21}H_{22}FN_2O_5P$: C, 58.33, H, 5.13, N, 6.48. Found: C, 58.1, H, 5.11, N, 6.25.

20

EXAMPLE 69

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-fluoro-
 benzonitrile

Prepared from (1, 4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 5-bromo-2-fluorobenzonitrile according to Procedure B. White
25 solid: mp 229-230 °C; 1H -NMR ($DMSO-d_6$) δ 10.4 (s, 1H), 8.15 (dd, 1H, $J = 7.39$, 2.12 Hz), 7.95-7.89 (m, 1H), 7.59-7.48 (m, 3H), 6.99 (d, 1H, $J = 8.1$ Hz), 1.7 (s, 6H); MS (APCI) m/z 297 ($[M + H]^+$, 100%); Anal. Calc. For $C_{17}H_{13}FN_2O_2$: C, 68.91, H, 4.42, N, 9.45. Found: C, 68.74, H, 4.83, N, 9.10.

EXAMPLE 70

8-Fluoro-4,4-dimethyl-dihydro-benzo[d][1,3]oxazin-2-one

N-(*tert*-Butoxycarbonylamino)-3-fluorobenzoic acid (Takagishi et al. *Synlett* 4, 360-2 (1992); mp 159-161 °C) was deprotected using trifluoroacetic acid to give *o*-amino benzoic acid which was treated with methylmagnesium bromide to afford *o*-amino dimethyl carbinol. The *o*-amino dimethyl carbinol (2.23 g, 13.2 mmol) was treated with 1,1'-carbonyldiimidazole (2.8 g, 17.2 mmol) in THF (20 mL) at 50 °C for 12 hours. Upon completion of reaction, it was cooled to rt and ethyl acetate (100 mL) added. The organic layer was washed with 10% aqueous HCl solution (2x25 mL), dried over MgSO₄ and concentrated. The residue was purified *via* chromatography (silica gel, 10% ethyl acetate/hexane) to give 8-fluoro-4,4-dimethyl-dihydro-benzo[d][1,3]oxazin-2-one as a white solid (1.3 g, 50%); mp 127-128 °C; ¹H-NMR (DMSO-*d*₆) δ 10.4 (s, 1H), 7.22-7.12 (m, 2H), 7.07-7.00 (m, 2H), 1.6 (s, 6H); MS (APCI) *m/z* 196 ([M + H]⁺, 100%); Anal. Calc. For C₁₀H₁₀FNO₂: C, 61.53, H, 5.16, N, 7.18. Found: C, 61.27, H, 5.37, N, 7.02.

EXAMPLE 71

6-(3-Chloro-4-fluoro-phenyl)-8-fluoro-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]-oxazin-2-one

To a solution of 8-fluoro-4,4-dimethyl-dihydro-benzo[d][1,3]oxazin-2-one (0.15g, 0.77 mmol) in acetic acid (5 mL) was added dropwise a solution of bromine (0.37g, 2.31 mmol) in acetic acid (5 mL) under nitrogen at rt. After stirred for 10 minutes, the mixture was concentrated and the residue obtained was purified by a silica gel column (hexane:ethyl acetate/4:1) to afford 6-bromo-8-fluoro-4,4-dimethyl-dihydro-benzo[d][1,3]oxazin-2-one as an off-white solid (0.176g, 84%) which was used in next step without further purification.

A mixture of 6-bromo-8-fluoro-4,4-dimethyl-dihydro-benzo[d][1,3]oxazin-2-one (0.176 g, 0.64 mmol), 4-fluoro-3-chlorophenyl boronic acid (0.15 g, 0.84 mmol),

tetrakis(triphenylphosphine)-palladium (0) (0.04 g, 0.032 mmol), and sodium carbonate (0.20 g, 1.92 mmol) in DME (10 mL) and water (5 mL) was subject to a blanket of nitrogen for 15 minutes at 50 °C and then was heated at 85 °C for 1 hour. The reaction mixture was cooled to room temperature and ethyl acetate (100 mL) was added. The organic layer was washed twice with aqueous ammonium chloride (100 mL) and once with brine (100 mL), dried over magnesium sulfate and concentrated. The residue was purified via chromatography (silica gel, 25% ethyl acetate/hexane) to give 6-(3-chloro-4-fluoro-phenyl)-8-fluoro-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]-oxazin-2-one as a white solid ((0.13 g, 66%): mp 246-248 °C; ¹H-NMR (DMSO-d₆) δ 10.5 (s, 1H), 8.00 (dd, 1H, *J* = 7.09, 2.32 Hz), 7.78-7.73 (m, 1H), 7.62 (dd, 1H, *J* = 11.86, 1.77 Hz), 7.7 (t, 2H, *J* = 9 Hz), 1.7 (s, 6H); MS (APCI) *m/z* 324 ([M+H]⁺, 100%); Anal. Calc. For C₁₆H₁₂F₂NO₂ 0.5 H₂O C, 57.76, H, 3.94, N, 4.21. Found: C, 57.49, H, 3.69, N, 4.03.

15

EXAMPLE 72

6-(3-Bromo-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1,3-dibromobenzene according to procedure B. A white solid: mp 174-175 °C; ¹H-NMR (DMSO-d₆) δ 10.35 (s, 1H), 7.88 (bs, 1H), 7.68 (d, 1H, *J* = 7.5 Hz), 7.6-7.51 (m, 3H), 7.4 (t, 1H, *J* = 7.5 Hz), 6.97 (d, 1H, *J* = 8.57 Hz), 1.64 (s, 6H); MS (EI) *m/z* 331([M⁺], 60%), 333([M⁺], 60%); Anal. Calc. For C₁₆H₁₄BrNO₂: C, 57.85, H, 4.25, N, 4.22. Found: C, 57.7, H, 4.36, N, 4.09.

25

EXAMPLE 73

4,4-Dimethyl-6-(3-trimethylsilanylethynyl-phenyl)-1,4-dihydro-benzo[d][1,3]oxazin-2-one

A mixture of 6-(3-bromo-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (0.8g, 2.4 mmol), trimethylsilylacetylene (1g, 10 mmol),

tetrakis(triphenylphosphine) palladium (0) (0.17g, 0.24 mmol), and cuprous (I) iodide (0.05g, .28 mmol) in triethyl amine (20 mL) was heated under nitrogen at 80 °C for 3 hours. The reaction mixture was cooled to rt and the solvent was removed. The residue was taken up in ethyl acetate (50 mL) and washed with 1N aqueous HCl (3x 5 20 mL) and brine (20 mL). The organic layer was separated and dried (MgSO₄). After removal of solvent, the residue was purified by a silica gel chromatography (hexane:ethyl acetate/3:1) to afford the title compound as a white solid (0.77g, 92%): mp 240-242 °C; ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 7.74-7.69 (m, 2H), 7.61-7.58 (m, 2H), 7.48-7.40 (m, 2H), 6.96 (d, 1H, *J* = 7.98 Hz), 1.67 (s, 6H), 0.25 (s, 9H); MS (EI) 10 *m/z* 349([M⁺], 50%); Anal. Calc. For C₂₁H₂₃NO₂Si·0.2 EtOAc: C, 71.32, H, 6.75, N, 3.82. Found: C, 71.08, H, 6.64, N, 3.82.

EXAMPLE 74

6-(3-Ethynyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

15 A mixture of 4,4-dimethyl-6-(3-trimethylsilanylethynyl-phenyl)-1,4-dihydro-benzo[d][1,3]oxazin-2-one (0.7g, 2 mmol) and potassium carbonate (2g, excess) in anhydrous methanol was stirred at rt under nitrogen for 4 hours. The mixture was treated with ice-water (100 mL) and extracted with ethyl acetate (2x80 mL). The 20 organic layers were washed with brine and dried with MgSO₄. The solvent was removed and the title compound was obtained as a off-white solid (0.4g, 72%): mp 171-172 °C; ¹H-NMR (DMSO-d₆) δ 10.3, (s, 1H), 7.78 (bs, 1H), 7.72-7.69 (m, 1H), 7.6-7.57 (m, 2H), 7.49-7.43 (m, 2H), 6.97 (d, 1H, *J* = 7.98 Hz), 4.25 (s, 1H), 1.67 (s, 6H); MS (EI) *m/z* 277([M⁺], 100%); Anal. Calc. For C₁₈H₁₅NO₂·0.2 EtOAc: C, 76.56, 25 H, 5.67, N, 4.75. Found: C, 76.34, H, 5.4, N, 4.7.

EXAMPLE 75

3-[3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-phenyl]-propynenitrile

To a stirred mixture of DMSO, acetonitrile and water (9 mL/3 mL/0.5 mL) was added at rt under nitrogen cuprous cyanide (0.193g, 2.2 mmol), sodium iodide (11 mg, 0.072 mmol), and 6-(3-ethynyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (0.2 g, 0.72 mmol). Chlorotrimethylsilane was then added
 5 to the above mixture in a dropwise manner. After addition, the mixture was heated at 50 °C for 72 hours. The reaction mixture was then cooled to rt and treated with 0.5 N aqueous HCl cold solution (50 mL). The precipitate obtained was collected on a filter and washed with water. The solid was purified on a silica gel column (hexane:ethyl acetate/2:1) to give the title compound as an off-white solid (10 mg, 4.6 %): mp 212-
 10 213 °C; ¹H-NMR (CHCl₃-d₆) δ 7.96 (s, 1H), 7.77 (s, 1H), 7.65 (d, 1H, *J* = 7.8 Hz), 7.60 (d, 1H, *J* = 7.69 Hz), 7.51 (d, 1H, *J* = 7.77 Hz), 7.45 (dd, 1H, *J* = 8.67, 2.21 Hz), 7.31 (d, 1H, *J* = 1.55 Hz), 6.91 (d, 1H, *J* = 8.19 Hz), 1.8 (s, 6H); MS (EI) *m/z* 302 ([M⁺], 30%).

15

EXAMPLE 76

6-(3-Fluoro-5-nitro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1-bromo-3-fluoro-5-nitrobenzene according to procedure B. A yellow solid: mp 260-261 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 8.37 (bs, 1H), 8.14-8.05 (m, 2H), 7.77-7.74 (m, 2H), 7.01 (d, 1H, *J* = 7.94 Hz), 1.7 (s, 6H); MS (ESI) *m/z* 315([M - H]⁻, 100%); Anal. Calc. For C₁₆H₁₃FN₂O₄: C, 60.76, H, 4.14, N, 8.86. Found: C, 60.34, H, 4.2, N, 8.61.

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EXAMPLE 77

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6-(3-Chloro-5-fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1-bromo-3-chloro-5-fluorobenzene according to procedure B. A white solid: mp 193-194 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.67-7.64 (m, 3H), 7.61-7.57

(m, 1H), 7.41-7.37 (m, 1H), 6.96 (d, 1H, $J = 8.72$ Hz), 1.7 (s, 6H); MS (APCI) m/z 306($[M + H]^+$, 100%); Anal. Calc. For $C_{16}H_{13}ClFNO_2$: C, 62.86, H, 4.29, N, 4.58. Found: C, 62.98, H, 4.1, N, 4.6.

5

EXAMPLE 78

3-Chloro-5-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1-bromo-3-chlorobenzonitrile according to procedure B. A white solid: mp 256-257 °C; 1H -NMR (DMSO- d_6) δ 10.4 (s, 1H), 8.22 (bs, 1H), 8.15 (bs, 1H), 7.98 (bs, 1H), 7.74-7.71 (m, 2H), 6.97 (d, 1H, $J = 8.09$ Hz), 1.7 (s, 6H); MS (ESI) m/z 311($[M - H]^+$, 100%); Anal. Calc. For $C_{17}H_{13}ClN_2O_2$: C, 65.29, H, 4.19, N, 8.96. Found: C, 65.25, H, 3.92, N, 8.71.

15

EXAMPLE 79

6-(3,5-Dinitro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1-bromo-3,5-dinitrobenzene according to procedure B. A yellow solid: mp 297-298 °C; 1H -NMR (DMSO- d_6) δ 10.4 (s, 1H), 8.88 (d, 2H, $J = 1.98$ Hz), 8.78 (bs, 1H), 7.78-7.82 (m, 2H), 7.04 (d, 1H, $J = 8.23$ Hz), 1.7 (s, 6H); MS (APCI) m/z 343($[M - H]^+$, 100%); Anal. Calc. For $C_{16}H_{13}N_3O_6$: C, 55.98, H, 3.82, N, 12.24. Found: C, 55.65, H, 3.7, N, 11.92.

EXAMPLE 80

25

5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-isophthalonitrile

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 5-bromoisophthalonitrile according to procedure B. A white solid: mp 288-289 °C; 1H -NMR (DMSO- d_6) δ 10.4 (s, 1H), 8.58 (s, 2H), 8.40 (d, 1H, $J = 0.77$ Hz),

7.80-7.75 (m, 2H), 6.99 (d, 1H, $J = 8.2$ Hz), 1.7 (s, 6H); MS (EI) m/z 303($[M]^+$, 20%); Anal. Calc. For $C_{18}H_{13}N_3O_2 \cdot 1.65 H_2O$: C, 64.92, H, 4.93, N, 12.62. Found: C, 64.74, H, 4.69, N, 12.32.

5

EXAMPLE 81

4,4-Dimethyl-6-(3-thiazol-2-yl-phenyl)-1,4-dihydro-benzo[d][1,3]oxazin-2-one

A mixture of 6-(3-bromo-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (0.25g, 0.75 mmol), tri-*n*-butyl-thiazol-2-yl tin (0.5g, 1.3 mmol) in DMF (5 mL) was degassed to remove oxygen and then heated under nitrogen at 90 °C for 3 hours. The reaction mixture was cooled to rt and treated with ice-water (70 mL). Ethyl acetate (100 mL) was added and organic layer was separated, washed with brine, and dried ($MgSO_4$). After removal of solvent, the residue was purified by a silica gel column (hexane:ethyl acetate/1:1) to give the title compound as a white solid (60 mg, 23%); mp 223-224 °C; 1H -NMR ($DMSO-d_6$) δ 10.4 (s, 1H), 9.13 (s, 1H), 8.45 (s, 1H), 7.94 (bs, 1H), 7.67-7.61 (m, 4H), 7.53 (t, 1H, $J = 7.68$ Hz), 7.00 (d, 1H, $J = 8.81$ Hz), 1.7 (s, 6H); MS (APCI) m/z 337($[M + H]^+$, 100%); Anal. Calc. For $C_{19}H_{16}N_2O_2S \cdot 0.25 H_2O$: C, 66.94, H, 4.88, N, 8.22. Found: C, 66.57, H, 4.65, N, 7.92.

20

EXAMPLE 82

6-(3-Fluoro-5-methoxy-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 3-bromo-5-fluoroanisole according to procedure B. A white solid: mp 181-182 °C; 1H -NMR ($DMSO-d_6$) δ 10.4 (s, 1H), 7.62-7.59 (m, 2H), 7.13-7.06 (m, 2H), 6.97-6.94 (d, 1H, $J = 8.89$ Hz), 6.80 (dt, 1H, $J = 10.95, 2.12$ Hz), 3.8 (s, 3H), 1.7 (s, 6H); MS (ESI) m/z 302 ($[M + H]^+$, 100%); Anal. Calc. For $C_{17}H_{16}FNO_3 \cdot 0.1 H_2O$: C, 67.36, H, 5.39, N, 4.62. Found: C, 67.11, H, 5.44, N, 4.48.

EXAMPLE 83

6-(3-Fluoro-5-trifluoromethyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1-bromo-3-fluoro-5-trifluoromethylbenzene according to procedure B. A white solid: mp 207-208 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.94-7.9 (m, 2H), 7.73-7.7 (m, 2H), 7.63 (d, 1H, *J* = 8.58 Hz), 6.99 (d, 1H, *J* = 8.68 Hz), 1.7 (s, 6H); MS (EI) *m/z* 339([M⁺], 60%); Anal. Calc. For C₁₇H₁₃F₄NO₂: C, 60.18, H, 3.86, N, 4.13. Found: C, 59.9, H, 3.99, N, 4.06.

EXAMPLE 84

6-(5-Bromo-pyridin-3-yl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 3,5-dibromopyridine according to procedure B. A white solid: mp 211-212 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 8.92 (d, 1H, *J* = 1.9 Hz), 8.66 (d, 1H, *J* = 2.09 Hz), 8.40 (t, 1H, *J* = 2.02 Hz), 7.72-7.68 (m, 2H), 6.99 (d, 1H, *J* = 8.1 Hz), 1.7 (s, 6H); MS (APCI) *m/z* 333([M + H]⁺, 100%), 335([M + H]⁺, 100%); Anal. Calc. For C₁₅H₁₃BrN₂O₂: C, 54.07, H, 3.93, N, 8.41. Found: C, 54.15, H, 3.89, N, 8.31.

EXAMPLE 85

6-(5-Bromo-1-oxy-pyridin-3-yl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

A mixture of 6-(5-bromo-pyridin-3-yl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (0.34g, 1 mmol), hydrogen peroxide (30%, 5 mL) in acetic acid (5 mL) was heated at 60 °C for 3 hours. The reaction mixture was cooled to rt and neutralized by addition of a cold saturated sodium bicarbonate solution. The white precipitate obtained was collected on a filter, washed with distilled water and dried to afford the title compound as a white solid (0.35g, 100%): mp 157-159 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 8.69 (s, 1H), 8.53 (s, 1H), 7.99 (s, 1H), 7.73-7.69

(m, 2H), 6.97 (d, 1H, $J = 8.18$ Hz), 1.7 (s, 6H); MS (APCI) m/z 349([M + H]⁺, 100%), 351([M + H]⁺, 100%); Anal. Calc. For C₁₅H₁₃BrN₂O₃·2.5 H₂O: C, 45.70, H, 4.60, N, 7.11. Found: C, 45.34, H, 4.64, N, 7.

5

EXAMPLE 86

6-(3-Cyano-5-fluoro-phenyl)-4,4-dimethyl-2-oxo-4H-benzo[d][1,3]oxazine-1-carboxylic acid tert-butyl ester

A mixture of 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluorobenzonitrile (0.3g, ~1 mmol), di-*tert*-butyl dicarbonate (0.33g, 1.5 mmol),
10 and DMAP (50mg) in anhydrous acetonitrile was stirred at rt under nitrogen for 4 minutes. The reaction mixture was washed with 1N aqueous HCl, brine, dried (MgSO₄). After removal of solvent, the title compound was obtained as a white solid (0.25g, 63%): mp 139-140 °C; ¹H-NMR (CDCl₃-d₆) δ 7.66-7.63 (m, 2H), 7.53-7.48 (m, 2H), 7.38-7.35 (m, 2H), 1.79 (s, 6H), 1.62 (s, 9H); MS (APCI) m/z 289([M - H]⁻,
15 100%); Anal. Calc. For C₂₂H₂₁FN₂O₄: C, 66.66, H, 5.34, N, 7.07. Found: C, 66.7, H, 5.41, N, 7.

EXAMPLE 87

5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-2-fluorobenzonitrile

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Prepared from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1-bromo-2-fluorobenzonitrile according to procedure B. A white solid: mp 255-256 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 8.30 (dd, 1H, $J = 6.15, 2.41$ Hz), 8.12-8.07 (m, 1H), 7.76-7.58 (m, 3H), 6.97 (d, 1H, $J = 8.22$ Hz), 1.7 (s, 6H); MS
25 (APCI) m/z 297 ([M+H]⁺, 100%); Anal. Calc. For C₁₇H₁₃FN₂O₂·0.1 H₂O: C, 68.50, H, 4.46, N, 9.40. Found: C, 68.27, H, 4.81, N, 9.1.

EXAMPLE 88

4-(8-Fluoro-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-
thiophene-2-carbonitrile

8-Fluoro-(1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid
5 was prepared from 6-bromo-8-Fluoro-4,4-dimethyl-dihydro-benzo[d][1,3]oxazin-2-one using the procedure of example 4.

The title compound was prepared from 8-fluoro-(1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 4-bromo-2-cyanothiophene according to procedure B. A white solid: mp 250-251 °C; ¹H-NMR (DMSO-d₆) δ 10.5 (s, 1H),
10 8.54 (d, 1H, *J* = 1.42 Hz), 8.43 (d, 1H, *J* = 1.35 Hz), 7.69 (dd, 1H, *J* = 11.71, 1.54 Hz), 7.58 (bs, 1H), 1.7 (s, 6H); MS (EI) *m/z* 302([M⁺], 50%); Anal. Calc. For C₁₅H₁₁FN₂O₂S·0.45 H₂O: C, 58.04, H, 3.86, N, 9.02 Found: C, 58.4, H, 3.89, N, 8.63.

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EXAMPLE 89

3-Fluoro-5-(8-fluoro-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile

Prepared from 8-fluoro-(1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 5-bromo-3-fluorobenzonitrile according to procedure B. A white
20 solid: mp 256-257 °C; ¹H-NMR (DMSO-d₆) δ 10.5 (s, 1H), 8.20 (bs, 1H), 8.06 (dt, 1H, *J* = 10.48, 2.16 Hz), 7.85-7.82 (m, 1H), 7.77 (dd, 1H, *J* = 11.89, 1.81 Hz), 7.63 (s, 1H), 1.7 (s, 6H); MS (EI) *m/z* 314([M⁺], 60%).

EXAMPLE 90

25 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-3-carbonitrile

Prepared according to procedure B from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 2-bromo-4-thiophenecarbonitrile. An off-white

solid: mp 255-260 °C; ¹H-NMR (DMSO-d₆) δ 10.36 (s, 1H), 8.48(d, 1H, *J* = 1.1 Hz), 7.88-7.87 (d, 1H *J* = 1.3 Hz), 7.63 (d, 1H *J* = 1.9 Hz), 7.56-7.54 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.93 (d, 1H, *J* = 8.1 Hz), 1.64 (s, 6H). MS(-ESI) *m/z* 283 (M-H)⁺.

5

EXAMPLE 91

2-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-3-carbonitrile

Prepared according to procedure B from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 2-bromo-3-thiophenecarbonitrile. An off-white solid: mp 200-202 °C; ¹H-NMR (DMSO-d₆) δ 10.49 (s, 1H), 7.75(m, 1H), 7.63(d, 1H, *J* = 2.2 Hz), 7.59 (m, 1H), 7.50 (m, 1H), 7.02 (d, 1H, *J* = 8.1 Hz), 1.63(s, 6H); MS(-ESI) *m/z* 283 (M-H)⁺.

10

EXAMPLE 92

6-(1,2,4-thiadiazol-3-yl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

A mixture of 5-[3-bromo-phenyl]-[1,3,4]oxathiazole-2-one (21.25 g, 82.3 mmol), ethylcyano formate (32.5 mL, 329 mmol) in o-xylene (500 mL) was heated to 150 °C for 60 hours. After the solvent was removed from the reaction mixture, the product was recrystallized from ethanol to give 3-[3-bromo-phenyl]-[1,2,4]thiadiazole-5-carboxylic acid ethyl ester as white crystals (17.5 g, 68%); mp 87-90 °C; ¹H-NMR (CDCl₃) δ 8.53 (t, 1H, *J* = 1.76 Hz), 8.28 (dt, 1H, *J* = 5.4, 1.2 Hz), 7.62 (dq, 1H, *J* = 5.1, 1.0 Hz), 7.36 (t, 1H, *J* = 7.9 Hz), 4.55 (q, 2H, *J* = 7.1 Hz), 1.48 (t, 3H, *J* = 7.1 Hz); MS ((+)APCI) [M+H]⁺ @ *m/z* 313/315. Anal. Calc. For C₁₁H₉BrN₂O₂S: C, 42.19, H, 2.90, N, 8.94. Found: C, 41.81, H, 3.08, N, 8.78.

20

25

A mixture of 3-[3-bromo-phenyl]-[1,2,4]thiadiazole-5-carboxylic acid ethyl ester (16.8 g, 53.5 mmol), sodium hydroxide (2.4 g, 58.8 mmol), distilled water (120

mL), and ethanol (20 mL) was heated to 100 °C for 2 hours. The reaction mixture was cooled to room temperature. Concentrated hydrochloric acid (5.1 mL) was added, and the reaction mixture re-heated to 100 °C for 3 hours. The solution was cooled to room temperature and extracted with diethyl ether (3x150 mL). The combined organic layers were washed with distilled water (3x100 mL), and dried over MgSO₄. After the solvent was removed, 3-[3-bromo-phenyl]-[1,2,4]thiadiazole was obtained as white needles (12.7 g, 99%): mp 69-71 °C; ¹H-NMR (CDCl₃) δ 9.89 (s, 1H), 8.52 (t, 1H, *J* = 1.8 Hz), 8.28 (dt, 1H, *J* = 5.2, 1.3 Hz), 7.61 (dq, 1H, *J* = 4.9, 1.1 Hz), 7.35 (t, 1H, *J* = 7.9 Hz); MS ((+)APCI) [M+H]⁺ @ *m/z* 241/243. Anal. Calc. For C₈H₅BrN₂S: C, 39.85, H, 2.09, N, 11.62. Found: C, 39.82, H, 2.43, N, 11.33.

According to procedure B, (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid was coupled with 3-[3-bromo-phenyl]-[1,2,4]thiadiazole to yield 6-(1,2,4-thiadiazol-3-yl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one as an off-white solid (0.5 g, 35%): mp 214-216 °C; ¹H-NMR (DMSO-d₆) δ 10.40 (s, 1H), 10.36 (s, 1H), 8.49 (s, 1H), 8.23 (d, 1H, *J* = 7.7 Hz), 7.83 (d, 1H, *J* = 7.9 Hz), 7.66 - 7.61 (m, 3H), 7.02 (t, 1H, *J* = 4.4 Hz), 1.70 (s, 6H); MS ((+)APCI) [M+H]⁺ @ *m/z* 338.

EXAMPLE 93

20 6-(3-Fluoro-5-thiophen-3-yl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared from 6-(3-bromo-5-fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one and 3-thiophene boronic acid according to procedure B. A brownish-orange solid: mp 200-203 °C; ¹H-NMR (CDCl₃) δ 8.62 (s, 1H), 7.53 (q, 1H, *J* = 1.4 Hz), 7.50 (d, 1H, *J* = 1.5 Hz), 7.49 (d, 1H, *J* = 2.0 Hz), 7.45 - 7.40 (m, 1H), 7.35 (d, 1H, *J* = 1.8 Hz), 7.27 - 7.24 (m, 2 H), 7.15 (dt, 1H, *J* = 5.8, 2.0 Hz), 6.94 (d, 1H, *J* = 8.2 Hz), 1.80 (s, 6H); MS ((-)APCI) [M-H]⁻ @ *m/z* 352. Anal. Calc. For C₂₀H₁₆FNO₂S·0.50 H₂O: C, 66.28, H, 4.73, N, 3.87. Found: C, 66.54, H, 5.03, N, 3.52.

EXAMPLE 94

2-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo [d] [1,3] oxazin-6-yl)-pyrrole-1-carboxylic acid tert-butyl ester

5 A solution of 6-bromo-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one (0.87 g, 3.4 mmol) and tetrakis(triphenylphosphine)palladium(0) (96 mg, 0.08 mmol) in toluene (40 mL) was stirred under a flow of nitrogen for 25 min. To the solution was added sequentially 1-t-butoxycarbonylpyrrole-2-boronic acid (1.4 g, 7.0 mmol) in absolute ethanol (10 mL) and potassium carbonate (0.94 g, 7.0 mmol) in water (10
10 mL). The mixture was heated at 80 °C for 16 h and allowed to cool to rt. The reaction mixture was poured into aqueous saturated sodium bicarbonate solution (100 mL) and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with water (100 mL) and brine (50 mL) and dried over magnesium sulfate. The solution was filtered, concentrated *in vacuo*, and the residue was purified
15 by flash column chromatography on silica gel (30% ethyl acetate/hexane) to give the title compound as an off-white powder (0.7 g, 62%); mp 176 °C. ¹H NMR (CDCl₃) δ 1.40 (s, 9 H), 1.73 (s, 6 H), 6.17 (dd, 1 H, *J* = 1.8, 3.3 Hz), 6.22 (dd, 1 H, *J* = 3.3, 3.3 Hz), 6.77 (d, 1 H, *J* = 8.1 Hz), 7.13 (d, 1 H, *J* = 1.8 Hz), 7.23 (dd, 1 H, *J* = 1.8, 8.1 Hz), 7.33 (dd, 1 H, *J* = 1.8, 3.3 Hz), 7.69 (bs, 1 H). MS ((-) ESI) *m/z* 341 [M-H]⁻.
20 Anal. Calcd for C₁₉H₂₂N₂O₄: C, 66.65; H, 6.48; N, 8.18. Found: C, 65.46; H, 6.51; N, 7.74.

EXAMPLE 95

2-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo [d] [1,3] oxazin-6-yl)-5-nitro-pyrrole-1-carboxylic acid tert-butyl ester

25 To a solution of 2-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo [d] [1,3]oxazin-6-yl)-pyrrole-1-carboxylic acid tert-butyl ester (0.7 g, 2.0 mmol) in acetonitrile (25 mL) and dichloromethane (1 mL) at room temperature was added silver nitrate (0.37 g, 2.1 mmol). After 5 min, acetyl chloride (0.15 mL, 2.0 mmol) in acetonitrile (3 mL)

was added and the solution was allowed to stir for 2 h. The reaction mixture was poured into water (50 mL) and extracted with ethyl ether (2 x 50 mL). The organic layers were combined, washed with brine (30 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 (30% ethyl acetate/hexane) to give a yellow oil which crystallized from 5% ethyl acetate/hexane to give the title compound as a bright yellow powder (350 mg, 45%): mp 125 °C. ¹H NMR (CDCl₃) δ 1.47 (s, 9 H), 1.75 (s, 6 H), 6.26 (d, 1 H, *J* = 4.2 Hz), 6.87 (d, 1 H, *J* = 8.1 Hz), 7.19 (d, 1 H, *J* = 4.2 Hz), 7.34 (d, 1 H, *J* = 2 Hz), 7.4 (dd, 1 H, *J* = 1.8, 8.1 Hz), 8.17 (bs, 1 H). MS ((+) APCI) *m/z* 388 [M + H]⁺. Anal. Calcd for C₁₉H₂₁N₃O₆: C, 58.91; H, 5.46; N, 10.85. Found: C, 58.4; H, 5.55; N, 10.18.

EXAMPLE 96

4,4-Dimethyl-6-(5-nitro-1H-pyrrol-2-yl)-1,4-dihydrobenzo [d][1,3]oxazin-2-one
2-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo [d] [1,3] oxazin-6-yl)-5-nitro-pyrrole-1-carboxylic acid tert-butyl ester (0.7 g, 1.8 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 180 °C. After 10 min at this temperature, the flask was removed from the oil bath and allowed to cool to rt. The brown residue was washed into a larger flask with dichloromethane/ethyl acetate and adsorbed onto a small amount of silica gel. Purification by flash column chromatography on silica gel (60% ethyl acetate/hexane) gave the title compound as a brown powder (200 mg, 40%): mp 265 °C (dec). ¹H NMR (DMSO-*d*₆) δ 1.65 (s, 6 H), 6.81 (d, 1 H, *J* = 4.4 Hz), 6.90 (d, 1 H, *J* = 8.6 Hz), 7.25 (d, 1 H, *J* = 4.2 Hz), 7.79 (dd, 1 H, *J* = 2, 8.3 Hz), 7.91 (d, 1 H, *J* = 2 Hz), 10.37 (s, 1 H), 13.17 (bs, 1 H). MS ((-) ESI) *m/z* 286 [M-H]⁻. Anal. Calcd for C₁₄H₁₃N₃O₄: C, 58.53; H, 4.56; N, 14.63. Found: C, 58.25; H, 5.10; N, 12.57.

EXAMPLE 97

4,4-Dimethyl-6-(1H-pyrrol-2-yl)-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

2-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo [d] [1,3] oxazin-6-yl)-pyrrole-1-
5 carboxylic acid tert-butyl ester (3.5 g, 10 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 180 °C . After 10 min at this
temperature, the flask was removed from the oil bath and allowed to cool. The brown
10 residue was washed into a larger flask with dichloromethane/ethyl acetate and
adsorbed onto a small amount of silica gel. Purification by flash column
chromatography on silica gel (60% ethyl acetate/hexane) gave the title compound as a
green solid (2 g, 80%): mp 202 °C (dec). ¹H NMR (CDCl₃) δ 1.75 (s, 6 H), 6.30 (m, 1
H), 6.45 (m, 1 H), 6.85 (d, 1 H, *J* = 8.5 Hz), 6.86 (m, 1 H), 7.24 (d, 1 H, *J* = 2 Hz),
15 7.33 (dd, 1 H, *J* = 2, 8.4 Hz), 8.44 (bs, 1 H), 8.66 (s, 1 H). MS ((+) APCI) *m/z* 243
[M+H]⁺. Anal. Calcd for C₁₄H₁₄N₂O₂: C, 69.41; H, 5.82; N, 11.56. Found: C,
69.20; H, 5.96; N, 11.29.

EXAMPLE 98

20 **4,4-Dimethyl-6-(1-methyl-1H-pyrrol-2-yl)-1,4-dihydro-benzo [d][1,3] oxazin-2-one**

To a mixture of 4,4-dimethyl-6-(1H-pyrrol-2-yl)-1,4-dihydro-
benzo[d][1,3]oxazin-2-one (1.5 g, 6.2 mmol) in dimethylformamide (20 mL) at room
temperature was added sequentially potassium carbonate (4.28 g, 31 mmol) and a
25 solution of methyl iodide (1.16 mL, 19 mmol) in dimethylformamide (5 mL). After 1
h, the reaction mixture was boiled. The reaction was cooled to room temperature,
poured into water (50 mL) and extracted with ethyl ether (2 x 50 mL). The organic
layers were combined, washed with brine (30 mL), dried over magnesium sulfate,
filtered and concentrated *in vacuo*. Purification by flash column chromatography on

silica gel (40% ethyl acetate/hexane) gave the title compound as an off-white powder (0.5 g, 31%) mp 230 °C. ¹H NMR (CDCl₃) δ 1.71 (s, 6 H), 3.42 (s, 3 H), 6.31 (dd, 1 H, *J* = 2.9, 5.9 Hz), 6.47 (m, 1 H), 6.88 (m, 1 H), 6.94 (d, 1 H, *J* = 8.6 Hz), 7.26 (d, 1 H, *J* = 2.2 Hz), 7.41 (dd, 1 H, *J* = 2.2, 8.6 Hz), 8.43 (bs, 1 H). MS ((-) ESI) *m/z* 255 [M-H]⁻. Anal. Calcd for C₁₅H₁₆N₂O₂: C, 70.29; H, 6.29; N, 10.93. Found: C, 68.59; H, 6.16; N, 10.49.

EXAMPLE 99

4,4-Dimethyl-6-(1-methyl-5-nitro-1H-pyrrol-2-yl)-1,4-dihydro-benzo[d][1,3]oxazin-2-one

To a solution of 4,4-dimethyl-6-(1-methyl-1H-pyrrol-2-yl)-1,4-dihydro-benzo[d][1,3] oxazin-2-one (0.3 g, 1.2 mmol) in acetonitrile (20 mL) was added silver nitrate (0.21 g, 1.26 mmol). The solution was cooled to -78 °C and treated with a solution of acetyl chloride (0.08 mL, 1.2 mmol) in acetonitrile (1 mL). The reaction mixture was allowed to warm to room temperature. After 1 h, the reaction mixture was poured into water (50 mL) and extracted with ethyl ether (2 x 50 mL). The organic layers were combined, washed with brine (30 mL), dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (40% ethyl acetate/hexane) gave the title compound (5 mg, 1%) as a yellow solid, mp 180-185 °C. ¹H NMR (CDCl₃) δ 1.75 (s, 6 H), 3.45 (s, 3 H), 6.57 (dd, 1 H, *J* = 2.9, 4.3 Hz), 7.04 (d, 1 H, *J* = 8.5 Hz), 7.22 (dd, 1 H, *J* = 2.5, 4.3 Hz), 7.36 (d, 1 H, *J* = 2.1 Hz), 7.56 (dd, 1 H, *J* = 2.1, 8.5 Hz), 9.67 (bs, 1 H). MS ((+) APCI) *m/z* 302 [M+H]⁺.

EXAMPLE 100

5-Bromo-4-ethylthiophene-2-carboxaldehyde

Prepared from 2-bromo-3-ethylthiophene in a similar manner to the example 19. ¹H-NMR(DMSO-d₆) δ 9.82 (s, 1H), 7.81 (s, 1H), 2.5 (q, 2H, *J* = 7.4 Hz), 1.15 (t, 3H, *J* = 7.5 Hz).

EXAMPLE 101

5-Bromo-4-ethylthiophene-2 carbonitrile

Prepared from 5-bromo-4-ethylthiophene-2-carboxaldehyde using the similar
5 procedure of example 18. IR(KBr) 2221 cm^{-1} ; $^1\text{H-NMR(DMSO-}d_6)$ δ 7.87 (S, 1H),
2.55 (q, 2H, $J = 7.3\text{ Hz}$), 1.18 (t, 3H, $J = 7.6\text{ Hz}$). MS (EI) m/z 215/217(M^+).

EXAMPLE 102

5-Bromo-4-*n*-propylthiophene-2-carboxaldehyde

10 Prepared from 2-bromo-3-*n*-propylthiophene in a similar manner to the
example 19. $^1\text{H-NMR(DMSO-}d_6)$ δ 9.82 (S, 1H), 2.6-2.5 (m, 2H), 1.65-1.51 (m, 2H),
1.0 (t, 3H, $J = 4.7\text{ Hz}$).

EXAMPLE 103

5-Bromo-4-*n*-propylthiophenecarbonitrile

15 Prepared from 5-bromo-4-*n*-propylthiophene-2-carboxaldehyde using the
similar procedure of example 18. $^1\text{H-NMR(DMSO-}d_6)$ δ 7.87 (S, 1H), 2.5 (t, 2H, $J =$
5.2 Hz), 1.64-1.5 (m, 2H), 1.91 (t, 3H, $J = 5.1\text{ Hz}$). MS(EI) m/z 229-231(M^+).

20

EXAMPLE 104

5-Bromo-4-*n*-butylthiophenecarboxaldehyde

Prepared from 2-bromo-3-*n*-butylthiophene in a similar manner to the example
19. IR(KBr) 1660 cm^{-1} . $^1\text{H-NMR (DMSO-}d_6)$ δ 9.78 (S, 1H), 7.85 (S, 1H), 2.57-2.53
25 (m, 2H), 1.57-1.53 (m, 2H), 1.32-1.25 (m, 2H), 0.88 (t, 3H, $J = 5.2\text{ Hz}$). MS (EI) m/z
246(M^+).

EXAMPLE 105

5-Bromo-4-*n*-butylthiophenecarbonitrile

Prepared from 5-bromo-4-*n*-butylthiophenecarboxaldehyde using the similar procedure of example 18. ¹H-NMR(DMSO-*d*₆) δ 7.87 (s, 1H), 2.58-2.44 (m, 2H), 1.65-1.48 (m, 2H), 1.38-1.23 (m, 2H), 0.89 (t, 3H, *J* = 5.3 Hz). MS (EI) *m/z* 243 (*M*⁺).

5

EXAMPLE 106

3-(1,2-Dihydro-2-oxospiro[4H-3,1-benzoxazine-4,1-cyclohexan]-6-yl)-benzonitrile

Prepared according to Procedure B from spiro-(4, 1'-cyclohexane-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl) boronic acid and 3-bromobenzonitrile. Tan powder: mp 245-247 °C. ¹H-NMR(DMSO-*d*₆) δ 10.31 (s, 1H), 8.21 (s, 1H), 8.02 (d, 1H, *J* = 8.0 Hz), 7.78 (d, 1H, *J* = 7.7 Hz), 7.68-7.61 (m, 3H), 6.97 (d, 1H, *J* = 8.2 Hz), 1.98-1.96 (m, 4H), 1.75-1.64 (m, 5H), 1.40-1.32 (m, 1H). MS (EI) *m/z* 318 [*M*⁺]. Anal. Calc. For C₂₀H₁₈N₂O₂·1/2 H₂O: C 73.38; H, 5.85; N, 8.56. Found: C, 73.86; H, 5.81; N, 8.22.

15

EXAMPLE 107

3-(1, 2-Dihydro-2-oxospiro[4H-3, 1-benzoxazine-4, 1-cyclohexan]-6-yl)-5-fluorobenzonitrile

Prepared according to Procedure B from spiro-(4, 1'-cyclohexane-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl) boronic acid and 3-bromo-5-fluorobenzonitrile. White powder: mp 250-253 °C. IR (KBr) 2220 cm⁻¹. ¹H-NMR (DMSO-*d*₆) δ 10.34 (s, 1H), 8.13 (s, 1H), 8.0 (d, 1H, *J* = 10.6 Hz), 7.80-7.7 (m, 3 H), 6.98-6.95 (d, 1H, *J* = 8.1 Hz), 1.99-1.97 (m, 4H), 1.76-1.65 (m, 6H), 1.37-1.33 (m, 1H). MS (EI) *m/z* 336 (*M*⁺). Anal. Calc. For C₂₀H₁₇FN₂O₂·H₂O: C, 67.78; H, 5.40; N, 7.90. Found: C, 67.9; H, 4.93; N, 7.67.

25

EXAMPLE 108

4-(1, 2-Dihydro-2-oxospiro[4H-3,1-benzoxazine-4,1-cyclohexan]-6-yl)-2-thiophenecarbonitrile

Prepared according to Procedure B from spiro-(4, 1'-cyclohexane-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl) boronic acid and 3-bromo-5-cyanothiophene. White crystals: mp 230-232 °C. IR (KBr) 2200 cm⁻¹. ¹H-NMR (DMSO-d₆) δ 10.29 (s, 1H), 8.49 (s, 1H), 8.33 (s, 1H), 7.69-7.63 (m, 2H), 6.93-6.91 (d, 1H, *J* = 8.2 Hz), 1.99-1.87 (m, 4H), 1.73-1.64 (m, 5H), 1.38-1.31 (m, 1H). MS(+)-APCI *m/z* 325 (M+H)⁺. Anal. Calc. For C₁₈H₁₆N₂O₂S1/4H₂O: C, 65.73; H, 5.06; N, 8.52. Found: C, 65.55; H, 5.06; N, 8.22.

EXAMPLE 109

10 5-(1, 2-Dihydro-2-oxospiro[4H-3, 1-benzoxazine-4,1-cyclohexan]-6-yl)-2-thiophenecarbonitrile

Prepared according to Procedure B from spiro-(4, 1'-cyclohexane-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl) boronic acid and 2-bromo-5-cyanothiophene Tan powder: mp 243-245 °C. ¹H-NMR(DMSO-d₆) δ 10.41(s, 1H), 7.98-7.97 (d, 1H, *J* = 3.9 Hz), 7.67-7.60 (m, 3H), 6.97-6.94 (d, 1H, *J* = 8.3 Hz), 1.98-1.92 (m, 4H), 1.74-1.64 (m, 5H), 1.45-1.21 (m, 1H). MS (EI) *m/z* 324 (M⁺). Anal. Calc. For C₁₈H₁₆N₂O₂S 1/2 H₂O: C, 65.08; H, 5.04; N, 8.18. Found: C, 64.84; H, 5.09; N, 8.40.

EXAMPLE 110

20 5-(1, 2-Dihydro-2-oxospiro[4H-3, 1-benzoxazine-4,1-cyclohexan]-6-yl)-4-methyl-2-thiophenecarbonitrile

Prepared according to Procedure B from spiro-(4, 1'-cyclohexane-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl) boronic acid and 2-bromo-3-methyl-5-cyanothiophene. White powder: mp 200-203 °C. ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 7.85 (s, 1H), 7.43-7.40 (m, 2H), 7.0 (d, 1H, *J* = 8.8 Hz), 2.27 (s, 3 H), 2.00-1.62 (m, 9H), 1.42-1.23 (m, 1H). MS(EI) *m/z* 338 (M⁺). Anal. Calc. For C₁₉H₁₈N₂O₂S: C, 67.43; H, 5.36, N, 8.28. Found: C, 67.12; H, 5.45; N, 8.05.

EXAMPLE 111

5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-ethyl-thiophene-2-carbonitrile

Prepared according to Procedure B from spiro-(4, 1'-cyclohexane-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl) boronic acid and 2-bromo-3-ethyl-5-cyanothiophene. White crystals: mp 160-162 °C. ¹H-NMR(DMSO-d₆) δ 10.46 (s, 1H), 7.96 (s, 1H), 7.40-7.38 (m, 2H), 7.02-6.99 (d, 1H, *J* = 8.8 Hz), 2.61 (q, 2H, *J* = 7.5 Hz), 1.64 (s, 6H), 1.16 (t, 3H, *J* = 7.6 Hz). MS (+) APCI *m/z* [M + H]⁺ 313. Anal. Calc. For C₁₇H₁₆N₂O₂S·1/4 H₂O: C, 64.43; H, 5.25; N, 8.84. Found: C, 64.77; H, 5.23; N, 8.68.

10

EXAMPLE 112

5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-*n*-propyl-thiophene-2-carbonitrile

Prepared according to Procedure B from spiro-(4, 1'-cyclohexane-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl) boronic acid and 2-bromo-3-*n*-propyl-5-thiophenecarbonitrile. White crystals: mp 160-162 °C. IR (KBr) 2220 cm⁻¹. ¹H-NMR(DMSO-d₆) δ 10.47 (s, 1H), 7.93 (s, 1H), 7.38-7.36 (m, 2H), 7.01 (d, 1H, *J* = 8.7 Hz), 2.59-2.48 (m, 2H), 1.64-1.51 (m, 2H), 0.85 (t, 3H, *J* = 7.3 Hz). MS(-ESI) *m/z* [M-H]⁻ 325. Anal. Calc. For C₁₈H₁₈N₂O₂S·3/4H₂O: C, 63.60; H, 5.78; N, 8.24. Found: C, 63.48; H, 5.59; N, 8.04.

20

EXAMPLE 113

5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-*n*-butyl-thiophene-2-carbonitrile

Prepared according to Procedure B from spiro-(4, 1'-cyclohexane-1,4-dihydro-2-oxo-2H-3,1-benzoxazin-6-yl) boronic acid and 2-bromo-3-*n*-butyl-5-thiophenecarbonitrile. White crystals: mp 167-168 °C. ¹H-NMR(DMSO-d₆) δ 10.46 (s, 1H), 7.93 (s, 1H), 7.38-7.36 (m, 2H), 7.01 (d, 1H, *J* = 8.7 Hz), 2.59 (t, 2H, *J* = 8.1 Hz), 1.63 (s, 6H), 1.58-1.51 (m, 2H), 1.48-1.17 (m, 2H), 0.82 (t, 3H, *J* = 7.4 Hz). MS(-ESI)

25

m/z [M-H]⁺ 339. Anal. Calc. For C₁₉H₂₀N₂O₂S·1/4 H₂O: C, 66.16; H, 5.99; N, 8.12. Found: C, 66.33; H, 5.92; N, 7.85.

EXAMPLE 114

5 6-(4-Cyano-3-fluoro)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]-
oxazin-2-one

A solution of 4-cyano-3-fluoro-bromobenzene (0.6 g, 3.0 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.2 g) in ethylene glycol dimethyl ether (20 mL) was stirred under N₂ for 20 minutes. To this mixture was then added (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid (1.0 g, 4.5 mmol) and sodium carbonate (1.1 g, 10.6 mmol) in water (5 mL). The solution was brought to reflux for 18 hours and then cooled to room temperature, poured into 2N NaOH and extracted with EtOAc (3x50 mL). The combined extracts were washed with water, brine, dried (MgSO₄), and evaporated. The residue was purified by column chromatography (SiO₂, EtOAc:hexane = 1:2) to afford the title compound (0.05 g, 6%) as an off-white solid. mp: 272 - 275 °C; ¹H-NMR (DMSO-d₆) δ 10.4 (s, 1H), 8.0 (t, 1 H, *J* = 7.7 Hz), 7.9 (dd, 1H, *J* = 10.3, 1.3 Hz), 7.8 (dd, 1H, *J* = 6.8, 1.4 Hz), 7.7 (m, 2H), 6.9 (d, 1H, *J* = 8.9 Hz), 1.7 (s, 6H); MS (EI) M⁺ @ m/z 296.

20 **EXAMPLE 115**

6-(4-Fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

Prepared according to Procedure B from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1-bromo-4-fluorobenzene. Off-white crystals: 25 mp 232-233 °C. ¹H-NMR(DMSO-d₆) δ 10.3 (s, 1H), 7.74 (m, 2H), 7.53 (m, 2H), 7.28 (m, 2H), 6.96 (d, 1H, *J* = 8.9 Hz), 1.63 (s, 6H).

EXAMPLE 116

6-(3,4-Difluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared according to Procedure B from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1-bromo-3, 4-difluorobenzene. Off-white crystals: mp 207-208 °C. ¹H-NMR(DMSO-d₆) δ 10.35 (s, 1H), 7.79 (m, 1H), 7.40-7.63 (m, 4H), 6.95 (d, 1H, *J* = 8.9 Hz), 1.62 (s, 6H).

5

EXAMPLE 117

6-(2-Fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one

Prepared according to Procedure B from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxin-6-yl)boronic acid and 1-bromo-2-fluorobenzene. Off-white crystals: mp 164-165 °C. ¹H-NMR(DMSO-d₆) δ 10.33 (s, 1H), 7.56 (m, 1H), 7.25-7.45 (m, 4H), 6.98 (d, 1H, *J* = 8.7 Hz), 1.64 (s, 6H).

10

EXAMPLE 118

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)phenylacetonitrile

15

Prepared from 3-bromophenylacetonitrile and (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-6-yl)boronic acid. White solid: mp 188-190 °C; ¹H-NMR (DMSO- d₆) δ 10.33 (s, 1H), 7.62 (m, 2H), 7.55 (m, 2H), 7.48 (d, 1H, *J* = 8.00 Hz), 7.33 (d, 1H, *J* = 7.57 Hz), 6.99 (d, 1H, *J* = 8.81 Hz), 4.09 (s, 2H), 1.67 (s, 6H); MS *m/z* 291(M-H).
Anal. Calc. For C₁₈H₁₆N₂O₂·0.3 H₂O: C, 72.61, H, 5.62, N, 9.41. Found: C, 73.00, H, 5.43, N, 8.81

20

EXAMPLE 119

5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-furan-2-carbonitrile

25

The title compound was prepared according to the procedure B from 2-bromo-5-cyanofuran (1.0 g, 5.6 mmol) (J. Med. Chem. (1997), 40(23), 3804-3819) and (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid (1.8 g, 8.18 mmol)

as a white solid (0.39 g, 1.45 mmol, 17%): mp. 257 - 260 °C; ¹H-NMR (DMSO-d₆) δ 10.48 (s, 1H), 7.73 - 7.70 (m, 3H), 7.19 (d, 1 H, *J* = 3.8 Hz), 6.98 (d, 1 H, *J* = 8.9 Hz), 1.66 (s, 6H); MS ((+)-APCI) *m/z* = 269 (M+H)⁺.

5

EXAMPLE 120

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-2-fluorobenzonitrile

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 Et₂O. the organic layer was washed with sat. sodium hydrogen carbonate solution, water, brine, dried (MgSO₄) and evaporated to give methyl 3-bromo-2-fluorobenzoate (0.195 g, 0.84 mmol, 84%): ¹H-NMR (CDCl₃) δ 7.90 - 7.85 (m, 1H), 7.71 - 7.65 (m, 1H), 7.10 (dt, 1H, *J* = 8.0, 1.0 Hz), 3.94 (s, 3H): MS (EI) 232 (M⁺).
15

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 a 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 RT, partitioned between EtOAc/H₂O, the aqueous layer was re-extracted with EtOAc, and the combined organic layers were washed with water, dried (MgSO₄) and evaporated to afford 3-bromo-2-fluorobenzaldehyde (2.63 g, 12.9 mmol, 98%), which was used without further purification: ¹H-NMR (CDCl₃) δ 10.35 (s, 1H), 7.82 (m, 2H), 7.18 (t, 7.8 Hz).
20

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/H₂O (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 (MgSO₄) and evaporated to give 3-bromo-2-fluorobenzaldoxime which was used without further characterization.
25

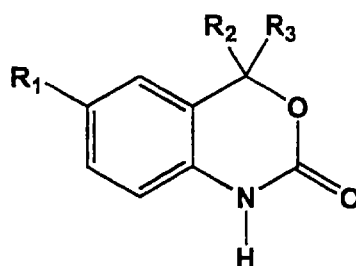
A solution of the last cited compound (0.75 g, 3.43 mmol) and tetrakis(triphenylphosphine) palladium(0) (0.2 g) were stirred in dimethoxy ethane (30 mL) at room temperature under nitrogen. After 15 min., (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid (1.1 g, 5.0 mmol) and sodium carbonate (1.35 g) in water (10 mL) were added and the mixture heated under reflux. After 16 h., the mixture was cooled, partitioned between water and EtOAc, the organic layer was washed with sat. sodium carbonate solution, brine, dried (MgSO₄) and evaporated. The residue was then dissolved in acetonitrile (50 mL), treated with copper acetate (0.2 g) and heated under reflux. After 16 h, the mixture was cooled and evaporated. The residue was partitioned between water and EtOAc, the organic layer was then washed with dilute sulfuric acid (1N), water, brine, dried (MgSO₄) and evaporated. The residue was then subjected to column chromatography (SiO₂, EtOAc/hexane, gradient elution), and then crystallized from EtOAc-hexane to afford the title compound (0.176 g, 0.59 mmol, 17%) as a white solid: mp. 192-198 °C; ¹H-NMR (CDCl₃) δ 9.15 (s, 1H), 7.69 - 7.58 (m, 2H), 7.42 - 7.31 (m, 3H), 6.99 (d, 1H, *J* = 8.2 Hz), 1.78 (s, 6H); MS ((+)ESI) 297 [M + H]⁺.

EXAMPLE 121 - PHARMACOLOGY

The compounds of this invention were tested in the relevant assay as described below and their potency are in the range of 0.01 nM to 5 μM in the *in vitro* assays and 0.001 to 300 mg/kg in the *in vivo* assays.

Table 1

Potency of the selected cyclocarbamate derivatives as PR antagonists in some *in vitro* and *in vivo* models:



5	Compound	R ₁	R ₂	R ₃	hPR	CV-1
					Decidualization IC ₅₀ (nM)	IC ₅₀ (mg/kg)
10	1	3-cyano-4-fluorophenyl	Me	Me	55	80%@1**
	2	3-fluoro-5-trifluoromethylphenyl	Me	Me	54	50%@1
15	3	3-fluorophenyl	Me	Me	6	80%@3
	4	3,5-dichlorophenyl	Me	Me	134	60%@1
20	5	5-cyano-2-fluorophenyl	Me	Me	68	60%@1
	6	3-fluoro-5-nitrophenyl	Me	Me	11.5	50%@1
25	7	4-(2-cyanofuryl)	Me	Me	30	75%@3
	8	3-bromo-5-fluorophenyl	Me	Me	11	50%@3

	9	3-cyano-4-fluorophenyl	Me	Me	13	6.96±0.84
5	10	5-(2-cyano-4-methylthiophenyl)	spirocyclohexyl		2.7	50%@10
	11	5-(2-cyanothiophenyl)	spirocyclohexyl		12	50%@10
10	12	5-(2-cyanothiophenyl)	Me	Me	19	3.34±0.22
	13	3-bromophenyl	Me	Me	11.5	3
15	14	3-chloro-5-fluorophenyl	Me	Me	22	50%@3
	15	3-cyano-5-fluorophenyl	cyclopropyl	cyclopropyl	22	3
20	16	5-(3-bromopyridyl)	Me	Me	26	50%@3
25	17	4-(2-cyanothiophenyl)	Me	Me	12.7	2.3±0.46
	18	5-(2-cyano-4-methylthiophenyl)	Me	Me	5.23	1.5
30	19	3-cyano-5-fluorophenyl	Me	Me	13.8	0.35
35	20	3-chloro-4-fluorophenyl	Me	Me	37	1

ND, not determined; **Percentage inhibition at the dose specified

40

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 1.2×10^7 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 μ l. 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 antiprogesterational 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 μ l 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 antiprogesterin. All reference compounds are run in full dose-response curves and the EC_{50} or IC_{50} values are calculated.

Table 2. Estimated EC_{50} , standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies

Compound	Exp.	<u>EC_{50}</u>	SE	<u>95% CI</u>	
		(nM)		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

5

Table 3. Estimated IC₅₀, standard error (SE), and 95% confident interval (CI) for the antiprogesterin, RU486 from three individual studies

10	Compound	Exp.	IC 50	SE	95% CI	
			(nM)		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

15 **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 ($p < 0.05$)

EC₅₀: Concentration of a compound that gives half-maximal increase PRE-luciferase activity (default-nM) with SE.

IC₅₀: 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
25 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. Progesterin and antiprogesterin reference compounds are run in full dose-response curves. The final concentration of vehicle is 0.1%. In control wells, cells receive vehicle only. Antiprogesterins are tested in the presence of 0.03 nM trimegestone, the reference progesterin 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 μ l 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 4. Estimated EC_{50} , standard error (SE), and 95% confidence intervals (CI) for individual studies

Compound	Exp	EC_{50} (nM)	SE	<u>95% CI</u>	
				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 5. Estimated IC_{50} , standard error, and 95% confident interval for the antiprogestin, RU486

IC_{50} 95% CI

Compound	Exp	(nM)	SE	lower	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

5

EC₅₀: Concentration of a compound that gives half-maximal increase in BrdU incorporation with SE; IC₅₀: Concentration of a compound that gives half-maximal decrease in 0.1 trimegestone induced BrdU incorporation with SE

4. T47D cell alkaline phosphatase assay

10 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),
15 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).

20

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
25 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% CO₂/humidified atmosphere for 24 hr.

d. Alkaline Phosphatase Enzyme Assay:

At the end of treatment, the medium was removed from the plate and fifty μ l of assay buffer I was added to each well. The plates were shaken in a titer plate shaker for 15 min. Then 150 μ l 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 6. 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	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

5 **Table 7. Estimated IC₅₀, standard error, and 95% confident interval for the reference antiprogesterin RU486 from three independent experiments**

Compound	Exp	IC 50 (nM)	SE	95% CI	
				lower	upper
10 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

15 **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.

20 1. Rat decidualization assay The objective of this procedure is used to evaluate the effect of progestins and antiprogesterins 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 (MazolaTM) 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.

30 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 EC₅₀ 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 CO₂ 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.

5 g. Reference Compounds:

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

10 **Table 8. Estimated EC_{50} , standard error (SE), and 95% confidence intervals for individual studies**

Compound	Exp	EC_{50}		95% CI	
		(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 9. Estimated average EC₅₀, standard error, and 95% confidence intervals for dose-response curves of 3 reference compounds

5	Compound	<u>EC₅₀</u>		<u>95% CI</u>	
		(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

10

Table 10. Estimated IC₅₀, standard error, and 95% confident interval for the antiprogesterin, RU 486

15	Compound	Exp.	<u>IC₅₀</u>		<u>95% CI</u>	
			(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)

20 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%

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

Antiprogestational activity: Compounds that decrease EC₅₀ progesterone induced decidualization significantly (p<0.05)

EC₅₀ for uterine weight: Concentration of compound that gives half-maximal increase in decidual response (default-mg/kg)

IC₅₀ for uterine weight: Concentration of compound that gives half-maximal decrease in EC₅₀ progesterone induced decidual response (default-mg/kg)

5

EXAMPLE 122

6-(3-Methoxyphenyl)spiro[4H-3,1-benzoxazine-4,1-cyclobutan]-2(1H)-one

A solution of Boc protected 4-chloroaniline (1.15g, 5 mmol) in anhydrous THF was treated at -78 °C under a blanket of nitrogen with *t*-butyllithium (7.4 mL, 12.5 mmol). The reaction solution was then slowly warmed to -20 °C, kept stirring for 1.5 hours, and treated with cyclobutanone (1mL, 13.4 mmol). The mixture was warmed to rt and quenched with brine (30 mL) and 1N aqueous hydrogen chloride solution (10 mL) was added. Ethyl acetate was added and the organic layer was separated and dried (MgSO₄). After removal of the solvent, the residue was purified by flash column chromatography (hexane:ethyl acetate/3:1) to give the alcohol which was used in next step without further purification.

To a solution of above product in ethanol was added potassium hydroxide (2g). The reaction mixture was stirred at rt for 18 hours, followed by the addition of brine (20 mL) and a cold 1N aqueous hydrogen chloride solution (20 mL). The precipitate was collected on a filter and washed with water to afford 6-chlorospiro[4H-3,1-benzoxazine-4,1-cyclobutan]-2(1H)-one as a white solid (0.13g, 12% for two steps): mp 183-184 °C; MS (ESI) *m/z* 222 [M - H].

A mixture of 6-chlorospiro[4H-3,1-benzoxazine-4,1-cyclobutan]-2(1H)-one (0.1g, 0.45 mmol), 3-methoxyphenyl boronic acid (0.1g, 0.66mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloronickel (II) (50 mg, 0.073 mmol), potassium phosphate (0.35g, 1.7 mmol) in dioxane (5 mL) was degassed to remove oxygen and then heated at 85 °C under a blanket of nitrogen for 72 hours. The reaction mixture was allowed to cool to rt. Ethyl acetate (30 mL) and brine (20 mL) were added. The organic layer was separated and dried (MgSO₄). After removal of solvent, the

residue was purified through a column chromatography (hexane:ethyl acetate/3:1) to yield 6-(3-methoxy-phenyl)spiro[4H-3,1-benzoxazine-4,1-cyclobutan]-2(1H)-one as white solid (18 mg, 14%): mp 145-146 °C; ¹H-NMR (DMSO-*d*₆) δ 8.04 (s, 1H), 7.69 (d, 1H, *J* = 1.6 Hz), 7.59 (dd, 1H, *J* = 8.2, 1.5 Hz), 7.36 (d, 1H, *J* = 7.9 Hz), 7.27 (d, 1H, *J* = 7.7 Hz), 7.22 (d, 1H, *J* = 2.2 Hz), 6.99 (d, 1H, *J* = 8.2 Hz), 6.92 (dd, 1H, *J* = 8.0, 2.4 Hz), 3.83 (s, 3H), 2.45-2.62(m, 4H), 1.81-2.12 (m, 2H)); MS ((+)APCI) *m/z* 296 [M + H]⁺.

EXAMPLE 123

10 8-Bromo-6-(3-chloro-4-fluorophenyl)-4,4-dimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one

To a mixture of 6-(3-chloro-4-fluorophenyl)-4,4-dimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (0.2g, 0.65 mmol) and sodium acetate (0.1g, 1.2 mmol) in acetic acid (5 mL) was added, at rt under nitrogen bromine (0.04 mL, 0.78 mmol).
15 The reaction mixture was stirred for 20 hours and poured into ice water (30 mL). The precipitate was collected on a filter and washed with water (3x5 mL) to yield 8-bromo-6-(3-chloro-4-fluorophenyl)-4,4-dimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as off-white solid (0.18, 72%): mp 194-195 °C; ¹H-NMR (DMSO-*d*₆) δ 9.77 (s, 1H), 8.02 (dd, 1H, *J* = 7.10, 1.81 Hz), 7.92 (s, 1H), 7.77 (m, 1H), 7.66 (s, 1H), 7.47-
20 7.53 (m, 1H), 1.71 (s, 6H). MS (ESI) *m/z* 384, 386 [M - H]⁻.

EXAMPLE 124

3-(8-Bromo-4,4-dimethyl-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-5-fluorobenzonitrile

25 Prepared according to the above procedure from 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-5-fluorobenzonitrile (0.5g, 1.7 mmol) as an off-white solid (0.48g, 75%): mp 216-217 °C; ¹H-NMR (DMSO-*d*₆) δ 9.78 (s, 1H), 8.18

(t, 1H, $J = 1.6$ Hz), 8.02-8.08 (m, 2H), 7.81 (m, 1H), 7.75 (d, 1H, $J = 1.8$ Hz), 1.66 (s, 6H). MS (ESI) m/z 373, 375 $[M - H]^+$.

EXAMPLE 125

5 5-(8-Bromo-4,4-dimethyl-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-2-fluorobenzonitrile

Prepared according to the above procedure from 5-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-2-fluorobenzonitrile (0.2g, 0.67 mmol) as an off-white solid (0.18g, 72%): mp 235-236 °C; $^1\text{H-NMR}$ (DMSO- d_6) δ 9.78 (s, 1H), 8.38 (dd, 1H, $J = 6.1, 2.4$ Hz), 8.14-8.20 (m, 1H), 7.98 (d, 1H, $J = 1.9$ Hz), 7.71 (d, 1H, $J = 1.8$ Hz), 7.62 (t, 1H, $J = 9.1$ Hz), 1.69 (s, 6H). MS (ESI) m/z 373, 375 $[M - H]^+$.

EXAMPLE 126

15 6-(3-Bromophenyl)-1,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one

To a solution of 6-(3-bromophenyl)-4,4-dimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (1g, 3.0 mmol) in anhydrous DMF was added, at rt under a blanket of nitrogen, sodium hydride (60% in mineral oil, 0.24g, 6.0 mmol). After stirring for 20 minutes, the reaction solution was treated with iodomethane and stirred for 1.5 hours. The mixture was poured into a saturated aqueous ammonium sulfate solution (40 mL) and ethyl acetate (40 mL) was added. The organic layer was separated, dried (MgSO_4), and evaporated to yield 6-(3-bromophenyl)-1,4,4-trimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as off-white solid (0.75g, 72%): mp 142-143 °C; $^1\text{H-NMR}$ (DMSO- d_6) δ 7.93 (s, 1H), 7.71 (m, 1H), 7.65 (s, 1H), 7.55 (d, 1H, $J = 8.0$ Hz), 7.42 (t 1H, $J = 7.7$ Hz), 7.18 (d, 1H, $J = 8.4$ Hz), 3.35 (s, 3H), 1.67 (s, 6H). MS (ESI) m/z 368, 370 $[M + \text{Na}]^+$.

EXAMPLE 127

25 6-(3-Fluorophenyl)-4-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one

4-Amino-3'-fluoro[1,1'-biphenyl]-3-carbonitrile was prepared from 3-fluorophenyl boronic acid and 2-amino-5-bromobenzonitrile according to procedure A. A solution of 4-amino-3'-fluoro[1,1'-biphenyl]-3-carbonitrile (6.65g, 31.3 mmol) in anhydrous THF (100 mL) was treated drop wise at rt under nitrogen with methylmagnesium bromide (3.0 M in ether, 21 mL, 63 mmol). After addition, the reaction mixture was heated at gentle reflux for 1.5 hours, cooled to rt, and treated with 3N aqueous hydrogen chloride solution (30 mL). The mixture was heated at reflux for 3 hours, cooled to ambient temperature, and adjusted to pH 5-6 by addition of a saturated aqueous sodium carbonate solution. Ethyl acetate (100 mL) was added, organic layer was separated and aqueous layer was extracted with ethyl acetate (3x50 mL). The combined organic layers were dried (MgSO₄) and evaporated. The residue was purified by a silica gel column chromatography (hexane:ethyl acetate/3:1) to afford 1-(4-amino-3'-fluoro[1,1'-biphenyl]-3-yl)ethanone (3.1g, 43%): mp 156-157°C.

A solution of 1-(4-amino-3'-fluoro[1,1'-biphenyl]-3-yl)ethanone (3g, 13 mmol) in anhydrous methanol (60 mL) was treated at rt under nitrogen with sodium borohydride in a portion wise manner. After addition, the reaction mixture was stirred for 4 hours, treated with a saturated aqueous ammonium sulfate solution (50 mL) and ethyl acetate (100 mL). The organic layer was separated, dried (MgSO₄) and evaporated. The residue was purified on a silica gel column chromatography (hexane:ethyl acetate/3:1) to yield 1-(4-amino-3'-fluoro[1,1'-biphenyl]-3-yl)ethanol as a white solid (2g, 67%): mp 136-137 °C.

A mixture of above alcohol (0.2g, 0.87 mmol) and triphosgene in anhydrous THF (20 mL) was stirred at rt under nitrogen. After 15 minutes, the mixture was treated with a saturated aqueous sodium bicarbonate solution (30 mL) and ethyl acetate (40 mL). The organic layer was separated, dried (MgSO₄), and evaporated to give 6-(3-fluorophenyl)-4-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as a white solid (0.18g, 81%): mp 160-161 °C; ¹H-NMR (DMSO-*d*₆) δ 10.31 (s, 1H), 7.62 (dd,

1H, $J = 8.2, 1.9$ Hz), 7.57 (s, 1H), 7.44-7.53 (m, 3H), 7.13-7.20 (m 1H), 6.97 (d, 1H, $J = 8.2$ Hz), 5.57 (q, 1H, $J = 6.6$ Hz), 1.63 (d, 3H, $J = 6.6$ Hz). MS (ESI) m/z 256 [M - H]⁻.

5

EXAMPLE 128

3-(4,4-Dimethyl-8-methoxy-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-5-fluorobenzonitrile

To a solution of 2-amino-3-methoxybenzoic acid (5g, 30 mmol) in anhydrous THF (100 mL) was added at ambient temperature under a blanket of nitrogen methylmagnesium bromide (3.0 M in THF, 50 mL, 150 mmol). The reaction mixture was heated at 50 °C for 18 hours, cooled to rt, and treated with a saturated aqueous ammonium chloride solution (50 mL). Ethyl acetate (100 mL) was added and organic layer was separated, dried (MgSO₄), and evaporated. The residue was dissolved in anhydrous THF (100 mL) and treated at ambient temperature under nitrogen with 1,1'-carbonyldiimidazole (5.4g, 33 mmol). After 24 hours, the mixture was quenched with 1N aqueous hydrogen chloride solution (30 mL). Ethyl acetate (100 mL) was added, organic layer was separated, dried (MgSO₄), and evaporated. The residue was purified by a silica gel column chromatography (hexane:ethyl acetate/3:1) to afford 8-methoxy-4,4-dimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one as white solid (3.5g, 56%): MS (ESI) m/z 208 [M + H]⁺.

To a mixture of 8-methoxy-4,4-dimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (2.1g, 10.1 mmol), sodium acetate (1.5g, 18 mmol) in acetic acid (30 mL) was added bromine (0.62 mL, 12 mmol) at ambient temperature. After 30 minutes, the solution was treated with a concentrated ammonium hydroxide solution (50 mL). The precipitate was collected on a filter and washed with water (3x20 mL) to yield 6-bromo-8-methoxy-4,4-dimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (2.7g, 93%) as off-white solid: MS (ESI) m/z 286, 288 [M + H]⁺.

A mixture of 6-bromo-8-methoxy-4,4-dimethyl-1,4-dihydro-2H-3,1-benzoxazin-2-one (1.6g, 5.6 mmol), bis(pinacolato)diboron (1.6 g, 6.3 mmol), potassium acetate (1.5g, 15.3 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]palladium (II) chloride (1:1 complex with methylene chloride, 0.5g, 0.6 mmol) in DMF (30 mL) was subject to a positive flow of nitrogen to remove oxygen and then heated at 85 °C under a blanket of nitrogen for 18 hours. The reaction mixture was allowed to cool to ambient temperature, treated with 3-bromo-5-fluoro-benzonitrile (1.2 g, 6 mmol), [1,1'-bis(diphenylphosphino)- ferrocene]palladium (II) chloride (1:1 complex with methylene chloride, 0.5g, 0.6 mmol), and sodium carbonate (2g, 19 mmol) in water (10 mL). The resulted solution was heated at 85 °C for 3 hours under a blanket of nitrogen, cooled to rt, and treated with brine (50 mL). Ethyl acetate (100 mL) was added, organic layer was separated, dried (MgSO₄), and evaporated. The residue was purified by a flash silica gel column chromatography (THF:hexane/2:3) to yield 3-(4,4-dimethyl-8-methoxy-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-5-fluorobenzonitrile as a white solid (0.6g, 33%): mp 252-253 °C; ¹H-NMR (DMSO-*d*₆) δ 9.76 (s, 1H), 8.21 (s, 1H), 8.07 (d, 1H, *J* = 10.6 Hz), 7.82 (m, 1H), 7.39 (s 1H), 7.36 (s, 1H), 3.93 (s, 3H), 1.66 (s, 6H). MS (ESI) *m/z* 325 [*M* - H].

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EXAMPLE 129

3-(4,4-Dimethyl-8-hydroxy-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-5-fluorobenzonitrile

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A mixture of 3-(4,4-dimethyl-8-methoxy-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-5-fluorobenzonitrile (0.1g, 0.31 mmol), Lithium iodide (0.3g, 2.24 mmol) in 2,4,6-collidine was heated at reflux under nitrogen for 5 hours. The solvent was removed *in vacuo* and the residue was taken in a mixture of brine (10 mL) and ethyl acetate (30 mL). The organic layer was separated, dried (MgSO₄), and evaporated. The resultant residue was purified on a silica gel column chromatography (hexane:ethyl acetate/1:1) to give the title compound as white plates

(0.03mg, 31%): mp 197-198 °C; ¹H-NMR (DMSO-*d*₆) δ 10.16 (s, 1H), 9.55 (s, 1H), 8.01 (s, 1H), 7.79-7.87 (m, 2H), 7.20 (s, 1H), 7.08 (d, 1H, *J* = 1.0 Hz), 1.65 (s, 6H). MS (ESI) *m/z* 311 [M - H]⁺.

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EXAMPLE 130

6-(2,3-Difluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared according to procedure B from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and 2,3-difluorobenzyltriflate. A yellow solid: mp 166-167 °C; ¹H-NMR (DMSO-*d*₆) δ 10.4 (s, 1H), 7.5-7.2 (m, 5H), 7.0 (m, 1H), 1.7 (s, 6H); MS (EI) *m/z* 289 ([M+H]⁺); Anal. Calc. For C₁₆H₁₃F₂NO₂: C, 66.43, H, 4.53, N, 4.84. Found: C, 66.15, H, 4.37, N, 4.64.

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EXAMPLE 131

3-(1-Ethyl-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluoro-benzonitrile

15

Prepared according to the procedure for example 125 from 3-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluoro-benzonitrile. A white solid: mp 154-155 °C; ¹H-NMR (DMSO-*d*₆) δ 8.17 (s, 1H), 8.03 (d, 1H, *J* = 10.5 Hz), 7.84-7.77 (m, 3H), 7.27 (d, 1H, *J* = 8.54 Hz), 3.97 (q, 2H, *J* = 6.89 Hz), 1.67 (s, 6H) 1.21 (t, 3H, *J* = 6.95 Hz); MS (EI) *m/z* 324 ([M + H]⁺); Anal. Calc. For C₁₉H₁₇FN₂O₂: C, 70.36, H, 5.28, N, 8.64. Found: C, 70.33, H, 5.51, N, 8.48.

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EXAMPLE 132

[6-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)pyridin-2-yl]acetonitrile

25

Prepared according to procedure B from (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid and (6-bromo-2-pyridyl)acetonitrile (*J. Org. Chem.* 1988, 53, 786-790). An off-white solid, mp 210-212.5 °C. ¹H NMR (DMSO-*d*₆) δ 1.68 (s, 6 H), 4.27 (s, 2 H), 7.00 (d, 1 H, *J* = 8.3 Hz), 7.34 (d, 1 H, *J* = 7.1 Hz),

7.89 – 7.96 (m, 2 H), 8.00 – 8.05 (m, 2 H), 10.42 (s, 1 H). MS (ESI) $[M-H]^+ = 292$.
Anal. calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 68.49; H, 5.19;
N, 13.74.

5

EXAMPLE 133

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)-5-fluoro-phenylacetonitrile

To a solution of 3-bromo-5-fluorobenzaldehyde(22.25g, 0.11 mole) in methanol at rt was added $NaBH_4$ (2.07g, 0.055 mole) stirred at rt for 2 hr. The
10 reaction was quenched with H_2O , and concentrated. The residue was diluted with diethyl ether, washed with 1 N HCl, brine, dried over $MgSO_4$, concentrated. 3-Bromo-5-fluorobenzyl alcohol as a colorless oil was collected (14.6 g, 65%). 1H NMR ($DMSO-d_6$) δ 4.50 (m, 2H), 5.44(t, 3H, $J = 5.93$ Hz), 7.16 (dd, 1H, $J = 1.09$, 8.79Hz), 7.36(s, 1H), 7.38 (dd, 1H, $J = 2.99$, 6.15Hz); Anal. Calc. For $C_7H_6Br_2FO$:
15 C, 41.01, H, 2.95 . Found: C, 41.30, H, 3.01.

To a solution of 3-Bromo-5-fluorobenzyl alcohol (2.3g, 0.011 mole) in CH_2Cl_2 (15mL) was added 12.4mL of 1.0M PBr_3 (3.33g, 0.0123 mole) in CH_2Cl_2 , stirred for 3 hr, diluted with ether (100mL), washed with H_2O (50ml,3X), dried over $MgSO_4$, concentrated. Purified by column chromatography using 1:9 ethyl
20 acetate/hexane as an eluant solvent system. 3-Bromo-5-fluorobenzyl bromide as a white crystalline material was obtained, mp 41-43°C. 1H NMR ($DMSO-d_6$) δ 4.69 (s, 2H), 7.52(d, 1H, $J = 1.76$ Hz) 7.54(d, 1H, $J = 1.91$ Hz), 7.56(s, 1H); MS(EI): M^+ . m/z 266 ; Anal. Calc. For $C_7H_5Br_2F$: C, 31.38, H, 1.88. Found: C, 31.75, H, 1.78.

25 To a solution of 3-bromo-5-fluorobenzyl bromide (3.2g, 0.0112 mole) in 1,4-dioxane (20mL) was added a solution of KCN (0.82g, 0.013 mole) in H_2O (5mL) and EtOH (5mL), refluxed for 2 hours. Extracted with ether, washed with brine, dried over $MgSO_4$, concentrated. Column chromatography using hexane/ethyl acetate (19:1). 3-Bromo-5-fluorophenylacetonitrile obtained was a colorless oil: 1H NMR

(DMSO- d_6) δ 4.15 (s, 2H), 7.29(d, 1H, $J = 9.37$ Hz), 7.47(s, 1H), 7.55(d, 1H, $J = 8.45$ Hz); MS(EI) $M + m/z$ 213 ; Anal. Calc. For C_8H_5BrFN : C, 44.89, H, 2.35, N, 6.54. Found: C, 44.88, H, 2.32, N, 6.46.

The title compound was prepared according to the procedure B from 3-bromo-5-fluorophenylacetonitrile and (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid. A white solid was obtained and recrystallized from ethanol/ether: mp 218-220. 1H NMR (DMSO- d_6) δ 1.67 (s, 6H), 4.11(s, 2H), 6.98(d, 1H, $J = 8.92$ Hz), 7.18(d, 1H, $J = 9.26$), 7.52-7.62(m, 3H), 10.37(s, 1H); MS(EI) (M-H) m/z 309; Anal. Calcd. For $C_{18}H_{15}FN_2O_2$: C, 69.67, H, 4.87, N, 9.03. Found: C, 69.78, H, 4.97, N, 8.36.

EXAMPLE 134

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)-4-fluorophenylacetonitrile

To a solution of 5-bromo-2-fluorotoluene (15g, 0.079 mole) in CCl_4 (150mL) was added NBS (14.2g, 0.080 mole). The resulting reaction solution was heated under reflux with the starting material being completely consumed within 2 hr. CCl_4 was removed under reduced pressure and the residue was diluted dissolved in ether, washed with brine (3X), dried over $MgSO_4$, concentrated. Chromatographed/hexane yielded 5-bromo-2-fluorobenzyl bromide. The product was immediately used for the reaction below.

5-Bromo-2-fluorobenzyl bromide (8.0g, 0.03 mole) was dissolved in 1,4-Dioxane (60mL) and added to a solution of KCN (2.04g, 0.031 mole) in H_2O (20mL) and ethanol (20mL). The resulting mixture was heated under reflux for 5 h. After cooling to rt, the product was extracted with ether (200mL), washed with brine, dried over $MgSO_4$, concentrated. Crystallized from ether/hexane to give 5-bromo-2-fluorophenylacetonitrile as a white crystalline material (5.6g, 88%): mp 55-58°C; 1H NMR (DMSO- d_6) δ 4.07 (s, 2H), 7.29(t, 1H, $J = 9.23$ Hz), 7.60-7.69(m,

2H); MS(EI) M+. m/z 213 ; Anal. Calc. For $C_8H_5Br_2FN$: C, 44.89, H, 2.35, N, 6.54. Found: C, 44.90, H, 2.24, N, 6.43.

The title compound was prepared from 5-Bromo-2-fluorophenylacetonitrile and (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid. White solid; mp 184-187 °C ; 1H NMR (DMSO- d_6) δ 1.67 (s, 6H), 4.11(s, 2H), 6.98(d, 1H, $J=8.92$ Hz), 7.36(t, 1H, $J=9.13$ Hz) 7.54 (d, 2H, $J=7.91$ Hz), 7.67-7.75(m, 2H), 10.37(s, 1H); MS(EI) (M-H) m/z 309; Anal. Calc. For $C_{18}H_{15}FN_2O_2$: C, 69.67, H, 4.87, N, 9.03. Found: C, 68.71, H, 4.80, N, 8.54.

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EXAMPLE 135

4-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3] oxazin-6-yl)-2-fluorophenylacetonitrile

Prepared according to procedure B from 4-bromo-2-fluorophenylacetonitrile (T. Alessi A.H.P. US Patent No: 4895862) and (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid. A grey solid; mp 253-256 °C 1HNMR (DMSO- d_6) δ 10.35 (s,1H) 7.67 -7.49(m,5H), 6.97(d,1H; $J=8.6$ Hz) 4.09 (s,2H) 1.67(s, 6H); MS [M-H] m/z 309. Anal. Calc. For $C_{18}H_{15}N_2FO_2 \cdot 0.15H_2O$: C,69.07, H, 4.93, N, 8.95. Found C,69.27, H 5.05, N, 8.50

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EXAMPLE 136

2-(4,4-Dimethyl 2- oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)phenylacetonitrile

Prepared according to procedure B from 2- bromophenylacetonitrile and (1, 4-dihydro-4,4-dimethyl-2-oxo- 2H-3,1-benzoxazin-6-yl)boronic acid. White solid ; mp 176-179°C; 1H -NMR (DMSO- d_6), δ 10.31 (s, 1H), 7.53 (m, 1H), 7.48(m,2H), 7.22-7.32(m,3H), 6.98(d,1H; $J=8.0$ Hz); 3.90(s,2H), 1.64(s,6H). MS (+)APCI [M+H] $^+$ m/z =293. Anal. Calc. For $C_{18}H_{16}N_2O_2$: C, 73.95, H, 5.52, N, 9.58. Found: C,73.51, H, 5.70, N, 9.39.

EXAMPLE 137

N-[4-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-3,1-benzoxazin-6-yl)-2-fluoro-phenyl]-acetamide

Prepared according to procedure B from 4'-bromo-2'-fluoroacetanilide and
5 (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid. Off white
solid; mp 245-247°C. ¹H-NMR (DMSO-d₆) δ 10.3 (s, 1H), 9.79 (s, 1H), 7.95
(t, 1H; J=8.4 Hz), 7.56-7.63(m, 3H), 7.47(dd, 1H J = 1.64, 8.47Hz), 6.95(d, 1H; J=8.9
Hz), 2.1(s, 3H), 1.67(s, 6H); MS +APCI [M+H]⁺ m/z 329. Anal. Calc. For C₁₈H₁₇N₂
FO₃: C, 65.85, H, 5.22, N, 8.53. Found: C, 65.46, H, 5.24, N, 8.12.

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EXAMPLE 138

6-(3-Fluoro-4-methoxy-phenyl)4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

Prepared according to procedure B from 4-bromo-2-fluoroanisole and (1, 4-
15 dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid. White solid: mp
210-211°C ¹H-NMR (DMSO-d₆) δ 10.27(s, 1H), 7.52-7.60 (m, 3H), 7.45(d, 1H,
J=8.6 Hz), 7.22 (t, 1H; J=8.9 Hz), 6.94(d, 1H, J=8.8 Hz), 3.87(s, 3H), 1.66(s, 6H).
MS [M-H]⁻ m/z = 300. Anal. Calc. For C₁₇H₁₆FN₂O₃: C, 67.76, H, 5.35, N, 4.65.
Found: C, 67.88, H, 5.39, N, 4.70.

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EXAMPLE 139

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)phenylacetonitrile

Prepared according to the procedure B from 3-bromophenylacetonitrile and
25 (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)boronic acid. White solid: mp 188-
190°C. ¹H-NMR (DMSO-d₆) δ 10.33(s, 1H), 7.62(m, 2H), 7.55 (m, 2H), 7.48 (d, 1H
J=8.00 Hz), 7.33 (d, 1H, J=7.57Hz), 6.99 (d, 1H, J=8.81 Hz) 4.09 (s, 2H), 1.67 (s,
6H); MS m/z 291(M-H). Anal. Calc. For C₁₈H₁₆N₂O₂·2.0.3 H₂O: C, 72.61, H, 5.62, N,
9.41. Found: C, 73.00, H, 5.43, N, 8.81

EXAMPLE 140

3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)benzenesulfonamide

- 5 Prepared according to procedure B from 3-bromobenzenesulfonamide and (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-6-yl)boronic acid. White solid: mp 242-244°C (dec) ¹H-NMR (DMSO-d₆) δ 10.28(s, broad 1H), 8.07(s, 1H), 7.9(d, 1H, J=7.80 Hz), 7.78 (d, 1H J=7.86Hz), 7.64 (t, 1H, J=7.79 Hz), 7.59 (m, 2H), 7.42(s, broad 2H), 7.02(d, 1H, J = 8.86Hz), 1.68(s, 6H); MS m/z 331(M+H). Anal. Calc. For
- 10 C₁₆H₁₆N₂O₄S): C, 57.82, H, 4.85, N, 8.43. Found: C, 57.49, H, 5.08, N, 8.05.

EXAMPLE 141

5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)-thiophene-2-sulfonamide

- 15 Prepared according to procedure B from 5-bromothiophene-2-sulphonamide and (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-6-yl)boronic acid. White solid: mp 258-260°C, ¹H-NMR (DMSO-d₆) δ 10.41(s, 1H), 7.71(s, 2H), 7.58(m, 2H), 7.52(d, 1H, J=3.9Hz), 7.48(d, 1H J=8.16Hz), 6.95(d, 1H J=8.16), 1.66(s, 6H); MS m/z 337(M-H). Anal. Calc. For C₁₄H₁₄N₂O₄S₂): C, 49.69, H, 4.17, N, 8.28. Found: C, 49.90, H, 4.28,
- 20 N, 8.12.

EXAMPLE 142

6-(6-Amino-pyridin-3-yl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazine-2-one

- 25 Prepared according to procedure B from 2-amino-5-bromopyridine and (1,4-dihydro-4,4-dimethyl-2-oxo-2H-3,1-6-yl)boronic acid. White crystals, mp 257-259°C. ¹H-NMR (DMSO-d₆) δ 10.20 (s, 1H), 8.22 (d, 1H, J=2.38 Hz) 7.69, 7.66 (dd, 1H, J=2.5, 2.5 Hz), 7.42 (m, 2H), 6.89 (d, 1H, J=8.8Hz), 6.49(d, 1H, J=8.64Hz), 6.02 (s, 2H), 1.64 (s, 6H); MS m/z 269 M+. Anal. Calcd. For C₁₅H₁₅N₃O₂ .17 H₂O: C, 66.15, H, 5.68, N, 15.43. Found: C, 66.10, H, 5.81, N, 15.02.

EXAMPLE 143

6-(5-Diethoxymethyl-furan-3-yl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one

5 Prepared according to procedure B from 4,4-dimethyl 2 oxo -1, 4 - dihydro 2 H - benzo [d] [1,3] oxazine -6- boronic acid and 3-bromo-5-diethoxymethyl furan. A brown gum: ¹H NMR (DMSO-d₆) δ 10.2 (s, 1H), 8.12(s, 1H), 7.54-7.49 (m, 2H), 6.93-6.88(m, 2H), 5.56(s, 1H), 3.60-3.38(m, 4H), 1.67(s, 6H), 1.2-1.14 (m, 6H). .MS (ESI) m/z 344 [M-H]⁺. Anal. Calcd. For C₁₉H₂₃NO₅·1/2 H₂O: C, 64.39; H, 6.77; N, 3.95. Found C, 64.90; H, 6.79; N, 3.78.

EXAMPLE 144

4-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3] oxazin-6-yl)-furan-2-carbaldehyde

A solution of 6-(5-diethoxymethyl-furan-3-yl)-4,4-dimethyl-1,4-dihydro-
15 benzo[d][1,3] oxazin-2-one (1.1g, 3 mmol) was stirred in THF (20 mL) and 2N HCl (2 mL) for 1 hour. The crystalline product was filtered and dried (0.52 g, 69%): mp 262-263 °C; ¹H NMR (DMSO-d₆) δ 10.3 (s, 1H), 9.65 (s, 1H), 8.59 (s, 1H), 8.04 (s, 1H), 7.65-7.64 (d, 1H, J = 1.5 Hz), 7.61-7.60 (d, 1H, J = 1.8 Hz), 7.59-7.58 (d, 1H, J = 1.8 Hz), 6.94-6.91 (d, 1H, J = 8.2 Hz), 1.65 (s, 6H). .MS (ESI) m/z 270 [M-
20 H]⁺.

EXAMPLE 145

4-(1,4-Dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)-2-furancarboxaldehyde oxime

25 A mixture of 4-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-furan-2-carbaldehyde (2.7 g, 10mmol), hydroxylamine hydrochloride (0.75 G, 10.6 mmol) and sodium acetate (0.87 g, 10.6 mmol) was heated at reflux in 80% ethanol (25 mL) for 2 hours. The title compound crystallized from the cooled reaction mixture as tan crystals (1.5g, 52.4%): mp 236-238°C. ¹H NMR (DMSO-d₆) δ 11.97(s,

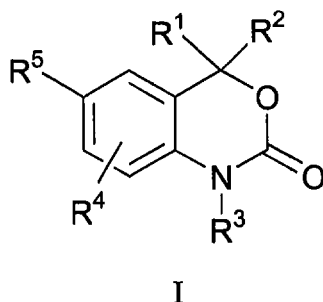
1H), 10.26 (s, 1H), 8.2 (s, 1H), 7.63 (s, 1H), 7.56-7.52 (m, 3H), 6.91-6.88 (d, 1H, J=8.1 Hz), 1.66 (s, 6H). MS ESI m/z 285 [M⁺H]. Anal. Calcd. For C₁₅H₁₄N₂O₄: C, 62.93; H, 4.93; N, 9.79. Found C, 62.77; H, 5.00; N, 9.79.

5

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
10 intended to fall within the scope of the appended claims.

CLAIMS

1. A compound of the formula:



- 5 wherein:

R^1 and R^2 are independent substituents selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A , and

- 10 $NR^B COR^A$;

or R^1 and R^2 are fused to form a ring selected from the group consisting of a), b), and c):

- a) a carbon-based 3 to 8 membered saturated spirocyclic ring;
- b) a carbon-based 3 to 8 membered spirocyclic ring having one or more
- 15 carbon-carbon double bonds;
- c) a 3 to 8 membered heterocyclic ring having in its backbone one to three heteroatoms selected from the group consisting of O, S and N;

- the rings of a), b), and c) being optionally substituted by from 1 to 4 groups selected from the group consisting of fluorine, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6
- 20 thioalkyl, CF_3 , OH, CN, NH_2 , $NH(C_1$ to C_6 alkyl), and $N(C_1$ to C_6 alkyl) $_2$;

R^A 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^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

- 5 R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_3 to C_6 alkenyl, alkynyl, substituted alkynyl, or COR^C ;

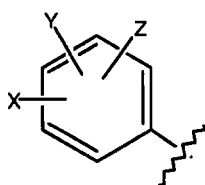
R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

- 10 R^4 is H, halogen, CN, NO_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, amino, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^5 is (i) or (ii):

(i) a substituted benzene ring containing the substituents X, Y and Z as

- 15 shown below:



wherein:

- X is selected from the group consisting of halogen, 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 thioalkoxy, substituted C_1 to C_3 thioalkoxy, amino, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing in its backbone 1 to 3 heteroatoms, COR^D , $OCOR^D$, and $NR^E COR^D$;
- 20

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;

5 Y and Z are independent substituents selected from the group consisting of H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_3 alkyl, and C_1 to C_3 thioalkoxy; or

(ii) a five or six membered ring having in its backbone 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO_2 and NR^6 and containing one or two
10 independent substituents selected from the group consisting of H, halogen, CN, NO_2 , amino, C_1 to C_3 alkyl, and C_1 to C_3 alkoxy;

 with the proviso that when R^5 is the five membered ring having in its backbone two NR^6 heteroatoms, R^1 and R^2 are not both H; and

 with the proviso that when R^5 is a five-membered ring having in its
15 backbone one NR^6 heteroatom, and wherein R^5 is attached at the two position on said ring, there is no CN substituent in the five position on said ring;

R^6 is H or C_1 to C_3 alkyl;

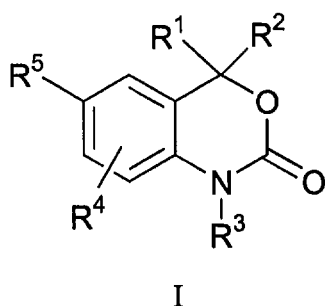
 with the proviso that when R^5 is the benzene ring a) substituted with one or two substituents or the 5 or 6 membered ring b) having in its backbone 1, 2, or 3
20 heteroatoms selected from the group consisting of O, S, and NR^6 , and R^1 is alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, R^2 is not alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl; or if R^2 is alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl, R^1 is not

alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, alkenyl, substituted alkenyl, alkynyl, and substituted alkynyl;

with the proviso that when R^5 is the benzene ring a) substituted with one or two substituents or the 5 or 6 membered ring b) having in its backbone 1, 2, or 3

- 5 heteroatoms selected from the group consisting of O, S, and NR^6 , and R^1 is alkyl or substituted alkyl, R^2 is not cycloalkyl or substituted cycloalkyl; or if R^2 is alkyl or substituted alkyl, R^1 is not cycloalkyl or substituted cycloalkyl;
or pharmaceutically acceptable salt thereof.

- 10 2. A compound of the formula:



wherein:

R^1 and R^2 are fused to form a ring selected from the group consisting of a), b), and c):

- 15 a) a carbon-based 3 to 8 membered saturated spirocyclic ring;
b) a carbon-based 3 to 8 membered spirocyclic ring having one or more carbon-carbon double bonds;
c) a 3 to 8 membered heterocyclic ring having in its backbone one to three heteroatoms selected from the group consisting of O, S and N;

the rings of a), b), and c) being optionally substituted by from 1 to 4 groups selected from the group consisting of fluorine, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to C₆ thioalkyl, CF₃, OH, CN, NH₂, NH(C₁ to C₆ alkyl), and N(C₁ to C₆ alkyl)₂;

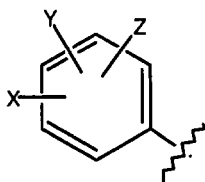
R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₃ to C₆ alkenyl, alkynyl, substituted alkynyl, or COR^C;

R^C is H, C₁ to C₄ alkyl, substituted C₁ to C₄ alkyl, aryl, substituted aryl, C₁ to C₄ alkoxy, substituted C₁ to C₄ alkoxy, C₁ to C₄ aminoalkyl, or substituted C₁ to C₄ aminoalkyl;

R⁴ is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆ aminoalkyl;

R⁵ is (i) or (ii):

(i) a substituted benzene ring containing the substituents X, Y and Z as shown below:



wherein:

X is selected from the group consisting of halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing in its backbone 1 to 3 heteroatoms, COR^D, OCOR^D, and 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;

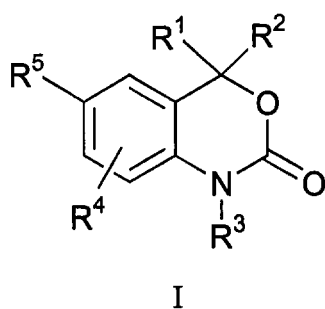
5 Y and Z are independent substituents selected from the group consisting of H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_3 alkyl, and C_1 to C_3 thioalkoxy; or

(ii) a five or six membered ring having in its backbone 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO_2 and NR^6 and containing one or two
10 independent substituents selected from the group consisting of H, halogen, CN, NO_2 , amino, C_1 to C_3 alkyl, and C_1 to C_3 alkoxy;

R^6 is H or C_1 to C_3 alkyl;

or pharmaceutically acceptable salt thereof.

15 3. A compound of the formula:



wherein:

R^1 and R^2 are independent substituents selected from the group consisting of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl,
20 C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8

cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, and NR^BCOR^A;

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃

5 aminoalkyl;

R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₃ to C₆ alkenyl, alkynyl, substituted alkynyl, or COR^C;

R^C is H, C₁ to C₄ alkyl, substituted C₁ to C₄ alkyl, aryl, substituted aryl, C₁ to C₄
10 alkoxy, substituted C₁ to C₄ alkoxy, C₁ to C₄ aminoalkyl, or substituted C₁ to C₄ aminoalkyl;

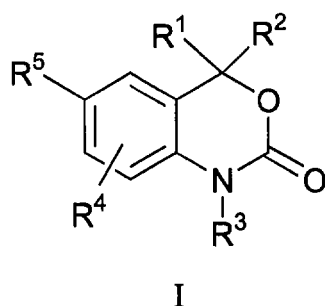
R⁴ is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆ aminoalkyl;

15 R⁵ is a five or six membered ring having in its backbone 1, 2, or 3 heteroatoms selected from the group consisting of SO and SO₂ and containing one or two independent substituents selected from the group consisting of H, halogen, CN, NO₂, amino, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

R⁶ is H or C₁ to C₃ alkyl;

20 or pharmaceutically acceptable salt thereof.

4. A compound of the formula:



wherein:

R^1 and R^2 are H;

5 R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_3 to C_6 alkenyl, alkynyl, substituted alkynyl, or COR^C ;

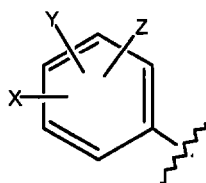
R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

10 R^4 is H, halogen, CN, NO_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, amino, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^5 is selected from the group consisting of (i), (ii), (iii), and (iv):

(i) a substituted benzene ring containing the substituents X, Y and Z as

15 shown below:



wherein:

X is selected from the group consisting of halogen, 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

thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing in its backbone 1 to 3 heteroatoms, COR^D, OCOR^D, and NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl,

- 5 C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

Y and Z are independent substituents selected from the group consisting of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, and C₁ to C₃ thioalkoxy;

- 10 (ii) a five membered ring having in its backbone 1 or 3 heteroatoms selected from the group consisting of O, S, and NR⁶ and containing one or two independent substituents selected from the group consisting of H, halogen, CN, NO₂, amino, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

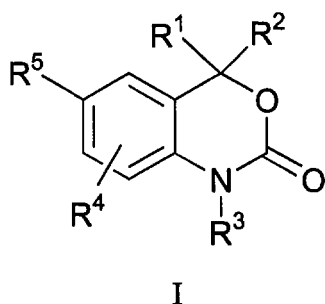
- (iii) a five membered ring having in its backbone 2 heteroatoms selected from
15 the group consisting of O and S and containing one or two independent substituents selected from the group consisting of H, halogen, CN, NO₂, amino, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy; and

- (iv) a six membered ring having in its backbone 1, 2, or 3 heteroatoms selected from the group consisting of O, S, and NR⁶ and containing one or two
20 independent substituents selected from the group consisting of H, halogen, CN, NO₂, amino, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

R⁶ is H or C₁ to C₃ alkyl;

or pharmaceutically acceptable salt thereof.

5. A compound of the formula:



wherein:

R^1 is H;

5 R^2 is C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A , or $NR^B COR^A$;

R^A 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^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

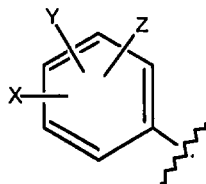
R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_3 to C_6 alkenyl, alkynyl, substituted alkynyl, or COR^C ;

15 R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

R^4 is H, halogen, CN, NO_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, amino, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

20 R^5 is (i) or (ii):

(i) a substituted benzene ring containing the substituents X, Y and Z as shown below:



wherein:

5 X is selected from the group consisting of halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing in its backbone 1 to 3 heteroatoms, COR^D, OCOR^D, and NR^ECOR^D;

10 R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

15 Y and Z are independent substituents selected from the group consisting of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, and C₁ to C₃ thioalkoxy; or

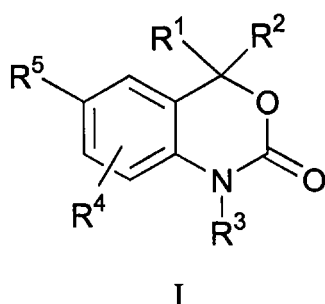
(ii) a five or six membered ring having in its backbone 1, 2, or 3 heteroatoms selected from the group consisting of O, S, and NR⁶ and containing one or two independent substituents selected from the group consisting of H, halogen, CN, NO₂, amino, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

20

R⁶ is H or C₁ to C₃ alkyl;

or pharmaceutically acceptable salt thereof.

6. A compound of the formula:



wherein:

R^1 and R^2 are independent substituents selected from the group consisting of C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A , and $NR^B COR^A$;

R^A 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;

10 R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

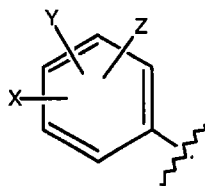
R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_3 to C_6 alkenyl, alkynyl, substituted alkynyl, or COR^C ;

R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

R^4 is H, halogen, CN, NO_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, amino, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^5 is (i) or (ii):

20 (i) a substituted benzene ring containing the substituents X, Y and Z as shown below:



wherein:

X is selected from the group consisting of halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing in its backbone 1 to 3 heteroatoms, COR^D, OCOR^D, and NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

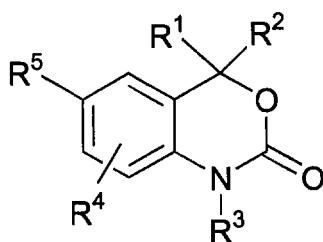
Y and Z are independent substituents selected from the group consisting of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, and C₁ to C₃ thioalkoxy; or

(ii) a five or six membered ring having in its backbone 1, 2, or 3 heteroatoms selected from the group consisting of O, S, and NR⁶ and containing one or two independent substituents selected from the group consisting of H, halogen, CN, NO₂, amino, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

R⁶ is H or C₁ to C₃ alkyl;

or pharmaceutically acceptable salt thereof.

7. A compound of the formula:



I

wherein:

R¹ is selected from the group consisting of C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, and substituted C₃ to C₈ cycloalkyl;

R² is selected from the group consisting of aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, and NR^BCOR^A;

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

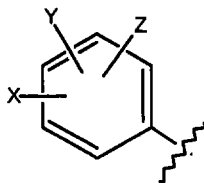
R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₃ to C₆ alkenyl, alkynyl, substituted alkynyl, or COR^C;

R^C is H, C₁ to C₄ alkyl, substituted C₁ to C₄ alkyl, aryl, substituted aryl, C₁ to C₄ alkoxy, substituted C₁ to C₄ alkoxy, C₁ to C₄ aminoalkyl, or substituted C₁ to C₄ aminoalkyl;

R⁴ is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆ aminoalkyl;

R⁵ is (i) or (ii):

(i) a substituted benzene ring containing the substituents X, Y and Z as shown below:



wherein:

5 X is selected from the group consisting of halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing in its backbone 1 to 3 heteroatoms, COR^D, OCOR^D, and NR^ECOR^D;

10 R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

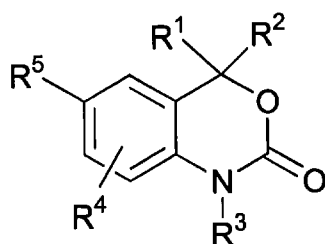
Y and Z are independent substituents selected from the group consisting
15 of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, and C₁ to C₃ thioalkoxy; or

(ii) a five or six membered ring having in its backbone 1, 2, or 3 heteroatoms selected from the group consisting of O, S, and NR⁶ and containing one or two independent substituents selected from the group consisting of H, halogen, CN, NO₂,
20 amino, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

R⁶ is H or C₁ to C₃ alkyl;

or pharmaceutically acceptable salt thereof.

8. A compound of the formula:



I

wherein:

R^1 and R^2 are C_3 to C_8 cycloalkyl or substituted C_3 to C_8 cycloalkyl;

5 R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_3 to C_6 alkenyl, alkynyl, substituted alkynyl, or COR^C ;

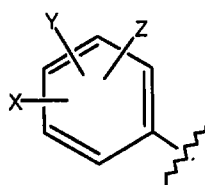
R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

10 R^4 is H, halogen, CN, NO_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, amino, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^5 is (i) or (ii):

(i) a substituted benzene ring containing the substituents X, Y and Z as

15 shown below:



wherein:

X is selected from the group consisting of halogen, 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

thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 membered heterocyclic ring containing in its backbone 1 to 3 heteroatoms, COR^D, OCOR^D, and NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl,
5 C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

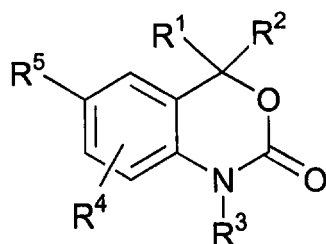
R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

Y and Z are independent substituents selected from the group consisting of H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, and C₁ to C₃ thioalkoxy; or
10

(ii) a five or six membered ring having in its backbone 1, 2, or 3 heteroatoms selected from the group consisting of O, S, and NR⁶ and containing one or two independent substituents selected from the group consisting of H, halogen, CN, NO₂, amino, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

15 R⁶ is H or C₁ to C₃ alkyl;
or pharmaceutically acceptable salt thereof.

9. A compound of the formula:



20

I

wherein:

$R^1 = R^2$ and are selected from the group consisting of C_1 to C_3 alkyl and substituted C_1 to C_3 alkyl, or R^1 and R^2 are fused to form a carbon-based 3 to 6 membered saturated spirocyclic ring;

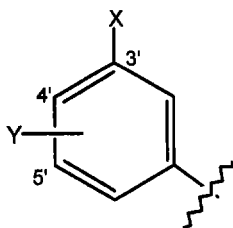
R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, or COR^C ;

5 R^C is H, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy;

R^4 is H, halogen, CN, NO_2 , C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, or substituted C_1 to C_3 alkoxy;

R^5 is selected from the group consisting of a), b) and c):

a) a substituted benzene ring of the formula shown below:



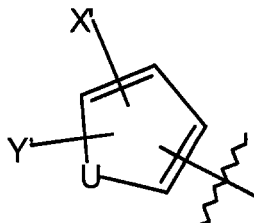
10

wherein:

X is 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 in its backbone 1 to 3 heteroatoms, or C_1 to C_3 thioalkoxy;

15 Y is H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_4 alkyl, or C_1 to C_3 thioalkoxy;

b) a five membered ring of the structure:



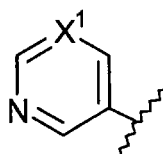
wherein:

U is O, S, or NR⁶;

X' is selected from the group consisting of halogen, CN, NO₂, C₁ to C₃ alkyl, and C₁ to C₃ alkoxy;

Y' is selected from the group consisting of H and C₁ to C₄ alkyl; and

5 c) a six membered ring of the structure:



wherein:

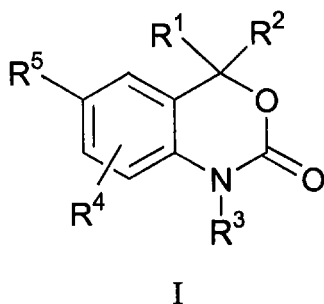
X¹ is CX²;

X² is halogen, CN, alkoxy, or NO₂;

10 R⁶ is H, C₁ to C₃ alkyl, or C₁ to C₄ CO₂alkyl;

or pharmaceutically acceptable salt thereof.

10. A compound of the formula:



15 wherein:

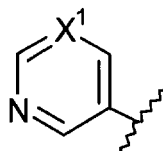
R¹ = R² and are selected from the group consisting of C₁ to C₃ alkyl and substituted C₁ to C₃ alkyl, or R¹ and R² are fused to form a carbon-based 3 to 6 membered saturated spirocyclic ring;

R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, or COR^C;

R^C is H, C_1 to C_4 alkyl, or C_1 to C_4 alkoxy;

R^4 is H, halogen, CN, NO_2 , C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, C_1 to C_3 alkoxy, or substituted C_1 to C_3 alkoxy;

R^5 is a six membered ring of the structure:



5

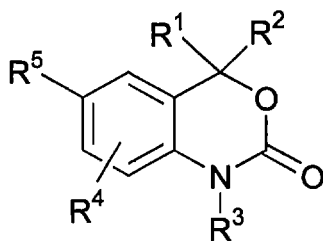
wherein:

X^1 is N;

or pharmaceutically acceptable salt thereof.

10

11. A compound of the formula:



I

$R^1 = R^2$ and are CH_3 or R^1 and R^2 are fused to form a carbon-based 6 membered saturated spirocyclic ring;

15

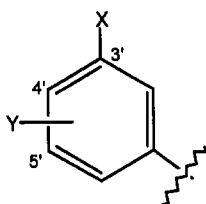
R^3 is H, OH, NH_2 , C_1 alkyl, substituted C_1 alkyl, or COR^C ;

R^C is H, C_1 to C_3 alkyl, or C_1 to C_4 alkoxy;

R^4 is H, halogen, NO_2 , CN, or C_1 to C_3 alkyl;

R^5 is (i) or (ii):

- (i) a substituted benzene ring of the formula:

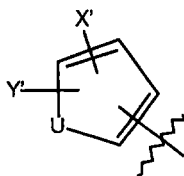


wherein:

- X is selected from the group consisting of halogen, CN, C₁ alkoxy, NO₂, or the
5 5-membered heterocyclic ring, wherein said heterocyclic ring is 2-thiazole;

Y is H or fluorine; or

- (ii) a five membered ring of the structure:



wherein:

- 10 U is O, S, or NH;
X' is halogen, CN, or NO₂, provided that when U is NH, then X' is not CN;
Y' is H or C₁ to C₄ alkyl;

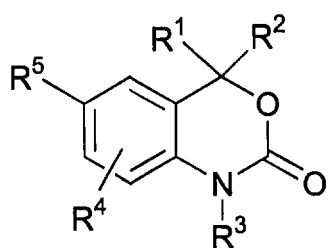
or a pharmaceutically acceptable salt thereof.

- 15 12. A compound selected from the group consisting of 2-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo [d] [1,3] oxazin-6-yl)-pyrrole-1-carboxylic acid tert-butyl ester, 2-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo [d] [1,3] oxazin-6-yl)-5-nitro-pyrrole-1-carboxylic acid tert-butyl ester, 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-*n*-butyl-thiophene-2-carbonitrile, and a pharmaceutically
20 acceptable salt thereof.

13. A compound selected from the group consisting of 4,4-Dimethyl-6-(3-trimethylsilanylethynyl-phenyl)-1,4-dihydro-benzo[d][1,3]oxazin-2-one, 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)benzensulfonamide, 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)-thiophene-2-sulfonamide, 4-(1,4-Dihydro-4,4-dimethyl-2-oxo-2H-3,1-benzoxazin-6-yl)-2-furancarboxaldehyde oxime, and a pharmaceutically acceptable salt thereof.

14. Use of a compound of any of claims 1 to 13, or pharmaceutically acceptable salt thereof, in preparing a medicament for administration to a mammalian subject for hormone replacement therapy.

15. Use of a compound of formula I, or pharmaceutically acceptable salt thereof, in preparing a medicament for administration to a mammalian subject for hormone replacement therapy, wherein said compound of formula I is of the structure:



I

wherein:

R¹ and R² are independent substituents selected from the group consisting of H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₂ to C₆ alkynyl, substituted C₂ to C₆ alkynyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈

cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A , and NR^BCOR^A ;

or R^1 and R^2 are fused to form:

- a) a carbon-based 3 to 8 membered saturated spirocyclic ring;
- 5 b) a carbon-based 3 to 8 membered spirocyclic ring having one or more carbon-carbon double bonds; or

c) a 3 to 8 membered heterocyclic ring containing in its backbone one to three heteroatoms selected from the group consisting of O, S and N;

- the rings of a), b) and c) being optionally substituted by from 1 to 4 groups
- 10 selected from the group consisting of fluorine, C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 thioalkyl, CF_3 , OH, CN, NH_2 , $\text{NH}(\text{C}_1$ to C_6 alkyl), and $\text{N}(\text{C}_1$ to C_6 alkyl) $_2$;

R^A 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;

- 15 R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

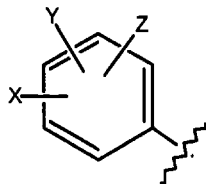
R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_3 to C_6 alkenyl, alkynyl, substituted alkynyl, or COR^C ;

- R^C 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;
- 20

R^4 is H, halogen, CN, NO_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, alkynyl, substituted alkynyl, C_1 to C_6 alkoxy, substituted C_1 to C_6 alkoxy, amino, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

R^5 is selected from the group consisting of a) and b):

a) a substituted benzene ring containing the substituents X, Y and Z as shown below:



wherein:

- 5 X is selected from the group consisting of halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing in its backbone 1 to 3
- 10 heteroatoms, COR^D, OCOR^D, and NR^ECOR^D;

R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

- 15 Y and Z are independent substituents selected from the group consisting of H, halogen, CN, NO₂, amino, aminoalkyl, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, and C₁ to C₃ thioalkoxy; and

- b) a five or six membered ring having in its backbone 1, 2, or 3 heteroatoms selected from the group consisting of O, S, SO, SO₂ and NR⁶ and containing one or two
- 20 independent substituents selected from the group consisting of H, halogen, CN, NO₂, amino, C₁ to C₃ alkyl, C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, COR^F, and NR^GCOR^F;

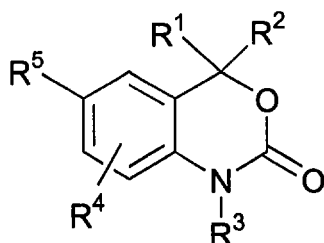
R^F is H, C_1 to C_3 alkyl, substituted C_1 to C_3 alkyl, aryl, substituted aryl, C_1 to C_3 alkoxy, substituted C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, or substituted C_1 to C_3 aminoalkyl;

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

5 R^6 is H or C_1 to C_3 alkyl;

or pharmaceutically acceptable salt thereof.

16. A compound of the formula (I):



I

10 wherein:

R^1 and R^2 are independent substituents selected from the group of H, C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_2 to C_6 alkenyl, substituted C_2 to C_6 alkenyl, C_2 to C_6 alkynyl, substituted C_2 to C_6 alkynyl, C_3 to C_8 cycloalkyl, substituted C_3 to C_8 cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A , or

15 $NR^B COR^A$;

or R^1 and R^2 are fused to form:

- a) an optionally substituted 3 to 8 membered spirocyclic alkyl ring;
- b) an optionally substituted 3 to 8 membered spirocyclic alkenyl ring; or
- c) an optionally substituted 3 to 8 membered heterocyclic ring containing

20 one to three heteroatoms from the group including O, S and N; the spirocyclic rings of

a), b) and c) being optionally substituted by from 1 to 4 groups selected from fluorine, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to C₆ thioalkyl, -CF₃, -OH, -CN, NH₂, -NH(C₁ to C₆ alkyl), or -N(C₁ to C₆ alkyl)₂;

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

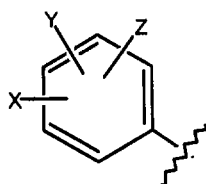
R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, or substituted alkynyl, COR^C;

R^C is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

R⁴ is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, alkynyl, or substituted alkynyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆ aminoalkyl;

R⁵ is selected from a) or b)

a) R⁵ is a trisubstituted benzene ring containing the substituents X, Y and Z as shown below:



wherein:

X is taken from the group including halogen, CN, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, C₁ to C₃ alkoxy,

substituted C₁ to C₃ alkoxy, C₁ to C₃ thioalkoxy, substituted C₁ to C₃ thioalkoxy, amino, C₁ to C₃ aminoalkyl, substituted C₁ to C₃ aminoalkyl, NO₂, C₁ to C₃ perfluoroalkyl, 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D, OCOR^D, or NR^ECOR^D;

5 R^D is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

 R^E is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

 Y and Z are independent substituents taken from the group including H, halogen,
10 CN, NO₂, amino, aminoalkyl, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy; or

 b) R⁵ is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR⁶ and containing one or two independent substituents from the group including H, halogen, CN, NO₂, amino, and C₁ to C₃ alkyl, C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, COR^F, or NR^GCOR^F;

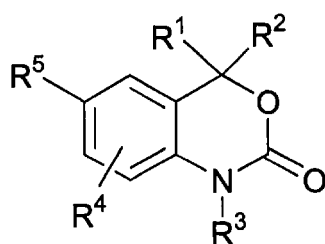
15 R^F is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;

 R^G is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;

 R⁶ is H or C₁ to C₃ alkyl;

20 or pharmaceutically acceptable salt thereof.

17. A compound of Claim 16 having the structure:

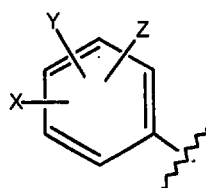


I

wherein:

- R¹ is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;
- R² is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₂ to C₆ alkenyl, substituted C₂ to C₆ alkenyl, C₃ to C₈ cycloalkyl, substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, COR^A, or NR^BCOR^A;
- R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃ alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃ aminoalkyl;
- R^B is H, C₁ to C₃ alkyl, or substituted C₁ to C₃ alkyl;
- R³ is H, OH, NH₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₆ alkenyl, substituted C₁ to C₆ alkenyl, alkynyl, or substituted alkynyl, COR^C;
- R^C is H, C₁ to C₄ alkyl, substituted C₁ to C₄ alkyl, aryl, substituted aryl, C₁ to C₄ alkoxy, substituted C₁ to C₄ alkoxy, C₁ to C₄ aminoalkyl, or substituted C₁ to C₄ aminoalkyl;
- R⁴ is H, halogen, CN, NO₂, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₁ to C₆ alkoxy, substituted C₁ to C₆ alkoxy, amino, C₁ to C₆ aminoalkyl, or substituted C₁ to C₆ aminoalkyl;

R^5 is the moiety:



X is taken from the group including halogen, 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 thioalkoxy, substituted C_1 to C_3 thioalkoxy, amino, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D , $OCOR^D$, or $NR^E COR^D$;

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;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_3 alkyl, or C_1 to C_3 thioalkoxy;

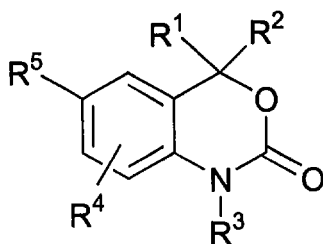
or

R^5 is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO_2 or NR^6 and containing one or two independent substituents from the group including H, halogen, CN, NO_2 , amino, and C_1 to C_3 alkyl, or C_1 to C_3 alkoxy;

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

or pharmaceutically acceptable salt thereof.

18. A compound of Claim 16 having the structure:



I

wherein:

R¹ is H, C₁ to C₆ alkyl, substituted C₁ to C₆ alkyl, C₃ to C₈ cycloalkyl,
5 substituted C₃ to C₈ cycloalkyl, aryl, substituted aryl, heterocyclic, substituted
heterocyclic, COR^A, or NR^BCOR^A;

R¹ and R² are fused to form spirocyclic alkyl as a 3 to 8 membered spirocyclic
ring, substituted spirocyclic alkyl constructed by fusing R¹ and R² to form a 3 to 8
membered spirocyclic ring, spirocyclic alkenyl constructed by fusing R¹ and R² to form
10 a 3 to 8 membered spirocyclic ring, substituted spirocyclic alkenyl constructed by
fusing R¹ and R² to form a 3 to 8 membered spirocyclic ring, spirocyclic alkyl
constructed by fusing R¹ and R² to form a 3 to 8 membered spirocyclic ring and
containing one to three heteroatoms from the group including O, S and N; substituted
spirocyclic alkyl constructed by fusing R¹ and R² to form a 3 to 8 membered spirocyclic
15 ring and containing one to three heteroatoms from the group including O, S and N; the
spirocyclic rings made by fusing R¹ and R² being optionally substituted by from 1 to 4
groups selected from fluorine, C₁ to C₆ alkyl, C₁ to C₆ alkoxy, C₁ to C₆ thioalkyl, -CF₃, -
OH, -CN, NH₂, -NH(C₁ to C₆ alkyl), or -N(C₁ to C₆ alkyl)₂;

R^A is H, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, aryl, substituted aryl, C₁ to C₃
20 alkoxy, substituted C₁ to C₃ alkoxy, C₁ to C₃ aminoalkyl, or substituted C₁ to C₃
aminoalkyl;

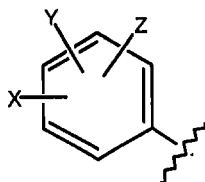
R^B is H, C_1 to C_3 alkyl, or substituted C_1 to C_3 alkyl;

R^3 is H, OH, NH_2 , C_1 to C_6 alkyl, substituted C_1 to C_6 alkyl, C_3 to C_6 alkenyl, substituted C_1 to C_6 alkenyl, alkynyl, or substituted alkynyl, COR^C ;

5 R^C is H, C_1 to C_4 alkyl, substituted C_1 to C_4 alkyl, aryl, substituted aryl, C_1 to C_4 alkoxy, substituted C_1 to C_4 alkoxy, C_1 to C_4 aminoalkyl, or substituted C_1 to C_4 aminoalkyl;

R^4 is H, halogen, CN, NO_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, amino, C_1 to C_6 aminoalkyl, or substituted C_1 to C_6 aminoalkyl;

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



X is taken from the group including halogen, 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 thioalkoxy, substituted C_1 to C_3 thioalkoxy, amino, C_1 to C_3 aminoalkyl, substituted C_1 to C_3 aminoalkyl, NO_2 , C_1 to C_3 perfluoroalkyl, 5 membered heterocyclic ring containing 1 to 3 heteroatoms, COR^D , $OCOR^D$, or $NR^E COR^D$;

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;

Y and Z are independent substituents taken from the group including H, halogen, CN, NO₂, C₁ to C₃ alkoxy, C₁ to C₃ alkyl, or C₁ to C₃ thioalkoxy;

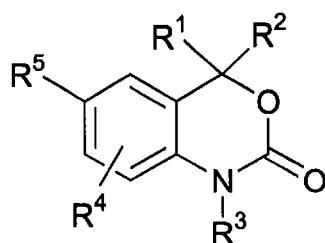
or

R⁵ is a five or six membered ring with 1, 2, or 3 heteroatoms from the group including O, S, SO, SO₂ or NR⁶ and containing one or two independent substituents from the group including H, halogen, CN, NO₂, amino, and C₁ to C₃ alkyl, or C₁ to C₃ alkoxy;

R⁶ is H, or C₁ to C₃ alkyl;

or pharmaceutically acceptable salt thereof.

19. A compound of Claim 16 having the formula:



I

wherein:

R¹ = R² and are selected from C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, or a 3 to 6 membered spirocyclic alkyl ring;

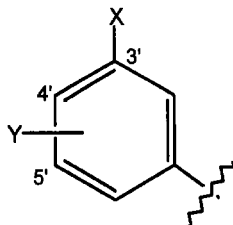
R³ is H, OH, NH₂, C₁ to C₆ alkyl, or substituted C₁ to C₆ alkyl, or COR^C;

R^C is H, C₁ to C₄ alkyl, or C₁ to C₄ alkoxy;

R⁴ is H, halogen, CN, NO₂, C₁ to C₃ alkyl, substituted C₁ to C₃ alkyl, C₁ to C₃ alkoxy, or substituted C₁ to C₃ alkoxy;

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

a) R^5 is the moiety:



X is halogen, CN, C_1 to C_3 alkoxy, C_1 to C_3 alkyl, NO_2 , C_1 to C_3 perfluoroalkyl,

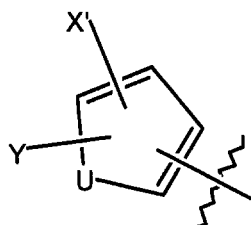
5 5 membered heterocyclic ring containing 1 to 3 heteroatoms, or C_1 to C_3 thioalkoxy;

Y is H, halogen, CN, NO_2 , C_1 to C_3 alkoxy, C_1 to C_4 alkyl, or C_1 to C_3

thioalkoxy;

or

b) R^5 is a five membered ring with the structure:



10

U is O, S, or NR^6 ,

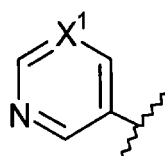
X' is from the group including halogen, CN, NO_2 , or C_1 to C_3 alkyl and C_1 to C_3

alkoxy;

Y' is from the group including H and C_1 to C_4 alkyl;

15 or

c) R^5 is a six membered ring with the structure:



X^1 is N or CX^2 ;

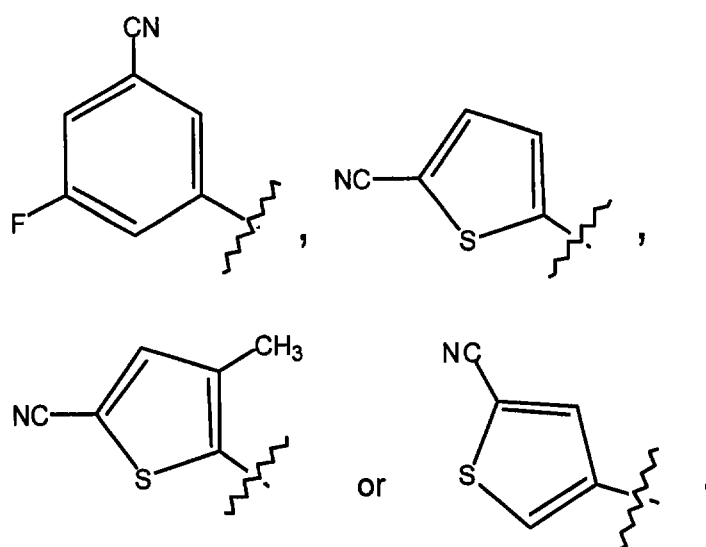
X^2 is halogen, CN, alkoxy, or NO_2 ;

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

or pharmaceutically acceptable salt thereof

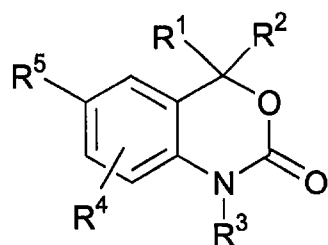
5

20. A compound of Claim 19 wherein R^5 is selected from the group of:



10

21. A compound of Claim 16 having the formula:



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wherein:

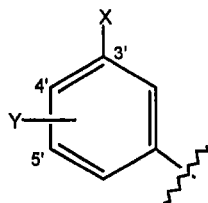
R^1 and R^2 are CH_3 or R^1 and R^2 are fused to form a alkyl a 6 membered

15 spirocyclic alkyl ring;

R^3 is H, OH, NH_2 , CH_3 , substituted methyl, or $-COH$, $CO(C_1$ to C_3 alkyl),
 $CO(C_1$ to C_4 alkoxy);

R^4 is H, halogen, NO_2 , CN, or C_1 to C_3 alkyl;

R^5 is a moiety of the formula:



5

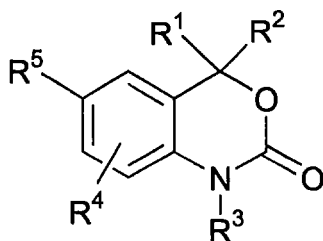
X is taken from the group including halogen, CN, methoxy, NO_2 , or 2-thiazole;

Y is H or F;

or a pharmaceutically acceptable salt thereof.

10

22. A compound of Claim 16 having the formula:



I

wherein:

R^1 and R^2 are CH_3 or R^1 and R^2 are fused to form a alkyl a 6 membered

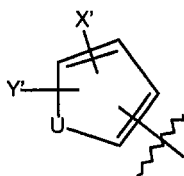
15

spirocyclic alkyl ring;

R^3 is H, OH, NH_2 , CH_3 , substituted methyl, or $-COH$, $CO(C_1$ to C_3 alkyl),
 $CO(C_1$ to C_4 alkoxy);

R^4 is H, halogen, NO_2 , CN, or C_1 to C_3 alkyl;

R⁵ is a five membered ring having the structure:



U is O, S, or NH,

X' is halogen, CN, or NO₂, provided that when U is NH, then X' is not CN;

5 Y' is H or C₁ to C₄ alkyl

or a pharmaceutically acceptable salt thereof.

23. A compound of Claim 16 which is selected from the group of:

10 a) 6-(3-Chlorophenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one;
b) 6-(3-Methoxy-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-
oxazin-2-one;

c) 6-(2-Chloro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;

15

d) 6-(4-Chloro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-
oxazin-2-one;

e) 6-(3-Chloro-phenyl)-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;

f) 6-(3-Chloro-phenyl)-4-ethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one; or

20 g) 6-(3-Chloro-phenyl)-4-phenyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;

or a pharmaceutically acceptable salt thereof.

24. A compound of Claim 16 which is selected from the group of:

- a) 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile;
- b) 4,4-Dimethyl-6-(3-nitrophenyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one;
- 5 c) 6-(3-Bromo-5-fluorophenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one;
- d) 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluorobenzonitrile;
- e) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-nicotinonitrile;
- 10 f) 4-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-2-carbonitrile;
- g) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-2-carbonitrile;
- 15 h) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-methyl-thiophene-2-carbonitrile;
- i) 4-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-furan-2-carbonitrile; or
- j) 4,4-Diethyl-6-(3-nitrophenyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one;
- 20
- or a pharmaceutically acceptable salt thereof.

25. A compound of Claim 16 which is selected from the group of:

- a) 6-(3-Chlorophenyl)-4,4-diethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one;

- b) 6-(3-Chlorophenyl)-spiro[4H-3, 1-benzoxazine-4, 1'-cyclohexane-2-(1H)-one;
- c) 6-(3-Chlorophenyl)-spiro-[4H-3, 1-benzoxazine-4, 1'-cyclopentane]-2(1H)-one;
- 5 d) 6-(3-Nitrophenyl)-spiro[4H-3,1-benzoxazine-4,1'-cyclohexan]-2(1H)-one;
- e) 4-Allyl-6-(3-chlorophenyl)-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- f) 6-(3-Chlorophenyl)-4-methyl-4-propyn-1-yl-1,4-dihydro-
- 10 benzo[d][1,3]oxazin-2-one; or
- g) 6-(3-Chlorophenyl)-4-ethynyl-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- or a pharmaceutically acceptable salt thereof.
- 15 26. A compound of Claim 16 which is selected from the group of:
- a) 6-(3-Chlorophenyl)-4-methyl-4-phenyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- b) 4-Benzyl-6-(3-chloro-phenyl)-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- 20 c) 6-(3-Chloro-phenyl)-4-cyclopropyl-4-methyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- d) 6-(3-Chloro-phenyl)-4-cyclopropyl-4-propyn-1-yl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;

- e) 6-(3-Chloro-phenyl)-4,4-dicyclopropyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- f) 6-(3-Chloro-phenyl)-4,4-dipropyn-1-yl-1,4-dihydrobenzo[d][1,3]oxazin-2-one;
- 5 g) 6-(3-Bromo-5-fluorophenyl)-1,4,4-trimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one;
- h) 6-Chloro-4-methyl-4-trifluoromethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- i) 6-(3-Methoxyphenyl)-4-methyl-4-trifluoromethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one; or
- 10 j) 7-(3-Methoxy-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one;
- or a pharmaceutically acceptable salt thereof.
- 15 27. A compound of Claim 16 which is selected from the group of:
- a) 6-(3-Acetyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]- oxazin-2-one;
- b) 6-(3-Acetyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]- oxazin-2-one;
- 20 c) 6-(3-Benzoyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]- oxazin-2-one;
- d) 4,4-Dimethyl-6-[3-(1H-tetrazol-5-yl)-phenyl]-1,4-dihydrobenzo[d][1,3]oxazin-2-one;

e) 4-(4,4-Dicyclopropyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-2-carbonitrile;

f) 6-(3-Bromo-5-fluoro-phenyl)-4,4-dicyclopropyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one;

5) 3-(4, 4-Dicyclopropyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluoro-benzonitrile;

h) 6-(3-Bromo-5-methyl-phenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one;

10 i) 6-(3-Bromo-5-trifluoromethoxy-phenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]-oxazin-2-one;

j) 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-methyl-benzonitrile;

or a pharmaceutically acceptable salt thereof.

15

28. A compound of Claim 16 which is selected from the group of:

a) 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-trifluoromethoxy-benzonitrile;

20 b) 6-(3,5-difluoro-phenyl)-4,4-dimethyl-1,4-dihydrobenzo-[d][1,3]oxazin-2-one;

c) 6-(3,5-dichloro-phenyl)-4,4-dimethyl-1,4-dihydrobenzo-[d][1,3]oxazin-2-one;

d) 6-(3,5-Bis-trifluoromethyl-phenyl)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]oxazin-2-one;

- e) 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-methoxy-benzonitrile;
- f) 6-(3-Fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]- oxazin-2-one;
- 5 g) 6-(3-Chloro-4-fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- h) 3-(1-Diethoxymethyl-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-5-fluoro-benzonitrile;
- i) 3-Fluoro-5-(1-methoxymethyl-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile;
- 10 j) 3-Fluoro-5-(1-methoxymethyl-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile;
- or a pharmaceutically acceptable salt thereof.
- 15 29. A compound of Claim 16 which is selected from the group of:
- a) Phosphoric acid 6-(3-cyano-5-fluoro-phenyl)-4,4-dimethyl-4H-benzo[d][1,3]oxazin-2-yl ester diethyl ether;
- b) 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-fluoro-benzonitrile;
- 20 c) 6-(3-Chloro-4-fluoro-phenyl)-8-fluoro-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]-oxazin-2-one;
- d) 6-(3-Bromo-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]- oxazin-2-one;

- e) 4,4-Dimethyl-6-(3-trimethylsilanylethynyl-phenyl)-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- f) 6-(3-Ethynyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]-oxazin-2-one;
- 5 g) 3-[3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-phenyl]-propynenitrile;
- h) 6-(3-Fluoro-5-nitro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- i) 6-(3-Chloro-5-fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-
- 10 benzo[d][1,3]oxazin-2-one;
- or a pharmaceutically acceptable salt thereof.

30. A compound of Claim 16 which is selected from the group of:

- a) 3-Chloro-5-(4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-
- 15 yl)-benzonitrile;
- b) 6-(3,5-Dinitro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- c) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-
- 20 isophthalonitrile;
- d) 4,4-Dimethyl-6-(3-thiazol-2-yl-phenyl)-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- e) 6-(3-Fluoro-5-methoxy-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;

- f) 6-(3-Fluoro-5-trifluoromethyl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- g) 6-(5-Bromo-pyridin-3-yl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- 5 h) 6-(5-Bromo-1-oxy-pyridin-3-yl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- i) 6-(3-Cyano-5-fluoro-phenyl)-4,4-dimethyl-2-oxo-4H-benzo[d][1,3]oxazine-1-carboxylic acid tert-butyl ester;
- j) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-2-
10 fluoro-benzonitrile;
- or a pharmaceutically acceptable salt thereof.
31. A compound of Claim 16 which is selected from the group of:
- 15 a) 4-(8-Fluoro-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-2-carbonitrile;
- b) 3-Fluoro-5-(8-fluoro-4,4-dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-benzonitrile;
- c) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-
20 thiophene-3-carbonitrile;
- d) 2-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-thiophene-3-carbonitrile;

- e) 6-(1,2,4-thiadiazol-3-yl-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- f) 6-(3-Fluoro-5-thiophen-3-yl-phenyl)-4,4-dimehtyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- 5 g) 2-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo [d] [1,3] oxazin-6-yl)-pyrrole-1-carboxylic acid tert-butyl ester;
- h) 2-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo [d] [1,3] oxazin-6-yl)-5-nitro-pyrrole-1-carboxylic acid tert-butyl ester;
- i) 4,4-Dimethyl-6-(5-nitro-1H-pyrrol-2-yl)-1,4-dihydrobenzo
- 10 [d][1,3]oxazin-2-one;
- j) 4,4-Dimethyl-6-(1H-pyrrol-2-yl)-1,4-dihydro-benzo[d][1,3]-oxazin-2-one;
- or a pharmaceutically acceptable salt thereof.
- 15 32. A compound of Claim 16 which is selected from the group of:
- a) 4,4-Dimethyl-6-(1-methyl-1H-pyrrol-2-yl)-1,4-dihydro-benzo [d][1,3]oxazin-2-one;
- b) 4,4-Dimethyl-6-(1-methyl-5-nitro-1H-pyrrol-2-yl)-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- 20 c) 3-(1,2-Dihydro-2-oxospiro[4H-3,1-benzoxazine-4,1-cyclohexan]-6-yl)-benzonitrile;
- d) 3-(1, 2-Dihydro-2-oxospiro[4H-3, 1-benzoxazine-4, 1-cyclohexan]-6-yl)-5-fluorobenzonitrile;

- e) 4-(1, 2-Dihydro-2-oxospiro[4H-3,1-benzoxazine-4,1-cyclohexan]-6-yl)-2-thiophenecarbonitrile;
- f) 5-(1, 2-Dihydro-2-oxospiro[4H-3, 1-benzoxazine-4,1-cyclohexan]-6-yl)-2-thiophenecarbonitrile;
- 5 g) 5-(1, 2-Dihydro-2-oxospiro[4H-3, 1-benzoxazine-4,1-cyclohexan]-6-yl)-4-methyl-2-thiophenecarbonitrile;
- h) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-ethyl-thiophene-2-carbonitrile;
- 10 i) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-*n*-propyl-thiophene-2-carbonitrile;
- or a pharmaceutically acceptable salt thereof.
33. A compound of Claim 16 which is selected from the group of:
- 15 a) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-4-*n*-butyl-thiophene-2-carbonitrile;
- b) 6-(4-Cyano-3-fluoro)-4,4-dimethyl-1,4-dihydrobenzo[d][1,3]- oxazin-2-one;
- c) 6-(4-Fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]- oxazin-2-
20 one;
- d) 6-(3,4-Difluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]oxazin-2-one;
- e) 6-(2-Fluoro-phenyl)-4,4-dimethyl-1,4-dihydro-benzo[d][1,3]- oxazin-2-one;

f) 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]-oxazin-6-yl)phenylacetonitrile;

g) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-furan-2-carbonitrile;

5 h) 5-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-furan-2-carbonitrile;

i) 3-(4,4-Dimethyl-2-oxo-1,4-dihydro-2H-benzo[d][1,3]oxazin-6-yl)-2-fluoro-benzonitrile;

or a pharmaceutically acceptable salt thereof.

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34. A pharmaceutical composition comprising a compound of Claim 16, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

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35. 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 16 or a pharmaceutically acceptable salt thereof.

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36. A method of treating hormone-dependent neoplastic disease in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of Claim 16 or a pharmaceutically acceptable salt thereof.

37. The method of Claim 36 wherein the hormone-dependent neoplastic disease is selected from the group of uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, and meningioma.

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38. A method of synchronizing estrus in a mammal, the method comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of Claim 16 or a pharmaceutically acceptable salt thereof.