

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
27 November 2008 (27.11.2008)

PCT

(10) International Publication Number
WO 2008/144483 A2(51) International Patent Classification: **Not classified**(21) International Application Number:
PCT/US2008/063857

(22) International Filing Date: 16 May 2008 (16.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/930,763 18 May 2007 (18.05.2007) US(71) Applicant (for all designated States except US): **ARMGO PHARMA, INC.** [US/US]; 3960 Broadway, New York, New York 10032 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GAO, Hongwu** [CN/CN]; No. 3 Building, 720 Cailun Rd., Pudong New Area Shanghai 201203 (CN). **BELVEDERE, Sandro** [IT/US]; 114 E 40th Street, #4A, New York, New York 10016 (US). **WEBB, Yael** [IL/US]; 3339 Curry St., Yorktown Heights, New York 10598 (US). **LANDRY, Donald** [US/US]; 29 Claremont Ave., #2-S, New York, New York10027 (US). **DENG, Shixian** [US/US]; 34 Ogden Ave., White Plains, New York 10605 (US). **CHENG, Zhen-zhuang** [CN/US]; 6404 Wetherole Street, FL 1, Rego Park, New York 11374 (US). **YAN, Jiaming** [CN/US]; 725 W 172nd Street, #4, New York, New York 10032 (US).(74) Agents: **FANUCCI, Allan, A.** et al.; Winston & Strawn LLP, Patent Department 1700 K Street, N.W., Washington, DC 20006-3817 (US).

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

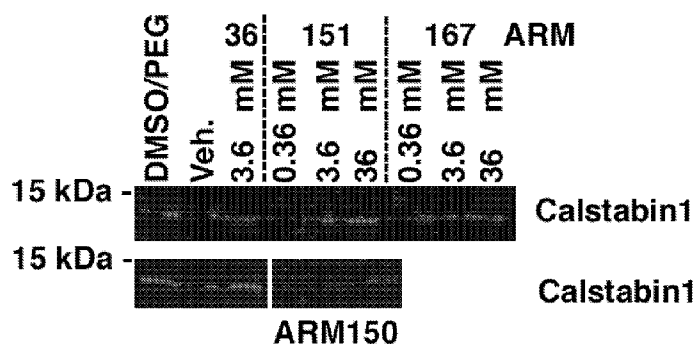
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH,

[Continued on next page]

(54) Title: AGENTS FOR TREATING DISORDERS INVOLVING MODULATION OF RYANODINE RECEPTORS

Figure 4A

RyR1 ISO Screen - Tibialis



(57) Abstract: The present invention provides new agents and compounds effective for treating disorders and diseases associated with RyRs, including cardiac, muscular and cognitive disorders and diseases. These agents are derivatives of benzoxazepines, benzodiazepines and benzazapines. More particularly, the invention provides compounds which include derivatives of benzoxazepine, and their enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, polymorphs, metabolites, and prodrugs thereof.

Figure 4B



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, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, 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:

— *without international search report and to be republished upon receipt of that report*

AGENTS FOR TREATING DISORDERS INVOLVING MODULATION OF RYANODINE RECEPTORS

FIELD OF THE INVENTION

5 This invention relates to compounds and their use to treat disorders and diseases associated with the ryanodine receptors (RyRs) that regulate calcium channel functioning in cells. More particularly, the invention discloses compounds that may be classified as derivatives of benzoxazepines, benzodiazepines and benzazepines, and are useful to treat cardiac, skeletal muscular and cognitive disorders. The invention also discloses
10 pharmaceutical compositions comprising the compounds and uses thereof to treat diseases and conditions associated with RyRs.

BACKGROUND OF THE INVENTION

 The sarcoplasmic reticulum (SR) is a structure in cells that functions, among other
15 things, as a specialized intracellular calcium (Ca^{2+}) store. RyRs are channels in the SR, which open and close to regulate the release of Ca^{2+} from the SR into the intracellular cytoplasm of the cell. Release of Ca^{2+} into the cytoplasm from the SR increases cytoplasmic Ca^{2+} concentration. Open probability of RyRs refers to the likelihood that a RyR channel is open at any given moment, and therefore capable of releasing Ca^{2+} into the cytoplasm from the SR.

20 There are three types of RyRs, all of which are highly-homologous Ca^{2+} channels: RyR1, RyR2, and RyR3. RyR1 is found predominantly in skeletal muscle as well as other tissues, RyR2 is found predominantly in the heart as well as other tissues, and RyR3 is found in the brain as well as other tissues. The RyR channels are formed by four RyR polypeptides in association with four FK506 binding proteins (FKBPs), specifically FKBP12 (calstabin1)
25 and FKBP12.6 (calstabin2). Calstabin1 binds to RyR1 and RyR3 while calstabin2 binds to RyR2. The calstabin1 binds to the RyR channel (one molecule per RyR subunit), stabilize the RyR channel function, facilitate coupled gating between neighboring RyR channels and prevent abnormal activation (Ca^{2+} leak) of the channel by stabilizing the channel's closed state.

30 Besides calstabin1, protein kinase A (PKA) also binds to the cytoplasmic surface of RyRs via the targeting protein mAKAP. Phosphorylation of RyRs by PKA results in partial dissociation of calstabin1 from RyRs, which in turn, causes increased open probability of RyRs, and increased Ca^{2+} release from the SR into the intracellular cytoplasm.

Ca^{2+} release from the SR in skeletal muscle and heart cells is a key physiological mechanism that controls muscle performance, because increased concentration of Ca^{2+} in the intracellular cytoplasm causes contraction of the muscle.

Excitation-contraction (EC) coupling in skeletal muscles involves electrical depolarization of the plasma membrane in the transverse tubule (T-tubule), which activates voltage-gated L-type Ca^{2+} channels (LTCCs). In skeletal muscle LTCCs trigger Ca^{2+} release from the SR through physical interaction with RyR1 resulting in muscle contraction, in cardiac muscle Ca^{2+} influx via the LTCC activates RyR2 to release Ca^{2+} resulting in muscle contraction. The resulting increase in cytoplasmic Ca^{2+} concentration induces actin-myosin interaction and muscle contraction. To enable relaxation, intracellular Ca^{2+} is pumped back into the SR via SR Ca^{2+} -ATPase pumps (SERCAs), which, in the heart, is regulated by phospholamban (PLB) depending on the muscle fiber type.

It has been shown that disease forms that result in sustained activation of the sympathetic nervous system and increased plasma catecholamine levels cause maladaptive activation of intracellular stress pathways resulting in destabilization of the RyR1 and RyR2 channel closed state and intracellular Ca^{2+} leak. SR Ca^{2+} leak via RyR1 or RyR2 channels has been found to deplete intracellular SR calcium stores, and to result in heart failure and impaired exercise capacity. The stress-induced muscle defect permanently reduces isolated muscle and *in vivo* performance particularly in situations of increased demand.

It also has been shown that destabilization of RyR1 closed state occurs under pathologic conditions of increased sympathetic activation and involves depletion of the stabilizing calstabin1 channel subunit. Experiments have shown that PKA activation as an end effector of the sympathetic nervous systems increases PKA phosphorylation of RyR1 at Ser-2843 which decreases the binding affinity of calstabin1 to RyR1 and increases channel open probability.

In cardiac striated muscle, RyR2 is the major Ca^{2+} -release channel required for EC coupling and muscle contraction. During EC coupling, depolarization of the cardiac-muscle cell membrane during phase zero of the action potential activates voltage-gated Ca^{2+} channels. Ca^{2+} influx through the open voltage-gated channels in turn initiates Ca^{2+} release from the SR via RyR2. This process is known as Ca^{2+} -induced Ca^{2+} release. The RyR2-mediated, Ca^{2+} -induced Ca^{2+} release then activates the contractile proteins in the cardiac cell, resulting in cardiac muscle contraction.

Phosphorylation of cardiac RyR2 by PKA is an important part of the "fight or flight" response that increases cardiac EC coupling gain by augmenting the amount of Ca^{2+} released for a given trigger. This signaling pathway provides a mechanism by which activation of the sympathetic nervous system, in response to stress, results in increased cardiac output. PKA phosphorylation of RyR2 increases the open probability of the channel by dissociating calstabin2 from the channel complex. This, in turn, increases the sensitivity of RyR2 to Ca^{2+} -dependent activation.

Despite advances in treatment, heart failure remains an important cause of mortality in Western countries. An important hallmark of heart failure is reduced myocardial contractility. In heart failure, contractile abnormalities result, in part, from alterations in the signaling pathway that allows the cardiac action potential to trigger Ca^{2+} release *via* RyR2 channels and muscle contraction. In particular, in failing hearts, the amplitude of the whole-cell Ca^{2+} transient is decreased and the duration prolonged.

Cardiac arrhythmia, a common feature of heart failure, results in many of the deaths associated with the disease. Atrial fibrillation (AF) is the most common cardiac arrhythmia in humans, and represents a major cause of morbidity and mortality. Structural and electrical remodeling – including shortening of atrial refractoriness, loss of rate-related adaptation of refractoriness, and shortening of the wavelength of re-entrant wavelets – accompany sustained tachycardia. This remodeling is likely important in the development, maintenance and progression of atrial fibrillation. Studies suggest that calcium handling plays a role in electrical remodeling in atrial fibrillation.

Approximately 50% of all patients with heart disease die from fatal cardiac arrhythmias. In some cases, a ventricular arrhythmia in the heart is rapidly fatal – a phenomenon referred to as "sudden cardiac death" (SCD). Fatal ventricular arrhythmias and SCD also occur in young, otherwise-healthy individuals who are not known to have structural heart disease. In fact, ventricular arrhythmia is the most common cause of sudden death in otherwise-healthy individuals.

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited disorder in individuals with structurally normal hearts. It is characterized by stress-induced ventricular tachycardia – a lethal arrhythmia that causes SCD. In subjects with CPVT, physical exertion and/or stress induce bidirectional and/or polymorphic ventricular tachycardias that lead to SCD even in the absence of detectable structural heart disease. CPVT is predominantly inherited in an autosomal-dominant fashion. Individuals with CPVT

have ventricular arrhythmias when subjected to exercise, but do not develop arrhythmias at rest. Studies have identified mutations in the human RyR2 gene, on chromosome 1q42-q43, in individuals with CPVT.

Failing hearts (*e.g.*, in patients with heart failure and in animal models of heart failure) are characterized by a maladaptive response that includes chronic hyperadrenergic stimulation. In heart failure, chronic beta-adrenergic stimulation is associated with the activation of beta-adrenergic receptors in the heart, which, through coupling with G-proteins, activate adenylyl cyclase and thereby increase intracellular cAMP concentration. cAMP activates cAMP-dependent PKA, which has been shown to induce hyperphosphorylation of RyR2. Thus, chronic heart failure is a chronic hyperadrenergic state that results in several pathologic consequences, including PKA hyperphosphorylation of RyR2.

PKA hyperphosphorylation of RyR2 has been proposed as a factor contributing to depressed contractile function and arrhythmogenesis in heart failure. Consistent with this hypothesis, PKA hyperphosphorylation of RyR2 in failing hearts has been demonstrated, *in vivo*, both in animal models and in patients with heart failure undergoing cardiac transplantation.

In failing hearts, the hyperphosphorylation of RyR2 by PKA induces the dissociation of calstabin2 from the RyR2 channel. This causes marked changes in the biophysical properties of the RyR2 channel, including increased open probability due to an increased sensitivity to Ca^{2+} -dependent activation; destabilization of the channel, resulting in subconductance states; and impaired coupled gating of the channels, resulting in defective EC coupling and cardiac dysfunction. Thus, PKA-hyperphosphorylated RyR2 is very sensitive to low-level Ca^{2+} stimulation, and this manifests itself as a diastolic SR Ca^{2+} leak through PKA hyperphosphorylated RyR2 channel.

The maladaptive response to stress in heart failure results in depletion of calstabin2 from the channel macromolecular complex. This leads to a shift to the left in the sensitivity of RyR2 to Ca^{2+} -induced Ca^{2+} release, resulting in channels that are more active at low-to-moderate Ca^{2+} concentrations. Over time, the increased "leak" through RyR2 results in resetting of the SR Ca^{2+} content to a lower level, which in turn reduces EC coupling gain and contributes to impaired systolic contractility.

Additionally, a subpopulation of RyR2 that are particularly "leaky" can release SR Ca^{2+} during the resting phase of the cardiac cycle, diastole. This results in depolarizations of

the cardiomyocyte membrane known as delayed after-depolarizations (DADs), which are known to trigger fatal ventricular cardiac arrhythmias.

In patients with CPVT mutations in their RyR2 and otherwise structurally-normal hearts, a similar phenomenon is at work. Specifically, it is known that exercise and stress induce the release of catecholamines that activate beta-adrenergic receptors in the heart. Activation of the beta-adrenergic receptors leads to PKA hyperphosphorylation of RyR2 channels. Evidence also suggests that PKA hyperphosphorylation of RyR2 resulting from beta-adrenergic-receptor activation renders mutated RyR2 channels more likely to open in the relaxation phase of the cardiac cycle, increasing the likelihood of arrhythmias.

Cardiac arrhythmias are known to be associated with diastolic SR Ca^{2+} leaks in patients with CPVT mutations in their RyR2 and otherwise structurally-normal hearts. In these cases, the most common mechanism for induction and maintenance of ventricular tachycardia is abnormal automaticity. One form of abnormal automaticity, known as triggered arrhythmia, is associated with aberrant release of SR Ca^{2+} , which initiates DADs. DADs are abnormal depolarizations in cardiomyocytes that occur after repolarization of a cardiac action potential. The molecular basis for the abnormal SR Ca^{2+} release that results in DADs has not been fully elucidated. However, DADs are known to be blocked by ryanodine, providing evidence that RyR2 plays a key role in the pathogenesis of this aberrant Ca^{2+} release.

U.S. Patent Application No. 2004/0229781 discusses JTV-519 (4-[3-(4-benzylpiperidin-1-yl)propionyl]-7-methoxy-2,3,4,5-tetrahydro-1,4-benzothiazepine monohydrochloride; also known as k201 or ICP-Calstan 100), a 1,4-benzothiazepine, as a new modulator of RyR calcium-ion channels. U.S. Published Patent Applications No. 2005/0187386 and 2005/0215540 discuss RyR2 as a target for treating and preventing heart failure and cardiac arrhythmias, including atrial fibrillation and cardiac arrhythmias that cause exercise-induced SCD. RyR2 channels with 7 different CPVT mutations (*e.g.*, S2246L, R2474S, N4104K, R4497C, P2328S, Q4201R, V4653F) were found to have functional defects that resulted in channels that became leaky (*i.e.*, a calcium leak) when stimulated during exercise. The mechanism for the VT in CPVT has been demonstrated to be the same as the mechanism for VT in heart failure.

It has been shown that exercise-induced arrhythmias and sudden cardiac death (in patients with CPVT) result from a reduced affinity of calstabin2 for RyR2, which is associated with calcium leak. Additionally, it has been demonstrated that exercise activates RyR2 as a

result of phosphorylation by 3', 5'-cyclic adenosine monophosphate (cAMP)-dependent protein kinase (PKA). Mutant RyR2 channels, which had normal function in planar lipid bilayers under basal conditions, were more sensitive to activation by PKA phosphorylation – exhibiting increased activity (open probability) and prolonged open states, as compared with wild-type channels. In addition, PKA-phosphorylated mutant RyR2 channels were resistant to inhibition by Mg^{2+} , a physiological inhibitor of the channel, and showed reduced binding to calstabin2, which stabilizes the channel in the closed state. These findings indicate that, during exercise, when RyR2 are PKA-phosphorylated, the mutant CPVT channels are more likely to open in the relaxation phase of the cardiac cycle, increasing the likelihood of arrhythmias triggered by SR Ca^{2+} leak.

Additionally, U.S. Published Patent Application No. 2003/0134331 discusses a method for regulating contraction of a subject's heart by administering a compound that regulates PKA phosphorylation of a RyR2 and specifically decreases PKA phosphorylation. U.S. Published Patent Application No. 2004/0048780 also discusses a method for treating and preventing atrial tachyarrhythmia and exercise- and stress-induced arrhythmias by administration of an agent which inhibits PKA phosphorylation of RyR2.

In view of the foregoing, there is a need to identify new compounds effective for treating disorders and diseases associated with RyRs, including skeletal muscular and cardiac disorders and diseases. More particularly, a need remains to identify new agents that can be used to treat RyR associated disorders by, for example, repairing the leak in RyR channels, and enhancing binding of calstabin proteins to PKA-phosphorylated RyRs, and to mutant RyRs that otherwise have reduced affinity for, or do not bind to, calstabins. The invention now provides solutions to these needs.

SUMMARY OF THE INVENTION

Accordingly, the present invention generally provides compounds that may be classified as derivatives of benzoxazepines, benzothiazepines and benzazepines. They are sometimes referred to as "RyCals."

More particularly, the present invention provides compounds which include derivatives of benzoxazepines, and their enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, polymorphs, metabolites, and prodrugs thereof.

Specifically preferred compounds include those compounds of formula I-a as disclosed herein, or compounds disclosed herein as ARM136, ARM137, ARM138, ARM139, ARM140, ARM146, ARM147, ARM148, ARM149, ARM150, ARM151, ARM152, ARM153, ARM156, ARM157, ARM159, ARM160, ARM161, ARM166, ARM167, ARM182, ARM186, ARM189, ARM203, ARM217, ARM251, ARM252, ARM258, ARM277, ARM279, ARM282, ARM291, ARM293, ARM296, ARM301, ARM302, ARM306, ARM311, ARM312, ARM313, ARM318, ARM322, ARM324, ARM326, ARM331, ARM335, ARM337, ARM351, ARM352, ARM353, ARM354, ARM397, ARM398, ARM399, ARM423, ARM454, ARM463, ARM466, ARM470, ARM473 and ARM477, and their enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, polymorphs, metabolites, and prodrugs thereof.

The compounds of the invention may optionally comprise a labeling group, such as a fluorescent, bioluminescent, chemiluminescent, colorimetric or radioactive labeling group.

The present invention also provides methods for the synthesis of compounds of the invention, and salts, hydrates, solvates, complexes, polymorphs, metabolites, and prodrugs thereof.

The present invention further provides a method of treating or preventing various disorders and diseases associated with RyRs, such as cardiac, muscular and cognitive disorders and diseases, comprising administering to a subject in need of such treatment an amount of a compound of the invention, and salts, hydrates, solvates, complexes, polymorphs, metabolites, and prodrugs thereof, effective to prevent or treat a disorder or disease associated with an RyR.

The present invention also provides a method of preventing or treating a leak in RyR (including RyR1, RyR2 and RyR3) in a subject, including administering to the subject an amount of a compound of the invention, and salts, hydrates, solvates, complexes, polymorphs, metabolites, and prodrugs thereof, effective to prevent or treat a leak in RyR. The methods of the invention can be practice on an *in vitro* system (*e.g.*, cultured cells or tissues) or *in vivo* (*e.g.*, in a non-human animal or a human).

In addition, the present invention provides a method of modulating the binding of RyRs and calstabin in a subject, including administering to the subject an amount of a compound of the invention, and salts, hydrates, solvates, complexes, polymorphs, metabolites, and prodrugs thereof, effective to modulate the amount of RyR-bound calstabin.

The present invention also provides pharmaceutical compositions comprising one or more of the compounds of the invention, and at least one additive selected from the group consisting of analgesic agents, antioxidants, aromatics, buffers, binders, colorants, disintegrants, diluents, emulsifiers, excipients, extenders, flavor-improving agents, gellants, glidants, preservatives, skin-penetration enhancers, solubilizers, stabilizers, suspending agents, sweeteners, tonicity agents, vehicles and viscosity-increasing agents. The said pharmaceutical composition is presented in capsules, granules, powders, solutions, suspensions, or tablets form. The articles of manufacture are packaged with indications for various disorders that the pharmaceutical compositions are capable of treating and/or preventing.

BRIEF DESCRIPTION OF THE FIGURES

Other features and advantages of the present invention will become apparent from the following detailed description and drawing figures, wherein:

FIGs. 1A-I Immunoblot with calstabin2 antibody showing binding of calstabin2 to PKA phosphorylated RyR2 in the absence (Neg) or presence of the indicated concentration of ARM140, ARM151, ARM 152 and ARM167 (**A**); ARM137 and ARM148 (**B**); ARM147 and ARM149 (**C**); ARM166 (**D**); ARM217 (**E**); ARM 258 (**F**); ARM291 and ARM296 (**G**); ARM138 (bottom panel) and ARM 139 (top panel) (**H**); and ARM251 (**I**). ARM036, a benzothiazepine described in US patent application publication No. 2005/0187386, is used as a control. Pos: positive control (non-PKA phosphorylated RyR2).

FIGs. 2A-D Immunoblot with calstabin1 antibody showing binding of calstabin1 to PKA phosphorylated RyR1 in the absence (Neg) or presence of compounds ARM148 and ARM150 (**A**); ARM140, ARM151 and ARM167 (**B**); ARM313 and ARM337 (**C**); and ARM 312 (**D**). ARM036 is used as a control. Pos: positive control (non-PKA phosphorylated RyR2).

FIGs. 3A-B Immunoblot with calstabin2 antibody showing the levels of calstabin2 in immunoprecipitated RyR2 complexes from heart lysates in mice administered vehicle (50:50 DMSO/PEG), isoproterenol alone (0) or isoproterenol together with ARM140 (**A**); and ARM151 and ARM167

(B) at the indicated concentrations. ARM036 is used as control at 3.6 mM.

FIGs. 4A-C Immunoblot with calstabin1 antibody showing the levels of calstabin1 in immunoprecipitated RyR1 complexes from tibialis lysates in mice administered vehicle (50:50 DMSO/PEG), isoproterenol alone or isoproterenol together with of ARM 150, ARM151 and ARM167 (A); ARM140 (B); and ARM148 (C) at the indicated concentrations. ARM036 is used as control at 3.6 mM.

DETAILED DESCRIPTION OF THE INVENTION

It should be understood, however, that the detailed description and the specific examples while indicating various embodiments of the invention are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural references unless the content clearly dictates otherwise. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The term "RyCals" refers to compounds of the general Formula I-a as provided by the invention, as well as the specific compounds designated "ARM" and numerical numbers 136 to 477 as provided by the invention, and herein collectively referred to as "compound(s) of the invention".

The term "alkyl" as used herein refers to a linear or branched, saturated hydrocarbon having from 1 to 6 carbon atoms. Representative alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl, and neohexyl.

The term "alkenyl" as used herein refers to a linear or branched hydrocarbon having from 2 to 6 carbon atoms and having at least one carbon-carbon double bond. In one embodiment, the alkenyl has one or two double bonds. The alkenyl moiety may exist in the E or Z conformation and the compounds of the present invention include both conformations.

The term "alkynyl" as used herein refers to a linear or branched hydrocarbon having from 2 to 6 carbon atoms and having at least one carbon-carbon triple bond.

The term "aryl" as used herein refers to an aromatic group containing 1 to 3 aromatic rings, either fused or linked containing 5-14 carbon atoms.

The term "cyclic" or "cyclic group" as used herein includes a cycloalkyl group and a heterocyclic group.

5 The term "cycloalkyl" or "cycloalkyl group" as used herein refers to a three- to seven-membered saturated or partially unsaturated carbon ring. Any suitable ring position of the cycloalkyl group may be covalently linked to the defined chemical structure. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The term "halogen" as used herein refers to fluorine, chlorine, bromine, and iodine.

10 The term "heterocyclic group" or "heterocyclic" or "heterocyclyl" or "heterocyclo" as used herein interchangeably refers to fully saturated, or partially or fully unsaturated, including aromatic (i.e., "heteroaryl") cyclic groups (for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 16 membered tricyclic ring systems) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the
15 heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system. Exemplary heterocyclic groups include, but are not
20 limited to, azepanyl, azetidiny, aziridiny, dioxolanyl, furanyl, furazanyl, homo piperaziny, imidazolidiny, imidazoliny, isothiazolyl, isoxazolyl, morpholiny, oxadiazolyl, oxazolidiny, oxazolyl, oxazolidiny, pyrimidiny, phenanthridiny, phenanthroliny, piperaziny, piperidiny, pyranly, pyraziny, pyrazolidiny, pyrazoliny, pyrazolyl, pyridaziny, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridiny, pyrimidiny, pyrrolidiny,
25 pyrroliny, quinuclidiny, tetrahydrofuranyl, thiadiaziny, thiadiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiomorpholiny, thiophenyl, triaziny, and triazolyl. Exemplary bicyclic heterocyclic groups include indolyl, isoindolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, quinuclidiny, quinoliny, tetrahydroisoquinoliny, isoquinoliny, benzimidazolyl, benzopyranly, indoliziny, benzofuryl, benzofurazanyl, chromonyl, coumariny, benzopyranly, cinnoliny, quinoxaliny, indazolyl,
30 pyrrolopyridyl, furopyridiny (such as furo[2,3-c]pyridiny, furo[3,2-b]pyridiny] or furo[2,3-b]pyridiny), dihydroisoindolyl, dihydroquinazoliny (such as 3,4-dihydro-4-oxo-quinazoliny), triazinylazepiny, tetrahydroquinoliny and the like. Exemplary tricyclic

heterocyclic groups include carbazolyl, benzidolyl, phenanthrolyl, acridinyl, phenanthridinyl, xanthenyl and the like.

The term "phenyl" as used herein refers to a substituted or unsubstituted phenyl group.

The aforementioned terms "alkyl," "alkenyl," "alkynyl," "aryl," "phenyl," "cyclic group," "cycloalkyl," "heterocyclyl," "heterocyclo," and "heterocycle" is further, optionally, substituted with one or more substituents. Exemplary substituents include, but are not limited to, one or more of the following groups: hydrogen, alkyl, halogen, CF_3 , OCF_3 , cyano, nitro, N_3 , oxo, cycloalkyl, alkenyl, alkynyl, heterocycle, aryl, alkylaryl, heteroaryl, OR_a , SR_a , S(=O)R_e , $\text{S(=O)}_2\text{R}_e$, $\text{P(=O)}_2\text{R}_e$, $\text{S(=O)}_2\text{OR}_a$, $\text{P(=O)}_2\text{OR}_a$, NR_bR_c , $\text{NR}_b\text{S(=O)}_2\text{R}_e$, $\text{NR}_b\text{P(=O)}_2\text{R}_e$, $\text{S(=O)}_2\text{NR}_b\text{R}_c$, $\text{P(=O)}_2\text{NR}_b\text{R}_c$, C(=O)OR_a , C(=O)R_a , $\text{C(=O)NR}_b\text{R}_c$, OC(=O)R_a , $\text{OC(=O)NR}_b\text{R}_c$, $\text{NR}_b\text{C(=O)OR}_a$, $\text{NR}_d\text{C(=O)NR}_b\text{R}_c$, $\text{NR}_d\text{S(=O)}_2\text{NR}_b\text{R}_c$, $\text{NR}_d\text{P(=O)}_2\text{NR}_b\text{R}_c$, $\text{NR}_b\text{C(=O)R}_a$, or $\text{NR}_b\text{P(=O)}_2\text{R}_e$, wherein R_a is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, alkylaryl, heteroaryl, heterocycle, or aryl; R_b , R_c and R_d are independently hydrogen, alkyl, cycloalkyl, alkylaryl, heteroaryl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and R_e is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, alkylaryl, heteroaryl, heterocycle, or aryl. In the aforementioned exemplary substituents, groups such as alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, alkylaryl, heteroaryl, heterocycle and aryl can themselves be optionally substituted with any of the aforementioned substituents.

Exemplary substituents may further optionally include at least one labeling group, such as a fluorescent, a bioluminescent, a chemiluminescent, a colorimetric and a radioactive labeling group. A fluorescent labeling group can be selected from bodipy, dansyl, fluorescein, rhodamine, Texas red, cyanine dyes, pyrene, coumarins, Cascade BlueTM, Pacific Blue, Marina Blue, Oregon Green, 4',6-Diamidino-2-phenylindole (DAPI), indopyra dyes, lucifer yellow, propidium iodide, porphyrins, arginine, and variants and derivatives thereof. For further information on fluorescent label moieties and fluorescence techniques, see, e.g., *Handbook of Fluorescent Probes and Research Chemicals*, by Richard P. Haughland, Sixth Edition, Molecular Probes, (1996), which is hereby incorporated by reference in its entirety. One of skill in the art can readily select a suitable labeling group, and conjugate such a labeling group to any of the compounds of the invention, without undue experimentation.

The term "quaternary nitrogen" refers to a tetravalent positively charged nitrogen atom including, for example, the positively charged nitrogen in a tetraalkylammonium group (e.g., tetramethylammonium, N-methylpyridinium and the like), the positively charged nitrogen in

protonated ammonium species (e.g., trimethyl-hydroammonium, N-hydropyridinium), the positively charged nitrogen in amine N-oxides (e.g., N-methyl-morpholine-N-oxide, pyridine-N-oxide), and the positively charged nitrogen in an N-amino-ammonium group (e.g., N-aminopyridinium).

5 Throughout the specification, unless otherwise noted, the nitrogen in the benzoxazepine ring of compounds of the present invention may optionally be a quaternary nitrogen. Compounds of the present invention may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

10 The term "prodrug" as employed herein denotes a compound that, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield compounds of the present invention.

 All stereoisomers of the compounds of the present invention (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers (e.g., as a pure or substantially pure optical isomer having a specified activity), or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the S or R configuration as defined by the IUPAC 1974 Recommendations. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

25 Certain preferred compounds of the invention are referred to using the prefix "ARM" and numerical numbers 136 to 477.

 Compounds of the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 90% of the compound, 95% of the compound, and even more preferably 99% of the compound ("substantially pure" compound), which is then used or formulated as described herein. Such "substantially pure" compounds of the present invention are also contemplated herein as part of the present invention.

All configurational isomers of the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention embraces both cis (*Z*) and trans (*E*) alkene isomers, as well as cis and trans isomers of cyclic hydrocarbon or heterocyclic rings.

5 Throughout the specifications, groups and substituents thereof may be chosen to provide stable moieties and compounds.

The present invention provides compounds that are capable of treating disorders and diseases associated with RyRs. More particularly, the present invention provides compounds that are capable of treating or preventing a leak in RyR channels. In one embodiment, the
10 compounds of the invention enhance association and/or inhibit dissociation of RyR and calstabin (e.g., RyR1 and calstabin1; RyR2 and calstabin2; and RyR3 and calstabin1).

"Disorders and diseases associated with RyRs" means disorders and diseases that can be treated and/or prevented by modulating RyRs. "Disorders and diseases associated with RyRs" include, without limitation, cardiac, muscular, and cognitive disorders and diseases, malignant
15 hyperthermia, diabetes, and sudden infant death syndrome.

Cardiac disorder and diseases include, but are not limited to, irregular heartbeat and exercise-induced irregular heartbeat disorders and diseases; sudden cardiac death; exercise-induced sudden cardiac death; congestive heart failure; chronic obstructive pulmonary disease; cardiac hypertrophy and high blood pressure. Irregular heartbeat disorders and
20 diseases include, but are not limited to, atrial and ventricular arrhythmia, atrial and ventricular fibrillation, atrial and ventricular tachyarrhythmia; atrial and ventricular tachycardia, CPVT, and exercise-induced variants thereof.

Muscular disorders and diseases include, but are not limited to, skeletal muscle fatigue, central core diseases, exercise-induced skeletal muscle fatigue, bladder disorders,
25 incontinence, age-associated muscle fatigue, congenital myopathy, myopathy with cores and rods, mitochondrial myopathies selected from the group consisting of Kearns-Sayre syndrome, MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke) syndrome, and MERRF (myoclonus epilepsy with ragged-red fibers) syndrome, endocrine myopathies, muscular glycogen storage diseases selected from the group consisting of
30 Pompe's disease, Andersen's disease, and Cori's diseases, myoglobinurias selected from the group consisting of McArdle's disease, Tarui disease, and DiMauro disease, dermatomyositis, myositis ossificans, familial periodic paralysis, polymyositis, inclusion body myositis, neuromyotonia, stiff-man syndrome, malignant hyperthermia, common muscle cramps, tetany,

facioscapulohumeral dystrophy, myasthenia gravis, muscular dystrophy selected from the group consisting of limb girdle muscular dystrophy, congenital muscular dystrophy, distal muscular dystrophy, Emery-Dreifuss muscular dystrophy, myotonic muscular dystrophy, and oculopharyngeal muscular dystrophy, Duchenne muscular dystrophy and Becker's muscular dystrophy.

Cognitive disorders and diseases include, but are not limited to,

(i) peripheral neuropathy or central neuropathy selected from the group consisting of vestibular neuropathy, optic neuropathy, optic nerve neuropathy, retinal neuropathy, diabetic neuropathy, alcoholic neuropathy, neuropathy caused by Charcot-Marie-Tooth disease (CMT), Friedreich's ataxia, Gullain-Barre syndrome, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, sjogren syndrome, HIV infection, syphilis infection, herpes infection, hepatitis infection, colorado tick fever infection, diphtheria infection, leprosy, Lyme disease, bacterial infection, viral infection, inflammatory processes, exposure to toxins, treatment with drugs, treatment with chemotherapeutic drugs, cancer, nutritional deficiency, vitamin B-12 deficiency, thiamine deficiency, trauma, pressure on a nerve, a heritable condition, demyelination, axonal damage, uremia, amyloidosis, arsenic poisoning, nitrous oxide exposure or heavy metal exposure;

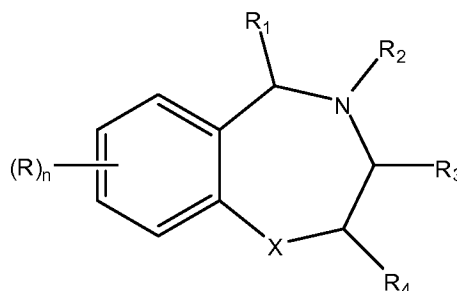
(ii) epilepsy or a non-epileptic seizure selected from the group consisting of epilepsy, partial onset seizures, focal onset seizures, distributed seizures, generalized seizures, simple partial seizures, complex partial seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, atonic seizures, petit mal seizures, grand mal seizures, Jacksonian seizures, psychomotor seizures, temporal-lobe seizures, non-epileptic seizures, unprovoked seizures, alcoholic seizures, infantile spasms, West syndrome, benign childhood epilepsy with centrotemporal spikes, benign rolandic epilepsy, benign childhood epilepsy with occipital paroxysms, juvenile myoclonic epilepsy (JME), temporal lobe epilepsy, frontal lobe epilepsy, Lennox-Gastaut syndrome, occipital lobe epilepsy, fetal alcohol spectrum disorder (FASD), psychogenic seizures, and febrile convulsions; and

(iii) a cognitive disorder selected from the group consisting of Alzheimer's Disease, memory disorders, age-dependent memory disorders, dementia, delirium, amnesia, aphasia, vascular dementia, multi-infarct dementia, Binswanger's disease, dementia with Lewy bodies (DLB), alcohol-induced persisting dementia, frontotemporal lobar degenerations (FTLD), Pick's disease, frontotemporal dementia, frontal variant FTLD, semantic dementia: temporal variant FTLD, progressive non-fluent aphasia, Creutzfeldt-Jakob disease, Huntington's

disease, Parkinson's disease, AIDS dementia complex, an attention disorder, attention-deficit disorder (ADD), attention-deficit hyperactivity disorder (ADHD), age-related cognitive dysfunction and stress-induced cognitive dysfunction including post-traumatic stress disorder.

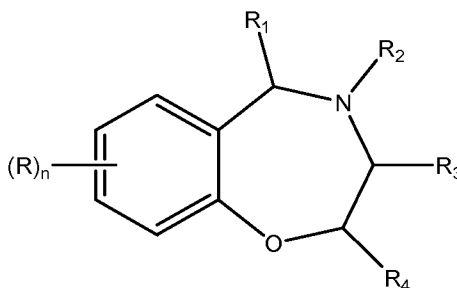
5 Compounds

In general, the compounds of the invention are defined by formula I



where **X** is O, -NR₅ or -C(R₅)₂ and where the substituents are as defined herein.

A preferred embodiment relates to compounds of Formula I-a:



I-a

wherein

n is 0, 1, 2, 3, or 4;

each R is independently selected from the group consisting of Z, R₅, -OR₅, -SR₅,
 15 -N(R₅)₂, -NR₅C(=O)OR₅, -C(=O)N(R₅)₂, -C(=O)OR₅, -C(=O)R₅, -OC(=O)R₅, NO₂,
 CN, -CZ₃, OCZ₃, -N₃, and -P(=O)R₈R₉;

R₁ and R₃ are each independently selected from the group consisting of oxo, R₅,
 -CH₂OR₅, -CH₂OC(=O)R₆, -C(=O)OR₅, -C(=O)NHR₅, -C(=O)R₅, and -OC(=O)R₅;

R₂ is selected from the group consisting of R₅, -C(=O)R₆, -C(=S)R₆, and -(CH₂)_mR₁₀,

20 wherein m is 1, 2, 3, 4, 5, or 6; or

R₁ and R₂ together with the carbon and nitrogen to which they are respectively
 attached, form an unsubstituted or substituted heterocycle; or

R₂ and R₃ together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine; or

R₃ and R₄ together with the carbon atoms to which they are respectively attached, form an unsubstituted or substituted cycloalkyl or heterocyclic ring; or

5 R₄ is selected from the group consisting of R₅ and oxo;

each R₅ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclalkyl, alkylaryl, and alkylheteroaryl;

10 R₆ is selected from the group consisting of R₅, -(CH₂)_bNR₁₃R₁₄, -NR₅OR₅, -OR₅, -C(=O)OR₅, -C(=O)NR₁₃R₁₄, -(CH₂)_cY, and -C(=O)R₅, wherein b is 0, 1, 2, 3, 4, 5, or 6 and c is 1, 2, 3, 4 or 5;

R₁₀ is selected from the group consisting of R₅, -OR₅, -SO₂R₁₁, -C(=O)R₁₂, -NH(C=O)R₁₂, -O(C=O)R₁₂, and -P(=O)R₈R₉;

15 R₈, R₉, R₁₁ and R₁₂ are independently selected from the group consisting of R₅, OR₅, and -N(R₅)₂;

Y is selected from the group consisting of Z, -CO₂R₅, -C(=O)NR₁₃R₁₄, and -OR₅;

Z is a halogen selected from F, Cl, Br and I;

20 R₁₃ and R₁₄ are independently selected from the group consisting of R₅, or R₁₃ and R₁₄ together with the N to which they are bonded may form an unsubstituted or substituted heterocycle; and

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclalkyl, alkylaryl, and alkylheteroaryl may be substituted or unsubstituted;

25 wherein the nitrogen in the benzoxazepine ring may optionally be a quaternary nitrogen; and

all enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, polymorphs, metabolites, and prodrugs thereof;

provided that, (i) when R is hydrogen at position 7 of the benzoxazepine ring, R₂ is not hydrogen, alkyl, haloalkyl or alkoxyalkyl, (ii) when R₃ is oxo, R₁ is not oxo or

30 -C(=O)NHR₅; (iii) when R₂ is H, R₁ is not phenyl; and (iv) when R₂ and R₃ together

with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle, R_1 is not oxo.

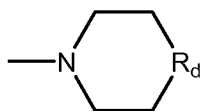
The invention further provides a number of more preferred structures that fall within the general structure of formula I-a. Preferred compounds of the present invention include:

- Compound of formula I-a wherein n , and R_1 - R_4 are as in formula I-a, and wherein each R is independently selected from the group consisting of Z , OCZ_3 , R_5 , OR_5 , CN , NO_2 , $N(R_5)_2$, $-C(=O)N(R_5)_2$, $-C(=O)OR_5$, and $-P(=O)R_8R_9$, wherein R_8 and R_9 are independently OR_5 , and wherein each R_5 is independently hydrogen, or an unsubstituted or substituted alkyl, alkylaryl, aryl, or heterocyclyl.

- Compound of formula I-a wherein R is OR_5 at position 7 of the benzoxazepine ring, n , and R_1 - R_4 are as in formula I-a, and wherein R_5 is selected from the group consisting of hydrogen, or an unsubstituted or substituted alkyl, alkylaryl, aryl, or heterocyclyl. In one most preferred embodiment, R is methoxy.

- Compound of formula I-a wherein n , R , R_1 , R_3 , and R_4 are as in formula I-a, and wherein R_2 is selected from the group consisting of (i) R_5 , (ii) $-C(=O)R_6$, and (iii) $-(CH_2)_mR_{10}$, wherein R_5 is hydrogen, or an unsubstituted or substituted alkyl, aryl, alkylaryl, heterocyclyl or heteroaryl; wherein R_6 is $-NR_{13}R_{14}$, $-C(=O)NR_{13}R_{14}$ or $-(C=O)OR_5$; and wherein R_{13} and R_{14} together with the N to which they are bonded form an unsubstituted or substituted heterocycle; and wherein m is 1, 2, 3, 4, 5, or 6, and wherein R_{10} is R_5 or $(C=O)OR_5$.

- Compound of formula I-a wherein n , R , R_1 , R_3 , and R_4 are as in formula I-a, and wherein R_2 is selected from the group consisting of R_5 , $-C(=O)(C=O)OR_5$, $-C(=O)NR_{13}R_{14}$, $-CH_2R_{10}$ and $-C(=O)C(=O)NR_{13}R_{14}$, wherein R_5 is hydrogen, or an unsubstituted or substituted alkyl, aryl, alkylaryl, heterocyclyl or heteroaryl; and wherein R_{13} and R_{14} are either



each H or are bonded to make N -benzo[1,3]dioxo-5-yl, or $N-C(=O)OC(R_5)_3$, wherein the nitrogen in R_d may optionally be a quaternary nitrogen; and wherein R_{10} is R_5 or $(C=O)OR_5$. In one most preferred embodiment, R_2 is $-C(=O)C(=O)OH$.

- Compounds of formula I-a wherein n , R , R_1 , and R_4 are as in formula I-a, and wherein R_2 and R_3 together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine.

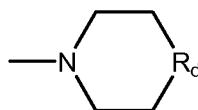
• Compounds of formula I-a wherein n, R, R₁ and R₂ are as in formula I-a, and wherein R₃ and R₄ together with the carbon atoms to which they are respectively attached, form an unsubstituted or substituted cycloalkyl or heterocyclic ring.

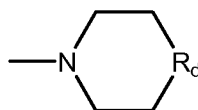
Still other preferred compounds of the present invention include those of formula I-a, wherein

(a) n is 1 or 2, R is Z, OCZ₃, R₅, OR₅, CN, NO₂, N(R₅)₂, -C(=O)N(R₅)₂, -C(=O)OR₅, or -P(=O)R₈R₉ at position 7 or 8 of the benzoxazepine ring; or

(b) n is 1, R is Z, OCZ₃, R₅, OR₅, CN, NO₂, -N(R₅)₂, -C(=O)N(R₅)₂, -C(=O)OR₅, or -P(=O)R₈R₉ at position 6 of the benzoxazepine ring; or

(c) R₂ is C(=O)R₆, wherein R₆ is selected from the group consisting of -C(=O)R₅, -C(=O)OR₅, -C(=O)NR₁₃R₁₄, and (CH₂)_bNR₁₃R₁₄, wherein b=0, and R₁₃ and R₁₄ are



either each H or are bonded to make , wherein R_d is O, CH₂, or NR_a; and R_a is H, alkoxy, C(=O)OC(CH₃)₃, or (C₁-C₆ alkyl)-aryl, wherein the aryl is a disubstituted phenyl or a benzo[1,3]dioxo-5-yl group, and wherein the nitrogen in NR_a may optionally be a quaternary nitrogen; or

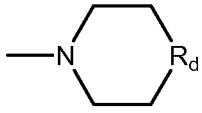
(d) R₂ is R₅ or (CH₂)_mR₁₀, wherein R₁₀ is selected from the group consisting of R₅, -C(=O)N(R₅)₂, -C(=O)OR₅, or -OR₅; and m is 1, 2, 3, 4, 5, or 6.

More preferred compounds of (a) include R₈ and R₉ being independently OR₅. Also in (a)-(d), more preferred compounds of (a)-(d) include each R₅ being independently hydrogen, or an unsubstituted or substituted alkyl, alkylaryl, aryl, or heterocyclyl.

The preferred compounds of the invention specifically include those of formula I-a, wherein n is 1 and R is OR₅, OCZ₃, Z, CN, R₅, N(R₅)₂, -C(=O)N(R₅)₂, -C(=O)OR₅, or -P(=O)(OR₅)₂, NO₂ at position 6, 7 or 8 of the benzoxazepine ring; or n is 2, each R is independently OR₅ at positions 7 and 8 of the benzoxazepine ring.

The more preferred compounds of the invention specifically include those of formula I-a, wherein:

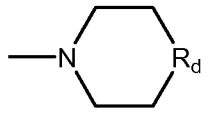
A) n is 1, R is OR₅ or OCZ₃ at position 7 of the benzoxazepine ring, and R₂ is (i) hydrogen; (ii) R₅, (iii) (CH₂)_mR₁₀, wherein m is 1, 2, 3, 4, 5, or 6, and wherein R₁₀ is R₅ or C(=O)OR₅; (iv) -C(=O)C(=O)OR₅; (v) -C(=O)NR₁₃R₁₄ or (vi) -C(=O)C(=O)NR₁₃R₁₄,

wherein R_{13} and R_{14} are either each H or are bonded to make , wherein R_d is CH_2 , NH, O, N-benzo[1,3]dioxo-5-yl, or $N-C(=O)OC(R_5)_3$, wherein the nitrogen in R_d may optionally be a quaternary nitrogen; or R_2 and R_3 together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted

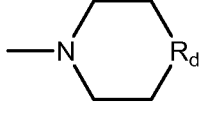
heterocycle other than a piperazine; or

B) n is 1, R is Z, CN, R_5 , $N(R_5)_2$, $-C(=O)N(R_5)_2$, $-C(=O)OR_5$, or $-P(=O)(OR_5)_2$ at position 7 of the benzoxazepine ring, and R_2 is R_5 ; or

C) n is 1, R is NO_2 at position 8 of the benzoxazepine ring, and R_2 is (i) hydrogen; (ii) R_5 , (iii) $-C(=O)C(=O)OR_5$; or (iv) $-C(=O)NR_{13}R_{14}$, wherein R_{13} and R_{14} are either each H or

are bonded to make , wherein R_d is CH_2 , NH, O, $NC(=O)OC(R_5)_3$, or N-benzo[1,3]dioxo-5-yl, wherein the nitrogen in R_d may optionally be a quaternary nitrogen; or R_2 and R_3 together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine; or

D) n is 2, each R is independently OR_5 at positions 7 and 8 of the benzoxazepine ring, and R_2 is (i) hydrogen; (ii) $C(=O)C(=O)OR_5$; or (iii) $-C(=O)NR_{13}R_{14}$, wherein R_{13} and R_{14} are

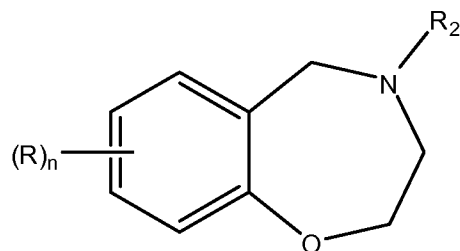
either each H or are bonded to make , wherein R_d is CH_2 , NH, O, N-benzo[1,3]dioxo-5-yl, or $N-C(=O)OC(R_5)_3$, wherein the nitrogen in R_d may optionally be a quaternary nitrogen; or

E) n is 1, R is OR_5 at position 6 of the benzoxazepine ring, and R_2 and R_3 together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine; or

F) each of R_1 , R_2 , R_3 , and R_4 is H, $n=1$, R is OR_5 , OCZ_3 , Z, CN, R_5 , $N(R_5)_2$, $-C(=O)N(R_5)_2$, $-C(=O)OR_5$, or $-P(=O)(OR_5)_2$, NO_2 and is at position 7 of the benzoxazepine ring.

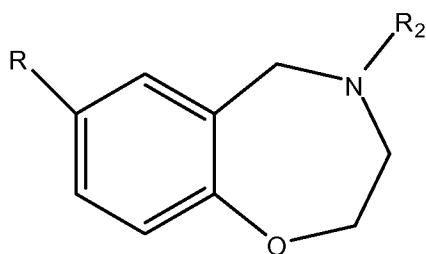
The most preferred compounds of (A)-(F) include R being OR_5 at position 7 of the benzoxazepine ring wherein each R_5 is independently hydrogen, or an unsubstituted or substituted alkyl, alkylaryl, aryl, or heterocyclyl.

Still other preferred compounds are those represented by the structure of any one or more of formula I-b, I-c, I-d, I-e, I-f, I-g, I-h, and I-i, and their pharmaceutically acceptable salts and hydrates.

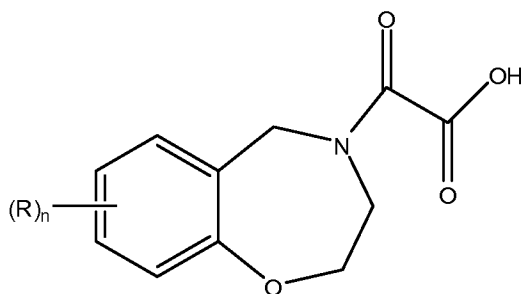


5

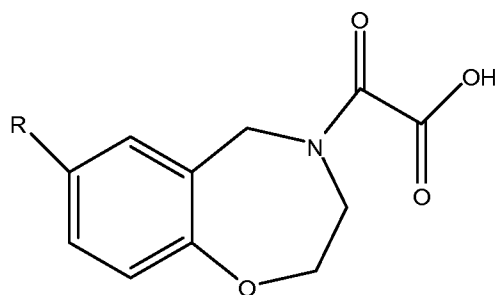
I-b



I-c

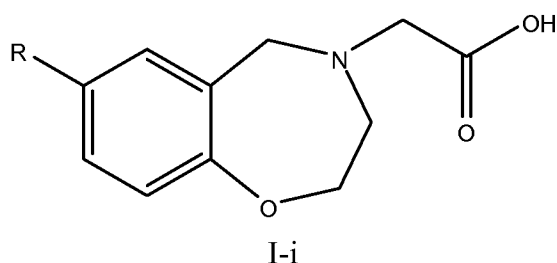
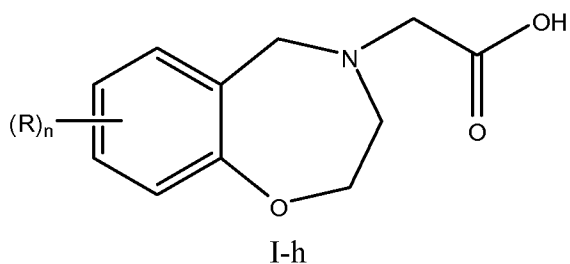
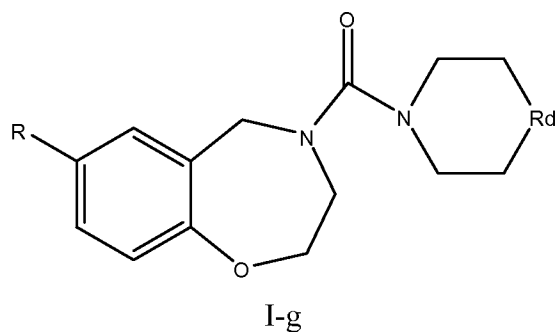
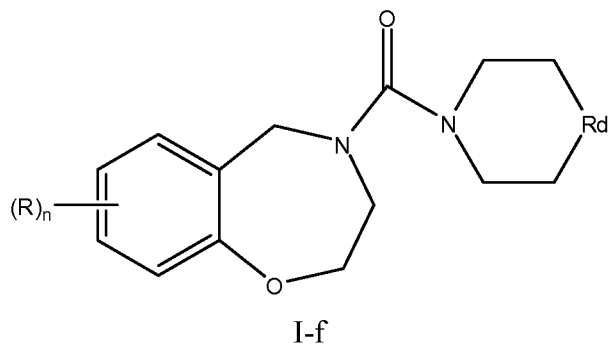


I-d



I-e

10

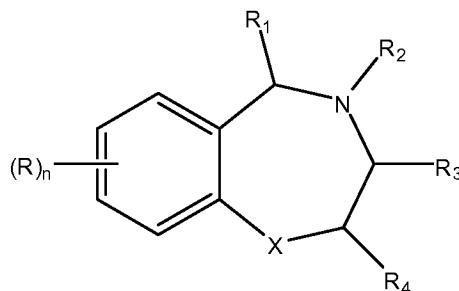


5

wherein R, n and R₂ are as in formula I-a and R_d is CH₂, NH, O, N-benzo[1,3]dioxo-5-yl, or
 10 N-C(=O)OC(R₅)₃, wherein the nitrogen in R_d may optionally be a quaternary nitrogen.

The most preferred compounds of formula I-b to I-i include those where R is OR₅ at position 7 of the benzoxazepine ring wherein each R₅ is independently hydrogen, or an unsubstituted or substituted alkyl, alkylaryl, aryl, or heterocyclyl. Preferably, R is methoxy at position 7 of the benzothiazepine ring.

In a more general embodiment, the present invention provides compounds of formula:

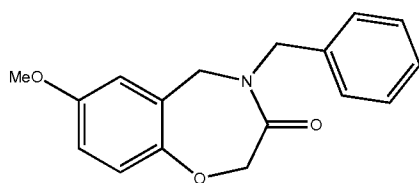


wherein n, R and R₁-R₄ are as defined herein, and wherein X is O, -NR₅ or -C(R₅)₂.

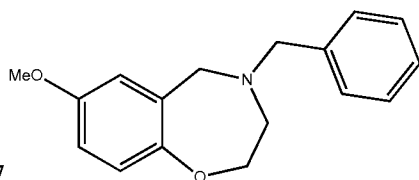
5 The claims have been carefully prepared so as to only recite compounds that to the knowledge of the inventors have not been known in the art. The inventors reserve the right to further exclude any compounds disclosed in prior art that may be cited against the claims in future office actions.

Specifically preferred compounds include those compounds of formula I-a, I-b, I-c, I-
 10 d, I-e, I-f, I-g, I-h and I-i as disclosed herein, or compounds disclosed herein as include, without limitation, ARM136, ARM137, ARM138, ARM139, ARM140, ARM146, ARM147, ARM148, ARM149, ARM150, ARM151, ARM152, ARM153, ARM156, ARM157, ARM159, ARM160, ARM161, ARM166, ARM167, ARM182, ARM186, ARM187, ARM189, ARM 200, ARM203, ARM 205, ARM217, ARM251, ARM252, ARM258,
 15 ARM277, ARM279, ARM282, ARM291, ARM293, ARM296, ARM301, ARM302, ARM306, ARM311, ARM312, ARM313, ARM318, ARM322, ARM324, ARM326, ARM331, ARM335, ARM337, ARM351, ARM352, ARM353, ARM354, ARM397, ARM398, ARM399, ARM423, ARM454, ARM463, ARM466, ARM470, ARM473 and ARM477. These compounds have the following structures:

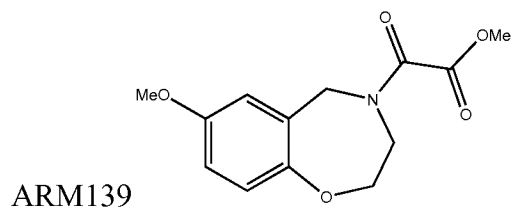
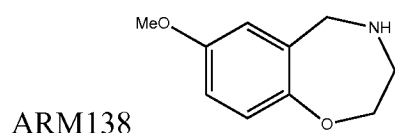
20



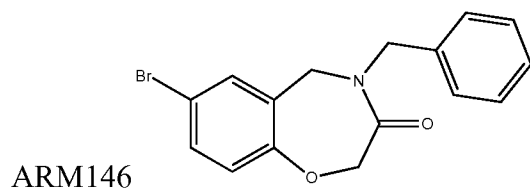
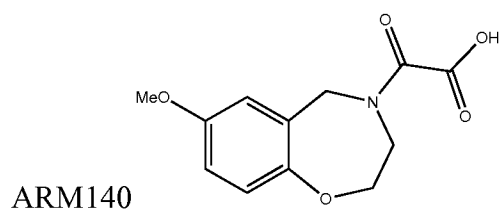
ARM136



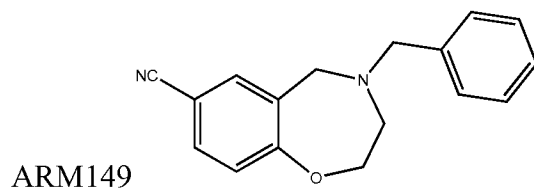
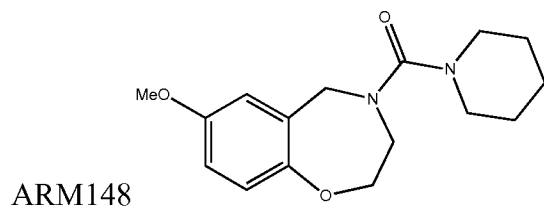
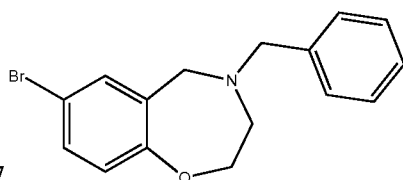
ARM137

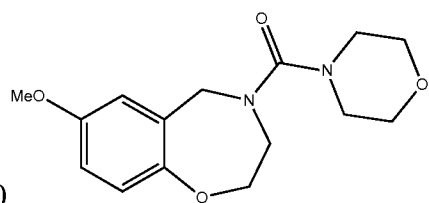


5

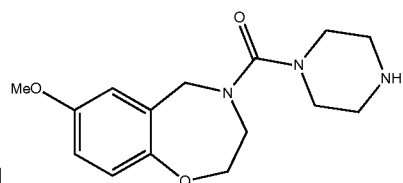


10 ARM147

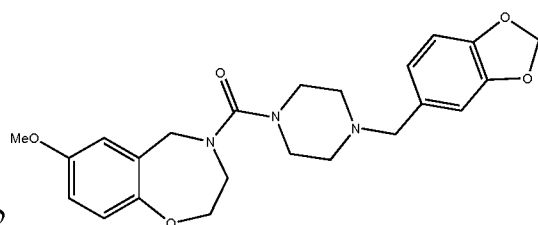




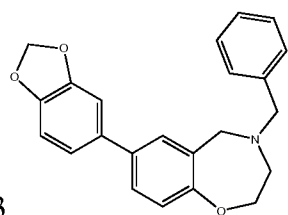
ARM150



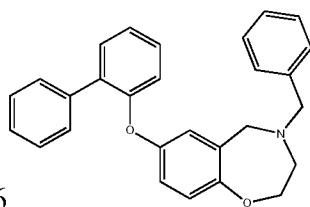
ARM151



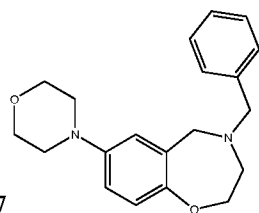
ARM152



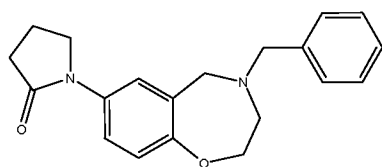
ARM153



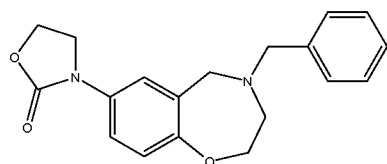
10 ARM156



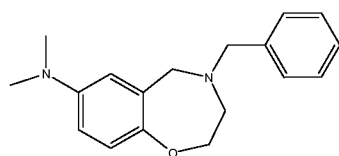
ARM157



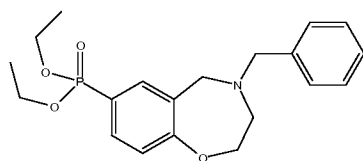
ARM159



5 ARM160

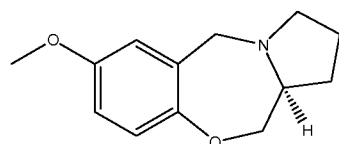


ARM161



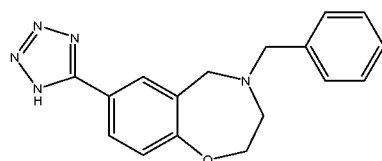
10

ARM166

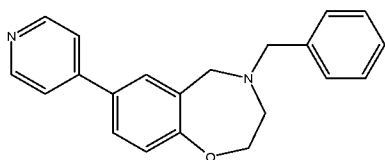


ARM167

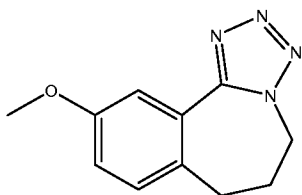
15



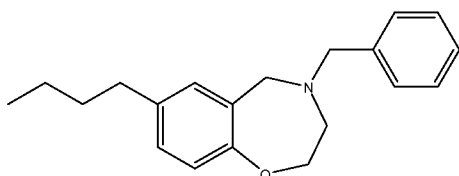
ARM182



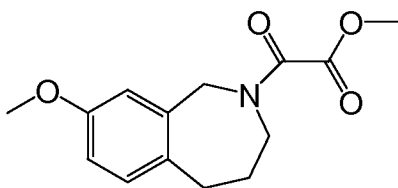
ARM186



5 ARM187

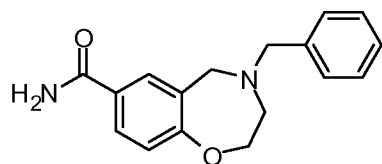


ARM189



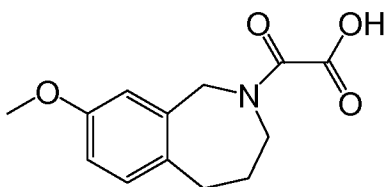
10

ARM200

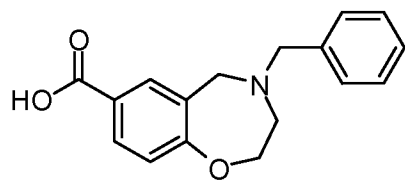


ARM203

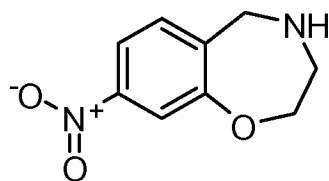
15



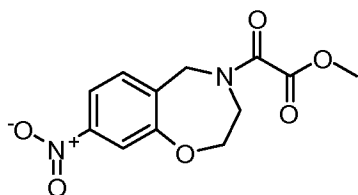
ARM205



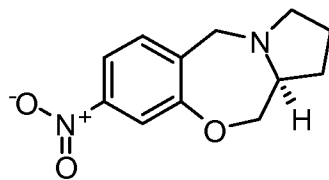
ARM217



5 ARM251

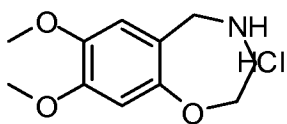


ARM252



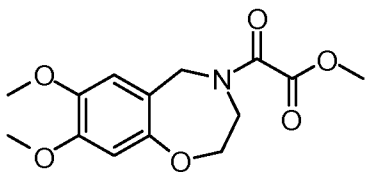
10

ARM258

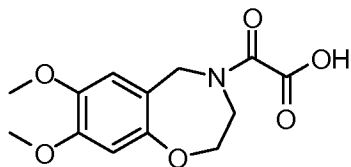


ARM277

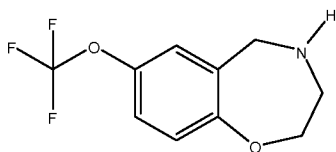
15



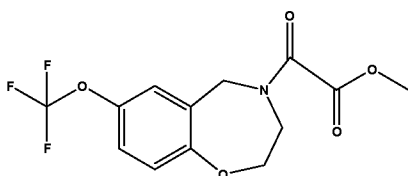
ARM279



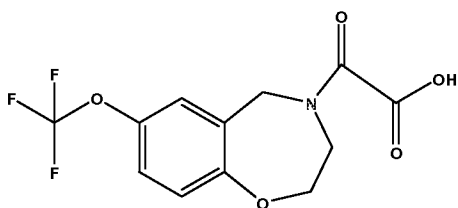
ARM282



5 ARM291

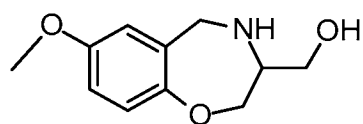


ARM293



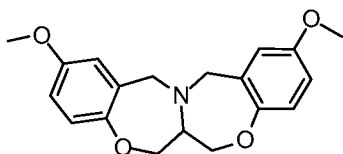
10

ARM296

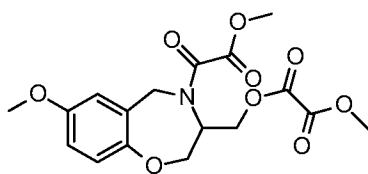


ARM301

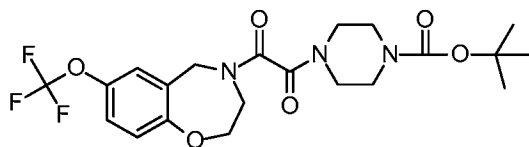
15



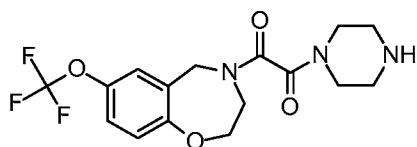
ARM302



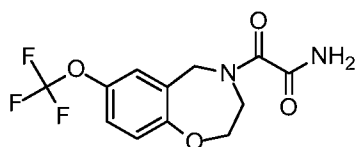
ARM306



5 ARM311

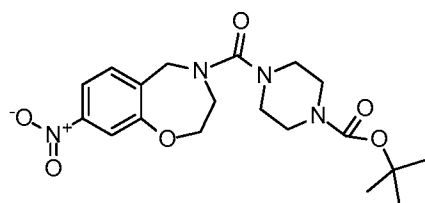


ARM312



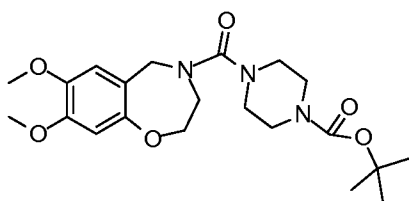
10

ARM313

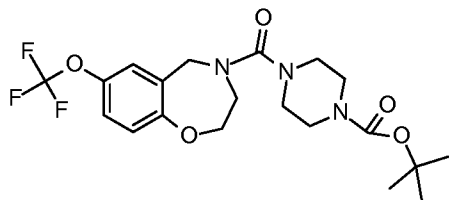


ARM318

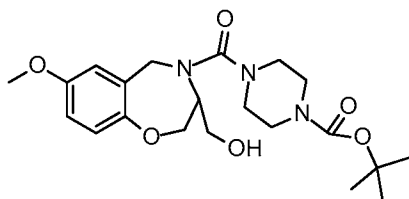
15



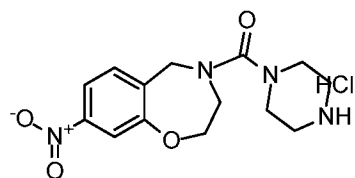
ARM322



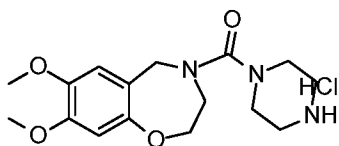
ARM324



5 ARM326

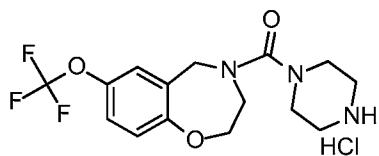


ARM331



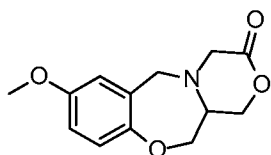
10

ARM335

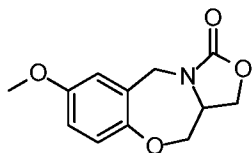


ARM337

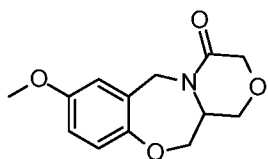
15



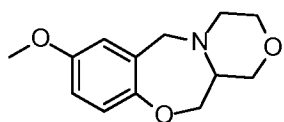
ARM351



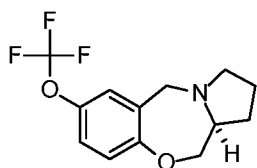
ARM352



5 ARM353

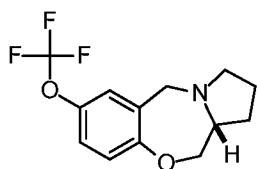


ARM354

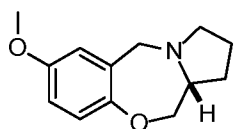


10

ARM397

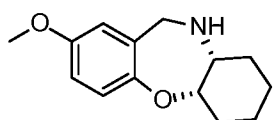


ARM398

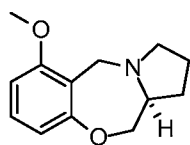


15

ARM399

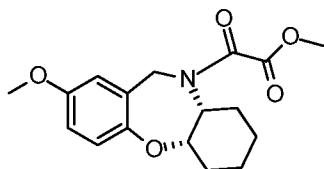


ARM423

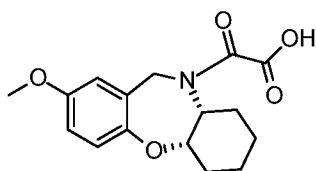


ARM454

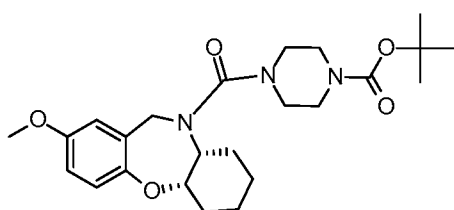
5



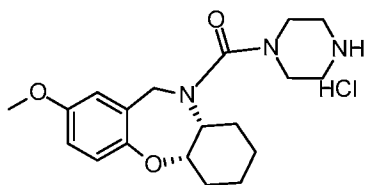
ARM463



10 ARM466

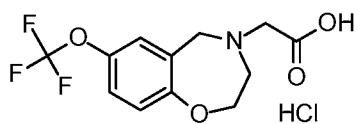


ARM470



15

ARM473



ARM477

Pharmaceutical Compositions

The compounds of the invention are formulated into pharmaceutical compositions for administration to human subjects in a biologically compatible form suitable for administration *in vivo*. According to another aspect, the present invention provides a pharmaceutical

5 composition comprising compounds of the invention in admixture with a pharmaceutically acceptable diluent and/or carrier. The pharmaceutically-acceptable carrier must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the recipient thereof. The pharmaceutically-acceptable carrier employed herein is selected from various organic or inorganic materials that are used as
10 materials for pharmaceutical formulations and which are incorporated as analgesic agents, buffers, binders, disintegrants, diluents, emulsifiers, excipients, extenders, gellants, glidants, skin-penetration enhancers, solubilizers, stabilizers, suspending agents, tonicity agents, vehicles and viscosity-increasing agents. If necessary, pharmaceutical additives, such as antioxidants, aromatics, colorants, flavor-improving agents, preservatives, and sweeteners, are
15 also added. Examples of acceptable pharmaceutical carriers include carboxymethyl cellulose, crystalline cellulose, glycerin, gum arabic, lactose, magnesium stearate, methyl cellulose, powders, saline, sodium alginate, sucrose, starch, talc and water, among others.

The pharmaceutical formulations of the present invention are prepared by methods well-known in the pharmaceutical arts. For example, the compounds of the invention are
20 brought into association with a carrier and/or diluent, as a suspension or solution. Optionally, one or more accessory ingredients (*e.g.*, buffers, flavoring agents, surface active agents, and the like) also are added. The choice of carrier is determined by the solubility and chemical nature of the compounds, chosen route of administration and standard pharmaceutical practice.

25 The compounds of the invention are administered to a subject by contacting target cells (*e.g.*, cardiac muscle cells) *in vivo* in the subject with the compounds. The compounds are contacted with (*e.g.*, introduced into) cells of the subject using known techniques utilized for the introduction and administration of proteins, nucleic acids and other drugs. Examples of methods for contacting the cells with (*i.e.*, treating the cells with) the compounds of the
30 invention include, without limitation, absorption, electroporation, immersion, injection, introduction, liposome delivery, transfection, transfusion, vectors and other drug-delivery vehicles and methods. When the target cells are localized to a particular portion of a subject, it is desirable to introduce the compounds of the invention directly to the cells, by injection or

by some other means (*e.g.*, by introducing the compounds into the blood or another body fluid). The target cells are contained in tissue of a subject and are detected by standard detection methods readily determined from the known art, examples of which include, without limitation, immunological techniques (*e.g.*, immunohistochemical staining), fluorescence
5 imaging techniques, and microscopic techniques.

Additionally, the compounds of the present invention are administered to a human or animal subject by known procedures including, without limitation, oral administration, sublingual or buccal administration, parenteral administration, transdermal administration, via inhalation or intranasally, vaginally, rectally, and intramuscularly. The compounds of the
10 invention are administered parenterally, by epifascial, intracapsular, intracranial, intracutaneous, intrathecal, intramuscular, intraorbital, intraperitoneal, intraspinal, intrasternal, intravascular, intravenous, parenchymatous, subcutaneous or sublingual injection, or by way of catheter. In one embodiment, the agent is administered to the subject by way of delivery to the subject's muscles including, but not limited to, the subject's cardiac muscles. In an
15 embodiment, the agent is administered to the subject by way of targeted delivery to cardiac muscle cells *via* a catheter inserted into the subject's heart.

For oral administration, a formulation of the compounds of the invention may be presented as capsules, tablets, powders, granules, or as a suspension or solution. The formulation has conventional additives, such as lactose, mannitol, cornstarch or potato starch.
20 The formulation also is presented with binders, such as crystalline cellulose, cellulose derivatives, acacia, cornstarch or gelatins. Additionally, the formulation is presented with disintegrators, such as cornstarch, potato starch or sodium carboxymethylcellulose. The formulation also is presented with dibasic calcium phosphate anhydrous or sodium starch glycolate. Finally, the formulation is presented with lubricants, such as talc or magnesium
25 stearate.

For parenteral administration (*i.e.*, administration by injection through a route other than the alimentary canal), the compounds of the invention are combined with a sterile aqueous solution that is isotonic with the blood of the subject. Such a formulation is prepared by dissolving a solid active ingredient in water containing physiologically-compatible
30 substances, such as sodium chloride, glycine and the like, and having a buffered pH compatible with physiological conditions, so as to produce an aqueous solution, then rendering said solution sterile. The formulation is presented in unit or multi-dose containers, such as sealed ampoules or vials. The formulation is delivered by any mode of injection,

including, without limitation, epifascial, intracapsular, intracranial, intracutaneous, intrathecal, intramuscular, intraorbital, intraperitoneal, intraspinal, intrasternal, intravascular, intravenous, parenchymatous, subcutaneous, or sublingual or by way of catheter into the subject's heart.

For transdermal administration, the compounds of the invention are combined with skin penetration enhancers, such as propylene glycol, polyethylene glycol, isopropanol, ethanol, oleic acid, *N*-methylpyrrolidone and the like, which increase the permeability of the skin to the compounds of the invention and permit the compounds to penetrate through the skin and into the bloodstream. The compound/enhancer compositions also may be further combined with a polymeric substance, such as ethylcellulose, hydroxypropyl cellulose, ethylene/vinylacetate, polyvinyl pyrrolidone, and the like, to provide the composition in gel form, which are dissolved in a solvent, such as methylene chloride, evaporated to the desired viscosity and then applied to backing material to provide a patch.

The composition may be provided in unit dose form such as a tablet, capsule or single-dose vial. Suitable unit doses, *i.e.*, therapeutically effective amounts, can be determined during clinical trials designed appropriately for each of the conditions for which administration of a chosen compound is indicated and will, of course, vary depending on the desired clinical endpoint. The present invention also provides articles of manufacture for treating and preventing disorders, such as cardiac disorders, in a subject. The articles of manufacture comprise a pharmaceutical composition of one or more of the compounds of the invention. The articles of manufacture are packaged with indications for various disorders that the pharmaceutical compositions are capable of treating and/or preventing. For example, the articles of manufacture comprise a unit dose of a compound disclosed herein that is capable of treating or preventing a muscular disorder, and an indication that the unit dose is capable of treating or preventing a certain disorder, for example an arrhythmia.

The present invention further provides compounds that may be classified as derivatives of benzoxazepines, including, by way of example and without limitation, the preferred compounds ARM136, ARM137, ARM138, ARM139, ARM140, ARM146, ARM147, ARM148, ARM149, ARM150, ARM151, ARM152, ARM153, ARM156, ARM157, ARM159, ARM160, ARM161, ARM166, ARM167, ARM182, ARM186, ARM189, ARM203, ARM217, ARM251, ARM252, ARM258, ARM277, ARM279, ARM282, ARM291, ARM293, ARM296, ARM301, ARM302, ARM306, ARM311, ARM312, ARM313, ARM318, ARM322, ARM324, ARM326, ARM331, ARM335, ARM337, ARM351, ARM352, ARM353, ARM354, ARM397, ARM398, ARM399, ARM423,

ARM454, ARM463, ARM466, ARM470, ARM473 and ARM477. These and any other compounds of the present invention can be associated with a pharmaceutically acceptable carrier, as described above, so as to form a pharmaceutical composition.

In accordance with the methods of the present invention, any of these compounds may be administered to the subject (or are contacted with cells of the subject) in an amount effective to limit or prevent a decrease in the level of RyR-bound calstabin in the subject, particularly in cells of the subject. This amount is readily determined by the skilled artisan, based upon known procedures, including analysis of titration curves established *in vivo* and methods and assays disclosed herein. A suitable amount of the compounds of the invention effective to limit or prevent a decrease in the level of RyR-bound calstabin in the subject ranges from about 0.01 mg/kg/day to about 20 mg/kg/day, and/or is an amount sufficient to achieve plasma levels ranging from about 300 ng/ml to about 1000 ng/ml. Alternatively, the amount of compounds from the invention ranges from about 10 mg/kg/day to about 20 mg/kg/day. Also included are amounts of from about 0.01 mg/kg/day or 0.05 mg/kg/day to about 5 mg/kg/day or about 10 mg/kg/day which can be administered.

Uses

The present invention provides a new range of therapeutic treatments for patients with various disorders involving modulation of RyRs, particularly skeletal muscular disorders (RyR1), cardiac disorders (RyR2), and cognitive disorders (RyR3).

In one embodiment of the present invention, the subject has not yet developed a disorder, such as exercise-induced cardiac arrhythmia. In another embodiment of the present invention, the subject is in need of treatment for a disorder, including different cardiac disorders.

Various disorders that the compounds of the invention treat or prevent are disorders associated with RyRs, as described above. One skilled in the art will recognize still other diseases, including but not limited to muscular and cardiac disorders, that the compounds of the invention can be useful to treat, in accordance with the information provided herein.

The amount of compounds of the invention effective to limit or prevent a decrease in the level of RyR2-bound calstabin2 in the subject is an amount effective to prevent exercise-induced cardiac arrhythmia in the subject. Cardiac arrhythmia is a disturbance of the electrical activity of the heart that manifests as an abnormality in heart rate or heart rhythm. As used herein, an amount of compounds of the invention "effective to prevent exercise-

induced cardiac arrhythmia" includes an amount of compounds of the invention, effective to prevent the development of the clinical impairment or symptoms of the exercise-induced cardiac arrhythmia (e.g., palpitations, fainting, ventricular fibrillation, ventricular tachycardia and sudden cardiac death). The amount of the compounds effective to prevent exercise-induced cardiac arrhythmia in a subject will vary depending upon the particular factors of each case, including the type of exercise-induced cardiac arrhythmia, the subject's weight, the severity of the subject's condition, and the mode of administration of the compounds. This amount is readily determined by the skilled artisan, based upon known procedures, including clinical trials, and methods disclosed herein. In one embodiment, the amount of the compounds of the invention effective to prevent the exercise-induced cardiac arrhythmia is an amount effective to prevent exercise-induced sudden cardiac death in the subject. In another embodiment, the compounds of the invention prevent exercise-induced cardiac arrhythmia and exercise-induced sudden cardiac death in the subject.

Because of its ability to stabilize RyR-bound calstabin and maintain or restore balance in the context of dynamic PKA phosphorylation and dephosphorylation of RyRs, the compounds of the invention are also useful in treating a subject who has already experienced clinical symptoms of these various disorders. For example, if the symptoms of the disorder are observed early enough, the compounds of the invention are effective in limiting or preventing a further decrease in the level of RyR-bound calstabin in the subject.

Additionally, the subject of the present invention is a candidate for exercise-induced cardiac disorders, such as exercise-induced cardiac arrhythmia. Exercise-induced cardiac arrhythmia is a heart condition (e.g., a ventricular fibrillation or ventricular tachycardia, including any that leads to sudden cardiac death) that develops during/after a subject has undergone physical exercise. A "candidate" for an exercise-induced cardiac disorder is a subject at risk for developing a cardiac disorder during/after physical exercise. Examples of candidates for exercise-induced cardiac arrhythmia include, without limitation, a subject with CPVT or and at risk for developing cardiac arrhythmia during/after physical exercise.

Accordingly, in still another embodiment of the present invention, the subject has been exercising, or is currently exercising, and has developed an exercise-induced disorder. In this case, the amount of the compounds of the invention effective to limit or prevent a decrease in the level of RyR-bound calstabin in the subject is an amount of compound effective to treat the exercise-induced disorder in the subject. As used herein, an amount of compounds of the invention "effective to treat an exercise-induced disorder" includes an amount of a compound

of the invention, effective to alleviate or ameliorate the clinical impairment or symptoms of the exercise-induced disorder (*e.g.*, in the case of cardiac arrhythmia, palpitations, fainting, ventricular fibrillation, ventricular tachycardia, and sudden cardiac death). The amount of the compounds of the invention effective to treat an exercise-induced disorder in a subject will vary depending upon the particular factors of each case, including the type of exercise-induced disorder, the subject's weight, the severity of the subject's condition, and the mode of administration of the compounds. This amount is readily determined by the skilled artisan, based upon known procedures, including clinical trials, and methods disclosed herein. In one embodiment, the compounds of the invention treat exercise-induced disorders in the subject.

The present invention further provides a method for treating exercise-induced disorders in a subject. The method comprises administering the compounds of the invention to the subject in an amount effective to treat the exercise-induced disorder in the subject. A suitable amount of the compounds effective to treat, for example, exercise-induced cardiac arrhythmia in the subject ranges from about 5 mg/kg/day to about 20 mg/kg/day, and/or is an amount sufficient to achieve plasma levels ranging from about 300 ng/ml to about 1000 ng/ml.

Additionally, the compounds prevent irregular heartbeat disorders in subjects with heterozygous defects in the calstabin2 gene.

The compounds of the invention, can be used alone, in combination with each other, or in combination with other agents that have cardiovascular activity including, but not limited to, diuretics, anticoagulants, antiplatelet agents, antiarrhythmics, inotropic agents, chronotropic agents, α and β blockers, angiotensin inhibitors, ACE inhibitors and vasodilators. Further, such combinations of the compounds of the present invention and other cardiovascular agents are administered separately or in conjunction. In addition, the administration of one element of the combination is prior to, concurrent to or subsequent to the administration of other agent(s).

In various embodiments of the above-described methods, the exercise-induced cardiac arrhythmia in the subject is associated with VT. In some embodiments, the VT is CPVT. In other embodiments of these methods, the subject is a candidate for exercise-induced cardiac arrhythmia, including candidates for exercise-induced sudden cardiac death.

In view of the foregoing methods, the present invention also provides use of the compounds of the invention in a method for limiting or preventing a decrease in the level of RyR-bound calstabin in a subject who is a candidate for a disorder. The present invention also provides use of the compounds of the invention in a method for treating or preventing a

muscular disorder in a subject. Furthermore, the present invention provides use of the compounds of the invention in a method for preventing treating or preventing exercise-induced muscular disorders in a subject.

Accordingly, the present invention further provides a method for assaying the effects of the compounds of the invention in preventing disorders and diseases associated with RyRs. The method comprises the steps of: (a) obtaining or generating a culture of cells containing RyR; (b) contacting the cells with one or more of the compounds of the invention; (c) exposing the cells to one or more conditions known to increase phosphorylation of RyR in cells; and (d) determining if the one or more compounds of the invention limits or prevents a decrease in the level of RyR-bound calstabin in the cells. As used herein, a cell "containing RyR" is a cell in which an RyR, including RyR1, RyR2, and RyR3, or a derivative or homologue thereof, is naturally expressed or naturally occurs. Conditions known to increase phosphorylation of RyR in cells include, without limitation, the presence of PKA.

In the method of the present invention, cells are contacted with one of the compounds of the invention by any of the standard methods of effecting contact between drugs/agents and cells, including any modes of administration described herein. The level of RyR-bound calstabin in the cell is measured by any known methods in the art or described herein. In one embodiment of the present invention, the one or more compounds of the invention prevents a decrease in the level of RyR-bound calstabin in the cells.

In one embodiment, the method of the present invention further comprises the steps of contacting one or more compounds of the invention with a culture of cells containing an RyR; and determining if the one or more compounds has an effect on an RyR-associated biological event in the cells. As used herein, a "RyR-associated biological event" includes a biochemical or physiological process in which RyR activity has been implicated, such as, without limitation, EC coupling and contractility in cardiac muscle cells. According to this method of the present invention, the one or more compounds are contacted with one or more cells (such as cardiac muscle cells) *in vitro*. For example, a culture of the cells is incubated with a preparation containing the one or more compounds of the invention. These compounds' effect on a RyR-associated biological event then is assessed by any biological assays or methods known in the art, including immunoblotting, single-channel recordings and any others disclosed herein.

The present invention is further directed to one or more compounds of the invention identified by the above-described identification method, as well as a pharmaceutical

composition comprising the compound and a pharmaceutically acceptable carrier and/or diluent. The compounds are useful for preventing exercise-induced sudden cardiac death in a subject, and for treating or preventing other RyR-associated conditions. As used herein, a "RyR-associated condition" is a condition, disease, or disorder in which RyR level or activity has been implicated, and includes an RyR-associated biological event. The RyR-associated condition is treated or prevented in the subject by administering to the subject an amount of the compound effective to treat or prevent the RyR-associated condition in the subject. This amount is readily determined by one skilled in the art. In one embodiment, the present invention provides a method for preventing exercise-induced sudden cardiac death in a subject, by administering the one or more compounds of the invention to the subject in an amount effective to prevent the exercise-induced sudden cardiac death in the subject.

The present invention also provides an *in vivo* method for assaying the effectiveness of the compounds of the invention in preventing disorders and diseases associated with RyRs. The method comprises the steps of: (a) obtaining or generating an animal containing RyR; (b) administering one or more of the compounds of the invention to the animal; (c) exposing the animal to one or more conditions known to increase phosphorylation of RyR in cells; and (d) determining the extent the compound limits or prevents a decrease in the level of RyR-bound calstabin in the animal. The method further comprises the steps of: (e) administering one or more of the compounds of the invention to an animal containing RyR; and (f) determining the extent of the effect of the compound on a RyR-associated biological event in the animal. Also provided is a pharmaceutical composition comprising this compound; and a method for preventing exercise-induced sudden cardiac death in a subject, by administering this compound to the subject in an amount effective to prevent the exercise-induced sudden cardiac death in the subject.

It has been demonstrated that compounds which block PKA activation would be expected to reduce the activation of the RyR channel, resulting in less release of calcium into the cell. Compounds that bind to the RyR channel at the calstabin binding site, but do not come off the channel when the channel is phosphorylated by PKA, would also be expected to decrease the activity of the channel in response to PKA activation or other triggers that activate the RyR channel. Such compounds would also result in less calcium release into the cell.

By way of example, the diagnostic assays screen for the release of calcium into cells *via* the RyR channel, using calcium-sensitive fluorescent dyes (*e.g.*, Fluo-3, Fura-2, and the

like). Cells are loaded with the fluorescent dye of choice, then stimulated with RyR activators to determine the reduction of the calcium-dependent fluorescent signal (Brillantes, *et al.*, Stabilization of calcium release channel (ryanodine receptor) function by FK506-binding protein. *Cell*, 77:513-23, 1994; Gillo, *et al.*, Calcium entry during induced differentiation in murine erythroleukemia cells. *Blood*, 81:783-92, 1993; Jayaraman, *et al.*, Regulation of the inositol 1,4,5-trisphosphate receptor by tyrosine phosphorylation. *Science*, 272:1492-94, 1996). Calcium-dependent fluorescent signals are monitored with a photomultiplier tube, and analyzed with appropriate software. This assay can easily be automated to screen the compounds of the invention using multiwell dishes.

To demonstrate that the compounds of inhibit the PKA-dependent activation of RyR-mediated intracellular calcium release, an assay involves the expression of recombinant RyR channels in a heterologous expression system, such as Sf9, HEK293, or CHO cells. RyR could also be co-expressed with beta-adrenergic receptors. This would permit assessment of the effect of compounds of the invention on RyR activation, in response to addition of beta-adrenergic receptor agonists.

The level of PKA phosphorylation of RyR2 which correlates with the degree of heart failure also is assayed and then used to determine the efficacy of the compounds of the invention to block the PKA phosphorylation of the RyR2 channel. Such an assay is based on the use of antibodies that are specific for the RyR2 protein. For example, the RyR2-channel protein is immunoprecipitated and then back-phosphorylated with PKA and [γ - 32 P]-ATP. The amount of radioactive [32 P] label that is transferred to the RyR2 protein then is measured using a phosphorimager (Marx, *et al.*, PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. *Cell*, 101:365-76, 2000).

Another assay of the compounds of the invention involves use of a phosphoepitope-specific antibody that detects RyR1 that is PKA phosphorylated on Ser 2843 or RyR2 that is PKA phosphorylated on Ser 2809. Immunoblotting with such an antibody can be used to assess efficacy of these compounds for therapy for heart failure and cardiac arrhythmias. Additionally, RyR2 S2809A and RyR2 S2809D knock-in mice are used to assess efficacy of therapy for heart failure and cardiac arrhythmias. Such mice further provide evidence that PKA hyperphosphorylation of RyR2 is a contributing factor in heart failure and cardiac arrhythmias by showing that the RyR2 S2809A mutation inhibits heart failure and arrhythmias, and that the RyR2 S2809D mutation worsens heart failure and arrhythmias.

Therefore, in a specific embodiment, the present invention provides a method of treating heart failure, atrial fibrillation or exercise-induced cardiac arrhythmia, comprising administering to an animal in need thereof, a therapeutically effective amount of a compound selected from the compounds of the invention.

5 Intracellular Ca^{2+} leak is proposed as a principal mediator of depressed muscle performance and dystrophic muscle remodeling. Muscular dystrophies are heterogeneous hereditary diseases characterized by weakness and progressive muscle wasting. Duchenne muscular dystrophy (DMD) is one of the most frequent genetic diseases (X-linked; 1 in 3,500 boys) with death usually occurring before age 30 by respiratory and/or cardiac failure in high
10 numbers of patients. Since genetic screening will not eliminate DMD due to a high incidence of sporadic cases, an effective therapy is highly desirable. Because alterations of intracellular Ca^{2+} concentrations in DMD myofibers are believed to represent a central pathogenic mechanism, development of a therapeutic intervention that prevents intracellular Ca^{2+} abnormalities as a cause of skeletal muscle degeneration is highly desirable. It has been
15 suggested that elevations of intracellular Ca^{2+} concentrations ($[\text{Ca}^{2+}]_i$) under resting conditions directly contributed to toxic muscle cell (myofiber) damage and concurrent activation of Ca^{2+} -dependent proteases, such as calpain. Therefore, preventing activation of calcium-dependent proteases by inhibiting intracellular Ca^{2+} elevations represents a strategy to prevent muscle wasting in DMD. Intracellular Ca^{2+} elevations are prevented by administration of a
20 pharmaceutical composition comprising a compound of the invention.

In accordance with the method of the present invention, the decrease in the level of RyR-bound calstabin is limited or prevented in the subject by decreasing the level of phosphorylated RyR in the subject. In one embodiment, the amount of the agent effective to limit or prevent a decrease in the level of RyR2-bound calstabin2 in the subject is an amount
25 of the agent effective to treat or prevent heart failure, atrial fibrillation and/or exercise-induced cardiac arrhythmia in the subject. In another embodiment, the amount of the agent effective to limit or prevent a decrease in the level of RyR2-bound calstabin2 in the subject is an amount of the agent effective to prevent exercise-induced sudden cardiac death in the subject.

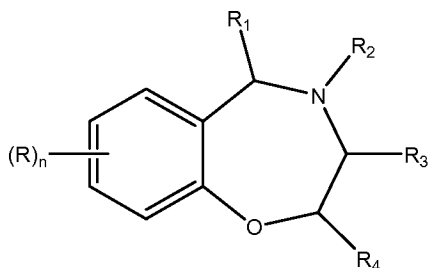
30 Methods of Synthesis

The present invention, provides, in a further aspect, processes for the preparation of a compound of the invention, and salts, solvates, hydrates, complexes, polymorphs, metabolites, and pro-drugs thereof, and pharmaceutically acceptable salts of such pro-drugs. More

particularly, the present invention provides processes for the preparation of the preferred compounds of ARM136, ARM137, ARM138, ARM139, ARM140, ARM146, ARM147, ARM148, ARM149, ARM150, ARM151, ARM152, ARM153, ARM156, ARM157, ARM159, ARM160, ARM161, ARM166, ARM167, ARM182, ARM186, ARM189, ARM203, ARM217, ARM251, ARM252, ARM258, ARM277, ARM279, ARM282, ARM291, ARM293, ARM296, ARM301, ARM302, ARM306, ARM311, ARM312, ARM313, ARM318, ARM322, ARM324, ARM326, ARM331, ARM335, ARM337, ARM351, ARM352, ARM353, ARM354, ARM397, ARM398, ARM399, ARM423, ARM454, ARM463, ARM466, ARM470, ARM473 and ARM477, and salts, solvates, hydrates, complexes, polymorphs, metabolites, and pro-drugs thereof, and pharmaceutically acceptable salts of such pro-drugs. The various synthetic routes to the compounds are described in the examples.

Some of the syntheses utilize solvents. In one embodiment, the solvent is an organic solvent. In another embodiment, the organic solvent is methylene chloride (CH_2Cl_2), chloroform (CCl_4), formaldehyde (CH_2O) or methanol (CH_3OH). Some of the syntheses also utilize a base catalyst. In one embodiment, the base catalyst is an amine compound. In another embodiment, the base catalyst is an alkylamine such as triethylamine (TEA). In still another embodiment, the base catalyst is pyridine. Some of the syntheses also utilize basic solutions. In one embodiment, the basic solution is sodium bicarbonate or calcium carbonate. In another embodiment, the basic solution is saturated sodium bicarbonate or saturated calcium carbonate. Some of the syntheses use acidic solutions. In one embodiment, the acidic solution is a sulfuric acid solution, a hydrochloric acid solution, or a nitric acid solution. In one embodiment, the solution is 1N HCl. The solvents, organic solvents, reactants, catalysts, wash solutions, and so forth are added at appropriate temperatures (*e.g.* room temperature or about 20°C - 25°C , 0°C , etc.).

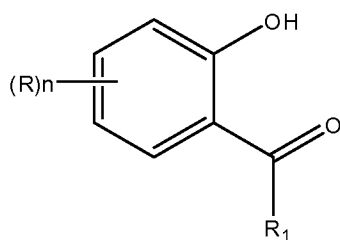
The compounds of the invention can be prepared by various chemical syntheses. In particular, the invention also relates to a method of synthesis of compounds of formula I-a:



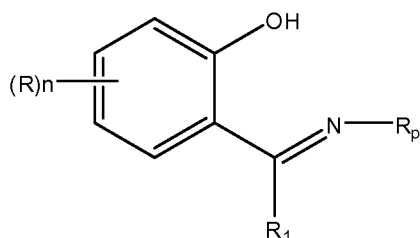
wherein the substituents are as disclosed herein for this formula.

When R_2 and R_3 are H, this method comprising the steps of:

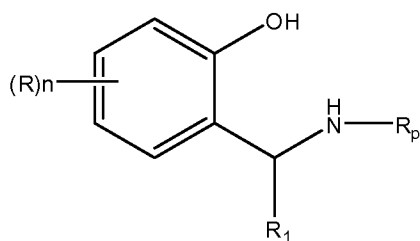
(a) treating a compound having the formula:



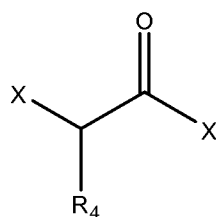
with a compound of formula: $-NH_2R_p$ wherein R_p represents a nitrogen protecting group, to
5 obtain a compound of formula:



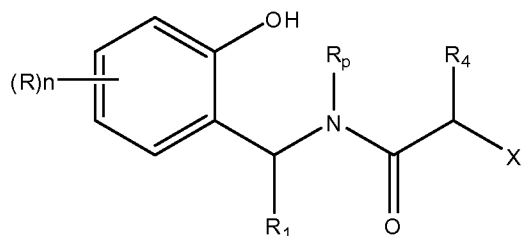
(b) reacting the compound formed in step (a) with a reducing agent to form a
compound of formula:



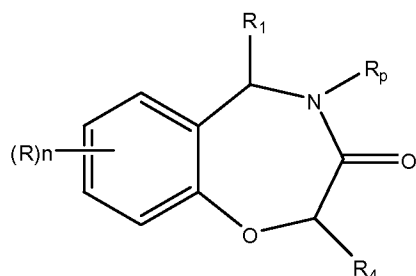
10 (c) reacting the compound formed in step (b) with a compound of the formula:



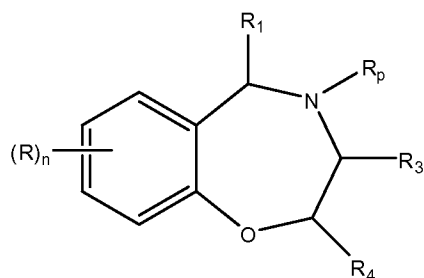
wherein each X is independently a halogen or a sulfonate, to form a compound of formula:



(d) reacting the compound formed in step (c) with a base to form a compound of formula:

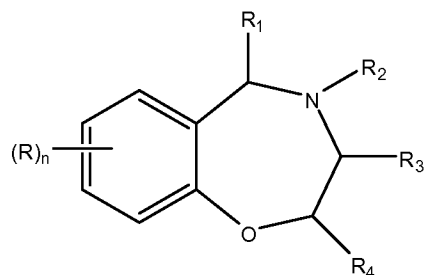


5 (e) treating the compound formed in step (d) with a reducing agent to form a compound of formula:



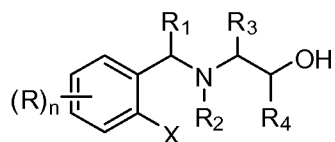
and

(f) removing the nitrogen protecting group R_p to form a compound of formula:

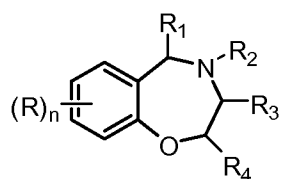


10

Another method of synthesis comprises the step of reacting a compound of formula:

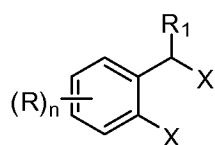


with a transition metal catalyst such as CuI under conditions sufficient to form a compound of formula:

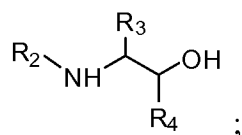


5 These methods can further comprise:

(i) treating a compound of the formula:

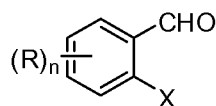


with a compound of formula:

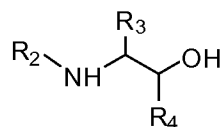


10 or

(ii) treating a compound of the formula:

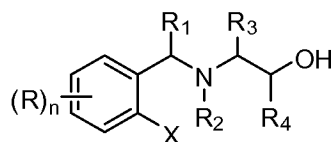


with a compound of formula:



15 under reductive amination conditions;

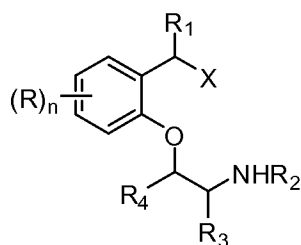
wherein the treating of (i) or (ii) forms compound of formula:



wherein X is independently a leaving group of a halogen or a sulfonate.

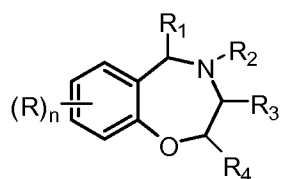
The synthesis methods can also comprise the steps of:

(a) treating a compound of formula

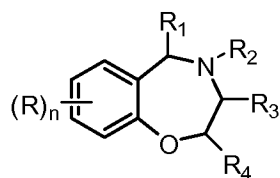


5

wherein X is a leaving group selected from a halogen and a sulfonate with a base, under conditions sufficient to form a compound of formula:

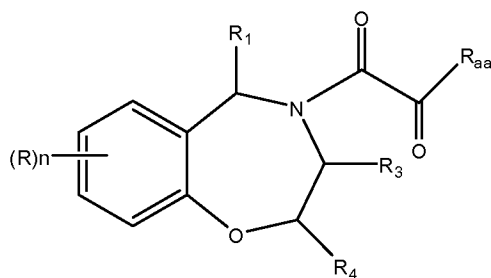


Another synthesis method comprises a step of reacting the compound of formula:

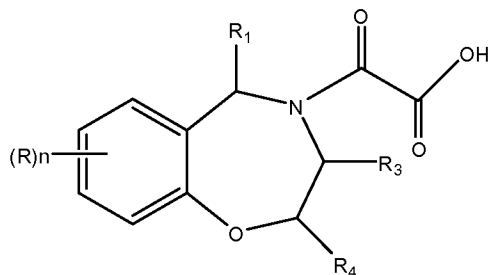


10

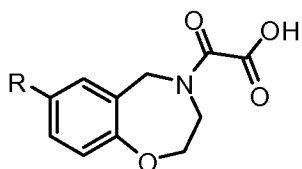
wherein R_2 is H, with an acid chloride of formula $Cl-C(=O)OR_{aa}$ under conditions sufficient to form a compound of the formula:



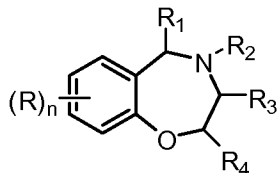
wherein R_{aa} is C_1 - C_4 alkyl or aryl. Subsequently, the previous compound that was formed can be reacted with an acid or a base under conditions sufficient to form a compound of the formula:



5 or its salts. A preferred compound is represented by the formula:

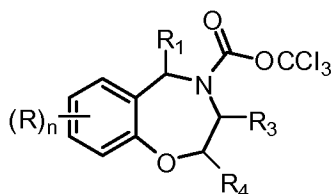


These synthesis methods can further comprise reacting a compound of the formula:



wherein R_2 is H, with either of:

10 (i) triphosgene and a base to form a compound of the formula



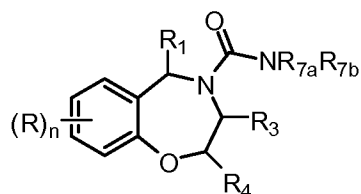
and further reacting that compound with one equivalent of an amine of formula $HNR_{7a}R_{7b}$,

or

15 (ii) a compound of formula $Cl-CO-NR_{7a}R_{7b}$,

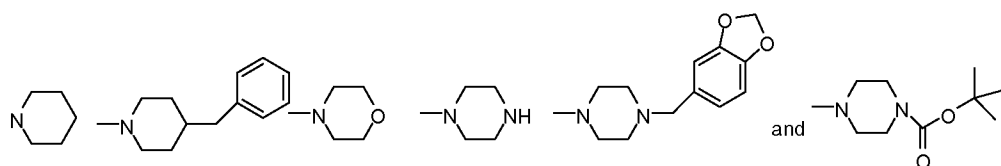
or

(iii) a compound of formula $\text{Cl}_3\text{CO}(\text{C}=\text{O})\text{NR}_{7a}\text{R}_{7b}$ under conditions sufficient to form the compound of formula

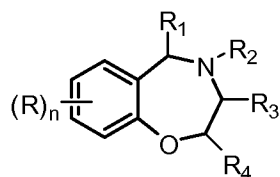


wherein NR_{7a} R_{7b} in (i), (ii), or (iii) is selected from the group consisting of NH₂, NEt₂,

5 NHCH₂Ph, NHOH,

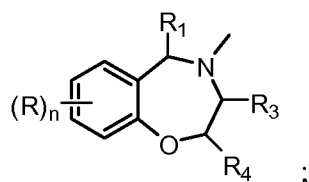


Other synthesis methods include reacting the compound of formula

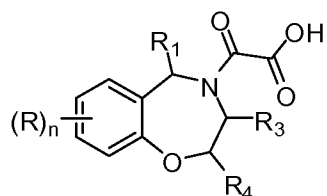


wherein R₂ is H, with formaldehyde (CH₂O) and sodium cyanoborohydride (NaBCNH₃)

10 under conditions sufficient to form a compound of the formula:

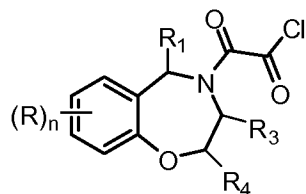


or treating the compound of formula:

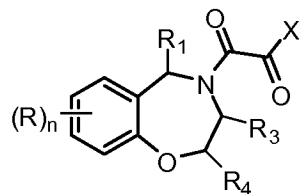


or its salts with thionyl chloride or oxalyl chloride under conditions sufficient to form a

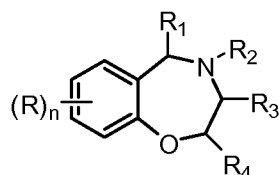
15 compound of the formula:



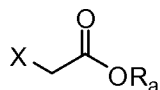
The latter compound can be reacted with a compound of the formula HX, wherein X is OCH₃ or NHEt, under conditions sufficient to form a compound of the formula:



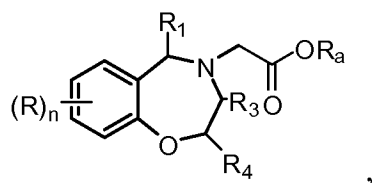
5 Additional synthesis methods include further reacting the compound of formula:



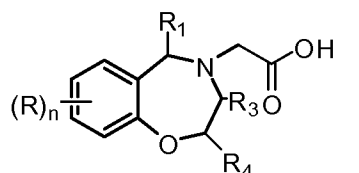
wherein R₂ is H, with a compound of formula:



wherein X is a halogen or a sulfonate, and R_a is a C₁-C₄ alkyl, under conditions sufficient to
10 form a compound of the formula:



and subsequently reacting that compound
with an acid or a base, to form a compound of formula:



Unless otherwise specifically disclosed in the description of the syntheses, the substituents for the compounds that are prepared are those defined in general herein for compounds of the general formula I-a or for the more specific compounds of formulae I-b to I-i.

The compounds of the invention are prepared in different forms, such as salts, hydrates, solvates, complexes, polymorphs, metabolites, pro-drugs or salts of pro-drugs and the invention includes all variant forms of the compounds.

A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or pharmaceutically acceptable salts, hydrates or pro-drugs thereof, with other chemical components, such as physiologically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

A "pro-drug" refers to an agent which is converted into the parent drug *in vivo*. Pro-drugs are often useful because, in some situations, they are easier to administer than the parent drug. They are bioavailable, for instance, by oral administration whereas the parent drug is not. The pro-drug also has improved solubility in pharmaceutical compositions over the parent drug. For example, the compound carries protective groups which are split off by hydrolysis in body fluids, *e.g.*, in the bloodstream, thus releasing active compound or is oxidized or reduced in body fluids to release the compound.

A compound of the present invention also can be formulated as a pharmaceutically acceptable salt, *e.g.*, acid addition salt or a base addition salt, and complexes thereof. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the agent without preventing its physiological effect. Examples of useful alterations in physical properties include, but are not limited to, lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

The term "pharmaceutically acceptable salt" means an acid addition salt which is suitable for or compatible with the treatment of a subject such as a human patient or an animal such as a dog.

The term "pharmaceutically acceptable acid addition salt" as used herein means any non-toxic organic or inorganic salt of any base compounds of the invention or any of their intermediates. Illustrative inorganic acids which form suitable acid addition salts include hydrochloric, hydrobromic, sulfuric and phosphoric acids, as well as metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic

acids that form suitable acid addition salts include mono-, di-, and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, acetic, trifluoroacetic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Either mono or di-acid salts can be formed, and such salts exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of compounds of the invention, are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of an appropriate salt will be known to one skilled in the art. Other non-pharmaceutically acceptable salts, *e.g.*, oxalates, are used, for example, in the isolation of compounds of the invention for laboratory use or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

The term "pharmaceutically acceptable acid base addition salt" as used herein means any non-toxic organic or inorganic salt of any acidic compounds of the invention or any of their intermediates. Illustrative examples include alkali metal salts (*e.g.*, lithium, sodium or potassium salts), alkali earth metal salts (*e.g.*, calcium or magnesium salts), ammonium salts, C₁-C₆ alkylamine (triethylamine and the like) salts, C₁-C₆ alkanolamine (diethanolamine, triethanolamine and the like) salts, procaine salts, cyclohexylamine (dicyclohexylamine and the like) salts, benzylamine (N-methylbenzylamine, N-ethylbenzylamine, N-benzyl-.beta.-phenethylamine, N,N-dibenzylethylenediamine, dibenzylamine and the like) salts, heterocyclic amine (morpholine, N-ethylpyridine, and the like) salts, and the like.

The compounds of the present invention form hydrates or solvates, which are included in the scope of the claims. When the compounds of the present invention exist as regioisomers, configurational isomers, conformers or diastereoisomeric forms, all such forms and various mixtures thereof are included in the scope of compounds of the present invention. It is possible to isolate individual isomers using known separation and purification methods, if desired. For example, when a compound of the present invention is a racemate, the racemate can be separated into the (S)-compound and (R)-compound by optical resolution. Individual optical isomers and mixtures thereof are included in the scope of compounds of the present invention.

The term "solvate" as used herein means a compound of the invention or a pharmaceutically acceptable salt thereof, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage

administered. Examples of suitable solvents are ethanol, water and the like. When water is the solvent, the molecule is referred to as a "hydrate."

The term "metabolite" as used herein refers to a byproduct produced in vivo, for example in a subject, from a chemical compound.

5 The term "polymorph" refers to a particular crystalline state of a substance, having particular physical properties such as X-ray diffraction, IR spectra, melting point, and the like.

10 The term an "effective amount," "sufficient amount" or "therapeutically effective amount" of an agent as used herein is that amount sufficient to effect beneficial or desired results, including clinical results and, as such, an "effective amount" depends upon the context in which it is being applied. The response is preventative and/or therapeutic. The term "effective amount" also includes the amount of a compound of the invention, which is "therapeutically effective" and which avoids or substantially attenuates undesirable side effects.

15 As used herein and as well understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state and remission (whether partial or total), whether
20 detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

25 The present invention further provides a composition, comprising radio labeled compounds of the invention. Labeling of the compounds is accomplished using one of a variety of different radioactive labels known in the art. The radioactive label of the present invention is, for example, a radioisotope. The radioisotope is any isotope that emits detectable radiation including, without limitation, ³⁵S, ¹²⁵I, ³H, or ¹⁴C. Radioactivity emitted by the radioisotope can be detected by techniques well known in the art. For example, gamma emission from the radioisotope is detected using gamma imaging techniques, particularly scintigraphic imaging.

30 By way of example, radio-labeled compounds of the invention are prepared as follows. A compound of the invention may be demethylated at the phenyl ring using BBr₃. The resulting phenol compound then is re-methylated with a radio-labeled methylating agent (such

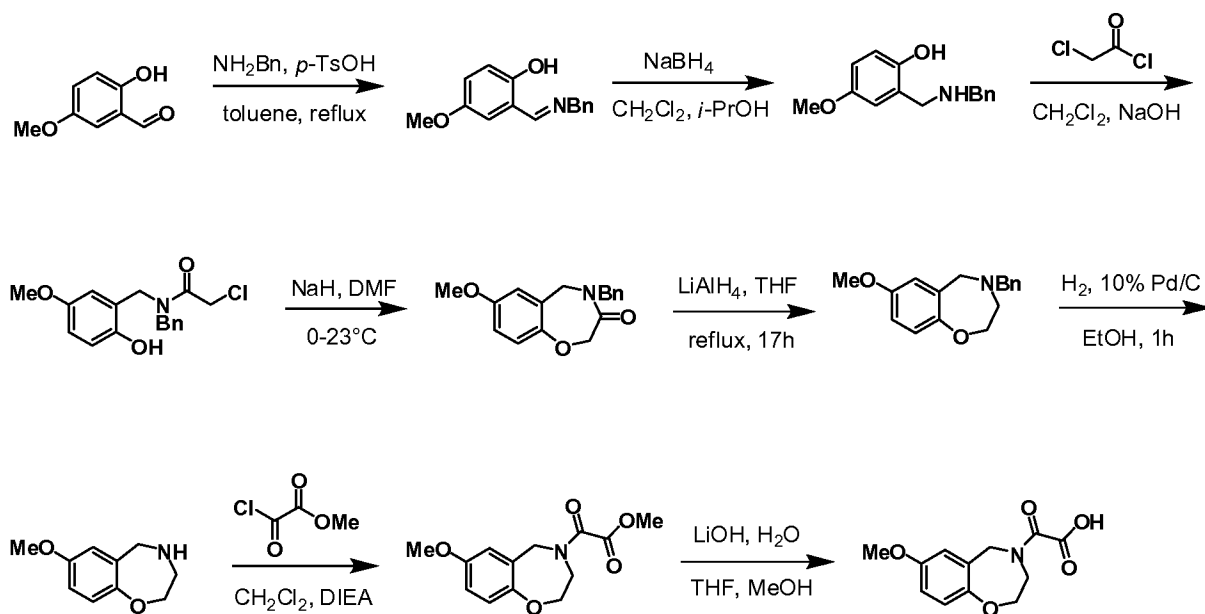
as ^3H -dimethyl sulfate) in the presence of a base (such as NaH) to provide ^3H -labeled compounds.

EXAMPLES

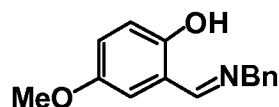
5 The following examples are provided as illustrations of the most preferred compounds according to the invention.

The following abbreviations are used in the exemplified synthetic procedures: DIEA= Diisopropylethylamine, DMAC= Dimethylacetamide, DMF= Dimethylformamide, DMSO=Dimethylsulfoxide, NBS= N-Bromosuccinimide, and THF= Tetrahydrofuran.

10 EXAMPLE 1: PREPARATION OF ARM136-140 (SCHEME 1)



2-((Benzylimino)methyl)-4-methoxyphenol



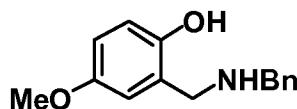
15 To a solution of 2-hydroxy-5-methoxybenzaldehyde (10.0 g, 65.7 mmol, 1.0 equiv.) in toluene (70 mL) was added *p*-toluenesulfonic acid monohydrate (100 mg, 0.526mmol, 0.008 equiv.) and benzylamine (6.84 mL, 62.6 mmol, 0.95 equiv.). The reaction mixture was refluxed for 17 h with dean-stark trap, cooled down to 23°C, and concentrated to give desired

compound as yellow solid. This product was directly used in next step without further purification.

^1H NMR (300 MHz, DMSO- d_6): 3.71 (s, 3H), 4.79 (s, 2H), 6.79 (d, $J=9.3$ Hz, 1H), 6.93 (dd, $J=3.0$ Hz, $J=8.7$ Hz, 1H), 7.06 (d, $J=9.3$ Hz, 1H), 7.34 (m, 5H), 8.65 (s, 1H).

5

2-((Benzylamino)methyl)-4-methoxyphenol

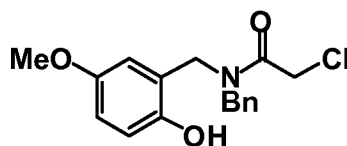


Compound 2-((benzylamino)methyl)-4-methoxyphenol (7.84 g, 32.5 mmol) was dissolved in CH_2Cl_2 (50 mL) and *i*-PrOH (50 mL) at 23°C and the solution was cooled down to 0°C . NaBH_4 (1.57 g, 44.9 mmol, 1.38 equiv.) was added in one portion and ice bath was removed. The reaction mixture was warmed to 23°C and stirred for 17h. The solvent was evaporated, the residue was dissolved with EtOAc (300 mL) and H_2O (200 mL) and the aqueous layer was extracted with EtOAc (2x150 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to give desired product. This product was directly used in the following step without further purification.

15

^1H NMR (300 MHz, CDCl_3): 3.73 (s, 3H), 3.80 (s, 2H), 3.96 (s, 2H), 6.55 (m, 1H), 6.76 (m, 2H), 7.29 (m, 5H).

N-Benzyl-2-chloro-N-(2-hydroxy-5-methoxybenzyl)acetamide



20

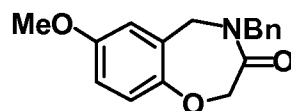
Compound 2-((benzylamino)methyl)-4-methoxyphenol (assumed 32.5 mmol) was dissolved in CH_2Cl_2 (250 mL) and aqueous NaOH (5.2 g, 130 mmol, 4.0 equiv. in H_2O 250 mL) was added in one portion. The resulting mixture was cooled down to 0°C and chloroacetyl chloride (5.4 mL, 68 mmol, 2.09 equiv.) was added over 5 min. The reaction mixture was continued to stir at 0°C for 30 min, concentrated and THF (200 mL) was added. The reaction mixture was stirred at 23°C for 1h, diluted with 1.0 M HCl (300 mL) and extracted with CH_2Cl_2 (3x150 mL). The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to give desired product. This product was directly used in next step without further purification.

25

¹H NMR (300 MHz, CDCl₃): 3.69 (m, 3H), 4.12 (s, 1H), 4.34 (s, 1H), 4.43 (s, 1H), 4.65 (s, 1H), 4.69 (s, 1H), 4.77 (s, 1H), 6.35 (d, *J*=2.7 Hz, 0.5 H), 6.49 (d, *J*=2.7 Hz, 0.5 H), 6.77 (m, 1H), 6.88 (d, *J*=8.7 Hz, 0.5 H), 7.00 (d, *J*=8.7 Hz, 0.5 H), 7.32 (m, 5H), 8.55 (bs, 0.5 H).

5

4-Benzyl-7-methoxy-4,5-dihydrobenzo[f][1,4]oxazepin-3(2H)-one (ARM136)

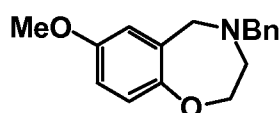


To a solution of compound N-benzyl-2-chloro-N-(2-hydroxy-5-methoxybenzyl) acetamide (8.6 g, 27 mmol) in DMF (50 mL) at 0°C was added NaH (1.6 g, 60% in mineral oil, 40 mmol, 1.48 equiv.) in one portion. The reaction mixture was continued to stir at 0°C for 30 min and another batch of NaH (1.5 g, 60% in mineral oil, 37.5 mmol, 1.39 equiv.) was added. The reaction mixture was stirred at 23°C for 30 min, diluted with 1.0 M HCl (300 mL), extracted with CH₂Cl₂ (3x100 mL). The combined organic layers were washed (brine), dried (Na₂SO₄), concentrated and the residue was purified by column chromatography (EtOAc/petroleum ether 0-30%) to give desired product.

15

¹H NMR (300 MHz, CDCl₃): 3.68 (s, 3H), 4.34 (s, 2H), 4.69 (s, 2H), 4.77 (s, 2H), 6.35 (d, *J*=3.0 Hz, 1H), 6.76 (dd, *J*=3.0 Hz, *J*=9.0 Hz, 1H), 7.00 (d, *J*=9.0 Hz, 1H), 7.29 (m, 5H).

4-Benzyl-7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM137)



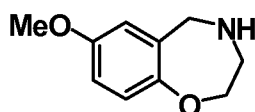
20

To a solution of 4-benzyl-7-methoxy-4,5-dihydrobenzo[f][1,4]oxazepin-3(2H)-one (3.5 g, 12.4 mmol, 1.0 equiv.) in anhydrous THF (120 mL) at 23°C was added LiAlH₄ (1.55 g, 40.7 mmol, 3.28 equiv.). The reaction mixture was refluxed for 17h and cooled down to 0°C by ice/H₂O bath. Solid Na₂SO₄•10H₂O was added slowly until the reaction mixture became a gel-like suspension. The ice bath was removed, THF (100 mL) was added and the reaction mixture was continued to stir for 30 min. Then, the mixture was filtered through Celite and the solid was washed by THF (2x100 mL). The filtrate was collected and concentrated to give desired product. This product was directly used in next step without further purification.

25

^1H NMR (300 MHz, CDCl_3): 3.08 (m, 2H), 3.63 (s, 2H), 3.74 (s, 3H), 3.78 (s, 2H), 4.02 (m, 2H), 6.53 (d, $J=3.0\text{ Hz}$, 1H), 6.68 (dd, $J=3.0\text{ Hz}$, $J=8.7\text{ Hz}$, 1H), 6.93 (d, $J=8.7\text{ Hz}$, 1H), 7.30 (m, 5H).

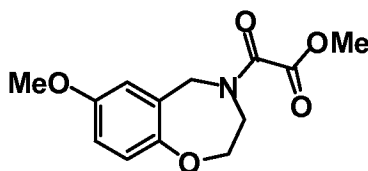
5 7-Methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM138)



To a solution of 4-benzyl-7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (3.4 g, assumed 12.4 mmol, 1.0 equiv.) in EtOH (66 mL) at 23°C was added 10% Pd/C (0.55 g). The reaction mixture was stirred under H_2 atmosphere for 1h, filtered through Celite and the solid was washed by MeOH (2x80 mL). The filtrate was collected and concentrated to give desired product. This product was directly used in next step without further purification.

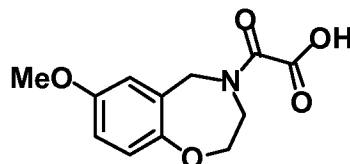
^1H NMR (300 MHz, CDCl_3): 3.20 (m, 2H), 3.76 (s, 3H), 3.91 (s, 2H), 3.97 (m, 2H), 6.67 (m, 2H), 6.94 (m, 1H).

15 Methyl 2-(7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)-2-oxoacetate (ARM139)



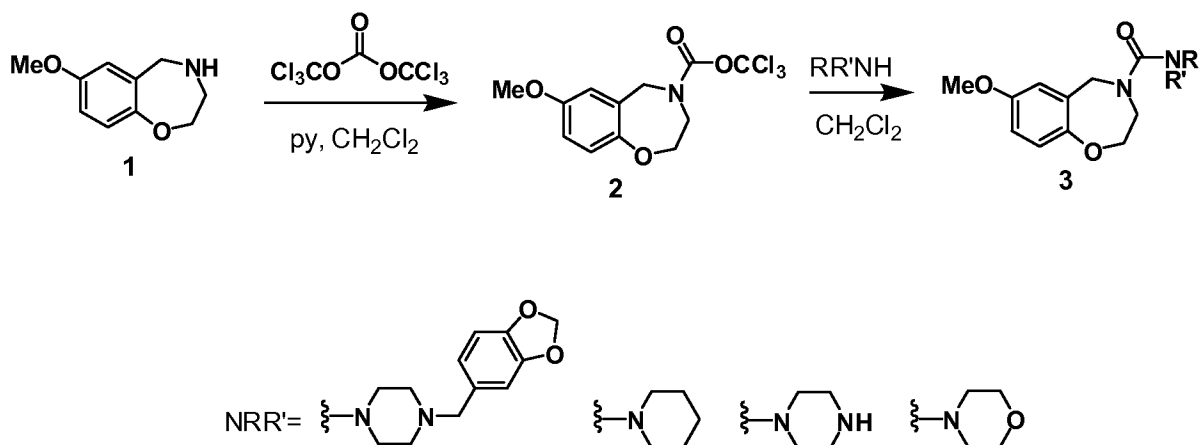
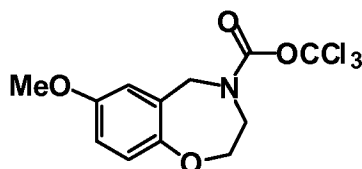
To a cold solution (0°C) of 7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (0.5 g, 2.79 mmol, 1.0 equiv.) in CH_2Cl_2 (100 mL) was added DIEA (1.46 mL, 8.38 mmol, 3.0 equiv.) and methyl chloroacetate (0.31 mL, 3.36 mmol, 1.2 equiv.). The reaction mixture was continued to stir at 0°C for 30 min, diluted with 1.0 M HCl (100 mL), extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were washed (brine), dried (Na_2SO_4), concentrated and the residue was purified by column chromatography (EtOAc/petroleum ether 0-50%) to give desired product.

^1H NMR (300 MHz, CDCl_3): 3.78 (m, 4H), 3.84 (s, 1.5 H), 3.91 (s, 1.5 H), 3.98-4.08 (m, 3H), 4.51 (s, 1H), 4.61 (s, 1H), 6.62 (d, $J=3.0\text{ Hz}$, 0.5 H), 6.73 (m, 1H), 6.87 (d, $J=3.0\text{ Hz}$, 0.5 H), 6.96 (m, 1H).

2-(7-Methoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)-2-oxoacetic acid (ARM140)

To a solution of methyl 2-(7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)-2-oxoacetate (0.32 g, 1.21 mmol, 1.0 equiv.) in MeOH (10 mL) and THF (10 mL) at 23°C was added aqueous LiOH•H₂O (250 mg, 5.95 mmol, 4.0 equiv. in H₂O 10 mL). The reaction mixture was continued to stir at the same temperature for 30 min, concentrated, diluted with H₂O (50 mL) and extracted by Et₂O (30 mL). The aqueous layer was neutralized by HCl aqueous to pH=3 and extracted with CH₂Cl₂ (3x50 mL). The combined organic layers were washed (brine), dried (Na₂SO₄), concentrated to give desired product.

¹H NMR (300 MHz, DMSO-d₆): 3.71 (m, 4H), 3.83 (m, 1H), 3.99 (m, 2H), 4.53 (m, 2H), 6.67 (m, 0.5 H), 6.76 (m, 1H), 6.85 (m, 0.5 H), 6.93 (m, 1H).

EXAMPLE 2: PREPARATION OF ARM148, 150, 151, 152 (SCHEME 2)Trichloromethyl 7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate

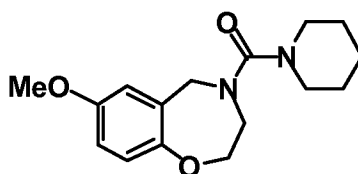
To a cold solution (-30°C) of triphosgene (2.5 g, 8.4 mmol, 1.88 equiv.) in CH₂Cl₂ (20 mL) was added a solution of 7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4] oxazepine (0.8 g,

4.47 mmol, 1.0 equiv.) and pyridine (2.1 mL, 25.75 mmol, 5.76 equiv.) in CH₂Cl₂ (10 mL) over 10 min. The reaction mixture was continued to stir at -20°C for 20 min, 0°C for 30 min, diluted with 0.5 M HCl (100 mL), extracted with CH₂Cl₂ (3x100 mL). The combined organic layers were washed (brine), dried (Na₂SO₄), and concentrated. The residue was purified by column chromatography (EtOAc/hexane 5-33%) to give desired product compound.

¹H NMR (300 MHz, CDCl₃): 3.78 (m, 3H), 3.97 (m, 1H), 4.05 (m, 3H), 4.58-4.66 (d, 2H), 6.76 (m, 1H), 6.84 (m, 1H), 6.99 (m, 1H).

(7-Methoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)(piperidin-1-yl)methanone

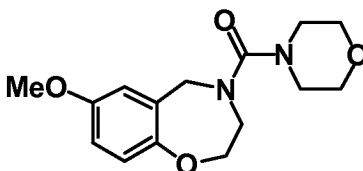
(ARM148)



Piperidine (5 mL, 50.6 mmol, 57.5 equiv) was added to compound trichloromethyl 7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate (0.3 g, 0.88 mmol, 1.0 equiv.) in a 25 mL flask at 23°C. The resulting white suspension was continued to stir for 17h at 23°C, diluted with ethyl acetate (200 mL), washed by 0.2 M HCl aqueous (3x50 mL), washed by brine, dried (Na₂SO₄), concentrated to give desired product.

¹H NMR (300 MHz, CDCl₃): 1.61 (bs, 6H), 3.21 (m, 4H), 3.64 (m, 2H), 3.80 (s, 3H), 4.07 (m, 2H), 4.31 (s, 2H), 6.72 (m, 2H), 6.93 (d, *J*=8.4 Hz, 1H).

(7-Methoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)(morpholino)methanone (ARM150)



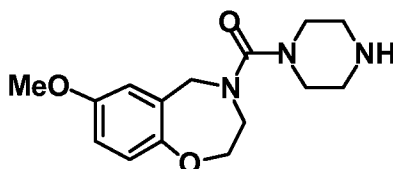
Morpholine (5 mL, 57 mmol, 108 equiv) was added to compound trichloromethyl 7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate (0.18 g, 0.53 mmol, 1.0 equiv.) in a 25 mL flask at 23°C. The resulting white suspension was continued to stir for 17h at 23°C, diluted with ethyl acetate (200 mL), washed by 0.2 M HCl aqueous (3x50 mL), washed by brine, dried (Na₂SO₄), concentrated to give desired product.

¹H NMR (300 MHz, CDCl₃): 3.28 (m, 4H), 3.68 (m, 6H), 3.77 (s, 3H), 4.08 (m, 2H), 4.33 (s, 2H), 6.71 (m, 2H), 6.95 (m, 1H).

¹³C NMR (67 MHz, CDCl₃): 47.85, 52.31, 53.15, 55.74, 66.76, 72.72, 113.32, 115.26, 121.63, 131.52, 153.39, 155.25, 164.05.

5

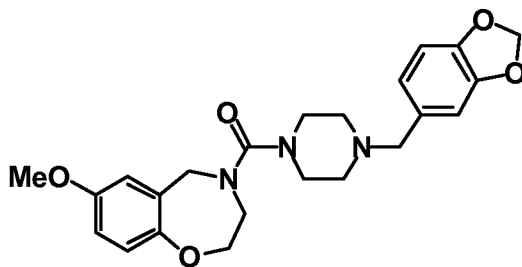
(7-Methoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)(piperazin-1-yl)methanone
(ARM151)



Piperazine (1.0 g, 11.6 mmol, 22 equiv) was added to a solution of compound
10 trichloromethyl 7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate (0.18 g, 0.53 mmol, 1.0 equiv.) in CH₂Cl₂ (5 mL) at 23°C. The resulting solution was continued to stir for 17h at 23°C and filtered. The filtrate was diluted with CHCl₃ (50 mL) and NaHCO₃ saturated aqueous solution. The aqueous layer was extracted with CHCl₃ (3x70 mL). The combined organic layers were washed (H₂O, brine), dried (Na₂SO₄) and concentrated to give
15 desired product compound.

¹H NMR (300 MHz, CDCl₃): 2.52 (m, 1H), 2.91 (m, 4H), 3.27 (m, 4H), 3.66 (m, 2H), 3.77 (s, 3H), 4.08 (m, 2H), 4.32 (s, 2H), 6.73 (m, 2H), 6.94 (d, *J*=7.8 Hz, 1H).

(4-(Benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)(7-methoxy-2,3 dihydrobenzo[f][1,4]
20 oxazepin-4(5H)-yl)methanone (ARM152)

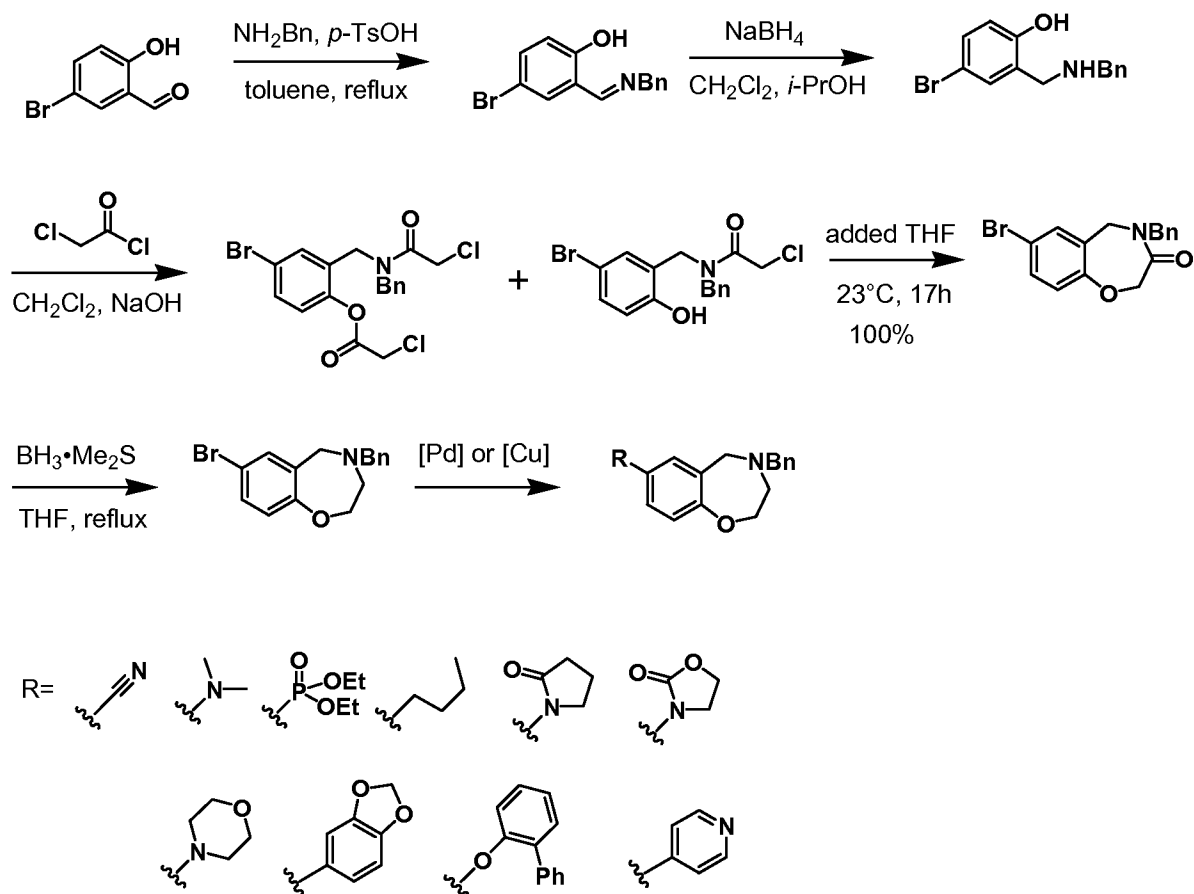


1-Piperonylpiperazine (0.37 g, 1.68 mmol, 3.0 equiv) was added to a solution of
compound trichloromethyl 7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepine-4(5H)-carboxylate
(0.19 g, 0.56 mmol, 1.0 equiv.) in CH₂Cl₂ (5 mL) at 23°C. The resulting solution was
25 continued to stir for 17h at 23°C, diluted with CH₂Cl₂ (150 mL), washed (NaHCO₃ aqueous,

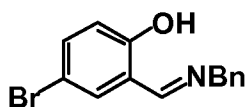
brine), dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (EtOAc/hexane 20-100%) to give desired product compound.

^1H NMR (300 MHz, CDCl_3): 2.44 (t, $J=4.8$ Hz, 4H), 3.29 (t, $J=4.8$ Hz, 4H), 3.43 (s, 2H), 3.64 (m, 2H), 3.76 (s, 3H), 4.07 (m, 2H), 4.30 (s, 2H), 5.94 (m, 2H), 6.72 (m, 4H), 6.84 (s, 1H), 6.95 (dd, $J=0.6$ Hz, $J=7.2$ Hz, 1H).

EXAMPLE 3: PREPARATION OF ARM146, 147, 149, 153, 156, 157, 159, 160, 161, 166, 186, 189 (SCHEME 3)



2-((Benzylimino)methyl)-4-bromophenol

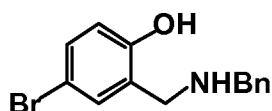


To a solution of 2-hydroxy-5-bromobenzaldehyde (52.8 g, 0.263 mol, 1.0 equiv.) in toluene (300 mL) was added *p*-toluenesulfonic acid monohydrate (300 mg, 1.58 mmol, 0.006

equiv.) and benzylamine (27.4 mL, 0.25 mol, 0.95 equiv.). The reaction mixture was refluxed for 17 h with dean-stark trap, cooled down to 23°C, and concentrated to give desired compound as yellow solid. This product was directly used in next step without further purification.

- 5 ¹H NMR (300 MHz, DMSO-d₆): 2.28 (s, 1H), 4.79 (s, 2H), 6.84 (d, *J*=8.7 Hz, 1H), 7.11-7.38 (m, 5H), 7.44 (dd, *J*=2.7 Hz, *J*=8.7 Hz, 1H), 7.68 (d, *J*=2.7 Hz, 1H), 8.66 (s, 1H).

2-((Benzylamino)methyl)-4-bromophenol

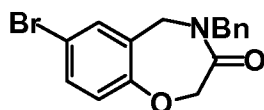


- 10 Compound 2-((benzylamino)methyl)-4-bromophenol (7.6 g, assumed 26.3 mmol) was dissolved in CH₂Cl₂ (16 mL) and *i*-PrOH (16 mL) at 23°C and the solution was cooled down to 0°C. NaBH₄ (1.4 g, 40 mmol, 1.52 equiv.) was added in one portion and ice bath was removed. The reaction mixture was warmed to 23°C and stirred for 17h and quenched by citric acid aqueous (10 mL). The solvent was evaporated, the residue was dissolved with
- 15 EtOAc (300 mL) and H₂O (200 mL) and the aqueous layer was extracted with EtOAc (2x150 mL). The combined organic layers were washed (brine), dried (Na₂SO₄) and concentrated to give desired product. This product was directly used in next step without further purification.

¹H NMR (300 MHz, CDCl₃): 3.79 (s, 2H), 3.96 (s, 2H), 6.72 (d, *J*=8.4 Hz, 1H), 7.08 (m, 1H), 7.33 (m, 6H).

20

4-benzyl-7-bromo-4,5-dihydrobenzo[f][1,4]oxazepin-3(2H)-one (ARM146)

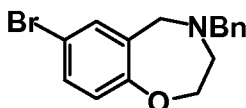


- 25 Compound 2-((benzylamino)methyl)-4-bromophenol (7.8 g, assumed 26.2 mmol) was dissolved in CH₂Cl₂ (250 mL) and NaOH aqueous (4.2 g, 105 mmol, 4.0 equiv. in H₂O 250 mL) was added in one portion. The resulting mixture was cooled down to 0°C and chloroacetyl chloride (4.18 mL, 52.4 mmol, 2.0 equiv.) was added over 5 min. The reaction mixture was continued to stir at 0°C for 30 min, concentrated and THF (200 mL) was added. The reaction mixture was stirred at 23°C for 17h, diluted with 1.0 M HCl (300 mL) and extracted with CH₂Cl₂ (3x150 mL). The combined organic layers were washed (brine), dried

(Na₂SO₄) and concentrated to give desired product. This product was directly used in next step without further purification. The analytical sample was purified by column chromatography (EtOAc/petroleum ether 0-30%) to give desired pure product.

¹H NMR (300 MHz, CDCl₃): 4.35 (s, 2H), 4.75 (s, 2H), 4.76 (s, 2H), 6.94 (m, 2H),
5 7.23 (m, 2H), 7.34 (m, 4H).

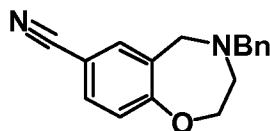
4-Benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM147)



To a solution of 4-benzyl-7-bromo-4,5-dihydrobenzo[f][1,4]oxazepin-3(2H)-one (8.8
10 g, 26.2 mmol, 1.0 equiv.) in anhydrous THF (150 mL) at 23°C was added BH₃•SMe₂ (9.0 mL,
94.8 mmol, 3.6 equiv.). The reaction mixture was refluxed for 14h and cooled down to 23°C.
The NaOH aqueous (3.0 M, 35 mL) was added slowly. The reaction mixture was refluxed for
1h, cooled down to 23°C and concentrated. The residue was diluted with NaHCO₃ aqueous
and extracted with EtOAc (3x150 mL). The combined organic layers were washed (brine),
15 dried (Na₂SO₄), concentrated and the residue was purified by column chromatography
(EtOAc/petroleum ether 0-20%) to give desired product.

¹H NMR (300 MHz, CDCl₃): 3.08 (m, 2H), 3.65 (s, 2H), 3.77 (s, 2H), 4.07 (m, 2H),
6.89 (d, *J*=8.4 Hz, 1H), 7.13 (d, *J*=2.4 Hz, 1H), 7.31 (m, 6H).

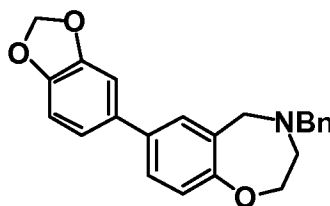
4-Benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carbonitrile (ARM149)



To a solution of 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (2.3 g,
7.23 mmol, 1.0 equiv.) in anhydrous DMAC (10 mL) at 23°C was added Na₂CO₃ (0.64 g, 6
mmol, 0.83 equiv.), K₄[Fe(CN)₆]•3H₂O (0.9 g, 2.13 mmol, 0.29 equiv.) and Pd(OAc)₂ (50 mg,
25 0.22 mmol, 0.03 equiv.). The reaction mixture was degassed, refilled with argon, stirred at
120°C for 3h and cooled down to 23°C. The reaction mixture was diluted with ethyl acetate
(300 mL) and filtered through Celite. The filtrate was concentrated and the residue was
purified by column chromatography (EtOAc/hexane 0-30%) to give desired product.

¹H NMR (300 MHz, CDCl₃): 3.10 (m, 2H), 3.66 (s, 2H), 3.78 (s, 2H), 4.15 (m, 2H), 7.07 (d, *J*=8.1 Hz, 1H), 7.30 (m, 6H), 7.49 (dd, *J*=2.1 Hz, *J*=8.1 Hz, 1H).

7-(Benzo[d][1,3]dioxol-5-yl)-4-benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM153)



5

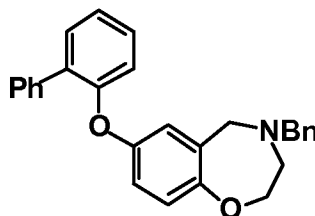
To a solution of 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (1.1 g, 3.46 mmol, 1.0 equiv.) in CH₃CN (40 mL) at 23°C was added K₂CO₃ aqueous (717 mg, 5.19 mmol, 1.5 equiv. in H₂O 12 mL), 3,4-(methylenedioxy)phenylboronic acid (640 mg, 3.86 mmol, 1.11 equiv.) and Pd(PPh₃)₄ (80 mg, 0.069 mmol, 0.02 equiv.). The reaction mixture was degassed, refilled with argon, refluxed for 17h and cooled down to 23°C. The reaction mixture was concentrated, diluted with EtOAc (300 mL), washed with NaHCO₃ aqueous, dried (Na₂SO₄), filtered, concentrated and the residue was purified by column chromatography (EtOAc/hexane 0-20%) to give desired product.

10

¹H NMR (300 MHz, CDCl₃): 3.13 (m, 2H), 3.71 (s, 2H), 3.88 (s, 2H), 4.13 (m, 2H), 5.99 (s, 2H), 6.86 (dd, *J*=0.6 Hz, *J*=7.8 Hz, 1H), 7.00 (m, 2H), 7.07 (d, *J*=8.1 Hz, 1H), 7.15 (d, *J*=2.4 Hz, 1H), 7.33 (m, 6H).

15

4-Benzyl-7-(biphenyl-2-yloxy)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM156)



To a solution of 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (1.0 g, 3.14 mmol, 1.0 equiv.) in anhydrous morpholine (5 mL, 57.4 mmol, 18.3 equiv.) at 23°C was added K₃PO₄ (1.3 g, 6.12 mmol, 2.0 equiv.), 2-phenylphenol (107 mg, 0.63 mmol, 0.2 equiv.) and CuI (30 mg, 0.157 mmol, 0.05 equiv.). The reaction mixture was degassed, refilled with argon, stirred at 100°C for 17h and cooled down to 23°C. The reaction mixture was diluted with NaHCO₃ aqueous and extracted with EtOAc (3x150 mL). The combined organic layers

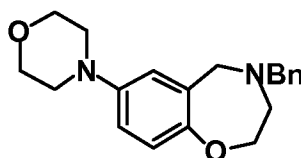
20

25

were washed (brine), dried (Na_2SO_4), concentrated and the residue was purified by column chromatography (EtOAc/hexane 0-50%) to give desired product.

^1H NMR (300 MHz, CDCl_3): 3.09 (m, 2H), 3.61 (s, 2H), 3.73 (s, 2H), 4.05 (m, 2H), 6.61 (d, $J=2.7$ Hz, 1H), 6.75 (dd, $J=2.7$ Hz, $J=8.4$ Hz, 1H), 6.92 (d, $J=8.4$ Hz, 1H), 6.96 (dd, $J=1.2$ Hz, $J=8.4$ Hz, 1H), 7.15-7.45 (m, 11 H), 7.53 (m, 2H).

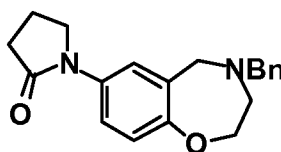
4-Benzyl-7-morpholino-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM157)



To a solution of 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (1.0 g, 3.14 mmol, 1.0 equiv.) in anhydrous morpholine (5 mL, 57.4 mmol, 18.3 equiv.) at 23°C was added K_3PO_4 (1.3 g, 6.12 mmol, 2.0 equiv.), 2-phenylphenol (107 mg, 0.63 mmol, 0.2 equiv.) and CuI (30 mg, 0.157 mmol, 0.05 equiv.). The reaction mixture was degassed, refilled with argon, stirred at 100°C for 17h and cooled down to 23°C . The reaction mixture was diluted with aqueous NaHCO_3 and extracted with EtOAc (3x150 mL). The combined organic layers were washed (brine), dried (Na_2SO_4), concentrated and the residue was purified by column chromatography (EtOAc/hexane 0-50%) to give desired product.

^1H NMR (300 MHz, CDCl_3): 3.08 (m, 6H), 3.66 (s, 2H), 3.81 (s, 2H), 3.86 (m, 4H), 4.04 (m, 2H), 6.56 (d, $J=3.0$ Hz, 1H), 6.74 (dd, $J=3.0$ Hz, $J=8.7$ Hz, 1H), 6.96 (d, $J=8.7$ Hz, 1H), 7.30 (m, 5H).

1-(4-Benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)pyrrolidin-2-one (ARM159)

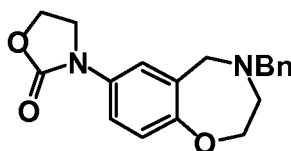


To a solution of 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (1.0 g, 3.14 mmol, 1.0 equiv.) in anhydrous dioxane (9 mL) at 23°C was added 2-pyrrolidinone (0.3 mL, 3.9 mmol, 1.25 equiv.), Cs_2CO_3 (1.4 g, 4.3 mol, 1.4 equiv.), Xantphos (110 mg, 0.19 mmol, 0.06 equiv.) and $\text{Pd}_2(\text{dba})_3$ (60 mg, 0.065 mmol, 0.02 equiv.). The reaction mixture was degassed, refilled with argon, stirred at 100°C for 17h and cooled down to 23°C . The reaction mixture was diluted with brine (100 mL) and extracted with ethyl acetate (3x100 mL). The

combined organic layers were washed (brine), dried (Na_2SO_4), concentrated and the residue was purified by column chromatography (EtOAc/hexane 10-100%) to give desired product.

^1H NMR (300 MHz, CDCl_3): 2.15 (m, 2H), 2.59 (t, $J=8.1$ Hz, 2H), 3.08 (m, 2H), 3.65 (s, 2H), 3.80 (t, $J=6.9$ Hz, 2H), 3.83 (s, 2H), 4.05 (m, 2H), 7.01 (d, $J=8.7$ Hz, 1H), 7.28 (m, 6H), 7.40 (dd, $J=3.0$ Hz, $J=8.4$ Hz, 1H).

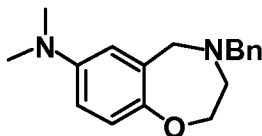
3-(4-Benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-yl)oxazolidin-2-one (ARM160)



To a solution of 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (1.0 g, 3.14 mmol, 1.0 equiv.) in anhydrous dioxane (9 mL) at 23°C was added K_2CO_3 (0.87 g, 6.29 mmol, 2.0 equiv.), 2-oxazolidinone (273 mg, 3.14 mmol, 1.0 equiv.), *trans*-1,2-diaminocyclohexane (0.04 mL, 0.3 mmol, 0.1 equiv.) and CuI (30 mg, 0.16 mmol, 0.05 equiv.). The reaction mixture was degassed, refilled with argon, stirred at 90°C for 17h and cooled down to 23°C . The reaction mixture was diluted with NaHCO_3 aqueous and extracted with EtOAc (3x150 mL). The combined organic layers were washed (brine), dried (Na_2SO_4), concentrated and the residue was purified by column chromatography (EtOAc/hexane 10-100%) to give desired product.

^1H NMR (300 MHz, CDCl_3): 3.09 (m, 2H), 3.65 (s, 2H), 3.83 (s, 2H), 4.05 (m, 4H), 4.47 (t, $J=7.5$ Hz, 2H), 7.02 (d, $J=8.7$ Hz, 1H), 7.19 (d, $J=3.0$ Hz, 1H), 7.31 (m, 6H).

4-Benzyl-N,N-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-amine (ARM161)

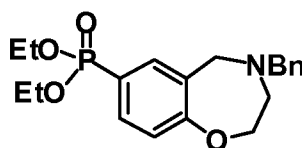


To a solution of 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (0.75 g, 2.25 mmol, 1.0 equiv.) in anhydrous toluene (14 mL) at 23°C was added Cs_2CO_3 (1.35 g, 4.14 mmol, 1.84 equiv.), Xantphos (110 mg, 0.19 mmol, 0.08 equiv.) and $\text{Pd}_2(\text{dba})_3$ (60 mg, 0.065 mmol, 0.03 equiv.). The reaction mixture was degassed, refilled with argon and dimethylamine (2.0 mL, 2.0 M in THF, 4.0 mmol, 1.8 equiv.) was added. The reaction mixture was sealed in a pressure tube, stirred at 110°C for 17h and cooled down to 23°C . The

reaction mixture was diluted with NaHCO₃ aqueous and extracted with EtOAc (3x150 mL). The combined organic layers were washed (brine), dried (Na₂SO₄), concentrated and the residue was purified by column chromatography (EtOAc/hexane 0-30%) to give desired product.

¹H NMR (300 MHz, CDCl₃): 3.88 (s, 6H), 3.10 (m, 2H), 3.66 (s, 2H), 3.82 (s, 2H), 4.02 (m, 2H), 6.40 (d, *J*=3.0 Hz, 1H), 6.57 (dd, *J*=3.0 Hz, *J*=9.0 Hz, 1H), 6.92 (d, *J*=8.4 Hz, 1H), 7.29 (m, 5H).

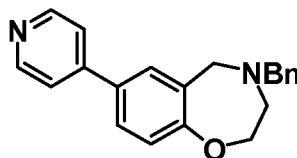
Diethyl 4-benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-7-ylphosphonate (ARM166)



To a solution of 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (1.7 g, 5.35 mmol, 1.0 equiv.) in anhydrous EtOH (20 mL) at 23°C was added Pd(OAc)₂ (24 mg, 0.107 mmol, 0.02 equiv.), PPh₃ (84 mg, 0.32 mmol, 0.06 equiv.), diethyl phosphate (0.83 mL, 6.45 mmol, 1.2 equiv.) and DIEA (1.4 mL, 8.05 mmol, 1.5 equiv.). The reaction mixture was degassed, refilled with argon, refluxed for 17h and cooled down to 23°C. The reaction mixture was concentrated. The residue was diluted with NaHCO₃ aqueous and extracted with EtOAc (3x150 mL). The combined organic layers were washed (brine), dried (Na₂SO₄), concentrated and the residue was purified by column chromatography (EtOAc/hexane 20-100%) to give desired product.

¹H NMR (300 MHz, CDCl₃): 1.32 (m, 6H), 3.06 (m, 2H), 3.65 (s, 2H), 3.83 (s, 2H), 4.00-4.17 (m, 6H), 7.06 (dd, *J*=3.9 Hz, *J*=8.4 Hz, 1H), 7.29 (m, 5H), 7.48 (dd, *J*=1.8 Hz, *J*=12.9 Hz, 1H), 7.62 (ddd, *J*=1.8 Hz, *J*=8.4 Hz, *J*=12.9 Hz, 1H).

4-Benzyl-7-(pyridin-4-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM186)

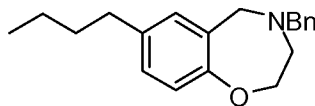


To a solution of 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (0.8 g, 2.52 mmol, 1.0 equiv.) in CH₃CN (40 mL) at 23°C was added K₂CO₃ aqueous (717 mg, 5.19 mmol, 2.1 equiv. in H₂O 12 mL), 4-pyridineboronic acid (640 mg, 5.2 mmol, 2.1 equiv.) and

Pd(PPh₃)₄ (80 mg, 0.069 mmol, 0.03 equiv.). The reaction mixture was degassed, refilled with argon, refluxed for 17h and cooled down to 23°C. The reaction mixture was concentrated, diluted with EtOAc (300 mL), washed with NaHCO₃ aqueous, dried (Na₂SO₄), filtered, concentrated and the residue was purified by column chromatography (EtOAc/hexane 10-100%) to give desired product.

¹H NMR (300 MHz, CDCl₃): 3.12 (m, 2H), 3.70 (s, 2H), 3.88 (s, 2H), 4.14 (m, 2H), 7.12 (d, *J*=8.1 Hz, 1H), 7.31 (m, 6H), 7.43 (dd, *J*=2.1 Hz, *J*=4.8 Hz, 2H), 7.48 (dd, *J*=2.4 Hz, *J*=8.1 Hz, 1H), 8.60 (dd, *J*=1.8 Hz, *J*=4.8 Hz, 2H).

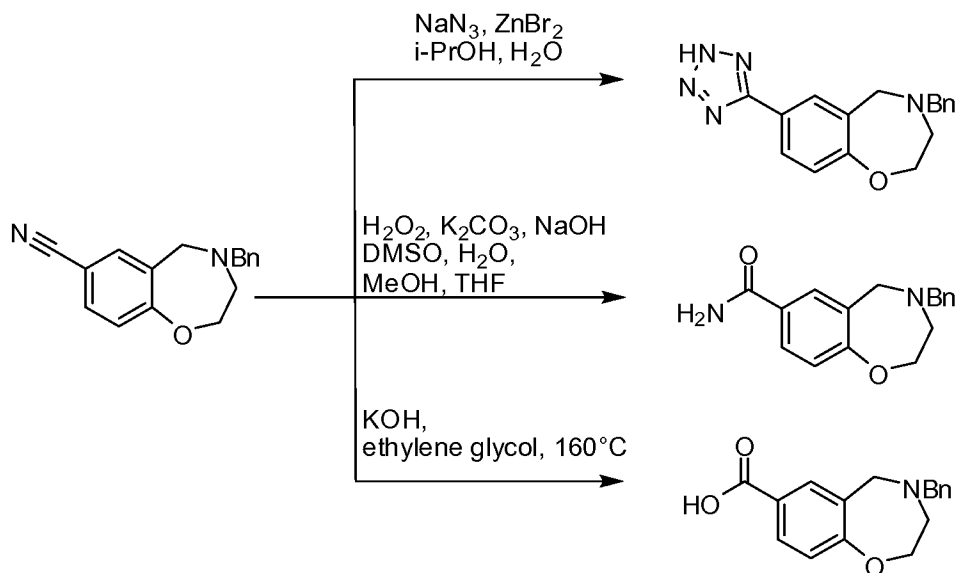
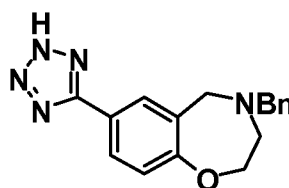
10 4-Benzyl-7-butyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM189)



To a solution of BuMgCl (0.625 mL, 1.25 mmol, 2.0 *M* solution in ether, 2.0 equiv.) in THF (5 mL) at 23°C was added ZnCl₂ (1.375 mL, 1.375 mmol, 1.0 *M* solution in ether 2.18 equiv.). The reaction mixture was stirred 23°C for 15 min, Pd(PPh₃)₂Cl₂ (22.5 mg, 0.03 mmol, 0.05 equiv.) was added, followed by 4-benzyl-7-bromo-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (200 mg, 0.63 mmol, 1.0 equiv.). The reaction mixture was refluxed for 17 hours, cooled down to 23°C, diluted with potassium sodium tartrate tetrahydrate aqueous and extracted by EtOAc (3x50 mL). The combined organic layers were washed with NaHCO₃ aqueous, dried (Na₂SO₄), filtered, concentrated and the residue was purified by column chromatography (EtOAc/Hexane 0-15%) to give desired product.

¹H NMR (300 MHz, CDCl₃): 0.95 (t, *J*=7.5 Hz, 3H), 1.37 (m, 2H), 1.58 (m, 2H), 2.54 (t, *J*=7.5 Hz, 2H), 3.10 (m, 2H), 3.65 (s, 2H), 3.80 (s, 2H), 4.07 (m, 2H), 6.81 (d, *J*=1.8 Hz, 1H), 6.98 (m, 2H), 7.31 (m, 5H).

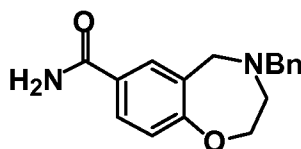
¹³C NMR (67 MHz, CDCl₃): 14.23, 22.57, 33.99, 35.04, 58.33, 58.45, 58.86, 70.28, 120.43, 127.19, 128.26, 128.35, 129.07, 130.76, 131.45, 137.86, 138.70, 157.87.

EXAMPLE 4: PREPARATION OF ARM182, 203, 217 (SCHEME 4)4-Benzyl-7-(1H-tetrazol-5-yl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM182)

5

To a solution of 4-benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carbonitrile (0.5 g, 1.89 mmol, 1.0 equiv.) in $i\text{-PrOH}$ (5 mL) at 23°C was added H_2O (5 mL), NaN_3 (246 mg, 3.78 mmol, 2.0 equiv.), and ZnBr_2 (425 mg, 1.89 mmol, 1.0 equiv.). The reaction mixture was refluxed for 17 hours, cooled down to 23°C , diluted with NH_4Cl (100 mL) and extracted with EtOAc (3x70 mL). The combined organic layers were washed with NaHCO_3 aqueous, dried (Na_2SO_4), filtered, concentrated and the residue was purified by column chromatography (MeOH/EtOAc 5-20%) to give desired product.

^1H NMR (300 MHz, CDCl_3): 3.22 (m, 2H), 3.93 (s, 2H), 3.99 (s, 2H), 4.14 (m, 2H), 6.91 (d, $J=8.4$ Hz, 1H), 7.26 (m, 5H), 7.68 (bs, 1H), 7.80 (dd, $J=1.8$ Hz, $J=8.4$ Hz, 1H).

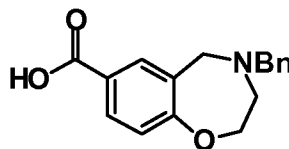
4-Benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxamide (ARM203)

To a solution of crude 4-benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carbonitrile compd (320 mg, 1.21 mmol, 1.0 equiv.) in DMSO (2 mL) at 23°C was added 30% H₂O₂ (0.15 mL, 1.4 mmol, 1.22 equiv.) and K₂CO₃ (25 mg, 0.18 mmol, 0.15 equiv.). The reaction mixture was stirred at the same temperature for 30 min and TLC only showed starting material. 30% H₂O₂ (1.5 mL, 14 mmol, 12.2 equiv.) and NaOH aqueous (1.5 mL, 3.0 M, 4.5 mmol, 3.7 equiv.) were added to reaction mixture, followed by addition of MeOH (5 mL) and THF (5 mL). The reaction mixture was continued to stir at 23°C for 20 min, diluted with brine (200 mL) and extracted by EtOAc (3x50 mL). The combined organic layers were washed with NaHCO₃ aqueous, dried (Na₂SO₄), filtered, concentrated and the residue was purified by column chromatography (EtOAc/Hexane 50-100%) to give desired product.

¹H NMR (300 MHz, CDCl₃): 3.07 (t, *J*=4.5 Hz, 2H), 3.65 (s, 2H), 3.83 (s, 2H), 4.11 (m, 2H), 6.15 (s, 2H), 7.03 (d, *J*=8.1 Hz, 1H), 7.30 (m, 5H), 7.51 (d, *J*=2.1 Hz, 1H), 7.62 (dd, *J*=2.1 Hz, *J*=8.1 Hz, 1H).

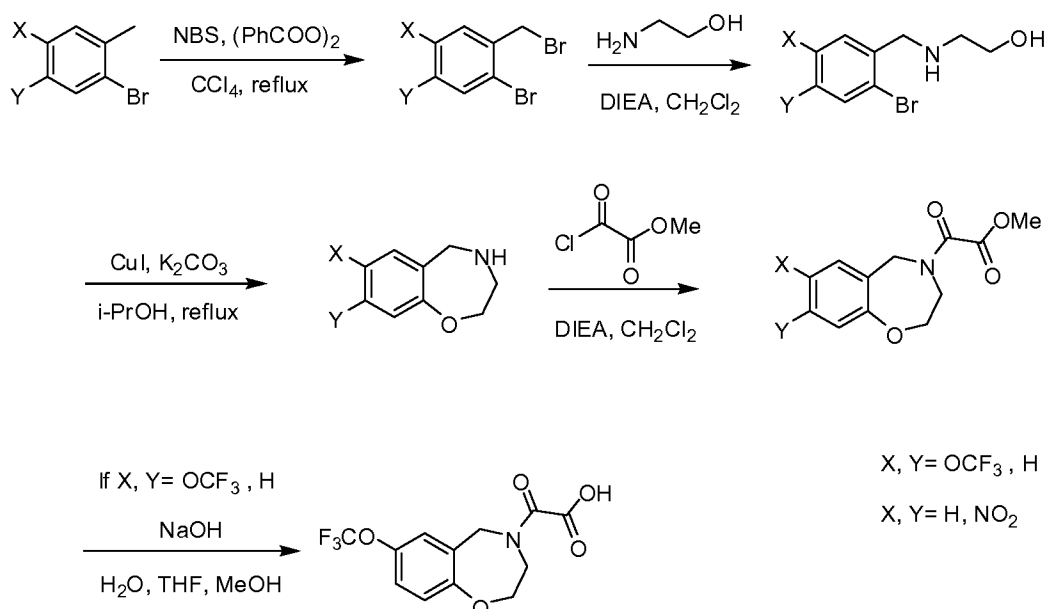
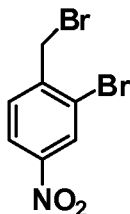
¹³C NMR (67 MHz, CDCl₃): 57.71, 58.53, 59.39, 70.81, 121.01, 127.35, 127.93, 128.26, 128.45, 128.92, 130.34, 131.86, 138.26, 163.05, 168.96.

4-Benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carboxylic acid (ARM217)



To a solid mixture of crude 4-benzyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-7-carbonitrile (150 mg, 0.57 mmol, 1.0 equiv.) and KOH (375 mg, 85% purity, 5.7 mmol, 10.0 equiv.) at 23°C was added ethylene glycol (10 mL). The reaction mixture was stirred at 160°C for 17 hours, cooled down to 23°C, diluted with 0.5 M HCl aqueous and extracted with ethyl acetate. The aqueous layer was neutralized by 3.0 M NaOH aqueous to pH=5 and extracted with CH₂Cl₂ (2x100 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered, concentrated and the residue was purified by column chromatography (MeOH/EtOAc 0-10%) to give desired product.

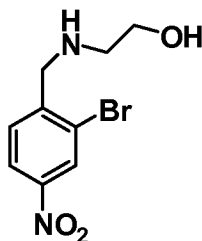
¹H NMR (300 MHz, CDCl₃): 3.12 (m, 2H), 3.77 (s, 2H), 3.93 (s, 2H), 4.17 (m, 2H), 7.13 (d, *J*=8.4 Hz, 1H), 7.29 (m, 5H), 7.83 (m, 1H), 7.92 (dd, *J*=1.8 Hz, *J*=8.4 Hz, 1H).

EXAMPLE 5: PREPARATION OF ARM251, 252, 291, 293, 296 (SCHEME 5)2-Bromo-1-(bromomethyl)-4-nitrobenzene

5

2-Bromo-4-nitrotoluene (25 g, 116 mmol), NBS (20.6 g, 116 mmol) and benzoyl peroxide (280 mg, 1.16 mmol) were suspended in carbon tetrachloride (180 mL). The mixture was refluxed for 16 hr and cooled to room temperature. The solid was removed by filtration. The filtrate was evaporated. This compound was directly used in the next step without any purification.

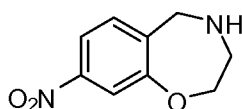
10

2-(2-Bromo-4-nitrobenzylamino)ethanol

To a solution of 2-aminoethanol (35 g, 580 mmol) and DIEA (20 mL, 116 mmol) in 200 mL CH₂Cl₂ was added 2-bromo-1-(bromomethyl)-4-nitrobenzene (116 mmol in 100 mL methylene chloride). The solution was stirred at room temperature for 3 hr. The solution was directly loaded onto a silica gel column. The column was washed with chloroform and chloroform/methanol 10/1 to obtain the desired product.

¹H NMR (300 MHz, CDCl₃): 8.42 (d, J = 2.1 Hz, 1H), 8.14 (dd, J = 8.4, 2.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.72 (m, 2H), 2.82 (m, 2H).

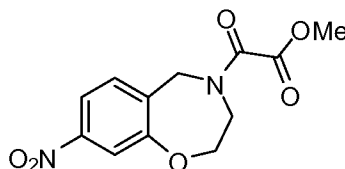
8-Nitro-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM251)



2-(2-Bromo-4-nitrobenzylamino)ethanol, (6.0 g, 21.8 mmol), copper(I) iodide (410 mmg) and potassium carbonate (4.62 g, 43.6 mmol) were mixed in 120 mL of *i*-PrOH. The solution was degassed for 5 min under vacuum and the flask was purged with argon twice. The solution was refluxed for 16 hr. After solution was cooled to room temperature, 400 ml of chloroform was added to dilute it. The solid was removed by filtration. The filtrate was evaporated to dryness. The pure compound was obtained by column chromatography (EtOAc/methanol, 5:1).

¹H NMR (300 MHz, CDCl₃): 7.80 (m, 2H), 7.28 (d, J = 8.7, 1H), 4.1-4.0 (m, 4H), 3.25 (m, 2H).

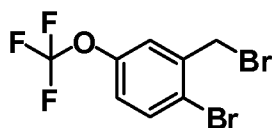
Methyl 2-(8-nitro-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)-2-oxoacetate (ARM252)



8-Nitro-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM251) (1.0 g, 5.15 mmol), methyl chlorooxoacetate (523 μ L, 5.66 mmol) and DIEA (1.6 mL, 11.2 mmol) were mixed in 10 mL of CH₂Cl₂. The solution was stirred at room temperature for 3 hours. The solution was directly loaded onto column. The column was washed with ethyl acetate. The title compound was thus obtained.

^1H NMR (300 MHz, CDCl_3): 7.94 (m, 2H), 7.54 (d, $J = 8.1$ Hz, 0.6H), 7.30 (d, $J = 8.1$ Hz, 0.4 H), 4.71, 4.64 (ss, 2H), 4.21 (m, 1.90H), 4.07 (m, 1.1 H), 3.85 (m, 4H).

1-Bromo-2-(bromomethyl)-4-(trifluoromethoxy)benzene



1-Bromo-2-methyl-4-(trifluoromethoxy)benzene (20 g, 78.3 mmol), NBS (15.3 g, 86 mmol) and benzoyl peroxide (380 mg, 1.56 mmol) were suspended in carbon tetrachloride (180 mL). The mixture was refluxed for 16 hr and cooled to room temperature. The solid was removed by filtration. The filtrate was evaporated. This compound was directly used in the next step without any purification.

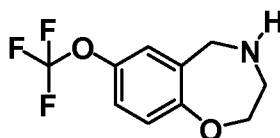
2-(2-Bromo-5-(trifluoromethoxy)benzylamino)ethanol



To a solution of 2-aminoethanol (5.8 ml, 96 mmol) and DIEA (8.4 ml, 48 mmol) in 200 mL dichloromethane was added a solution of 1-bromo-2-(bromomethyl)-4-(trifluoromethoxy)benzene (24 mmol) in 100 mL of methylene chloride. The solution was stirred at room temperature overnight. The solution was directly loaded onto silica gel column. The column was washed with chloroform, chloroform/methanol 10/1. The title compound was obtained.

^1H NMR (300 MHz, CDCl_3): 7.56 (d, $J = 8.4$ Hz, 1H), 7.28 (d, $J = 2.4$ Hz, 1H), 6.99 (dd, $J = 8.4, 2.1$ Hz, 1H), 3.96 (s, 2H), 3.69 (m, 2H), 2.81 (m, 2H).

7-(Trifluoromethoxy)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (ARM291)

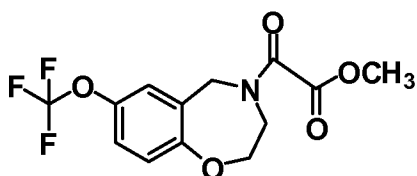


Compound 2-(2-Bromo-5-(trifluoromethoxy)benzylamino)ethanol, (4.4 g, 14 mmol), copper(I) iodide (530 mg, 2.8 mmol) and potassium carbonate (4.0 g, 28 mmol) were mixed in

120 mL of i-PrOH. The solution was degassed for 5 min under vacuum and the flask was purged with argon twice. The solution was refluxed for 16 hr. The solution was cooled to room temperature, and 400 mL of chloroform was added. The solid was removed by filtration. The filtrate was evaporated to dryness. The pure compound was obtained by column chromatography (EtOAc/methanol, 5:1).

¹HNMR (300 MHz, CDCl₃): 7.00 (m, 3H), 4.02 (m, 2H), 3.92 (s, 2H), 3.25 (m, 2H).

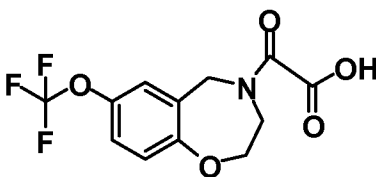
Methyl 2-oxo-2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetate
(ARM293)



Compound 7-(Trifluoromethoxy)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (400 mg, 1.61 mmol), methyl chlorooxoacetate (221 μ L, 2.4 mmol) and DIEA (0.6 mL, 5.6 mmol) were mixed in 5 mL of methylene chloride. The solution was stirred at room temperature for 3 hours. The solution was directly loaded onto column. The column was washed with ethyl acetate. The title compound was obtained.

¹HNMR (300 MHz, CDCl₃): 7.22 (m, 0.5H), 7.04 (m, 2H), 6.96 (m, 0.5 H), 4.71, 4.64 (ss, 2H), 4.14 (m, 2H), 4.01 (m, 1.1 H), 3.85 (m, 4H).

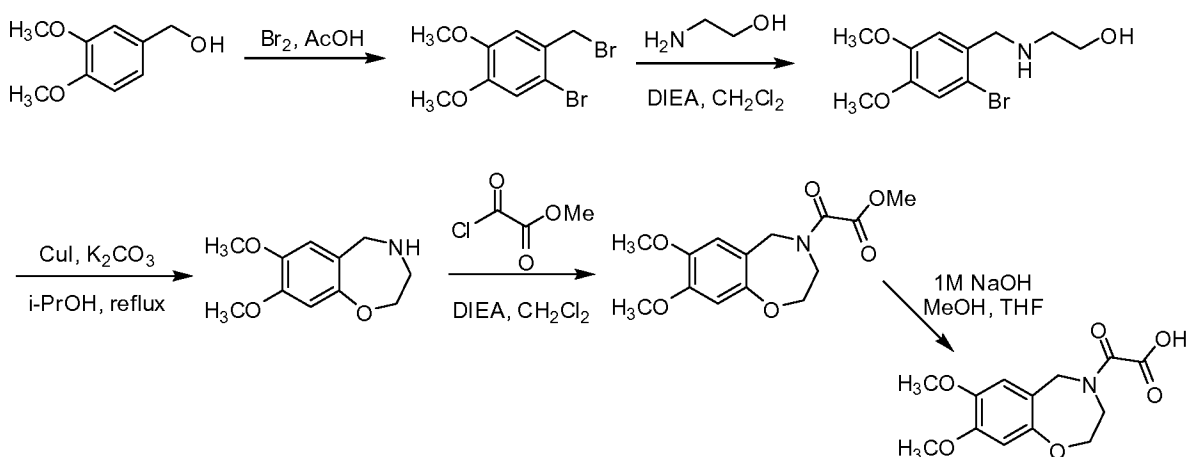
2-Oxo-2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetic acid
(ARM296)



Methyl 2-oxo-2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetate (200 mg) was dissolved in 15 mL of a mixture of THF, methanol and 1 M NaOH (1:1:1, v/v). The solution was stirred at room temperature for three hours and acidified to pH 2. The solvent was removed and the solid was collected and dried under vacuum. The title compound was obtained.

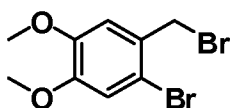
^1H NMR (300 MHz, DMSO- d_6): 7.40-7.00 (m, 3H), 4.62 (ss, 2H), 4.16 (m, 2H), 3.87 (m, 0.8H), 3.74 (m, 1.2H).

EXAMPLE 6: PREPARATION OF ARM277, 279, 282 (SCHEME 6)



5

1-Bromo-2-(bromomethyl)-4,5-dimethoxybenzene

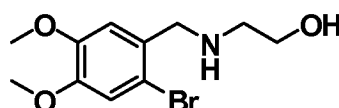


3, 4-Dimethoxybenzyl alcohol (100 g) was dissolved in 200 mL of glacial acetic acid. To this solution was slowly added a solution of bromine (36.4 mL) in 100 mL of acetic acid. The reaction was stirred at room temperature overnight. The solid was collected and washed with methanol. The title product was obtained.

10

^1H NMR (300 MHz, CDCl_3): 6.99 (s, 1H), 6.89 (s, 1H), 4.54 (s, 2H), 3.87 (ss, 6H).

2-(2-Bromo-4,5-dimethoxybenzylamino)ethanol



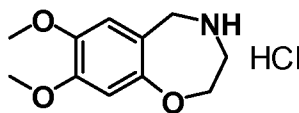
15

1-Bromo-2-(bromomethyl)-4,5-dimethoxybenzene (48 mmol), ethanolamine (194 mmol) and DIEA (112 mmol) were stirred in 200 mL of acetonitrile at room temperature for one hour. The solvent was removed and the residue was loaded onto a column directly. The column was washed with chloroform, followed by ethyl acetate. The title compound was thus obtained.

20

^1H NMR (300 MHz, CDCl_3): 6.97 (s, 1H), 6.84 (s, 1H), 3.86 (ss, 6H), 3.80 (s, 2H), 3.66 (t, $J = 6.3\text{Hz}$, 2H), 2.81 (t, $J = 6.3\text{ Hz}$, 2H).

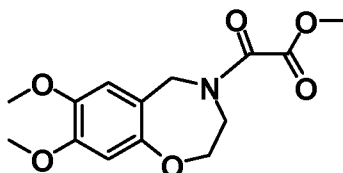
7,8-Dimethoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine hydrochloride (ARM277)



2-(2-Bromo-4,5-dimethoxybenzylamino)ethanol (45 mmol) was mixed with CuI (850 mg, 4.5 mmol) and potassium carbonate (12.5 g, 89 mmol) in 150 ml of *i*-PrOH. The mixture was stirred under reflux overnight. After cooling to room temperature, 300 mL dichloromethane was added and the solid was removed by filtration. The desired compound was obtained by column chromatography with 10/1 - 5/2 chloroform/methanol as eluent. The compound was obtained. The title compound was then converted to hydrochloride salt by addition of 15 mL of a 4M solution of HCl in dioxane.

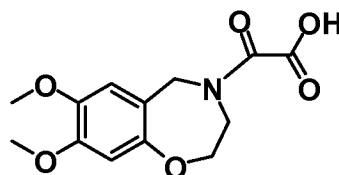
^1H NMR (300 MHz, $\text{DMSO}-d_6$): 9.66 (br, 2H), 7.06 (s, 1H), 6.72 (s, 1H), 4.12 (m, 4H), 3.73 (ss, 6H), 3.39 (m, 2H).

Methyl 2-(7,8-dimethoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)-2-oxoacetate (ARM279)



7,8-Dimethoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine hydrochloride (ARM277) (1.52 mmol), methyl chlorooxoacetate (200 μL , 2.14 mmol) and DIEA (5.47 mmol) were mixed in 10 mL of CH_2Cl_2 . The solution was stirred at room temperature for 3 hours. The resulting solution was directly loaded onto a column. The column was washed with ethyl acetate. The title compound was obtained

^1H NMR (300 MHz, CDCl_3): 6.82 (s, 0.7H), 6.60 (m, 1.3H), 4.57 (ss, 2H), 4.06 (m, 2H), 3.95-3.78 (m, 11H).

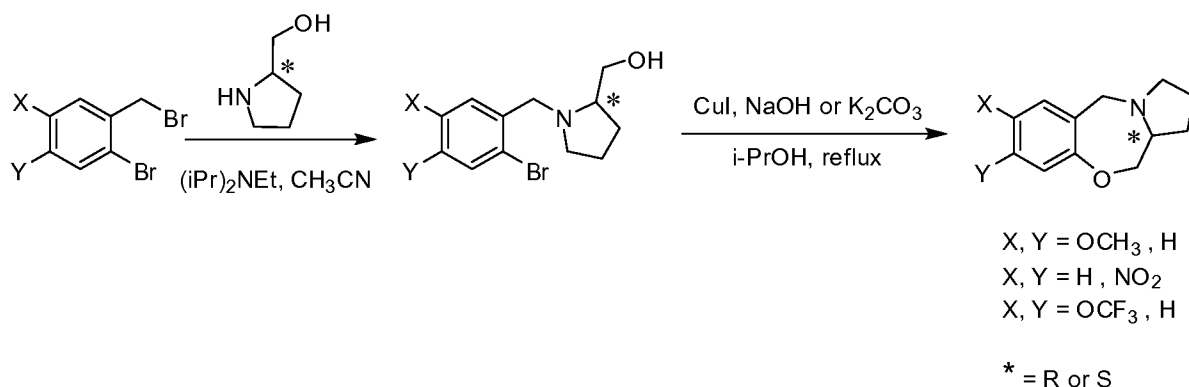
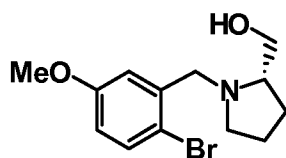
2-(7,8-Dimethoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)-2-oxoacetic acid (ARM282)

Methyl 2-(7,8-dimethoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)-2-oxoacetate (220 mg) was dissolved in 15 mL of a mixture of THF, methanol and 1 M NaOH (1:1:1, v/v).

- 5 The solution was stirred at room temperature for three hour and acidified to pH 2. The solvent was removed and the solid was collected and dried under vacuum. The title compound was obtained.

¹H NMR (300 MHz, DMSO-d₆): 6.85 (s, 6H), 6.63 (m, 1.4H), 4.50 (m, 2H), 4.03 (m, 2H), 3.82-3.66 (m, 8H).

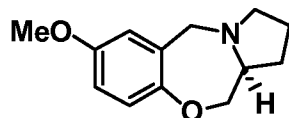
10

EXAMPLE 7: PREPARATION OF ARM167, 258, 397, 398, 399 (SCHEME 7)(S)-(1-(2-Bromo-5-methoxybenzyl)pyrrolidin-2-yl)methanol

- 15 To a solution of (S)-(+)-2-pyrrolidinemethanol (3.6 g, 35.6 mmol, 1.03 equiv.) in anhydrous CH₃CN (25 mL) at 23°C was added DIEA (20 mL, 115 mmol, 3.3 equiv.), followed by 2-bromo-5-methoxybenzyl bromide (9.7 g, 34.6 mmol, 1.0 equiv.). The reaction mixture was stirred at 23°C for 1 hour, concentrated, diluted with NaHCO₃ aqueous and extracted with EtOAc (3x250 mL). The combined organic layers were washed (brine), dried
- 20 (Na₂SO₄) and concentrated to give desired product.

¹H NMR (300 MHz, CDCl₃): 1.75 (m, 2H), 1.90 (m, 2H), 2.33 (m, 1H), 2.78 (m, 2H), 2.99 (m, 1H), 3.43 (m, 2H), 3.72 (dd, *J*=3.3 Hz, *J*=11.1 Hz, 1H), 3.80 (s, 3H), 4.00 (d, *J*=13.5 Hz, 1H), 6.69 (dd, *J*=3.0 Hz, *J*=8.7 Hz, 1H), 6.94 (d, *J*=3.0 Hz, 1H), 7.42 (d, *J*=8.4 Hz, 1H).

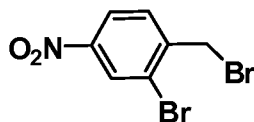
5 (S)-7-methoxy-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine (ARM167)



To a solution of (S)-(1-(2-bromo-5-methoxybenzyl)pyrrolidin-2-yl)methanol (1.0 g, 3.33 mmol, 1.0 equiv.) in anhydrous *i*-PrOH (10 mL) at 23°C was added NaOH (0.3 g, 7.5 mmol, 2.25 equiv.) and CuI (60 mg, 0.32 mmol, 0.1 equiv.). The reaction mixture was
10 degassed, refilled with argon, refluxed for 17h and cooled down to 23°C. The reaction mixture was diluted with MeOH (100 mL), filtered through Celite and concentrated. The residue was purified by column chromatography (EtOAc/hexane 50-100%) to give desired product.

¹H NMR (300 MHz, CDCl₃): 1.42 (m, 1H), 1.86 (m, 3H), 2.51 (q, *J*=8.7 Hz, 1H), 2.73
15 (m, 1H), 3.17 (m, 1H), 3.47 (dd, *J*=9.3 Hz, *J*=11.7 Hz, 1H), 3.70 (s, 2H), 3.76 (s, 3H), 4.30 (dd, *J*=2.4 Hz, *J*=12.0 Hz, 1H), 6.70 (m, 2H), 6.95 (m, 1H).

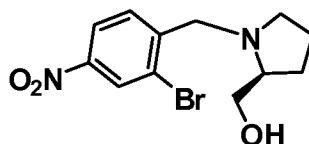
2-Bromo-1-(bromomethyl)-4-nitrobenzene



20 2-Bromo-4-nitro toluene (25 g, 116 mmol), benzoyl peroxide (280 mg, 1.16 mmol) and NBS (20.6 g, 116 mmol) were mixed and refluxed in 200 ml CCl₄ overnight. After the mixture was cooled to room temperature, the solid was filtered off. The filtrate was evaporated to dryness. The compound was directly used in the next step without any further purification.

25

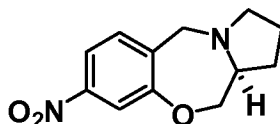
(S)-(1-(2-Bromo-4-nitrobenzyl)pyrrolidin-2-yl)methanol



2-Bromo-1-(bromomethyl)-4-nitrobenzene (35.2 mmol), (s)-(+)-2-pyrrolidinemethanol (4.27 g, 42.3 mmol) and DIEA (14.7 ml, 84.6 mmol) were stirred in 200 ml acetonitrile at room temperature for one hour. The solvent was removed and the residue was loaded onto column directly. The column was washed with chloroform, followed by ethyl acetate. The title compound was obtained.

¹HNMR (300 MHz, CDCl₃): 8.41 (d, J= 2.1 Hz, 1H), 8.15 (dd, J= 8.4, 2.1 Hz, 1H), 7.60 (d, J= 8.4, Hz, 1H), 4.08 (d, J= 14.4 Hz, 1H), 3.70-3.58 (m, 2H), 3.47 (dd, J= 13.5, 2.7 Hz, 1H), 2.90 (m, 2H), 2.46 (m, 1H), 2.00-1.70 (m, 5H).

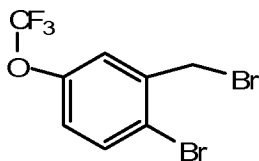
10 (S)-8-Nitro-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine (ARM258)



(S)-(1-(2-Bromo-4-nitrobenzyl)pyrrolidin-2-yl)methanol (3.0 g, 9.55 mmol), copper(I) iodide (180 mg, 0.955 mmol) and potassium carbonate (2.6 g, 19 mmol) were mixed in 150 mL of i-PrOH. The mixture was degassed for 5 min and heated to reflux under argon overnight. After the solution was cooled to room temperature, 200 mL ethyl acetate was added. The inorganic solid was removed by filtration. The solvent was removed and the residue was loaded onto column. The column was washed with EtOAc / methanol (10:1). The title compound was thus obtained.

¹HNMR (300 MHz, CDCl₃): 7.86 (m, 2H), 7.30 (d, J= 7.2 Hz, 1H), 4.41 (dd, J= 12.3, 2.4 Hz, 1H), 3.84 (dd, J = 42, 13.8 Hz, 2H), 3.54 (m, 1H), 3.15 (m, 1H), 2.81 (m, 1H), 2.58 (m, 1H), 1.89 (m, 3H), 1.40 (m, 1H).

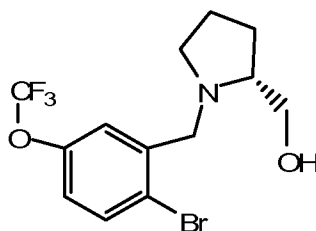
1-bromo-2-(bromomethyl)-4-(trifluoromethoxy)benzene



1-bromo-2-methyl-4-(trifluoromethoxy)benzene (10.09 g, 39.6 mmol) was dissolved in carbon tetrachloride (100 mL) and treated successively with NBS (7.74 g, 43.5 mmol, 1.1 equiv) and benzoyl peroxide (190 mg, 0.78 mmol). The reaction mixture was stirred under refluxing conditions overnight. All the volatiles were removed under reduced pressure. The

residue was filtered through a short pad of silica gel (hexanes:ethyl acetate, 10:1) to provide 1-bromo-2-(bromomethyl)-4-(trifluoromethoxy)benzene as a pale yellow oil.

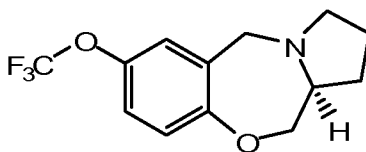
(R)-(1-(2-bromo-5-(trifluoromethoxy)benzyl)pyrrolidin-2-yl)methanol



To a solution of (S)-pyrrolidin-2-ylmethanol (0.30 mL, 3.08 mmol) in anhydrous acetonitrile (15 mL), DIEA (3.3 equiv) was added. The reaction mixture was stirred at ambient temperature for 10 min and then 1-bromo-2-(bromomethyl)-4-(trifluoromethoxy)benzene (1.0 g, 2.99 mmol) was added. The reaction mixture was stirred at ambient temperature for 3 hours. All the volatiles were removed under reduced pressure and the residue was treated with a saturated sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (silica, hexanes:ethyl acetate, 9:1 to 6:1 to 3:1) to provide (R)-(1-(2-bromo-5-(trifluoromethoxy)benzyl)pyrrolidin-2-yl)methanol as a yellow oil.

^1H NMR (300 MHz, CDCl_3) δ 7.58 (d, J = 8.7 Hz, 1H), 7.36 (br s, 1H), 7.03 (dd, J = 8.7 and 2.1 Hz, 1H), 4.09 (d, J = 13.8 Hz, 1H), 3.73 (dd, J = 11.4 and 3.3 Hz, 1H), 3.59 (d, J = 14.1 Hz, 1H), 3.50 (dd, J = 11.4 and 2.7 Hz, 1H), 3.04 (br m, 1H), 2.89 (br s, 1H), 2.39 (br m, 1H), 2.06 - 1.74 (m, 4H).

(S)-7-(trifluoromethoxy)-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine (ARM397)

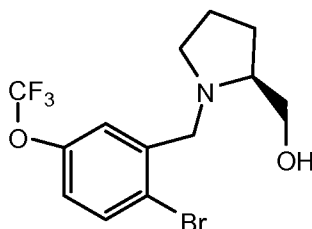


(R)-(1-(2-bromo-5-(trifluoromethoxy)benzyl)pyrrolidin-2-yl)methanol (0.55 g, 1.55 mmol), copper iodide (59 mg, 0.31 mmol, 0.2 equiv) and potassium carbonate (428 mg, 3.1 mmol, 2.0 equiv) were transferred into the reaction flask. The mixture was suspended in dry

isopropanol (20 mL) and degassed. It was stirred under refluxing conditions overnight. After cooling to room temperature, chloroform was added in small portions and the mixture was filtered thru a short pad of silica gel. The filtrate was concentrated under reduced pressure and the residue was flash chromatographed (silica, hexanes:ethyl acetate, 3:1) to provide (S)-7-(trifluoromethoxy)-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine.

^1H NMR (300 MHz, CDCl_3) δ 7.01 (m, 3H), 4.35 (dd, $J = 12.3$ and 2.4 Hz, 1H), 3.73 (ABq, $J = 13.8$ and 3.3 Hz, 2H), 3.53 (dd, $J = 12$ and 9.6 Hz, 1H), 3.17 (m, 1H), 2.78 (m, 1H), 2.54 (dt, $J = 8.7$ Hz, 1H), 1.97 – 1.79 (m, 3H), 1.45 (m, 1H).

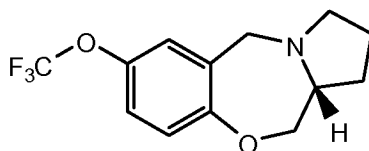
10 (S)-(1-(2-bromo-5-(trifluoromethoxy)benzyl)pyrrolidin-2-yl)methanol



To a solution of (R)-pyrrolidin-2-ylmethanol (0.33 g, 3.26 mmol) in anhydrous acetonitrile (5 mL), DIEA (1.84 mL, 10.6 mmol, 3.3 equiv) was added. The reaction mixture was stirred at ambient temperature for 10 min and then 1-bromo-2-(bromomethyl)-4-(trifluoromethoxy)benzene (1.07 g, 3.20 mmol) was added. The reaction mixture was stirred at ambient temperature for 3 hours. All the volatiles were removed under reduced pressure and the residue was treated with a saturated sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica, hexanes:ethyl acetate, 9:1 to 6:1 to 3:1) to provide (S)-(1-(2-bromo-5-(trifluoromethoxy)benzyl)pyrrolidin-2-yl)methanol.

^1H NMR (300 MHz, CDCl_3) δ 7.58 (d, $J = 8.7$ Hz, 1H), 7.36 (br s, 1H), 7.03 (dd, $J = 8.7$ and 2.1 Hz, 1H), 4.09 (d, $J = 14.1$ Hz, 1H), 3.73 (dd, $J = 11.4$ and 3.3 Hz, 1H), 3.59 (d, $J = 13.2$ Hz, 1H), 3.50 (dd, $J = 11.1$ and 2.4 Hz, 1H), 3.04 (br m, 1H), 2.89 (br s, 1H), 2.39 (br m, 1H), 2.06 - 1.74 (m, 4H).

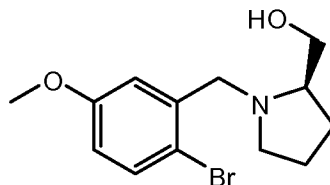
(R)-7-(trifluoromethoxy)-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine
(ARM398)



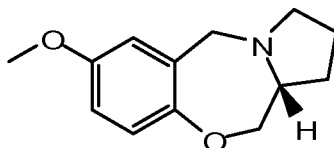
(S)-(1-(2-bromo-5-(trifluoromethoxy)benzyl)pyrrolidin-2-yl)methanol (0.63 g, 1.78 mmol), copper iodide (68 mg, 0.2 equiv) and potassium carbonate (492 mg, 2.0 equiv) were transferred into a reaction flask. The mixture was suspended in dry isopropanol (20 mL) and degassed. It was stirred under refluxing conditions overnight. After cooling to room temperature, chloroform was added in small portions and the mixture was filtered through a short pad of silica gel. The filtrate was concentrated under reduced pressure and the residue was flash chromatographed (silica, hexanes:ethyl acetate, 3:1) to provide (R)-7-(trifluoromethoxy)-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine.

¹H NMR (300 MHz, CDCl₃) δ7.01 (m, 3H), 4.35 (dd, J = 12.3 and 2.4 Hz, 1H), 3.73 (ABq, J = 13.8 and 3.3 Hz, 2H), 3.53 (dd, J = 12 and 9.6 Hz, 1H), 3.17 (m, 1H), 2.78 (m, 1H), 2.54 (dt, J = 8.7 Hz, 1H), 1.97 – 1.79 (m, 3H), 1.45 (m, 1H).

(R)-(1-(2-bromo-5-methoxybenzyl)pyrrolidin-2-yl)methanol

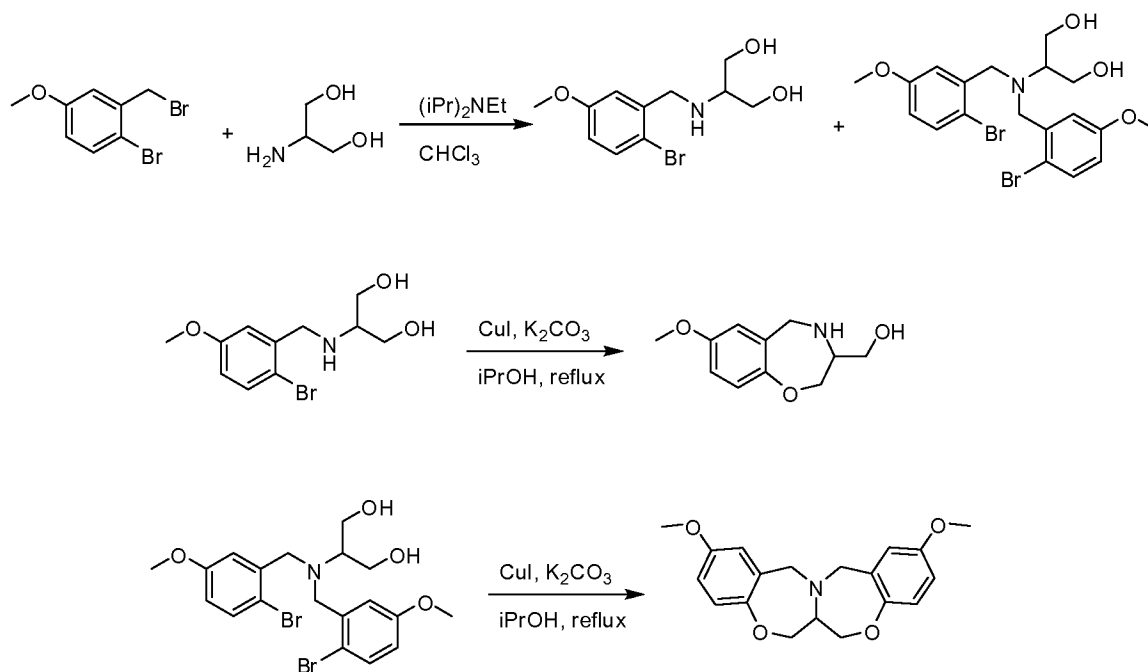


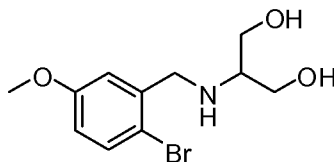
To a solution of (R)-pyrrolidin-2-ylmethanol (3.29 mL, 33.7 mmol) in anhydrous acetonitrile (25 mL), DIEA (18.8 mL, 108 mmol, 3.3 equiv) was added. The reaction mixture was stirred at ambient temperature for 10 min and then 1-bromo-2-(bromomethyl)-4-methoxybenzene (9.16 g, 32.7 mmol) was added in four equal portions. The reaction mixture was stirred at ambient temperature for 3 hours. All the volatiles were removed under reduced pressure and the residue was treated with a saturated sodium bicarbonate solution (50 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica, hexanes:ethyl acetate, 4:1 to 3:1 to 1:1) to provide (R)-(1-(2-bromo-5-methoxybenzyl)pyrrolidin-2-yl)methanol as a pale yellow oil.

(R)-7-methoxy-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine (ARM399)

(R)-(1-(2-bromo-5-methoxybenzyl)pyrrolidin-2-yl)methanol (0.61 g, 2.03 mmol), copper iodide (77 mg, 0.406 mmol, 0.2 equiv) and potassium carbonate (562 mg, 4.06 mmol, 2.0 equiv) were transferred into a reaction flask. The mixture was suspended in dry isopropanol (20 mL) and degassed. It was stirred under refluxing conditions overnight. After cooling to room temperature, chloroform was added in small portions and the mixture was filtered through a short pad of silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (silica, hexanes:ethyl acetate, 3:1) to provide (R)-7-methoxy-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine.

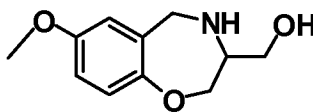
^1H NMR (300 MHz, CDCl_3) δ 6.93 (m, 1H), 6.70 (m, 2H), 4.29 (dd, 1H), 3.75 (s, 3H), 3.70 (s, 2H), 3.46 (dd, 1H), 3.15 (m, 1H), 2.74 (m, 1H), 2.51 (dt, 1H), 1.95 – 1.75 (m, 3H), 1.42 (m, 1H).

EXAMPLE 8: PREPARATION OF ARM301, 302 (SCHEME 8)

2-(2-Bromo-5-methoxybenzylamino)propane-1,3-diol

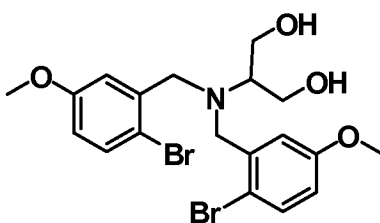
To a solution of serinol (9.9 g, 109 mmol) and DIEA (38 mL, 218 mmol) in 200 mL of chloroform was added a solution of 2-bromo-5-methoxy benzyl bromide (28 g, 100 mmol) in 100 mL of chloroform. The solution was stirred at 50 °C overnight. It was loaded onto silica a gel column. The column was washed with chloroform and eluted with ethyl acetate/methanol (100%-80%). The title compounds was obtained.

¹H NMR (300 MHz, CDCl₃): 7.40 (d, J = 9.0 Hz, 1H), 6.96 (d, J = 3.0 Hz, 1H), 6.64 (dd, J = 8.7, 2.7 Hz, 1H), 3.85 (s, 2H), 3.76 (m, 5H), 3.59 (dd, J = 5.1, 11.1 Hz, 2H), 2.90 (m, 1H).

(7-Methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-3-yl)methanol (ARM301)

2-(2-Bromo-5-methoxybenzylamino)propane-1,3-diol (18.9 g, 65 mmol), copper(I) iodide (1.23 g, 6.5 mmol) and potassium carbonate (18 g, 130 mmol) were mixed in 120 mL *i*-butanol. The solution was degassed for 5 minutes under vacuum and the flask was purged with argon twice. The solution was refluxed for 48 hr. It was cooled to r.t., and was diluted with 400 mL of chloroform. The solid was removed by filtration and the filtrate was evaporated to dryness. The pure compound was obtained by column chromatography (EtOAc/methanol, 5:1).

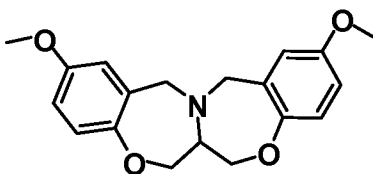
¹H NMR (300 MHz, CDCl₃): 6.94 (d, J = 8.1 Hz, 1H), 6.68 (m, 2H), 4.25 (dd, J = 12.6, 2.7 Hz, 1H), 3.94 (m, 2H), 3.78-3.42 (m, 6H), 3.26 (m, 2H).

2-(Bis(2-bromo-5-methoxybenzyl)amino)propane-1,3-diol

To a solution of serinol (9.9 g, 109 mmol) and DIEA (38 mL, 218 mmol) in 200 mL chloroform was added a solution of 2-bromo-5-methoxy benzyl bromide (28 g, 100 mmol) in 100 mL of chloroform. The solution was stirred at 50 °C overnight. The solution was directly loaded onto silica gel column. The column was washed with chloroform, ethyl acetate/methanol (100%-80%). The title product was obtained.

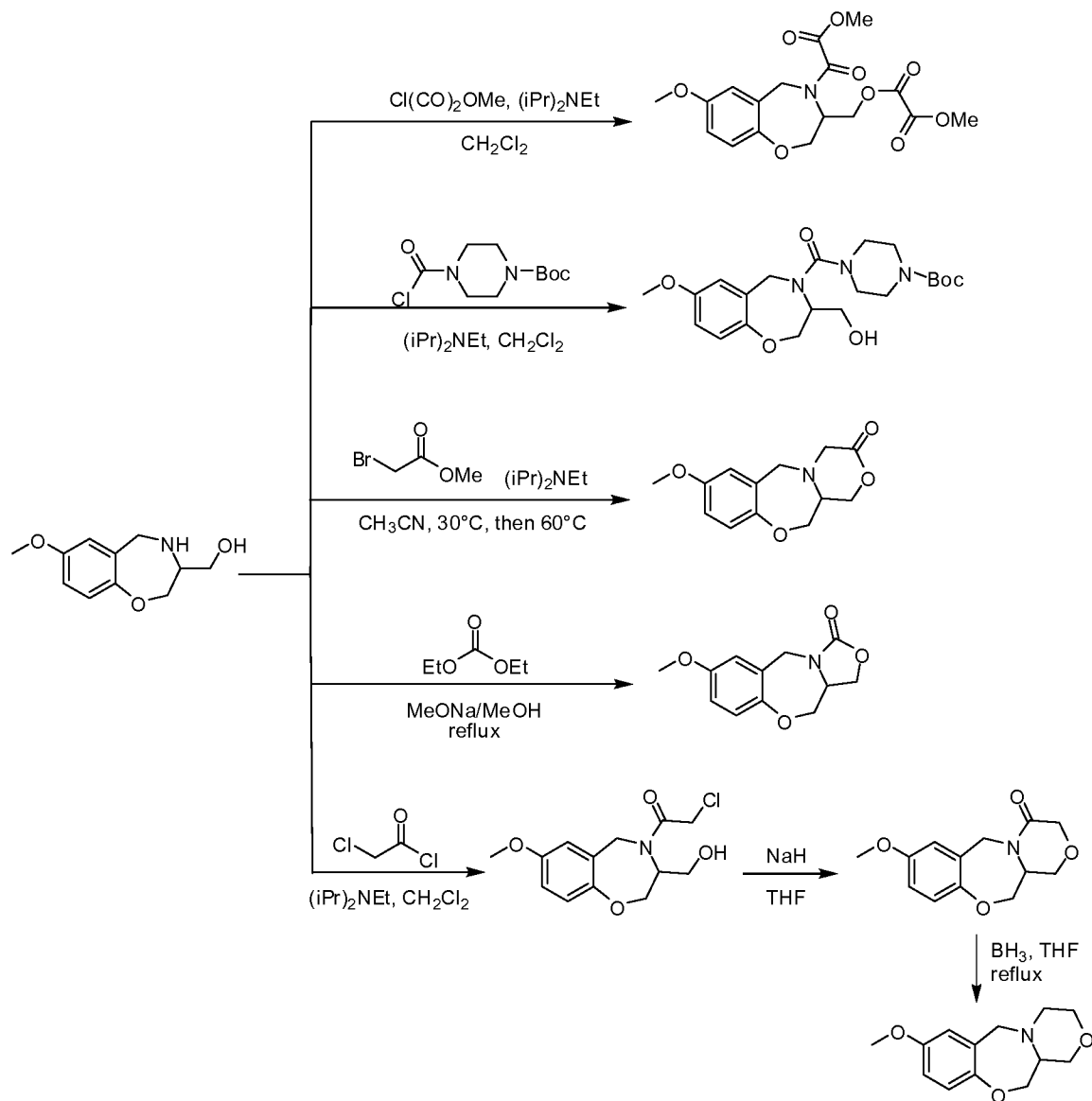
¹H NMR (300 MHz, CDCl₃): 7.36 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 3.3 Hz, 2H), 6.64 (dd, J = 9.0, 2.7 Hz, 2H), 3.85 (s, 5H), 3.76 (m, 9H), 3.00 (m, 1H), 2.1 (br, 2H).

(ARM302)

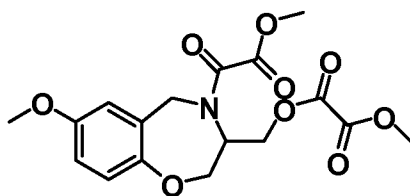


2-(Bis(2-bromo-5-methoxybenzyl)amino)propane-1,3-diol (9.0 g, 18.4 mmol), copper(I) iodide (700 mg, 3.68 mmol) and potassium carbonate (10 g, 73 mmol) were mixed in 120 mL of *i*-butanol. The solution was degassed for 5 min under vacuum and the flask was purged with argon twice. The solution was refluxed for 48 hr. The solution was cooled to r.t., and diluted with 400 mL of chloroform. The solid was removed by filtration and the filtrate was evaporated to dryness. The pure compound was obtained by column chromatography (EtOAc/chloroform, 1:1).

¹H NMR (300 MHz, CDCl₃): 6.94 (d, J = 8.1 Hz, 2H), 6.68 (m, 4H), 4.24 (dd, J = 12.6, 2.7 Hz, 2H), 4.10 (m, 2H), 3.88-3.66 (m, 10H), 3.58 (m, 1H).

EXAMPLE 9: PREPARATION OF ARM306, 326, 351, 352, 353, 534 (SCHEME 9)

5 (7-Methoxy-4-(2-methoxy-2-oxoacetyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-3-yl)methyl methyl oxalate (ARM306)

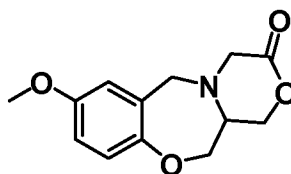


(7-Methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-3-yl)methanol (400 mg, 1.90 mmol), methyl chlorooxoacetate (470 μL , 4.56 mmol) and DIEA (1.0 mL, 5.7 mmol) were

mixed in 5 mL of methylene chloride. The solution was stirred at r.t. for 3 hours. The solution was loaded onto a silica column and eluted with ethyl acetate.

¹H NMR (300 MHz, CDCl₃): 6.98-6.92 (m, 1.6H), 6.83 (m, 1H), 6.58 (d, J= 2.4Hz, 0.4 H), 5.10 (m, 1H), 4.82 (m, 1H), 4.64 (m, 1.4H), 4.40 (m, 2H), 4.21 (m, 0.6H), 4.00-3.76 (m, 10 H).

8-Methoxy-4,6,12,12a-tetrahydrobenzo[f][1,4]oxazino[3,4-c][1,4]oxazepin-3(1H)-one (ARM351)

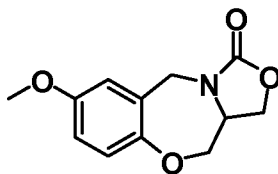


To a solution of (7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-3-yl)methanol (300 mg, 1.44 mmol) and DIEA (0.5 mL, 2.88 mmol) in 10 mL of anhydrous acetonitrile was added methyl bromoacetate (132 µl, 1.44mmol). The solution was stirred at 30 °C overnight, then 60 °C for 4 hr. The solvent was removed and the residue was dissolved in methylene chloride and loaded onto silica gel. The column was washed with ethyl acetate/hexane(1:1).

The title product was obtained.

¹H NMR (300 MHz, CDCl₃): 6.94 (d, J = 8.7 Hz, 1H), 6.70 (m, 2H), 4.38 (dd, J= 4.0, 11.4Hz, 1H), 4.12 (m, 3H), 3.76 (m, 4H), 3.53 (m, 2H), 3.28 (d, J= 18Hz, 1H), 3.20 (m, 1H).

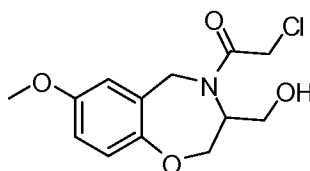
7-Methoxy-11,11a-dihydro-1H-benzo[f]oxazolo[4,3-c][1,4]oxazepin-3(5H)-one (ARM352)



(7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-3-yl)methanol (300 mg, 1.44 mmol), diethyl carbonate (1.7 mL, 14.3 mmol) and sodium methoxide (4.37M in MeOH, 0.65 mL, 2.86 mmol) were mixed in 10 mL anhydrous ethanol. The solution was refluxed overnight. The solution was acidified with TFA and the solvent was removed. The pure title compound was obtained by column chromatography (ethyl acetate/ hexane, 1:1).

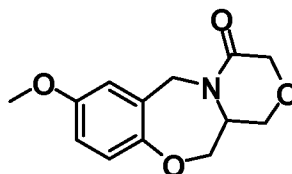
¹H NMR (300 MHz, CDCl₃): 6.94 (d, J = 8.7 Hz, 1H), 6.70 (m, 2H), 4.64 (d, J= 15Hz, 1H), 4.35 (m, 4H), 3.86 (m, 1H), 3.75 (s, 3H), 3.60 (m, 1H).

2-Chloro-1-(3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)ethanone



(7-Methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepin-3-yl)methanol (627 mg, 3.0 mmol) and DIEA (575 μ l, 3.3 mmol) were mixed in 10 mL dichloromethane. The solution was cooled with an ice-methanol bath. To the cooled solution was added a solution of chloroacetyl chloride (263 μ l, 3.3 mmol) in 5.0 mL of methylene chloride. The solution was stirred for 30 minutes, then allowed to reach to r.t. overnight. The title compound was obtained by column chromatography.

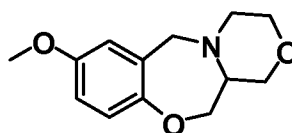
8-Methoxy-3,6,12,12a-tetrahydrobenzo[f][1,4]oxazino[3,4-c][1,4]oxazepin-4(1H)-one (ARM353)



To a solution of 2-chloro-1-(3-(hydroxymethyl)-7-methoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)ethanone in 10 mL of anhydrous THF was added sodium hydride (60%, 90 mg, 2.2 mmol). The mixture was stirred at r.t. overnight. The solvent was removed. The desired compound was obtained by column chromatography.

^1H NMR (300 MHz, CDCl_3): 6.96 (d, $J = 9.0$ Hz, 1H), 6.86 (d, $J = 3.0$ Hz, 1H), 6.70 (dd, $J = 8.7, 3.0$ Hz, 1H), 5.28 (d, $J = 14.4$ Hz, 1H), 4.30 (m, 1H), 4.10-3.75 (m, 10H).

8-Methoxy-1,3,4,6,12,12a-hexahydrobenzo[f][1,4]oxazino[3,4-c][1,4]oxazepine (ARM354)

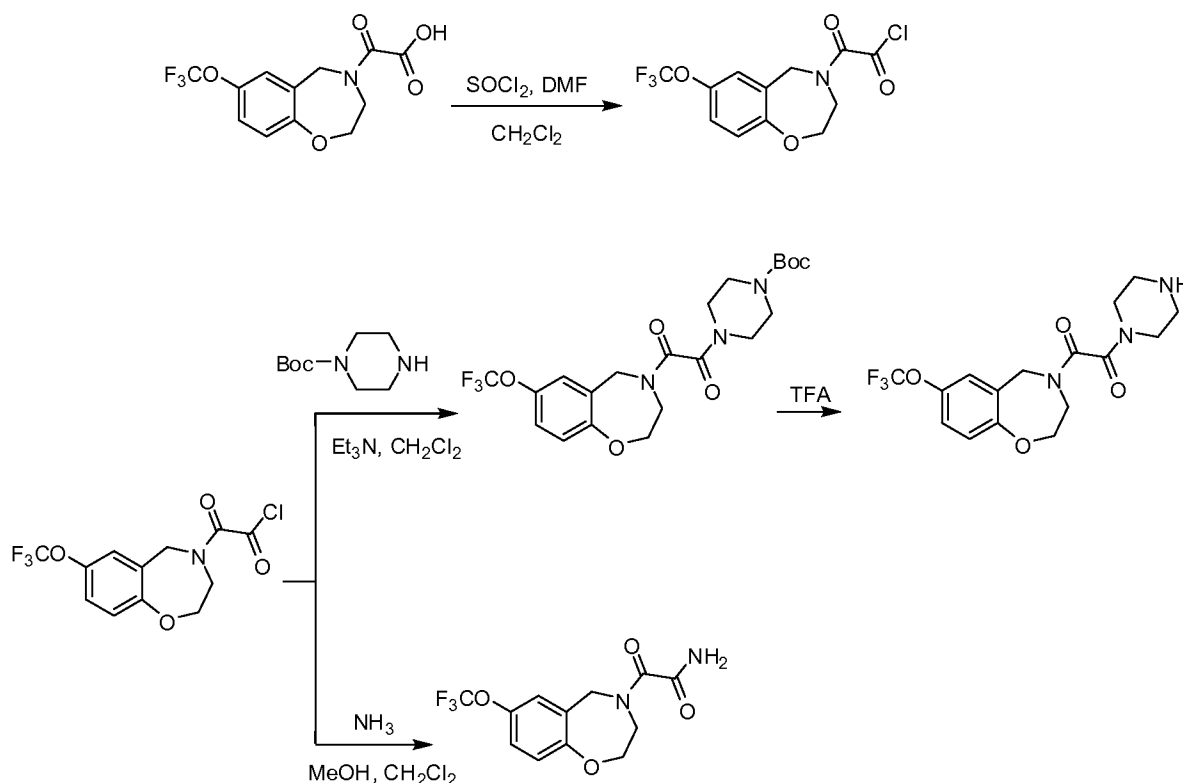


To a solution of 8-methoxy-3,6,12,12a-tetrahydrobenzo[f][1,4]oxazino[3,4-c][1,4]oxazepin-4(1H)-one (280 mg, 1.12 mmol) in 5 mL in anhydrous THF was added a 1M

borane/THF complex (5.0 mL). The solution was refluxed overnight. The excess of borane was decomposed by adding 2 mL of methanol and refluxing for 3 hr. The solvent was removed and the column separation afforded the title compound.

^1H NMR (300 MHz, CDCl_3): 6.94 (d, $J = 9.0$ Hz, 1H), 6.70 (m, 2H), 4.48-3.60 (m, 9H), 3.29 (d, $J = 13.5$ Hz, 1H), 3.26 (m, 1H), 2.79 (m, 2H), 2.51 (m, 1H).

EXAMPLE 10: PREPARATION OF ARM311, 312, 313. (SCHEME 10).



10 2-Oxo-2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetyl chloride

To a solution of 2-oxo-2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetic acid (50 mg, 0.16 mmol) in CH_2Cl_2 (5 ml) was added SOCl_2 (0.5 ml, excess) and DMF (0.05 ml). The reaction mixture was stirred overnight at r. t. The solvents were removed by evaporation under reduced pressure to give title acyl chloride. It was dissolved in 10 ml of CH_2Cl_2 and used for the next reactions without further purification.

tert-Butyl 4-(2-oxo-2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetyl)piperazine-1-carboxylate (ARM311)

To the acyl chloride CH_2Cl_2 solution (6.6 ml, 0.11 mmol) was added 4-Boc-piperazine (20 mg, 0.12 mmol) and Et_3N (0.5 ml, excess). The reaction mixture was stirred at r. t. for 2 h, and washed with 1N HCl (3 ml x 2) and sat. NaHCO_3 (3 ml x 2). The solvents were removed by evaporation and the product ARM 311 was purified by chromatography (SiO_2 , $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) as an oil.

^1H NMR (CDCl_3): 7.2 (s, broad, 1H), 7.05 (s, 1H), 6.9 (s, broad, 1H), 4.65 (s, ~1H), 4.60 (s, ~1H), 4.2 (m), 4.08 (m), 3.8 (m), 3.6 (m), 3.4 (m), 3.3 (m), 3.2 (m), 2.9 (m), 1.4 (m, 9H).

1-(Piperazin-1-yl)-2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)ethane-1,2-dione (ARM312)

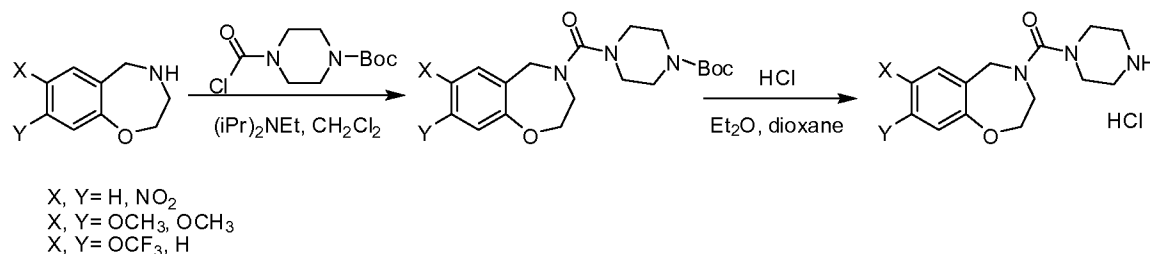
To a solution of tert-butyl 4-(2-oxo-2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetyl)piperazine-1-carboxylate (9.08 mg) was dissolved in CH_2Cl_2 (3 ml) was added TFA (0.5 ml). The reaction mixture was stirred at r. t. for 24 h. The solvents were removed by evaporation under reduced press to give ARM 312 as an oil.

^1H NMR (CDCl_3): 7.2 (s, broad, 1H), 7.0 (s, broad, 1H), 6.9 (s, broad, 1H), 4.6 (s, broad, ~1H), 4.4 (s, broad, ~1H), 4.2-3.8 (m), 3.4 - 3.0 (m).

2-Oxo-2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetamide (ARM313)

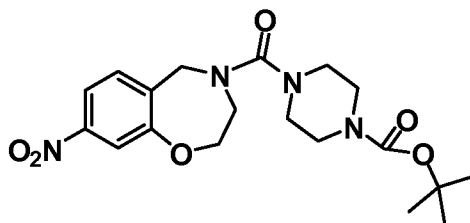
The title compound was prepared by reaction of corresponding acyl chloride (CH_2Cl_2 solution prepared in step 1, 3.3 ml) with a methanolic NH_3 solution (20%, 0.5 ml).

^1H NMR (CDCl_3): 7.3 (s, broad, 1H), 7.2 (s, 1H), 7.0 (s, broad, 1H), 5.6 (s, broad, NH_2), 5.05 (s, 1H), 4.6 (s, 1H), 4.4 (m, 1H), 4.1 (m, 2H), 4.0 (m, 1H).

EXAMPLE 11: PREPARATION OF ARM318, 322, 324, 331, 335, 337. (SCHEME 11).Preparation of ARM318, 322, 324, 326: General Procedure

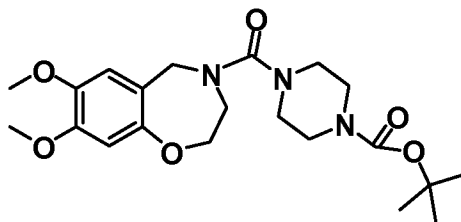
5 Amine or amine hydrochloride (1.1 mmol), DIEA (0.7 mL, 3.7 mmol) and 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester (300 mg, 1.2 mmol) were mixed in 5 mL dichloromethane. The solution was stirred at r.t. for 24 hr. The solution was evaporated to dryness, the residue was dissolved in 2 mL of methylene chloride, loaded onto column and eluted with ethyl acetate/ hexane, giving the following pure products:

10 tert-Butyl 4-(8-nitro-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-4-carbonyl)piperazine-1-carboxylate (ARM318)



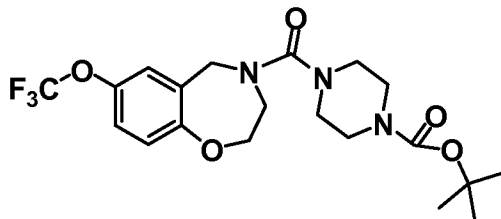
15 ¹H NMR (300 MHz, CDCl₃): 7.86 (m, 2H), 7.35 (d, J = 8.4 Hz, 1H), 4.43 (s, 2H), 4.21 (m, 2H), 3.72 (m, 2H), 3.42 (m, 4H), 3.18 (m, 4H), 1.44 (s, 9H).

tert-Butyl 4-(7,8-dimethoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-4-carbonyl)piperazine-1-carboxylate (ARM322)



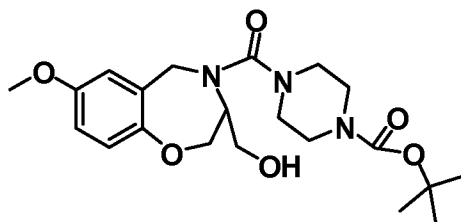
20 ¹H NMR (300 MHz, CDCl₃): 6.66 (s, 1H), 6.56 (s, 1H), 4.30 (s, 2H), 4.10 (m, 2H), 3.82 (s, 6H), 3.66 (m, 2H), 3.42 (m, 4H), 3.20 (m, 4H), 1.44 (s, 9H).

tert-Butyl 4-(7-(trifluoromethoxy)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-4-carbonyl)piperazine-1-carboxylate (ARM324)



5 ^1H NMR (300 MHz, CDCl_3): 7.24 (m, 1H), 7.01 (m, 2H), 4.34 (s, 2H), 4.12 (m, 2H), 3.66 (m, 2H), 3.42 (m, 4H), 3.19 (m, 4H), 1.44 (s, 9H).

tert-Butyl 4-(3-(hydroxymethyl)-7-methoxy-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-4-carbonyl)piperazine-1-carboxylate (ARM326)



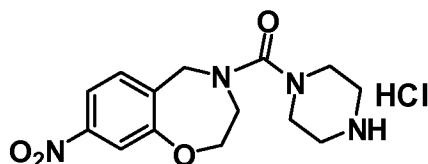
10

^1H NMR (300 MHz, CDCl_3): 6.88 (d, $J = 8.4\text{ Hz}$, 1H), 6.72 (dd, $J = 8.7, 3.0\text{ Hz}$, 1H), 6.60 (d, $J = 3.0\text{ Hz}$, 1H), 4.67 (ss, 1H), 4.34 (m, 0.8H), 4.21 (m, 1.2H), 4.06 (m, 4H), 3.77 (m, 4H), 3.42 (m, 4H), 3.14 (m, 4H), 1.44 (s, 9H).

15 Preparation of ARM331, 335, 337: General Procedure

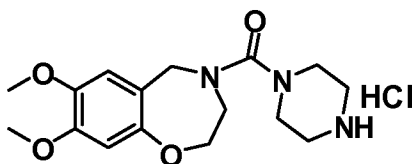
To a solution of a Boc-protected piperazine compound in 3.0 mL of diethyl ether was added 5.0 mL of a 4M HCl solution in dioxane. The solution was stirred for 3 hr, the solvent and excess of HCl were removed and the residue was triturated with 10 mL of diethyl ether and sonicated for 5 min. The supernatant clear solvent was discarded. The solid was dissolved
20 in a mixture of dichloromethane and methanol, and transferred to a vial. Removal of solvent provided the target product.

(8-Nitro-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)(piperazin-1-yl)methanone
hydrochloride (ARM331)



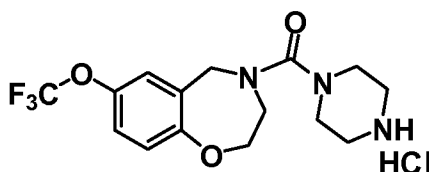
¹H NMR (300 MHz, DMSO-d₆): 9.40 (br, 2H), 7.86 (dd, J= 8.1, 2.1 Hz, 1H), 7.65 (d, J= 2.1 Hz, 1H), 7.53 (d, J= 8.1Hz, 1H), 4.54 (s, 2H), 4.32 (t, J= 4.2Hz, 2H), 3.66 (t, J= 5.1Hz, 2H), 3.62 (m, 2H), 3.28 (m, 4H), 3.06 (m, 4H).

(7,8-Dimethoxy-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)(piperazin-1-yl)methanone
hydrochloride (ARM335)

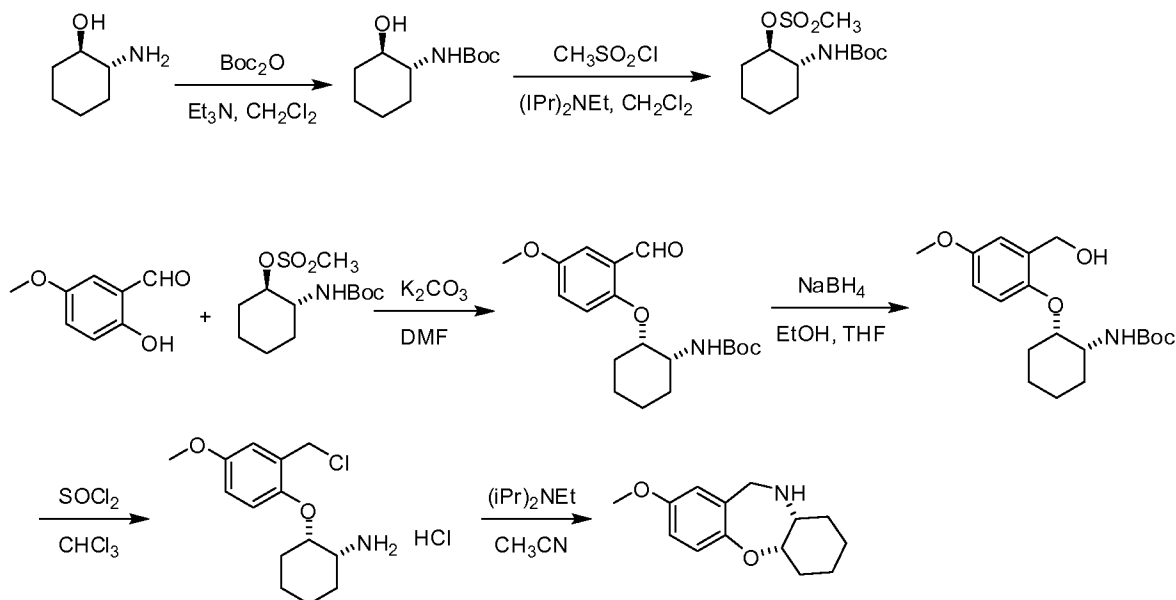
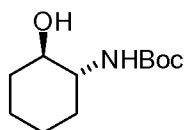


¹H NMR (300 MHz, DMSO-d₆): 9.20 (br, 2H), 6.83 (s, 1H), 6.58 (s, 1H), 4.32 (s, 2H), 4.07 (m, 2H), 3.69 (ss, 6H), 3.55 (m, 2H), 3.27 (m, 4H), 3.10 (m, 4H).

Piperazin-1-yl(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)methanone
hydrochloride (ARM337)



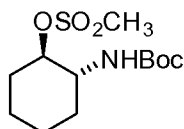
¹H NMR (300 MHz, DMSO-d₆): 9.20 (br, 2H), 7.31 (d, J=2.1Hz, 1H), 7.14 (dd, J= 8.4, 3.0Hz, 1H), 6.98 (d, J= 8.7Hz, 1H), 4.43 (s, 2H), 4.20 (m, 2H), 3.62 (m, 2H), 3.24 (m, 4H), 3.07 (m, 4H).

EXAMPLE 12: PREPARATION OF ARM423 (SCHEME 12)tert-Butyl (1R,2R)-2-hydroxycyclohexylcarbamate

5

To a solution of trans-2-aminocyclohexanol hydrochloride (15.8 g, 104.2 mmol) and triethylamine (36.5 mL, 260 mmol) in 200 mL of dichloromethane was added Boc anhydride (22.7 g, 104.2 mmol). The solution was stirred at r.t. overnight, diluted with 400 mL dichloromethane, and extracted with 120 mL of 1M aqueous HCl. The organic solution was dried over sodium sulfate. Removal of solvent provided the title compound.

¹H NMR (300 MHz, CDCl₃): 4.56(br, 1H), 3.28 (m, 2H), 1.99 (m, 2H), 1.72 (m, 2H), 1.49-1.16 (m, 13H).

(1R,2R)-2-(tert-Butoxycarbonylamino)cyclohexyl methanesulfonate

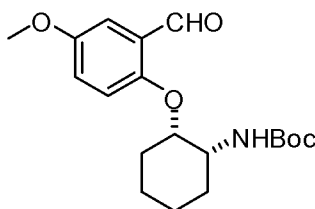
15

To a stirred solution of tert-butyl (1R,2R)-2-hydroxycyclohexylcarbamate (22 g, 102 mmol) and DIEA (26.3 mL, 153 mmol) in 100 mL of dichloromethane cooled to 0 °C was added methanesulfonyl chloride (10.3 mL, 133 mmol) dropwise. After addition, the solution

was stirred for 1 hr at 0 °C and at r.t. for 2 hr. The solution was diluted with 400 mL of dichloromethane and extracted with 200 mL of 0.1 M aqueous HCl. The organic layer was dried over sodium sulfate and the solvent was removed. The title compound was obtained by column chromatography (EtOAc/hexane, 1:1).

- 5 ^1H NMR (300 MHz, CDCl_3): 4.65(br, 1H), 4.40 (m, 1H), 3.59 (m, 1H), 3.00 (s, 3H), 2.10 (m, 2H), 1.72-1.16 (m, 15H).

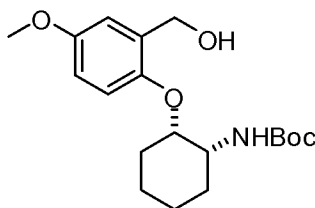
tert-butyl (1R,2S)-2-(2-Formyl-4-methoxyphenoxy)cyclohexylcarbamate



- 10 (1R,2R)-2-(tert-Butoxycarbonylamino)cyclohexyl methanesulfonate (10.5 g, 35.8 mmol), 2-hydroxy-5-methoxy benzaldehyde (7.1 g, 46.6 mmol) (26.3 mL, 153 mmol) and potassium carbonate (13 g, 93.2 mmol) were mixed in 100 mL of anhydrous DMF. The mixture was stirred at 80 °C overnight under argon. It was diluted with 200 mL of ethyl acetate and washed with 200 mL of water. The aqueous layer was extracted with ethyl acetate
15 (2 x 60 mL). The combined organics were dried over sodium sulfate. Removal of solvent provided a mixture of title compound and starting material.

^1H NMR (300 MHz, CDCl_3): 10.42 (s, 1H), 7.28 (d, $J = 8.4\text{ Hz}$, 1H), 7.10-7.00 (m, 2H), 4.60 (br, 1H), 4.10 (m, 1H), 3.79 (m, 4H), 2.05 (m, 2H), 1.72-1.16 (m, 15H).

- 20 tert-Butyl (1R,2S)-2-(2-(hydroxymethyl)-4-methoxyphenoxy)cyclohexylcarbamate



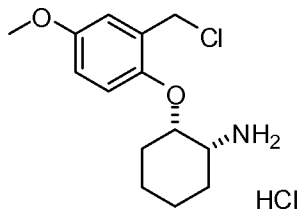
- To a solution of tert-butyl (1R,2S)-2-(2-formyl-4-methoxyphenoxy)cyclohexylcarbamate (35.8 mmol) in 100 mL of anhydrous ethanol/THF (1:1) was added sodium borohydride (1.37 g, 36 mmol) in three portions in 30 min. The
25 solution was stirred at r.t. for 3 hrs and the solvent was removed. The residue was mixed with 200 mL of water and extracted with chloroform (3 x 250 mL). The combined organic fractions

were dried over Na₂SO₄. The title compound was obtained by column chromatography (silica gel).

¹H NMR (300 MHz, CDCl₃): 6.74 (m, 3H), 4.80 (m, 1H), 4.50 (d, J= 8.1Hz, 1H), 4.34 (br, m, 1H), 3.97 (m, 1H), 3.73 (s, 3H), 3.27 (br, 1H), 2.06 (m, 2H), 1.67-1.21 (m, 15H).

5

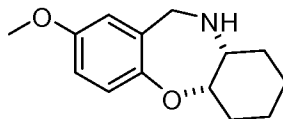
(1R,2S)-2-(2-(Chloromethyl)-4-methoxyphenoxy)cyclohexanamine hydrochloride



To a solution of tert-butyl (1R,2S)-2-(2-(hydroxymethyl)-4-methoxyphenoxy)cyclohexylcarbamate (8.6 g, 24.6 mmol) in 20 mL of chloroform was added thionyl chloride (6.4 mL, 450 mmol) at 0 °C. The solution was stirred at r.t. overnight, then heated to 50 °C for 2 hours. After cooling to r.t., methanol (10mL) was added at 0 °C to the above solution to decompose the thionyl chloride. The solvent was removed under reduced pressure, chloroform (80 mL) was added, and evaporated again to give a solid that was mixed with 200 mL diethyl ether and stirred for 2 hr. The title compound was obtained as a yellow solid collected by filtration.

¹H NMR (300 MHz, DMSO-d₆): 8.21 (s, br, 3H), 6.98-6.90 (m, 2H), 6.79 (dd, J= 9.0, 1.0, Hz, 1H), 5.03 (d, J= 11.7 Hz, 1H), 4.41 (m, 2H), 3.73 (s, 3H), 2.76 (br, 1H), 2.10 (m, 2H), 1.65-1.10 (m, 6H).

20 (5aS,9aR)-2-Methoxy-5a,6,7,8,9,9a,10,11-octahydrodibenzo[b,f][1,4]oxazepine (ARM423)



(1R,2S)-2-(2-(Chloromethyl)-4-methoxyphenoxy)cyclohexanamine hydrochloride (6.60 g, 21.6 mmol) and DIEA (7.7 mL, 43 mmol) were mixed in 400 mL of acetonitrile. The mixture was stirred at r.t. overnight. The solvent was removed under reduced pressure and the residue was dissolved in 300 mL of a pH 2 aqueous solution, and extracted with ethyl acetate (2 x 200 mL). The aqueous was basified and extracted with dichloromethane (3 x 150 mL).

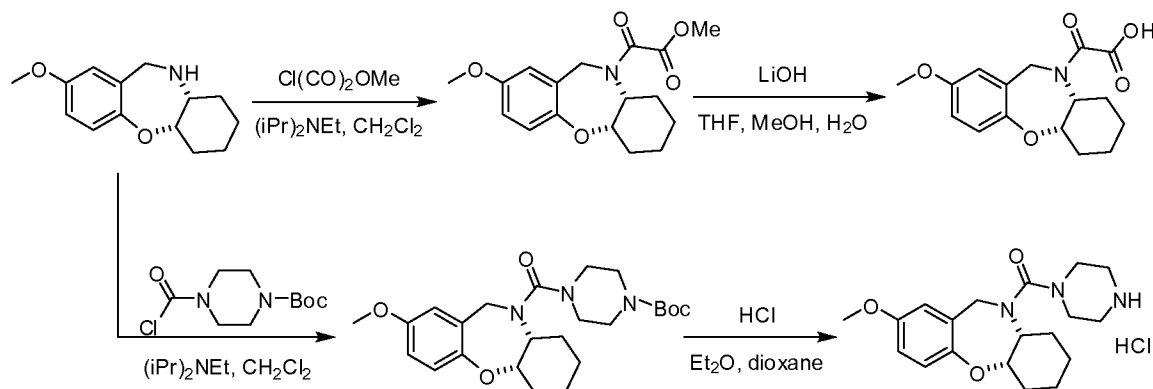
25

The dichloromethane solution was dried over Na_2SO_4 . Removal of the solvent gave the title compound.

^1H NMR (300 MHz, CDCl_3): 6.95 (d, $J = 9.0$ Hz, 1H), 6.65 (m, 2H), 4.16 (d, $J = 14.7$ Hz, 1H), 3.76 (m, 4H), 3.15 (m, 1H), 2.76 (m, 1H), 2.16 (m, 1H), 1.98-1.00 (m, 7H).

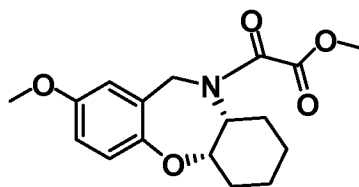
5

EXAMPLE 13: PREPARATION OF ARM463, 466, 470, 473. (SCHEME 13)



Methyl 2-((5aS,9aR)-2-methoxy-5a,6,7,8,9,9a-hexahydrodibenzo[b,f][1,4]oxazepin-10(11H)-yl)-2-oxoacetate (ARM463)

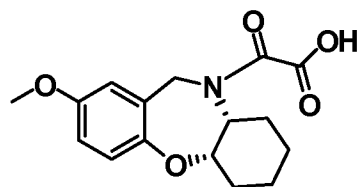
10



To a solution of (5aS,9aR)-2-methoxy-5a,6,7,8,9,9a,10,11-octahydrodibenzo[b,f][1,4]oxazepine (372 mg, 1.6 mmol) and DIEA (0.6 mL, 3.5 mmol) in 10 mL dichloromethane was added methyl chloroformate (162 μL , 2.4 mmol). The solution was stirred at 0°C for 4 hours. The title compound was obtained after column chromatography (EtOAc/hexane).

15

2-((5aS,9aR)-2-Methoxy-5a,6,7,8,9,9a-hexahydrodibenzo[b,f][1,4]oxazepin-10(11H)-yl)-2-oxoacetic acid (ARM466)

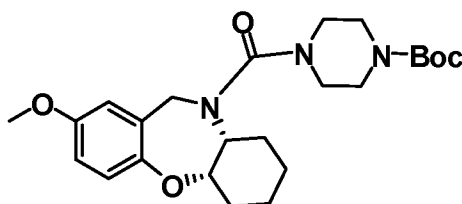


20

A solution of methyl 2-((5aS,9aR)-2-methoxy-5a,6,7,8,9,9a-hexahydrodibenzo[b,f][1,4]oxazepin-10(11H)-yl)-2-oxoacetate (210 mg) in 30 mL of a mixture of THF, methanol and 1 M LiOH (1:1:1) was stirred at r.t. for 6 hr and acidified with 1 N HCl. The organic solvent was removed and the resulting precipitate was collected via filtration and washed with water. The solid was dried under vacuum to give the title compound.

¹H NMR (300 MHz, DMSO-d₆): 6.8-6.7 (m, 3H), 5.06 (d, J= 16.2 Hz, 0.5H), 4.88 (d, J= 16.2Hz, 0.5H), 4.65 (d, J= 16.2Hz, 0.5H), 4.32 (m, 1.4H), 4.04 (m, 0.5H), 3.67 (ss, 36H), 3.37 (m, 2H), 2.1-1.2 (m, 8H).

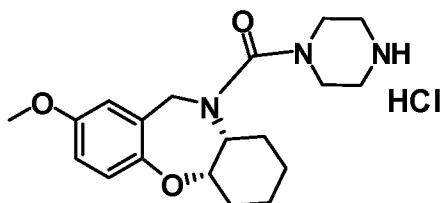
tert-Butyl 4-((5aS,9aR)-2-methoxy-5a,6,7,8,9,9a,10,11-octahydrodibenzo[b,f][1,4]oxazepine-10-carbonyl)piperazine-1-carboxylate (ARM470)



A solution of (5aS,9aR)-2-methoxy-5a,6,7,8,9,9a,10,11-octahydrodibenzo[b,f][1,4]oxazepine (256 mg, 1.1 mmol), DIEA (0.3 mL, 1.32 mmol) and 4-chlorocarbonyl-piperazine-1-carboxylic acid tert-butyl ester (290 mg, 1.16 mmol) in 5 mL dichloromethane was stirred at r.t. for 24 hr. The reaction solution was evaporated to dryness, the residue was dissolved in 2 mL of dichloromethane and loaded onto a column and eluted with ethyl acetate/hexane to give the title compound.

¹H NMR (300 MHz, CDCl₃): 6.84 (d, J= 8.7Hz, 1H), 6.68 (dd, J= 9.0, 3.0Hz, 1H), 6.55 (d, J= 3.0Hz, 1H), 4.56 (d, J= 17.1Hz, 1H), 4.44 (d, J= 17.4Hz, 1H), 3.86 (m, 1H), 3.67 (m, 4H), 3.31 (m, 4H), 2.99 (m, 4H), 2.12 (m, 2H), 1.80-1.23 (m, 15H).

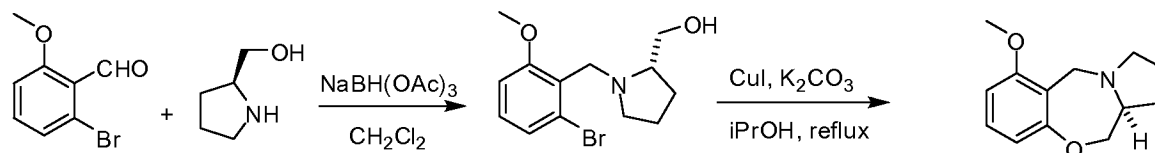
((5aS,9aR)-2-Methoxy-5a,6,7,8,9,9a-hexahydrodibenzo[b,f][1,4]oxazepin-10(11H)-yl)(piperazin-1-yl)methanone hydrochloride (ARM473)



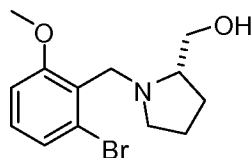
To a solution of tert-butyl 4-((5a*S*,9a*R*)-2-methoxy-5a,6,7,8,9,9a,10,11-octahydrodibenzo[*b,f*][1,4]oxazepine-10-carbonyl)piperazine-1-carboxylate (270 mg) in 3.0 mL of diethyl ether added a 4M solution of HCl in dioxane (5.0 mL). The reaction was stirred for 3 hr, the solvent and excess of HCl were removed, and the residue was treated with 10 mL of diethyl ether and sonicated for 5 min. The supernatant clear solvent was discarded. The solid was dissolved in a dichloromethane/methanol mixture and transferred to vial. Removal of solvent provided the title compound.

¹H NMR (300 MHz, DMSO-*d*₆): 9.17 (br, 2H), 6.84-6.65 (m, 3H), 4.72 (d, *J*=17.1Hz, 1H), 4.44 (d, *J*=17.4Hz, 1H), 4.06 (m, 1H), 3.67 (s, 3H), 3.50 (m, 1H), 3.10-2.96 (m, 8H), 1.99 (m, 2H), 1.67 (m, 2H), 1.49 (m, 2H), 1.29 (m, 2H).

EXAMPLE 14: Preparation of ARM454 (SCHEME 14)



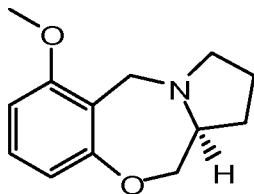
15 (S)-(1-(2-Bromo-6-methoxybenzyl)pyrrolidin-2-yl)methanol



2-Bromo-6-methoxybenzaldehyde (1.65 g, 7.67 mmol) and (S)-pyrrolidin-2-ylmethanol (0.85 g, 8.44 mmol) were dissolved in dichloromethane (70 mL), the solution was stirred at ambient temperature for 1 hour and then treated with sodium(triacetoxy)borohydride (4.28 g, 2.5 equiv). The reaction mixture was stirred at room temperature overnight. Ethyl acetate and a saturated solution of sodium bicarbonate were added successively to the reaction mixture. Following extraction, the layers were separated and the organic phase was dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica, hexanes:ethyl acetate, 1:3 to neat ethyl acetate) to provide (R)-(1-(2-bromo-6-methoxybenzyl)pyrrolidin-2-yl)methanol.

^1H NMR (300 MHz, CDCl_3) δ 7.18 – 7.06 (m, 2H), 6.82 (dd, 1H), 3.99 (d, 1H), 3.84 (s, 3H), 3.78 (dd, 1H), 3.71 (d, 1H), 3.37 (dd, 1H), 2.88 – 2.72 (m, 2H), 2.56 (ddd, 1H), 1.97 – 1.84 (m, 1H), 1.82 – 1.55 (m, 3H).

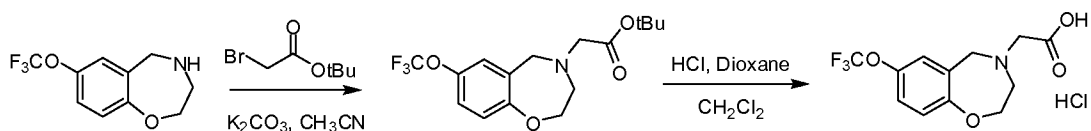
5 (S)-6-Methoxy-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine (ARM454)



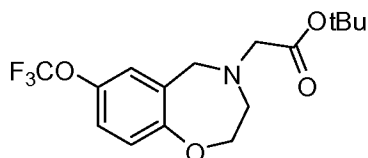
(S)-(1-(2-Bromo-6-methoxybenzyl)pyrrolidin-2-yl)methanol (0.35 g, 1.16 mmol), copper iodide (44 mg, 0.23 mmol, 0.2 equiv) and potassium carbonate (322 mg, 2.33 mmol, 2.0 equiv) were transferred into a reaction flask. The mixture was suspended in dry isopropanol (15 mL) and degassed. It was stirred under refluxing conditions for 6 hours. After cooling to room temperature, chloroform was added in small portions and the mixture was filtered through a short pad of silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (silica, ethyl acetate) to provide (S)-6-methoxy-1,2,3,5,11,11a-hexahydrobenzo[f]pyrrolo[2,1-c][1,4]oxazepine.

15 ^1H NMR (300 MHz, CDCl_3) δ 7.10 (dd, 1H), 6.63 (m, 2H), 4.56 (d, 1H), 4.35 (dd, 1H), 3.78 (s, 3H), 3.54 (dd, 1H), 3.36 – 3.10 (br m, 2H), 2.78 (br s, 1H), 2.56 (br d, 1H), 1.98 – 1.72 (m, 3H), 1.45 (br m, 1H).

EXAMPLE 15: PREPARATION OF ARM477 (SCHEME 15)



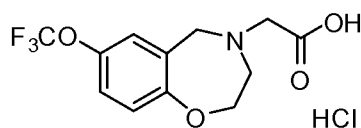
tert-Butyl 2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetate



To a mixture of 7-(trifluoromethoxy)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine (590 mg, 2.53 mmol) and K_2CO_3 (1.75 g, 12.65 mmol) in a round bottom flask was added

anhydrous CH₃CN (15 mL), followed by *tert*-butyl bromoacetate (0.37 mL, 2.53 mmol). The reaction mixture was stirred at ambient temperature for 20 h. The reaction mixture was partitioned between water (~50 mL) and ethyl acetate (~50 mL). The organics were dried over Na₂SO₄, concentrated *in vacuo*, and purified by column chromatography (silica gel, 25% EtOAc/Hexanes) to give the title product.

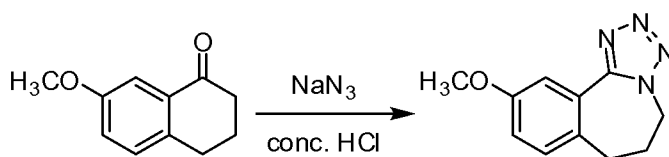
2-(7-(Trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetic acid hydrochloride (ARM477)



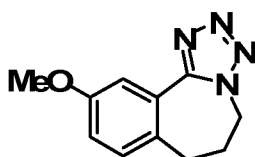
To a solution of *tert*-butyl 2-(7-(trifluoromethoxy)-2,3-dihydrobenzo[f][1,4]oxazepin-4(5H)-yl)acetate (776 mg, 2.23 mmol) in anhydrous CH₂Cl₂ (7.0 mL) was added HCl (4 M solution in dioxane, 2.80 mL, 11.2 mmol). The reaction mixture was stirred at ambient temperature for 18 h. Insoluble white solid was formed. The solid was isolated by filtration and washing with ether to the title product as a white powder.

¹H-NMR (300 MHz, DMSO-*d*₆) δ = 7.40-7.42 (m, 2H), 7.19-7.22 (d, *J* = 10.2 Hz, 1H), 4.51 (bs, 2H), 4.32 (bs, 2H), 4.16 (bs, 2H), 3.69 (bs, 2H) (NH⁺ and COOH signal not observed due to relatively large amount of H₂O in DMSO-*d*₆).

EXAMPLE 16: PREPARATION OF ARM187 (SCHEME 16)



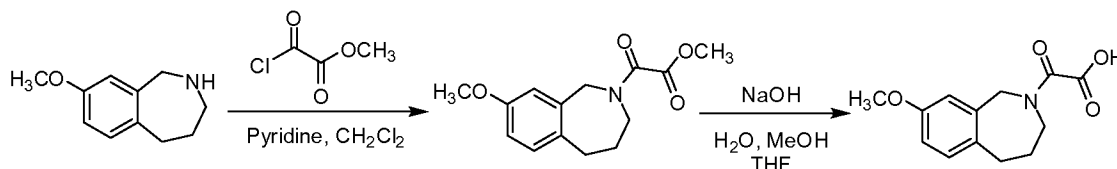
10-Methoxy-6,7-dihydro-5H-benzo[c]tetrazolo[1,5-a]azepine (ARM187)



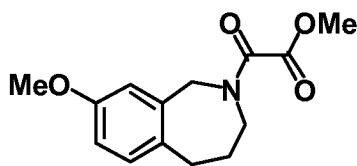
To a cold suspension of 7-methoxy-1-tetralone (5.21 g, 29.56 mmol, 1.0 equiv.) in *conc.* HCl (26 mL) at 0°C was added NaN₃ (1.98 g, 30.46 mmol, 1.03 equiv.) over 30 min. Then, the reaction mixture was stirred 23°C for 2 hours and cooled down to 0°C by ice water.

NaN₃ (4.5 g, 69.22 mmol, 2.34 equiv.) was added over 1 hour. The reaction mixture was warmed to 23°C and stirred for 17 hours. The reaction mixture was poured into ice, neutralized to pH 7 by aqueous NaOH (3.0 M) and extracted by EtOAc (3x200 mL). The combined organic layers were washed with NaHCO₃ aqueous, dried (Na₂SO₄), filtered, concentrated and the residue was purified by column chromatography (EtOAc/Hexane 10-100%) to give desired product.

EXAMPLE 17: PREPARATION OF ARM200, 205 (SCHEME 17)



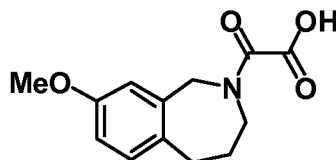
Methyl 2-(8-methoxy-4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)-2-oxoacetate (ARM200)



To a cold solution (0°C) of crude 8-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine (assumed 14.7 mmol, 1.0 equiv. prepared according to *J. Med. Chem.* **2005**, 48, 3586-3604) in CH₂Cl₂ (200 mL) at 0°C was added pyridine (2.38 mL, 29.4 mmol, 2.0 equiv.) and methyl chloroacetate (1.6 mL, 17.3 mmol, 1.2 equiv.). The reaction mixture was continued to stir at 0°C for 30 min, diluted with 1.0 M HCl (100 mL), extracted with CH₂Cl₂ (3x100 mL). The combined organic layers were washed (brine), dried (Na₂SO₄), concentrated and the residue was purified by column chromatography (EtOAc/hexane 0-50%) to give desired product.

¹H NMR (300 MHz, CDCl₃): 1.87 (m, 2H), 2.94 (m, 2H), 3.65 (t, *J*=5.4 Hz, 2H), 3.80 (m, 3H), 3.85 (m, 3H), 4.55 (m, 2H), 6.60 (d, *J*=2.7 Hz, 1/3H), 6.72 (dd, *J*=2.7 Hz, *J*=8.1 Hz, 1H), 6.94 (d, *J*=2.4 Hz, 2/3H), 7.07 (m, 1H).

MS (ESI): 263.9 [M+1]⁺, 304.9 [M+CH₃CN]⁺

2-(8-methoxy-4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)-2-oxoacetic acid (ARM205)

To a solution of methyl 2-(8-methoxy-4,5-dihydro-1H-benzo[c]azepin-2(3H)-yl)-2-oxoacetate (0.17 g, 0.65 mmol, 1.0 equiv.) in MeOH (5 mL) and THF (5 mL) at 23°C was added aqueous NaOH (70 mg, 1.75 mmol, 2.7 equiv. in H₂O 4 mL). The reaction mixture was continued to stir at the same temperature for 15 min, concentrated, diluted with H₂O (50 mL) and extracted by Et₂O (30 mL). The aqueous layer was neutralized by HCl aqueous to pH 3 and extracted with CH₂Cl₂ (3x50 mL). The combined organic layers were washed (brine), dried (Na₂SO₄), concentrated and residue was purified by column chromatography (MeOH/CH₂Cl₂ 0-10% with 1% HOAc). The desired fractions were collected, concentrated, dissolved in CH₂Cl₂ and washed by brine. The organic layer was dried (Na₂SO₄), concentrated and residue was freezing-dried to give title compound.

¹H NMR (300 MHz, DMSO-d₆): 1.65 (m, 2H), 2.84 (m, 2H), 3.57 (m, 2H), 3.68 (m, 3H), 4.36 (m, 2H), 6.66 (m, 2/3H), 6.68 (m, 2/3H), 6.77 (m, 2/3H), 7.04 (m, 1H).

Compound 155 can be prepared as described in the literature, for example in Novel vasopressin V2 receptor-selective antagonists: pyrrolo[2,1-a]quinoxaline and pyrrolo[2,1-c][1,4]benzodiazepine derivatives. Ohtake, Yasuhiro; Naito, Akira; Hasegawa, Hisashi; Kawano, Katsuhiro; Morizono, Daisuke; Taniguchi, Makoto; Tanaka, Yoko; Matsukawa, Hidehiko; Naito, Kenji; Oguma, Touru; Ezure, Yohji; Tsuruya, Yoshihiro. Sagami Research Laboratories, Wakamoto Pharmaceutical Co., Ltd., Kanagawa, Japan. Bioorganic & Medicinal Chemistry (1999), 7(6), 1247-1254; and Lewis Acid-Induced Internal Proton Return in Enolate Complexes with Chiral Amines. Vedejs, Edwin; Lee, Namkyu. Chemistry Department, University of Wisconsin, Madison, WI, USA. Journal of the American Chemical Society (1995), 117(3), 891-900. The contents of the aforementioned references are incorporated by reference herein.

EXAMPLE 18: Binding of calstabin2 to PKA phosphorylated RyR2

Cardiac SR membranes were prepared, as previously described (Marx et al., PKA phosphorylation dissociates FKBP12.6 from the calcium release channel (ryanodine receptor): defective regulation in failing hearts. Cell, 101:365-76, 2000; Kaftan et al., Effects of

rapamycin on ryanodine receptor/ Ca^{2+} -release channels from cardiac muscle. Circ. Res., 78:990-97, 1996). Immunoblotting of microsomes (50 ug) was performed as described, with anti-calstabin antibody (1:1,000) (Jayaraman et al., FK506 binding protein associated with the calcium release channel (ryanodine receptor). J. Biol. Chem., 267:9474-77, 1992) for 1 h at room temperature (Reiken et al., Beta-blockers restore calcium release channel function and improve cardiac muscle performance in human heart failure. Circulation, 107:2459-66, 2003). After incubation with HRP-labeled anti-rabbit IgG (1:5,000 dilution; Transduction Laboratories, Lexington, Ky.), the blots were developed using ECL (Amersham Pharmacia, Piscataway, N.J.) or equipment from Li-Cor Biosciences (model Odyssey). EC50 values were calculated by quantifying the blots as known in the art.

As shown in **FIGs. 1A-I**, the presence of any one of the compounds ARM137, ARM138, ARM139, ARM140, ARM147, ARM148, ARM149, ARM151, ARM152, ARM166, ARM167, ARM217, ARM 251, ARM258, ARM291 and ARM296, prevented the dissociation of calstabin2 from PKA phosphorylated RyR2, and/or enhanced the association of calstabin2 to PKA phosphorylated RyR2.

An example of EC50 values derived from the RyR2 Rycal screen data is shown in TABLE 1.

TABLE 1

	EC50		EC50
ARM140	50nM	ARM147	800 nM
ARM148	1500 nM	ARM149	1000 nM
ARM151	60 nM	ARM152	175 nM
ARM167	40 nM		

In addition, the following compounds were also found to prevent dissociation of calstabin2 from PKA phosphorylated RyR2, when tested in the aforementioned calstabin2 rebinding assay: ARM150, ARM189 and ARM203.

EXAMPLE 19: Binding of calstabin1 to PKA phosphorylated RyR1

SR membranes from skeletal muscle were prepared in a manner similar to Example 8, and as further described in US patent application publication No. 2004/0224368, the contents of which are incorporated by reference herein. Immunoblotting of microsomes (50 μg) was

performed as described, with anti-calstabin antibody (1:1,000). The blots were developed and quantified as described in Example 18.

As shown in **FIGs. 2A, B, C and D**, the presence of any one of the compounds ARM140, ARM148, ARM150, ARM151, ARM167, ARM312, ARM313 and ARM337, prevented the dissociation of calstabin1 from PKA phosphorylated RyR1, and/or enhanced the association of calstabin1 to PKA phosphorylated RyR1.

An example of the EC50 values derived from RyR1 Rycal screen data is shown in TABLE 2.

TABLE 2

	EC50
ARM140	45 nM
ARM150	125 nM
ARM151	65 nM
ARM167	100 nM

EXAMPLE 20: Calstabin2 Rebinding to RyR2 in Isoproterenol Treated Mice

Isoproterenol, a beta adrenergic receptor agonist, induces heart failure in mice via overstimulation of the beta adrenergic receptor. Concurrent with this is the activation of PKA, phosphorylation of the RyR2 on the sarcoplasm reticulum, and decreased interaction of calstabin-2 (FKBP12.6) to RyR2. A similar cascade of events occurs in skeletal muscle, wherein PKA activation by isoproterenol induces phosphorylation of the RyR1, leading to decreased binding of calstabin-1 (FKBP12) to RyR1.

As described in detail in International application No. PCT/US2007/085289, the contents of which are incorporated by reference herein, the inventors found that chronic isoproterenol treatment to a wild-type mouse offers a faster and more reliable method for inducing changes in RyR biochemistry that could be readily quantified. These changes include increased RyR phosphorylation and concomitant decreased calstabin binding.

MATERIALS AND METHODS

Animals and Reagents

C57Bl/6 mice were maintained and studied according to approved protocols. The synthetic beta-adrenergic agonist, isoproterenol (ISO) was obtained from Sigma (I65627) and prepared as a 100 mg/ml stock in water. Lysis buffer was made by adding sucrose (1 mM),

dithiothreitol (320 mM), and 1 protease inhibitor tablet (10X) to 10 ml stock solution (10 mM HEPES, 1 mM EDTA, 20 mM NaF, 2 mM Na₃VO₄).

Osmotic Pump Preparation and Surgical Implantation

5 Mice were continually infused for seven days with 10 mg/ml isoproterenol (1 µl/hr) by means of a subcutaneously implanted osmotic infusion pump (Alzet MiniOsmotic pump, Model 2001, Durect Corporation, Cupertino, CA).

10 For drug loading, the osmotic pump was held vertically and 200 µl drug solution was injected into the pump via a 1 ml syringe (attached to a cannula) that contained an excess of drug solution (~ 250-300 µl). The drug solution was injected slowly downward, while the syringe was slowly lifted, until the pump was overfilled. Overflow of displaced fluid upon capping the pump confirmed that the pump was properly filled.

The loaded osmotic pumps were implanted subcutaneously by the following steps. The recipient mouse was anesthetized with 1.5-2% isoflurane in O₂ administered at 0.6
15 L/min, and its weight was then measured and recorded. The mouse was then placed chest-down on styrofoam, its face in the nose cone. The fur was clipped on the back of the neck, extending behind the ears to the top of the head. The area was wiped gently with 70% alcohol, and a small incision was made at the midline on the nape of head/neck. A suture holder was swabbed with alcohol, inserted into the cut, and opened to release the skin from
20 the underlying tissue. To accommodate the pump, this opening was extended back to the hindquarters. The loaded pump was inserted into the opening, with its release site positioned away from the incision, and was allowed to settle underneath the skin with minimal tension. The incision was closed with 5.0 nylon suture, requiring about 5-6 sutures, and the area was wiped gently with 70% alcohol. Following surgery, mice were placed in individual cages to
25 minimize injury and possible activation of the sympathetic nervous system.

Isolation of Heart Tissue and Homogenate Preparation

The heart was removed from the peritoneal cavity, isolated from the pericardium, removed of any remaining fat, and then frozen in liquid nitrogen. For each tissue sample,
30 three standard microfuge tubes and one 5 ml tube were labeled. Tissue was transferred to 5 ml tube in approximately 0.5-0.7 ml fresh lysis buffer depending on the tissue size. The tissue was homogenized until a uniform lysate was formed without large tissue chunks. The homogenate was transferred to a microfuge tube and centrifuged at 4°C for 15 minutes at

4,000 x g. The supernatant was transferred to a new microfuge tube and centrifuged at 4°C for 15 min at 10,000 x g. The supernatant was removed and transferred to a new microfuge tube. A small aliquot was removed to measure the protein concentration, and the remaining sample was frozen at -80°C.

5

RyR2 Immunoprecipitation from Tissue Lysates

RyR2 was immunoprecipitated from samples by incubating 200-500 µg of homogenate with 2 µl anti-RyR antibody (RyR2-5029; Jayaraman et al., *J. Biol. Chem.* 1992;267:9474-77) in 0.5 ml of a modified RIPA buffer (50 mM Tris-HCl (pH 7.4), 0.9% NaCl, 5.0 mM NaF, 1.0 mM Na₃VO₄, 0.5% Triton-X100, and protease inhibitors) at 4°C for 1.5 hr. The samples were then incubated with Protein A sepharose beads (Amersham Pharmacia Biotech, Piscataway, NJ) at 4°C for 1 hour, after which the beads were washed three times with RIPA. Samples were heated to 95°C and size fractionated by SDS-PAGE (6% for SDS-PAGE RyR and 15% SDS-PAGE for calstabin). Immunoblots were developed using an anti-RyR antibody (RyR2-5029) at a 1:5,000 dilution, a phospho-specific antibody (RyR2-P2809, Zymed Laboratories, San Francisco, CA) at a 1:10,000 dilution or an anti-FKBP antibody (FKBB12/12/6, Jayaraman et al., *J. Biol. Chem.* 1992;267:9474-77) at a 1:2,000 dilution. The antibodies were diluted in 5% milk or TBS-T (20 mM Tris-HCl, pH 7.5, 0.5 M NaCl, 0.05% Tween® 20, 0.5% Triton X-100).

20

RESULTS

The efficacy of compounds ARM140, ARM151 and ARM 167 in enhancing calstabin2 binding to RyR2 were examined in isoproterenol treated mice. Each compound was administered in an osmotic pump at the indicated concentrations. At day 6, each mouse was sacrificed, and heart tissue was isolated and used to analyze calstabin2 binding in RyR2 immunoprecipitates.

25

As shown in **FIGs. 3A and B**, each of these compounds enhanced levels of calstabin2 in isoproterenol treated mice to a level similar to that observed by administration of 3.6 mM ARM036, which has been shown to be effective in both the primary screen and the isoproterenol screen.

30

EXAMPLE 21: Calstabin1 Rebinding to RyR1 in Isoproterenol Treated Mice

The efficacy of compounds ARM140, ARM148, ARM150, ARM151 and ARM 167 in enhancing calstabin1 binding to RyR1 were examined in isoproterenol treated mice as described in Example 19.

- 5 Mouse skeletal muscle tissue was isolated as follows. The leg muscles were exposed by cutting the skin at the ankle and pulling upward. The tissue was kept moistened with Tyrode's buffer (10 mM HEPES, 140 mM NaCl, 2.68 mM KCl, 0.42 mM Na₂HPO₄, 1.7 mM MgCl₂, 11.9 mM NaHCO₃, 5 mM glucose, 1.8 mM CaCl₂, prepared by adding 20 mg CaCl₂ to 100 ml 1X buffer made from a 10X solution without CaCl₂). The following muscles were
- 10 isolated and frozen in liquid nitrogen. The extensor digitoralis longus (EDL) was isolated by inserting scissors between lateral tendon and the X formed by the EDL and tibialis tendons, cutting upward toward the knee; cutting the fibularis muscle to expose the fan-shaped tendon of gastrocnemius; inserting forceps under X and under the muscle to loosen the EDL tendon; cutting the EDL tendon and pulling up the muscle; and finally cutting loose the EDL. The
- 15 soleus was isolated by removing the fibularis muscle from top of gastrocnemius; exposing the soleus on the underside of the gastrocnemius by cutting and lifting up the Achilles tendon; cutting the soleus at the top of the muscle behind the knee; and finally pulling the soleus and cutting it away from the gastrocnemius muscle. The tibialis was isolated by cutting the tibialis tendon from the front of ankle, pulling the tendon upwards, and cutting it away from the tibia.
- 20 The vastus (thigh muscle) was isolated from both legs, by cutting the muscle just above the knee and removing the muscle bundle. The samples were frozen in liquid nitrogen.

Muscle tissue homogenates were prepared as in Example 18.

- Each compound was administered at the indicated concentrations. At day 5, each mouse was sacrificed, and tibialis tissue was isolated and used to analyze calstabin binding in
- 25 RyR1 immunoprecipitates.

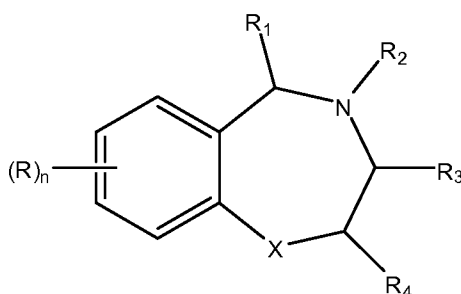
As shown in **FIGs. 4A and B**, each of these compounds enhanced levels of calstabin1 in isoproterenol treated mice to a level similar to that observed by administration of 3.6 mM ARM036, which has been shown to be effective in both the primary screen and the isoproterenol screen.

- 30 All publications, references, patents and patent applications cited herein are incorporated by reference in their entirety to the same extent as if each individual application, patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety.

THE CLAIMS

What is claimed is:

- 5 1. A compound of formula I:



wherein

n is 0, 1, 2, 3, or 4;

X is O, -NR₅ or -C(R₅)₂;

- 10 each R is independently selected from the group consisting of Z, R₅, -OR₅, -SR₅, -N(R₅)₂, -NR₅C(=O)OR₅, -C(=O)N(R₅)₂, -C(=O)OR₅, -C(=O)R₅, -OC(=O)R₅, NO₂, CN, -CZ₃, OCZ₃, -N₃, and -P(=O)R₈R₉;

R₁ and R₃ are each independently selected from the group consisting of oxo, R₅, -CH₂OR₅, -CH₂OC(=O)R₆, -C(=O)OR₅, -C(=O)NHR₅, -C(=O)R₅, and -OC(=O)R₅;

- 15 R₂ is selected from the group consisting of R₅, -C(=O)R₆, -C(=S)R₆, and -(CH₂)_mR₁₀, wherein m is 1, 2, 3, 4, 5, or 6; or

R₁ and R₂ together with the carbon and nitrogen to which they are respectively attached, form an unsubstituted or substituted heterocycle; or

- 20 R₂ and R₃ together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine; or

R₃ and R₄ together with the carbon atoms to which they are respectively attached, form an unsubstituted or substituted cycloalkyl or heterocyclic ring; or

R₄ is selected from the group consisting of R₅ and oxo;

- 25 each R₅ is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclalkyl, alkylaryl, and alkylheteroaryl;

R₆ is selected from the group consisting of R₅, -(CH₂)_bNR₁₃R₁₄, -NR₅OR₅, -OR₅, -C(=O)OR₅, -C(=O)NR₁₃R₁₄, -(CH₂)_cY, and -C(=O)R₅, wherein b is 0, 1, 2, 3, 4, 5, or 6 and c is 1, 2, 3, 4 or 5;

R₁₀ is selected from the group consisting of R₅, -OR₅, -SO₂R₁₁, -C(=O)R₁₂,
5 -NH(C=O)R₁₂, -O(C=O)R₁₂, and -P(=O)R₈R₉;

R₈, R₉, R₁₁ and R₁₂ are independently selected from the group consisting of R₅, OR₅, and -N(R₅)₂;

Y is selected from the group consisting of Z, -CO₂R₅, -C(=O)NR₁₃R₁₄, and -OR₅;

Z is a halogen selected from F, Cl, Br and I;

10 R₁₃ and R₁₄ are independently selected from the group consisting of R₅, or R₁₃ and R₁₄ together with the N to which they are bonded may form an unsubstituted or substituted heterocycle; and

wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, cycloalkylalkyl, heterocyclylalkyl, alkylaryl, and alkylheteroaryl may be substituted or
15 unsubstituted;

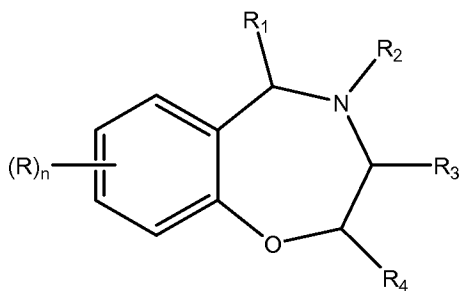
wherein the nitrogen in the benzoxazepine ring may optionally be a quaternary nitrogen; and

all enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, polymorphs, metabolites, and prodrugs thereof;

20 provided that, (i) when R is hydrogen at position 7 of the benzoxazepine ring, R₂ is not hydrogen, alkyl, haloalkyl or alkoxyalkyl, (ii) when R₃ is oxo, R₁ is not oxo or -C(=O)NHR₅; (iii) when R₂ is H, R₁ is not phenyl; and (iv) when R₂ and R₃ together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle, R₁ is not oxo.

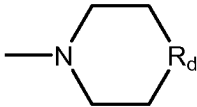
25

2. The compound of claim 1, having formula I-a



3. The compound of claim 1 or 2, wherein

- 5 (a) n is 1 or 2, R is Z, OCZ₃, R₅, OR₅, CN, NO₂, N(R₅)₂, -C(=O)N(R₅)₂, -C(=O)OR₅, or -P(=O)R₈R₉ at position 7 or 8 of the benzoxazepine ring;
- (b) n is 1, R is Z, OCZ₃, R₅, OR₅, CN, NO₂, -N(R₅)₂, -C(=O)N(R₅)₂, -C(=O)OR₅, or -P(=O)R₈R₉ at position 6 of the benzoxazepine ring;
- (c) R₂ is C(=O)R₆, wherein R₆ is selected from the group consisting of -C(=O)R₅,
 10 -C(=O)OR₅, -C(=O)NR₁₃R₁₄, and (CH₂)_bNR₁₃R₁₄, wherein b=0, and R₁₃ and R₁₄ are either

each H or are bonded to make , wherein R_d is O, CH₂, or NR_a; and R_a is H, alkoxy, C(=O)OC(CH₃)₃, or (C₁-C₆ alkyl)-aryl, wherein the aryl is a disubstituted phenyl or a benzo[1,3]dioxo-5-yl group, and wherein the nitrogen in NR_a may optionally be a quaternary nitrogen;

- 15 (d) R₂ is R₅ or (CH₂)_mR₁₀, wherein R₁₀ is selected from the group consisting of R₅, -C(=O)N(R₅)₂, -C(=O)OR₅, or -OR₅; and m is 1, 2, 3, 4, 5, or 6; or
- (e) R₂ and R₃ together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine; or
- (f) R₃ and R₄ together with the carbon atoms to which they are respectively attached, form
 20 an unsubstituted or substituted ring.

wherein,

in (a), R₈ and R₉ are independently OR₅; and

in (a)-(d), each R₅ is independently hydrogen, or an unsubstituted or substituted alkyl, alkylaryl, aryl, or heterocyclyl.

4. The compound of claim 1 or 2 wherein R_2 is

(i) hydrogen;

(ii) R_5 ,

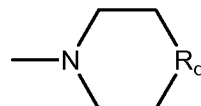
(iii) $(CH_2)_m R_{10}$, wherein m is 1, 2, 3, 4, 5, or 6, and wherein R_{10} is R_5 or $(C=O)OR_5$;

(iv) $-C(=O)C(=O)OR_5$;

(v) $-C(=O)NR_{13}R_{14}$ or

(vi) $-C(=O)C(=O)NR_{13}R_{14}$

wherein R_{13} and R_{14} are either each H or are bonded to make



, wherein R_d is CH_2 , NH, O, N-benzo[1,3]dioxo-5-yl, or $N-C(=O)OC(R_5)_3$, wherein the nitrogen in R_d may optionally be a quaternary nitrogen;

or R_2 and R_3 together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine.

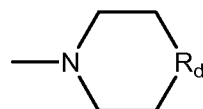
5. The compound of claim 4, wherein n is 1 and R is OR_5 , OCZ_3 , Z, CN, R_5 ,

$N(R_5)_2$, $-C(=O)N(R_5)_2$, $-C(=O)OR_5$, or $-P(=O)(OR_5)_2$, NO_2 at position 6, 7 or 8 of the benzoxazepine ring, or n is 2, each R is independently OR_5 at positions 7 and 8 of the benzoxazepine ring.

6. The compound of claim 1 or 2, wherein:

A) n is 1, R is OR_5 or OCZ_3 at position 7 of the benzoxazepine ring, and R_2 is (i) hydrogen; (ii) R_5 , (iii) $(CH_2)_m R_{10}$, wherein m is 1, 2, 3, 4, 5, or 6, and wherein R_{10} is R_5 or $(C=O)OR_5$; (iv) $-C(=O)C(=O)OR_5$; (v) $-C(=O)NR_{13}R_{14}$ or (vi) $-C(=O)C(=O)NR_{13}R_{14}$,

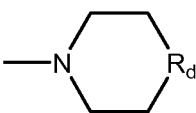
wherein R_{13} and R_{14} are either each H or are bonded to make



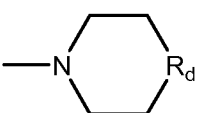
, wherein R_d is CH_2 , NH, O, N-benzo[1,3]dioxo-5-yl, or $N-C(=O)OC(R_5)_3$, wherein the nitrogen in R_d may optionally be a quaternary nitrogen; or R_2 and R_3 together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine; or

B) n is 1, R is Z, CN, R_5 , $N(R_5)_2$, $-C(=O)N(R_5)_2$, $-C(=O)OR_5$, or $-P(=O)(OR_5)_2$ at position 7 of the benzoxazepine ring, and R_2 is R_5 ; or

C) n is 1, R is NO_2 at position 8 of the benzoxazepine ring, and R_2 is (i) hydrogen; (ii) R_5 , (iii) $-\text{C}(=\text{O})\text{C}(=\text{O})\text{OR}_5$; or (iv) $-\text{C}(=\text{O})\text{NR}_{13}\text{R}_{14}$, wherein R_{13} and R_{14} are either each H or

are bonded to make , wherein R_d is CH_2 , NH , O , $\text{NC}(=\text{O})\text{OC}(\text{R}_5)_3$, or N -benzo[1,3]dioxo-5-yl, wherein the nitrogen in R_d may optionally be a quaternary nitrogen; or R_2 and R_3 together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine; or

D) n is 2, each R is independently OR_5 at positions 7 and 8 of the benzoxazepine ring, and R_2 is (i) hydrogen; (ii) $\text{C}(=\text{O})\text{C}(=\text{O})\text{OR}_5$; or (iii) $-\text{C}(=\text{O})\text{NR}_{13}\text{R}_{14}$, wherein R_{13} and R_{14} are

either each H or are bonded to make , wherein R_d is CH_2 , NH , O , N -benzo[1,3]dioxo-5-yl, or $\text{N}-\text{C}(=\text{O})\text{OC}(\text{R}_5)_3$, wherein the nitrogen in R_d may optionally be a quaternary nitrogen; or

E) n is 1, R is OR_5 at position 6 of the benzoxazepine ring, and R_2 and R_3 together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine; or

F) each of R_1 , R_2 , R_3 , and R_4 is H, $n=1$, R is OR_5 , OCZ_3 , Z , CN , R_5 , $\text{N}(\text{R}_5)_2$, $-\text{C}(=\text{O})\text{N}(\text{R}_5)_2$, $-\text{C}(=\text{O})\text{OR}_5$, or $-\text{P}(=\text{O})(\text{OR}_5)_2$, NO_2 and is at position 7 of the benzoxazepine ring.

wherein each R_5 is independently hydrogen, or an unsubstituted or substituted alkyl, alkylaryl, aryl, or heterocyclyl.

7. The compound of claim 1 or 2, wherein R is selected from the group consisting of Z , OCZ_3 , R_5 , OR_5 , CN , NO_2 , $\text{N}(\text{R}_5)_2$, $-\text{C}(=\text{O})\text{N}(\text{R}_5)_2$, $-\text{C}(=\text{O})\text{OR}_5$, and $-\text{P}(=\text{O})\text{R}_8\text{R}_9$.

8. The compound of claim 7, wherein R is OR_5 at position 7 of the benzoxazepine ring.

9. The compound of claim 1 or 2, wherein R_2 is selected from the group consisting of (i) R_5 , (ii) $-\text{C}(=\text{O})\text{R}_6$, and (iii) $-(\text{CH}_2)_m\text{R}_{10}$, wherein R_5 is H, or an unsubstituted or substituted alkyl, aryl, alkylaryl, heterocyclyl or heteroaryl; wherein R_6 is $-\text{NR}_{13}\text{R}_{14}$,

-C(=O)NR₁₃R₁₄ or -(C=O)OR₅; and wherein R₁₃ and R₁₄ together with the N to which they are bonded form an unsubstituted or substituted heterocycle.

10. The compound of claim 9, wherein R₂ is R₅, -C(=O)(C=O)OR₅,
5 -C(=O)NR₁₃R₁₄, -CH₂R₁₀ or -C(=O)C(=O)NR₁₃R₁₄.

11. The compound of claim 1 or 2, wherein R₂ and R₃ together with the nitrogen and carbon to which they are respectively attached, form an unsubstituted or substituted heterocycle other than a piperazine.

12. The compound of claim 1 or 2, wherein R₃ and R₄ together with the carbon atoms to which they are respectively attached, form an unsubstituted or substituted cycloalkyl or heterocyclic ring.

13. The compound of claim 1, wherein the compound is selected from the group consisting of ARM136, ARM137, ARM138, ARM139, ARM140, ARM146, ARM147, ARM148, ARM149, ARM150, ARM151, ARM152, ARM153, ARM156, ARM157, ARM159, ARM160, ARM161, ARM166, ARM167, ARM182, ARM186, ARM189, ARM203, ARM217, ARM251, ARM252, ARM258, ARM277, ARM279, ARM282, ARM291, ARM293, ARM296, ARM301, ARM302, ARM306, ARM311, ARM312, ARM313, ARM318, ARM322, ARM324, ARM326, ARM331, ARM335, ARM337, ARM351, ARM352, ARM353, ARM354, ARM397, ARM398, ARM399, ARM423, ARM454, ARM463, ARM466, ARM470, ARM473 and ARM477.

14. A pharmaceutical composition comprising a compound according to any of claims 1 to 13, and at least one additive selected from the group consisting of analgesic agents, antioxidants, aromatics, buffers, binders, colorants, disintegrants, diluents, emulsifiers, excipients, extenders, flavor-improving agents, gellants, glidants, preservatives, skin-penetration enhancers, solubilizers, stabilizers, suspending agents, sweeteners, tonicity agents, vehicles and viscosity-increasing agents.

15. The pharmaceutical composition of claim 14, in the form of a capsule, granule, powder, solution, suspension, or tablet and is designed for administration by an oral,

sublingual, buccal, parenteral, intravenous, transdermal, inhalation, intranasal, vaginal, intramuscular, or rectal mode.

16. A method for making a pharmaceutical composition for the treatment or prevention of disorders and diseases associated with Ryanodine receptors (RyRs) that regulate calcium channel functioning in cells which comprises associating a compound according to any of claims 1 to 13 with at least one additive selected from the group consisting of analgesic agents, antioxidants, aromatics, buffers, binders, colorants, disintegrants, diluents, emulsifiers, excipients, extenders, flavor-improving agents, gellants, glidants, preservatives, skin-penetration enhancers, solubilizers, stabilizers, suspending agents, sweeteners, tonicity agents, vehicles, and viscosity-increasing agents.

17. The method of claim 16, wherein the disorders and diseases are selected from the group consisting of cardiac, muscular and cognitive disorders and diseases, malignant hyperthermia, diabetes, and sudden infant death syndrome.

18. The method of claim 17, wherein the cardiac disorders and diseases are selected from the group consisting of irregular heartbeat disorders and diseases; exercise-induced irregular heartbeat disorders and diseases; sudden cardiac death; exercise-induced sudden cardiac death; congestive heart failure; chronic obstructive pulmonary disease; and high blood pressure.

19. The method of claim 18, wherein the irregular heartbeat disorders and diseases and exercise-induced irregular heartbeat disorders and diseases are selected from the group consisting of atrial and ventricular arrhythmia; atrial and ventricular fibrillation; atrial and ventricular tachyarrhythmia; atrial and ventricular tachycardia; catecholaminergic polymorphic ventricular tachycardia (CPTV); and exercise-induced variants thereof.

20. The method of claim 17, wherein the muscular disorders and diseases are selected from the group consisting of skeletal muscle fatigue, exercise-induced skeletal muscle fatigue, muscular dystrophy, bladder disorders, and incontinence.

21. The method of claim 17, wherein the cognitive disorders and diseases are selected from the group consisting of Alzheimer's Disease, forms of memory loss, and age-dependent memory loss.

5 22. The use of a compound according to any of claims 1 to 13 for preparing a pharmaceutical composition for treating disorders and diseases associated with Ryanodine receptors (RyRs) that regulate calcium channel functioning in cells.

10 23. The use of a compound according to any of claims 1 to 13 for the treatment of disorders and diseases associated with ryanodine receptors (RyRs) that regulate calcium channel functioning in cells.

15 24. The use of claims 22 or 23, wherein the disorders and diseases are selected from the group consisting of cardiac, muscular and cognitive disorders and diseases, malignant hyperthermia, diabetes, and sudden infant death syndrome.

20 25. The use of claim 24, wherein the cardiac disorders and diseases are selected from the group consisting of irregular heartbeat disorders and diseases; exercise-induced irregular heartbeat disorders and diseases; sudden cardiac death; exercise-induced sudden cardiac death; congestive heart failure; chronic obstructive pulmonary disease; and high blood pressure.

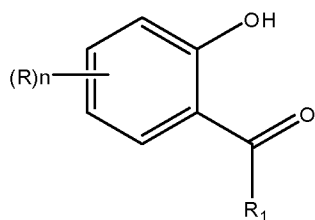
25 26. The use of claim 25, wherein the irregular heartbeat disorders and diseases and exercise-induced irregular heartbeat disorders and diseases are selected from the group consisting of atrial and ventricular arrhythmia; atrial and ventricular fibrillation; atrial and ventricular tachyarrhythmia; atrial and ventricular tachycardia; catecholaminergic polymorphic ventricular tachycardia (CPTV); and exercise-induced variants thereof.

30 27. The use of claim 24, wherein the muscular disorders and diseases are selected from the group consisting of skeletal muscle fatigue, central core diseases, exercise-induced skeletal muscle fatigue, muscular dystrophy, bladder disorders, and incontinence.

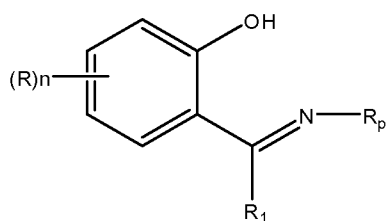
28. The use of claim 24, wherein the cognitive disorders and diseases are selected from the group consisting of Alzheimer's Disease, forms of memory loss, and age-dependent memory loss.

5 29. A method of synthesis of a compound according to claim 2, wherein R_2 and R_3 are H, comprising the steps of:

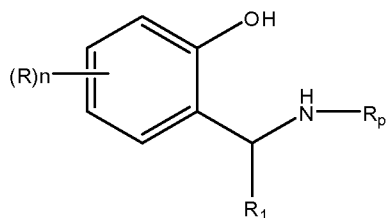
(a) treating a compound having the formula:



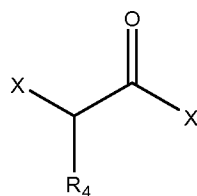
10 with a compound of formula: $-NH_2R_p$ wherein R_p represents a nitrogen protecting group, to obtain a compound of formula:



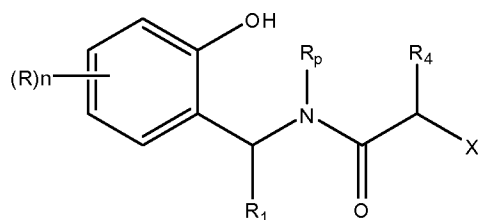
(b) reacting the compound formed in step (a) with a reducing agent to form a compound of formula:



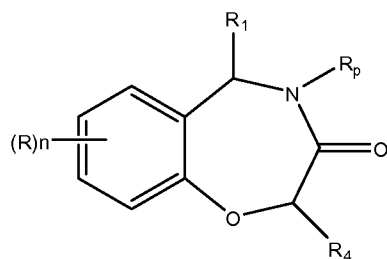
15 (c) reacting the compound formed in step (b) with a compound of the formula:



wherein each X is independently a halogen or a sulfonate, to form a compound of formula:

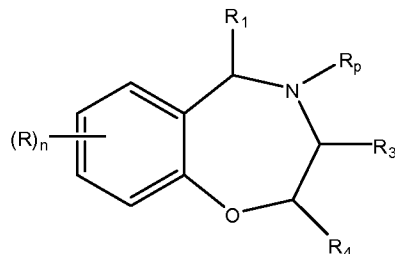


(d) reacting the compound formed in step (c) with a base to form a compound of formula:



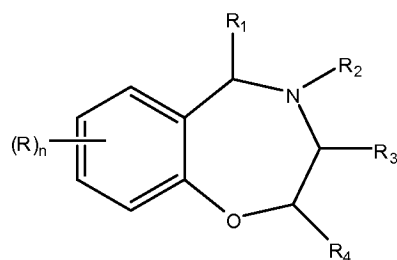
5

(e) treating the compound formed in step (d) with a reducing agent to form a compound of formula:

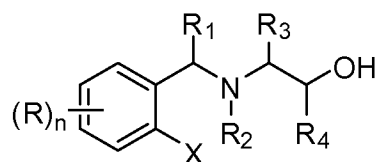


and

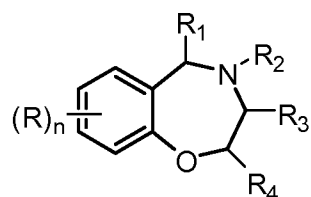
10 (f) removing the nitrogen protecting group R_p to form a compound of formula:



30. A method of synthesis of a compound according to claim 2, comprising the step of reacting a compound of formula:

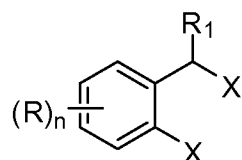


with a transition metal catalyst under conditions sufficient to form a compound of formula:

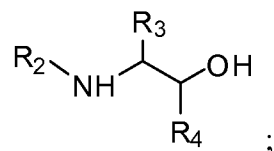


5 31. The method of claim 30, which further comprises:

(i) treating a compound of the formula:

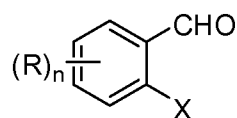


with a compound of formula:

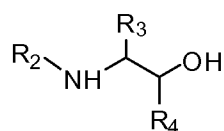


10 or

(ii) treating a compound of the formula:

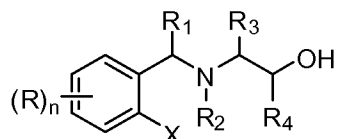


with a compound of formula:



under reductive amination conditions;

wherein the treating of (i) or (ii) forms compound of formula:



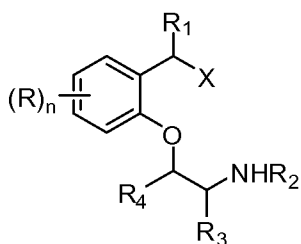
wherein X is independently a leaving group of a halogen or a sulfonate.

5

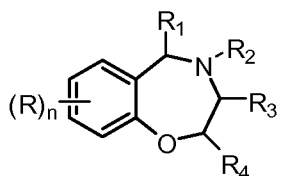
32. The method of claim 30, wherein the transition metal catalyst is CuI.

33. A method of synthesis of a compound according to claim 2, comprising the steps of:

10 (a) treating a compound of formula

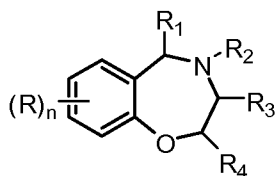


wherein X is a leaving group selected from a halogen and a sulfonate with a base, under conditions sufficient to form a compound of formula:

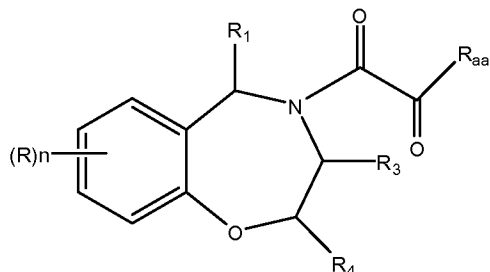


15

34. The method of any of claims 29 to 33, which further comprises a step of reacting the compound of formula:



wherein R_2 is H, with an acid chloride of formula Cl-C(=O)OR_{aa} under conditions sufficient to form a compound of the formula:

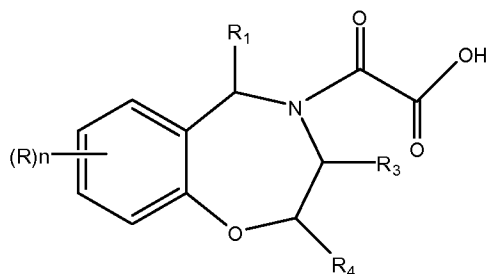


5

wherein R_{aa} is $\text{C}_1\text{-C}_4$ alkyl or aryl.

35. The method of claim 34, which further comprises reacting the compound formed in that claim with an acid or a base under conditions sufficient to form a compound of the formula:

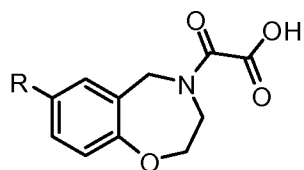
10



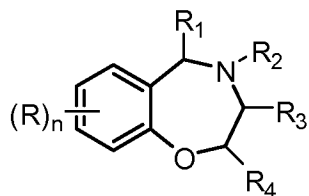
or its salts.

15

36. The method of claim 35, wherein the compound is represented by the formula:

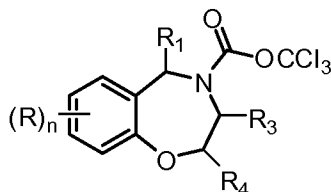


37. The method of any of claims 29 to 33, which further comprises reacting a compound of the formula:



wherein R_2 is H, with either of:

(i) triphosgene and a base to form a compound of the formula



5

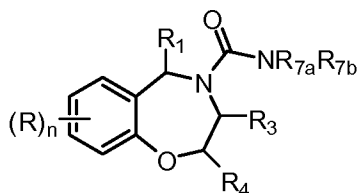
and further reacting that compound with one equivalent of an amine of formula $\text{HNR}_{7a} \text{R}_{7b}$,

or

(ii) a compound of formula $\text{Cl-CO-NR}_{7a} \text{R}_{7b}$,

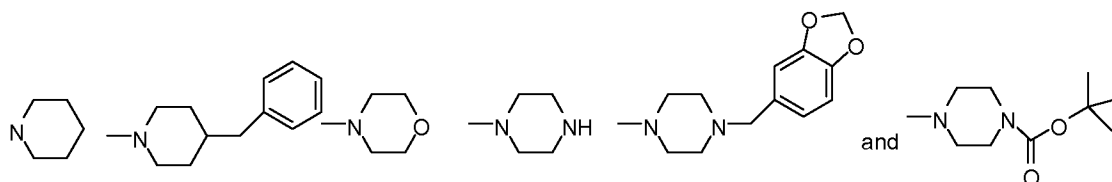
10 or

(iii) a compound of formula $\text{Cl}_3\text{CO}(\text{C}=\text{O})\text{NR}_{7a} \text{R}_{7b}$ under conditions sufficient to form the compound of formula

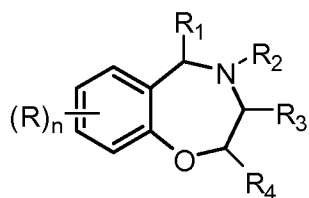


wherein $\text{NR}_{7a} \text{R}_{7b}$ in (i), (ii), or (iii) is selected from the group consisting of NH_2 , NEt_2 ,

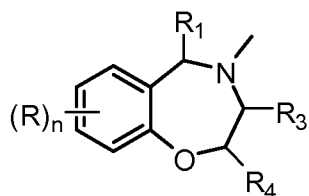
15 NHCH_2Ph , NHOH ,



38. The method of any of claims 29 to 33, which further comprises reacting the compound of formula

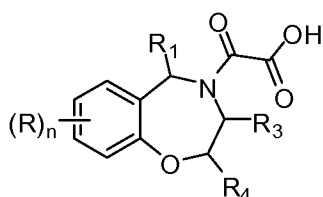


wherein R_2 is H, with formaldehyde (CH_2O) and sodium cyanoborohydride (NaBCNH_3) under conditions sufficient to form a compound of the formula:



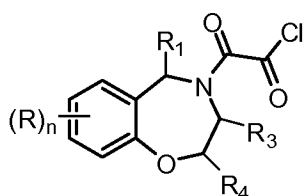
5

39. The method of claim 35, which further comprises treating the compound of formula:

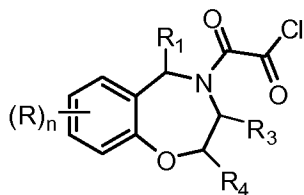


or its salts with thionyl chloride or oxalyl chloride under conditions sufficient to form a compound of the formula:

10

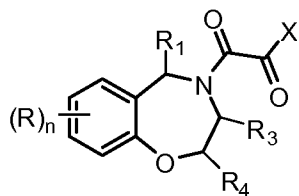


40. The method of claim 39, which further comprises a step of reacting of the formula:

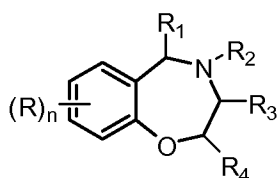


15

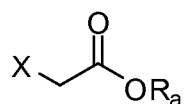
with a compound of the formula HX , wherein X is OCH_3 or NHEt , under conditions sufficient to form a compound of the formula:



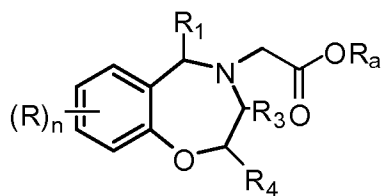
41. The method of any of claims 29 to 33, which further reacting the compound of formula:



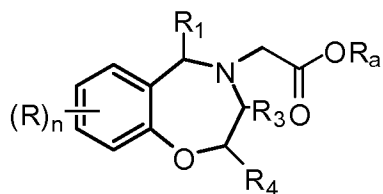
wherein R₂ is H, with a compound of formula:



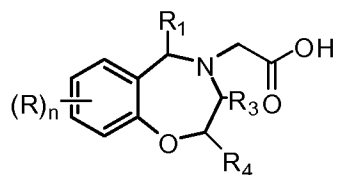
wherein X is a halogen or a sulfonate, and R_a is a C₁-C₄ alkyl, under conditions sufficient to form a compound of the formula:

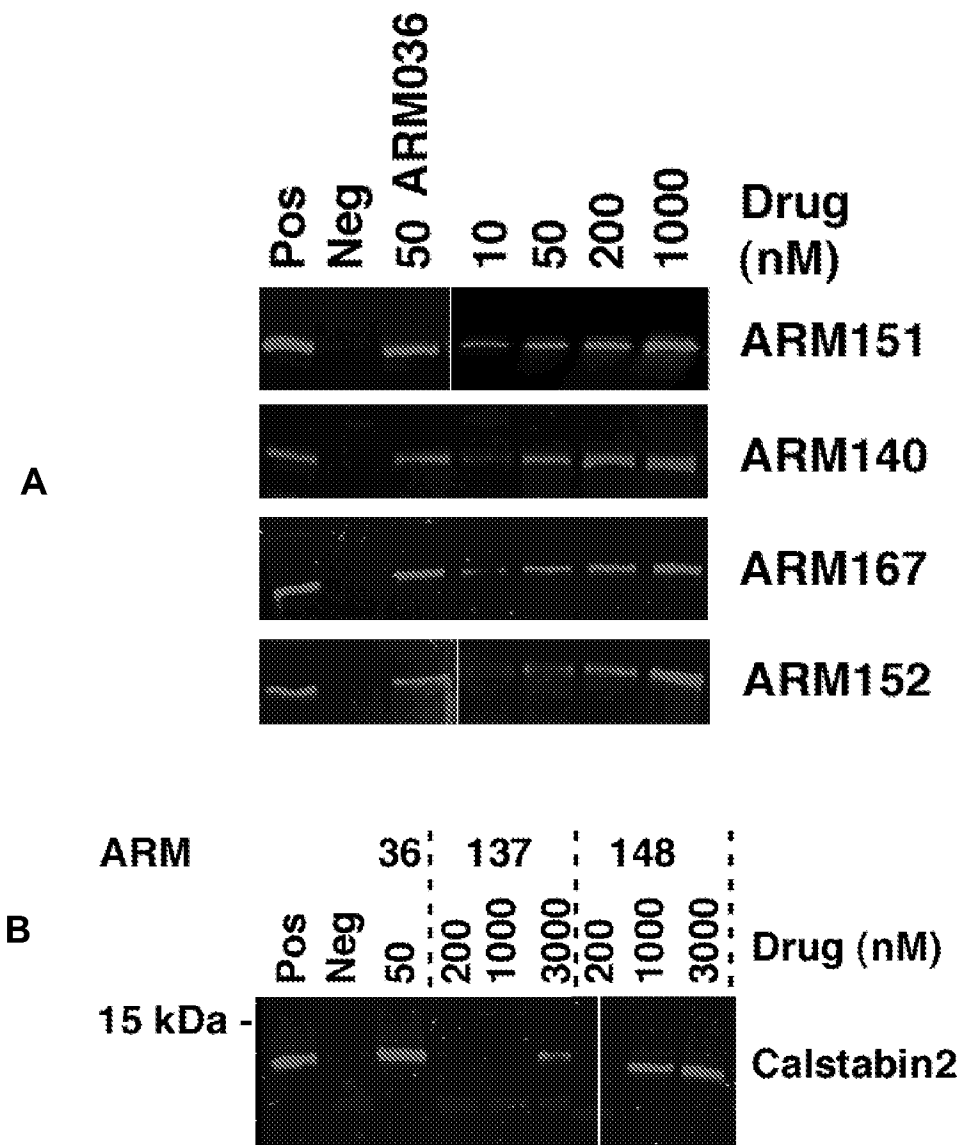


42. The method of claim 41, further comprising reacting the compound of the formula:



with an acid or a base, to form a compound of formula:





Figures 1 A-B

2/11

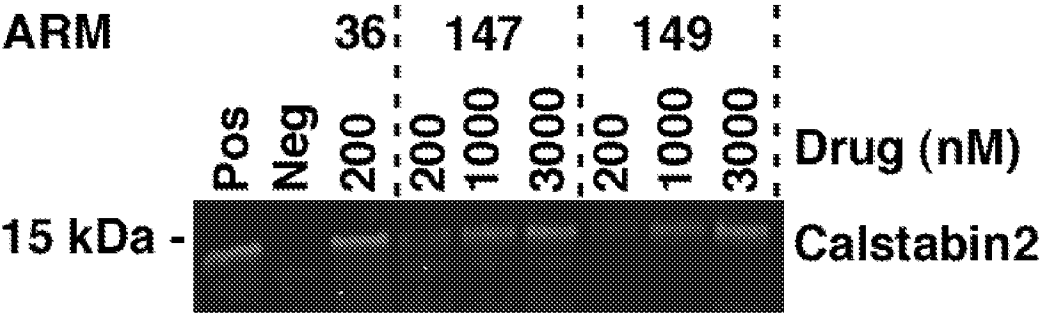


Figure 1C

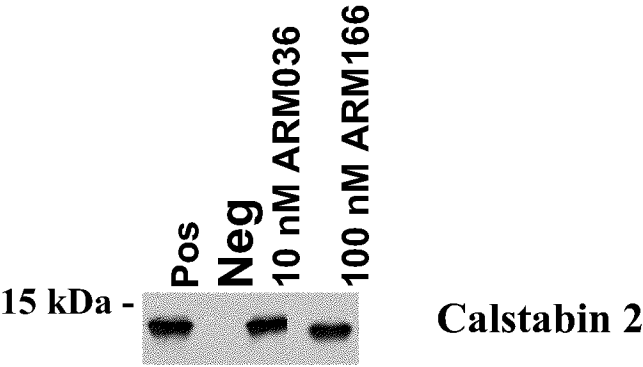


Figure 1D

3/11

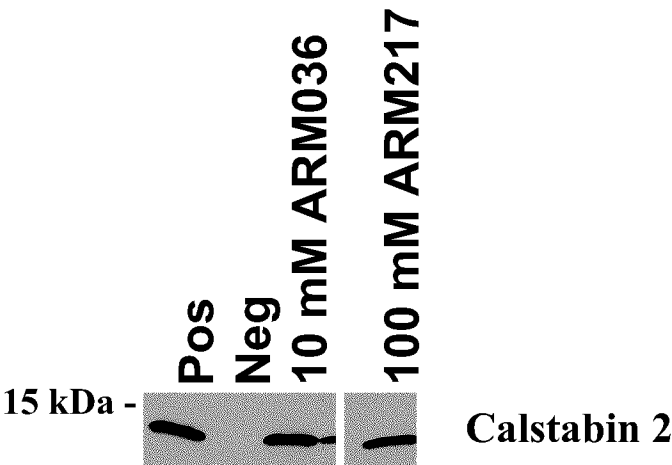


Figure 1E

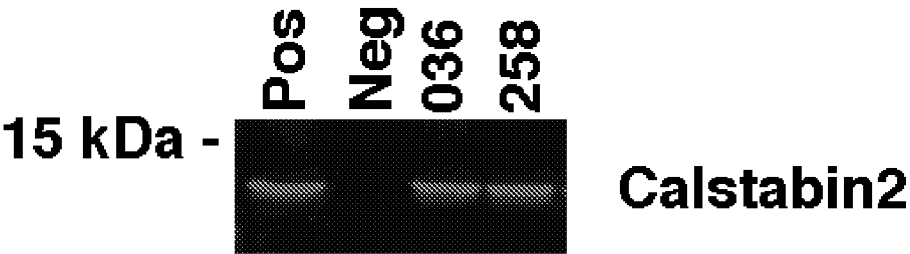


Figure 1F

4/11

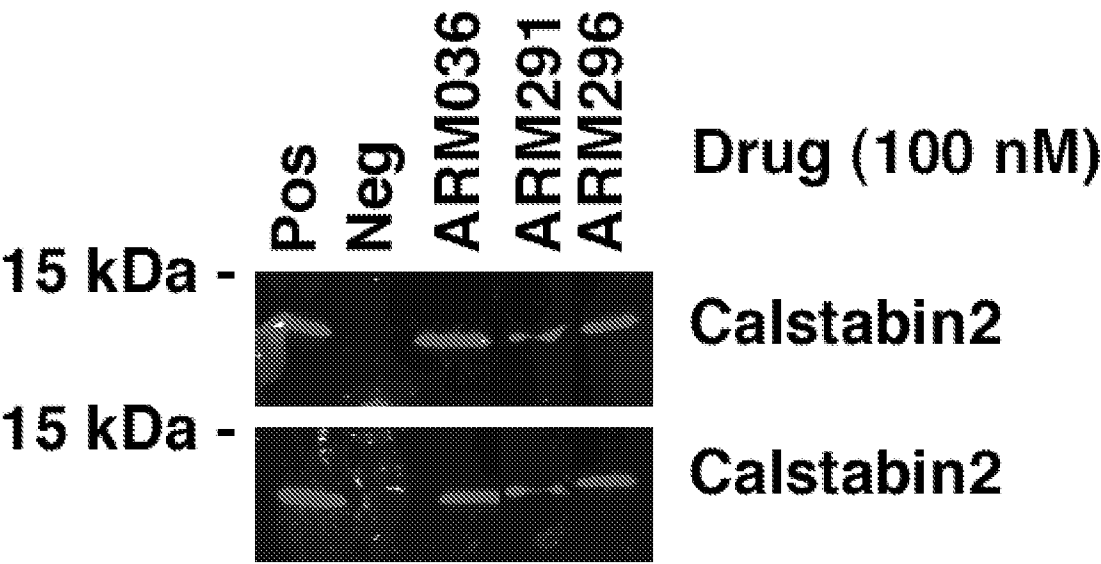


Figure 1G

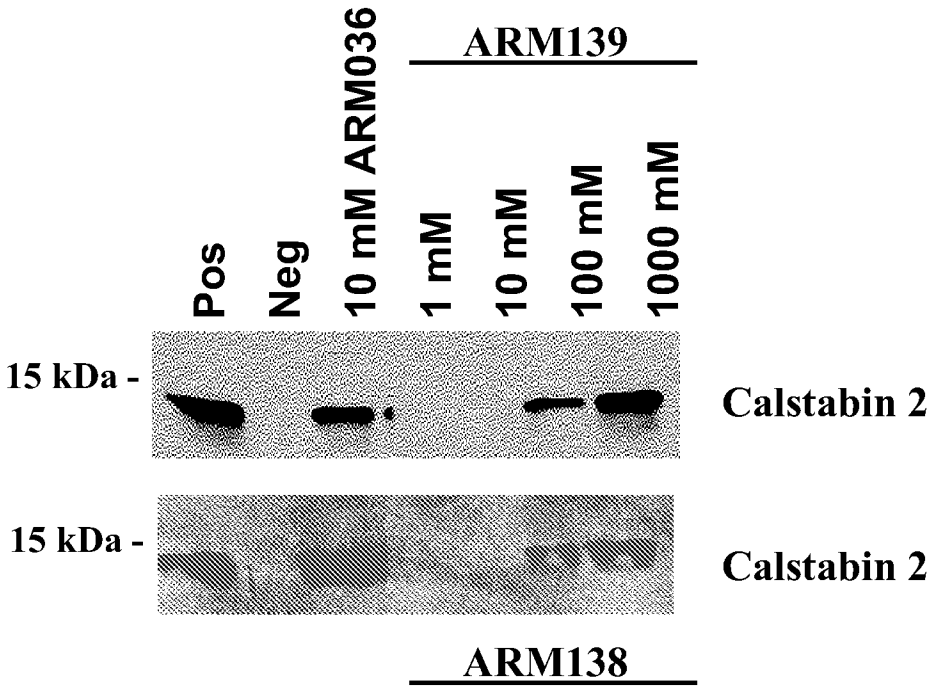


Figure 1H

5/11

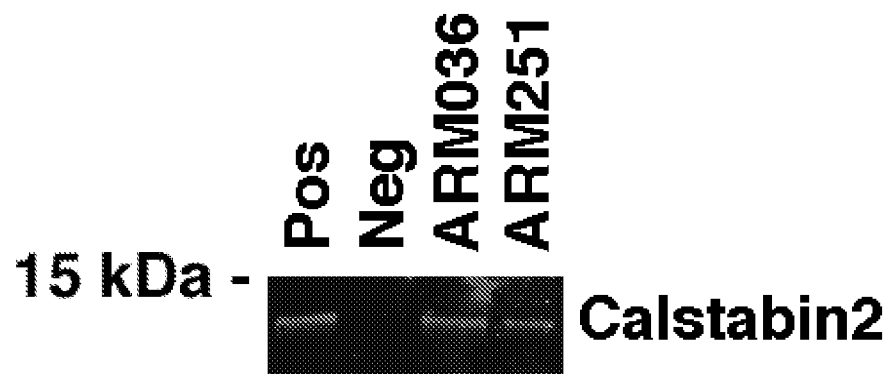


Figure 1I

6/11

RyR1 Primary Screen

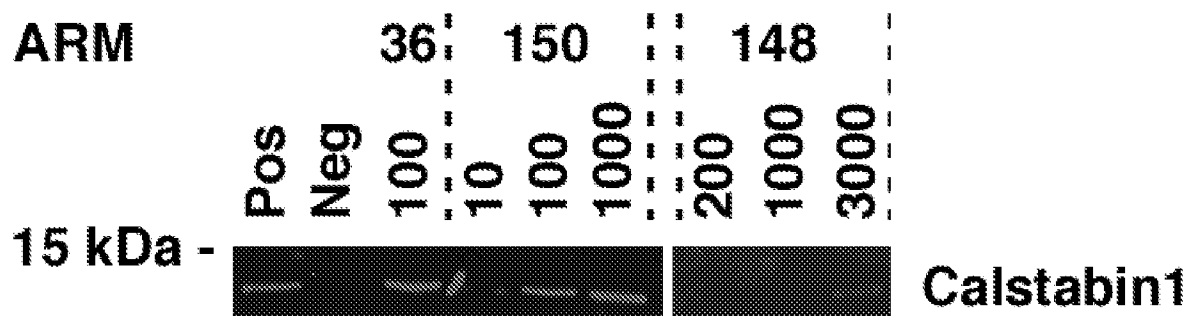


Figure 2A

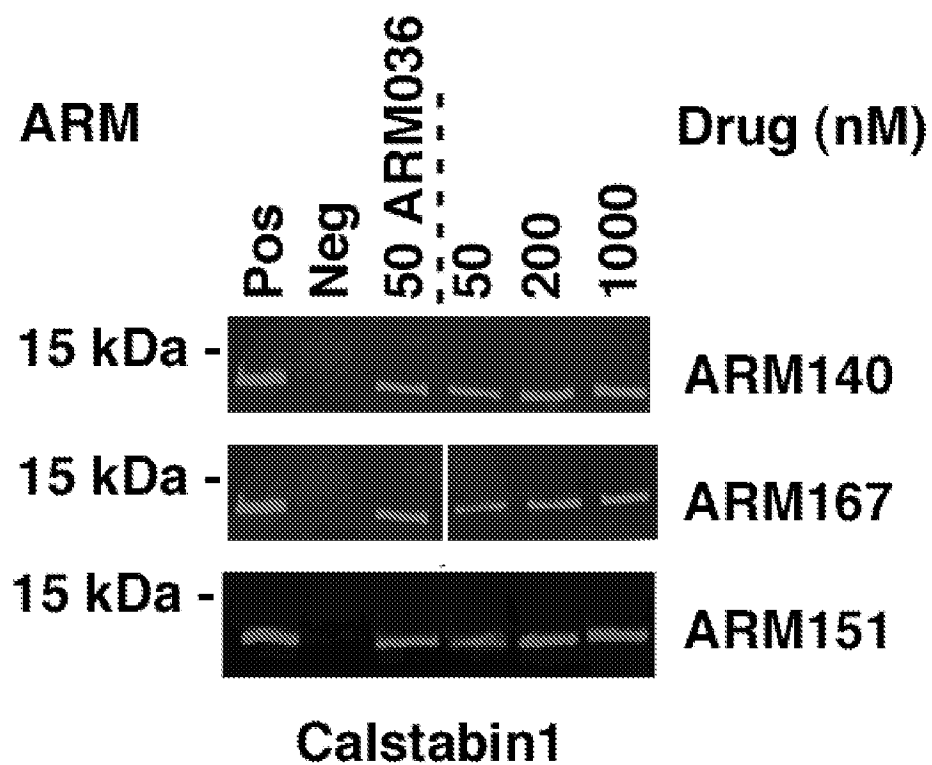


Figure 2B

7/11

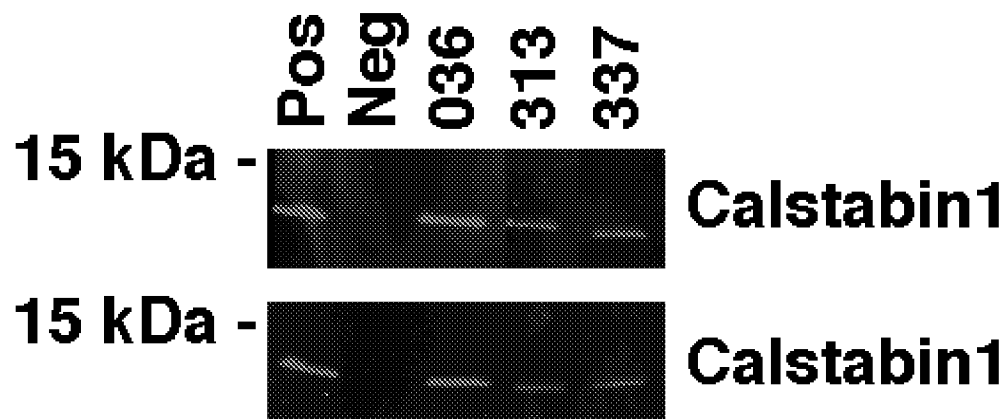


Figure 2C

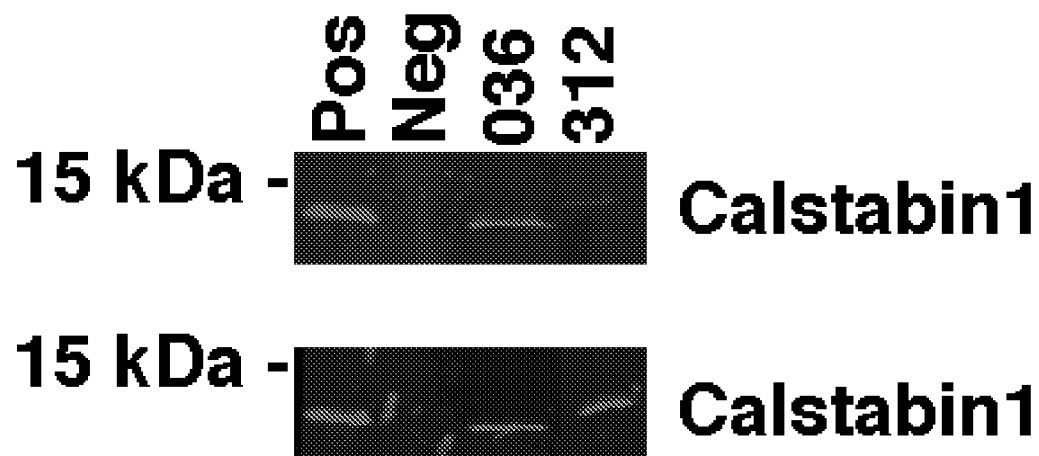


Figure 2D

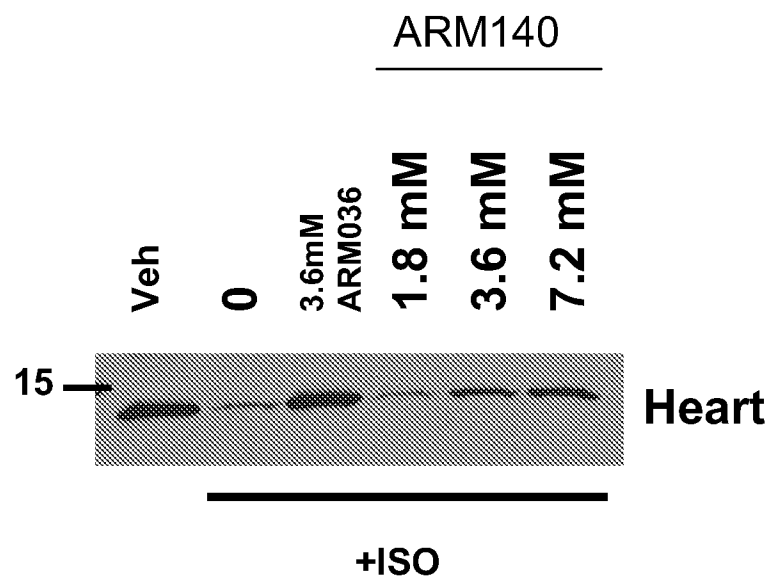


Figure 3A

9/11

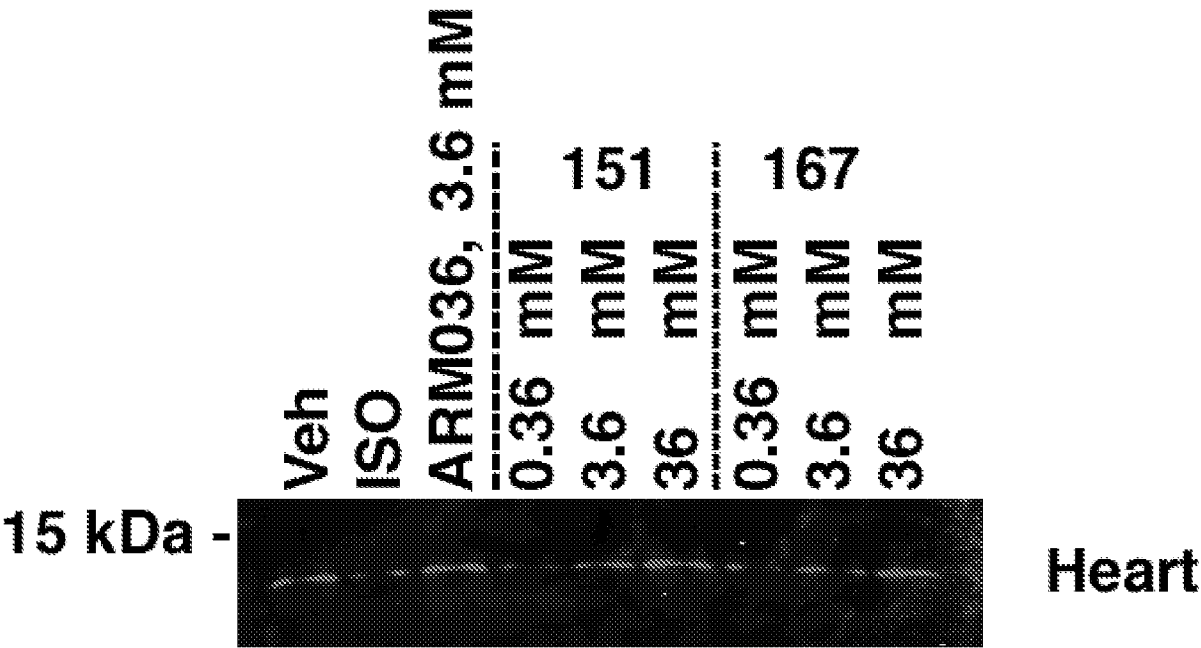


Figure 3B

10/11

Figure 4A

RyR1 ISO Screen - Tibialis

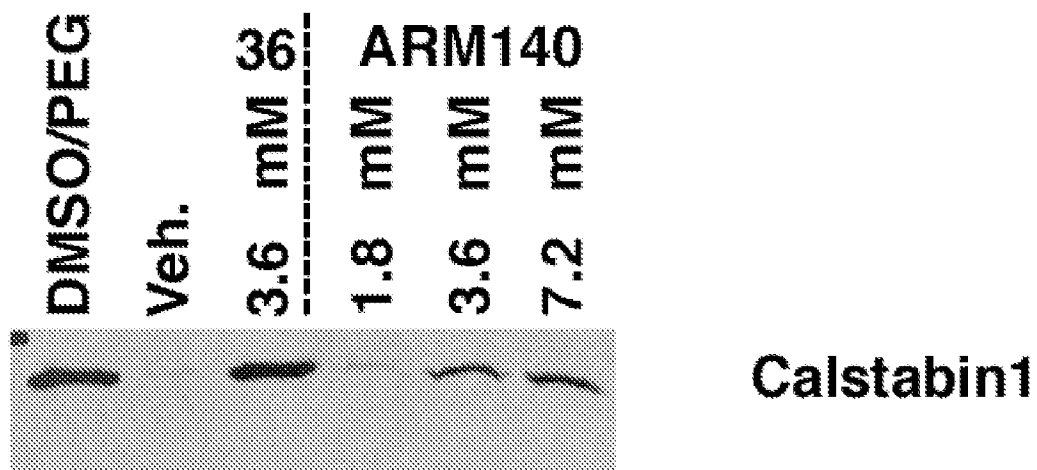
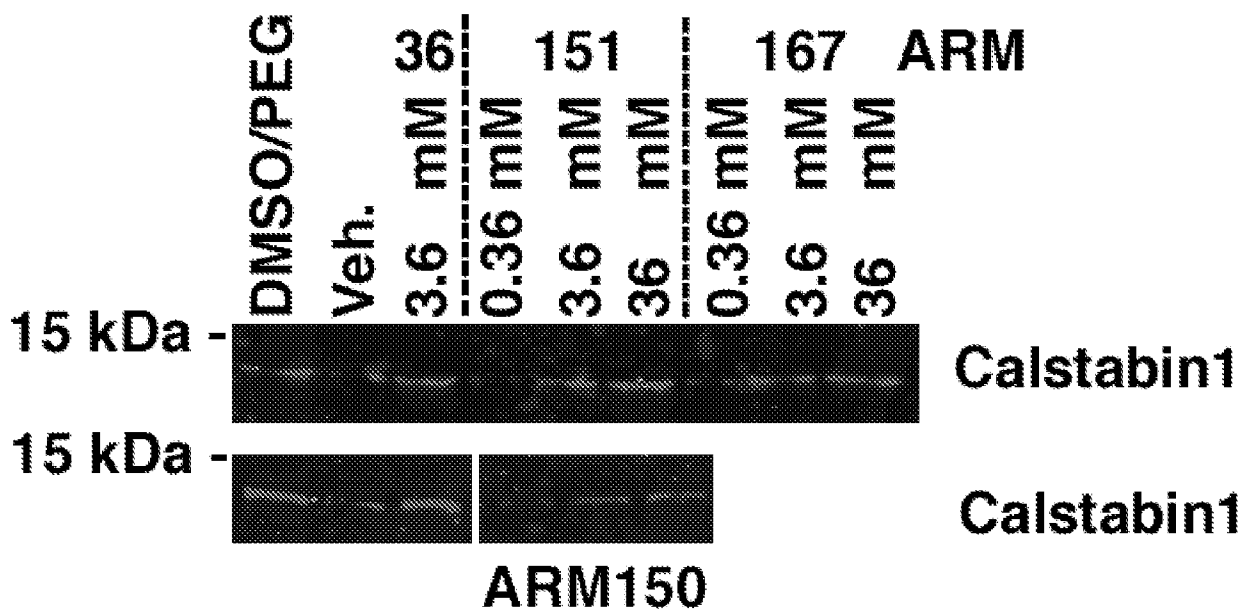


Figure 4B

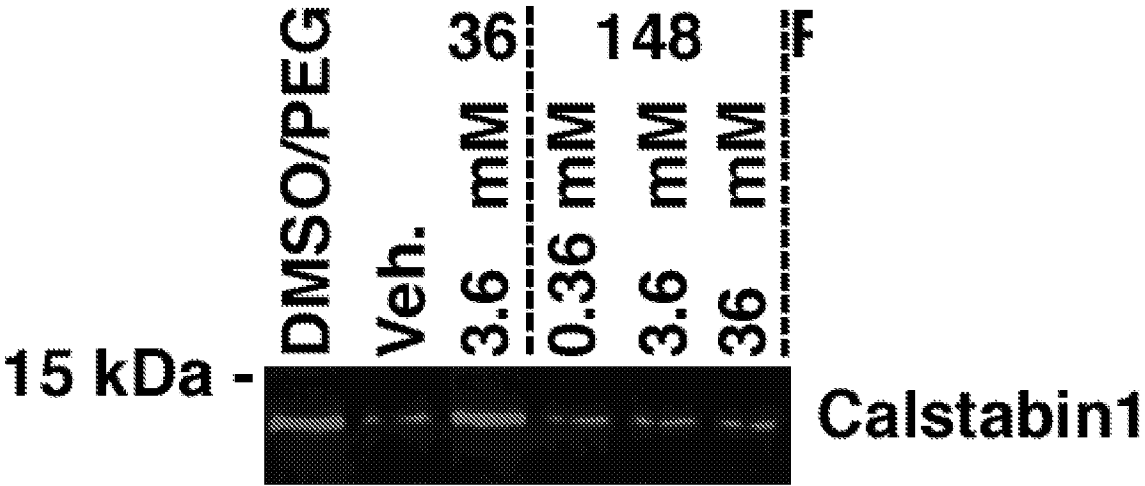


Figure 4C