(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 October 2005 (13.10.2005)

PCT

(10) International Publication Number
WO 2005/095366 A1

(51) International Patent Classification[7]: C07D 267/14, 413/14, 417/14, 413/04, A61K 31/553, A61P 15/00, 35/00

(21) International Application Number: PCT/US2005/009756

(22) International Filing Date: 23 March 2005 (23.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/555,945	24 March 2004 (24.03.2004)	US
11/087,051	22 March 2005 (22.03.2005)	US

(71) Applicant *(for all designated States except US)*: **WYETH** [US/US]; Five Giralda Farms, Madison, NJ 07940 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ZHANG, Puwen** [US/US]; 7004 Oriole Court, Audubon, PA 19403 (US). **WROBEL, Jay, Edward** [US/US]; 15 Rosetree Lane, Lawrence, NJ 08468 (US). **TEREFENKO, Eugene, Anthony** [US/US]; 266 Live Oak Drive, Quakertown, PA 18951 (US). **KERN, Jeffrey, Curtis** [US/US]; 1344 Second Avenue, Gilbertsville, PA 19525 (US).

(74) Agents: **LUCCI, Joseph** et al.; Woodcock Washburn LLP, One Liberty Place - 46th Floor, Philadelphia, PA 19103 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

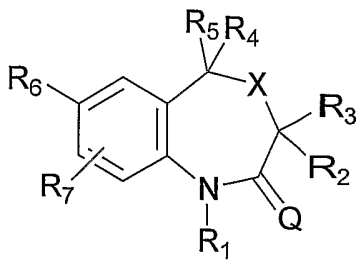
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/095366 A1

(54) Title: 7-ARYL 1,5-DIHYDRO-4,1-BENZOXAZEPIN-2(3*H*)-ONE DERIVATIVES AND THEIR USE AS PROGESTERONE RECEPTOR MODULATORS



(57) Abstract: This invention provides progesterone receptor modulators having the structure: wherein R^1 to R^7, X, and Q are as defined in the specification; or a pharmaceutically acceptable salt thereof.

7-ARYL 1,5-DIHYDRO-4,1-BENZOXAZEPIN-2(3*H*)-ONE DERIVATIVES AND THEIR USE AS PROGESTERONE RECEPTOR MODULATORS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Application No. _____ filed _____, 2005, which claims the benefit of U.S. Application No. 60/555,945, filed on March 24, 2004, the disclosures of both are herein incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] This invention relates to agonists and antagonists of the progesterone receptor, their preparation and their use as progesterone receptor modulators.

BACKGROUND OF THE INVENTION

[0003] Intracellular receptors (IR) form a class of structurally related gene regulators known as "ligand dependent transcription factors" (Mangelsdorf, D. J. etc. *Cell*, **83**, 835, 1995). 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).

[0004] The natural hormone, or ligand, for the PR is the steroid progesterone. Synthetic compounds, such as medroxyprogesterone acetate or levonorgestrel, can also serve as PR ligands. Once a ligand is present in the fluid surrounding a cell, it passes through the membrane *via* passive diffusion, and binds to the IR to create a receptor/ligand complex. This complex binds to specific gene promoters present in the cell's DNA. Once bound to the DNA the complex modulates the production of mRNA and the protein encoded by that gene.

[0005] 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.

[0006] PR agonists (natural and synthetic) are known to play an important role in the health of women. PR agonists are used in birth control formulations, either along or in the presence of an ER agonist. ER agonists are used to treat the symptoms of menopause, but have been associated with a proliferative effect on the uterus which can lead to an increased risk of uterine cancers. Co-administration of a PR agonist reduces/ablates that risk.

[0007] PR antagonists may also 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 (U.S. Patent No. 5,719,136).

[0008] PR antagonists may also be useful for the treatment of hormone dependent breast cancers (Horwitz, et al, *Horm. Cancer*, 283, **1996**, 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 uterine fibroids (Murphy, et al, *J. Clin. Endo. Metab.*, **76**, 513, 1993) and endometriosis (Kettel, et al., *Fertility and Sterility*, **56**, 402, 1991).

[0009] PR antagonists may also be useful in hormone replacement therapy for post menopausal patients in combination with a partial ER antagonist such as tamoxifen (U.S. Patent No. 5,719,136).

[0010] 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).

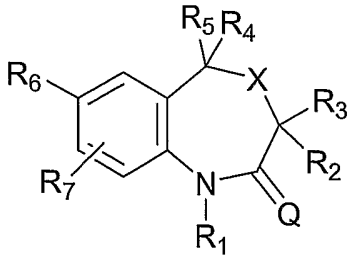
[0011] PR ligands have been described, for example, in Zhi, *et al,* (*Bioorg. & Med.Chem. Lett.* 10, 415, 2000 and *J. Med. Chem.*, 41, 291, 1998), Tegley, *et al* (*J. Med. Chem.* 41, 4357, 1998), Combs, *et al.* (*J. Med. Chem.*, **38**, 4880, 1995), Perlman, *et. al.* (*Tet. Letters*, **35**, 2295, 1994), Hamann, *et al* (*Ann. N.Y. Acad. Sci.*, **761**, 383, 1995), Chen, *et al* (Chen, et al, POI-37, 16th Int. Cong. Het. Chem., Montana, 1997), Kurihari, *et. al.*, described the PR ligand **12** (*J. Antibiotics*, **50**, 360, 1997).

[0012] Zhang, *et al.*, described several PR modulators (U.S. Patent Nos. 6,432,949, 6,380,235, and 6,358,948). Other PR modulators are described in Fensome, *et al.* (U.S. Patent Nos. 6,391,907 and 6,355,648), Santilli, *et al* (U.S. Patent No. 6,306,851), Zhang, *et al.* (U.S. Patent No. 6,369,056), Ullrich, *et al.* (U.S. Patent No. 6,417,214), and Collins, *et al.* (U.S. Patent Nos. 6,407,101 and 6,339,098).

[0013] Certain 4,1-benzoxazepinones are disclosed in the art. PCT Patent Application WO 99/11635 describes the use of some 5,5-disubstituted-1,5-dihydro-4,1-benzoxazepinones as HIV reverse transcriptase inhibitors. PCT Patent Application WO 97/48701 discloses certain squalene synthetase inhibitor 4,1-benzoxazepinones with a linked carboxyl group at position 3. Japanese Patent Application JP 08-259447 and European Patent Application EP 0567026 disclose certain 4,1-benzoxazepinones. U.S. Patent No. 4,476,133 describe the use of some 5-substituted-4,1-benzoxazepinones as CNS agents. European Patent Application EP 0142361 discloses phospholipase A_2 inhibitor benzoxazepinones.

SUMMARY OF THE INVENTION

[0014] The present invention relates to agonists and antagonists of the progesterone receptor, their preparation and their use as progesterone receptor modulators. In some aspects, the invention relates to compounds of Formula I:



wherein:

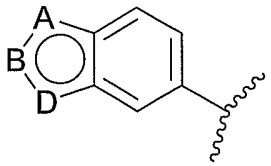
R_1 is H, C_{1-3} alkyl, or COR^A; where R^A is H, C_{1-4} alkyl, C_{1-4} alkoxy, or C_{1-3} aminoalkyl;

R_2 and R_3 are each independently H, CF_3, or C_{1-3} alkyl;

R_4 and R_5 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-3} perfluoroalkyl, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, or together with the carbon atom to which they are attached form a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N;

R_6 is substituted phenyl containing 1 to 3 substituents or a 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms and 1 to 3 substituents, said heteroatoms being O, S, SO, SO_2 or N and said substituents independently being H, halogen, CN, NO_2, OH, amino, and C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, $C{=}NOR^C$, COR^D, or NR^CCOR^D; or

R_6 is a benzofused heterocyclic ring of the following formula



where A, B, and D are each independently CH, N, O, or S;

R^C is H, C_{1-4} alkyl, substituted C_{1-4} alkyl, or COR^D;

R^D is H, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} aminoalkyl;

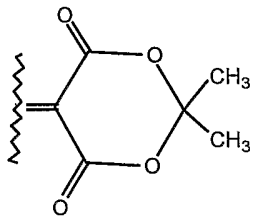
R_7 is H, halogen, CN, NO_2, OH, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, amino, or C_{1-3} aminoalkyl;

Q is O, S, NR_8, CR_9R_{10}, or $R_{13}R_{14}$;

R_8 is CN, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic, SO_2CF_3, OR_{11} or $NR_{11}R_{12}$;

R_9 and R_{10} are independently H, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, CN, or CO_2R_{11};

or CR_9R_{10} comprises a six membered ring of the structure:



R_{11} and R_{12} are independently each H, C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, acyl or sulfonyl;

R_{13} and R_{14} are each independently H, C_{1-3} lower alkyl, C_{1-3} lower perfluoroalkyl, aryl, heterocyclic, a 3 to 6 membered alkylspirocyclic ring comprising R_{13} and R_{14}, a 3 to 6 membered heterospirocyclic ring comprising R_{13} and R_{14} and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2 or N;

X is O, S, NR^E, or CR^ER^F; where R^E and R^F are each independently H or C_{1-4} alkyl;

or pharmaceutically acceptable salt thereof.

[0015] In certain embodiments, when X is O and Q is O or S, then at least one of R_4 and R_5 is H, CF_3, CF_2CF_3, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within said spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N. In some embodiments, each of R_4 and R_5 are selected from the aforementioned atoms or groups.

[0016] In yet other embodiments, when X is NR^E, Q is O or S, R_6 is a 5 or 6 membered heterocyclic ring, and R_4 is cyclopropyl or C_1 to C_3 alkyl, then R_5 is H, CF_3, CF_2CF_3, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, or a substituted

heterocycle;

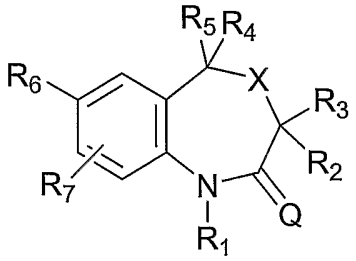
[0017] In certain embodiments, when X is O, Q is O or S, and R_4 is CF_3, then R_5 is H, CF_3, CF_2CF_3, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle.

[0018] The invention is also directed to pharmaceutical compositions comprising such compounds and the use of such compounds in the treatment of diseases, hormone replacement therapy, or in inducing contraception.

DETAILED DESCRIPTION OF THE INVENTION

[0019] In one aspect, the present invention is directed to compounds that act as competitive inhibitors of progesterone binding to the PR and act as agonists and/or antagonists in functional models, either/or *in vitro* and *in vivo*. These compounds may be used for contraception, in the treatment of uterine fibroids, endometriosis, dysmenorrhea, breast, uterine, ovarian and prostate cancer, meningloma, and post menopausal hormone replacement therapy.

[0020] In one aspect the invention concerns compounds of Formula I:



wherein:

R_1 is H, C_{1-3} alkyl, or COR^A; where R^A is H, C_{1-4} alkyl, C_{1-4} alkoxy, or C_{1-3} aminoalkyl;

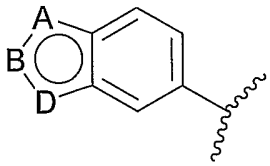
R_2 and R_3 are each independently H, CF_3, or C_{1-3} alkyl;

R_4 and R_5 are each independently H, C^{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-3} perfluoroalkyl, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, or together with the carbon atom to which they are attached form a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms

within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N;

R_6 is substituted phenyl containing 1 to 3 substituents or a 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms and 1 to 3 substituents, said heteroatoms being O, S, SO, SO_2 or N and said substituents independently being H, halogen, CN, NO_2, OH, amino, and C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, $C{=}NOR^C$, COR^D, or NR^CCOR^D; or

R_6 is a benzofused heterocyclic ring of the following formula



where A, B, and D are each independently CH, N, O, or S;

R^C is H, C_{1-4} alkyl, substituted C_{1-4} alkyl, or COR^D;

R^D is H, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} aminoalkyl;

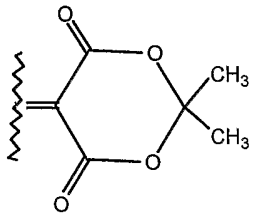
R_7 is H, halogen, CN, NO_2, OH, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, amino, or C_{1-3} aminoalkyl;

Q is O, S, NR_8, CR_9R_{10}, or $R_{13}R_{14}$;

R_8 is CN, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic, SO_2CF_3, OR_{11} or $NR_{11}R_{12}$;

R_9 and R_{10} are independently H, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, CN, or CO_2R_{11};

or CR_9R_{10} comprises a six membered ring of the structure:



R_{11} and R_{12} are independently each H, C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, acyl or sulfonyl;

R_{13} and R_{14} are each independently H, C_{1-3} lower alkyl, C_{1-3} lower perfluoroalkyl, aryl, heterocyclic, a 3 to 6 membered alkylspirocyclic ring

comprising R_{13} and R_{14}, a 3 to 6 membered heterospirocyclic ring comprising R_{13} and R_{14} and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2 or N;

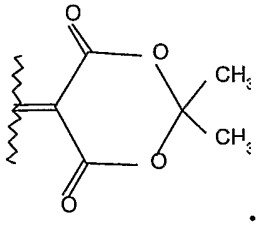
X is O, S, NR^E, or CR^ER^F; where R^E and R^F are each independently H or C_{1-4} alkyl;

provided that when X is O and Q is O or S, then at least one of R_4 and R_5 is H, CF_3, CF_2CF_3, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within said spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N;

provided that when X = NR^E, Q = O or S, R_6 is a 5 or 6 membered heterocyclic ring, and R_4 is cyclopropyl or C_1 to C_3 alkyl, then R_5 is H, CF_3, CF_2CF_3, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, or a substituted heterocycle;

or pharmaceutically acceptable salt thereof.

[0021] In some embodiments, R_1, R_2, and R_3 are each H. In other embodiments, R_4 is H, C_{1-6} alkyl, CF_3, CF_2CF_3, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, substituted aryl, heterocycle, or substituted heterocycle. In yet other embodiments, R_5 is aryl, substituted aryl, heterocycle, or substituted heterocycle. In certain embodiments, R_4 and R_5 are a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N. In still other embodiments, R_8 is CN, C_{1-3} alkyl, SO_2CF_3, OR_{11} or $NR_{11}R_{12}$. In some embodiments, R_9 and R_{10} are each, independently, H, C_{1-3} alkyl, NO_2, CN, or CO_2R_{11}; or CR_9R_{10} comprise a six membered ring as shown by the structure:

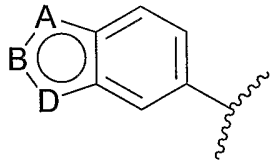


In other embodiments, R_{11} and R_{12} are each, independently, H, C_{1-3} alkyl, acyl (such

as alkylcarbonyl) or sulfonyl. In yet other embodiments, R_{13} and R_{14} are each, independently, H, C_{1-3} lower alkyl, or C_{1-3} perfluoroalkyl.

[0022] In some aspects, the invention relates to compounds where R_7 is H, halogen, CN, or NO_2. In other aspects, R_8 is selected from the group of CN, SO_2CF_3, or OR_{11}. In some compositions, R_9 and R_{10} are each, independently, NO_2, CN, or CO_2R_{11}. In other compositions, R_{11} and R_{12} are each, independently, H or C_{1-3} alkyl. In yet other compositions, R_{13} and R_{14} are each, independently, H, C_{1-3} alkyl, or C_{1-3} lower perfluoroalkyl.

[0023] In some compounds, R_6 is substituted phenyl containing 1 to 2 substituents, where said substituents are halogen, CN, NO_2, OH, C=NOH; or R_6 is a 5 or 6 membered heterocyclic ring containing 1 to 2 heteroatoms substituted with 1 to 2 substituents from the group including halogen, CN, NO_2, OH, and C_1 to C_3 alkyl, C=NOH, said heteroatoms being O, S, SO, SO_2 or N; or R_6 is a benzofused heterocyclic ring of the following formula



;

A and D are each independently CH, O, or S; B is N; and X is O.

[0024] Certain preferred compounds of the invention are:
4-methyl-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile,

tert-butyl 2-cyano-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-[5-methyl-2-oxo-5-(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-[5-methyl-2-oxo-5-(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,
5-(1,5-dimethyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,
tert-butyl 2-cyano-5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,
5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,
1-methyl-5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,
2'-Cyano-5'-[(2-oxo-1,2,3,5-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-(5-spiro-1"-cyclohexane)]-pyrrole-1'-carboxylic acid *tert*-butyl ester,
5'-[(2-Oxo-1,2,3,5-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-(5-spiro-1"-cyclohexane)]-1*H*-pyrrole-2'-carbonitrile,
tert-butyl 2-cyano-5-[5-methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,
tert-butyl 2-cyano-5-[2-oxo-5,5-di(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,
tert-butyl 2-cyano-5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,
5-[5-methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,
tert-butyl 2-cyano-5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,
5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,
1-methyl-5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,
5-[1,5-dimethyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,
5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-

carbonitrile,

1-methyl-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-(1,5-dimethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

7-(3-chlorophenyl)-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chlorophenyl)-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

tert-butyl 2-cyano-5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

tert-butyl 2-cyano-5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(5-methyl-5-thien-3-yl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-methyl-5-thien-3-yl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-benzyl-5-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

9*H*-fluoren-9-ylmethyl 7-(5-cyano-1*H*-pyrrol-2-yl)-5-methyl-5-thien-2-yl-2,3-dihydro-4,1-benzoxazepine-1(5*H*)-carboxylate,

5-[(5*S*)-5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

1-ethyl-5-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1,2-dicarbonitrile,

5-(5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-fluorobenzonitrile,

tert-butyl 2-cyano-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-[(5*R*)-5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-

pyrrole-2-carbonitrile,

1-methyl-5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(9-fluoro-5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

7-(3-chloro-4-fluorophenyl)-5-isopropyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-fluoro-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

5-(9-fluoro-5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

3-fluoro-5-(5-isopropyl-5-thien-2-yl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

7-(3-chloro-4-fluorophenyl)-5-propyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-fluoro-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

5-methyl-7-(3-methylphenyl)-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-aminophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-methoxyphenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(2-chlorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chlorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(4-chlorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

7-(3,5-difluorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-methyl-5,7-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-methyl-5-thien-2-yl-7-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-methyl-5-thien-2-yl-7-[3-(trifluoromethyl)phenyl]-1,5-dihydro-4,1-benzoxazepin-

2(3*H*)-one,

5-methyl-7-(3-nitrophenyl)-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-4-fluorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(2-furyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-4-fluorophenyl)-5-ethyl-5-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

tert-butyl 2-cyano-5-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

3-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-fluorobenzonitrile,

7-(3-chloro-4-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

tert-butyl 2-cyano-5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

3-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

5-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

5-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

4-methyl-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile,

2-fluoro-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile,

4-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile,

5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile,

5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-4-methylthiophene-2-carbonitrile,

4-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile,

4-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile,

tert-butyl 2-cyano-5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

4-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile,

5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile,

3-fluoro-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-4-fluorophenyl)-4,5,5-trimethyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one,

1-ethyl-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-benzyl-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

3-fluoro-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

tert-butyl 2-cyano-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1 -benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

7-(3-chloro-4-fluorophenyl)-5,5-dithien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole–2-carbonitrile,

3-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

tert-butyl 2-[5,5-bis(5-bromothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5–cyano-1*H*-pyrrole-1-carboxylate,

7-(3-chloro-4-fluorophenyl)-5,5-bis(5-chlorothien-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-[5,5-bis(5-bromothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl– 1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5–cyano-1*H*-pyrrole-1-carboxylate,

5-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole–2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-di(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

tert-butyl 2-cyano-5-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

3-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

5-[5,5-bis(5-chlorothien-2-yl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1–methyl-1*H*-pyrrole-2-carbonitrile,

3-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-

2(3*H*)-one,

tert-butyl 2-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-1*H*-pyrrole-1-carboxylate,

5-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-diphenyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-[(5*R*)-5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

tert-butyl 2-cyano-5-[(5*S*)-5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

5-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-1*H*-pyrrole-1-carboxylate,

5-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-bis(3-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-[5,5-bis(5-cyanothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

5-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

5-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-

methyl-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(1-methyl-2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-bis(4-methoxyphenyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

5-[(5*R*)-5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-[(5*S*)-5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-[5,5-di(3-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-[5-(4-methoxyphenyl)-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

3-[5,5-di(3-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

5-[5,5-bis(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

7-(3,5-dichlorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-ethyl-7-(2-fluorophenyl)-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3,4-difluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-ethyl-7-(4-fluorophenyl)-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-4-fluorophenyl)-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

4-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-2-furonitrile,

7-(2,3-difluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(4-chloro-3-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-5-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

4-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-2-fluorobenzonitrile,

7-(3-bromo-5-chlorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-chloro-5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]benzonitrile,

7-(3-bromo-5-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-fluoro-5-[5-(2-furyl)-2-oxo-5-(pentafluoroethyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]benzonitrile,

1-methyl-5-(5-methyl-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5,5-dimethyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile, or

5-(1-acetyl-5,5-dimethyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile.

[0025] The compounds of this invention may contain an asymmetric carbon atom. Some of the compounds 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, other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. The present invention also includes the pro-drug of compounds of formula I and pharmaceutically acceptable salts thereof.

[0026] The term "alkyl" is used herein as a group or part of a group, e.g., alkylamino, to refer to both straight- and branched-chain saturated aliphatic hydrocarbon groups having at least one carbon atoms, e.g., 1 to 6 carbon atoms; "alkenyl" is intended to include both straight- and branched-chain alkyl group with at least one carbon-carbon double bond, e.g., having 2-6 carbon atoms; "alkynyl"

group is intended to cover both straight- and branched-chain alkyl group with at least one carbon-carbon triple bond, e.g., having 2-6 carbon atoms.

[0027] The terms "substituted alkyl", "substituted alkenyl", and "substituted alkynyl" refer to alkyl, alkenyl, and alkynyl as just described having one or more substituents from the group including halogen, CN, OH, NO_2, amino, aryl, heterocyclic, substituted aryl, substituted heterocyclic, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, arylthio. These substituents may be attached to any carbon of alkyl, alkenyl, or alkynyl group provided that the attachment constitutes a stable chemical moiety.

[0028] The term "aryl" as a group or part of a group, e.g., aryloxy, arylthio, is used herein to refer to an aromatic system , e.g., of 6 to 14 carbon atoms, 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.

[0029] The term "substituted aryl" refers to aryl as just defined having one or more, e.g., 1 to 5 or 1-3, substituents from the group including halogen, CN, OH, NO_2, amino, alkyl, cycloalkyl, alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

[0030] 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, e.g., fused benzene 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.

[0031] The term "substituted heterocyclic" is used herein to describe the heterocyclic just defined having one or more substituents selected from the group which includes halogen, CN, OH, NO_2, amino, alkyl, substituted alkyl, cycloalkyl, e.g., of 3-8 carbon atoms, alkenyl, substituted alkenyl, alkynyl, alkoxy, aryloxy, substituted alkyloxy, alkylcarbonyl, alkylcarboxy, alkylamino, or arylthio.

[0032] The term "alkoxy" is used herein to refer to the OR group, where R is alkyl or substituted alkyl.

[0033] The term "aryloxy" is used herein to refer to the OR group, where R is aryl or substituted aryl.

[0034] The term "alkylcarbonyl" is used herein to refer to the RCO group, where R is alkyl or substituted alkyl.

[0035] The term "alkylcarboxy" is used herein to refer to the COOR group, where R is alkyl or substituted alkyl.

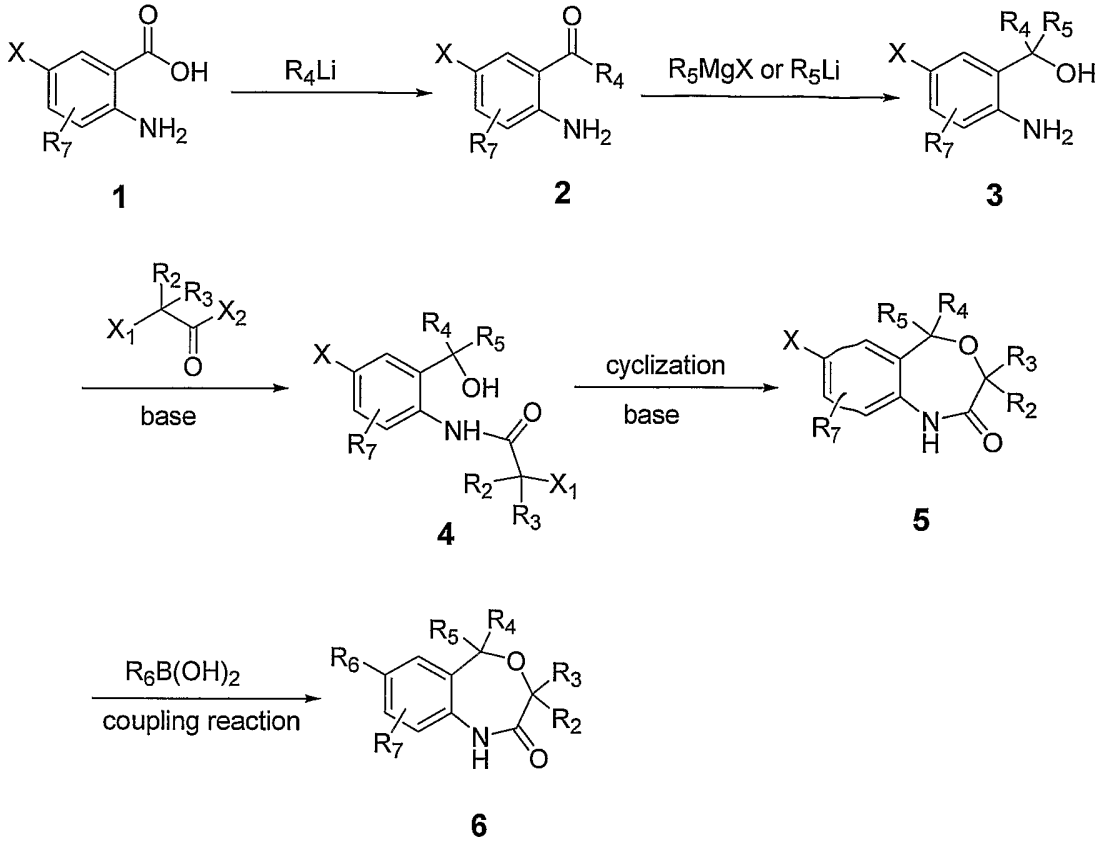
[0036] The term "aminoalkyl" refers to both secondary and *tert*iary amines wherein the alkyl or substituted alkyl groups may be either same or different and the point of attachment is on the nitrogen atom.

[0037] The term "halogen" refers to Cl, Br, F, and I.

[0038] The term "lower perfluoroalkyl" is used herein to refer to C_{1-3} alkyl groups where each hydrogen atom is replaced with a fluorine atom. Examples include CF_3 and CF_2CF_3 groups.

[0039] The compounds of the present invention can be synthesized following the schemes described below or variations thereof as appreciated by those of skill in the art.

Scheme I

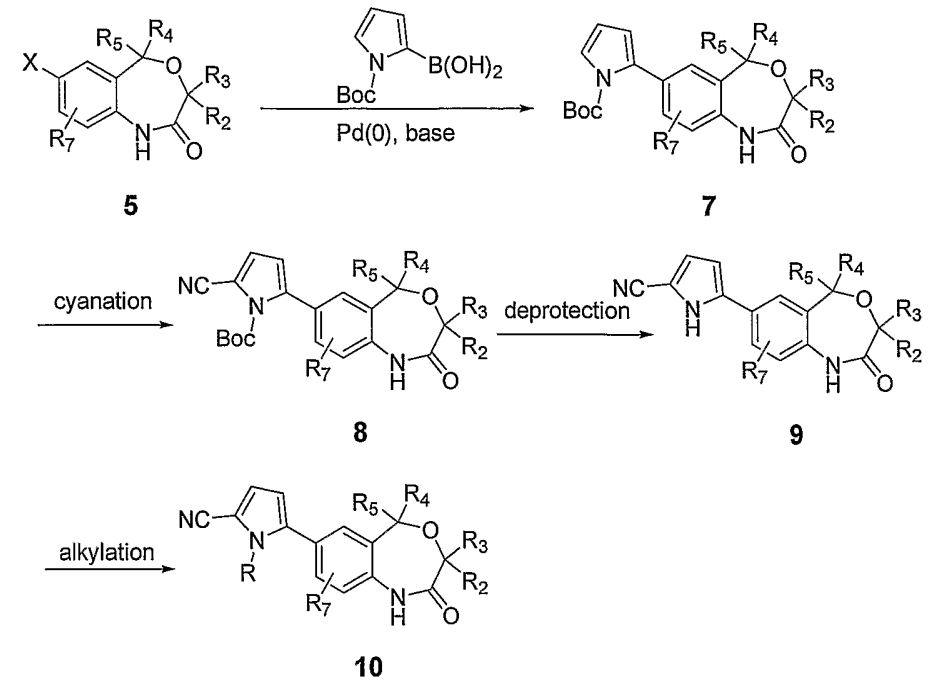


[0040] Scheme I illustrates a general synthesis of the compounds of the present invention. The 7-aryl (R_6) group was assembled *via* a coupling reaction such as Suzuki coupling reaction and is critical to the PR activity of compounds in the present invention. As illustrated in Scheme I, access to ketones **2** can be achieved by reaction of an appropriately substituted anthranilic acids **1** with a suitable organo lithium reagent. The reaction can be executed in an aprotic solvent including but not limited to THF or diethyl ether at a suitable temperature such as 0 °C or room temperature under a blanket of inert atmosphere such as nitrogen or argon. To prevent the formation of carbinol side products, a reversing quenching procedure (pouring the reaction mixture to a diluted aqueous acidic solution such as hydrogen chloride solution) is preferred. An alternative way to work up the reaction included

but not limited to an addition of trialkylsilyl chloride or equivalent to the reaction before quenching the reaction mixture with a diluted aqueous acidic solution. Treatment of ketones **2** to give carbinols **3** is effected with a suitable organo metallic reagent including but not limited to Grignard or lithium reagents. The reaction can be performed in an aprotic solvent such as diethyl ether or THF at low temperature ranging from -78 °C to room temperature under an inert atmosphere such as argon or nitrogen. Formation of amide **4** can be achieved by treatment of carbinols **3** with an appropriate acylation reagent including but not limited to substituted chloro or bromoacetyl chloride or bromide. A suitable base such as triethyl amine, Hünig's base, potassium carbonate, or sodium carbonate and an aprotic solvent including but not limited to THF or diethyl ether can be used and the reaction temperature ranges from -78 °C to room temperature under an inert atmosphere such as argon or nitrogen. The ring closure to **5** can be effected by treatment of **4** with a suitable base such as sodium hydride, potassium carbonate, or triethyl amine. The reaction can be carried out in an aprotic solvent such as DMF, HMPA, or THF at the temperature ranging from 0 °C to room temperature. The coupling product **6** from **5** can be effected by a number of coupling reactions such as Suzuki and Stille procedures. 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, dppf, or dppe. Under this catalytic condition, an appropriately substituted nucleophilic reagent, e.g., aryl boronic acid, arylstannane, or aryl zinc compound, can be coupled with **5** to produce the compounds of the present invention, 7-aryl benzoxazepinones **6**. The commonly used bases in the reaction include but not limited to sodium bicarbonate, sodium carbonate, potassium phosphate, barium carbonate, cesium fluoride, and potassium acetate. The most commonly used solvents in these reactions include benzene, toluene, DMF, isopropanol, ethanol, DME, and ether. The coupling reaction is generally executed under an inert atmosphere such as nitrogen or argon at temperatures ranging from room temperature to 95 °C. In the case when the 7-aryl boronic acid is not available, the 7-halogen of **5** can be converted to the borate or stannane, which can be coupled

with an appropriate aryl halide such as aryl bromide or aryl iodide using any coupling reaction described above.

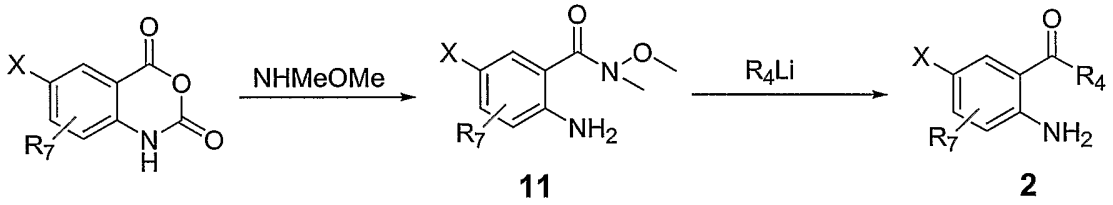
Scheme IA



[0041] Scheme IA describes a general synthesis of 7-(5-cyanopyrrol-2-yl) benzoxazepinones. An appropriately protected pyrrole moiety was coupled with **5** to yield **7** using the coupling procedure described above. Cyanation of pyrrole moiety at 5'-position can be readily effected by treatment of **7** with a suitable cyanating reagent such as chlorosulfonyl isocyanate in a non-protic solvent including but not limited to THF. When chlorosulfonyl isocyanate is used, the complex was formed and DMF can be used to break up the complex to install cyano moiety on the 5'-position of pyrrole ring. The reaction can be effected at -78 °C under an inert atmosphere such as nitrogen or argon and then treated with DMF to yield **8**. There are other means known to those of skill in the art to install cyano moiety on the pyrrole ring including but not limited to a coupling reaction of cyano group to the pyrrole moiety catalyzed by a transition metal. In this procedure, the pyrrole moiety is substituted with bromine, iodine, or triflate serving as a leaving group to effect the

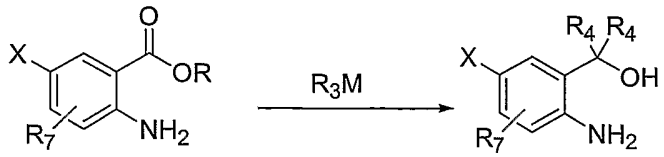
coupling with cyano nucleophile. Removal of protecting group from 1'-position of pyrrole can be effected *via* various means depending on the nature of protecting group by ones of skill in the art. For example, Boc group can be removed by a number of conditions. These include ones such as treatment of **8** with base or acid or by thermo condition of simply heating neat material of **8** under an inert atmosphere such as nitrogen or argon at high temperature such as 165 °C to give the unprotected compounds of the present invention **9**. Transformation at the 1'-position of pyrrole moiety included but not limited to alkylation and acylation. The alkylation such as methylation of the 1'-position on the pyrrole moiety to give **10** can be effected by treatment of **9** with an appropriate methylating reagent such as iodomethane. An aprotic solvent such as DMF and a suitable base such as potassium carbonate or potassium bicarbonate are often used and reaction is executed at 0 °C to room temperature.

Scheme II



[0042] Scheme II described an alternative route leading to ketones **2** by treatment of an appropriately substituted Weinreb amide **11** with organo metallic reagents such as Grignard or lithium reagents. The reaction can be most effectively executed in a suitable nonprotic solvent including but not limited to THF or diethyl ether at the temperature ranging from –78 °C to 0 °C under an inert atmosphere such as nitrogen or argon. The Weinreb amide **11** can be effected by the reaction of an appropriately substituted isatoic anhydride with *N, O*-dimethylhydroxylamine hydrochloride salt in a protic solvent such as ethanol or methanol at reflux.

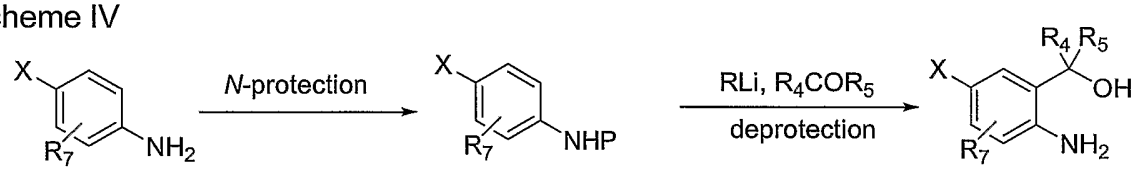
Scheme III



12 3

[0043] Scheme III illustrates an alternative procedure for preparation of the symmetrical carbinaol **3**. The substituted anthranilic acids can be treated with Grignard reagent to give **3**. When the ester is used, both Grignard and organo lithium species can be used to effect the formation of carbinols **3** in good yield. The commonly used solvent in this transformation is an aprotic solvent including but not limited to THF and diethyl ether. The reaction can be executed at the temperature ranging from –78 °C to room temperature under an inert atmosphere such as argon or nitrogen.

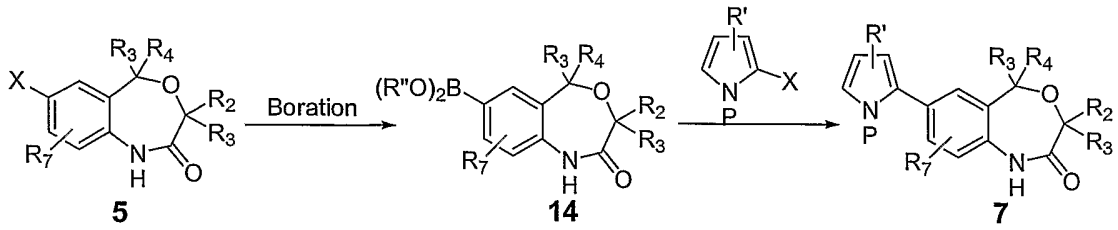
Scheme IV



13 3

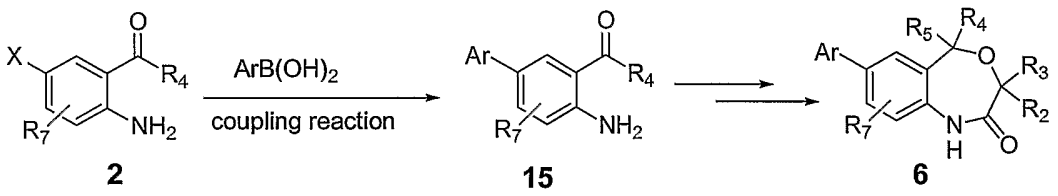
[0044] Amino carbinol **3** can also be effected as illustrated in Scheme IV. A substituted aniline is protected with a suitable protecting group to give **13**. The *t*-butoxylcarbonyl protecting group is preferred but other protecting groups including but not limited to *t*-butylcarbonyl and acetyl aniline can be used. The protected aniline **13** is treated with a suitable organo lithium base such as *n*-butyllithium and then quenched with a suitable ketone to afford *n*-protected amino carbinol. The reaction is executed in an aprotic solvent such as diethyl ether or THF at –78 °C under an inert atmosphere such as argon or nitrogen. Removal of the protecting group to give carbinol **3** can be effected by a number of ways known to those of skill in the art.

Scheme V



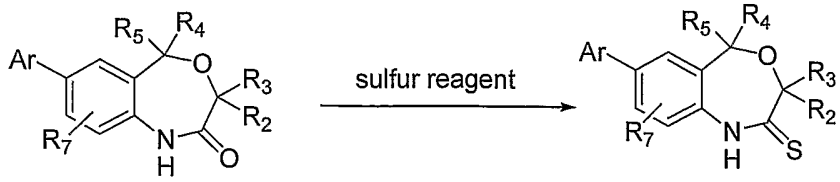
[0045] Scheme V depicts an alternative approach for the preparation of 7-pyrrolyl benzoxazepinone **7**. A benzoxazepinone **5** is converted into a suitable nucleophile such as borate species by means well known by those of skill in the art. For example, the borate moiety can be effected by a boration procedure catalyzed by a transition metal similar to one reported by Murata et al. (M. Murata et al., *J. Org. Chem.*, **62**, 6458-6459, 1997). The borate **14** is then coupled with a suitable pyrrole such as a protected 2-bromo- or 2-iodopyrrole using the procedure described above for the preparation of **7** in Scheme IA.

Scheme VI



[0046] Scheme VI illustrates another approach for synthesizing compounds in the present invention. Ketone **2** can be coupled with aryl moiety to give **15** using the coupling procedure described above. Following the procedures described in Scheme I, compounds **6** of the present invention can be effected in a multi-step synthesis.

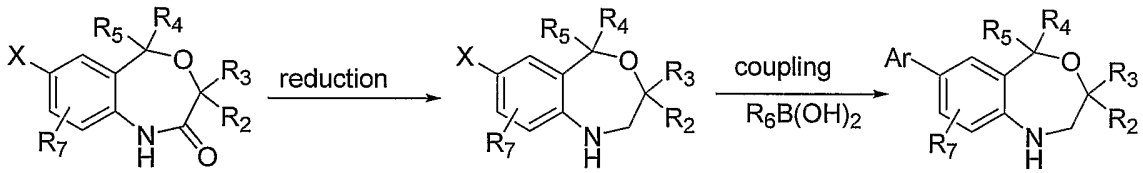
Scheme VII



6 16

[0047] The preparation of 7-aryl benzoxazepin-2-thione **16**, the compounds of present invention, is depicted in Scheme VII. The transformation of 7-aryl benzoxazepinone **6** into **16** can be often effected using a sulfur reagent including but not limited to Lawesson's reagent or phosphorus pentasulfide in a suitable solvent such as toluene, chlorobenzene, or xylene at about 120 °C under nitrogen or argon.

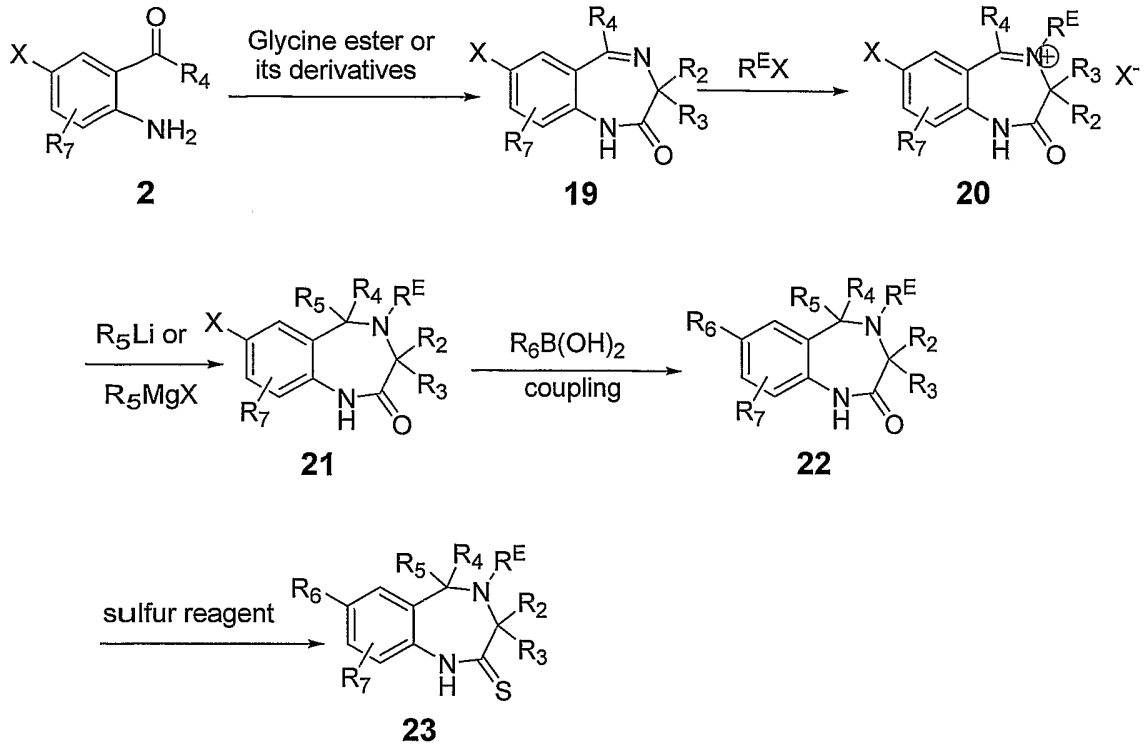
Scheme VIII



5 17 18

[0048] Scheme VIII illustrates a synthesis of 7-aryl benzoxazepines. Benzoxazepinones **5** can be readily reduced to produce **17** by a suitable reducing reagent including but not limit to lithium aluminum hydride in an aprotic solvent such as THF at the ambient temperature under a blanket of inert atmosphere such as nitrogen or argon. Coupling of **17** with various aryl boronic acids using the coupling protocols described in Scheme I can readily effect the compounds of the present invention, 7-aryl benzoxazepines (**18**). Following the similar procedures described in Scheme IA, benzoxazepines substituted with 7-pyrrole moiety can be prepared.

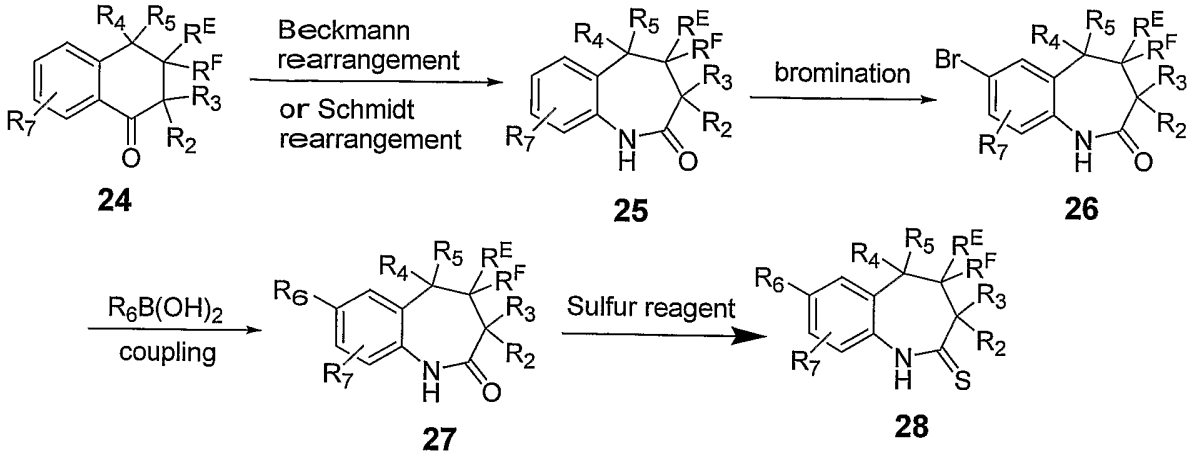
Scheme IX



[0049] A general synthesis of 7-aryl benzodiazepinones is depicted in Scheme IX. Ring closure of ketone **2** to benzodiazepinones **19** can be effected by condensing **2** with a suitable glycine ester or its derivatives in an aprotic solvent such as pyridine or toluene at reflux under nitrogen or argon. Addition of organo metallic reagent at position-5 can be difficulty without the activation of 4-nitrogen. In this regard, compound **19** can be readily alkylated and activated to give **20** by an appropriate alkylating reagent such as alkyl iodide in a suitable solvent such as acetonitrile under nitrogen or argon. Addition of an appropriate organo metallic reagent such as alkyllithium or Grignard reagent at position-5 to yield **21** can be easily achieved in an aprotic solvent such as diethyl ether or THF from ambient temperature to boiling point of the solvent under nitrogen or argon. In a similar manner as mentioned in Scheme I, the coupling reaction can be most efficiently used to convert **21** to the compounds of the present invention, 7-aryl benzodiazepinones (**22**). Following the

procedure described in Scheme VII, 7-aryl benzodiazepin-2-thiones (**23**), the compounds of the present invention, can be readily effected.

Scheme X



[0050] Scheme X describes a synthesis of 7-aryl benzoazepinones. Aryl ketone **24**, which can be readily prepared from the appropriately substituted arenes and lactones *via* Friedel-Crafts reactions, can be converted to benzoazepinones **25** by reacting with hydroxylamine (Beckmann rearrangement) under an acidic condition. Benzoazepinones **25** can also be prepared by treatment of **24** with sodium azide under acidic conditions (Schmidt rearrangement). 7-Bromobenzoazepinones **26** can be effected by treatment of **25** with bromine and a suitable base such as sodium acetate in an acidic solvent such as acetic acid at 0 °C to the ambient temperature. The compounds of present invention, 7-aryl benzoazepinones (**27**), can be produced most efficiently from **26** and a suitable substituted arene nucleophile by a coupling reaction such as ones described in Scheme I.

[0051] Using the procedure illustrated in Scheme VII, 7-aryl benzoazepin-2-thiones (**28**), claimed in the presentation invention, can be prepared.

[0052] 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.

[0053] This invention includes pharmaceutical compositions and treatments which comprise administering to a mammal a pharmaceutically effective amount of one or more compounds as described above as antagonists of the progesterone receptor.

[0054] The progesterone receptor antagonists of this invention, used alone or in combination, can be utilized in methods of contraception and the treatment and/or prevention of benign and malignant neoplastic disease. Specific uses of the compounds and pharmaceutical compositions of invention include the treatment and/or prevention of uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy; carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma and other hormone-dependent tumors. Additional uses of the present progesterone receptor antagonists include the synchronization of the estrus in livestock.

[0055] When the compounds are employed for the above utilities, they may be combined with one or more pharmaceutically acceptable carriers or excipients, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

[0056] 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.

[0057] These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvents customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

[0058] 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.

[0059] 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.

[0060] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of

sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringe ability exits. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

[0061] The present invention may be further understood by the following non-limiting examples.

Example 1

tert-Butyl 2-cyano-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate

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

[0062] To a solution of 5-bromo anthranilic acid (50g, 0.231 mol) in anhydrous THF (500 mL) at 0 °C under nitrogen was added in a dropwise manner methyllithium (1.4 M in diethyl ether, 661 mL, 0.926 mol). After addition, the reaction mixture was slowly allowed to warm to room temperature, stirred overnight, and treated with aqueous saturated ammonium chloride solution (1000 mL). Ethyl acetate (400 mL) was added and organic layer was separated. The aqueous layer was extracted with ethyl acetate (3x200 mL). The combined organic layers were dried (Mg_2SO_4) and concentrated. The residue was purified by a flash chromatography on silica gel (hexane:ethyl acetate/9:1) to afford the title compound as a brown solid (29.3g, 59%). MS (ES) *m/z* 214/216 ($[M + H]^+$, 100%).

1-(2-Amino-5-bromo-phenyl)-1-thiophen-2-yl-ethanol

[0063] To a solution of 1-(2-amino-5-bromo-phenyl)–ethanone (3g, 14 mmol) in anhydrous THF (50 mL) was added at –78 °C under nitrogen 2-thienyl lithium (1.0 mol in THF, 28 mL, 28 mmol). The reaction mixture was slowly allowed to warm to –20 °C, treated with aqueous saturated ammonium chloride solution (50 mL).

Ethyl acetate (50 mL) was added and organic layer was separated, dried (Mg_2SO_4), and concentrated. The residue was used in next step without further purification. ^{1}H-NMR (DMSO-d_6) δ 7.4 (d, J = 4.9 Hz, 1H), 7.07-7.11 (m, 2H), 6.94 (m, 1H), 6.84 (dd, J = 3.5, 0.5 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 6.36 (s, 1H), 5.31 (s, 2H), 1.85 (s, 3H).

N-[4-Bromo-2-(1-hydroxy-1-thien-2-ylethyl)phenyl]-2-chloroacetamide

[0064] To a solution of 1-(2-amino-5-bromo-phenyl)-1-thiophen-2-yl-ethanol (3.9g, 13 mmol) in a mixture of anhydrous THF and diethyl ether (20 mL/20 mL) at 0 °C under nitrogen was added triethyl amine (4 mL, 28.7 mmol) and chloroacetyl chloride (1.6 mL, 20 mmol). After addition, the reaction mixture was slowly warmed to room temperature (rt), stirred for 3 h, and treated with a cold 1N hydrogen chloride aqueous solution (70 mL). Ethyl acetate (100 mL) was added and organic layer separated, dried (Mg_2SO_4), concentrated to yield the title compound as a white solid (4.7g, 94%). ^{1}H-NMR (DMSO-d_6) δ 10.78 (s, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.51 (dd, J = 8.7, 2.2 Hz, 1H), 7.43 (d, J = 5.0 Hz, 1H), 7.37 (m, 2H), 6.95 (m, 1H), 6.88 (dd, J = 3.4, 0.8 Hz, 1H), 4.26 (d, J = 6.9 Hz, 2H), 1.94 (s, 3H).

7-Bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one

[0065] To a solution of N-[4-bromo-2-(1-hydroxy-1-thien-2-ylethyl)phenyl]-2-chloroacetamide (1.29g, 3.44 mmol) in anhydrous THF (20 mL) was added at 0 ° under nitrogen sodium hydride (60% in mineral oil, 0.38g, 9.5 mmol). After addition, the reaction mixture was stirred for 3 h, treated with an aqueous saturated ammonium chloride solution (30 mL). Ethyl acetate (50 mL) was added and organic layer separated, dried (Mg_2SO_4), and concentrated to yield the title compound as a white solid (1.1g, 96%). ^{1}H-NMR (DMSO-d_6) δ 10.13 (s, 1H), 7.57 (dd, J = 5.0, 1.0 Hz, 1H), 7.47 (dd, J = 8.6, 1.4 Hz, 1H), 7.39 (d, J = 1.67 Hz, 1H), 7.11 (d, J = 8.4 Hz, 1H), 7.00 (m, 1H), 6.88 (dd, J = 2.6, 0.9 Hz, 1H), 4.18 (d, J = 15.8 Hz, 1H), 4.03 (d, J = 16.3 Hz, 1H), 1.99 (s, 3H). MS (ES) m/z 338/340 ([M + H]$^+$, 100%).

[0066] A mixture of 7-bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one (1.2g, 3.55 mmol), 2-borono-1H-pyrrole-1-carboxylic acid,

1-*tert*-butyl ester (1.2g, 5.69 mmol), tetrakis(triphenylphosphine) palladium (0) (0.2g, 0.17 mmol), sodium carbonate (1.2g, 11.32 mmol) in a mixture of DME and water (20 mL and 5 mL) was degassed to remove air and then heated at 90 °C under nitrogen for 4 h. The mixture was allowed to cool to rt, treated with a saturated aqueous ammonium sulfate solution (50 mL). Ethyl acetate (80 mL) was added and organic layer separated, dried (Mg_2SO_4), and concentrated. The residue was purified by a flash chromatography on a silica gel column (Hexane:ethyl acetate/3:1) to give the coupling product as an oil which was used in next step without further purification.

[0067] To a solution of the above coupling product in anhydrous THF (30 mL) at –78 °C under nitrogen was added chlorosulfonyl isocyanate (0.46 mL, 5.3 mmol). After kept at –78 °C for 3 h, the reaction solution was treated with anhydrous DMF (5 mL), slowly warmed to rt, and quenched with a saturated aqueous ammonium chloride solution (30 mL). Ethyl acetate (60 mL) was added and organic layer separated, dried (Mg_2SO_4), and concentrated. The residue was purified by a flash chromatography on a silica gel column (hexane:THF/3:1) to give *tert*-butyl 2-cyano-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate as a white solid (0.35g, 22% for two steps). ^{1}H-NMR (DMSO-d_6) δ 10.16 (s, 1H), 7.54 (d, J = 5.1 Hz, 1H), 7.31-7.36 (m, 2H), 7.29 (dd, J = 3.8, 0.7 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 6.96 (td, J = 4.8, 0.6 Hz, 1H), 6.87 (d, J = 3.5 Hz, 1H), 6.43 (dd, J = 3.8, 0.5 Hz, 1H), 4.15 (d, J = 15.8 Hz, 1H), 4.05 (d, J = 15.9 Hz, 1H), 2.00 (s, 3H), 1.39 (s, 9H). MS (ES) *m/z* 450 ($[M + H]^+$, 100%). Anal. Calc. For $C_{24}H_{23}N_3O_4S$: C, 64.13, H, 5.16, N, 9.35. Found: C, 63.69, H, 5.10, N, 9.14.

Example 2

5-[5-Methyl-2-oxo-5-(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile

[0068] A neat *tert*-butyl 2-cyano-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate (0.25g, 0.56 mmol)

was placed in a flask under nitrogen and heated at 165 °C for 2 minutes until gas evolution ceased. The solid obtained was triturated in small amount of THF and collected on a filter to yield the title compound as a grayish solid (0.18g, 92%). ^{1}H-NMR (DMSO-d_6) δ 12.56 (s, 1H), 10.11 (s, 1H), 7.64-7.70 (m, 2H), 7.56 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 8.4 Hz, 1H), 6.98 (m, 2H), 6.85 (d, J = 3.5 Hz, 1H), 6.69 (d, J = 3.8 Hz, 1H), 4.13 (d, J = 15.8 Hz, 1H), 4.01 (d, J = 15.8 Hz, 1H), 2.07 (s, 3H). MS (ES) *m/z* 348 ([M - H]$^-$, 100%).

Example 3

1-Methyl-5-[5-methyl-2-oxo-5-(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile

[0069] To a solution of 5-[5-methyl-2-oxo-5-(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile (0.1g, 0.29 mmol) in anhydrous DMF (5mL) at rt under nitrogen was added potassium carbonate (1g, 7.23 mmol) and iodomethane (0.5 mL, 8 mmol). The reaction mixture was stirred for 2 h and treated with brine (30 mL). Ethyl acetate (50 mL) was added and organic layer separated, dried (Mg_2SO_4), and concentrated. The residue was purified by a flash chromatography on a silica gel column (hexane:ethyl acetate/2:1) to afford the title compound as a white solid (23mg, 22%): mp 197-198 °C; ^{1}H-NMR (DMSO-d_6) δ 10.21 (s, 1H), 7.55 (d, J = 4.8, 1H), 7.43 (dd, J = 8.4, 1.8 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 4.1 Hz, 1H), 6.98 (d, J = 4.9 Hz, 1H), 6.93 (d, J = 3.0 Hz, 1H), 6.31 (d, J = 4.1 Hz, 1H), 4.21 (d, J = 15.9 Hz, 1H), 4.07 (d, J = 15.9 Hz, 1H), 3.65 (s, 3H), 2.04 (s, 3H). MS (ES) *m/z* 362 ([M – H]$^-$, 100%).

Example 4

tert-Butyl 2-cyano-5-[5-methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate

1-(2-Amino-5-bromo-phenyl)-1-thiazol-2-yl-ethanol

[0070] Prepared from 1-(2-amino-5-bromo-phenyl)-ethanone and 2-thiazolyl lithium generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 7.70 (d, J = 3.3 Hz, 1H), 7.64 (d, J = 3.2 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H), 7.10 (dd, J = 8.5, 2.4 Hz, 1H), 6.92 (s, 1H), 6.55 (d, J = 8.5 Hz, 1H), 5.50 (s, 2H), 1.90 (s, 3H).

***N*-{4-Bromo-2-[1-hydroxy-1-(1,3-thiazol-2-yl)ethyl]phenyl}-2-chloroacetamide**

[0071] Prepared from amino-5-bromo-phenyl)- 1-thiazol-2-yl-ethanol and chloro acetyl chloride generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.88 (s, 1H), 7.91 (d, J = 8.7 Hz, 1H), 7.73 (m, 2H), 7.69, (d, J = 3.2 Hz, 1H), 7.59 (d, J = 2.3 Hz, 1H), 7.52 (dd, J = 8.7, 2.4 Hz, 1H), 4.33 (d, J = 5.3 Hz, 2H), 1.95 (s, 3H). Anal. Calc. For $C_{13}H_{12}BrClN_2O_2S$: C, 41.56, H, 3.22, N, 7.46. Found: C, 41.79, H, 3.21, N, 7.04.

7-Bromo-5-methyl-5-(1,3-thiazol-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(3H)-one

[0072] Prepared from *N*-{4-bromo-2-[1-hydroxy-1-(1,3-thiazol-2-yl)ethyl]phenyl}-2-chloroacetamide generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.12 (s, 1H), 7.79 (d, J = 3.24 Hz, 1H), 7.75 (d, J = 3.24 Hz, 1H), 7.53 (d, J = 2.2 Hz, 1H), 7.48 (dd, J = 8.6, 2.3 Hz, 1H), 7.06 (d, J = 8.5 Hz, 1H), 4.42 (d, J = 15.0 Hz, 1H), 4.20 (d, J = 15.0 Hz, 1H), 2.0 (s, 3H). MS (ES) *m/z* 337/339 ([M - H]$^-$, 100%). Anal. Calc. For $C_{13}H_{11}BrN_2O_2S$: C, 46.03, H, 3.27, N, 8.26. Found: C, 46.19, H, 3.38, N, 8.01.

***tert*-Butyl 2-[5-methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate**

[0073] Prepared from 7-bromo-5-methyl-5-(1,3-thiazol-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(3H)-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.12 (s, 1H), 7.75 (d, J = 3.3 Hz, 1H), 7.70 (d, J = 3.1 Hz, 1H), 7.23-7.32 (m, 3H), 7.09 (d, J = 8.2 Hz, 1H), 6.24 (t, J = 3.3 Hz, 1H), 6.19 (m, 1H), 4.42 (d, J = 15.0 Hz, 1H), 4.25 (d, J = 14.9 Hz, 1H), 2.01 (s, 3H), 1.31 (s, 9H). MS (ES)

m/z 424 ([M - H]$^-$, 100%).

[0074] *tert*-Butyl 2-cyano-5-[5-methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate was prepared from *tert*-butyl 2-[5-methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.22 (s, 1H), 7.73 (d, *J* = 3.2 Hz, 1H), 7.71 (d, *J* = 3.1 Hz, 1H), 7.39(d, *J* = 2.3 Hz, 1H), 7.32 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.19 (d, *J* = 4.1 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.42 (d, *J* = 4.2 Hz, 1H), 4.42 (d, *J* = 15.0 Hz, 1H), 4.25 (d, *J* = 14.9 Hz, 1H), 2.02 (s, 3H), 1.32 (s, 9H). MS (ES) *m/z* 449 ([M - H]$^-$, 100%).

Example 5

5-[5-Methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile

[0075] Prepared from *tert*-butyl 2-cyano-5-[5–methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate generally according to the procedure of example 2. ^{1}H-NMR (DMSO-d_6) δ 12.65 (s, 1H), 10.12 (s, 1H), 7.78 (d, *J* = 1.9 Hz, 1H), 7.75 (d, *J* = 3.2 Hz, 1H), 7.71 (d, *J* = 3.3 Hz, 1H), 7.64 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 1H), 6.97 (d, *J* = 3.9 Hz, 1H), 6.65 (d, *J* = 3.9 Hz, 1H), 4.37 (d, *J* = 14.9 Hz, 1H), 4.15 (d, *J* = 14.8 Hz, 1H), 2.10 (s, 3H). MS (ES) *m/z* 349 ([M - H]$^-$, 100%).

Example 6

tert-Butyl 2-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate

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

[0076] 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 ($MgSO_4$). 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; ^{1}H-NMR ($CDCl_3$) 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).

N-[4-Bromo-2-(1-hydroxy-1-methyl-ethyl)-phenyl]-2-chloro-acetamide

[0077] Prepared from 2-(2-amino-5-bromophenyl)propan-2-ol and chloro acetyl chloride generally according to the procedure described in example 1. An off-white solid: mp 133-134 °C. ^{1}H-NMR (DMSO-d_6) δ 11.21 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.46 (dd, J = 8.6, 2.3 Hz, 1H), 7.44 (d, J = 2.3 Hz, 1H), 6.28 (s, 1H), 4.43 (s, 2H), 1.53 (s, 6H).

7-Bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one

[0078] Prepared from N-[4-bromo-2-(1-hydroxy-1-methyl-ethyl)-phenyl]-2-chloro-acetamide generally according to the procedure described in example 1. An off-white solid: mp 120-121 °C. ^{1}H-NMR (DMSO-d_6) δ 10.01 (s, 1 H), 7.46 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 8.6, 2.3 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 4.23 (s, 2H), 1.53 (s, 6H).

[0079] *tert*-Butyl 2-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate was prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.96 (s, 1H), 7.32 (m, 1H), 7.23 (m, 1H), 7.15 (d, J = 8.24 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.25 (m, 2H), 4.23 (s, 2H), 1.55 (s, 6H), 1.36 (s, 9H); MS (ES) m/z 357 ($[M + H]^+$, 100%).

Example 7

tert-Butyl-2-cyano-5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate

[0080] Prepared from *tert*-butyl-2-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.03 (s, 1H), 7.35 (d, J = 1.79 Hz, 1H), 7.31 (d, J = 3.8 Hz, 1H), 7.23 (dd, J = 1.79, 8.31 Hz, 1H), 7.12 (d, J = 8.36 Hz, 1H), 6.44 (d, J = 3.81 Hz, 1H), 4.25 (s, 2H), 1.55 (s, 6H), 1.39 (s, 9H).

Example 8

5-(5,5-Dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile

[0081] Prepared from *tert*-butyl-2-cyano-5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate generally according to the procedure of example 2.

^{1}H-NMR (DMSO-d_6) δ 12.58 (s, 1H), 9.98 (s, 1H), 7.63 (d, J = 1.65 Hz, 1H), 7.55 (dd, J = 1.62, 8.45 Hz, 1H), 7.12 (d, J = 8.43 Hz, 1H), 6.99 (m, 1H), 6.70 (m, 1H), 4.23 (s, 2H), 1.60 (s, 6H); MS (ES) *m/z* 280 ([M - H]$^-$, 100%)

Example 9

5-(5,5-Dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile

[0082] Prepared from 5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile and iodomethane generally according to the procedure of example 3. ^{1}H-NMR (DMSO-d_6) δ 10.06 (s, 1H), 7.40 (d, J = 1.87 Hz, 1H), 7.34 (dd, J = 1.87, 8.32 Hz, 1H), 7.20 (d, J = 8.38 Hz, 1H), 7.03 (d, J = 3.99 Hz,1H), 6.35 (d, J = 4.00, 1H), 4.27 (s, 2H), 3.71 (s, 3H), 1.58 (s, 6H); MS

(FI) *m/z* 294 ([M - H]$^-$, 100%)

Example 10

5-(5,5-Dimethyl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile

[0083] To a solution of 5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile (0.4g, 1.4 mmol) in a mixture of toluene (20 mL) and THF (10mL, help to dissolve the starting material) was added at rt under nitrogen the Lawesson's reagent (0.29g, 0.71 mmol). The mixture was heated at 100 °C for 10 minutes, cooled to rt, and concentrated. The residue was purified by a flash chromatography on silica gel column (hexane:THF/4:1) to give the title compound as a yellowish solid (0.25g, 60%). ^{1}H-NMR (DMSO-d_6) δ 12.66 (s, 1H), 11.96 (s, 1H), 7.69 (d, J = 1.49 Hz, 1H), 7.64 (dd, J = 1.48, 8.44 Hz, 1H), 7.35 (d, J = 8.51 Hz, 1H), 7.01 (m, 1H), 6.79 (m, 1H), 4.49 (s, 2H), 1.60 (s, 6H); MS (FI) *m/z* 296 ([M - H]$^-$, 100%)

Example 11

tert-Butyl 2-cyano-5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate

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

[0084] To a solution of 1-(2-amino-5-bromo-phenyl)-ethanone (2.4g, 11.2 mmol) in anhydrous methanol (50 mL) was added sodium borohydride (1g, 26 mmol) at rt under nitrogen. The mixture was stirred for 1 h, poured onto ice water, and extracted with ethyl acetate (3x30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to yield the title compound as an off-white solid (2.1 g, 86%): mp 95-96 °C.

N-[4-bromo-2-(1-hydroxyethyl)phenyl]-2-chloroacetamide

[0085] Prepared by from 1-(2-amino-5-bromo-phenyl)-ethanol and chloroacetyl chloride generally according to the procedure described in Example 1. ^{1}H-NMR (DMSO-d_6) δ 10.11 (s, 1H), 7.64 (d, J = 8.63 Hz, 1H), 7.57 (d, J = 2.31 Hz, 1H), 7.44 (dd, J = 2.34, 8.57 Hz, 1H), 5.77 (d, J = 3.88 Hz, 1H), 4.93-4.89 (m, 1H), 4.35, (s, 2H), 1.31 (d, J = 6.45 Hz, 3H); MS (ES) *m/z* 290/292/294 ([M - H]$^-$, 100%).

7-Bromo-5-methyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one

[0086] Prepared from *N*-[4-bromo-2-(1-hydroxyethyl)phenyl]-2-chloroacetamide generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.25 (s, 1H), 7.44 (dd, J = 2.19, 8.53 Hz, 1H), 7.36 (d, J = 2.09 Hz, 1H), 7.07 (d, J = 8.54 Hz, 1H), 4.79 (q, J = 6.47 Hz, 1H), 4.45 (d, J = 16.43 Hz, 1H), 4.33 (d, J = 16.46 Hz, 1H), 1.49 (d, J = 6.5 Hz, 3H); MS (ES) *m/z* 256/258 ([M + H]$^+$, 40%); Anal. Calc. For $C_{10}H_{10}BrNO_2$: C:46.90 H:3.94 N:5.47. Found: C:49.96 H:4.01 N:5.38.

***tert*-Butyl-2-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate**

[0087] Prepared from 7-bromo-5-methyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.22 (s, 1H), 7.33 (m, 1H), 7.22 (dd, J = 1.83, 8.18 Hz, 1H), 7.15-7.09 (m, 2H), 6.72-6.23 (m, 2H), 4.81 (q, J = 6.53 Hz, 1H), 4.43 (d, J = 16.17 Hz, 1H), 4.32 (d, J = 16.22 Hz, 1H), 1.51 (d, J = 6.48 Hz, 3H), 1.34 (s, 9H); MS (ES) *m/z* 341 ([M - H]$^-$, 100%)

[0088] *tert*-Butyl-2-cyano-5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate was prepared from *tert*-butyl-2-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate according to the cyanation procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.30 (s, 1H), 7.37-7.25 (m, 3H), 7.16 (d, J = 8.26 Hz, 1H), 6.46 (d, J = 3.77 Hz, 1H), 4.81 (q, J = 6.14 Hz, 1H), 4.47 (d, J = 16.42 Hz, 1H), 4.36 (d, J = 16.44 Hz, 1H), 1.51 (d, J = 6.48 Hz, 3H), 1.37 (s, 9H); MS (ES) *m/z* 366 ([M - H]$^-$, 100%).

Example 12

5-(5-Methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile

[0089] Prepared from. *tert*-butyl-2-cyano-5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate generally according to the procedure of example 2. ^{1}H-NMR (DMSO-d_6) δ 12.61 (s, 1H), 10.25 (s, 1H), 7.62-7.58 (m, 2H), 7.16 (d, J = 8.26 Hz, 1H), 6.99 (m, 1H), 6.68 (m, 1H), 4.82 (q, J = 6.52 Hz, 1H), 4.47 (d, J = 16.41 Hz, 1H), 4.35 (d, J = 16.43 Hz, 1H), 1.58 (d, J = 6.48 Hz, 3H); MS (FI) *m/z* 266 ([M - H]$^-$, 100%).

Example 13

1-Methyl-5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile

[0090] Prepared from 5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile generally according to the procedure of example 3. ^{1}H-NMR (DMSO-d_6) δ 10.32 (s, 1H), 7.42-7.39 (m, 1H), 7.32 (bs, 1H), 7.23 (d, J = 8.25 Hz, 1H), 7.03 (d, J = 3.59 Hz, 1H), 6.35 (d, J = 3.61 Hz, 1H), 4.85 (q, J = 6.51 Hz, 1H), 4.49 (d, J = 16.54 Hz, 1H), 4.37 (d, J = 16.55 Hz, 1H), 3.71 (s, 3H), 1.54 (d, J = 6.47 Hz, 3H); MS (FI) *m/z* 280 ([M - H]$^-$, 100%).

Example 14

tert-Butyl 2-cyano-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate

1-(2-amino-5-bromophenyl)-1-phenylethanol

[0091] Prepared from 1-(2-amino-5-bromo-phenyl)-ethanone and phenyl magnesium bromide generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 7.32-7.16 (m, 6H), 7.11 (dd, J = 2.03, 8.48 Hz, 1H), 6.49 (d,

J = 8.55 Hz, 1H), 6.02 (s, 1H), 5.16 (s, 2H), 1.74 (s, 3H); MS (ES) *m/z* 274/276 ([M + H]$^+$, 100%); Anal. Calc. For $C_{14}H_{14}BrNO$: C: 57.55 H:4.83 N:4.79. Found: C:57.67 H:4.83 N:4.79.

_N_-[4-Bromo-2-(1-hydroxy-1-phenylethyl)phenyl]-2-chloroacetamide

[0092] Prepared from 1-(2-amino-5-bromophenyl)-1-phenylethanol and chloroacetyl chloride according to the acylation procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.42 (s, 1H), 7.93 (d, J = 8.71 Hz, 1H), 7.64 (d, J = 1.86 Hz, 1H), 7.52 (dd, J = 1.77, 8.71 Hz, 1H), 7.33-7.18 (m, 5H), 6.99 (s, 1H), 4.17 (d, J = 14.92 Hz, 1H), 3.99 (d, J = 14.98 Hz, 1H), 1.84 (s, 3H); MS (ES) *m/z* 366/368/370 ([M - H]$^-$, 100%); Anal. Calc. For $C_{16}H_{15}BrClNO_2$: C:52.13 H:4.10 N:3.80. Found: C:52.18 H:4.05 N:3.77.

7-Bromo-5-methyl-5-phenyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one

[0093] Prepared from *N*-[4-bromo-2-(1-hydroxy-1-phenylethyl)phenyl]-2-chloroacetamide according to the ring closure procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.00 (s, 1H), 7.53-7.47 (m, 2H), 7.36-7.27 (m, 3H), 7.25-7.20 (m, 2H), 7.04 (d, J = 8.52 Hz, 1H), 4.22 (d, J = 14.82 Hz, 1H), 3.98 (d, J = 14.82 Hz, 1H), 1.88 (s, 3H); MS (ES) *m/z* 332/334 ([M + H]$^+$, 100%)

***tert*-Butyl-2-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate**

[0094] Prepared from 7-bromo-5-methyl-5-phenyl-1,5-dihydro-4,1-benzoxazepin-2(3H)-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.94 (s, 1H), 7.34-7.23 (m, 8H), 7.06 (d, J = 7.98 Hz, 1H), 6.27 (d, J = 2.44 Hz, 2H), 4.19 (d, J = 14.36 Hz, 1H), 3.99, (d, J = 14.38 Hz, 1H), 1.86 (s, 3H), 1.36 (s, 9H); MS (ES) *m/z* 419 ([M + H]$^+$, 30%).

[0095] *tert*-Butyl-2-cyano-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate was prepared from *tert*-butyl-2-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-

carboxylate and chlorosulfonyl isocyanate according to the cyanation procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.02 (s, 1H), 7.42-7.38 (m, 2H), 7.32-7.10 (m, 7H), 6.49 (d, J = 3.80 Hz, 1H), 4.20 (d, J = 14.63 Hz, 1H), 3.99, (d, J = 14.41 Hz, 1H), 1.87 (s, 3H), 1.39 (s, 9H); MS (ES) *m/z* 442 ([M - H]$^-$, 100%).

Example 15

5-(5-Methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile

[0096] Prepared from *tert*-butyl-2-cyano-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate generally according to the procedure of example 2. ^{1}H-NMR (DMSO-d_6) δ 12.64 (s, 1H), 9.98 (s, 1H), 7.74-7.68 (m, 2H), 7.35-7.22 (m, 5H), 7.13 (d, J = 8.35 Hz, 1H), 7.00 (m, 1H), 6.72 (m, 1H), 4.19 (d, J = 14.73 Hz, 1H), 3.95, (d, J = 14.77 Hz, 1H), 1.97 (s, 3H); MS (ES) *m/z* 342 ([M - H]$^-$, 100%).

Example 16

1-Methyl-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile

[0097] Prepared from 5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile generally according to the procedure of example 3. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 7.48-7.42 (m, 2H), 7.36-7.19 (m, 6H), 7.03 (d, J = 4.03 Hz, 1H), 6.35 (d, J = 4.06 Hz, 1H), 4.27 (d, J = 14.95 Hz, 1H), 3.68 (d, J = 14.91 Hz, 1H), 3.68, (s, 3H), 1.94 (s, 3H); MS (ES) *m/z* 358 ([M + H]$^+$, 100%).

Example 17

tert-Butyl 2-cyano-5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate

1-(2-Amino-5-bromophenyl)-1-(2-furyl)ethanol

[0098] Prepared from 1-(2-amino-5-bromo-phenyl)-ethanone and 2-furyl lithium generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 7.6 (m, 1H), 7.08 (dd, J = 2.73, 10.91 Hz, 1H), 6.8 (d, J = 2.73 Hz, 1H), 6.56 (d, J = 8.18 Hz, 1H), 6.45-6.38 (m, 2H), 6.14 (s, 1H), 5.3 (s, 2H), 1.76 (s, 3H); MS (ES) *m/z* 280/282 ([M - H]$^-$, 30%).

***N*-{4-Bromo-2-[1-(2-furyl)-1-hydroxyethyl]phenyl}-2-chloroacetamide**

[0099] Prepared from 1-(2-amino-5-bromophenyl)-1-(2-furyl)ethanol and chloroacetyl chloride generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.84 (s, 1H), 8.07 (d, J = 8.76 Hz. 1H), 7.57 (bs, 1H), 7.50 (dd, J = 2.33, 8,76 Hz, 1H), 7.12 (s, 1H), 7.09 (d, J = 2.31 Hz, 1H), 6.46-6.42 (m, 2H), 4.35 (d, J = 1.69 Hz, 2H), 1.85 (s, 3H); MS (ES) *m/z* 356/358 ([M - H]$^-$, 100%).

7-Bromo-5-(2-furyl)-5-methyl-1,5-dihydro-4,1-benzoxazepin-2(*3H*)-one

[0100] Prepared from *N*-{4-bromo-2-[1-(2-furyl)-1-hydroxyethyl]phenyl}-2-chloroacetamide generally according to the ring closure procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.15 (s, 1H), 7.73 (bs, 1H), 7.47 (dd, J = 4.29, 8,57 Hz, 1H), 7.23 (d, J = 4.29 Hz, 1H), 7.13 (d, J = 8.57 Hz, 1H), 6.49 (m, 1H), 6.30 (d, J = 4.29 Hz, 1H), 4.14 (d, J = 16.67 Hz, 1H), 4.03 (d, J = 16.67 Hz, 1H), 1.87 (s, 3H).

***tert*-Butyl-2-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate**

[0101] Prepared from 7-bromo-5-(2-furyl)-5-methyl-1,5-dihydro-4,1-benzoxazepin-2(*3H*)-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.10 (s, 1H), 7.70 (bs, 1H), 7.30-7.23 (m, 2H), 7.17-7.14 (m, 1H), 7.02 (m, 1H), 6.43 (m, 1H), 6.28-6.17 (m, 3H), 4.08 (m, 2H), 1.88 (s, 3H), 1.36 (s, 9H); MS (ES) *m/z* 407 ([M - H]$^-$, 30%).

[0102] *tert*-Butyl-2-cyano-5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate was prepared from *tert*-butyl-2-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate generally according to the cyanation procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.17 (s, 1H), 7.71 (d, J = 1.46 Hz, 1H), 7.34 (dd, J = 1.93, 8.34, Hz, 1H), 7.28 (d, J = 3.79 Hz, 1H), 7.21 (d, J = 8.42 Hz, 1H), 7.16 (d, J = 1.94 Hz, 1H), 6.44-6.41 (m, 2H), 6.24 (d, J = 3.18 Hz, 1H), 4.13 (d, J = 16.14 Hz, 1H), 4.01 (d, J = 16.11 Hz, 1H), 1.89 (s, 3H), 1.38 (s, 9H); MS (ES) *m/z* 434 ([M + H]$^+$, 100%)

Example 18

5-[5-(2-Furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile

[0103] Prepared from *tert*-butyl-2-cyano-5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate generally according to the procedure of example 2. ^{1}H-NMR (DMSO-d_6) δ 12.56 (s, 1H), 10.11 (s, 1H), 7.74 (m, 1H), 7.65 (dd, J = 1.99, 8.46 Hz, 1H), 7.56 (d, J = 1.95 Hz, 1H), 7.21 (d, J = 8.56 Hz, 1H), 6.97 (dd, J = 2.17, 3.85 Hz, 1H), 6.65 (dd, J = 2.51, 3.79 Hz, 1H), 6.45 (dd, J = 1.89, 3.32 Hz, 1H), 6.21 (d, J = 3.3 Hz, 1H), 4.12 (d, J = 16.18 Hz, 1H), 3.96 (d, J = 16.22, 1H), 1.97 (s, 3H); MS (ES) *m/z* 334 ([M + H]$^+$, 100%).

Example 19

5-[5-(2-Furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile

[0104] Prepared from *tert*-butyl-2-cyano-5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate generally according to the procedure of example 3. ^{1}H-NMR (DMSO-d_6) δ 10.21 (s, 1H), 7.72 (d, J = 1.16 Hz, 1H), 7.44 (dd, J = 1.99, 8.38 Hz, 1H), 7.29 (d, J = 8.45 Hz, 1H), 7.21 (d, J = 1.97 Hz, 1H), 7.01 (d, J = 4.07 Hz, 1H), 6.45 (dd, J = 1.79, 3.26 Hz, 1H), 6.30 (m,

2H), 4.16 (d, J = 16.12 Hz, 1H), 4.06 (d, J = 16.13 Hz, 1H), 3.64 (s, 3H), 1.93 (s, 3H); MS (ES) *m/z* 348 ([M + H]$^+$, 100%).

Example 20

tert-Butyl 2-cyano-5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate

1-(2-amino-5-bromophenyl)-1-thien-3-ylethanol

[0105] Prepared from 1-(2-amino-5-bromo-phenyl)-ethanone and 3-thienyllithium generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d$_6$) δ 7.43 (dd, J = 2.98, 4.98 Hz, 1H), 7.33 (dd, J = 1.27, 2.94 Hz, 1H), 7.07 (dd, J = 2.37, 8.47 Hz, 1H), 7.04 (d, J = 2.33 Hz, 1H), 6.92 (dd, J = 1.26, 4.98 Hz, 1H), 6.52 (d, J = 8.38 Hz, 1H), 5.99 (bs, 1H), 5.32 (bs, 2H), 1.78 (s, 3H).

N-{4-Bromo-2-[1-hydroxy-1-(3-thienyl)ethyl]phenyl}-2-chloroacetamide

[0106] Prepared from 1-(2-amino-5-bromophenyl)-1-thien-3-ylethanol and chloroacetyl chloride generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d$_6$) δ 10.80 (s, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.52-7.43 (m, 2H), 7.40 (m, 2H), 7.00 (s, 1H), 6.93 (m, 1H), 4.30 (d, J = 15.00 Hz, 1H), 4.23 (d, J = 15.00 Hz, 1H), 1.90 (s, 3H); MS (ES) *m/z* 372/374/376 ([M - H]$^-$, 100%).

7-Bromo-5-methyl-5-(3-thienyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0107] Prepared from *N*-{4-bromo-2-[1-hydroxy-1-(3-thienyl)ethyl]phenyl}-2-chloroacetamide generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d$_6$) δ 10.1 (s, 1H), 7.56 (dd, J = 2.95, 5.05 Hz, 1H), 7.45 (dd, J = 2.32, 8.65 Hz, 1H), 7.30 (d, J = 2.28 Hz, 1H), 7.22 (dd, J = 1.31, 2.9 Hz, 1H), 7.11 (d, J = 8.71 Hz, 1H), 7.05 (dd, J = 1.31, 5.05 Hz, 1H), 4.17 (d, J = 16.36 Hz, 1H), 4.01 (d, J = 16.36 Hz, 1H), 1.91 (s, 3H); MS (ES) *m/z* 336/338 ([M - H]$^-$, 100%).

tert-Butyl-2-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate

[0108] Prepared from 7-bromo-5-methyl-5-(3-thienyl)-1,5-dihydro-4,1-benzoxazepin-2(*3H*)-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.03 (s, 1H), 7.53 (dd, J = 2.95, 5.04 Hz, 1H), 7.30 (dd, J = 1.78, 3.22 Hz, 1H), 7.26-7.21 (m, 2H), 7.14-7.12 (m, 2H), 7.04 (dd, J = 1.24, 5.02 Hz, 1H), 6.25-6.20 (m, 2H), 4.13 (d, J = 15.58 Hz, 1H), 4.02 (d, J = 15.60 Hz, 1H), 1.90 (s, 3H), 1.37 (s, 9H); MS (ES) *m/z* 425 ([M + H]$^+$, 100%).

[0109] *tert*-Butyl-2-cyano-5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate was prepared from *tert*-butyl-2-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate and chlorosulfonyl isoyanate generally according to the cyanation procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.11 (s, 1H), 7.54 (dd, J = 2.96, 5.02 Hz, 1H), 7.33 (dd, J = 1.91, 8.30 Hz, 1H), 7.29 (d, J = 3.78 Hz, 1H), 7.26-7.17 (m, 3H), 7.05 (dd, J = 1.27, 5.01 Hz, 1H), 6.43 (d, J = 3.82 Hz, 1H), 4.14 (d, J = 15.79 Hz, 1H), 4.01 (d, J = 15.78 Hz, 1H), 1.91 (s, 3H), 1.39 (s, 9H); MS (ES) *m/z* 448 ([M - H]$^-$, 20%).

Example 21

5-[5-Methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile

[0110] Prepared from *tert*-butyl-2-cyano-5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate generally according to the procedure of example 2. ^{1}H-NMR (DMSO-d_6) δ 12.58 (s, 1H), 10.06 (s, 1H), 7.66 (m, 2H), 7.57 (dd, J = 2.98, 5.04 Hz, 1H), 7.19 (m, 1H), 7.14 (dd, J = 1.22, 2.88 Hz, 1H), 7.08 (dd, J = 1.23, 5.03 Hz, 1H), 6.98 (dd, J = 2.07, 3.81 Hz, 1H), 6.67 (dd, 2.51, 3.82 Hz, 1H), 4.12 (d, J = 15.85 Hz, 1H), 3.95 (d, J = 15.85 Hz, 1H), 1.99 (s, 3H); MS (ES) *m/z* 348 ([M - H]$^-$, 20%).

Example 22

1-Methyl-5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-

7-yl]-1*H*-pyrrole-2-carbonitrile

[0111] Prepared from 5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile and iodomethane generally according to the procedure of example 3. ^{1}H-NMR (DMSO-d_6) δ 10.16 (s, 1H), 7.56 (dd, J = 2.92, 5.02 Hz, 1H), 7.42 (dd, J = 1.90, 8.42 Hz, 1H), 7.28-7.23 (m, 3H), 7.09 (dd, J = 1.06, 4.83 Hz, 1H), 7.01 (d, J = 4.06 Hz, 1H), 6.30 (d, J = 4.08 Hz, 1H), 4.20 (d, J = 15.95 Hz, 1H), 4.05 (d, J = 15.93 Hz, 1H), 3.65 (s, 3H), 1.96 (s, 3H); MS (ES) *m/z* 362 ([M - H]$^-$, 100%).

Example 23

5'-[(2-Oxo-1,2,3,5,-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-(5-spiro-1"-cyclohexane)]-1*H*-pyrrole-2'-carbonitrile

***N*-[4-bromo-2-(1-hydroxycyclohexyl)phenyl]-2-chloroacetamide**

[0112] 1-(2-Amino-5-bromo-phenyl)-cyclohexanol was prepared generally according to the procedure described in Example 6 from 2-amino-5-bromobenzoic acid and pentamethylenebis(magnesium bromide). The crude product was used in the next step without extensive purification and characterization. The title compound was prepared from 1-(2-amino-5-bromo-phenyl)-cyclohexanol and chloroacetyl chloride generally according to the procedure of Example 1. ^{1}H-NMR ($CDCl_3$) δ 10.87 (s, 1H), 8.19 (d, J = 8.3Hz, 1H), 7.41 (m, 2H), 4.15 (s, 2H), 2.27 (s, 1H), 2.07 (d, J = 7.3 Hz, 2H), 1.77 (m, 6H), 1.38 (m, 2H); MS (ES) *m/z* 344 (M-H)$^-$; Anal. Calc. For $C_{14}H_{17}BrClNO_2$: C, 48.51, H, 4.94, N, 4.04. Found: C, 48.63, H, 4.86, N, 4.00.

7-Bromo-1,5-dihydro-(5-spiro-1'-cyclohexane)-benzo[*e*][1,4]oxazepin-2-one

[0113] Prepared from *N*-[4-bromo-2-(1-hydroxycyclohexyl)phenyl]-2-chloroacetamide generally according to the procedure of Example 1. ^{1}H-NMR ($CDCl_3$) δ 7.80 (br s, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.29 (dd, J = 8.3, 2.4 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 2.08 (d, J = 12.7 Hz, 2H), 1.77 (m, 6H), 1.34 (m, 2H), 1.25 (s, 2H); MS (ES) *m/z* 310 (M+H)$^+$; Anal Calc. For $C_{14}H_{16}BrNO_2$: C, 54.21, H, 5.20,

N, 4.52. Found: C, 54.20, H, 5.44, N, 4.20.

2'-[(2-Oxo-1,2,3,5,-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-(5-spiro-1"-cyclohexane)]-pyrrole-1'-carboxylic acid *tert*-butyl ester

[0114] Prepared from 7-bromo-1,5-dihydro-(5-spiro-1'-cyclohexane)-benzo[*e*][1,4]oxazepin-2-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the procedure of Example 1. ^{1}H-NMR ($CDCl_3$) δ 7.78 (s, 1H), 7.33 (m, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.18 (dd, J = 7.9, 1.6 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.22 (m, 1H), 6.18 (m, 1H), 4.34 (s, 2H), 2.11 (d, J = 13.5 Hz, 2H), 1.82 (m, 6H), 1.41 (s, 9H), 1.28 (m, 2H).

2'-Cyano-5'-[(2-oxo-1,2,3,5,-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-(5-spiro-1"-cyclohexane)]-pyrrole-1'-carboxylic acid *tert*-butyl ester

[0115] Prepared from 2'-[(2-oxo-1,2,3,5,-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-(5-spiro-1"-cyclohexane)]-pyrrole-1'-carboxylic acid *tert*-butyl ester and chlorosulfonyl isocyanate generally according to the procedure of Example 1. ^{1}H-NMR (DMSO-d_6) δ 9.94 (s, 1H), 7.39 (s, 1H), 7.31 (d, J = 3.4 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 7.10 (d, J = 8.8 Hz, 1H), 6.44 (d, J = 3.9 Hz, 1H), 4.20 (s, 2H), 1.94 (d, J = 13.1 Hz, 2H), 1.87 (m, 2H), 1.62 (m, 4H), 1.38 (s, 9H), 1.35 (m, 2H); MS (ES) *m/z* 420 (M-H)$^-$.

[0116] The title compound was prepared from 2'-cyano-5'-[(2-oxo-1,2,3,5,-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-(5-spiro-1"-cyclohexane)]-pyrrole-1'-carboxylic acid *tert*-butyl ester generally according to the procedure of Example 1. ^{1}H-NMR (DMSO-d_6) δ 12.59 (s, 1H), 9.88 (s, 1H), 7.67 (d, J = 2.7 Hz, 1H), 7.57 (dd, J = 8.2, 2.7 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.98 (d, J = 5.5 Hz, 1H), 6.79 (d, J = 2.7 Hz, 1H), 4.20 (s, 2H), 2.00 (m, 4H), 1.70 (m, 6H); MS (ES) *m/z* 320 (M-H)$^-$.

Example 24

tert-Butyl 2-cyano-5-[2-oxo-5,5-di(2-thienyl)-,1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate

(2-Amino-5-bromophenyl)(dithien-2-yl)methanol

[0117] Prepared from methyl 2-amino-5-bromobenzoate and 2-thienyllithium using the procedure similar to example 6. ^{1}H-NMR ($CDCl_3$) δ 7.35 (dd, J = 5.3, 1.1 Hz, 2H), 7.26 (dd, J = 8.4, 2.3 Hz, 1H), 6.98 (m, 2H), 6.82 (d, J = 2.3 Hz, 1H), 6.79 (m, 2H), 6.62 (d, J = 8.4 Hz, 1H), 5.45 (br s, 1H), 3.86 (br s, 2H); Anal. Calc. For $C_{15}H_{12}BrNOS_2$: C, 49.18, H, 3.30, N, 3.82. Found: C, 49.62, H, 3.47, N, 3.60.

2-Bromo-*N*-{4-bromo-2-[hydroxy(dithien-2-yl)methyl]phenyl}acetamide

[0118] Prepared from (2-amino-5-bromophenyl)(dithien-2-yl)methanol and bromoacetyl chloride using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.22 (s, 1H), 8.42 (s, 1H), 8.05 (d, J = 9.0 Hz, 1H) 7.59 (m, 3H), 7.05 (m, 2H), 6.87 (m, 2H), 6.78 (d, J = 3 Hz, 1H), 3.92 (s, 2H); MS (ES) *m/z* 484 $(M-H)^-$.

7-Bromo-5,5-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0119] Prepared from 2-bromo-N-{4-bromo-2-[hydroxy(dithien-2-yl)methyl]phenyl}acetamide using the similar procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 8.08 (br s, 1H), 7.40 (d, J = 4.0 Hz, 2H), 7.37 (d, J = 2.1 Hz, 1H), 7.14 (d, J = 2.2 Hz, 1H), 6.99 (m, 2H), 6.89 (d, J = 3.6 Hz, 2H), 6.83 (d, J = 8.5 Hz, 1H), 4.35 (s, 1H); MS (ES) *m/z* 404 $(M-H)^-$; Anal Calc. For $C_{17}H_{12}BrNO_2S_2$: C, 50.25, H, 2.98, N, 3.45. Found: C, 50.57, H, 3.01, N, 3.25.

***tert*-Butyl 2-[2-oxo-5,5-di(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate**

[0120] Prepared from 7-bromo-5,5-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 7.70 (br s, 1H), 7.38 (m, 2H), 7.27 (m, 2H), 7.09 (d, J = 1.5 Hz, 1H), 6.96 (m, 4H), 6.88 (d, J = 9.0 Hz, 1H), 6.19 (t, J = 3.0 Hz, 1H), 6.06 (m, 1H), 4.36 (s, 2H), 1.41 (s, 9H); MS (ES) *m/z* 491$(M-H)^-$; Anal. Calc. For $C_{26}H_{24}N_2O_4S_2$: C, 63.39, H, 4.91, N, 5.69. Found: C, 62.59, H, 4.99, N, 5.35.

[0121] The title compound was prepared from *tert*-butyl 2-[2-oxo-5,5-di(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate generally according to the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 7.87 (br s, 1H), 7.38 (dd, J = 5.0, 1.2 Hz, 2H), 7.25 (dd, J = 8.4, 2.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.96 (m, 6H), 6.08 (d, J = 3.7 Hz, 1H), 4.37 (s, 2H), 1.50 (s, 9H); MS (ES) *m/z* 516 $(M-H)^-$.

Example 25

5-(2-Oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile

[0122] Prepared from *tert*-butyl 2-cyano-5-[2-oxo-5,5-di(2-thienyl)-,1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate generally according to the procedure of example 2. ^{1}H-NMR (DMSO-d_6) δ 12.57 (s, 1H), 10.21 (s, 1H), 7.66 (m, 1H), 7.62 (dd, J = 5.0, 1.2 Hz, 2H), 7.42 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H) 7.05 (m, 4H), 6.93 (d, J = 3.8 Hz, 1H), 6.41 (d, J = 3.9 Hz, 1H), 4.15 (s, 2H); MS (ES) *m/z* 418 $(M+H)^+$.

Example 26

1-Methyl-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile

[0123] Prepared from 5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile and iodomethane generally according to the procedure of example 3. ^{1}H-NMR (DMSO-d_6) δ 10.33 (s, 1H), 7.63 (dd, J = 5.0, 1.1 Hz, 2H), 7.50 (dd, J = 8.3, 2.1 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.03 (m, 4H), 6.89 (dd, J = 3.6, 1.1 Hz, 2H), 6.18 (d, J = 4.0 Hz, 1H), 4.25 (s, 2H), 3.49 (s, 3H); MS (ES) *m/z* 432 $(M+H)^+$.

Example 27

3-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-

fluorobenzonitrile

[0124] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-cyano-5-fluorophenyl boronic acid generally according to the coupling procedure described in example 1. A white solid: mp 238-239 °C; ^{1}H NMR (DMSO-d_6): δ 10.1 (s, 1H), 8.14 (t, J = 1.5 Hz, 1H), 7.98 (m, 1H), 7.80 (m, 1H), 7.69 (d, J = 1.9 Hz, 1H), 7.64 (dd, J = 8.3, 2.0 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 4.27 (s, 2H), 1.63 (s, 6H). MS *m/z* 309 ([M-H]-); Anal. calcd for $C_{18}H_{15}FN_2O_2$: C:69.67 H:4.87 N:9.03 Found: C:69.51 H:4.63 N:9.07

Example 28

7-(3-Chlorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0125] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-chlorophenyl boronic acid generally according to the coupling procedure described in example 1. A white solid: mp 152-153 °C; ^{1}H NMR (DMSO-d_6): δ 10.02 (s, 1H), 7.76 (s, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.38-7.58 (m, 4H), 7.18 (d, J = 8.3 Hz, 1H), 4.28 (s, 2H), 1.64 (s, 6H); MS *m/z* 300, ([M-H]-); Anal. calcd for $C_{17}H_{16}ClNO_2$: C:67.66 H:5.34 N:4.64 Found: C:66.79 H:5.23 N:4.50.

Example 29

7-(3-Chlorophenyl)-3,5,5-trimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

7-Bromo-3,5,5-trimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0126] Prepared from 2-(2-amino-5-bromophenyl)propan-2-ol and 2-bromopropylonyl chloride in two steps generally according to the procedure described in example 1. A white solid: ^{1}H NMR (DMSO-d_6): δ 9.88 (s, 1H), 7.48 (d, J = 2.3 Hz, 1H), 7.36 (dd, J = 8.6 , 2.3 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 4.34, (q, J = 6.4 Hz, 1H), 1.65 (s, 3H),1.39 (s, 3H), 1.18 (d, J = 6.5 Hz, 3H); MS (ESI) *m/z* 284/286 ([M+H]+); MS (ESI) *m/z* 282/284
([M-H]-); Anal. calcd for $C_{12}H_{14}BrNO_2$: C:50.72 H:4.97 N:4.93 Found: C:50.44

H:4.84 N:4.95.

[0127] The title compound was prepared from 7-bromo-3,5,5-trimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-chlorophenyl boronic acid generally according to the coupling procedure described in example 1. white solid: mp 169-170 °C; ^{1}H NMR (DMSO-d_6): δ 9.91 (s, 1H), 7.74 (d, J = 1.7 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.53 (dd, J = 8.4, 2.0 Hz, 1H), 7.46 (t, J = 7.7 Hz, 1H), 7.38, (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 4.37 (q, J = 6.5 Hz, 1H), 1.74 (s, 3H), 1.47 (s, 3H), 1.21 (d, J = 6.5 Hz, 3H). MS *m/z* 314/316 ([M-H]-). Anal. calcd for $C_{18}H_{18}ClNO_2$: C:68.46 H:5.75 N:4.44 Found: C: 68.32 H: 5.60 N: 4.24.

Example 30

5-[1,5-dimethyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-*H*-pyrrole-2-carbonitrile

[0128] Prepared from 5-[5-mthyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile and iodomethane generally according to the procedure described in example 3. A white solid: ^{1}H NMR (DMSO-d_6): δ 7.75 (d, J = 1.9 Hz, 1H), 7.71 (dd, J = 8.3, 1.9 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.50 (d, J = 8.3 Hz, 1H), 7.09 (d, J = 4.1 Hz, 1H), 6.52 (d, J = 4.1 Hz, 1H), 4.09 (m, 2H), 3.81 (s, 3H), 2.72 (s, 3H), 1.92 (s, 3H). MS *m/z* 379 ([M+H]+).

Example 31

tert-Butyl 2-cyano-5-(3,5,5-trimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate

tert-Butyl 2-(3,5,5-trimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate

[0129] Prepared from 7-bromo-3,5,5-trimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6):

δ 9.85 (s, 1H), 7.32 (m, 1H), 7.24 (d, J = 1.8 Hz, 1H), 7.13 (dd, J = 8.3, 1.9 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.20-6.27 (m, 2H), 4.32 (q, J = 6.4 Hz, 1H), 1.68 (s, 3H), 1.41 (s, 3H), 1.38 (s, 9H), 1.22 (d, J = 6.5 Hz, 3H). MS (ESI) *m/z* 371 ([M+H]+); MS (ESI) *m/z* 369 ([M-H]-); Anal. calcd for $C_{21}H_{26}N_2O_4$: C:68.09 H:7.07 N:7.56 Found: C:67.80 H:6.85 N:7.18.

[0130] The title compound was prepared from *tert*-butyl 2-(3,5,5-trimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate generally according to the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 9.92 (s, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.32 (d, J = 3.8 Hz, 1H), 7.25 (dd, J = 8.3, 1.9 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 5.94 (d, J = 3.8 Hz, 1H), 4.32 (q, J = 6.3 Hz, 1H), 1.65 (s, 3H), 1.41 (s, 3H), 1.38 (s, 9H), 1.21 (d, J = 6.5 Hz, 3H); MS (ESI) *m/z* 394 ([M-H]-).

Example 32

5-(3,5,5-Trimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0131] Prepared from *tert*-butyl 2-cyano-5-(3,5,5-trimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate generally according to the procedure of example 2. ^{1}H NMR (DMSO-d_6): δ 12.58 (s, 1H), 9.88 (s, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.54 (dd, J = 8.5, 1.9 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 6.98 (m, 1H), 4.34 (q, J = 6.6 Hz, 1H), 1.72 (s, 3H), 1.45 (s, 3H), 1.22 (d, J = 6.5 Hz, 3H); MS (ESI) *m/z* 296 ([M+H]+).

Example 33

5-(1,5-Dimethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-*H*-pyrrole-2-carbonitrile

[0132] Prepared from 5-[5-methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile and iodomethane generally according to the procedure of example 3. ^{1}H NMR (DMSO-d_6): δ 7.72 (s, 1H), 7.70

(dd, J = 8.2, 1.9 Hz, 1H), 7.51 (d, J = 9.0 Hz, 1H), 7.33 (dd, J = 5.0, 1.1 Hz, 1H), 7.08 (d, J = 4.1 Hz, 1H), 6.88 (m, 1H), 6.60 (dd, 3.5, 1.2 Hz, 1H), 6.51 (d, J = 4.1 Hz, 1H), 4.03 (q, J = 2.3 Hz, 1H), 3.81 (s, 3H), 2.81 (s, 3H), 1.93 (s, 3H); MS (ESI) *m/z* 422 ([M+FORMATE).

Example 34

tert-Butyl 2-cyano-5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate

N-[4-Bromo-2-(1-hydroxy-1-thien-2-ylbutyl)phenyl]-2-chloroacetamide

[0133] Prepared from the 5-bromo anthranilic acid in multiple steps generally according to the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.93 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.47 (dd, J = 8.8, 2.3 Hz, 1H), 7.41 (m, 2H), 7.15 (s, 1H), 6.94 (m, 2H), 4.28 (m, 2H), 2.15-2.40 (m, 2H), 1.25-1.40 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). MS (ESI) *m/z* 400/402/404 ([M-H]–); Anal. calcd for C16H17BrClNO2S: C:47.72 H:4.25 N:3.48 Found: C:47.76 H:4.39 N:3.46.

7-Bromo-5-propyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0134] Prepared from N-[4-bromo-2-(1-hydroxy-1-thien-2-ylbutyl)phenyl]-2-chloroacetamide generally according to the procedure described in example 1. A white solid, ^{1}H NMR (DMSO-d_6): δ 10.06 (s, 1H), 7.58 (dd, J = 5.1, 1.1 Hz, 1H), 7.45 (dd, J = 8.7, 2.2 Hz, 1H), 7.36 (d, J = 2.3 Hz, 1H), 7.12 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 5.1, 3.6 Hz, 1H), 6.92 (dd, J = 3.6, 1.1 Hz, 1H), 4.08 (d, J = 15.4 Hz, 1H), 3.91 (d, J = 15.3 Hz, 1H), 2.32 (m, 2H), 1.43 (m, 1H), 0.92 (m, 1H), 08.84 (t, J = 7.2 Hz, 3H); MS (ESI) *m/z* 366/368 ([M+H]+); MS (ESI) *m/z* 364/366 ([M-H]-); Anal. calcd for $C_{16}H_{16}BrNO_2S$: C:52.47 H:4.40 N:3.82 Found: C:52.37 H:4.21 N:3.77.

***tert*-Butyl 2-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate**

[0135] Prepared from 7-bromo-5-propyl-5-thien-2-yl-1,5-dihydro-4,1-

benzoxazepin-2(*H*)-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester using the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.54 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.31 (dd, *J* = 3.2, 1.7 Hz, 1H), 7.24 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.12 (m, 2H), 6.90-7.00 (m, 2H), 6.23 (t, *J* = 3.3 Hz, 1H), 6.19 (m, 1H), 4.12 (d, *J* = 15.2 Hz, 1H), 3.87 (d, *J* = 15.2 Hz, 1H), 2.31 (m, 2H), 1.45 (m, 1H), 1.42 (s, 9H), 1.12 (m, 1H), 0.83 (t, *J* = 7.2 Hz, 3H); MS (ESI) *m/z* 453 ([M+H]+); MS (ESI) *m/z* 451 ([M-H]-); Anal. calcd for $C_{25}H_{28}N_2O_4S$: C:66.35 H:6.24 N:6.19 Found: C:65.89 H:6.13 N:5.89.

[0136] The title compound was prepared from *tert*-butyl 2-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate using the similar procedure described in example. A white solid: mp 163-164 °C; ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 7.57 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.33 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.28 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.89 (dd, *J* = 3.6, 1.1 Hz, 1H), 6.41 (d, *J* = 3.9 Hz, 1H), 4.12 (d, *J* = 15.3 Hz, 1H), 3.92 (d, *J* = 15.3 Hz, 1H), 2.43 (m, 2H), 1.43 (s, 9H), 1.42 (m, 1H), 1.01 (m, 1H), 0.86 (t, *J* = 7.1 Hz, 3H); MS *m/z* 00-1894-IMS; Anal. calcd for $C_{26}H_{27}N_3O_4S$: C:65.39 H:5.70 N:8.80 Found: C:65.32 H:5.74 N:8.45.

Example 35

5-(2-Oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0137] Prepared from *tert*-butyl 2-cyano-5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate generally according to the procedure of example 2. A off-white solid: mp 245-246 °C; ^{1}H NMR (DMSO-d_6): δ 12.56 (s, 1H), 10.04 (s, 1H), 7.65 (m, 2H), 7.57 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.21 (d, *J* = 9.2 Hz, 1H), 6.95-7.02 (m, 2H), 6.92 (dd, *J* = 3.6, 1.1 Hz, 1H), 6.68 (, dd, *J* = 3.8, 2.5 Hz, 1H), 4.05 Z(d, *J* = 15.5 Hz, 1H), 3.89 (d, *J* = 15.4 Hz, 1H), 2.43 (m, 2H), 1.48 (m, 1H), 0.95 (m, 1H), 0.83 (t, *J* = 6.9 Hz, 3H); MS *m/z* 00-1901-IMS; Anal. calcd for $C_{21}H_{19}N_3O_2S$: C:66.82 H:5.07 N:11.13 Found: C:66.09 H:5.01

N:10.82.

Example 36

1-Methyl-5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0138] Prepared from 5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile and iodomethane using the procedure of example 3. A white solid, ^{1}H NMR (DMSO-d_6): δ 10.13 (s, 1H), 7.56 (dd, J = 4.9, 1.1 Hz, 1H), 7.42 (dd, J = 8.3, 1.8 Hz, 1H), 7.35 (d, J = 1.8 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 6.95-7.05 (m, 3H), 6.31 (d, J = 4.1 Hz, 1H), 4.12 (d, J = 15.4 Hz, 1H), 3.98 (d, J = 15.4 Hz, 1H), 3.66 (s, 3H), 2.37 (m, 2H), 1.48 (m, 1H), 1.04 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H); MS (ESI) *m/z* 392 ([M+H]+); MS (ESI) *m/z* 390 ([M-H]-); Anal. calcd for $C_{22}H_{21}N_3O_2S$: C:67.50 H:5.41 N:10.73 Found: C:66.73 H:5.30 N:10.48.

Example 37

7-(3-Chloro-4-fluorophenyl)-5-propyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0139] Prepared from 7-bromo-5-propyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-chloro-4-fluorophenyl boronic acid using the procedure described in example 1. A white solid: mp 183-184 °C; ^{1}H NMR (DMSO-d_6): δ 10.07 (s, 1H), 7.83 (dd, J = 7.1, 2.2 Hz, 1H), 7.51-7.68 (m, 4H), 7.47 (t, J = 9.0 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.02 (t, J = 5.0 Hz, 1H), 6.96 (dd, J = 3.5, 1.0 Hz, 1H), 4.09 (d, J = 15.3 Hz, 1H), 3.90 (d, J = 15.3 Hz, 1H), 2.45 (m, 2H), 1.48 (m, 1H), 0.98 (m, 1H), 0.86 (t, J = 7.2 Hz, 3H); Anal. calcd for $C_{22}H_{19}ClFNO_2S$: C:63.53 H:4.60 N:3.37 Found: C:61.60 H:4.32 N:3.25.

Example 38

7-(3-Chloro-4-fluorophenyl)-4,5-dimethyl-2-oxo-2,3-dihydro-*H*-

1,4-benzodiazepin-4-ium

7-Bromo-5-methyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

[0140] A mixture of 1-(2-amino-5-bromo-phenyl)-ethanone (8g, 37 mmol) and glycine ethyl ester hydrogen chloride (6.7g, 48 mmol) in pyridine was heated at reflux for 24 hrs under nitrogen. The reaction mixture was cooled, solvent removed, and residue was treated with a saturated aqueous ammonium chloride solution (200 mL). Ethyl acetate (300 mL) was added and organic layer was separated, dried ($MgSO_4$), concentrated, and the residue purified on silica gel column (hexane:ethyl acetate/1:1) to give 7-bromo-5-methyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one as a brown solid (1.51g, 16%). ^{1}H NMR (DMSO-d_6): δ 10.49 (s, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.66 (dd, J = 8.7, 2.1 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 3.91 (s, 2H), 2.39 (s, 3H). MS (ESI) *m/z* 253/255 ([M+H]+); Anal. calcd for $C_{10}H_9BrN_2O$: C:47.46 H:3.58 N:11.07 Found: C:47.58 H:3.52 N:10.95.

7-(3-Chloro-4-fluorophenyl)-5-methyl-1,3-dihydro-*H*-1,4-benzodiazepin-2-one

[0141] Prepared from 7-bromo-5-methyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one and 3-chloro-4-fluorophenyl boronic acid using the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.52 (s, 1H), 8.02 (d, J = 2.2 Hz, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.83 (dd, J = 8.5, 2.2 Hz, 1H), 7.76 (m, 1H), 7.52 (t, J = 8.76 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 3.91 (s, 2H), 2.48 (s, 3H); MS (ESI) *m/z* 303/305 ([M+H]+); MS (ESI) *m/z* 301/303 ([M-H]-); Anal. calcd for $C_{16}H_{12}ClFN_2O$: C:63.48 H:4.00 N:9.25 Found: C:63.16 H:4.02 N:8.85.

[0142] A mixture of 7-(3-chloro-4-fluorophenyl)-5-methyl-1,3-dihydro-*H*-1,4-benzodiazepin-2-one (0.4g, 1.32 mmol) and iodomethane (0.125 mL, 2 mmol) in anhydrous acetonitrile (20 mL) was heated at 50 °C under nitrogen for 24 hrs. The solvent was removed and residue triturated in ethyl acetate to give the title compound as greenish solid (60 mg, 14%). ^{1}H NMR (DMSO-d_6): δ 11.52 (s, 1H), 8.24 (d, J = 2.0 Hz, 1H), 8.13 (dd, J = 5.2, 2.2 Hz, 1H), 8.06 (dd, J = 7.0, 2.3 Hz, 1H), 7.81 (m, 1H), 7.58 (t, J = 9.0 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 4.48 (bs, 2H), 3.84 (s, 3H), 2.98 (s, 3H). MS (ESI) *m/z* 317/319 ([M]+); Anal. calcd for

$C_{17}H_{15}ClFN_2O$ I: C:45.92 H:3.40 N:6.30 Found: C:45.50 H:3.39 N:6.55.

Example 39

7-(3-chloro-4-fluorophenyl)-4,5,5-trimethyl-1,3,4,5-tetrahydro-*H*-1,4-benzodiazepin-2-one

[0143] A mixture of 7-(3-chloro-4-fluorophenyl)-4,5-dimethyl-2-oxo-2,3-dihydro-*H*-1,4-benzodiazepin-4-ium (0.2g, 0.63mmol) and methyl magnesium bromide (1mL in diethyl ether, 3M, 3mmol) in anhydrous diethyl ether (20 mL) was heated at reflux under nitrogen for 3 hrs. The reaction mixture was treated with a saturated aqueous ammonium chloride solution (30 mL). The organic layer was separated and aqueous layer was extracted with ethyl acetate (3x30 mL). The organic extracts were combined, dried ($MgSO_4$), concentrated, and residue purified on a silica gel column (hexane:ethyl acetate/3:1) to give the title compound as a white solid (11mg, 5.2%). ^{1}H NMR (DMSO-d_6): δ 10.06 (s, 1H), 7.92 (dd, J = 7.1, 2.2 Hz, 1H), 7.68 (m, 1H), 7.45-7.53 (m, 3H), 7.26 (d, J = 8.2 Hz, 1H), 3.78 (s, 2H), 2.18 (s, 3H), 1.52 (s, 6H). MS (ESI) *m/z* 333/335 ([M+H]+).

Example 40

3-[5,5-Bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile

7-Bromo-5,5-bis(5-chlorothien-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0144] Prepared from 2-amino-5-bromobenzoic acid in multiple steps following the procedure described in example 6. ^{1}H NMR (DMSO-d_6): δ 10.15 (s, 1H), 7.91 (dd, J = 8.8, 2.4 Hz, 1H), 7.18 (d, J = 8.8 HZ, 1H), 7.10 (d, J = 2.6 Hz, 1H), 7.06 (d, J = 3.9 Hz, 2H), 6.78 (d, J = 3.9 Hz, 2H), 4.22 (s, 2H). MS (ESI) *m/z* 472/474/476 ([M-H]-); Anal. calcd for $C_{17}H_{10}BrCl_2NO_2S_2$: C:42.97 H:2.12 N:2.95 Found: C:43.34 H:2.17 N:2.78.

[0145] The title compound was prepared from 7-bromo-5,5-bis(5-chlorothien-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-cyano-5-fluorophenyl boronic

acid generally according to the coupling procedure of example 1. ^{1}H NMR (DMSO-d_6): δ 10.32 (s, 1H), 7.89 (t, J = 1.5 Hz, 1H), 7.73-7.82 (m, 3H), 7.48 (d, J = 2.5 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 3.9 Hz, 2H), 6.98 (d, J = 3.9 Hz, 2H), 4.22 (s, 2H); MS (ESI) *m/z* 513/515/517 ([M-H]-); Anal. calcd for $C_{24}H_{13}Cl_2FN_2O_2S_2$: C:55.93 H:2.54 N:5.44 Found: C:56.34 H:2.64 N:5.36.

Example 41

7-(3-Chloro-4-fluorophenyl)-5,5-bis(5-chlorothien-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0146] Prepared from 7-bromo-5,5-bis(5-chlorothien-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-chloro-4-fluorophenyl boronic acid generally according to the coupling procedure of example 1. ^{1}H NMR (DMSO-d_6): δ 10.30 (s, 1H), 7.71 (t, J = 1.9 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.44-7.50 (m, 2H), 7.29 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 3.9 Hz, 2H), 6.89 (d, J = 3.9 Hz, 2H), 4.24 (s, 2H); MS (ESI) *m/z* 522/524/526 ([M-H]-).

Example 42

tert-Butyl 2-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-*H*-pyrrole-1-carboxylate

tert-Butyl 2-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate

[0147] Prepared from 7-bromo-5,5-bis(5-chlorothien-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the coupling procedure of example 1. ^{1}H NMR (DMSO-d_6): δ 10.23 (s, 1H), 7.35 (dd, J = 8.3, 2.4 Hz, 1H), 7.29 (m, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.01 (d, J = 4.0 Hz, 2H), 6.96 (d, J = 2.0 Hz, 1H), 6.72 (d, J = 3.9 Hz, 2H), 6.23 (t, J = 3.4 Hz, 1H), 6.13 (m, 1H), 4.24 (s, 2H), 1.38 (s, 9H); MS (ESI) *m/z* 561/563 ([M+H]+); MS (ESI) *m/z* 559/561 ([M-H]-); Anal. calcd for

$C_{26}H_{22}Cl_2N_2O_4S_2$: C:55.62 H:3.95 N:4.99 Found: C:56.61 H:4.18 N:4.40.

[0148] The title compound was prepared from *tert*-butyl 2-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate using the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.31 (s, 1H), 7.43 (dd, J = 8.3, 2.4 Hz, 1H), 7.27 (d, J = 3.9 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 2.4 Hz, 1H), 7.03 (d, J = 3.9 Hz, 2H), 6.77 (d, J = 3.9 Hz, 2H), 6.34 (d, J = 3.9 Hz, 1H), 4.23 (s, 2H), 1.38 (s, 9H); MS (ESI) *m/z* [M+H]+ (586/588); MS (ESI) *m/z* [M-H]- (584/586); Anal. calcd for $C_{27}H_{21}Cl_2N_3O_4S_2$: C:55.29 H:3.61 N:7.16 Found: C:55.52 H:3.63 N:6.97.

Example 43

5-[5,5-Bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-2-carbonitrile

[0149] Prepared from *tert*-butyl 2-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-*H*-pyrrole-1-carboxylate generally according to the procedure of example 2. ^{1}H NMR (DMSO-d_6): δ 12.5 (brs, 1H), 10.23 (s, 1H), 7.70 (dd, J = 8.5., 2.2 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.09 (d, J= 3.9 Hz, 2H), 6.96 (d, J= 3.9 Hz, 1H), 6.94 (d, J = 3.9 Hz, 2H), 6.54 (d, J = 3.8 Hz, 1H), 4.21 (s, 2H). MS (ES) *m/z* 484/486 ([M-H]-); Anal. calcd for $C_{22}H_{13}Cl_2N_3O_2S_2$: C:54.33 H:2.69 N:8.64 Found: C:52.62 H:3.30 N:7.95.

Example 44

5-[5,5-Bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-*H*-pyrrole-2-carbonitrile

[0150] Prepared from 5-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-2-carbonitrile and iodomethane generally according to the procedure of example 3. ^{1}H NMR (DMSO-d_6): δ 10.04 (s, 1H), 7.53 (dd, J = 8.3, 2.4 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.11 (d, J = 4.2 Hz, 1H), 7.05 (d, J = 3.8 Hz, 2H), 6.99 (d, J = 3.9 Hz, 1H), 6.83 (d, J = 3.9 Hz, 2H), 6.23 (d, J = 4.4 Hz, 1H),

4.27 (s, 2H), 3.56 (s, 3H); MS (ESI) *m/z* 498/500 ([M-H]-).

Example 45

7-(3-Chloro-4-fluorophenyl)-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

1-(2-Amino-5-bromophenyl)-2,2,3,3,3-pentafluoropropan-1-one

[0151] A solution of BOC protected aniline (14g, 72 mmol) in anhydrous ether (150 mL) at -15 °C under nitrogen was treated with a solution of *t*-butyllithium (1.7 M in pentane, 106 mL, 183 mmol). The reaction mixture was stirred at –15 °C for 4 hrs, cooled to –78 °C, and treated with ethyl pentafluoropropionate (13 mL, 88 mmol). The mixture was allowed to slowly warm to rt and brine (500 mL) was added. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was taken up in methylene chloride (100 mL) and treated with TFA (5 mL) at 0 °C under nitrogen. After 1.5 hrs, the solution was treated with a cold sodium bicarbonate solution (3N, 100 mL) and organic layer was separated, dried ($MgSO_4$), and concentrated. The crude residue (5g, 21 mmol) was then taken up in methylene chloride (80 mL) and treated with NBS (3.6g, 20 mmol) in portions at rt under nitrogen. After 1hr, the solution was washed with aqueous 3N sodium bicarbonate solution (3x 20 mL), dried ($MgSO_4$), and concentrated to give 1-(2-amino-5-bromophenyl)-2,2,3,3,3-pentafluoropropan-1-one as a yellow solid (6g, 25% in three steps). ^{1}H NMR (DMSO-d_6): δ 7.97 (s, 2H), 7.67 (d, J = 2.3 Hz, 1H), 7.56 (dd, J = 9.2, 2.2 Hz, 1H), 6.94 (d, J = 9.3 Hz, 1H); MS (ESI) *m/z* 318/320 ([M+H]+); MS (ESI) *m/z* 316/318 ([M-H]-); Anal. calcd for $C_9H_5BrF_5NO$: C:33.99 H:1.58 N:4.40 Found: C:34.27 H:1.75 N:4.22.

N-{4-Bromo-2-[2,2,3,3,3-pentafluoro-1-(2-furyl)-1-hydroxypropyl]phenyl}-2-chloroacetamide

[0152] To a solution of furan (13g, 190 mmol) in anhydrous THF (150 mL) was added *n*-butyllithium (2.5 M in hexane, 40 mL, 100 mmol) at 0 °C under nitrogen. The solution was stirred at 0 °C for 30 minutes, cooled to –78 °C, and treated with a

solution of 1-(2-amino-5-bromophenyl)-2,2,3,3,3-pentafluoropropan-1-one. The mixture was allowed to warm to –30 °C, a saturated ammonium chloride solution (100 mL) was added and mixture was warmed to rt. Ethyl acetate (300 mL) was added and organic layer separated, dried ($MgSO_4$), and concentrated. The residue was dissolved in anhydrous THF. The resultant solution was cooled to 0 °C, treated with triethylamine followed by addition of chloroacetyl chloride following the procedure described in example 1 to give *N*-{4-bromo-2-[2,2,3,3,3-pentafluoro-1-(2-furyl)-1-hydroxypropyl]phenyl}-2-chloroacetamide as a white solid. ^{1}H NMR (DMSO-d_6): δ 10.54 (s, 1H), 9.11 (s, 1H), 8.18 (d, J = 9.0 Hz, 1H), 7.79 (m, 1H), 7.64 (dd, J = 8.8, 2.4 Hz, 1H), 7.21 (d, J = 1.7 Hz, 1H), 6.71 (s, 1H), 6.58 (m, 1H), 4.35 (d, J = 1.5 Hz, 2H). MS (ESI) *m/z* 462/464 ([M+H]+); MS (ESI) *m/z* 460/462 ([M-H]-).

7-Bromo-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0153] Prepared from *N*-{4-bromo-2-[2,2,3,3,3-pentafluoro-1-(2-furyl)-1-hydroxypropyl]phenyl}-2-chloroacetamide using the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.33 (s, 1H), 7.93 (s, 1H), 7.68 (dd, J = 8.6, 2.0 Hz, 1H), 7.49 (s, 1H), 7.20 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 2.9 Hz, 1H), 6.64 (m, 1H), 4.49 (d, J = 14.8 Hz, 1H), 4.14 (d, J = 14.9 hz, 1H); MS (ESI) *m/z* 426/428 ([M+H]+); MS (ESI) *m/z* 424/426 ([M-H]-).

[0154] The title compound was prepared from 7-bromo-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-chloro-4-fluorophenyl boronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.36 (s, 1H), 7.93 (d, J = 1.3 Hz, 1H), 7.82 (dd, J = 8.5, 2.1 Hz, 1H), 7.72 (dd, J = 7.8, 1.8 Hz, 1H), 7.45-7.58 (m, 3H), 7.36 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 3.4 Hz, 1H), 6.63 (dd, J = 3.5, 1.8 Hz, 1H), 4.49 (d, J = 14.8 Hz, 1H), 4.12 (d, J = 14.8 Hz, 1H); MS (ESI) *m/z* 474/476 ([M-H]-).

Example 46

3-Fluoro-5-[5-(2-furyl)-2-oxo-5-(pentafluoroethyl)-1,2,3,5-tetrahydro-4,1-

benzoxazepin-7-yl]benzonitrile

[0155] Prepared from 7-bromo-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-cyano-5-fluorophenyl boronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.41 (s, 1H), 7.84-7.94 (m, 4H), 7.76 (td, *J* = 10.1, 2.1 Hz, 1H), 7.68 (d, *J* = 1.7 Hz, 1H), 7.36 (d, J= 8.6 Hz, 1H), 6.84 (d, *J* = 3.4 Hz, 1H), 6.64 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.45 (d, *J* = 14.9 Hz, 1H), 4.14 (d, J= 14.8 Hz, 1H); MS (ESI) *m/z* 467 ([M+H]+); MS (ESI) *m/z* 465 ([M-H]-); Anal. calcd for $C_{22}H_{12}F_6N_2O_3$: C:56.66 H:2.59 N:6.01 Found: C:56.64 H:2.85 N:5.61.

Example 47

7-(3-Chloro-4-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0156] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-chloro-4-fluorophenyl boronic acid generally according to the coupling procedure described in example 1. A white solid: mp 170-171 °C; ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.93 (dd, J= 8.1, 2.3 Hz, 1H), 7.68 (m, 1H), 7.44-7.59 (m, 3H), 7.18 (d, *J* = 8.4 Hz, 1H), 4.25 (s, 2H), 1.63 (s, 6H). MS (ESI) *m/z* 318 ([M-H]-); Anal. calcd for $C_{17}H_{15}ClFNO_2$: C:63.86 H:4.73 N:4.38 Found: C:63.54 H:4.72 N:4.11.

Example 48

7-(3-Fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0157] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-fluorophenyl boronic acid generally according to the coupling procedure described in example 1. A white solid: mp 196-197 °C; ^{1}H NMR (DMSO-d_6): δ 9.98 (s, 1H), 7.43-7.58 (m, 5H), 7.12-7.20 (m, 2H), 4.23 (s, 2H), 1.63 (s, 6H). MS (ESI) *m/z* 286 ([M+H]+); Anal. calcd for $C_{17}H_{16}FNO_2$: C:71.56 H:5.65 N:4.91

Found: C:71.54 H:5.77 N:4.82.

Example 49

H-Fluoren-9-ylmethyl 7-(5-cyano-*H*-pyrrol-2-yl)-5-methyl-5-thien-2-yl-2,3-dihydro-4,1-benzoxazepine-1(*H*)-carboxylate

7-Bromo-5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepine

[0158] To a solution of 7-bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one (5g, 14.6 mmol) in anhydrous THF (100 mL) was added lithium aluminum hydride (0.2g, 5.2 mmol) at rt under nitrogen. After addition, the mixture was stirred for 3 hrs and treated with aqueous ammonium chloride solution (200 mL). Ethyl acetate (300 mL) was added. Organic layer was separated, dried ($MgSO_4$), and concentrated to afford 7-bromo-5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepine as an oil (4g, 85%). A white solid as a HCl salt: ^1H NMR (DMSO-d_6): δ 7.52 (dd, J = 5.0, 0.8 Hz, 1H), 7.31 (dd, J = 8.5, 2.1 Hz, 1H), 7.12 (d, J = 2.1 Hz, 1H), 6.95-7.04 (m, 2H), 6.78 (dd, J = 3.5, 0.9 Hz, 1H), 3.61-3.85 (m, 4H), 3.12 (m, 2H), 2.93 (s, 3H); MS (ESI) *m/z* 324/326 ({M+H]+); Anal. calcd for $C_{14}H_{14}BrNOS$ HCl: C:46.62 H:4.19 N:3.88 Found: C:46.70 H:3.99 N:3.83.

tert-Butyl 2-(5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate

[0159] Prepared from 7-bromo-5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepine and 2-borono-1*H*-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester using the coupling procedure described in example 1. ^1H NMR (DMSO-d_6): δ 7.46 (dd, J= 5.0, 0.8 Hz, 1H), 7.23 (dd, J = 3.2, 1.8 Hz, 1H), 7.02 (dd, J = 8.1, 1.9 Hz, 1H), 6.91 (dd, J = 5.0, 3.6 Hz, 1H), 6.87 (m, 2H), 6.72 (dd, J= 3.4, 0.8 Hz, 1H), 6.18 (t, J = 3.3 Hz, 1H), 6.08 (dd, J= 3.2, 1.7 Hz, 1H), 5.68 (m, 1H), 3.85 (m, 1H), 3.72 (m, 1H), 3.02 (m, 2H), 1.94 (m, 3H), 1.35 (s, 9H); MS (ESI) *m/z* 411 ([M+H]+); Anal. calcd for $C_{23}H_{26}N_2O_3S$: C:67.29 H:6.38 N:6.82 Found: C:67.20 H:6.32 N:6.74.

H-Fluoren-9-ylmethyl 7-(5-cyano-*H*-pyrrol-2-yl)-5-methyl-5-thien-2-yl-2,3-

dihydro-4,1-benzoxazepine-1(*H*)-carboxylate

[0160] A mixture of *tert*-butyl 2-(5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate (4g, 9.74 mmol), 9-fluorenylmethyl chloroformate (3.8, 15 mmol), and a saturated sodium bicarbonate solution (50 mL) in dioxane (50 mL) was stirred for 3 hrs. A saturated aqueous ammonium chloride solution (100 mL) and ethyl acetate (200 mL) were added. Organic layer was separated, dried ($MgSO_4$), and concentrated. The residue obtained was dissolved in anhydrous THF and treated with chlorosulfonyl isocyanate following the procedure described in example 1. Using the deprotection procedure described in example 1, the BOC group of cyanation product was removed to afford *H*-fluoren-9-ylmethyl 7-(5-cyano-*H*-pyrrol-2-yl)-5-methyl-5-thien-2-yl-2,3-dihydro-4,1-benzoxazepine-1(*H*)-carboxylate as off-white solid: MS (ESI) *m/z* 558 ([M+H]+); MS (ESI) *m/z* 556 ([M-H]-).

Example 50

1-Methyl-5-(5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0161] Methylation of *H*-fluoren-9-ylmethyl 7-(5-cyano-*H*-pyrrol-2-yl)-5-methyl-5-thien-2-yl-2,3-dihydro-4,1-benzoxazepine-1(*H*)-carboxylate was effected generally according to the procedure described in example 3. The crude methylation product (0.2g, 0.035 mmol) was dissolved in DMF (16 mL) and piperidine (4 mL) was added at rt under nitrogen. The reaction solution was stirred at rt under nitrogen for 50 minutes. A saturated aqueous sodium bicarbonate solution (20 mL) and ethyl acetate (50 mL) were added. The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was purified on a silica gel column (hexane:ethyl acetate/3:1) to give the title compound as a white solid (25mg, 20 %). ^{1}H NMR (DMSO-d_6): δ 7.49 (dd, J= 5.0, 0.9 Hz, 1H), 7.18 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.96 (m, 3H), 6.78 (dd, *J* = 3.4, 0.9 Hz, 1H), 6.18 (d, *J* = 4.0 Hz, 1H), 5.96 (s, 1H), 3.86 (m, 1H), 3.75 (m, 1H), 3.61 (s, 3H), 3.02 (m, 2H), 1.95 (s, 3H); MS (ESI) *m/z* 350 ([M+H]+).

Example 51

5-(5-Methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0162] Prepared from *H*-fluoren-9-ylmethyl 7-(5-cyano-*H*-pyrrol-2-yl)-5-methyl-5-thien-2-yl-2,3-dihydro-4,1-benzoxazepine-1(*H*)-carboxylate using the deprotection procedure described in example 50. ^{1}H NMR (DMSO-d_6): δ 12.38 (s, 1H), 7.41-7.54 (m, 3H), 6.85-6.94 (m, 3H), 6.63 (dd, J = 3.4, 1.1 Hz, 1H), 6.45 (dd, J = 3.6, 2.5 Hz, 1H), 3.72 (m, 1H), 3.61 (m, 1H), 2.91-3.13 (m, 2H), 2.01 (s, 3H). MS (ESI) *m/z* 336 ([M+H]+); MS (ESI) *m/z* 334, ([M-H]-).

Example 52

tert-Butyl 2-cyano-5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate

(2-Amino-5-bromophenyl)(2-thienyl)methanone

[0163] Prepared from 5-bromo anthranilic acid using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 7.86 (d, J = 2.3 Hz, 1H), 7.71 (dd, J = 5.0, 1.0 Hz, 1H), 7.59 (dd, J = 3.8, 1.0 Hz, 1H), 7.39 (dd, J = 8.8, 2.4 Hz, 1H), 7.19 (m, 1H), 6.66 (d, J = 8.8 Hz, 1H), 5.71 (s, 2H); MS (ES) *m/z* 280 $(M-H)^-$.

N-[4-Bromo-2-(1-hydroxy-1-thien-2-ylpropyl)phenyl]-2-chloroacetamide

[0164] 1-(2-Amino-5-bromophenyl)-1-thiophen-2-yl-propan-1-ol was prepared from (2-amino-5-bromophenyl)(2-thienyl)methanone using the procedure described in example 1.

[0165] The title compound was prepared from 1-(2-amino-5-bromophenyl)-1-thiophen-2-yl-propan-1-ol and chloroacetyl chloride using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 10.23 (s, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.46 (dd, J = 8.7, 2.3 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.29 (dd, J = 5.1, 1.0 Hz, 1H), 6.97 (m, 1H), 6.90 (dd, J = 3.5, 1.0 Hz, 1H), 4.09 (m, 2H), 2.80 (s, 1H), 2.43 (m, 2H), 1.03 (t,

J = 7.3 Hz, 3H); MS (ES) *m/z* 386 (M-H)$^-$; Anal Calc. For $C_{15}H_{15}BrClNO_2S$: C, 46.35, H, 3.89, N, 3.60. Found: C, 46.67, H, 3.80, N, 3.52.

7-Bromo–5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0166] Prepared from N-[4-bromo-2-(1-hydroxy-1-thien-2-ylpropyl)phenyl]-2-chloroacetamide using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 7.80 (br s, 1H), 7.39 (m, 3H), 6.97 (m, 1H), 6.81 (m, 2H), 4.19 (d, J = 16.0 Hz, 1H), 4.05 (d, J = 16.0 Hz, 1H), 2.58 (m, 1H), 2.31 (m, 1H), 0.87 (t, J = 7.2 Hz, 3H); MS (ES) *m/z* 350 (M-H)$^-$.

***tert*-Butyl 2-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate**

[0167] Prepared from 7-bromo-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-tert-butyl ester using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 7.58 (br s, 1H), 7.34 (t, J = 3.1 Hz, 1H), 7.29 (m, 3H), 6.91 (d, J = 3.1 Hz, 2H), 6.85 (d, J = 8.1 Hz, 1H), 6.20 (t, J = 3.3 Hz, 1H), 6.16 (m, 1H), 4.22 (d, J = 15.8 Hz, 1H), 4.06 (d, J = 15.8 Hz, 1H), 2.54 (m, 1H), 2.30 (m, 1H), 1.46 (s, 9H), 0.89 (t, J = 7.2 Hz, 3H); MS (ES) *m/z* 437 (M-H)$^-$; Anal Calc. For $C_{24}H_{26}N_2O_4S$: C, 65.73, H, 5.98, N, 6.39. Found: C, 65.64, H, 5.81, N, 6.36.

[0168] The title compound was prepared from *tert*-butyl 2-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 7.68 (br s, 1H), 7.36 (d, J = 4.9 Hz, 1H), 7.27 (m, 1H), 7.22 (d, J = 1.8 Hz, 1H), 6.95 (d, J = 3.7 Hz, 1H), 6.92 (m, 3H), 6.23 (d, J = 3.7 Hz, 1H), 4.21 (d, J = 16.1 Hz, 1H), 4.07 (d, J = 16.1 Hz, 1H), 2.56 (m, 1H), 2.28 (m, 1H), 1.57 (s, 9H), 0.88 (t, J = 7.2 Hz, 3H); MS (ES) *m/z* 462 (M-H)$^-$; Anal. Calc. For $C_{25}H_{25}N_3O_4S$: C, 64.78, H, 5.44, N, 9.06. Found: C, 64.88, H, 5.40, N, 8.89.

Example 53

5-(5-Ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-

pyrrole-2-carbonitrile

[0169] Prepared from *tert*-butyl 2-cyano-5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.57 (s, 1H), 10.05 (s, 1H), 7.67 (m, 2H), 7.58 (d, J = 5.0 Hz, 1H), 7.20 (d, J = 4.5 Hz, 1H), 7.01 (m, 2H), 6.90 (d, J = 3.2 Hz, 1H), 6.69 (d, J = 3.8 Hz, 1H), 4.08 (d, J = 15.5 Hz, 1H), 3.98 (d, J = 15.5 Hz, 1H), 2.50 (m, 2H), 0.78 (t, J = 7.0 Hz, 3H); MS (ES) *m/z* 362 (M-H)$^-$.

Example 54

5-(5-Ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1H-pyrrole-2-carbonitrile

[0170] Prepared from 5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile using the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.14 (s, 1H), 7.56 (d, J = 4.8 Hz, 1H), 7.44 (dd, J = 8.3, 1.6 Hz, 1H), 7.33 (s, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.01 (m, 3H), 6.30 (d, J = 4.0 Hz, 1H), 4.14 (d, J = 15.4 Hz, 1H), 4.00 (d, J = 15.4 Hz, 1H), 3.65 (s, 3H), 2.50 (m, 2H), 0.79 (t, J = 7.0 Hz, 3H); MS (ES) *m/z* 376 (M-H)$^-$.

Example 55

7-(3-Chloro-4-fluoro-phenyl)-5-ethyl-5-thiophen-2-yl-1,5-dihydro-benzo[*e*][1,4]oxazepin-2-one

[0171] Prepared from 7-bromo-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-chloro-4-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 7.85 (dd, J = 7.1, 2.2 Hz, 1H), 7.65 (m, 2H), 7.57 (dd, J = 5.0, 1.0 Hz, 1H), 7.52 (m, 2H), 7.26 (d, J = 8.5 Hz, 1H), 7.01 (m, 2H), 4.11 (d, J = 15.4 Hz, 1H), 3.95 (d, J = 15.4 Hz, 1H), 2.41 (m, 2H), 0.78 (t, J = 7.0 Hz, 3H); MS (ES) *m/z* 400 (M-H)$^-$.

Example 56

3-(5-ethyl-2-oxo-5-thiophen-2-yl-1,2,3,5-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-5-fluoro-benzonitrile

[0172] Prepared from 7-bromo-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 5-fluoro-3-cyanobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.12 (s, 1H), 8.07 (s, 1H), 7.95 (dt, *J* = 10.3, 2.0 Hz, 1H), 7.81 (m, 2H), 7.69 (d, *J* = 2.0 Hz, 1H), 7.57 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.01 (m, 1H), 6.95 (m, 1H), 4.10 (d, *J* = 15.5 Hz, 1H), 4.01 (d, *J* = 15.5 Hz, 1H), 2.65 (m, 2H), 0.78 (t, *J* = 7.0 Hz, 3H); MS (ES) *m/z* 391 (M-H)$^-$.

Example 57

tert-Butyl 2-cyano-5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate

(2-Amino-5-bromophenyl)(2-thienyl)methanol

[0173] Prepared from (2-amino-5-bromophenyl)(2-thienyl)methanone using the procedure described in example 11. ^{1}H-NMR ($CDCl_3$) δ 7.33 (m, 2H), 7.25 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.00 (m, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 6.0 (s, 1H), 3.95 (br s, 2H), 2.75 (br s, 1H); MS (ES) *m/z* 266 $(M-H_2O)^+$; Anal. Calc. For $C_{11}H_{10}BrNOS$: C, 46.49, H, 3.55, N, 4.93. Found: C, 46.77, H, 3.54, N, 4.68.

7-Bromo-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0174] Prepared from (2-amino-5-bromophenyl)(2-thienyl)methanol in two steps using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 8.30 (s, 1H), 7.42 (m, 2H), 7.14 (d, *J* = 2.2 Hz, 1H), 7.05 (m, 1H), 6.90 (d, *J* = 3.6 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 6.09 (s, 1H), 4.53 (m, 2H); MS (ES) *m/z* 322 (M-H)$^-$.

tert-Butyl 2-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate

[0175] Prepared from 7-bromo-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.37 (dd, J = 5.0, 1.0 Hz, 1H), 7.30 (m, 2H), 7.01 (m, 2H), 6.93 (m, 2H), 6.19 (t, J = 3.3 Hz, 1H), 6.14 (s, 1H), 6.12 (m, 1H), 4.56 (m, 2H), 1.41 (s, 9H); MS (ES) *m/z* 409 $(M-H)^-$; Anal. Calcd. For $C_{22}H_{22}N_2O_4S$: C, 64.37, H, 5.4, N, 6.82. Found: C, 64.05, H, 5.4, N, 6.7.

[0176] The title compound was prepared from *tert*-butyl 2-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 8.27 (s, 1H), 7.40 (dd, J = 5.0, 1.0 Hz, 1H), 7.29 (m, 1H), 7.02 (m, 3H), 6.94 (d, J = 3.7 Hz, 2H), 6.18 (d, J = 3.7 Hz, 1H), 6.14 (s, 1H), 4.58 (m, 2H), 1.49 (s, 9H); MS (ES) *m/z* 434 $(M-H)^-$.

Example 58

5-(2-Oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile

[0177] Prepared from *tert*-butyl 2-cyano-5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.56 (s, 1H), 10.34 (s, 1H), 7.65 (m, 2H), 7.41 (d, J = 1.8 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.07 (m, 1H), 6.97 (m, 2H), 6.50 (d, J = 3.8 Hz, 1H), 6.30 (s, 1H), 4.48 (d, J = 16.3 Hz, 1H), 4.20 (d, J = 16.3 Hz, 1H); MS (ES) *m/z* 334 $(M-H)^-$.

Example 59

1-Methyl-5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile

[0178] Prepared from 5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile using the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.44 (s, 1H), 7.62 (d, J = 5.0 Hz, 1H), 7.47 (dd, J = 8.3, 2.0

Hz, 1H), 7.30 (d, J = 8.3 Hz, 1H), 7.08 (m, 1H), 7.04 (m, 2H), 6.33 (s, 1H), 6.22 (d, J = 4.0 Hz, 1H), 4.56 (d, J = 16.5 Hz, 1H), 4.32 (d, J = 16.5 Hz, 1H), 3.61 (s, 3H); MS (ES) m/z 348 $(M-H)^-$.

Example 60

7-(3-Chlorophenyl)-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0179] Prepared from 7-bromo-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-chlorobenzeneboronic acid generally according to the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 8.26 (br s, 1H), 7.51 (dd, J = 8.3, 2.1 Hz, 1H), 7.45 (d, J = 0.9 Hz, 1H), 7.42 (dd, J = 5.1, 0.9 Hz, 1H), 7.36 (m, 3H), 7.24 (d, J = 2.0 Hz, 1H), 7.05 (m, 2H), 6.93 (d, J = 3.5 Hz, 1H), 6.24 (s, 1H), 4.56 (d, J = 17.0 Hz, 1H), 4.47 (d, J = 17.0 Hz, 1H); MS (ES) m/z 356 $(M+H)^+$; Anal. Calc. For $C_{19}H_{14}ClNO_2S$: C, 64.13, H, 3.97, N, 3.94. Found: C, 64.1, H, 3.83, N, 3.99.

Example 61

tert-Butyl 2-cyano-5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate

1-(2-Amino-5-bromophenyl)-1-pyridin-2-ylethanol

[0180] Prepared from 2-amino-5-bromophenyl methyl ketone and 2-pyridyllithium generally according to the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 8.5 (d, J = 3.99 Hz, 1H), 7.77 (dt, J = 7.77, 1.79 Hz, 1H), 7.64 (d, J = 7.96 Hz, 1H), 7.30 (d, J = 2.37 Hz, 1H), 7.21-7.25 (m, 1H), 7.06 (dd, J = 8.49, 2.36 Hz, 1H), 6.47 (d, J = 8.51 Hz, 1H), 6.18 (s, 1H), 5.26 (s, 2H), 1.8 (s, 3H); MS (ESI) m/z 293/295, 1 Br pattern ($[M+H]^+$).

N-[4-Bromo-2-(1-hydroxy-1-pyridin-2-ylethyl)phenyl]-2-chloroacetamide

[0181] Prepared from 1-(2-amino-5-bromophenyl)-1-pyridin-2-ylethanol using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 10.00 (s, 1H), 8.58 (d, J = 4.9 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.63 (m, 2H), 7.52 (dd, J = 8.7, 2.2 Hz, 1H),

7.26 (m, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.05 (s, 1H), 3.97 (d, J = 15.2 Hz, 1H), 3.66 (d, J = 15.2 Hz, 1H), 1.87 (s, 3H); MS (ES) *m/z* 367 $(M-H)^-$.

7-Bromo-5-methyl-5-pyridin-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0182] Prepared from N-[4-bromo-2-(1-hydroxy-1-pyridin-2-ylethyl)phenyl]-2-chloroacetamide using the procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 8.50 (dt, J = 4.8, 0.8 Hz, 1H), 7.72 (td, J = 7.5, 1.6 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.55 (m, 2H), 7.42 (dd, J = 8.4, 2.1 Hz, 1H), 7.20 (m, 1H), 6.79 (d, J = 8.5 Hz, 1H), 4.37 (d, J = 14.5 Hz, 1H), 4.30 (d, J = 14.5 Hz, 1H), 1.97 (s, 3H); MS (ES) *m/z* 333 $(M-H)^+$; Anal. Calc. For $C_{15}H_{13}BrN_2O_2$: C, 54.07, H, 3.93, N, 8.14. Found: C, 53.96, H, 4.02, N, 8.14.

***tert*-Butyl 2-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate**

[0183] Prepared from 7-bromo-5-methyl-5-pyridin-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester using the coupling procedure described in example 1. ^{1}H-NMR ($CDCl_3$) δ 8.52 (d, J = 0.6 Hz, 1H), 7.69 (td, J = 7.9, 1.8 Hz, 1H), 7.60 (m, 1H), 7.35 (m, 3H), 7.26 (m, 1H), 7.18 (m, 1H), 6.86 (d, J = 8.2 Hz, 1H), 6.22 (m, 1H), 6.18 (m, 1H), 4.36 (s, 2H), 2.01 (s, 3H), 1.41 (s, 9H); MS (ES) *m/z* 418 $(M-H)^-$.

[0184] The title compound was prepared from *tert*-butyl 2-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.05 (s, 1H), 8.46 (d, J = 1.3 Hz, 1H), 7.80 (td, J = 2.7, 1.6 Hz, 1H), 7.55 (d, J = 4.0 Hz, 1H), 7.35 (m, 4H), 7.11 (d, 8.2 Hz, 1H), 6.45 (d, J = 4.0 Hz, 1H), 4.35 (d, J = 14.3 Hz, 1H), 4.18 (d, J = 14.3 Hz, 1H), 1.9 (s, 3H), 1.39 (s, 9H); MS (ES) *m/z* 443 $(M-H)^-$.

Example 62

5-(5-Methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile

[0185] Prepared from *tert*-butyl 2-cyano-5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.64 (s, 1H), 9.94 (s, 1H), 8.47 (d, J = 3.9 Hz, 1H), 7.81 (td, J = 7.7, 1.8 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.65 (dd, J = 8.3, 1.9 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.29 (m, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 3.8 Hz, 1H), 6.66 (d, J = 3.8 Hz, 1H), 4.30 (d, J = 14.4 Hz, 1H), 4.10 (d, J = 14.4 Hz, 1H), 1.99 (s, 3H); MS (ES) *m/z* 343 $(M-H)^-$.

Example 63

1-Methyl-5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile

[0186] Prepared from 5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile using the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.07 (s, 1H), 8.50 (d, J = 4.7 Hz, 1H), 7.82 (td, J = 7.8, 1.8 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.42 (m, 2H), 7.30 (m, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.02 (d, J = 4.1 Hz, 1H), 6.30 (d, J = 4.1 Hz, 1H), 4.38 (d, J = 14.7 Hz, 1H), 4.20 (d, J = 14.7 Hz, 1H), 3.65 (s, 3H), 1.99 (s, 3H); MS (ES) *m/z* 357 $(M-H)^-$.

Example 64

tert-Butyl 2-cyano-5-(9-fluoro-5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate

tert-Butyl 2-acetyl-4-bromo-6-fluorophenylcarbamate

[0187] Prepared from 5-bromo-2-[(*tert*-butoxycarbonyl)amino]-3-fluorobenzoic acid generally according to the procedure described in the literature (Zhang et al. *Tetrahedron Lett.* (2001), 42(11), 2097-2099). ^{1}H-NMR (DMSO-d_6) δ 9.18 (s, 1H), 7.80 (dd, J = 9.5, 2.2 Hz, 1H), 7.63 (d, J = 1.6 Hz, 1H), 2.46 (s, 3H), 1.44 (s, 9H); MS (ES) *m/z* 332 $(M+H)^+$.

1-(2-Amino-5-bromo-3-fluorophenyl) ethnanone

[0188] Prepared from *tert*-butyl 2-acetyl-4-bromo-6-fluorophenylcarbamate by treatment with TFA in methylene chloride. ^{1}H-NMR (DMSO-d_6) δ 7.75 (s, 1H), 7.58 (dd, J = 9.5, 2.2 Hz, 1H), 7.09 (br s, 2H), 2.55 (s, 3H); MS (ES) *m/z* 390 (M-H)$^-$

N-[4-Bromo-2-fluoro-6-(1-hydroxy-1-thien-2-ylethyl)phenyl]-2-chloroacetamide

[0189] Prepared from 1-(2-amino-5-bromo-3-fluorophenyl) ethnanone in two steps using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.27 (s, 1H), 7.63 (dd, J = 9.3, 2.1 Hz, 1H), 7.53 (s. 1H), 7.40 (dd, J = 5.1, 1.1 Hz, 1H), 6.90 (m, 1H), 6.81 (s, 1H), 6.76 (dd, J = 3.5, 1.1 Hz, 1H), 4.13 (d, J = 14.3 Hz, 1H), 4.04 (d, J = 14.3 Hz, 1H), 1.89 (s, 3H); MS (ES) *m/z* 390 (M-H)$^-$; Anal. Calc. For $C_{14}H_{12}BrClFNO_2S$: C, 42.82, H, 3.08, N, 3.57. Found: C, 42.76, H, 3.03, N, 3.41.

7-Bromo-9-fluoro-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0190] Prepared from N-[4-bromo-2-fluoro-6-(1-hydroxy-1-thien-2-ylethyl)phenyl]-2-chloroacetamide using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.66 (s, 1H), 7.65 (dd, J = 10.0, 2.2 Hz, 1H), 7.53 (dd, J = 5.0, 1.1 Hz, 1H), 7.34 (m, 1H), 6.99 (m, 1H), 6.90 (m, 1H), 4.23 (d, J = 14.8 Hz, 1H), 4.11 (d, J = 14.8 Hz, 1H), 1.98 (s, 3H); MS (ES) *m/z* 354 (M-H)$^-$; Anal. Calc. For $C_{14}H_{11}BrFNO_2S$: C, 47.21, H, 3.11, N, 3.93. Found: C, 47.03, H, 3.07, N, 3.82.

***tert*-Butyl 2-(9-fluoro-5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate**

[0191] Prepared from 7-bromo-9-fluoro-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.63 (s, 1H), 7.50 (dd, J = 5.0, 1.1 Hz, 1H), 7.35 (m, 2H), 7.12 (s, 1H), 6.95 (m, 1H), 6.89 (dd, J = 3.6, 1.2 Hz, 1H), 6.31 (m, 1H), 6.27 (m, 1H), 4.20 (d, J = 14.6 Hz, 1H), 4.12 (d, J = 14.6 Hz, 1H), 1.98 (s, 3H), 1.38 (s, 9H); MS (ES) *m/z* 441 (M-H)$^-$;

Anal. Calc. For $C_{23}H_{23}FN_2O_4S$: C, 62.43, H, 5.24, N, 6.33. Found: C, 62.08, H, 5.33, N, 6.15.

[0192] The title compound was prepared from *tert*-butyl 2-(9-fluoro-5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.70 (s, 1H), 7.51 (m, 2H), 7.32 (d, J = 3.8 Hz, 1H), 7.25 (s, 1H), 6.96 (dd, J = 5.0, 3.6 Hz, 1H), 6.87 (dd, J = 3.5, 1.1 Hz, 1H), 6.50 (d, J = 3.8 Hz, 1H), 4.21 (d, J = 14.7 Hz, 1H), 4.12 (d, J = 14.7 Hz, 1H), 1.99 (s, 3H), 1.40 (s, 9H); MS (ES) *m/z* 466 $(M-H)^-$; Anal. Calc. For $C_{24}H_{22}FN_3O_4S$: C, 61.66, H, 4.74, N, 8.99. Found: C, 61.62, H, 4.6, N, 8.65.

Example 65

5-(9-Fluoro-5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile

[0193] Prepared from *tert*-butyl 2-cyano-5-(9-fluoro-5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.7 (s, 1H), 9.61 (s, 1H), 7.73 (dd, J = 11.9, 1.8 Hz, 1H), 7.60 (s, 1H), 7.52 (dd, J = 5.0, 1.0 Hz, 1H), 7.0 (d, J = 3.9 Hz, 1H), 6.97 (m, 1H), 6.87 (dd, J = 3.5, 1.0 Hz, 1H), 6.81 (d, J = 3.9 Hz, 1H), 4.20 (d, J = 14.8 Hz, 1H), 4.12 (d, J = 14.8 Hz, 1H), 2.06 (s, 3H); MS (ES) *m/z* 366 $(M-H)^-$.

Example 66

tert-Butyl 2-cyano-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate

N-[4-Bromo-2-(1-hydroxy-2-methyl-1-thien-2-ylpropyl)phenyl]-2-chloroacetamide

[0194] Prepared from (2-amino-5-bromophenyl)(2-thienyl)methanone in two steps using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 11.25 (s, 1H),

8.14 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 2.3 Hz, 1H), 7.46 (dd, J = 8.8, 2.3 Hz, 1H), 7.40 (dd, J = 5.0, 1.1 Hz, 1H), 7.02 (d, J = 3.5, 1.1 Hz, 1H), 6.96 (m, 2H), 4.36 (d, J = 15.0 Hz, 1H), 4.30 (d, J = 15.0 Hz, 1H), 2.86 (m, 1H), 0.94 (dd, J = 22.0, 6.6 Hz, 6H); MS (ES) *m/z* 400 $(M-H)^-$; Anal. Calc. For $C_{16}H_{17}BrClNO_2S$: C, 47.72, H, 4.25, N, 3.48. Found: C, 47.89, H, 4.14, N, 3.37.

7-Bromo-5-isopropyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0195] Prepared from N-[4-bromo-2-(1-hydroxy-2-methyl-1-thien-2-ylpropyl)phenyl]-2-chloroacetamide using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.01 (s, 1H), 7.56 (dd, J = 4.9, 1.0 Hz, 1H), 7.52 (dd, J = 8.6, 2.2 Hz, 1H), 7.44 (d, J = 2.2 Hz, 1H), 7.10 (d, J = 8.6 Hz, 1H), 7.03 (m, 2H), 4.22 (d, J = 14.4 Hz, 1H), 3.87 (d, J = 14.4 Hz, 1H), 2.69 (m, 1H), 0.93 (dd, J = 17.8, 6.8 Hz, 6H); MS (ES) *m/z* 364 $(M-H)^-$.

***tert*-Butyl 2-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate**

[0196] Prepared from 7-bromo-5-isopropyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.97 (s, 1H), 7.53 (dd, J = 5.0, 0.9 Hz, 1H), 7.32 (dd, J = 3.2, 1.7 Hz, 1H), 7.30 (m, 2H), 7.13 (d, J = 8.9 Hz, 1H), 7.01 (dd, J = 3.5, 1.0 Hz, 1H), 6.98 (m, 1H), 6.26 (t, J = 3.3 Hz, 1H), 6.20 (m, 1H), 4.19 (d, J = 14.3 Hz, 1H), 3.85 (d, J = 14.3 Hz, 1H), 2.64 (m, 1H), 1.38 (s, 9H), 0.89 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H); MS (ES) *m/z* 453 $(M+H)^+$; Anal. Calc. for $C_{25}H_{28}N_2O_4S$: C, 66.35, H, 6.24, N, 6.19. Found: C, 66.41, H, 5.95, N, 6.07.

[0197] The title compound was prepared from *tert*-butyl 2-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.04 (s, 1H), 7.52 (dd, J = 4.6, 1.5 Hz, 1H), 7.38 (m, 2H), 7.30 (d, J = 3.8 Hz, 1H), 7.17 (m, 1H), 6.99 (m, 2H), 6.41 (d, J = 3.8 Hz, 1H), 4.19 (d, J = 14.4 Hz, 1H), 3.89 (d, J = 14.4 Hz, 1H), 2.67 (m, 1H), 1.42 (s, 9H), 0.89 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H);

MS (ES) *m/z* 478 $(M+H)^+$; Anal. Calc. for $C_{26}H_{27}N_3O_4S$: C, 65.39, H, 5.70, N, 8.80. Found: C, 65.05, H, 5.39, N, 8.68.

Example 67

5-(5-Isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile

[0198] Prepared from *tert*-butyl 2-cyano-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.64 (s, 1H), 9.97 (s, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.69 (dd, J = 8.4, 1.9 Hz, 1H), 7.51 (dd, J = 4.9, 1.2 Hz, 1H), 7.16 (d, J = 8.5 Hz, 1H), 7.01 (m, 3H), 6.65 (d, J = 3.9 Hz, 1H), 4.16 (d, J = 14.4 Hz, 1H), 3.92 (d, J = 14.4 Hz, 1H), 2.79 (m, 1H), 0.93 (m, 6H); MS (ES) *m/z* 378 $(M+H)^+$.

Example 68

5-(5-Isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1H-pyrrole-2-carbonitrile

[0199] Prepared from 5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile using the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 7.52 (dd, J = 4.9, 1.2 Hz, 1H), 7.49 (dd, J = 8.3, 1.9 Hz, 1H), 7.43 (d, J = 1.8 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.02 (m, 3H), 6.30 (d, J = 4.1 Hz, 1H), 4.24 (d, J = 14.4 Hz, 1H), 3.93 (d, J = 14.4 Hz, 1H), 3.70 (s, 3H), 2.70 (m, 1H), 0.90 (m, 6H); MS (ES) *m/z* 390 $(M-H)^-$.

Example 69

7-(3-Chloro-4-fluorophenyl)-5-isopropyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0200] Prepared from 7-bromo-5-isopropyl-5-thien-2-yl-1,5-dihydro-4,1-

benzoxazepin-2(3*H*)-one and 3-chloro-4-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.02 (s, 1H), 7.83 (dd, J = 7.1, 2.2 Hz, 1H), 7.67 (dd, J = 8.4, 2.0 Hz, 1H), 7.60 (m, 2H), 7.53 (m, 1H), 7.52 (m, 1H), 7.23 (d, J = 8.5 Hz, 1H), 7.05 (dd, J = 3.6, 1.3 Hz, 1H), 7.02 (dd, J = 5.0, 3.7 Hz, 1H), 4.21 (d, J = 14.4 Hz, 1H), 3.90 (d, J = 14.4 Hz, 1H), 2.81 (m, 1H), 0.91 (m, 6H); Anal. Calc. for $C_{22}H_{19}ClFNO_2S$: C, 63.53, H, 4.60, N, 3.37. Found: C, 63.34, H, 4.92, N, 2.97.

Example 70

3-Fluoro-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile

[0201] Prepared from 7-bromo-5-isopropyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-cyano-5-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.07 (s, 1H), 8.03 (s, 1H), 7.90 (m, 1H), 7.84 (m, 1H), 7.77 (m, 2H), 7.51 (dd, J = 5.0, 1.2 Hz, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.04 (m, 2H), 4.20 (d, J = 14.4 Hz, 1H), 3.96 (d, J = 14.4 Hz, 1H), 2.90 (m, 1H), 0.92 (t, J = 6.4 Hz, 6H); MS (ES) *m/z* 407 $(M+H)^+$.

Example 71

3-Fluoro-5-(5-isopropyl-5-thien-2-yl-2-thioxo-1,2,3,5-tetrahydo-4,1-benzoxazepin-7-yl)benzonitrile

[0202] Prepared by heating a mixture of 3-fluoro-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile and Lawesson's reagent at reflux in toluene generally according to example 10. ^{1}H-NMR (DMSO-d_6) δ 12.09 (s, 1H), 8.1 (s, 1H), 7.96 (d, J = 10.1 Hz, 1H), 7.88 (m, 2H), 7.83 (dd, J = 8.5, 1.8 Hz, 1H), 7.48 (dd, J = 4.9, 0.66 Hz, 1H), 7.40 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 2.6 Hz, 1H), 7.00 (m, 1H), 4.48 (d, J = 14.1 Hz, 1H), 4.37 (d, J = 14.1 Hz, 1H), 2.96 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.5 Hz, 3H); MS (ES) *m/z* 421 $(M-H)^-$.

Example 72

tert-Butyl 2-cyano-5-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate

N-[4-Bromo-2-(1-hydroxy-1-thien-3-ylpropyl)phenyl]-2-chloroacetamide

[0203] Prepared from 1-(2-amino-5-bromophenyl)-propan-1-one using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.95 (s, 1H), 8.05 (dd, J = 6.8, 2.9 Hz, 1H), 7.47 (m, 2H), 7.42 (m, 1H), 7.40 (m, 1H), 6.88 (dd, J = 4.9, 1.0 Hz, 1H), 6.74 (s, 1H), 4.32 (d, J = 31.7, 1H), 4.25 (d, J = 31.7 Hz, 1H), 2.30 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 386 $(M+H)^+$; Anal. Calc. for $C_{15}H_{15}BrClNO_2S$: C, 46.35, H, 3.89, N, 3.60. Found: C, 46.03, H, 3.73, N, 3.55.

7-Bromo-5-ethyl-5-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0204] Prepared from N-[4-bromo-2-(1-hydroxy-1-thien-3-ylpropyl)phenyl]-2-chloroacetamide using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.03 (s, 1H), 7.57 (dd, J = 4.9, 3.0 Hz, 1H), 7.45 (dd, J = 8.5, 2.2 Hz, 1H), 7.28 (d, J = 2.2 Hz, 1H), 7.26 (dd, J = 2.7, 1.4 Hz, 1H), 7.12 (dd, J = 5.2, 1.4 Hz, 1H), 7.10 (d, J = 8.5 Hz, 1H), 4.05 (d, J = 15.4 Hz, 1H), 3.93 (d, J = 15.4 Hz, 1H), 2.51 (m, 1H), 2.20 (m, 1H), 0.73 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 352 $(M+H)^+$; Anal. Calc. for $C_{15}H_{14}BrNO_2S$: C, 51.15, H, 4.01, N, 3.98. Found: C, 51.38, H, 4.09, N, 3.82.

tert-Butyl 2-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate

[0205] Prepared from 7-bromo-5-ethyl-5-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester one using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.97 (s, 1H), 7.55 (dd, J = 4.9, 2.9 Hz, 1H), 7.29 (m, 1H), 7.25 (m, 2H), 7.14 (m, 3H), 6.24 (m, 1H), 6.21 (m, 1H), 4.03 (d, J = 15.1 Hz, 1H), 3.90 (d, J = 15.1 Hz, 1H), 2.42 (m, 1H), 2.14 (m, 1H), 1.39 (s, 9H), 0.75 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 439 $(M+H)^+$.

[0206] The title compound was prepared from *tert*-butyl 2-(5-ethyl-2-oxo-5-thien-

3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.05 (s, 1H), 7.55 (dd, J = 5.4, 2.9 Hz, 1H), 7.34 (dd, J = 8.3, 2.0 Hz, 1H), 7.29 (d, J = 3.9 Hz, 1H), 7.23 (d, J = 2.0 Hz, 1H), 7.21 (dd, J = 2.9, 1.0 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.11 (dd, J = 5.4, 1.5 Hz, 1H), 6.42 (d, J = 3.9 Hz, 1H), 4.02 (d, J = 15.1 Hz, 1H), 3.93 (d, J = 15.1 Hz, 1H), 2.44 (m, 1H), 2.18 (m, 1H), 1.39 (s, 9H), 0.74 (t, J = 6.8 Hz, 3H); MS (ES) *m/z* 464 $(M+H)^+$.

Example 73

5-(5-Ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile

[0207] Prepared from *tert*-butyl 2-cyano-5-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-1-carboxylate using the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.57 (s, 1H), 10.00 (s, 1H), 7.65 (dd, J = 8.5, 1.9 Hz, 1H), 7.61 (d, J = 2.2 Hz, 1H), 7.58 (dd, J = 4.9, 2.7 Hz, 1H), 7.19 (m, 2H), 7.16 (dd, J = 5.2, 1.4 Hz, 1H), 6.97 (d, J = 3.8 Hz, 1H), 6.68 (d, J = 3.8 Hz, 1H), 3.99 (d, J = 15.4 Hz, 1H), 3.91 (d, J = 15.4 Hz, 1H), 2.53 (m, 1H), 2.32 (m, 1H), 0.75 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 364 $(M+H)^+$.

Example 74

5-(5-Ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1H-pyrrole-2-carbonitrile

[0208] Prepared from 5-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile using the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.09 (s, 1H), 7.56 (dd, J = 4.9, 2.9 Hz, 1H), 7.41 (dd, J = 8.3, 2.0 Hz, 1H), 7.27 (m, 3H), 7.16 (dd, J = 5.4, 1.5 Hz, 1H), 7.00 (d, J = 3.9 Hz, 1H), 6.30 (d, J = 3.9 Hz, 1H), 4.07 (d, J = 15.1 Hz, 1H), 3.98 (d, J = 15.1 Hz, 1H), 3.64 (s, 3H), 2.51 (m, 1H), 2.25 (m, 1H), 0.76 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 378 $(M+H)^+$.

Example 75

3-(5-Ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-fluorobenzonitrile

[0209] Prepared from 7-bromo-5-ethyl-5-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-cyano-5-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.07 (s, 1H), 8.07 (t, J = 1.5 Hz, 1H), 7.94 (dt, J = 10.3, 2.0 Hz, 1H), 7.80 (m, 1H), 7.73 (dd, J = 8.3, 2.0 Hz, 1H), 7.63 (d, J = 2.4 Hz, 1H), 7.57 (dd, J = 4.9, 2.9 Hz, 1H), 7.27 (m, 2H), 7.17 (dd, J = 4.9, 1.5 Hz, 1H), 4.02 (d, J = 15.6 Hz, 1H), 3.96 (d, J = 15.6 Hz, 1H), 2.54 (m, 1H), 2.49 (m, 1H), 0.74 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 393 $(M+H)^+$.

Example 76

7-(3-Chloro-4-fluorophenyl)-5-ethyl-5-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0210] Prepared from 7-bromo-5-ethyl-5-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-chloro-4-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.03 (s, 1H), 7.84 (dd, J = 6.9, 2.2 Hz, 1H), 7.62 (m, 2H), 7.56 (dd, J = 5.2, 3.0 Hz, 1H), 7.48 (m, 2H), 7.27 (m, 1H), 7.24 (d, J = 8.5 Hz, 1H), 7.16 (dd, J = 5.2, 1.4 Hz, 1H), 4.04 (d, J = 15.4 Hz, 1H), 3.94 (d, J = 15.4 Hz, 1H), 2.53 (m, 1H), 2.35 (m, 1H), 0.75 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 402 $(M+H)^+$;

Example 77

tert-Butyl 2-cyano-5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-H-pyrrole-1-carboxylate

N-{4-Bromo-2-[1-(2-furyl)-1-hydroxypropyl]phenyl}-2-chloroacetamide

[0211] Prepared from 1-(2-amino-5-bromophenyl)-propan-1-one in two steps

using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.96 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.60 (d, J = 1.0 Hz, 1H), 7.49 (dd, J = 8.8, 2.4 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 6.95 (s, 1H), 6.47 (m, 2H), 4.35 (s, 2H), 2.23 (q, 7.3 Hz, 2H), 0.82 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 372 $(M-H)^-$.

7-Bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one

[0212] Prepared from N-{4-bromo-2-[1-(2-furyl)-1-hydroxypropyl]phenyl}-2-chloroacetamide using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 7.72 (t, J = 1.0 Hz, 1H), 7.47 (dd, J = 8.8, 2.4 Hz, 1H), 7.17 (d, J = 2.4 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 6.48 (dd, J = 2.4, 1.0 Hz, 1H), 6.34 (d, J = 2.4 Hz, 1H), 4.21 (d, J = 15.1 Hz, 1H), 3.95 (d, J = 15.1 Hz, 1H), 2.45 (m, 1H), 2.10 (m, 1H), 0.73 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 336 $(M+H)^+$.

***tert*-Butyl 2-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-H-pyrrole-1-carboxylate**

[0213] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.02 (s, 1H), 7.69 (dd, J = 1.9, 0.8 Hz, 1H), 7.29 (dd, J = 3.3, 1.6 Hz, 1H), 7.26 (dd, J = 8.2, 1.9 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 6.97 (d, J = 2.2 Hz, 1H), 6.43 (dd, J = 3.3, 1.9 Hz, 1H), 6.32 (dd, J = 3.3, 0.8 Hz, 1H), 6.23 (m, 1H), 6.16 (dd, J = 3.3, 1.9 Hz, 1H), 4.20 (d, J = 15.4 Hz, 1H), 3.93 (d, J = 15.4 Hz, 1H), 2.43 (m, 1H), 2.07 (m, 1H), 1.37 (s, 9H), 0.75 (t, J = 7.1 Hz, 3H); Anal. Calc. for $C_{24}H_{26}N_2O_5$: C, 68.23, H, 6.20, N, 6.63. Found: C, 68.06, H, 6.24, N, 6.30.

[0214] The title compound was prepared from *tert*-butyl 2-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-H-pyrrole-1-carboxylate using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.10 (s, 1H), 7.70 (s, 1H), 7.35 (dd, J = 8.5, 1.9 Hz, 1H), 7.28 (d, J = 3.8 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.09 (d, J = 1.9 Hz, 1H), 6.43 (m, 1H), 6.39 (d, J = 3.8 Hz, 1H), 6.28 (d, J = 3.0 Hz, 1H), 4.17 (d, J = 15.4 Hz, 1H), 3.95 (d, J = 15.4 Hz, 1H), 2.46 (m, 1H), 2.11 (m, 1H), 1.41 (s, 9H), 0.74 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 448 $(M+H)^+$; Anal. Calc.

for $C_{25}H_{25}N_3O_5$: C, 67.10, H, 5.63, N, 9.39. Found: C, 66.98, H, 5.47, N, 9.30.

Example 78

5-[5-Ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-H-pyrrole-2-carbonitrile

[0215] Prepared from *tert*-butyl 2-cyano-5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-H-pyrrole-1-carboxylate using the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.55 (s, 1H), 10.04 (s, 1H), 7.72 (d, J = 1.1 Hz, 1H), 7.65 (dd, J = 8.5, 1.9 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 3.6 Hz, 1H), 6.63 (d, J = 3.8 Hz, 1H), 6.46 (m, 1H), 6.26 (d, J = 3.3 Hz, 1H), 4.11 (d, J = 15.6 Hz, 1H), 3.93 (d, J = 15.6 Hz, 1H), 2.55 (m, 1H), 2.25 (m, 1H), 0.75 (t, J = 7.4 Hz, 3H); MS (ES) *m/z* 348 $(M+H)^+$.

Example 79

5-[5-Ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-H-pyrrole-2-carbonitrile

[0216] Prepared from 5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-H-pyrrole-2-carbonitrile using the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.14 (s, 1H), 7.71 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 7.16 (s, 1H), 7.00 (d, J = 3.9 Hz, 1H), 6.46 (m, 1H), 6.34 (d, J = 3.4 Hz, 1H), 6.28 (d, J = 3.9 Hz, 1H), 4.23 (d, J = 15.1 Hz, 1H), 3.98 (d, 15.1 Hz, 1H), 3.62 (s, 3H), 2.47 (m, 1H), 2.18 (m, 1H), 0.75 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 362 $(M+H)^+$.

Example 80

7-(3-Chloro-4-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one

[0217] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-

2(H)-one and 3-chloro-4-fluorobenzeneboronic acid using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 8.32 (s, 1H), 7.81 (dd, J = 7.1, 2.5 Hz, 1H), 7.72 (s, 1H), 7.63 (dd, J = 8.5, 2.2 Hz, 1H), 7.47 (t, J = 9.0 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 6.47 (m, 1H), 6.32 (d, J = 3.3 Hz, 1H), 4.19 (d, J = 15.4 Hz, 1H), 3.95 (d, J = 15.4 Hz, 1H), 2.52 (m, 1H), 2.26 (m, 1H), 0.75 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 386 $(M+H)^+$.

Example 81

3-[5-Ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile

[0218] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 3-cyano-5-fluorobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.13 (s, 1H), 8.03 (s, 1H), 7.90 (dt, J = 10.5, 2.2 Hz, 1H), 7.80 (m, 1H), 7.74 (m, 2H), 7.52 (d, J = 2.2 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 6.46 (m, 1H), 6.29 (d, J = 3.3 Hz, 1H), 4.14 (d, J = 15.6 Hz, 1H), 3.96 (d, J = 15.6 Hz, 1H), 2.54 (m, 1H), 2.49 (m, 1H), 0.75 (t, J = 7.4 Hz, 3H); MS (ES) *m/z* 753 $(2M+H)^+$.

Example 82

7-(3-Bromo-5-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

5-Ethyl-5-(2-furyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0219] To a stirred solution of 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one (5.0g, 14.8mmol) in DMF (100 mL) was added potassium acetate (4.5g, 44.4 mmol), bis(pinacolato)diboron (7.5g, 29.6 mmol), and [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium (II) (0.6g, 0.8 mmol) at rt under nitrogen. The mixture was heated at reflux under nitrogen overnight. The solution was allowed to cool to room temperature and partitioned between

ammonium chloride solution (sat.) (100 mL) and ethyl acetate (150 mL). The aqueous layer was extracted with ethyl acetate (3x50 mL). The organic layers were combined, dried over magnesium sulfate, filtered through silica gel and triturated with ether to give 5-ethyl-5-(2-furyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one as a white solid (2.9g, 50%). ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 7.71 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.16 (d, J = 8.1 Hz, 1H), 6.48 (d, J = 3.2 Hz, 1H), 6.30 (d, J = 3.2 Hz, 1H), 4.21 (d, J = 15.4 Hz, 1H), 4.04 (d, J = 15.4 Hz, 1H), 2.45 (m, 1H), 2.00 (m, 1H), 1.25 (s, 8H), 0.71 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 384 $(M+H)^+$; Anal. Calc. for $C_{21}H_{26}BNO_5$: C:65.81 H:6.84 N:3.65 Found: C:65.51 H:6.96 N:3.51.

[0220] The title compound was prepared from 5-ethyl-5-(2-furyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 1,3-dibromo-5-fluorobenzene using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.05 (s, 1H), 7.68 (s, 1H), 7.63 (m, 2H), 7.46 (d, J = 9.8 Hz, 2H), 7.35 (s, 1H), 7.23 (d, J = 8.6 Hz, 1H), 6.44 (m, 1H), 6.28 (m, 1H), 4.15 (d, J = 15.3 Hz, 1H), 3.93 (d, J = 15.3 Hz, 1H), 2.47 (m, 1H), 2.29 (m, 1H), 0.72 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 430 $(M+H)^+$; Anal. Calc. for $C_{21}H_{17}BrFNO_3$: C:58.62 H:3.98 N:3.26 Found: C:58.26 H:3.87 N:2.95.

Example 83

7-(3-Bromo-5-chlorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0221] Prepared from 5-ethyl-5-(2-furyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 1,3-dibromo-5-chlorobenzene using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 7.75 (m, 1H), 7.71 (m, 1H), 7.65 (m, 3H), 7.39 (d, J = 2.3 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 6.47 (m, 1H), 6.32 (d, J = 3.3 Hz, 1H), 4.18 (d, J = 15.4 Hz, 1H), 4.04 (d, J = 15.4 Hz, 1H), 2.51 (m, 1H), 2.35 (m, 1H), 0.76 (t, J = 7.0 Hz, 3H); MS (ES) *m/z* 448 $(M+H)^+$; Anal. Calc. for $C_{21}H_{17}BrClNO_3$: C:56.46 H:3.84 N:3.14 Found: C:56.87 H:3.95 N:3.05.

Example 84

3-Chloro-5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]benzonitrile

[0222] To a stirred solution of 7-(3-bromo-5-chlorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one (0.6g, 1.3 mmol) in DMF (15mL) was added zinc cyanide (0.19g, 1.6 mmol), tris(dibenzylideneacetone)dipalladium (0.06g, 0.07mmol), and diphenylphosphinoferrocene (0.04g, 0.07mmol). The resulting solution was heated for 2 hr. at 120 °C. The solution was allowed to cool to room temperature and partitioned between ammonium chloride solution (sat.) and ethyl acetate. The organic layer was dried over magnesium sulfate, concentrated and purified using silica gel flash column (25% ethyl acetate/ hexane) to give 0.23g of the title compound as an off-white solid (45%). ^{1}H-NMR (DMSO-d_6) δ 10.10 (s, 1H), 8.12 (t, J = 1.5 Hz, 1H), 8.03 (t, J = 2.0 Hz, 1H), 7.97 (dd, J = 2.0, 1.5 Hz, 1H), 7.74 (m, 2H), 7.51 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 6.47 (dd, J = 3.4, 2.0 Hz, 1H), 6.30 (dd, J = 3.2, 0.7 Hz, 1H), 4.15 (d, J = 15.6 Hz, 1H), 3.97 (d, J = 15.6 Hz, 1H), 2.56 (m, 1H), 2.48 (m, 1H), 0.76 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 393 $(M+H)^+$; Anal. Calc. for $C_{22}H_{17}ClN_2O_3$: C:67.26 H:4.36 N:7.13 Found: C:67.18 H:4.05 N:6.87.

Example 85

4-[5-Ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-2-fluorobenzonitrile

[0223] Prepared from 5-ethyl-5-(2-furyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 4-bromo-2-fluorobenzonitrile using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.15 (s, 1H), 7.97 (m, 1H), 7.83 (dd, J = 11.2, 1.7 Hz, 1H), 7.76 (dd, J = 8.5, 2.2 Hz, 1H), 7.72 (m, 1H), 7.68 (m, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 6.47 (m, 1H), 6.32 (dd, J = 3.4, 1.0 Hz, 1H), 4.19 (d, J = 15.4 Hz,

1H), 3.98 (d, J = 15.4 Hz, 1 H), 2.56 (m, 1H), 2.34 (m, 1H), 0.76 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 377 $(M+H)^+$; Anal. Calc. for $C_{22}H_{17}FN_2O_3$: C:70.21 H:4.55 N:7.44 Found: C:69.30 H:4.39 N:7.13.

Example 86

7-(3-Chloro-5-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0224] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 3-chloro-5-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.09 (s, 1H), 7.72 (m, 1H), 7.68 (dd, J = 8.3, 2.2 Hz, 1H), 7.52 (m, 1H), 7.48 (m, 1H), 7.40 (m, 2H), 7.27 (d, J = 8.5 Hz, 1H), 6.47 (m, 1H), 6.32 (dd, J = 3.4, 1.0 Hz, 1H), 4.19 (d, J = 15.4 Hz, 1H), 3.97 (d, J = 15.4 Hz, 1H), 2.53 (m, 1H), 2.33 (m, 1H), 0.76 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 386 $(M+H)^+$; Anal. Calc. for $C_{21}H_{17}ClFNO_3$: C:65.38 H:4.44 N:3.63 Found: C:64.76 H:4.44 N:3.42.

Example 87

7-(4-Chloro-3-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0225] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 3-chloro-4-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 8.34 (s, 1H), 7.71 (m, 3H), 7.45 (dd, J = 8.4, 2.1 Hz, 1H), 7.38 (d, J = 2.1 Hz, 1H), 7.28 (dd, J = 8.7, 2.0 Hz, 1H), 6.47 (m, 1H), 6.33 (m, 1H), 4.20 (d, J = 15.3 Hz, 1H), 3.97 (d, J = 15.3 Hz, 1H), 2.51 (m, 1H), 2.28 (m, 1H), 0.76 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 368 $(M+H)^+$; Anal. Calc. for $C_{21}H_{17}ClFNO_3$: C:65.38 H:4.44 N:3.63 Found: C:61.12 H:4.05 N:2.49.

Example 88

7-(2,3-Difluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0226] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 2,3-difluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.11 (s, 1H), 7.71 (s, 1H), 7.64 (m, 1H), 7.57 (m, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.43 (m, 1H), 7.28 (m, 2H), 6.47 (dd, J = 3.6, 1.8 Hz, 1H), 6.35 (d, J = 3.6 Hz, 1H), 4.25 (d, J = 14.9 Hz, 1H), 3.97 (d, J = 14.9 Hz, 1H), 2.52 (m, 1H), 2.14 (m, 1H), 0.76 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 370 $(M+H)^+$; Anal. Calc. for $C_{21}H_{17}F_2NO_3$: C:68.29 H:4.64 N:3.79 Found: C:66.40 H:4.43 N:3.33.

Example 89

4-[5-Ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-2-furonitrile

[0227] Prepared from 5-ethyl-5-(2-furyl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 4-bromo-furan-2-carbonitrile using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.02 (s, 1H), 8.55 (d, J = 2.2 Hz, 1H), 8.10 (d, J = 2.0 Hz, 1H), 7.71 (d, J = 1.9 Hz, 1H), 7.58 (m, 1H), 7.41 (s, 1H), 7.24 (dd, J = 8.4, 2.7 Hz, 1H), 6.45 (s, 1H), 6.25 (d, J = 2.7 Hz, 1H), 4.11 (d, J = 15.6 Hz, 1H), 3.96 (d, J = 15.6 Hz, 1H), 2.50 (m, 1H), 2.33 (m, 1H), 0.75 (m, 3H); MS (ES) *m/z* 349 $(M+H)^+$; Anal. Calc. for $C_{20}H_{16}N_2O_4$: C:68.96 H:4.63 N:8.04 Found: C:68.38 H:4.73 N:7.84.

Example 90

7-(3,4-Difluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0228] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 3,4-difluorobenzeneboronic acid using the coupling procedure

described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.06 (s, 1H), 7.73 (s, 1H), 7.71 (m, 1H), 7.53 (m, 3H), 7.33 (s, 1H), 7.26 (d, J = 8.4 Hz, 1H), 6.47 (m, 1H), 6.33 (s, 1H), 4.21 (d, J = 15.4 Hz, 1H), 3.96 (d, J = 15.4 Hz, 1H), 2.51 (m, 1H), 2.27 (m, 1H), 0.76 (t, J = 7.0 Hz, 3H); MS (ES) *m/z* 370 $(M+H)^+$; Anal. Calc. for $C_{21}H_{17}F_2NO_3$: C:68.29 H:4.64 N:3.79 Found: C:66.29 H:4.49 N:3.33.

Example 91

5-Ethyl-7-(4-fluorophenyl)-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0229] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 4-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.04 (s, 1H), 7.71 (s, 1H), 7.58 (m, 3H), 7.31 (m, 4H), 6.47 (dd, J = 3.2, 1.8 Hz, 1H), 6.35 (m, 1H), 4.24 (d, J = 15.2 Hz, 1H), 3.96 (d, J = 15.2 Hz, 1H), 2.51 (m, 1H), 2.24 (m, 1H), 0.75 (t, J = 6.0 Hz, 3H); MS (ES) *m/z* 352 $(M+H)^+$; Anal. Calc. for $C_{21}H_{18}FNO_3$: C:71.78 H:5.16 N:3.99 Found: C:70.73 H:4.93 N:3.77.

Example 92

5-Ethyl-7-(2-fluorophenyl)-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0230] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 2-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 7.70 (s, 1H), 7.64 (m, 1H), 7.51 (m, 3H), 7.28 (m, 3H), 6.47 (dd, J = 3.3, 1.9 Hz, 1H), 6.35 (dd, J = 3.2, 0.7 Hz, 1H), 4.27 (d, J = 15.2 Hz, 1H), 3.97 (d, J = 15.2 Hz, 1H), 2.51 (m, 1H), 2.13 (m, 1H), 0.77 (t, J = 7.3 Hz, 3H); MS (ES) *m/z* 352 $(M+H)^+$; Anal. Calc. for $C_{21}H_{18}FNO_3$: C:71.78 H:5.16 N:3.99 Found: C:68.53 H:4.91 N:3.35.

Example 93

7-(3,5-Dichlorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0231] Prepared from 7-bromo-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 3,5-dichlorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.09 (s, 1H), 7.71 (d, J = 0.7 Hz, 1H), 7.68 (dd, J = 8.4, 2.1 Hz, 1H), 7.64 (d, J = 1.9 Hz, 2H), 7.57 (m, 1H), 7.43 (d, J = 4.6 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 6.47 (m, 1H), 6.32 (dd, J = 3.2, 0.6 Hz, 1H), 4.18 (d, J = 15.5 Hz, 1H), 3.92 (d, J = 15.5 Hz, 1H), 2.51 (m, 1H), 2.35 (m, 1H), 0.76 (t, J = 7.1 Hz, 3H); MS (ES) *m/z* 402 $(M+H)^+$; Anal. Calc. for $C_{21}H_{17}Cl_2NO_3$: C:62.70 H:4.26 N:3.48 Found: C:61.70 H:4.46 N:3.02.

Example 94

tert-Butyl 2-cyano-5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-1-carboxylate

[0232] Prepared from 2-(5-ethyl-1-methyl-2-oxo-5-thiophen-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-pyrrole-1-carboxylic acid *tert*-butyl ester and chlorosulfonyl isocyanate using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 7.64 (d, J = 1.8 Hz, 1H), 7.60 (dd, J = 8.3, 1.8 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.36 (m, 2H), 6.92 (dd, J = 5.0, 3.6 Hz, 1H), 6.62 (dd, J = 3.5, 1.2 Hz, 1H), 6.59 (d, J = 3.8 Hz, 1H), 4.07 (d, J = 12.3 Hz, 1H), 4.00 (d, J = 12.3 Hz, 1H), 2.75 (s, 3H), 2.31 (m, 1H), 2.18 (m, 1H), 1.40 (s, 9H), 0.83 (t, J = 7.2 Hz, 3H); MS (ES) *m/z* 478 $(M+H)^+$.

Example 95

5-(5-Ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-2-carbonitrile

[0233] Prepared from *tert*-butyl 2-cyano-5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-1-carboxylate using the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.82 (s, 1H), 7.97 (d, J = 1.8 Hz, 1H), 7.89 (dd, J = 8.4, 1.9 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.34 (dd, J =

5.0, 1.1 Hz, 1H), 7.05 (d, J = 3.8 Hz, 1H), 6.91 (dd, J = 5.0, 3.6, Hz, 1H), 6.83 (d, J = 3.9 Hz, 1H), 6.63 (dd, J = 3.5, 1.1 Hz, 1H), 4.04 (s, 2H), 2.71 (s, 3H), 2.45 (m, 1H), 2.29 (m, 1H), 0.87 (t, J = 7.1 Hz, 3H); MS (ES) m/z 378 $(M+H)^+$.

Example 96

5-(5-Ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-H-pyrrole-2-carbonitrile

[0234] Prepared from 5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-2-carbonitrile using the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 7.67 (m, 2H), 7.50 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 5.0 Hz, 1H), 7.08 (d, J = 4.0 Hz, 1H), 6.93 (t, J = 4.7 Hz, 1H), 6.66 (d, J = 3.5 Hz, 1H), 6.48 (d, J = 4.0 Hz, 1H), 4.05 (s, 2H), 3.76 (s, 3H), 2.79 (s, 3H), 2.38 (m, 1H), 2.29 (m, 1H), 0.86 (t, J = 7.0 Hz, 3H); MS (ES) m/z 392 $(M+H)^+$; Anal. Calc. for $C_{22}H_{21}N_3O_2S$: C, 67.50, H, 5.41, N, 10.73. Found: C, 67.34, H, 5.46, N, 10.41.

Example 97

1-Ethyl-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1 -benzoxazepin-7-yl)-H-pyrrole-2-carbonitrile

[0235] Prepared from 5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile and iodoethane using the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.33 (s, 1 H), 7.62 (dd, J = 5.4, 1.5 Hz, 2H), 7.43 (dd, J = 8.3, 2.0 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.01 (dd, J = 4.9, 3.4, 2H), 6.98 (d, J = 3.9 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 3.9, 1.5 Hz, 2H), 6.17 (d, J = 3.9 Hz, 1H), 4.24 (s, 2H), 3.86 (q, J = 7.3 Hz, 2H), 1.17 (t, J = 7.3 Hz, 3H); MS (ES) m/z 446 $(M+H)^+$.

Example 98

1-Benzyl-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-2-carbonitrile

[0236] Prepared from 5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1 -benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile and benzyl bromide using the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.28 (s, 1H), 7.58 (dd, *J* = 4.9, 1.0 Hz, 2H), 7.40 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.26 (m, 4H), 7.11 (d, *J* = 3.9 Hz, 1H), 6.94 (dd, *J* = 4.9, 3.4 Hz, 2H), 6.90 (d, *J* = 2.0 Hz, 1H), 6.66 (dd, *J* = 7.3, 1.0 Hz, 2H), 6.52 (dd, *J* = 3.4, 1.0 Hz, 2H), 6.31 (d, *J* = 3.9 Hz, 1H), 5.16 (s, 2H), 4.13 (s, 2H); MS (ES) *m/z* 508 $(M+H)^+$.

Example 99

7-(3-Chloro-4-fluorophenyl)-5,5-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(H)-one

[0237] Prepared from 7-bromo-5,5-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-chloro-4-fluorobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.27 (s, 1H), 7.68 (m, 4H), 7.48 (t, *J* = 8.8 Hz, 1H), 7.38 (m, 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.16 (d, *J* = 2.1 Hz, 1H), 7.04 (dd, *J* = 5.0, 3.6 Hz, 2H), 6.93 (dd, *J* = 3.6, 1.2 Hz, 2H), 4.22 (s, 2H); MS (ES) *m/z* 456 $(M+H)^+$; Anal. Calc. For $C_{23}H_{15}ClFNO_2S_2$: C, 60.59, H, 3.32, N, 3.07. Found: C, 60.35, H, 3.28, N, 2.91.

Example 100

3-Fluoro-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile

[0238] Prepared from 7-bromo-5,5-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3i)-one and 5-fluoro-3-cyanobenzeneboronic acid using the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.32 (s, 1H), 7.81 (m, 3H), 7.63 (m, 3H), 7.30 (m, 2H), 7.05 (m, 4H), 4.21 (s, 2H); MS (ES) *m/z* 445 $(M-H)^-$.

Example 101

tert-Butyl 2-[5,5-bis(5-bromothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-_H_-pyrrole-1-carboxylate

[0239] To a stirred mixture of *tert*-butyl 2-cyano-5-[2-oxo-5,5-di(2-thienyl)-,1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1H-pyrrole-1-carboxylate (0.5 g, 0.97 mmol) and potassium acetate (0.38 g, 3.7 mmol) in glacial acetic acid (12 mL) was added bromine (0.1 mL, 1.9 mmol) at room temperature. After 1hr, reaction mixture was slowly quenched with sodium bicarbonate solution (sat.) and extracted with ethyl acetate (3x40 mL). The combined organic layers were washed with water, brine and dried over magnesium sulfate. The solvent was removed *in vacuo* and residue purified on silica gel column (30% ethyl acetate in hexane) to give the title compound as yellowish solid (0.16g, 25%). ^{1}H-NMR (DMSO-d_6) δ 10.29 (s, 1H), 7.43 (dd, J = 8.3, 2.0 Hz, 1H), 7.26 (d, J = 3.9 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 7.12 (d, J = 3.9 Hz, 2H), 7.05 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 3.9 Hz, 2H), 6.33 (d, J = 3.4 Hz, 1H), 4.23 (s, 2H), 1.37 (s, 9H); MS (ES) *m/z* 674 (M-H)$^-$; Anal. Calc. for $C_{27}H_{21}Br_2N_3O_4S_2$: C:48.01 H:3.13 N:6.22 Found: C:47.94 H:3.16 N:5.92.

Example 102

5-[5,5-Bis(5-bromothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-_H_-pyrrole-2-carbonitrile

[0240] Prepared from *tert*-butyl 2-[5,5-bis(5-bromothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-*H*-pyrrole-1-carboxylate in two steps using the procedure described in examples 2 and 3. ^{1}H-NMR (DMSO-d_6) δ 10.38 (s, 1H), 7.62 (dd, J = 5.0, 1.0 Hz, 2H), 7.46 (dd, J = 8.3, 1.9 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.05 (m, 3H), 6.88 (d, J = 2.4 Hz, 2H), 4.26 (s, 2H), 3.49 (s, 3H); MS (ES) *m/z* 588 (M-H)$^-$; Anal. Calc. for $C_{23}H_{15}Br_2N_3O_2S_2$: C:46.88 H:2.57 N:7.13 Found: C:47.23 H:2.60 N:7.10.

Example 103

5-[5,5-Bis(5-cyanothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-

***H*-pyrrole-2-carbonitrile**

[0241] Prepared from 5-[5,5-Bis-(5-bromo-thiophen-2-yl)-2-oxo-1,2,3,5-tetrahydro-benzo[e][1,4]oxazepin-7-yl]-1H-pyrrole-2-carbonitrile generally according to example 84. ^{1}H-NMR (DMSO-d_6) δ 12.55 (s, 1H), 10.30 (s, 1H), 7.93 (d, J = 3.8 Hz, 2H), 7.78 (dd, J = 8.2, 2.2 Hz, 1H), 7.46 (d, J = 2.2 Hz, 1H), 7.21 (m, 3H), 6.97 (dd, J = 3.8, 2.2 Hz, 1H), 6.58 (dd, J = 3.8, 2.7 Hz, 1H), 4.28 (s, 2H); MS (ES) *m/z* 466 $(M-H)^-$.

Example 104

7-(3-Chloro-4-fluorophenyl)-5,5-dimethyl-1,3,4,5-tetrahydro-H-1-benzazepin-2-one

5,5-Dimethyl-1,3,4,5-tetrahydro-H-1-benzazepin-2-one

[0242] To a stirred solution of levulinic acid (2.8g, 19.5 mmol) in 65 mL of ether at 0 °C was slowly added methyl magnesium bromide (3M, 13 mL, 39 mmol). The resulting solution was allowed to stir overnight at room temperature. The solution was cooled to 0 °C, decomposed with 50% sulfuric acid, extracted with ether, dried over magnesium sulfate, and concentrated to give 5,5-dimethyl-dihydro-furan-2-one (400 mg, 18%) as a brown oil.

[0243] To a stirred solution of aluminum chloride (25.5g, 191.7 mmol) in benzene (100 mL) at 0 °C was added a solution of above brown oil (7.3g, 63.9 mmol) in 50mL of benzene. The resulting solution was then heated to reflux 3 h. The solution was then cooled to rt, quenched slowly in 1N HCl and ice. The benzene layer was successively washed with dilute 1N HCl, water, sodium carbonate solution, dried over magnesium sulfate, and concentrated to give 4,4-dimethyl-3,4-dihydro-2H-naphthalen-1-one (8.4g 75%).

[0244] A mixture of 4,4-dimethyl-3,4-dihydro-2H-naphthalen-1-one (0.5g, 2.9mmol), sodium azide (0.32g, 4.9 mmol), and polyphosphoric acid (50mL) was stirred via a mechanical stirrer at 60 °C overnight. The solution was then poured on ammonium hydroxide with cooling and extracted with ethyl acetate. The organic

layer was dried ($MgSO_4$), concentrated, and purified on a silica gel flash column (ethyl acetate:hexane/2:5) to give the title compound (0.07g, 13%). ^{1}H-NMR (DMSO-d_6) δ 9.52 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 7.4 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 7.7 Hz, 1H), 2.19 (t, J = 6.8 Hz, 2H), 2.00 (t, J = 7.3 Hz, 2H), 1.32 (s, 6H); MS (ES) *m/z* 190 $(M+H)^+$; Anal. Calc. For $C_{12}H_{15}NO$: C, 76.16, H, 7.99, N, 7.40. Found: C, 76.07, H, 8.09, N, 7.43.

7-Bromo-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one

[0245] To a mixture of glacial acetic acid (6 mL) and potassium acetate (0.2 g, 2.1 mmol) was added 5,5-dimethyl-1,3,4,5-tetrahydro-H-1-benzazepin-2-one (0.1 g, 0.5 mmol). Bromine (0.1 mL, 1.9 mmol) was added and the solution was allowed to stir overnight at room temperature. The solution was partitioned between brine and ethyl acetate. The organic layer was separated, dried over magnesium sulfate, and concentrated. The product was crystallized from ether to give 7-bromo-5,5-dimethyl-1,3,4,5-tetrahydro-2H-1-benzazepin-2-one as an off-white solid (0.07 g, 50%). ^{1}H-NMR (DMSO-d_6) δ 9.62 (s, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.41 (dd, J = 8.8, 2.4 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 2.20 (t, J = 6.8 Hz, 2H), 2.00 (t, J = 7.8 Hz, 2H), 1.33 (s, 6H); MS (ES) *m/z* 268 $(M+H)^+$; Anal. Calc. For $C_{12}H_{14}BrNO$: C, 53.75, H, 5.26, N, 5.22. Found: C, 49.14, H, 4.57, N, 4.68.

[0246] The title compound was prepared from 5,5-dimethyl-1,3,4,5-tetrahydro-H-1-benzazepin-2-one and 3-chloro-4-fluorobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.65 (s, 1H), 7.89 (dd, J = 7.3, 2.4 Hz, 1H), 7.69 (m, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.53 (m, 2H), 7.05 (d, J = 7.8 Hz, 1H), 2.25 (t, J = 6.8 Hz, 2H), 2.03 (t, J = 7.3 Hz, 2H), 1.39 (s, 6H); MS (ES) *m/z* 318 $(M+H)^+$.

Example 105

3-(5,5-Dimethyl-2-oxo-2,3,4,5-tetrahydro-H-1-benzazepin-7-yl)-5-fluorobenzonitrile

[0247] Prepared from 5,5-dimethyl-1,3,4,5-tetrahydro-H-1-benzazepin-2-one and

5-fluoro-3-cyanobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 9.70 (s, 1H), 8.10 (t, J = 1.5 Hz, 1H), 7.97 (dt, J = 10.3, 2.0 Hz, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.64 (dd, J = 7.8, 2.0 Hz, 1H), 7.08 (d, J = 8.3 Hz, 1H), 2.26 (t, J = 7.3 Hz, 2H), 2.03 (t, J = 7.3 Hz, 2H), 1.40 (s, 6H); MS (ES) *m/z* 309 $(M+H)^+$.

Example 106

7-(3-Chloro-4-fluorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(H)-one

[0248] Prepared from 7-bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-chloro-4-fluorobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.13 (s, 1H), 7.86 (dd, J = 6.8, 2.0 Hz, 1H), 7.64 (m, 2H), 7.55 (m, 2H), 7.48 (t, J = 8.8 Hz, 1H), 7.25 (d, J = 8.3 Hz, 1H), 6.99 (dd, J = 4.9, 3.4 Hz, 1H), 6.91 (dd, J = 3.4, 1.0 Hz, 1H), 4.16 (d, J = 16.1 Hz, 1H), 4.06 (d, J = 16.1 Hz, 1H), 2.08 (s, 3H); MS (ES) *m/z* 388 $(M+H)^+$; Anal. Calc. For $C_{20}H_{15}ClFNO_2S$: C, 61.93, H, 3.90, N, 3.61. Found: C, 61.88, H, 3.99, N, 3.35.

Example 107

3-Fluoro-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile

[0249] Prepared from 7-bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 5-fluoro-3-cyanobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.18 (s, 1H), 8.09 (s, 1H), 7.96 (dt, J = 9.8, 2.4 Hz, 1H), 7.80 (dt, J = 8.3, 1.5 Hz, 1H), 7.76 (dd, J = 8.3, 2.0 Hz, 1H), 7.72 (d, J = 2.0 Hz, 1H), 7.55 (dd, J = 5.4, 1.5 Hz, 1H), 7.28 (d, J = 8.3 Hz, 1H), 6.99 (dd, J = 4.9, 3.4 Hz, 1H), 6.89 (dd, J = 3.4, 1.5 Hz, 1H), 4.17 (d, J = 16.1 Hz, 1H), 4.04 (d, J = 16.1 Hz, 1H), 2.12 (s, 3H); MS (ES) *m/z* 379 $(M+H)^+$.

Example 108

4-Methyl-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile

[0250] Prepared from 7-bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 5-bromo-4-methylthiophene-2-carbonitrile generally according to the coupling procedure described in examples 82 and 1. ^{1}H-NMR (DMSO-d_6) δ 10.26 (s, 1H), 7.83 (s, 1H), 7.56 (dd, J = 4.9, 1.1 Hz, 1H), 7.47 (dd, J = 8.5, 2.2 Hz, 1H), 7.32 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 7.00 (m, 1H), 6.96 (m, 1H), 4.23 (d, J = 15.9 Hz, 1H), 4.13 (d, J = 15.9 Hz, 1H), 2.19 (s, 3H), 2.03 (s, 3H); MS (ES) *m/z* 381 $(M+H)^+$; Anal. Calc. For $C_{20}H_{16}N_2O_2S_2$: C, 63.14, H, 4.24, N, 7.36. Found: C, 62.85, H, 4.16, N, 7.09.

Example 109

2-Fluoro-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile

[0251] Prepared from 7-bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 5-bromo-2-fluorobenzonitrile generally according to the coupling procedure described in examples 82 and 1. ^{1}H-NMR (DMSO-d_6) δ 10.14 (s, 1H), 8.27 (dd, J = 5.6, 2.4 Hz, 1H), 8.06 (m, 1H), 7.68 (dd, J = 8.8, 2.4 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.60 (t, J = 9.3 Hz, 1H), 7.55 (dd, J = 5.4, 1.5 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 6.98 (m, 1H), 6.89 (dd, J = 3.9, 1.5 Hz, 1H), 4.16 (d, J = 15.6 Hz, 1H), 4.05 (d, J = 15.6 Hz, 1H), 2.10 (s, 3H); MS (ES) *m/z* 379 $(M+H)^+$.

Example 110

4-(5-Methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile

[0252] Prepared from 7-bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-

benzoxazepin-2(3*H*)-one and 4-bromofuran-2-carbonitrile generally according to the coupling procedure described in examples 82 and 1. ^{1}H-NMR (DMSO-d_6) δ 10.09 (s, 1H), 8.60 (s, 1H), 8.16 (s, 1H), 7.61 (m, 2H), 7.54 (dd, J = 4.9, 1.0 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 6.97 (dd, J = 5.4, 3.9 Hz, 1H), 6.84 (dd, J = 3.4, 1.0 Hz, 1H), 4.16 (d, J = 15.6 Hz, 1H), 4.00 (d, J = 15.6 Hz, 1H), 2.07 (s, 3H); MS (ES) *m/z* 351 $(M+H)^+$.

Example 111

5-(5,5-Dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile

[0253] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 5-bromo-2-fluorobenzonitrile generally according to the coupling procedure described in examples 82 and 1. ^{1}H-NMR (DMSO-d_6) δ 10.02 (s, 1H), 8.32 (dd, J = 6.3, 2.4 Hz, 1H), 8.11 (m, 1H), 7.62 (m, 1H), 7.58 (m, 2H), 7.19 (d, J = 8.8 Hz, 1H), 4.26 (s, 2H), 1.62 (s, 6H); MS (ES) *m/z* 311 $(M+H)^+$.

Example 112

4-(5,5-Dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile

[0254] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 4-bromofuran-2-carbonitrile generally according to the coupling procedure described in examples 82 and 1. ^{1}H-NMR (DMSO-d_6) δ 9.96 (s, 1H), 8.61 (s, 1H), 8.19 (s, 1H), 7.56 (d, J = 1.9 Hz, 1H), 7.50 (dd, J = 8.3, 2.0 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 4.24 (s, 2H), 1.59 (s, 6H); MS (ES) *m/z* 283 $(M+H)^+$.

Example 113

***tert*-Butyl 2-cyano-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-1-carboxylate**

2-Bromo-N-{4-bromo-2-[hydroxy(dithien-3-yl)methyl]phenyl}acetamide

[0255] Prepared from methyl 2-amino-5-bromobenzoate in two steps generally according to the procedures described in example 24. ^{1}H-NMR (DMSO-d_6) δ 10.26 (s, 1H), 8.03 (d, J = 5.3 Hz, 1H), 7.73 (s, 1H), 7.59 (m, 3H), 7.09 (m, 2H), 6.98 (dd, J = 5.0, 1.3 Hz, 2H), 6.72 (d, J = 2.4 Hz, 1H), 3.91 (s, 2H); MS (ES) *m/z* 486 (M-H)$^-$; Anal. Calc. For $C_{17}H_{13}Br_2NO_2S_2$: C, 41.91, H, 2.69, N, 2.87. Found: C, 41.62, H, 2.71, N, 2.72.

7-Bromo-5,5-dithien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(H)-one

[0256] Prepared from 2-bromo-N-{4-bromo-2-[hydroxy(dithien-3-yl)methyl]phenyl}acetamide generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.21 (s, 1H), 7.60 (dd, J = 4.9, 2.9 Hz, 2H), 7.50 (dd, J = 8.8, 2.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.08 (dd, J = 3.4, 1.5 Hz, 2H), 6.90 (dd, J = 4.9, 1.5 Hz, 2H), 6.75 (d, J = 2.4 Hz, 1H), 4.19 (s, 2H); MS (ES) *m/z* 408 (M+H)$^+$.

***tert*-Butyl 2-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-1-carboxylate**

[0257] Prepared from 7-bromo-5,5-dithien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.13 (s, 1H), 7.55 (dd, J = 4.9, 2.9 Hz, 2H), 7.27 (m, 2H), 7.16 (d, J = 8.3 Hz, 1H), 7.07 (dd, J = 2.9, 1.5 Hz, 2H), 6.89 (dd, J = 4.9, 1.5 Hz, 2H), 6.70 (d, J = 2.4 Hz, 1H), 6.19 (m, 1H), 6.06 (m, 1H), 4.17 (s, 2H), 1.36 (s, 9H); MS (ES) *m/z* 493 (M+H)$^+$.

[0258] The title compound was prepared from *tert*-butyl 2-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-1-carboxylate and chlorosulfonyl isocyanate steps generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.20 (s, 1H), 7.56 (dd, J = 4.9, 2.9 Hz, 2H), 7.35 (dd, J = 8.3, 2.0 Hz, 1H), 7.23 (m, 2H), 7.07 (dd, J = 2.9, 1.5 Hz, 2H), 6.89 (dd, J = 5.4, 1.5 Hz, 2H), 6.74 (d, J = 2.0 Hz, 1H), 6.26 (d, J = 3.4 Hz, 1H), 4.18 (s, 2H), 1.38 (s, 9H); MS (ES) *m/z* 518 (M+H)$^+$.

Example 114

5-(2-Oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-2-carbonitrile

[0259] Prepared from *tert*-butyl 2-cyano-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-1-carboxylate generally according to the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.49 (s, 1H), 10.14 (s, 1H), 7.61 (dd, J = 8.5, 2.2 Hz, 1H), 7.57 (dd, J = 5.2, 3.0 Hz, 2H), 7.23 (d, J = 8.5 Hz, 1H), 7.16 (m, 3H), 6.96 (dd, J = 5.2, 1.4 Hz, 2H), 6.91 (d, J = 3.8 Hz, 1H), 6.30 (d, J = 3.8 Hz, 1H), 4.12 (s, 2H); MS (ES) *m/z* 418 $(M+H)^+$.

Example 115

1-Methyl-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-2-carbonitrile

[0260] Prepared from 5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-H-pyrrole-2-carbonitrile and iodomethane generally according to the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.26 (s, 1H), 7.59 (dd, J = 5.2, 3.0 Hz, 2H), 7.45 (dd, J = 8.2, 2.2 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.10 (dd, J = 3.0, 1.4 Hz, 2H), 6.95 (m, 3H), 6.79 (d, J = 2.2 Hz, 1H), 6.14 (d, J = 4.1 Hz, 1H), 4.20 (s, 2H), 3.45 (s, 3H); MS (ES) *m/z* 432 $(M+H)^+$.

Example 116

3-Fluoro-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile

[0261] Prepared from 7-bromo-5,5-dithien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 5-fluoro-3-cyanobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.25 (s, 1H), 7.78 (m, 1H), 7.73 (m, 2H), 7.59 (m, 3H), 7.31 (d, J = 8.3 Hz, 1H), 7.18 (dd, J = 2.9,

1.5 Hz, 2H), 7.06 (d, J = 2.4 Hz, 1H), 6.97 (dd, J = 4.9, 1.5 Hz, 2H), 4.18 (s, 2H); MS (ES) *m/z* 447 $(M+H)^+$.

Example 117

7-(3-Chloro-4-fluorophenyl)-5,5-dithien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(H)-one

[0262] Prepared from 7-bromo-5,5-dithien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(H)-one and 3-chloro-4-fluorobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.20 (s, 1H), 7.62 (dd, J = 8.3, 2.0 Hz, 1H), 7.58 (m, 3H), 7.45 (t, J = 8.8 Hz, 1H), 7.34 (m, 1H), 7.28 (d, J = 8.3 Hz, 1H), 7.13 (dd, J = 2.9, 1.5 Hz, 2H), 6.95 (d, J = 1.0 Hz, 1H), 6.94 (d, J = 1.5 Hz, 2H), 4.18 (s, 2H); MS (ES) *m/z* 456 $(M+H)^+$.

Example 118

tert-Butyl 2-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-*H*-pyrrole-1-carboxylate

N-{2-[Bis(3-chlorophenyl)(hydroxy)methyl]-4-bromophenyl}-2-bromoacetamide

[0263] Prepared from Prepared from methyl 2-amino-5-bromobenzoate in two steps generally according to the procedure described in example 24. ^{1}H-NMR (DMSO-d_6) δ 9.89 (s, 1H), 8.01 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.61 (dd, J = 8.8, 2.4 Hz, 1H), 7.43 (m, 4H), 7.35 (t, J = 1.5 Hz, 2H), 7.05 (dt, J = 7.3, 1.5 Hz, 2H), 6.60 (d, J = 2.4 Hz, 1H), 3.82 (s, 2H); MS (ES) *m/z* 542 $(M-H)^-$; Anal. Calc. for $C_{21}H_{15}Br_2Cl_2NO_2$: C:46.36 H:2.78 N:2.57 Found: C:46.63 H:2.77 N:2.57.

7-Bromo-5,5-bis(3-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0264] Prepared from *N*-{2-[bis(3-chlorophenyl)(hydroxy)methyl]-4-bromophenyl}-2-bromoacetamide generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.13 (s, 1H), 7.62 (dd, J = 8.8, 2.4 Hz, 1H),

7.47 (m, 4H), 7.21 (t, J = 2.0 Hz, 2H), 7.10 (d, J = 8.3 Hz, 1H), 7.02 (dt, J = 7.3, 1.5 Hz, 2H), 6.61 (d, J = 2.4 Hz, 1H), 4.28 (s, 2H); MS (ES) *m/z* 464 $(M+H)^+$; Anal. Calc. for $C_{21}H_{14}BrCl_2NO_2$: C:54.46 H:3.05 N:3.02 Found: C:54.54 H:3.49 N:2.67.

***tert*-Butyl 2-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate**

[0265] Prepared from 7-bromo-5,5-bis(3-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.10 (s, 1H), 7.43 (m, 5H), 7.25 (dd, J = 2.9, 1.5 Hz, 1H), 7.20 (t, J = 1.5 Hz, 2H), 7.14 (d, J = 8.3 Hz, 1H), 7.06 (dt, J = 7.3, 1.5 Hz, 2H), 6.50 (d, J = 2.0 Hz, 1H), 6.20 (t, J = 3.4 Hz, 1H), 6.08 (dd, J = 3.4, 2.0 Hz, 1H), 4.29 (s, 2H), 1.35 (s, 9H); MS (ES) *m/z* 547 $(M-H)^-$; Anal. Calc. for $C_{30}H_{26}Cl_2N_2O_4$: C:65.58 H:4.77 N:5.10 Found: C:64.81 H:4.92 N:4.53.

[0266] The title compound was prepared from *tert*-butyl 2-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.20 (s, 1H), 7.47 (dd, J = 8.2, 2.2 Hz, 1H), 7.44 (m, 4H), 7.24 (d, J = 3.8 Hz, 1H), 7.20 (m, 3H), 7.06 (dt, J = 7.7, 1.1 Hz, 2H), 6.56 (d, J = 2.2 Hz, 1H), 6.28 (d, J = 3.8 Hz, 1H), 4.28 (s, 2H), 1.37 (s, 9H); MS (ES) *m/z* 574 $(M+H)^+$; Anal. Calc. for $C_{31}H_{25}Cl_2N_3O_4$: C:64.82 H:4.39 N:7.31 Found: C:64.56 H:4.62 N:7.00.

Example 119

5-[5,5-Bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-2-carbonitrile

[0267] Prepared from *tert*-butyl 2-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-*H*-pyrrole-1-carboxylat generally according to the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.53 (s, 1H), 10.14 (s, 1H), 7.70 (dd, J = 8.2, 2.2 Hz, 1H), 7.46 (m, 4H), 7.27 (d, J = 1.6 Hz,

2H), 7.21 (d, J = 8.2 Hz, 1H), 7.16 (dt, J = 6.6, 2.2 Hz, 2H), 7.03 (d, J = 1.6 Hz, 1H), 6.92 (d, J = 3.8 Hz, 1H), 6.30 (d, J = 3.8 Hz, 1H), 4.19 (s, 2H); MS (ES) *m/z* 472 $(M-H)^-$; Anal. Calc. for $C_{26}H_{17}Cl_2N_3O_2$: C:65.84 H:3.61 N:8.86 Found: C:65.60 H:3.50 N:8.78.

Example 120

5-[5,5-Bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-*H*-pyrrole-2-carbonitrile

[0268] Prepared from 5-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-2-carbonitrile and iodomethane generally according to the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.22 (s, 1H), 7.55 (dd, J = 8.2, 2.2 Hz, 1H), 7.45 (m, 4H), 7.27 (m, 3H), 7.09 (dt, J = 7.1, 1.6 Hz, 2H), 6.96 (d, J = 3.8 Hz, 1H), 6.67 (d, J = 2.2 Hz, 1H), 6.17 (d, J = 3.8 Hz, 1H), 4.28 (s, 2H), 3.48 (s, 3H); MS (ES) *m/z* 486 $(M-H)^-$; Anal. Calc. for $C_{27}H_{19}Cl_2N_3O_2$: C:66.40 H:3.92 N:8.60 Found: C:66.07 H:4.32 N:7.86.

Example 121

5-[5,5-Bis(3-chlorophenyl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-*H*-pyrrole-2-carbonitrile

[0269] Prepared from 5-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-2-carbonitrile and iodomethane generally according to the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 7.76 (dd, J = 8.2, 2.2 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.42 (m, 4H), 7.37 (s, 2H), 7.09 (m, 2H), 6.99 (d, J = 3.8 Hz, 1H), 6.58 (d, J = 2.2 Hz, 1H), 6.24 (d, J = 3.8 Hz, 1H), 4.25 (s, 2H), 3.58 (s, 3H), 2.65 (s, 3H); MS (ES) *m/z* 504 $(M+H)^+$; Anal. Calc. for $C_{28}H_{21}Cl_2N_3O_2$: C:66.94 H:4.21 N:8.36 Found: C:66.38 H:4.44 N:8.15.

Example 122

3-[5,5-Bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-

fluorobenzonitrile

[0270] Prepared from 7-bromo-5,5-bis(3-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 5-fluoro-3-cyanobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.23 (s, 1H), 7.80 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.78 (m, 1H), 7.62 (dt, *J* = 9.9, 2.7 Hz, 1H), 7.46 (m, 5H), 7.29 (m, 3H), 7.17 (dt, *J* = 7.1, 1.6 Hz, 2H), 6.96 (d, *J* = 2.2 Hz, 1H), 4.25 (s, 2H); MS (ES) *m/z* 501 $(M-H)^-$; Anal. Calc. for $C_{28}H_{17}Cl_2FN_2O_2$: C:66.81 H:3.40 N:5.57 Found: C:66.47 H:3.31 N:5.40.

Example 123

7-(3-Chloro-4-fluoro-phenyl)-5,5-bis-(3-chloro-phenyl)-1,5-dihydro-benzo[e][1,4]oxazepin-2-one

[0271] Prepared from 7-bromo-5,5-bis(3-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-chloro-4-fluorobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.17 (s, 1H), 7.73 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.60 (dd, *J* = 7.1, 2.7 Hz, 1H), 7.46 (m, 5H), 7.33 (m, 1H), 7.27 (t, *J* = 1.6 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.11 (dt, *J* = 7.1, 1.6 Hz, 2H), 6.80 (d, *J* = 2.2 Hz, 1H), 4.28 (s, 2H); MS (ES) *m/z* 510 $(M-H)^-$; Anal. Calc. for $C_{27}H_{17}Cl_3FNO_2$: C:63.24 H:3.34 N:2.73 Found: C:60.08 H:3.00 N:2.28.

Example 124

tert-Butyl 2-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-*H*-pyrrole-1-carboxylate

N-{2-[Bis(4-chlorophenyl)(hydroxy)methyl]-4-bromophenyl}-2-bromoacetamide

[0272] Prepared from methyl 2-amino-5-bromobenzoate in two steps generally according to the procedure described in example 24. ^{1}H-NMR (DMSO-d_6) δ 10.01

(s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.94 (s, 1H), 7.59 (dd, J = 8.8, 2.4 Hz, 1H), 7.44 (m, 4H), 7.19 (m, 4H), 6.58 (d, J = 2.4 Hz, 1H), 3.84 (s, 2H); MS (ES) *m/z* 542 (M-H)$^-$; Anal. Calc. for $C_{21}H_{15}Br_2Cl_2NO_2$: C:46.36 H:2.78 N:2.57 Found: C:46.59 H:2.82 N:2.36.

7-Bromo-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0273] Prepared from *N*-{2-[bis(4-chlorophenyl)(hydroxy)methyl]-4-bromophenyl}-2-bromoacetamide generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.13 (s, 1H), 7.58 (dd, J = 8.3, 2.0 Hz, 1H), 7.46 (m, 4H), 7.14 (m, 4H), 7.10 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 4.24 (s, 2H); MS (ES) *m/z* 462 (M-H)$^-$; Anal. Calc. for $C_{21}H_{14}BrCl_2NO_2$: C:54.46 H:3.05 N:3.02 Found: C:54.54 H:3.00 N:2.78.

***tert*-Butyl 2-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate**

[0274] Prepared from 7-bromo-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.08 (s, 1H), 7.42 (m, 4H), 7.35 (dd, J = 8.3, 2.4 Hz, 1H), 7.25 (dd, J = 2.9, 1.5 Hz, 1H), 7.16 (m, 5H), 6.51 (d, J = 2.0 Hz, 1H), 6.19 (t, J = 3.4 Hz, 1H), 6.08 (dd, J = 3.4, 2.0 Hz, 1H), 4.24 (s, 2H), 1.35 (s, 9H); MS (ES) *m/z* 547 (M-H)$^-$; Anal. Calc. for $C_{30}H_{26}Cl_2N_2O_4$: C:65.58 H:4.77 N:5.10 Found: C:64.81 H:4.80 N:4.80.

[0275] The title compound was prepared from *tert*-butyl 2-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate generally according to the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.18 (s, 1H), 7.43 (m, 5H), 7.23 (d, J = 3.9 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.15 (m, 4H), 6.58 (d, J = 2.0 Hz, 1H), 6.26 (d, J = 3.9 Hz, 1H), 4.23 (s, 2H), 1.35 (s, 9H); MS (ES) *m/z* 572 (M-H)$^-$; Anal. Calc. for $C_{31}H_{25}Cl_2N_3O_4$: C:64.82 H:4.39 N:7.31 Found: C:63.79 H:4.52 N:7.31.

Example 125

5-[5,5-Bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-2-carbonitrile

[0276] Prepared from *tert*-butyl 2-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-*H*-pyrrole-1-carboxylate generally according to the procedure described in example 2. ^{1}H-NMR (DMSO-d_6) δ 12.49 (s, 1H), 10.14 (s, 1H), 7.67 (dd, J = 8.2, 1.9 Hz, 1H), 7.46 (m, 4H), 7.25 (m, 4H), 7.20 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 1.9 Hz, 1H), 6.92 (d, J = 3.8 Hz, 1H), 6.30 (d, J = 3.8 Hz, 1H), 4.15 (s, 2H); MS (ES) *m/z* 472 $(M-H)^-$; Anal. Calc. for $C_{26}H_{17}Cl_2N_3O_2$: C:65.84 H:3.61 N:8.86 Found: C:65.14 H:4.56 N:7.41.

Example 126

5-[5,5-Bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-*H*-pyrrole-2-carbonitrile

[0277] Prepared from 5-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-2-carbonitrile and iodomethane generally according to the procedure described in example 3. ^{1}H-NMR (DMSO-d_6) δ 10.23 (s, 1H), 7.52 (dd, J = 8.3, 2.0 Hz, 1H), 7.45 (m, 4H), 7.26 (d, J = 8.3 Hz, 1H), 7.19 (m, 4H), 6.95 (d, J = 3.9 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 6.14 (d, J = 4.4 Hz, 1H), 4.25 (s, 2H), 3.46 (s, 3H); MS (ES) *m/z* 486 $(M-H)^-$; Anal. Calc. for $C_{27}H_{19}Cl_2N_3O_2$: C:66.40 H:3.92 N:8.60 Found: C:65.97 H:4.40 N:7.85.

Example 127

3-[5,5-Bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile

[0278] Prepared from 7-bromo-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 5-fluoro-3-cyanobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ

10.24 (s, 1H), 7.79 (m, 3H), 7.59 (dt, J = 9.8, 2.0 Hz, 1H), 7.46 (m, 4H), 7.28 (d, J = 8.3 Hz, 1H), 7.26 (m, 4H), 6.93 (d, J = 2.0 Hz, 1H), 4.20 (s, 2H); MS (ES) *m/z* 501 $(M-H)^-$; Anal. Calc. for $C_{28}H_{17}Cl_2FN_2O_2$: C:66.81 H:3.40 N:5.57 Found: C:66.46 H:3.43 N:5.48.

Example 128

7-(3-Chloro-4-fluorophenyl)-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0279] Prepared from 7-bromo-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and 3-chloro-4-fluorobenzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.17 (s, 1H), 7.69 (dd, J = 8.3, 2.4 Hz, 1H), 7.58 (dd, J = 6.8, 2.4 Hz, 1H), 7.46 (m, 5H), 7.31 (m, 1H), 7.24 (d, J = 8.3 Hz, 1H), 7.22 (m, 4H), 6.78 (d, J = 2.0 Hz, 1H), 4.23 (s, 2H); MS (ES) *m/z* 510 $(M-H)^-$; Anal. Calc. for $C_{27}H_{17}Cl_3FNO_2$: C:63.24 H:3.34 N:2.73 Found: C:62.75 H:3.58 N:2.72.

Example 129

7-(3,5-Difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0280] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3,5-difluorobenzene boronic acid generally according to the coupling procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.04 (s, 1H), 7.61-7.57 (m, 2H), 7.52-7.45 (m, 2H), 7.23-7.17 (m, 2H), 4.72 (s, 2H), 1.60 (s, 6H); MS (FI) *m/z* 304 $[M + H]^+$.

Example 130

7-(3,5-Difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-thione

[0281] Prepared from 7-(3,5-difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and Lawesson's Reagent using the procedure of example 10. ^{1}H-NMR (DMSO-d_6) δ 12.01 (s, 1H), 7.70-7.63 (m, 2H), 7.59-7.48 (m, 2H), 7.41 (d, J = 8.82 Hz, 1H), 7.28-7.18 (m, 1H), 4.51 (s, 2H), 1.62 (s, 6H); MS (FI) *m/z* 318 [M - H]$^-$.

Example 131

5-(5,5-Dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1–benzoxazepin-7-yl)-4-methylthiophene-2-carbonitrile

[0282] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 5-bromo-4-methyl-thiophene-2-carbonitrile using the coupling procedures in examples 82 and 1. ^{1}H-NMR (DMSO-d6) δ 10.13 (s, 1H), 7.87 (s, 1H), 7.41-7.36 (m, 2H), 7.22 (d, J = 8.32 Hz, 1H), 4.29 (s, 2H), 2.29 (s, 3H), 1.58 (s, 6H); MS (FI) *m/z* 311 ([M - H]$^-$, 20%).

Example 132

4-Methyl-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile

[0283] Prepared from 7-bromo-5-methyl-5-phenyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 5-bromo-4-methyl-thiophene-2-carbonitrile using the coupling procedures of examples 82 and 1. ^{1}H-NMR (DMSO-d6) δ 10.15 (s, 1H), 7.85 (s, 1H), 7.49 (m, 1H), 7.38-7.21 (m, 7H), 4.29 (d, J = 15.19 Hz, 1H), 4.04 (d, J = 15.05 Hz, 1H), 2.22, (s, 3H), 1.93 (s, 3H); MS (ES) *m/z* 375 ([M + H]$^+$, 100%).

Example 133

5-(1,5-Dimethyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1H-pyrrole-2-carbonitrile

[0284] Prepared from 5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-

benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile generally according to procedure of example 3. ^{1}H-NMR (DMSO-d_6) δ 7.84 (d, J = 1.71 Hz, 1H), 7.71 (dd, J = 8.32, 1.54 Hz, 1H), 7.47 (d, J = 8.25 Hz, 1H), 7.19-7.28 (m, 3H), 7.06-7.11 (m, 3H), 6.56 (d, J = 3.77 Hz, 1H), 3.99 (s, 2H), 3.83 (s, 3H), 2.42, (s, 3H), 1.77 (s, 3H); Anal. Calc. For $C_{23}H_{21}N_3O_2$: C:74.37 H:5.70 N:11.31 Found: C:74.29 H:5.56 N:11.06.

Example 134

1-Methyl-5-(5-methyl-5-thien-3-yl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile

[0285] Prepared from 1-methyl-5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1H-pyrrole-2-carbonitrile and Lawesson's reagent generally according to example 10. ^{1}H NMR (DMSO-d_6): δ 12.11 (s, 1H), 7.45-7.54 (m, 3H), 7.37 (d, , J = 1.62 Hz, 1H), 7.29 (dd, J = 2.87, 1.3 Hz, 1H), 7.06 (dd, J = 5.02, 1.28 Hz, 1H), 7.03 (d, J = 4.09 Hz, 1H), 6.37 (d, J = 4.09 Hz, 1H), 4.46 (d, J = 15.33 Hz, 1H), 4.35 (d, J = 15.33 Hz, 1H), 3.70 (s, 3H), 1 .99 (s, 3H); MS (ESI) *m/z* 378 ([M-H]-); Anal. calcd for $C_{20}H_{17}N_3OS_2$: C:63.3 H:4.52 N:11.07 Found: C:63.06 H:4.76 N:10.29.

Example 135

5-(5-Methyl-5-thien-3-yl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1H-pyrrole-2-carbonitrile

[0286] Prepared from 5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1H-pyrrole-2-carbonitrile and Lawesson's reagent generally according to example 10. ^{1}H NMR (DMSO-d_6): δ 12.67 (s, 1H), 12.01 (s, 1H), 7.71-7.74 (m, 2H), 7.54 (dd, J = 5.08, 2.99 Hz, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.2 (dd, J = 2.87, 1.3 Hz, 1H), 7.05 (dd, J = 5.04, 1.31 Hz, 1H), 7.00 (dd, J = 3.84, 2.1 Hz, 1H), 6.76 (dd, J = 3.79, 2.51 Hz, 1H), 4.4 (d, J = 15.34 Hz, 1H), 4.27 (d, J = 15.33 Hz, 1H), 1.98 (s, 3H); MS (ESI) *m/z* 366 ([M+H]+); MS (ESI) *m/z* 364 ([M-H]-). Anal. calcd for $C_{19}H_{15}N_3OS_2$: C:62.44 H:4.14 N:11.5 Found: C:61.9 H:4.14

N:11.27.

Example 136

1-Ethyl-5-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0287] Prepared from 5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1H-pyrrole-2-carbonitrile generally according to the procedure described in example 3. An off-white solid: mp 179-180 °C; ^{1}H NMR (DMSO-d_6): δ 10.19 (s, 1H), 7.56 (dd, J = 5.04, 2.94 Hz, 1H), 7.37 (dd, J = 8.35, 1.94 Hz, 1H), 7.66-7.22 (m, 2H), 7.16 (d, J = 1.91 Hz, 1H), 7.08 (dd, J = 5.14, 1.28 Hz, 1H), 7.03 (d, J = 4.02 Hz, 1H), 6.26 (d, J = 4.02 Hz, 1H), 4.20 (d, J = 15.95 Hz, 1H), 4.09 (d, J = 15.98 Hz, 1H), 3.98 (q, J = 7.28 Hz, 2H), 1.95 (s, 3H), 1.16 (t, J = 7.16 Hz, 3H); MS (ESI) *m/z* 378 ([M+H]+); MS (ESI) *m/z* 755 ([2M+H]$^+$); Anal. calcd for $C_{21}H_{19}N_3O_2S$: C:66.82 H:5.07 N:11.13 Found: C:66.38 H:4.94 N:10.71.

Example 137

5-(5-Methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1,2-dicarbonitrile

[0288] Prepared from 5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1H-pyrrole-2-carbonitrile and cyanogenbromide using the similar procedure of example 3. An off-white solid: mp 226-227 °C; ^{1}H NMR (DMSO-d_6): δ 10.25 (s, 1H), 7.62-7.65 (m, 2H), 7.57 (dd, J = 5.03, 2.93 Hz, 1H), 7.52 (d, J = 4.03 Hz, 1H), 7.32 (d, J = 9.04 Hz, 1H), 7.19 (dd, J = 2.85, 1.25 Hz, 1H), 7.09 (dd, J = 5.05, 1.23 Hz, 1H), 6.83 (d, J = 4.04 Hz, 1H), 4.17 (d, J = 16.03 Hz, 1H), 4.02 (d, J = 16.06 Hz, 1H), 1.96 (s, 3H); MS (ESI) *m/z* [M-H]- (373); MS (ESI) *m/z* [M+H]+ (375); MS (ESI) *m/z* [2M+H]+ (749); Anal. calcd for $C_{20}H_{14}N_4O_2S$: C:64.16 H:3.77 N:14.96 Found: C:62.78 H:3.75 N:13.94.

Example 138

7-(2-Furyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0289] Prepared from 7-bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-furylboronic acid generally according to the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.14 (s, 1H), 7.56-6.89 (m, 9H), 4.17 (d, *J* = 15.62 Hz, 1H), 4.05 (d, *J* = 15.62 Hz, 1H), 2.0 (s, 3H).

Example 139

5-(5-Ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile

[0290] Prepared from 7-bromo-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 5-bromo-2-fluorobenzonitrile generally according to the procedures described in examples 82 and 1. An off-white solid: mp 197-199 °C; ^{1}H NMR (DMSO-d_6): δ 10.09 (s, 1H), 8.25 (dd, *J* = 6.35, 2.44 Hz, 1H), 8.02-8.05 (m, 1H), 7.68 (dd, *J* = 8.3, 1.95 Hz, 1H), 7.61 (d, *J* = 1.95 Hz, 1H), 7.7 (dd, J_{HF} = 9.28 Hz, J_{HH} = 9.28 Hz, 1H), 7.56 (dd, *J* = 5.37, 1.47 Hz, 1H), 7.27 (d, *J* = 8.79 Hz, 1H), 7.0 (dd, *J* = 4.88, 3.42 Hz, 1H), 6.95 (dd, *J* = 3.9, 1.47 Hz, 1H), 4.08 (d, *J* = 15.62 Hz, 1H), 3.94 (d, *J* = 15.13 Hz, 1H), 2.46-2.57 (m, 2H), 0.76 (t, *J* = 6.83 Hz, 3H); MS (ESI) *m/z* 393 ($[M+H]^+$); MS (ESI) *m/z* 391 ($[M-H]^-$); Anal. calcd for $C_{22}H_{17}FN_2O_2S$: C:67.33 H:4.37 N:7.14 Found: C:67.26 H:4.38 N:6.90.

Example 140

5-(5-Ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-4-methylthiophene-2-carbonitrile

[0291] Prepared from 7-bromo-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 5-bromo-4-methyl-thiophene-2-carbonitrile generally according to the procedures described in examples 82 and 1. An off-white solid: mp 182-184 °C; ^{1}H NMR (DMSO-d_6): δ 10.19 (s, 1H), 7.83 (s, 1H), 7.57 (dd, *J* = 4.88, 0.98 Hz, 1H), 7.46 (dd, *J* = 8.3, 1.95 Hz, 1H), 7.33 (d, *J* = 1.95 Hz, 1H), 7.29 (d, *J* = 8.3 Hz, 1H),

7.07 (dd, J = 4.88, 3.42 Hz, 1H), 6.98 (dd, J = 3.42, 0.98 Hz, 1H), 4.14 (d, J = 15.6 Hz, 1H), 3.98 (d, J = 15.13 Hz, 1H), 2.47 (m, 1H), 2.35 (m, 1H), 2.21 (s, 3H), 0.77 (t, J = 6.84 Hz, 3H); MS (ESI) *m/z* 395 ($[M+H]^+$); MS (ESI) *m/z* 393 ($[M-H]^-$); Anal. calcd for $C_{21}H_{18}N_2O_2S_2$: C:63.93 H:4.60 N:7.10 Found: C:60.33 H:4.13 N:6.65.

Example 141

4-(5-Ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile

[0292] Prepared from 7-bromo-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 4-bromo-2-cyanofuran generally according to the procedures described in examples 82 and 1. A white solid: mp 99-100 °C; ^{1}H NMR (DMSO-d_6): δ 10.04 (s,1H), 8.60 (s, 1H), 8.17 (s, 1H), 7.54-7.61 (m, 3H), 7.22 (d, J = 8.45 Hz, 1H), 6.99 (dd, J = 4.99, 3.60 Hz, 1H), 6.90 (dd, J = 3.48, 1.02 Hz, 1H), 4.40, (d, J = 15.42, 1H), 3.94 (d, J = 15.47 Hz, 1H), 2.5 (m, 2H), 0.76 (t, J = 7.02 Hz, 3H); MS (ESI) *m/z* 365 ($[M+H]^+$); MS (ESI) *m/z* 363 ($[M-H]^-$); Anal. calcd for $C_{20}H_{16}N_2O_3S$: C:65.92 H:4.43 N:7.69 Found: C:64.84 H:4.59 N:6.98.

Example 142

5-(5-Ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile

[0293] Prepared from 5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile generally according to example 3. ^{1}H NMR (DMSO-d_6): δ 8.43 (dd, J = 5.86, 2.44 Hz, 1H), 8.18-8.21 (m, 1H), 7.91 (d, J = 1.95 Hz, 1H), 7.88 (dd, J = 8.3, 1.95 Hz, 1H), 7.66 (t, J = 8.79 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.34 (dd, J = 4.88, 1.46 Hz, 1H), 6.91 (dd, J = 4.88, 3.42 Hz, 1H), 6.65 (dd, J = 3.42, 0.98 Hz, 1H), 4.05 (s, 2H), 2.75 (s, 3H), 2.46 (m, 1H), 2.35 (m, 1H), 0.85 (t, J = 7.32 Hz, 3H); MS (ESI) *m/z* 407 ($[M+H]^+$).

Example 143

4-(5-Ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile

[0294] Prepared from 7-bromo-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 4-bromo-2-cyanothiophene generally according to the procedures described in examples 82 and 1. A yellowish solid: mp 202-204 °C; ^{1}H NMR (DMSO-d_6): δ 10.06 (s, 1H), 8.48 (s, 1H), 8.33 (s, 1H), 7.64-7.7 (m, 2H), 7.55 (d, *J* = 5.0 Hz, 1H), 7.23 (d, *J* = 8.48 Hz, 1H), 6.92-7.03 (m, 2H), 4.06 (d, *J* = 15.52 Hz, 1H), 3.94 (d, *J* = 15.44 Hz, 1H), 3.37 (m, 1H), 2.5 (m, 1H), 0.76 (t, *J* = 6.79 Hz, 1H); MS (ESI) *m/z* 381 ([M+H]+); MS (ESI) *m/z* 379 ([M-H]-); Anal. calcd for $C_{20}H_{16}N_2O_2S_2$: C:63.14 H:4.24 N:7.36 Found: C:62.53 H:4.25 N:7.12.

Example 144

1-Benzyl-5-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0295] Prepared from 5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1H-pyrrole-2-carbonitrile and benzylbromide generally according to example 3. ^{1}H NMR (DMSO-d_6): δ 10.12 (s, 1H), 7.53 (dd, *J* = 5.03, 2.97 Hz, 1H), 7.36 (dd, *J* = 8.33, 1.78 Hz, 1H), 7.24-7.28 (m, 3H), 7.20 (d, *J* = 8.42 Hz, 1H), 7.15 (d, *J* = 4.03 Hz, 1H), 7.05 (d, *J* = 1.84 Hz, 1H), 6.93-6.98 (m, 2H), 6.76-6.79 (m, 2H), 6.42 (d, *J* = 4.04 Hz, 1H), 5.27 (s, 2H), 4.11 (d, *J* = 15.9 Hz, 1H), 3.96 (d, *J* = 15.9 Hz, 1H), 1.66 (s, 3H); MS (ESI) *m/z* 440 ($[M+H]^+$); MS (ESI) *m/z* 438 ($[M-H]^-$).

Examples 145-156

[0296] The following examples were prepared from 7-bromo-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and corresponding aryl boronic acid generally according to the procedure described in example 1. The compound was purified on HPLC using YMC combi pro C18 Column (5 micron, 12 nm, 50 X 4.4

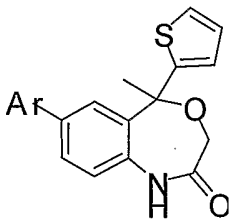
mm).

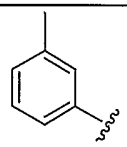
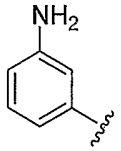
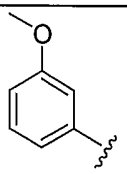
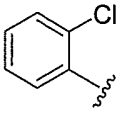
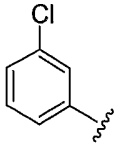
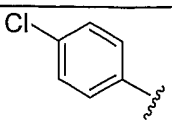
Mobile Phase A: acetonitrile with 0.1% TFA

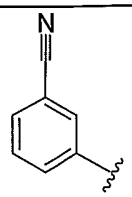
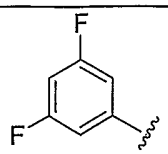
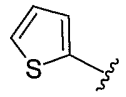
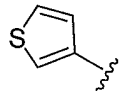
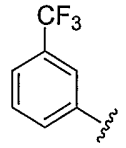
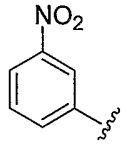
Mobile Phase B: Water with 0.1% TFA

Conditions: 1 mL/ min., 10% A to 100% A 10 minute linear gradient, 100% A for 3 minutes.

UV detection at 220 and 254 nm.



Compounds	R	Retention Time	MS (ES) *m/z*
5-Methyl-5-thiophen-2-yl-7-m-tolyl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		9.88	349
7-(3-Amino-phenyl)-5-methyl-5-thiophen-2-yl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		5.49	350
7-(3-Methoxy-phenyl)-5-methyl-5-thiophen-2-yl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		7.36	365
7-(2-Chloro-phenyl)-5-methyl-5-thiophen-2-yl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		9.84	369
7-(3-Chloro-phenyl)-5-methyl-5-thiophen-2-yl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		10.23	369
7-(4-Chloro-phenyl)-5-methyl-5-thiophen-2-yl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		10.28	369

3-(5-Methyl-2-oxo-5-thiophen-2-yl-1,2,3,5-tetrahydro-benzo[e][1,4]oxazepin-7-yl)-benzonitrile		8.66	360
7-(3,5-Difluoro-phenyl)-5-methyl-5-thiophen-2-yl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		10.00	371
5-Methyl-5,7-di-thiophen-2-yl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		9.09	341
5-Methyl-5-thiophen-2-yl-7-thiophen-3-yl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		9.05	341
5-Methyl-5-thiophen-2-yl-7-(3-trifluoromethyl-phenyl)-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		10.42	403
5-Methyl-7-(3-nitro-phenyl)-5-thiophen-2-yl-1,5-dihydro-benzo[e][1,4]oxazepin-2-one		9.30	380

Example 157

tert-Butyl 2-cyano-5-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate

N-(4-Bromo-2-[di(2-furyl)(hydroxy)methyl]phenyl}-2-chloroacetamide

[0297] Prepared from methyl 2-amino-5-bromobenzoate in two step generally according to the procedure described in example 24. ^{1}H-NMR (DMSO-d_6) δ 10.4 (s, 1H), 8.06 (d, J = 8.79 Hz, 1H), 8.04 (s, 1H), 7.70-7.71 (m, 2H), 7.55 (dd, J = 8.79, 2.44 Hz, 1H), 6.67 (d, J = 2.44 Hz, 1H), 6.49-6.50 (m, 2H), 6.23-6.24 (m, 2H), 4.23 (s, 2H); MS (ES) *m/z* 408/410/412 ([M - H]$^-$, 100%).

7-Bromo-5,5-di(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0298] Prepared from N-(4-bromo-2-[di(2-furyl)(hydroxy)methyl]phenyl}-2-chloroacetamide using the procedure described in example 1. ^{1}H-NMR (DMSO-d_6) δ 10.27 (s, 1H), 7.78 (d, J = 0.98 Hz, 2H), 7.52 (dd, J = 8.79, 2.44 Hz, 1H), 7.18 (d, J = 8.79 Hz, 1H), 6.73 (d, J = 2.44 Hz, 1H), 6.51 (dd, J = 3.42, 1.95 Hz, 2H), 6.24 (dd, J = 3.42, 0.98 Hz, 2H), 4.1 (s, 2H); MS (ES) *m/z* 372/374 ([M - H]$^-$, 100%); MS (ES) *m/z* 374/376 ([M + H]$^+$, 100%).

***tert*-Butyl 2-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate**

[0299] Prepared from 7-bromo-5,5-di(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the coupling procedure of example 1. ^{1}H NMR (DMSO-d_6): δ 10.21 (s, 1H), 7.73 (m, 2H), 7.30(dd, J = 8.3, 1.95 Hz, 1H), 7.26 (dd, J = 3.42, 1.47 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 1.95 Hz, 1H), 6.47 (dd, J = 3.42, 1.95 Hz, 2H), 6.19-6.20 (m, 3H), 6.06 (dd, J = 3.42, 1.95 Hz, 1H), 4.15 (s, 2H), 1.35 (s, 9H); MS (ESI) *m/z* 461 ([M+H]+); MS (ESI) *m/z* 459 ([M-H]-).

[0300] The title compound was prepared from *tert*-butyl 2-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate generally according to the procedure of example 1. ^{1}H NMR (DMSO-d_6): δ 10.29 (s, 1H), 7.74 (dd, J = 1.95, 0.98 Hz, 2H), 7.40 (dd, J = 8.3, 1.95 Hz, 1H), 7.26 (d, J = 8.3 Hz, 1H), 7.24 (d, J = 3.91 Hz, 1H), 6.67 (d, J = 1.95 Hz) , 1H, 6.48 (d, J = 1.95 Hz, 1H), 6.48 (dd, J = 3.42, 1.95 Hz, 2H), 6.20 (dd, J = 3.42, 0.98 Hz, 2H), 4.16 (s, 2H), 1.37 (s, 9H); MS (ESI) *m/z* 486 ([M+H]+); MS (ESI) *m/z* 484 ([M-H]-).

Example 158

7-(3-Chloro-4-fluorophenyl)-5,5-di(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0301] Prepared from 7-bromo-5,5-di(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-chloro-4-fluoro benzeneboronic acid generally according to the

coupling procedure of example 1. ^{1}H NMR (DMSO-d_6): δ 10.28 (s, 1H), 7.77 (dd, *J* = 1.95, 0.98 Hz, 2H), 7.66 (dd, *J* = 8.3, 1.95 Hz, 1H), 7.59 (dd, *J* = 7.32, 2.44 Hz, 1H), 7.45 (dd, $J_{HF} = J_{HH}$ = 8.79 Hz, 1H), 7.33-7.36 (m, 1H), 7.32 (d, *J* = 8.79 Hz, 1H), 6.89 (d, *J* = 2.44 Hz, 1H), 6.51 (dd, *J* = 3.42, 1.95 Hz, 2H), 6.27 (dd, *J* = 3.42, 0.98 Hz, 2H), 4.17 (s, 2H); MS (ESI) *m/z* 422/424 ([M-H]-); Anal. calcd for $C_{23}H_{15}ClFNO_4$: C:65.18 H:3.57 N:3.30 Found: C:64.16 H:3.66 N:2.78.

Example 159

3-[5,5-Di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile

[0302] Prepared from 7-bromo-5,5-di(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-cyano-5-fluorobenzeneboronic acid generally according to the coupling procedure of example 1. ^{1}H NMR (DMSO-d_6): δ 10.34 (s, 1H), 7.73-7.87 (m, 5H), 7.59 (dt, *J* = 10.25, 1.95 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 6.98 (d, *J* = 1.95 Hz, 1H), 1H, 6.52 (dd, *J* = 3.42, 1.95 Hz, 2H), 6.29 (dd, *J* = 3.42, 0.98 Hz, 2H), 4.16 (s, 2H); MS (ESI) *m/z* 415 ([M+H]+); MS (ESI) *m/z* 413 ([M-H]-); Anal. calcd for $C_{24}H_{15}FN_2O_4$: C:69.56 H:3.65 N:6.76 Found: C:67.60 H:3.77 N:5.81.

Example 160

5-[5,5-Di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-2-carbonitrile

[0303] Prepared from *tert*-butyl 2-cyano-5-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate generally according to example 2. ^{1}H NMR (DMSO-d_6): δ 12.61 (s, 1H), 10.3 (s, 1H), 7.84 (dd, *J* = 1.92, 0.82 Hz, 2H), 7.72 (dd, *J* = 8.51, 2.20 Hz, 1H), 7.33 (d, *J* = 8.51 Hz, 1H), 7.15 (d, *J* = 2.20 Hz, 1H), 6.99 (d, *J* = 3.85 Hz, 1H), 6.57 (dd, *J* = 3.30, 1.92 Hz, 2H), 6.40 (d, *J* = 3.85 Hz, 1H), 6.32 (dd, *J* = 3.30, 0.82 Hz, 2H), 4.18 (s, 2H); MS (ESI) *m/z* 386 ([M+H]+); MS (ESI) *m/z* 384 ([M-H]-); Anal. calcd for $C_{22}H_{15}N_3O_4$: C:68.57 H:3.92 N:10.90 Found: C:65.05 H:3.97 N:9.41.

Example 161

5-[5,5-Di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-*H*-pyrrole-2-carbonitrile

[0304] Prepared from 5-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-2-carbonitrile generally according to example 3. ^{1}H NMR (DMSO-d_6): δ 10.34 (s, 1H), 7.77 (m, 2H), 7.49 (dd, J = 8.3, 2.44 Hz, 1H), 7.33 (d, J = 8.30 Hz, 1H), 6.97 (d, J = 3.91 Hz, 1H), 6.76 (d, J = 1.95 Hz, 1H), 6.50 (dd, J = 3.42, 1.95 Hz, 2H), 6.25 (dd, J = 3.42, 0.98 Hz, 2H), 6.16 (d, J = 3.91 Hz, 1H), 4.18 (s, 2H), 3.54 (s, 3H); MS (ESI) *m/z* 400 ([M+H]+); MS (ESI) *m/z* 398 ([M-H]-); Anal. calcd for $C_{23}H_{17}N_3O_4$: C:69.17 H:4.29 N:10.52 Found: C:68.09 H:4.45 N:10.09.

Example 162

7-(4-Fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0305] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 4-fluoro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 9.92 (s, 1H), 7.64-7.67 (m, 2H), 7.41-7.46 (m, 2H), 7.17-7.25 (m, 2H), 7.12 (s, J = 2.26 Hz, 1H), 4.21 (s, 2H), 1.57 (s, 6H); MS (ESI) *m/z* 286 ([M+H]+); MS (ESI) *m/z* 284 ([M-H]-).

Example 163

7-(2-Fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0306] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-fluoro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.63 (m, 1H), 7.51-7.57 (m, 1H), 7.36-7.43 (m, 2H), 7.25-7.30 (m, 2H), 7.19 (d, J = 8.32 Hz, 1H), 4.27 (s, 2H), 1.59 (s, 6H); MS (ESI) *m/z* 286 ([M+H]+); MS (ESI) *m/z* 284 ([M-H]-).

Example 164

7-(3,4-Difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0307] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3,4-difluoro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 9.98 (s, 1H), 7.76-7.83 (m, 1H), 7.60-7.67 (m, 1H), 7.49-7.56 (m, 3H), 7.17 (d, J = 8.32 Hz, 1H), 4.26 (s, 2H), 1.61 (s, 6H); MS (ESI) *m/z* 304 ([M+H]+); MS (ESI) *m/z* 302 ([M-H]-).

Example 165

7-(3,5-Dichlorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0308] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3,5-dichloro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.02 (s, 1H), 7.76 (s, 2H), 7.55-7.64 (m, 3H), 7.18 (d, J = 8.45 Hz, 1H), 4.26 (s, 2H), 1.62 (s 6H); MS (ESI) *m/z* 336/338/340 ([M+H]+); MS (ESI) *m/z* 334/336/338 ([M-H]-).

Example 166

7-(2,3-Difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0309] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2,3-difluoro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.04 (s, 1H), 7.2-7.45 (m, 6H), 4.28 (s, 2H), 1.59 (s, 6H); MS (ESI) *m/z* 304 ([M+H]+); MS (ESI) *m/z* 302 ([M-H]-).

Example 167

7-(4-Chloro-3-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0310] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 4-chloro-3-fluoro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.79 (dd, J = 11.23, 1.95 Hz, 1H), 7.54-7.65 (m, 4H), 7.18 (d, J = 8.3 Hz, 1H), 4.26 (s, 2H), 1.61 (s, 6H); MS (ESI) *m/z* 320/322 ([M+H]+); MS (ESI) *m/z* 318/320 ([M-H]-).

Example 168

4-(5,5-Dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile

[0311] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-bromo-2-fluorobenzonitrile generally according to the coupling procedure described in examples 82 and 1. ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 1H), 7.92-7.99 (m, 2H), 7.77-7.79 (m, 1H), 7.64-7.69 (m, 2H), 7.22 (d, J = 8.39 Hz, 1H), 4.28 (s, 2H), 1.62 (s, 6H). MS (ESI) *m/z* 311 ([M+H]+); MS (ESI) *m/z* 309 ([M-H]-).

Example 169

7-(3-Bromo-5-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0312] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 1,3-dibromo-5-fluorobenzene generally according to the coupling procedure described in examples 82 and 1. ^{1}H NMR (DMSO-d_6): δ 10.0 (s, 1H), 7.6 (m, 1H), 7.56-7.63 (m, 3H), 7.48-7.51 (m, 1H), 7.18 (d, J = 8.3 Hz, 1H), 4.27 (s, 2H), 1.53 (s, 6H); MS (ESI) *m/z* 364/366 ([M+H]+); MS (ESI) *m/z* 362/364 ([M-H]-).

Example 170

7-(3-Chloro-5-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0313] Prepared from 7-bromo-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-

one and 3-bromo-5-chloro-1-fluorobenzene generally according to the coupling procedure described in examples 82 and 1. ^{1}H NMR (DMSO-d_6): δ 10.01 (s, 1H), 7.61-7.65 (m, 4H), 7.36-7.39 (m, 1H), 7.18 (d, J = 8.54 Hz, 1H), 4.26 (s, 2H), 1.62 (s, 6H); MS (ESI) *m/z* 320/322 ([M+H]+); MS (ESI) *m/z* 318/320 ([M-H]-). Anal. calcd for $C_{17}H_{15}ClFNO_2$: C:63.86 H:4.73 N:4.38 Found: C:62.53 H:4.55 N:3.50.

Example 171

3-Chloro-5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile

[0314] Prepared from 7-(3-bromo-5-chlorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one and zinc cyanide generally according to example 84. ^{1}H NMR (DMSO-d_6): δ 10.03 (s, 1H), 8.22 (m, 1H), 8.14 (m, 1H), 7.97 (m, 1H), 7.69 (m, 1H), 7.64 (dd, J = 8.54, 2.44 Hz, 1H), 7.20 (d, J = 8.54 Hz, 1H), 4.27 (s, 2H), 1.63 (s, 6H); MS (ESI) *m/z* 327/329 ([M+H]+); MS (ESI) *m/z* 325/327 ([M-H]-).

Example 172

tert-Butyl 2-cyano-5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate

N-{4-Bromo-2[hydroxyl(diphenyl)methyl]phenyl}-2-chloroacetamide

[0315] Prepared from methyl 2-amino-5-bromobenzoate in two step generally according to the procedure described in example 24. ^{1}H NMR (DMSO-d_6): δ 10.28 (s, 1H), 8.00 (d, J = 8.79 Hz, 1H), 7.78 (s, 1H), 7.54 (dd, J = 8.79, 2.44 Hz, 1H), 7.29-7.37 (m,, 6H), 7.17-7.19 (m, 4H), 6.56 (d, J = 2.44 Hz, 1H), 3.93 (s, 2H); MS (ESI) *m/z* 428/430/432 ([M-H]-).

7-Bromo-5,5-diphenyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0316] Prepared from N-{4-bromo-2[hydroxyl(diphenyl)methyl]phenyl}-2-chloroacetamide generally according to the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.13 (s, 1H), 7.53 (dd, J = 8.3, 1.95 Hz, 1H), 7.35-7.40 (m,

6H), 7.09-7.12 (m, 5H), 6.58 (d, J = 2.44 Hz, 1H), 4.26 (s, 2H). MS (ESI) *m/z*394 ([M+H]+); MS (ESI) *m/z* 398 ([M-H]-).

***tert*-Butyl 2-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate**

[0317] Prepared from 7-bromo-5,5-diphenyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butyl ester generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.07 (s, 1H), 7.36-7.38 (m, 7H), 7.22 (dd, J = 3.42, 1.95 Hz, 1H), 7.12-7.14 (m, 5H), 6.49 (d, J = 2.44 Hz, 1H), 6.16 (t, J = 3.42 Hz, 1H), 5.99 (dd, J = 2.93, 1.46 Hz, 1H), 4.26 (s, 2H), 1.35 (s, 9H); MS (ESI) *m/z* 481 ([M+H]+); MS (ESI) *m/z* 479 ([M-H]-).

[0318] The title compound was prepared from *tert*-butyl 2-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate and chlorosulfonyl isocyanate generally according to the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.17 (s, 1H), 7.32-7.4 (m, 7H), 7.19-7.20 (m, 2H), 7.13-7.14 (m, 4H), 6.52 (d, J = 1.95 Hz, 1H), 6.19 (d, J = 3.42 Hz, 1H), 4.26 (s, 2H), 1.39 (s, 9H); MS (ESI) *m/z* 506 ([M+H]+); MS (ESI) *m/z* 504 ([M-H]-). Anal. calcd for $C_{31}H_{27}N_3O_4$: C:73.65 H:5.38 N:8.31 Found: C:70.80 H:5.27 N:7.99.

Example 173

5-(2-Oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0319] Prepared from *tert*-butyl 2-cyano-5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-1-carboxylate generally according to example 2. ^{1}H NMR (DMSO-d_6): δ 12.5 (s, 1H), 10.13 (s, 1H), 7.62 (dd, J = 8.79, 2.20 Hz, 1H), 7.33-7.40 (m, 6H), 7.20-7.22 (m, 5H), 6.95 (d, J = 1.65 Hz, 1H), 6.88 (dd, J = 3.85, 2.20 Hz, 1H), 6.14 (dd, J = 3.85, 2.75 Hz, 1H), 4.17 (s, 2H). MS (ESI) *m/z* 406 ([M+H]+); MS (ESI) *m/z* 404 ([M-H]-); Anal. calcd for $C_{26}H_{19}N_3O_2$: C:77.02 H:4.72 N:10.36 Found: C:75.34 H:4.80 N:9.84.

Example 174

1-Methyl-5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0320] Prepared from 5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole–2-carbonitrile generally according to example 3. ^{1}H NMR (DMSO-d_6): δ 10.23 (s, 1H), 7.48 (dd, J = 8.24, 2.20 Hz, 1H), 7.35-7.39 (m, 6H), 7.27 (d, J = 8.24 Hz, 1H), 7.15-7.17 (m, 4H), 6.93 (d, J = 4.39 Hz, 1H), 6.59 (d, J = 2.20 Hz, 1H), 6.10 (d, J = 4.39 Hz, 1H), 4.28 (s, 2H), 3.39 (s, 3H); MS (ESI) *m/z* 420 ([M+H]+); MS (ESI) *m/z* 418 ([M-H]-).

Example 175

1-Methyl-5-(1–methyl-2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole-2-carbonitrile

[0321] Prepared from 5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-*H*-pyrrole–2-carbonitrile generally according to example 3. ^{1}H NMR (DMSO-d_6): δ 7.70 (dd, J = 8.24, 2.20 Hz, 1H), 7.55 (d, J = 8.24 Hz, 1H), 7.29-7.37 (m, 6H), 7.19 (d, J = 7.69 Hz, 4H), 6.97 (d, J = 4.39 Hz, 1H), 6.56 (d, J = 2.20 Hz, 1H), 6.19 (d, J = 3.85 Hz, 1H), 4.26 (s, 2H), 3.53, (s, 3H), 2.60 (s, 3H); MS (ESI) *m/z* 434 ([M+H]+).

Example 176

7-(3-Chloro-4–fluorophenyl)-5,5-diphenyl-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0322] Prepared from 7-bromo-5,5-diphenyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one and 3-chloro-4-fluoro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.17 (s, 1H), 7.65 (dd, J = 8.3, 2.44 Hz, 1H), 7.50 (dd, J = 7.32, 2.44 Hz, 1H), 7.34-7.43 (m, 7H), 7.25 (d, J

= 8.3 Hz, 1H), 7.22-7.24 (m, 1H), 7.16-7.19 (m, 4H), 6.75 (d, 1.95 Hz, 1H), 4.26 (s, 2H); MS (ESI) *m/z* 442/444 ([M-H]-); Anal. calcd for $C_{27}H_{19}ClFNO_2$: C:73.06 H:4.31 N:3.16 Found: C:72.67 H:4.36 N:2.89.

Example 177

2-[5,5-Bis-(4-methoxy-phenyl)-2-oxo-1,2,3,5-tetrahydro-benzo[e][1,4]oxazepin-7-yl]-5-cyano-pyrrole-1-carboxylic acid *tert*-butyl ester

N-(4-Bromo-2-{hydroxy[bis(4-methoxyphenyl]methyl}phenyl)-2-chloroacetamide

[0323] Prepared from methyl 2-amino-5-bromobenzoate in two steps generally according to the procedures described in example 24. ^{1}H NMR (DMSO-d_6): δ 10.45 (s, 1H), 8.07 (d, *J* = 8.24 Hz, 1H), 7.58 (s, 1H), 7.53 (dd, *J* = 8.24, 2.20 Hz, 1H), 7.07 (d, *J* = 7.14 Hz, 4H), 6.90 (d, *J* = 8.79 Hz, 4H), 6.60 (d, *J* = 2.75 Hz, 1H), 4.03 (s, 2H), 3.75 (s, 6H); MS (ESI) *m/z* 488/490/492 ([M-H]-).

7-Bromo-5,5-bis(4-methoxyphenyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one

[0324] Prepared from N-(4-bromo-2-{hydroxy[bis(4-methoxyphenyl]methyl}phenyl)-2-chloroacetamide following the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.13 (s, 1H), 7.49 (dd, *J* = 8.79, 2.20 Hz, 1H), 7.11 (d, *J* = 8.79 Hz, 1H), 6.92-7.0 (m, 8H), 6.59 (d, *J* = 2.20 Hz, 1H), 4.21 (s, 2H), 3.76 (s, 6H); MS (ESI) *m/z* 454/456 ([M+H]+); MS (ESI) *m/z* 452/454 ([M-H]-).

tert-Butyl 2-[5,5-bis(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate

[0325] Prepared from 7-bromo-5,5-bis(4-methoxyphenyl)-15-dihydro-4,1-benzoxazepin-2(H)-one and 2-borono-1H-pyrrole-1-carboxylic acid, 1-*tert*-butylester generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.68 (s, 1H), 7.25 (dd, *J* = 8.24, 2.20 Hz, 1H), 7.22 (dd, *J* = 3.30, 1.65 Hz, 1H), 7.13 (d, *J* = 8.24 Hz, 1H), 7.02 (d, *J* = 9.34 Hz, 4H), 6.88 (d, *J* =

9.34 Hz, 4H), 6.51 (d, J = 1.65 Hz, 1H), 6.17 (m, 1H), 6.00 (m, 1H), 4.2 (s, 2H), 3.73 (s, 6H), 1.35 (s, 9H); MS (ESI) *m/z* 541 ([M+H]+).

[0326] The title compound was prepared from *tert*-butyl 2-[5,5-bis(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole-1-carboxylate generally according to the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 11.8 (s, 1H), 10.2 (s, 1H), 7.35 (dd, J = 8.30, 2.05 Hz, 1H), 7.18-7.23 (m, 1H), 7.02 (d, J = 8.88 Hz, 4H), 6.90 (d, J = 8.93 Hz, 4H), 6.54 (d, J = 1.98 Hz, 1H), 6.20 (d, J=3.80 Hz, 1H), 4.21 (s, 2H), 3.75 (s, 6H), 1.37 (s, 9H); MS (ESI) *m/z* 564 ([M-H]-).

Example 178

7-(3-Chloro-4-fluorophenyl)-5,5-bis(4-methoxyphenyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0327] Prepared from 7-bromo-5,5-bis(4-methoxyphenyl)-15-dihydro-4,1-benzoxazepin-2(H)-one and 3-chloro-4-fluoro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.16 (s, 1H), 7.60-7.62 (m, 1H), 7.49-7.52 (m, 1H), 7.42 (m, 1H), 7.25 (m, 2H), 7.07 (d, J = 4.94 Hz, 4H), 6.93 (d, J = 4.94 Hz, 4H), 6.77 (d, J = 2.20 Hz, 1H), 4.20 (s, 2H), 3.75 (s, 6H); MS (ESI) *m/z* 504/506 ([M+H]+); MS (ESI) *m/z* 502/504 ([M-H]-).

Example 179

5-[5,5-Bis-(4-methoxy-phenyl)-2-oxo-1,2,3,5-tetrahydro-benzo[e][1,4]oxazepin-7-yl]-1H-pyrrole-2-carbonitrile

[0328] Prepared from 2-[5,5-Bis-(4-methoxy-phenyl)-2-oxo-1,2,3,5-tetrahydro-benzo[e][1,4]oxazepin-7-yl]-5-cyano-pyrrole-1-carboxylic acid *tert*-butyl ester following example 2. ^{1}H NMR (DMSO-d_6): δ 12.5 (s, 1H), 10.14 (s, 1H), 7.59 (dd, J = 8.41, 1.99 Hz, 1H), 6.90-7.22 (m, 3H), 7.16 (d, J = 8.81 Hz, 4H), 6.93 (d, J = 8.92 Hz, 4H), 6.20 (d, J = 3.59 Hz, 1H), 4.11 (s, 2H), 3.76 (s, 6H); MS (ESI) *m/z*

466 ([M+H]+); MS (ESI) *m/z* 464 ([M-H]-).

Example 180

5-[5,5-Bis(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-*H*-pyrrole-2-carbonitrile

[0329] Prepared from 2-cyano-5-[5-(4-methoxyphenyl)-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-*H*-pyrrole generally according to example 3. ^{1}H NMR (DMSO-d_6): δ 10.21 (s, 1H), 7.44 (dd, *J* = 8.23, 1.97 Hz, 1H), 7.27 (d, *J* = 8.46 Hz, 1H), 7.05 (d, *J* = 8.92 Hz, 4H), 6.92 (d, *J* = 8.92 Hz, 4H), 6.94 (s, 1H), 6.61 (s, 1H), 6.11 (d, *J* = 4.06 Hz, 1H), 4.22 (s, 2H), 3.75 (s, 6H), 3.42 (s, 3H); MS (ESI) *m/z* 480 ([M+H]+).

Example 181

5-[5,5-Di(3-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-*H*-pyrrole-2-carbonitrile

(2-Amino-5-bromophenyl)[di(3-furyl)]methanol

[0330] Prepared from methyl 2-amino-5-bromobenzoate and 3-furyllithiumfollowing the procedure described in example 24. ^{1}H NMR (DMSO-d_6): δ 7.6 (t, *J* = 1.73 Hz, 2H), 7.25 (q, *J* = 1.51, 0.81 Hz, 2H), 7.10 (q, *J* = 8.46, 2.43 Hz, 1H), 6.79 (d, *J* = 2.43 Hz, 1H), 6.56 (d, *J* = 8.46 Hz, 1H), 6.46 (d, *J* = 8.46 Hz, 1H), 6.39 (q, *J* = 1.73, 0.81 Hz, 2H), 5.35 (s, 2H); MS (ESI) *m/z* 332/334 ([M-H]-).

N-{4-Bromo-2-[di(3-furyl)(hydroxy)methyl]phenyl}-2-chloroacetamide

[0331] Prepared from (2-amino-5-bromophenyl)[di(3-furyl)]methanol and chloroacetyl chloride generally according to procedure of described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.69 (s, 1H), 8.14 (d, *J* = 8.74 Hz, 1H), 7.69 (t, *J* = 1.68 Hz, 2H), 7.54 (q, *J* = 8.74 Hz, 1H), 7.51 (s, 1H), 7.32 (s, 2H), 7.02 (d, *J* = 2.37 Hz, 1H), 6.43 (d, *J* = 1.03 Hz, 2H), 4.26 (s, 2H); MS (ESI) *m/z* 408/410/412 ([M-H]-).

7-Bromo-5,5-di(3-furyl)-1,5-dihydro-4.1-benzoxazepin-2(3*H*)-one

[0332] Prepared from N-{4-bromo-2-[di(3-furyl)(hydroxy)methyl]phenyl}-2-chloroacetamide following the procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.2 (s, 1H), 7.74 (s, 2H), 7.47 (dd, J = 8.63, 2.27 Hz, 1H), 7.36 (s, 2H), 7.14 (d, J = 8.67 Hz, 1H), 7.01 (d, J = 2.2 Hz, 1H), 6.40 (s, 2H), 4.20 (s, 2H); MS (ESI) *m/z* 374/376 ([M+H]+); MS (ESI) *m/z* 372/374 ([M-H]-).

[0333] The title compound was prepared from 7-bromo-5-di(3-furyl)benzoxazepinone and 5-cyano-1-methyl-1H-pyrrol-2-ylboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.27 (s, 1H), 7.72 (t, J = 1.62 Hz, 2H), 7.43 (dd, J = 8.37, 1.99 Hz, 1H), 7.38 (s, 2H), 7.29 (d, J = 8.42 Hz, 1H), 7.03 (d, J = 1.92 Hz, 1H), 6.98 (d, J = 4.09 Hz, 1H), 6.43 (d, J = 0.93 Hz, 2H), 6.19 (d, J = 4.09 Hz, 1H), 4.22 (s, 2H), 3.55 (s, 3H); MS (ESI) *m/z* 400 ([M+H]+); MS (ESI) *m/z* 398 ([M-H]-); Anal. calcd for $C_{23}H_{17}N_3O_4$: C:69.17 H:4.29 N:10.52 Found: C:68.72 H:4.42 N:10.27.

Example 182

3-[5,5-Di(3-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile

[0334] Prepared from 7-bromo-5-di(3-furyl) benzoxazepinone and 3-cyano-5-fluoro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.22 (s, 1H), 7.28-7 .83 (m, 11H), 6.45 (s, 1H), 4.19 (s, 2H); MS (ESI) *m/z* 415 ([M+H]+); MS (ESI) *m/z* 413 ([M-H]-).

Example 183

7-(3-Chloro-4-fluorophenyl)-5,5-di(3-furyl)-1,5-dihydro-4,1-benzoxazepin-2(*H*)-one

[0335] Prepared from 7-bromo-5-di(3-furyl) benzoxazepinone and 3-chloro-4-fluoro benzeneboronic acid generally according to the coupling procedure described in example 1. ^{1}H NMR (DMSO-d_6): δ 10.18 (s, 1H), 7.71 (m, 2H), 7.59-7.66 (m,

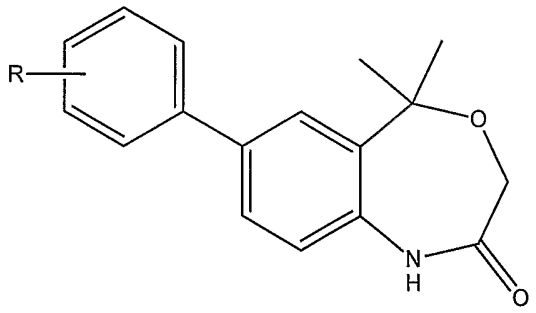
2H), 7.40-7.45 (m, 4H), 7.28 (d, J = 8.46 Hz, 1H), 7.19 (s, 1H), 6.43 (m, 2H), 4.19 (s, 2H); MS (ESI) *m/z* 424/426 ([M+H]+); MS (ESI) *m/z* 422/424 ([M-H]-).

Example 184

Assay Tests

[0336] 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 selected 5,5-dimethyl 7-aryl benzoxazepinones as PR modulators in some *in vitro* and *in vivo* assays

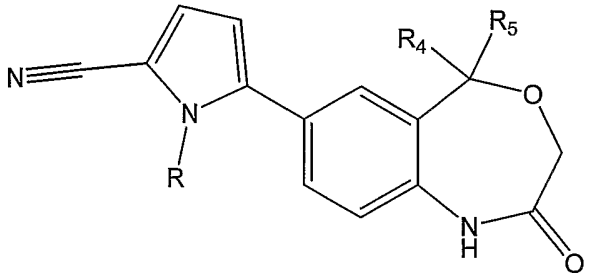


Compound	R	Alk. Phos. IC_{50} (nM)	Decidualization IC_{50} (mg/kg)
1	3'-Cl, 4'-F	30.5	>3
2	3'-F	14.9	ND*
3	3'-CN, 5'-F	22.5	40%@3
4	3'-F, 5'-F	30.0	>3
5	3'-Cl	120.5	ND
6	3'-CN, 4'-F	42.1	ND
7	4'-F	100.0	ND
8	2'-F	62.1	ND
9	3'-F, 4'-F	29.3	ND

10	3'-Cl, 5'-Cl	29.1	ND
11	2'-F, 3'-F	15.7	ND
12	4'-Cl, 3'-F	33.1	ND
13	3'-CN, 5'-Cl	34.6	ND

* ND: not determined.

Table 2. Potency of selected 5-(-benzoxazepin-7-yl)-pyrrole-2-carbonitrileas PR modulators in some *in vitro* and *in vivo* assays



Compound	R	R_4	R_5	Alk. Phos. EC_{50} (nM)	Alk. Phos. IC_{50} (nM)
1	BOC	Me	Me	4.8	
2	H	Me	Me	3.3	
3	Me	Me	Me	3.3	
4	BOC	Me	2-thienyl	1.45	
5	H	Me	2-thienyl	0.8	
6	Me	Me	2-thienyl	0.8	
7	BOC	Me	Phenyl	15.8	
8	H	Me	Phenyl	11.2	
9	Me	Me	Phenyl	247.5	
10	BOC	H	Me	149.2	
11	H	H	Me	245.8	
12	Me	H	Me	137.7	
13	H	2-thienyl	2-thienyl		43.9

14	Me	2-thienyl	2-thienyl	11.3
15	BOC	Phenyl	Phenyl	532
16	H	Phenyl	Phenyl	51
17	Me	Phenyl	Phenyl	11.5
18	H	Et	2-thienyl	78.1
19	Me	Et	2-thienyl	14.6

Pharmacology

(1) T47D cell proliferation assay

Objective:

[0337] Determination of progestational and antiprogestational potency by using a cell proliferation assay in T47D cells. A compound's effect on DNA synthesis in T47D cells is measured.

Methods:

A. REAGENTS:

[0338] Growth medium: DMEM:F12 (1:1) (GIBCO, BRL) supplemented with 10% (v/v) fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100 mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

[0339] 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).

B. CELL CULTURE:

[0340] Stock T47 D cells are maintained in growth medium. For BrdU

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

C. CELL PROLIFERATION ASSAY:

[0341] At the end of BrdU labeling, the medium is removed and BrdU incorporation is measured using a cell proliferation ELISA kit (#RPN 250, Amersham Life Science) according to manufacturer's instructions. Briefly, cells are fixed in an ethanol containing fixative for 30 min, followed by incubation in a blocking buffer for 30 min to reduce background. Peroxidase-labeled anti-BrdU antibody is added to the wells and incubated for 60 min. The cells are rinsed three times with PBS and incubated with 3,3'5,5'-tetramethylbenzidine (TMB) substrate for 10-20 min depending upon the potency of tested compounds. Then 25 µl of 1 M sulfuric acid is added to each well to stop color reaction and optical density is read in a plate reader at 450 nm within 5 min.

Analysis of Results:

[0342] 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.

Reference Compounds:

[0343] Trimegestone and medroxyprogesterone acetate (MPA) were reference progestins and RU486 is the reference antiprogestin. All reference compounds were run in full dose-response curves and the EC_{50} or IC_{50} values were calculated.

Table 1. Estimated EC_{50}, standard error (SE), and 95% confidence intervals (CI) for individual studies

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

Table 2. 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

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

(2) Rat decidualization assay

Objective:

[0344] This procedure was used to evaluate the effect of progestins and antiprogestins on rat uterine decidualization and compare the relative potencies of various test compounds.

Methods:

A. Reagents

[0345] Test compounds were dissolved in 100% ethanol and mixed with corn oil (vehicle). Stock solutions of the test compounds in oil (Mazola^{TM}) were then prepared by heating (~80 ^{o}C) the mixture to evaporate ethanol. Test compounds were subsequently diluted with 100% corn oil or 10% ethanol in corn oil prior to the treatment of animals. No difference in decidual response was found when these two vehicles were compared.

B. Animals (RACUC protocol #5002)

[0346] Ovariectomized mature female Sprague-Dawley rats (~60-day old and 230g) were obtained from Taconic (Taconic Farms, NY) following surgery. Ovariectomy was performed at least 10 days prior to treatment to reduce circulating sex steroids. Animals were housed under 12 hr light/dark cycle and given standard rat chow and water *ad libitum.*

C. Treatment

[0347] Rats were weighed and randomly assigned to groups of 4 or 5 before treatment. Test compounds in 0.2 mL vehicle were administered by subcutaneous injection in the nape of the neck or by gavage using 0.5 ml. The animals were treated once daily for seven days. For testing antiprogestins, animals were given the test compounds and a EC_{50} dose of progesterone (5.6 mg/kg) during the first three days of treatment. Following decidual stimulation, animals continued to receive progesterone until necropsy four days later.

D. Dosing

[0348] Doses were prepared based upon mg/kg mean group body weight. In all studies, a control group receiving vehicle was included. Determination of dose-response curves was carried out using doses with half log increases (e.g. 0.1, 0.3, 1.0, 3.0 mg/kg...).

E. Decidual induction

[0349] Approximately 24 hr after the third injection, decidualization was induced in one of the uterine horns by scratching the antimesometrial luminal epithelium with a blunt 21 G needle. The contralateral horn was not scratched and served as an unstimulated control. Approximately 24 hr following the final treatment, rats were sacrificed by CO_2 asphyxiation and body weight measured. Uteri were removed and trimmed of fat. Decidualized (D-horn) and control (C-horn) uterine horns were weighed separately.

Analysis of Results:

[0350] The increase in weight of the decidualized uterine horn was calculated by D-horn/C-horn and logarithmic transformation was used to maximize normality and homogeneity of variance. The Huber M-estimator was 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.) was used for both one-way ANOVA and non-linear dose-response analyses.

Reference Compounds:

[0351] All progestin reference compounds were run in full dose-response curves and the EC_{50} for uterine wet weight was calculated.

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

		EC_{50}		95% CI	
Compound	Exp	(mg/kg, s.c.)	SE	lower	upper

Progesterone	1	5.50	0.77	4.21	7.20
	2	6.21	1.12	4.41	8.76
3-Ketodesogestrel	1	0.11	0.02	0.07	0.16
	2	0.10	0.05	0.11	0.25
	3	0.06	0.03	0.03	0.14
Levonorgestrel	1	0.08	0.03	0.04	0.16
	2	0.12	0.02	0.09	0.17
	3	0.09	0.02	0.06	0.13
	4	0.09	0.02	0.06	0.14
MPA	1	0.42	0.03	0.29	0.60
	2	0.39	0.05	0.22	0.67
	3	0.39	0.04	0.25	0.61

Table 4. Estimated average EC_{50}, standard error, and 95% confidence intervals for dose-response curves of 3 reference compounds

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

Table 5. Estimated IC_{50}, standard error, and 95% confident interval for the antiprogestin, RU 486

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

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

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

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

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

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

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

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

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

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

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

(3) PRE-luciferase assay in CV-1 cells

Objective:

[0352] 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.

Methods:

A. REAGENTS:

Culture medium:

[0353] Growth medium: 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).

[0354] Experimental medium: 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).

Cell culture, transfection, treatment, and luciferase assay

[0355] Stock CV-1 cells were maintained in growth medium. Co-transfection was done using $1.2x10^7$ cells, 5 mg pLEM plasmid with hPR-B inserted at Sph1 and BamH1 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 was carried out at 260 V and 1,000 mF in a Biorad Gene Pulser II. After electroporation, cells were resuspended in growth medium and plated in 96-well plate at 40,000 cells/well in 200 µl. Following overnight incubation, the medium was changed to experimental medium. Cells were then treated with reference or test compounds in experimental medium. Compounds were tested for antiprogestational activity in the presence of 3 nM progesterone. Twenty-four hr. after treatment, the medium was discarded, cells were washed three times with D-PBS (GIBCO, BRL). Fifty ml of cell lysis buffer (Promega, Madison, WI) was added to each well and the plates were shaken for 15 min in a Titer Plate Shaker (Lab Line Instrument, Inc.). Luciferase activity was measured using luciferase reagents from Promega.

Analysis of Results:

[0356] Each treatment consists of at least 4 replicates. Log transformed data were used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting was used to downweight the effects of outliers. EC_{50} or IC_{50} values were calculated from the retransformed values. JMP software (SAS Institute, Inc.) was used for both one-way analysis of variance and non-linear response analyses.

Reference Compounds:

[0357] Progesterone and trimegestone were reference progestins and RU486 was the reference antiprogestin. All reference compounds were run in full dose-response curves and the EC_{50} or IC_{50} values were calculated.

Table 6. Estimated EC_{50}, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three individual studies

		EC50		95% CI	
Compound	Exp.	(nM)	SE	lower	upper
Progesterone	1	0.616	0.026	0.509	0.746
	2	0.402	0.019	0.323	0.501
	3	0.486	0.028	0.371	0.637
Trimegestone	1	0.0075	0.0002	0.0066	0.0085
	2	0.0081	0.0003	0.0070	0.0094
	3	0.0067	0.0003	0.0055	0.0082

Table 7. Estimated IC_{50}, standard error (SE), and 95% confident interval (CI) for the antiprogestin, RU486 from three individual studies

		IC50		95% CI	
Compound	Exp.	(nM)	SE	lower	upper
RU486	1	0.028	0.002	0.019	0.042
	2	0.037	0.002	0.029	0.048
	3	0.019	0.001	0.013	0.027

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

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

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

IC_{50}: Concentration of a compound that gives half-maximal decrease in 3

nM progesterone induced PRE-luciferase activity (default-nM) with SE.

(4) T47D cell alkaline phosphatase assay

Purpose:

[0358] To identify progestins or antiprogestins by determining a compound's effect on alkaline phosphatase activity in T47D cells.

Methods:

A. REAGENTS:

Culture medium:

[0359] DMEM:F12 (1:1) (GIBCO, BRL) supplemented with 5% (v/v) charcoal stripped fetal bovine serum (not heat-inactivated), 100U/ml penicillin, 100mg/ml streptomycin, and 2 mM GlutaMax (GIBCO, BRL).

Alkaline phosphatase assay buffer:

[0360] I. 0.1 M Tris-HCl, pH 9.8, containing 0.2% Triton X-100

[0361] II. 0.1 M Tris-HCl, pH 9.8 containing 4 mM p-nitrophenyl phosphate (Sigma).

B. CELL CULTURE AND TREATMENT:

[0362] Frozen T47D cells were thawed in a 37 °C water bath and diluted to 280,000 cells/ml in culture medium. To each well in a 96-well plate (Falcon, Becton Dickinson Labware), 180 µl of diluted cell suspension was added. Twenty µl of reference or test compounds diluted in the culture medium was then added to each well. When testing for progestin antagonist activity, reference antiprogestins or test compounds were added in the presence of 1 nM progesterone. The cells were incubated at 37°C in a 5% CO_2/humidified atmosphere for 24 hr.

Note: For high throughput screening, one concentration of each compound was tested at 0.3 mg/ml. Based on an average molecular weight of 300 g/mol for the compounds in the library, the concentration was approximately 1 mM. Subsequently, active

compounds were tested in dose response assays to determine EC_{50} or IC_{50}

C. ALKALINE PHOSPHATASE ENZYME ASSAY:

[0363] At the end of treatment, the medium was removed from the plate. Fifty µl of assay buffer I was added to each well. The plates were shaken in a titer plate shaker for 15 min. Then 150 µl of assay buffer II was added to each well. Optical density measurements were taken at 5 min intervals for 30 min at a test wavelength of 405 nM.

Analysis of Results:

Analysis of dose-response data

[0364] For reference and test compounds, a dose response curve was generated for dose (X-axis) vs. the rate of enzyme reaction (slope) (Y-axis). Square root-transformed data were used for analysis of variance and nonlinear dose response curve fitting for both agonist and antagonist modes. Huber weighting was used to downweight the effects of outliers. EC_{50} or IC_{50} values were calculated from the retransformed values. JMP software (SAS Institute, Inc.) was used for both one-way analysis of variance and non-linear dose response analyses in both single dose and dose response studies.

Reference Compounds:

[0365] Progesterone and trimegestone were reference progestins and RU486 was the reference antiprogestin. All reference compounds were run in full dose response curves and the EC_{50} or IC_{50} values were calculated.

Table 8. Estimated EC_{50}, standard error (SE), and 95% confidence intervals (CI) for reference progestins from three independent experiments

		EC50		95% CI	
Compound	Exp.	(nM)	SE	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

Table 9. Estimated IC_{50}, standard error, and 95% confident interval for the reference antiprogestin RU486 from three independent experiments

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

[0366] 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.*

[0367] When the compounds are employed for the above utilities, they may be combined with one or more pharmaceutically acceptable carriers, for example, solvents, diluents and the like, and may be administered orally in such forms as tablets, capsules, dispersible powders, granules, or suspensions containing, for example, from about 0.05 to 5% of suspending agent, syrups containing, for example, from about 10 to 50% of sugar, and elixirs containing, for example, from

about 20 to 50% ethanol, and the like, or parenterally in the form of sterile injectable solutions or suspensions containing from about 0.05 to 5% suspending agent in an isotonic medium. Such pharmaceutical preparations may contain, for example, from about 25 to about 90% of the active ingredient in combination with the carrier, more usually between about 5% and 60% by weight.

[0368] 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.

[0369] These active compounds may be administered orally as well as by intravenous, intramuscular, or subcutaneous routes. Solid carriers include starch, lactose, dicalcium phosphate, microcrystalline cellulose, sucrose and kaolin, while liquid carriers include sterile water, polyethylene glycols, non-ionic surfactants and edible oils such as corn, peanut and sesame oils, as are appropriate to the nature of the active ingredient and the particular form of administration desired. Adjuvents customarily employed in the preparation of pharmaceutical compositions may be advantageously included, such as flavoring agents, coloring agents, preserving agents, and antioxidants, for example, vitamin E, ascorbic acid, BHT and BHA.

[0370] 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.

[0371] These active compounds may also be administered parenterally or

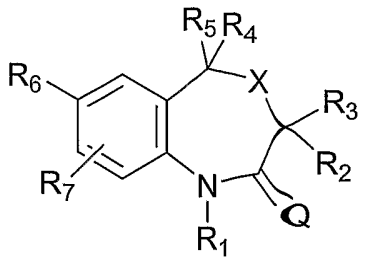
intraperitoneally. Solutions or suspensions of these active compounds as a free base or pharmacologically acceptable salt can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid, polyethylene glycols and mixtures thereof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

[0372] The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringe ability exits. It must be stable under conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacterial and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oil.

[0373] All patents, publications, and other documents cited herein are hereby incorporated by reference in their entirety.

What is claimed:

1. A compound of the formula:



wherein:

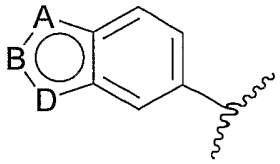
R_1 is H, C_{1-3} alkyl, or COR^A; where R^A is H, C_{1-4} alkyl, C_{1-4} alkoxy, or C_{1-3} aminoalkyl;

R_2 and R_3 are each independently H, CF_3, or C_{1-3} alkyl;

R_4 and R_5 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, CF_3, CF_2CF_3, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, or together with the carbon atom to which they are attached form a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N;

R_6 is substituted phenyl containing 1 to 3 substituents or a 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms and 1 to 3 substituents, said heteroatoms being O, S, SO, SO_2 or N and said substituents independently being H, halogen, CN, NO_2, OH, amino, and C_1 to C_3 alkyl, C_1 to C_3 alkoxy, C_1 to C_3 aminoalkyl, $C{=}NOR^C$, COR^D, or NR^CCOR^D; or

R_6 is a benzofused heterocyclic ring of the following formula



where A, B, and D are each independently CH, N, O, or S;

R^C is H, C_{1-4} alkyl, substituted C_{1-4} alkyl, or COR^D;

R^D is H, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} aminoalkyl;

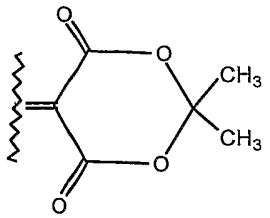
R_7 is H, halogen, CN, NO_2, OH, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, amino, or C_{1-3} aminoalkyl;

Q is O, S, NR_8, CR_9R_{10}, or $R_{13}R_{14}$;

R_8 is CN, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic, SO_2CF_3, OR_{11} or $NR_{11}R_{12}$;

R_9 and R_{10} are independently H, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, CN, or CO_2R_{11};

or CR_9R_{10} comprises a six membered ring of the structure:



R_{11} and R_{12} are independently each H, C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, acyl or sulfonyl;

R_{13} and R_{14} are each independently H, C_{1-3} lower alkyl, C_{1-3} lower perfluoroalkyl, aryl, heterocyclic, a 3 to 6 membered alkylspirocyclic ring comprising R_{13} and R_{14}, a 3 to 6 membered heterospirocyclic ring comprising R_{13} and R_{14} and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2 or N;

X is O, S, NR^E, or CR^ER^F; where R^E and R^F are each independently H or C_{1-4} alkyl;

provided that when X = O and Q = O or S, then at least one of R_4 and R_5 is H, CF_3, CF_2CF_3, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, or together with the carbon atom to which they are attached form a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N;

provided that when X = NR^E, Q = O or S, R_6 is a 5 or 6 membered heterocyclic ring, and R_4 is cyclopropyl or C_1 to C_3 alkyl, then R_5 is H, CF_3, CF_2CF_3,

C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, or a substituted heterocycle;

or pharmaceutically acceptable salt thereof.

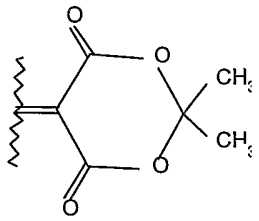
2. A compound according to claim 1 wherein R_1, R_2, and R_3 are each H;

3. A compound according to claim 1 or claim 2 wherein Q is NR_8, CR_9R_{10}, or $R_{13}R_{14}$.

4. A compound according to claim 3 wherein R_8 is CN, C_{1-3} alkyl, SO_2CF_3, OR_{11} or $NR_{11}R_{12}$.

5. A compound according to claim 3 wherein R_8 is CN, SO_2CF_3, or OR_{11}.

6. A compound according to claim 3 wherein R_9 and R_{10} are each, independently, H, C_{1-3} alkyl, NO_2, CN, or CO_2R_{11};
or CR_9R_{10} comprise a six membered ring as shown by the structure:



7. A compound according to claim 3 wherein R_9 and R_{10} are each, independently, NO_2, CN, or CO_2R_{11}.

8. A compound according to claim 3 wherein R_{11} and R_{12} are each independently, H, C_{1-3} alkyl, acyl or sulfonyl;

9. A compound according to claim 3 wherein R_{11} and R_{12} are each

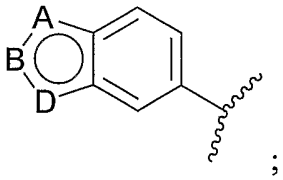
independently, H or C_{1-3} alkyl.

10. A compound according to claim 3 wherein R_{13} and R_{14} are each, independently, H, C_{1-3} lower alkyl, or C_{1-3} perfluoroalkyl.

11. A compound according to anyone of claims 1 to 10 wherein R_6 is substituted phenyl containing 1 to 2 substituents, where said substituents are selected from halogen, CN, NO_2, OH, C=NOH; or

R_6 is a 5 or 6 membered heterocyclic ring containing 1 to 2 heteroatoms substituted with 1 to 2 substituents from the group including halogen, CN, NO_2, OH, and C_1 to C_3 alkyl, C=NOH, said heteroatoms being O, S, SO, SO_2 or N; or

R_6 is a benzofused heterocyclic ring of the following formula



;

A and D are each independently CH, O, or S; and

B is N.

12. A compound according to anyone of claims 1 to 11 wherein R_4 is H, C_{1-6} alkyl, CF_3, CF_2CF_3, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, substituted aryl, heterocycle, or substituted heterocycle;

R_5 is aryl, substituted aryl, heterocycle, or substituted heterocycle; or

R_4 and R_5 together with the carbon to which they are attached are a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N.

13. A compound according to anyone of claims 1 to 12 wherein R_7 is H, halogen, CN or NO_2.

14. A compound according to anyone of claims 1 to 13 wherein X is O.

15. A compound according to claim 1 wherein:

R_1, R_2, and R_3 are each H;

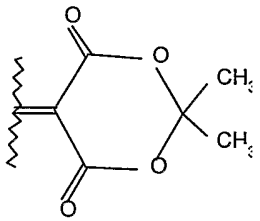
R_4 is H, C_{1-6} alkyl, CF_3, CF_2CF_3, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, substituted aryl, heterocycle, or substituted heterocycle;

R_5 is aryl, substituted aryl, heterocycle, or substituted heterocycle; or

R_4 and R_5 are a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N;

R_8 is CN, C_{1-3} alkyl, SO_2CF_3, OR_{11} or $NR_{11}R_{12}$;

R_9 and R_{10} are each, independently, H, C_{1-3} alkyl, NO_2, CN, or CO_2R_{11}; or CR_9R_{10} comprise a six membered ring as shown by the structure:



R_{11} and R_{12} are each, independently, H, C_{1-3} alkyl, acyl or sulfonyl; and

R_{13} and R_{14} are each, independently, H, C_{1-3} lower alkyl, or C_{1-3} perfluoroalkyl.

16. A compound according to claim 1 wherein:

R_7 is H, halogen, CN, or NO_2,

R_8 is selected from the group of CN, SO_2CF_3, or OR_{11};

R_9 and R_{10} are each, independently, NO_2, CN, or CO_2R_{11};

R_{11} and R_{12} are each, independently, H or C_{1-3} alkyl; and

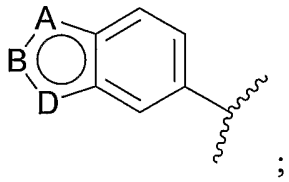
R_{13} and R_{14} are each, independently, H, C_{1-3} alkyl, or C_{1-3} perfluoroalkyl.

17. A compound according to claim 1 wherein:

R_6 is substituted phenyl containing 1 to 2 substituents, where said substituents are halogen, CN, NO_2, OH, C=NOH; or

R_6 is a 5 or 6 membered heterocyclic ring containing 1 to 2 heteroatoms substituted with 1 to 2 substituents from the group including halogen, CN, NO_2, OH, and C_1 to C_3 alkyl, C=NOH, said heteroatoms being O, S, SO, SO_2 or N; or

R_6 is a benzofused heterocyclic ring of the following formula



;

A and D are each independently CH, O, or S;

B is N; and

X is O.

18. A compound according to claim 1 wherein said compound is one of the following:

4-methyl-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile,

tert-butyl 2-cyano-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-[5-methyl-2-oxo-5-(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-[5-methyl-2-oxo-5-(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(5-methyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(1,5-dimethyl-2-oxo-5-phenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-

methyl-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

2'-Cyano-5'-[(2-oxo-1,2,3,5-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-(5-spiro-1"-cyclohexane)]-pyrrole-1'-carboxylic acid *tert*-butyl ester,

5'-[(2-Oxo-1,2,3,5-tetrahydro-benzo[*e*][1,4]oxazepin-7-yl)-(5-spiro-1"-cyclohexane)]-1*H*-pyrrole-2'-carbonitrile,

tert-butyl 2-cyano-5-[5-methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

tert-butyl 2-cyano-5-[2-oxo-5,5-di(2-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

tert-butyl 2-cyano-5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

5-[5-methyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-[5-methyl-2-oxo-5-(3-thienyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

5-[1,5-dimethyl-2-oxo-5-(1,3-thiazol-2-yl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

5-[5-(2-furyl)-5-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-(1,5-dimethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

7-(3-chlorophenyl)-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chlorophenyl)-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

tert-butyl 2-cyano-5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

tert-butyl 2-cyano-5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(5-methyl-2-oxo-5-pyridin-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(5-methyl-5-thien-3-yl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-methyl-5-thien-3-yl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-benzyl-5-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-

1*H*-pyrrole-2-carbonitrile,

9*H*-fluoren-9-ylmethyl 7-(5-cyano-1*H*-pyrrol-2-yl)-5-methyl-5-thien-2-yl-2,3-dihydro-4,1-benzoxazepine-1(5*H*)-carboxylate,

5-[(5*S*)-5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

1-ethyl-5-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1,2-dicarbonitrile,

5-(5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(5-methyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5-ethyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-fluorobenzonitrile,

tert-butyl 2-cyano-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-[(5*R*)-5-methyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(2-oxo-5-propyl-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(9-fluoro-5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

7-(3-chloro-4-fluorophenyl)-5-isopropyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-fluoro-5-(5-isopropyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

5-(9-fluoro-5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

3-fluoro-5-(5-isopropyl-5-thien-2-yl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

7-(3-chloro-4-fluorophenyl)-5-propyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-fluoro-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

5-methyl-7-(3-methylphenyl)-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-aminophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-methoxyphenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(2-chlorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chlorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(4-chlorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

7-(3,5-difluorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-methyl-5,7-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-methyl-5-thien-2-yl-7-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-methyl-5-thien-2-yl-7-[3-(trifluoromethyl)phenyl]-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-methyl-7-(3-nitrophenyl)-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-4-fluorophenyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-

2(3*H*)-one,

7-(2-furyl)-5-methyl-5-thien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-4-fluorophenyl)-5-ethyl-5-thien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

tert-butyl 2-cyano-5-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

3-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-fluorobenzonitrile,

7-(3-chloro-4-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

tert-butyl 2-cyano-5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

3-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

5-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

5-(5-ethyl-2-oxo-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

4-methyl-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile,

2-fluoro-5-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile,

4-(5-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile,

5-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-4-

methylthiophene-2-carbonitrile,

4-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile,

tert-butyl 2-cyano-5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile,

4-(5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)thiophene-2-carbonitrile,

5-(5-ethyl-1-methyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile,

3-fluoro-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-dithien-2-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-4-fluorophenyl)-4,5,5-trimethyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one,

1-ethyl-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-benzyl-5-(2-oxo-5,5-dithien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

3-fluoro-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile,

tert-butyl 2-cyano-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

7-(3-chloro-4-fluorophenyl)-5,5-dithien-3-yl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(2-oxo-5,5-dithien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

3-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

tert-butyl 2-[5,5-bis(5-bromothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-1*H*-pyrrole-1-carboxylate,

7-(3-chloro-4-fluorophenyl)-5,5-bis(5-chlorothien-2-yl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-[5,5-bis(5-bromothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-1*H*-pyrrole-1-carboxylate,

5-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-di(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

tert-butyl 2-cyano-5-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

3-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

5-[5,5-bis(5-chlorothien-2-yl)-1-methyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

3-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-bis(4-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

tert-butyl 2-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-1*H*-pyrrole-1-carboxylate,

5-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-diphenyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-[5,5-bis(5-chlorothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-[5,5-bis(4-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-[(5*R*)-5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

tert-butyl 2-cyano-5-[(5*S*)-5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

5-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate,

5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-cyano-1*H*-pyrrole-1-carboxylate,

5-[5,5-di(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-bis(3-chlorophenyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-[5,5-bis(5-cyanothien-2-yl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

5-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-2-carbonitrile,

5-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

1-methyl-5-(1-methyl-2-oxo-5,5-diphenyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile,

7-(3-chloro-4-fluorophenyl)-5,5-bis(4-methoxyphenyl)-1,5-dihydro-4,1-

benzoxazepin-2(3*H*)-one,

3-[5,5-bis(3-chlorophenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

5-[(5*R*)-5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-[(5*S*)-5-ethyl-2-oxo-5-thien-2-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

5-[5,5-di(3-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

tert-butyl 2-cyano-5-[5-(4-methoxyphenyl)-5-(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1*H*-pyrrole-1-carboxylate,

3-[5,5-di(3-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-5-fluorobenzonitrile,

5-[5,5-bis(4-methoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-1-methyl-1*H*-pyrrole-2-carbonitrile,

7-(3,5-dichlorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-ethyl-7-(2-fluorophenyl)-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3,4-difluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

5-ethyl-7-(4-fluorophenyl)-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-4-fluorophenyl)-5-(2-furyl)-5-(pentafluoroethyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

4-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-2-furonitrile,

7-(2,3-difluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(4-chloro-3-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

7-(3-chloro-5-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

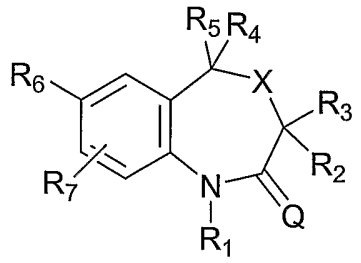
4-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]-2-fluorobenzonitrile,

7-(3-bromo-5-chlorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,

3-chloro-5-[5-ethyl-5-(2-furyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]benzonitrile,
7-(3-bromo-5-fluorophenyl)-5-ethyl-5-(2-furyl)-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one,
3-fluoro-5-[5-(2-furyl)-2-oxo-5-(pentafluoroethyl)-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl]benzonitrile, or
1-methyl-5-(5-methyl-5-thien-3-yl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile;
or a pharmaceutically acceptable salt thereof..

19. A pharmaceutical composition comprising a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

20. A method of inducing contraception comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formula:



wherein:

R_1 is H, C_{1-3} alkyl, or COR^A; where R^A is H, C_{1-4} alkyl, C_{1-4} alkoxy, or C_{1-3} aminoalkyl;

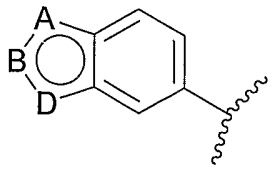
R_2 and R_3 are each independently H, CF_3, or C_{1-3} alkyl;

R_4 and R_5 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-3} perfluoroalkyl, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, or together with the carbon atom to which they are attached form a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms

within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N;

R_6 is substituted phenyl containing 1 to 3 substituents or a 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms and 1 to 3 substituents, said heteroatoms being O, S, SO, SO_2 or N and said substituents independently being H, halogen, CN, NO_2, OH, amino, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} aminoalkyl, $C{=}NOR^C$, COR^D, or NR^CCOR^D; or

R_6 is a benzofused heterocyclic ring of the following formula



where A, B, and D are each independently CH, N, O, or S;

R^C is H, C_{1-4} alkyl, substituted C_{1-4} alkyl, or COR^D;

R^D is H, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} aminoalkyl;

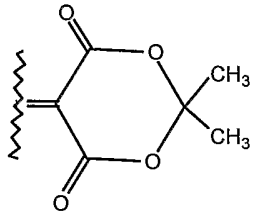
R_7 is H, halogen, CN, NO_2, OH, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, amino, or C_{1-3} aminoalkyl;

Q is O, S, NR_8, CR_9R_{10}, or $R_{13}R_{14}$;

R_8 is CN, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic, SO_2CF_3, OR_{11} or $NR_{11}R_{12}$;

R_9 and R_{10} are independently H, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, CN, or CO_2R_{11};

or CR_9R_{10} comprises a six membered ring of the structure:



R_{11} and R_{12} are independently H, C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, acyl or sulfonyl;

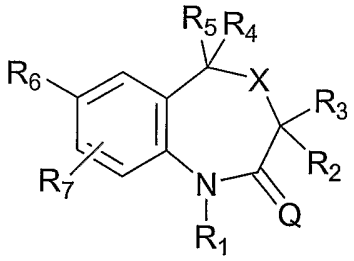
R_{13} and R_{14} are each independently H, C_{1-3} alkyl, C_{1-3} perfluoroalkyl, aryl, heterocyclic, a 3 to 6 membered alkylspirocyclic ring comprising R_{13} and R_{14}, a 3 to

6 membered heterospirocyclic ring comprising R_{13} and R_{14} and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2 or N; and

X is O, S, NR^E, or CR^ER^F; where R^E and R^F are each independently H or C_{1-4} alkyl.

21. A method according to claim 20 wherein the compound is administered orally.

22. A method of treating or preventing benign or malignant neoplastic disease comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formula:



wherein:

R_1 is H, C_{1-3} alkyl, or COR^A; where R^A is H, C_{1-4} alkyl, C_{1-4} alkoxy, or C_{1-3} aminoalkyl;

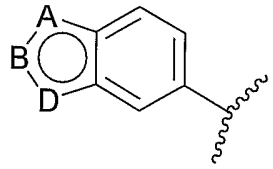
R_2 and R_3 are each independently H, CF_3, or C_{1-3} alkyl;

R_4 and R_5 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-3} perfluoroalkyl, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, or together with the carbon atom to which they are attached form a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N;

R_6 is substituted phenyl containing 1 to 3 substituents or a 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms and 1 to 3 substituents, said heteroatoms being O, S, SO, SO_2 or N and said substituents independently being H,

halogen, CN, NO_2, OH, amino, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} aminoalkyl, $C{=}NOR^C$, COR^D, or NR^CCOR^D; or

R_6 is a benzofused heterocyclic ring of the following formula



where A, B, and D are each independently CH, N, O, or S;

R^C is H, C_{1-4} alkyl, substituted C_{1-4} alkyl, or COR^D;

R^D is H, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} aminoalkyl;

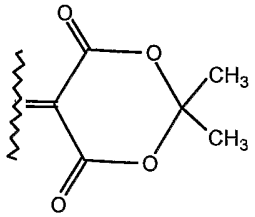
R_7 is H, halogen, CN, NO_2, OH, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, amino, or C_{1-3} aminoalkyl;

Q is O, S, NR_8, CR_9R_{10}, or $R_{13}R_{14}$;

R_8 is CN, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic, SO_2CF_3, OR_{11} or $NR_{11}R_{12}$;

R_9 and R_{10} are independently H, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, CN, or CO_2R_{11};

or CR_9R_{10} comprises a six membered ring of the structure:



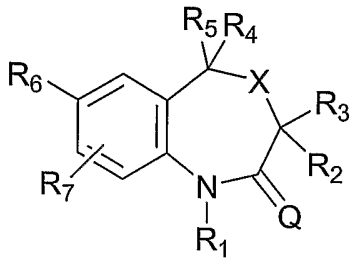
R_{11} and R_{12} are independently H, C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, acyl or sulfonyl;

R_{13} and R_{14} are each independently H, C_{1-3} alkyl, C_{1-3} perfluoroalkyl, aryl, heterocyclic, a 3 to 6 membered alkylspirocyclic ring comprising R_{13} and R_{14}, a 3 to 6 membered heterospirocyclic ring comprising R_{13} and R_{14} and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2 or N; and

X is O, S, NR^E, or CR^ER^F; where R^E and R^F are each independently H or C_{1-4} alkyl.

23. The method of claim 22 wherein the benign or malignant neoplastic disease is uterine myometrial fibroids, endometriosis, benign prostatic hypertrophy, carcinomas and adenocarcinomas of the endometrium, ovary, breast, colon, prostate, pituitary, meningioma or other hormone-dependent tumors.

24. A method of hormone replacement therapy comprising administering to a mammal in need thereof a pharmaceutically effective amount of a compound of the formula:



wherein:

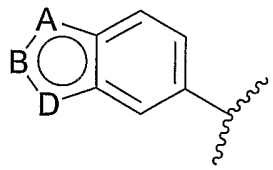
R_1 is H, C_{1-3} alkyl, or COR^A; where R^A is H, C_{1-4} alkyl, C_{1-4} alkoxy, or C_{1-3} aminoalkyl;

R_2 and R_3 are each independently H, CF_3, or C_{1-3} alkyl;

R_4 and R_5 are each independently H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-3} perfluoroalkyl, C_{3-6} cycloalkyl, aryl, substituted aryl, heterocycle, substituted heterocycle, or together with the carbon atom to which they are attached form a 3 to 6 membered alkylspirocyclic ring comprising R_4 and R_5, or a 3 to 6 membered heterospirocyclic ring comprising R_4 and R_5 and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2, or N;

R_6 is substituted phenyl containing 1 to 3 substituents or a 5 or 6 membered heterocyclic ring containing 1 to 3 heteroatoms and 1 to 3 substituents, said heteroatoms being O, S, SO, SO_2 or N and said substituents independently being H, halogen, CN, NO_2, OH, amino, C_{1-3} alkyl, C_{1-3} alkoxy, C_{1-3} aminoalkyl, $C{=}NOR^C$, COR^D, or NR^CCOR^D; or

R_6 is a benzofused heterocyclic ring of the following formula



where A, B, and D are each independently CH, N, O, or S;

R^C is H, C_{1-4} alkyl, substituted C_{1-4} alkyl, or COR^D;

R^D is H, C_{1-3} alkyl, C_{1-3} alkoxy, or C_{1-3} aminoalkyl;

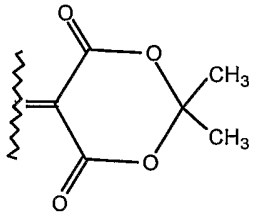
R_7 is H, halogen, CN, NO_2, OH, C_{1-3} alkyl, C_{2-3} alkenyl, C_{2-3} alkynyl, C_{1-3} alkoxy, amino, or C_{1-3} aminoalkyl;

Q is O, S, NR_8, CR_9R_{10}, or $R_{13}R_{14}$;

R_8 is CN, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, or substituted heterocyclic, SO_2CF_3, OR_{11} or $NR_{11}R_{12}$;

R_9 and R_{10} are independently H, C_{1-6} alkyl, substituted C_{1-6} alkyl, C_{3-8} cycloalkyl, substituted C_{3-8} cycloalkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, NO_2, CN, or CO_2R_{11};

or CR_9R_{10} comprises a six membered ring of the structure:



R_{11} and R_{12} are independently H, C_{1-6} alkyl, substituted C_{1-6} alkyl, aryl, substituted aryl, heterocyclic, substituted heterocyclic, acyl or sulfonyl;

R_{13} and R_{14} are each independently H, C_{1-3} alkyl, C_{1-3} perfluoroalkyl, aryl, heterocyclic, a 3 to 6 membered alkylspirocyclic ring comprising R_{13} and R_{14}, a 3 to 6 membered heterospirocyclic ring comprising R_{13} and R_{14} and containing one to three heteroatoms within the spirocyclic ring, said heteroatoms being O, S, SO, SO_2 or N; and

X is O, S, NR^E, or CR^ER^F; where R^E and R^F are each independently H or C_{1-4} alkyl.

25. The method of any one of claims 20 to 24 wherein said compound is one of the following:

7-(4-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

7-(2-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

7-(3,4-difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

7-(3,5-dichlorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

7-(2,3-difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

7-(4-chloro-3-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

4-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile;

7-(3-bromo-5-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

4-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile;

7-(3-chloro-5-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

3-chloro-5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)benzonitrile;

3-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-fluorobenzonitrile;

tert-butyl 2-cyano-5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate;

5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile;

5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile;

5-(5,5-dimethyl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile;

7-(3,5-difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

7-(3,5-difluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepine-2(3*H*)-thione;

5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-4-methylthiophene-2-carbonitrile;

7-(3-chlorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

7-(3-chlorophenyl)-3,5,5-trimethyl-1,5-dihydro-4,1-benzoxazepine-2(3*H*)-thione;

tert-butyl 2-cyano-5-(3,5,5-trimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-1-carboxylate;

5-(3,5,5-trimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1*H*-pyrrole-2-carbonitrile;

7-(3-chloro-4-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

7-(3-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepin-2(3*H*)-one;

7-(3-chloro-4-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepine-2(3*H*)-thione;

7-(3-fluorophenyl)-5,5-dimethyl-1,5-dihydro-4,1-benzoxazepine-2(3*H*)-thione;

3-(5,5-dimethyl-2-thioxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-5-fluorobenzonitrile;

5-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-fluorobenzonitrile;

4-(5,5-dimethyl-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-2-furonitrile;

5-(5,5-dimethyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile; or

5-(1-acetyl-5,5-dimethyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-7-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile; or a pharmaceutically acceptable salt thereof..

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/009756

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D267/14 C07D413/14 C07D417/14 C07D413/04 A61K31/553
A61P15/00 A61P35/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, BEILSTEIN Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AUGUSTINE, ROBERT L. ET AL: "Synthesis of dl-deethylibogamine" JOURNAL OF ORGANIC CHEMISTRY , 34(4), 1070-5 CODEN: JOCEAH; ISSN: 0022-3263, 1969, XP002331119 see compounds 5,6	1-3,10 , 13,16
X	ROBERTSON, DAVID W. ET AL: "Synthesis of a tritium-labeled indolidan analog and its use as a radioligand for phosphodiesterase-inhibitor cardiotonic binding sites" JOURNAL OF MEDICINAL CHEMISTRY , 32(7), 1476-80 CODEN: JMCMAR; ISSN: 0022-2623, 1989, XP002331120 see compound 14	1,2,11 , 13,19

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 June 2005	17/06/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scruton-Evans, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/009756

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/100327 A (ANTEXPHARMA, INC; TOMAZIC, ALENKA; LIREN, HUANG; CLANCY, JOANNA) 19 December 2002 (2002-12-19) see general formulae I,II,III,VI defintions and examples (eg 56,240,239)	1,2,11, 19
X	WO 99/15524 A (FUJISAWA PHARMACEUTICAL CO., LTD; TSUJI, KIYOSHI; TABUCHI, SEIICHIRO;) 1 April 1999 (1999-04-01) see general formula, defintions of R1 and R4	1
X	EP 0 294 647 A (MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG; MERCK PATENT GESEL) 14 December 1988 (1988-12-14) see general formula and defintions of and examples 6 and 10	1,2,11, 13, 19
X	WO 86/03749 A (RORER INTERNATIONAL INC) 3 July 1986 (1986-07-03) see general formula, page 5, 3rd formula, page 28 6th full named cmpound and last compound on page 27	1,2,11, 19
X	EP 0 077 983 A (FUJISAWA PHARMACEUTICAL CO., LTD) 4 May 1983 (1983-05-04) see general formula and examples 69,78,79	1,2,11, 19
X	US 3 900 501 A (NING ET AL) 19 August 1975 (1975-08-19) see examples 5,6,7,10	1,2, 11—13,19
X	WO 99/11635 A (DU PONT PHARMACEUTICALS COMPANY) 11 March 1999 (1999-03-11) cited in the application see general formula and defintions of R4	1,2, 11—17,19
A	ZHI L L ET AL: "Nonsteroidal progesterone receptor antagonists based on 6-thiophenehydroquinolines" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 10, no. 5, March 2000 (2000-03), pages 415-418, XP004202428 ISSN: 0960-894X cited in the application the whole document	1-25
Y	WO 00/66564 A (AMERICAN HOME PRODUCTS CORPORATION; LIGAND PHARMACEUTICALS, INC; ZHANG) 9 November 2000 (2000-11-09) cited in the application the whole document	1-25

-/--

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/009756

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00/66570 A (AMERICAN HOME PRODUCTS CORPORATION; LIGAND PHARMACEUTICALS, INC; ZHANG) 9 November 2000 (2000-11-09) cited in the application the whole document	1-25
Y	WO 00/66581 A (AMERICAN HOME PRODUCTS CORPORATION; LIGAND PHARMACEUTICALS, INC; COLLI) 9 November 2000 (2000-11-09) cited in the application the whole document	1-25
Y	WO 00/66554 A (AMERICAN HOME PRODUCTS CORPORATION; LIGAND PHARMACEUTICALS, INC; ULLRI) 9 November 2000 (2000-11-09) cited in the application the whole document	1-25

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/009756

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02100327 A	19-12-2002	CA 2447687 A1	19-12-2002
		EP 1392317 A2	03-03-2004
		JP 2004536079 T	02-12-2004
		WO 02100327 A2	19-12-2002
WO 9915524 A	01-04-1999	AU 9096698 A	12-04-1999
		WO 9915524 A1	01-04-1999
		JP 2001517666 T	09-10-2001
EP 0294647 A	14-12-1988	DE 3719031 A1	22-12-1988
		DE 3744149 A1	06-07-1989
		AT 91685 T	15-08-1993
		AU 614965 B2	19-09-1991
		AU 1664688 A	08-12-1988
		CA 1340362 C	02-02-1999
		DE 3882444 D1	26-08-1993
		EP 0294647 A2	14-12-1988
		ES 2056854 T3	16-10-1994
		HK 43096 A	22-03-1996
		HU 51272 A2	28-04-1990
		IE 62113 B1	14-12-1994
		JP 2694535 B2	24-12-1997
		JP 63310886 A	19-12-1988
		KR 9700953 B1	21-01-1997
		MX 9203247 A1	01-09-1992
		US 4916128 A	10-04-1990
		ZA 8804019 A	22-02-1989
WO 8603749 A	03-07-1986	US 4721721 A	26-01-1988
		AU 5238886 A	22-07-1986
		EP 0207140 A1	07-01-1987
		JP 62501417 T	11-06-1987
		WO 8603749 A1	03-07-1986
		US 4818755 A	04-04-1989
EP 0077983 A	04-05-1983	AU 8926982 A	28-04-1983
		DE 3276164 D1	04-06-1987
		DK 453882 A	23-04-1983
		EP 0077983 A1	04-05-1983
		ES 8401042 A1	16-02-1984
		ES 8601934 A1	01-03-1986
		ES 8500247 A1	01-01-1985
		FI 823544 A	23-04-1983
		GR 76714 A1	29-08-1984
		JP 58099468 A	13-06-1983
		NO 823506 A	25-04-1983
		OA 7236 A	30-04-1984
		US 4616014 A	07-10-1986
		ZA 8207310 A	31-08-1983
US 3900501 A	19-08-1975	AR 193632 A1	11-05-1973
		AT 331254 B	10-08-1976
		AT 847074 A	15-11-1975
		AT 847174 A	15-01-1975
		AT 332876 B	25-10-1976
		AT 847274 A	15-02-1976
		AT 847374 A	15-02-1975
		AT 329069 B	26-04-1976

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/009756

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 3900501 A		AT 847474 A	15-07-1975
		AT 847574 A	15-02-1975
		AT 847674 A	15-02-1975
		AT 322556 B	26-05-1975
		AT 325628 B	27-10-1975
		AT 326133 B	25-11-1975
		AT 326134 B	25-11-1975
		AT 326135 B	25-11-1975
		AU 458983 B2	13-03-1975
		AU 3715371 A	28-06-1973
		BE 777097 A1	22-06-1972
		BE 777098 A1	22-06-1972
		BG 17804 A3	25-12-1973
		CA 935157 A1	09-10-1973
		CA 948629 A1	04-06-1974
		CH 582162 A5	30-11-1976
		CH 565775 A5	29-08-1975
		CS 158717 B2	25-11-1974
		DD 95384 A5	05-02-1973
		DE 2163522 A1	13-07-1972
		DE 2163625 A1	13-07-1972
		DE 2163642 A1	13-07-1972
		ES 398222 A1	01-06-1975
		FR 2119070 A1	04-08-1972
		FR 2154391 A1	11-05-1973
		FR 2119071 A5	04-08-1972
		GB 1321938 A	04-07-1973
		GB 1325630 A	08-08-1973
		HU 164249 B	28-01-1974
		IL 38416 A	25-04-1975
		JP 56010310 B	06-03-1981
		LU 64491 A1	16-07-1973
		NL 7117480 A	27-06-1972
		NL 7117760 A	27-06-1972
		NL 7117761 A	27-06-1972
		NL 7117762 A	27-06-1972
		PL 83080 B1	31-12-1975
		RO 70586 A1	30-07-1981
		SU 466660 A3	05-04-1975
WO 9911635 A	11-03-1999	AU 9023998 A	22-03-1999
		BR 9814933 A	30-01-2001
		CA 2303295 A1	11-03-1999
		CN 1268944 A	04-10-2000
		EP 1009742 A1	21-06-2000
		HR 980482 A1	31-10-1999
		JP 2001514256 T	11-09-2001
		WO 9911635 A1	11-03-1999
		US 6140320 A	31-10-2000
		US 6489320 B1	03-12-2002
		ZA 9807539 A	21-02-2000
WO 0066564 A	09-11-2000	US 6380235 B1	30-04-2002
		CA 2366805 A1	09-11-2000
		CN 1349511 A ,C	15-05-2002
		EP 1173423 A1	23-01-2002
		JP 2003517459 T	27-05-2003
		WO 0066564 A1	09-11-2000

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/009756

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0066564 A		US 2002115853 A1	22-08-2002
		AU 4688700 A	17-11-2000
		MX PA01011290 A	01-08-2003
WO 0066570 A	09-11-2000	US 6436929 B1	20-08-2002
		AU 766801 B2	23-10-2003
		AU 4811900 A	17-11-2000
		BG 106080 A	31-05-2002
		BR 0010214 A	13-02-2002
		CA 2371712 A1	09-11-2000
		CN 1131856 C	24-12-2003
		CZ 20013952 A3	15-05-2002
		EA 4511 B1	29-04-2004
		EP 1175411 A1	30-01-2002
		HU 0203332 A2	28-01-2003
		JP 2002543192 T	17-12-2002
		MX PA01011287 A	14-07-2003
		NO 20015381 A	03-01-2002
		NZ 515353 A	26-03-2004
		PL 351083 A1	10-03-2003
		SK 15922001 A3	10-09-2002
		TR 200103285 T2	21-02-2002
		WO 0066570 A1	09-11-2000
		US 2003092711 A1	15-05-2003
WO 0066581 A	09-11-2000	US 6407101 B1	18-06-2002
		AU 4980000 A	17-11-2000
		CA 2372560 A1	09-11-2000
		CN 1349531 A ,C	15-05-2002
		EP 1173433 A1	23-01-2002
		JP 2002543197 T	17-12-2002
		MX PA01011295 A	14-07-2003
		WO 0066581 A1	09-11-2000
		US 2002068735 A1	06-06-2002
		US 2003158182 A1	21-08-2003
WO 0066554 A	09-11-2000	US 6417214 B1	09-07-2002
		AT 273951 T	15-09-2004
		AU 4806200 A	17-11-2000
		CA 2371629 A1	09-11-2000
		CN 1349500 A	15-05-2002
		DE 60013114 D1	23-09-2004
		EP 1175397 A1	30-01-2002
		ES 2226838 T3	01-04-2005
		HK 1043986 A1	01-04-2005
		JP 2002543181 T	17-12-2002
		MX PA01011299 A	14-07-2003
		WO 0066554 A1	09-11-2000
		US 2003008909 A1	09-01-2003