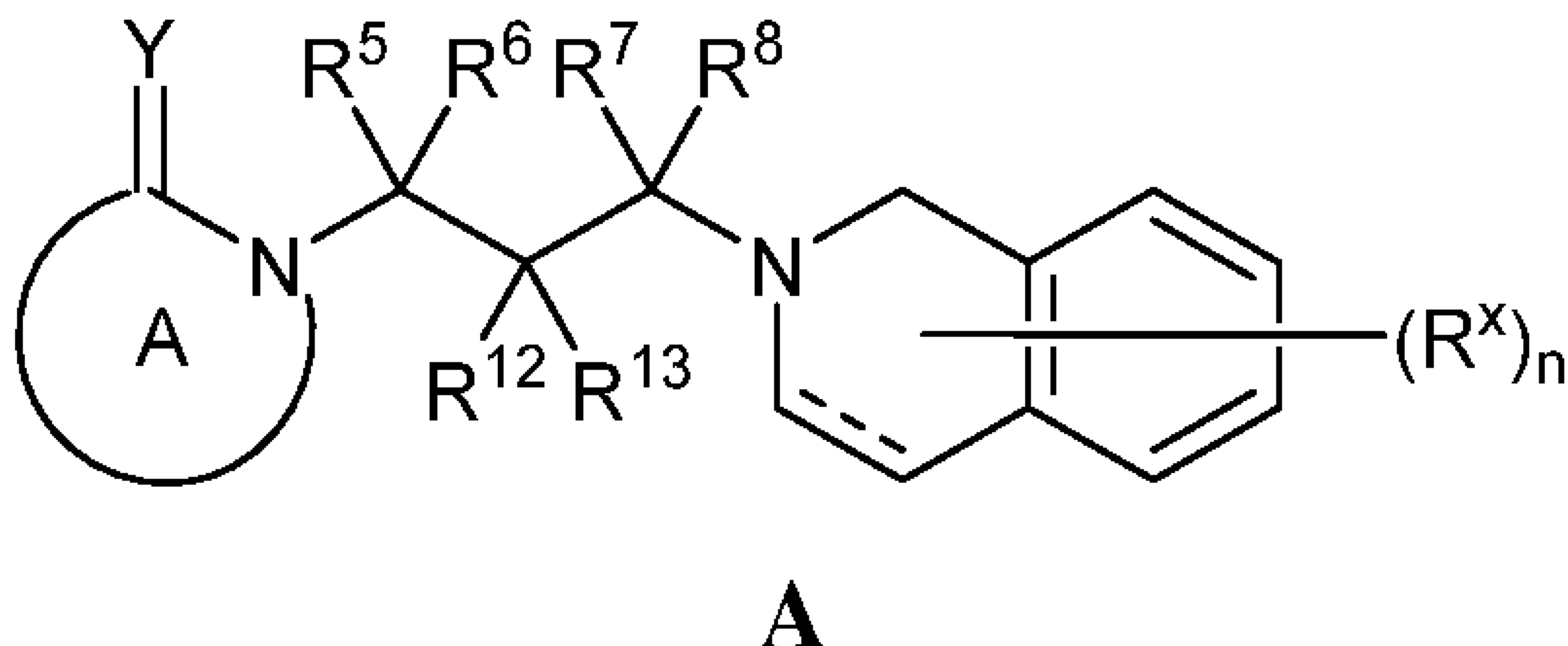




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(54) Title: PRMT5 INHIBITORS AND USES THEREOF



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Described herein are compounds of Formula (A), pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof. Compounds of the present invention are useful for inhibiting PRMT5 activity. Methods of using the compounds for treating PRMT5-mediated disorders are also described.

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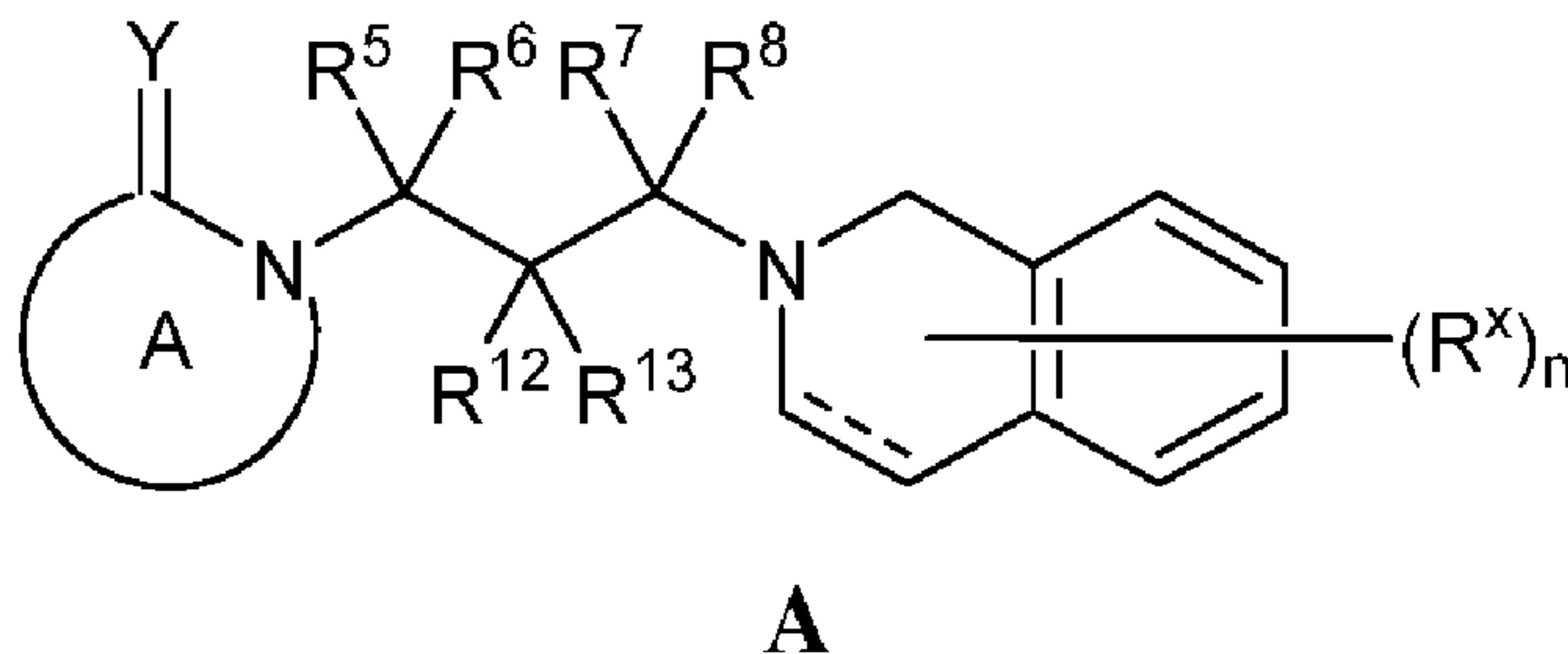
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(54) Title: PRMT5 INHIBITORS AND USES THEREOF



(57) Abstract: Described herein are compounds of Formula (A), pharmaceutically acceptable salts thereof, and pharmaceutical compositions thereof. Compounds of the present invention are useful for inhibiting PRMT5 activity. Methods of using the compounds for treating PRMT5-mediated disorders are also described.

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PRMT5 Inhibitors and Uses Thereof

Related Applications

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent applications, U.S.S.N. 61/745,477, filed December 21, 2012, and U.S.S.N. 61/785,025, filed March 14, 2013, the entire contents of each of which are incorporated herein by reference.

Background of the Invention

[0002] Epigenetic regulation of gene expression is an important biological determinant of protein production and cellular differentiation and plays a significant pathogenic role in a number of human diseases.

[0003] Epigenetic regulation involves heritable modification of genetic material without changing its nucleotide sequence. Typically, epigenetic regulation is mediated by selective and reversible modification (*e.g.*, methylation) of DNA and proteins (*e.g.*, histones) that control the conformational transition between transcriptionally active and inactive states of chromatin. These covalent modifications can be controlled by enzymes such as methyltransferases (*e.g.*, PRMT5), many of which are associated with specific genetic alterations that can cause human disease.

[0004] Disease-associated chromatin-modifying enzymes (*e.g.*, PRMT5) play a role in diseases such as proliferative disorders, metabolic disorders, and blood disorders. Thus, there is a need for the development of small molecules that are capable of inhibiting the activity of PRMT5.

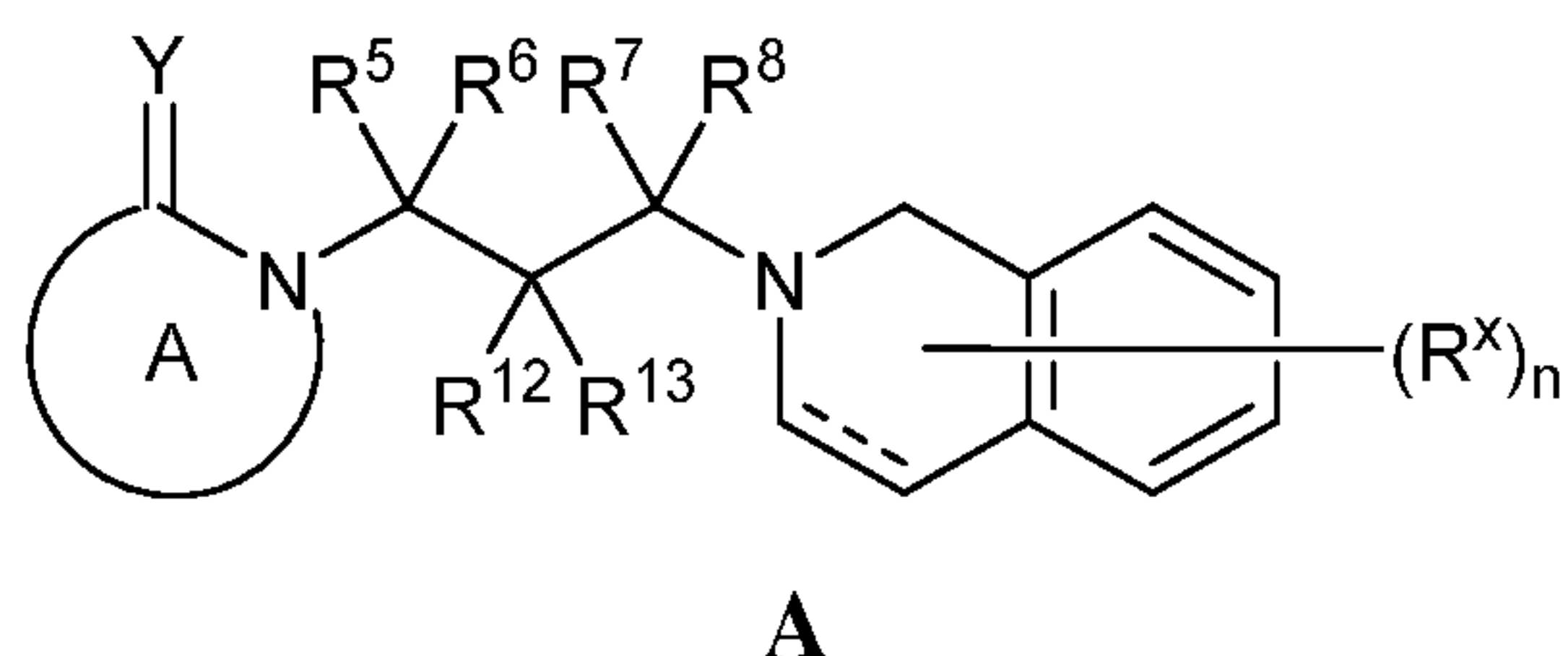
Detailed Description of Certain Embodiments

[0005] Protein arginine methyltransferase 5 (PRMT5) catalyzes the addition of two methyl groups to the two ω -guanidino nitrogen atoms of arginine, resulting in ω -NG, N'G symmetric dimethylation of arginine (sDMA) of the target protein. PRMT5 functions in the nucleus as well as in the cytoplasm, and its substrates include histones, spliceosomal proteins, transcription factors (See *e.g.*, Sun *et al.*, *PNAS* (2011) 108: 20538-20543). PRMT5 generally functions as part of a molecule weight protein complex. While the protein complexes of PRMT5 can have a variety of components, they generally include the protein

MEP50 (methylosome protein 50). In addition, PRMT5 acts in conjunction with cofactor SAM (S-adenosyl methionine).

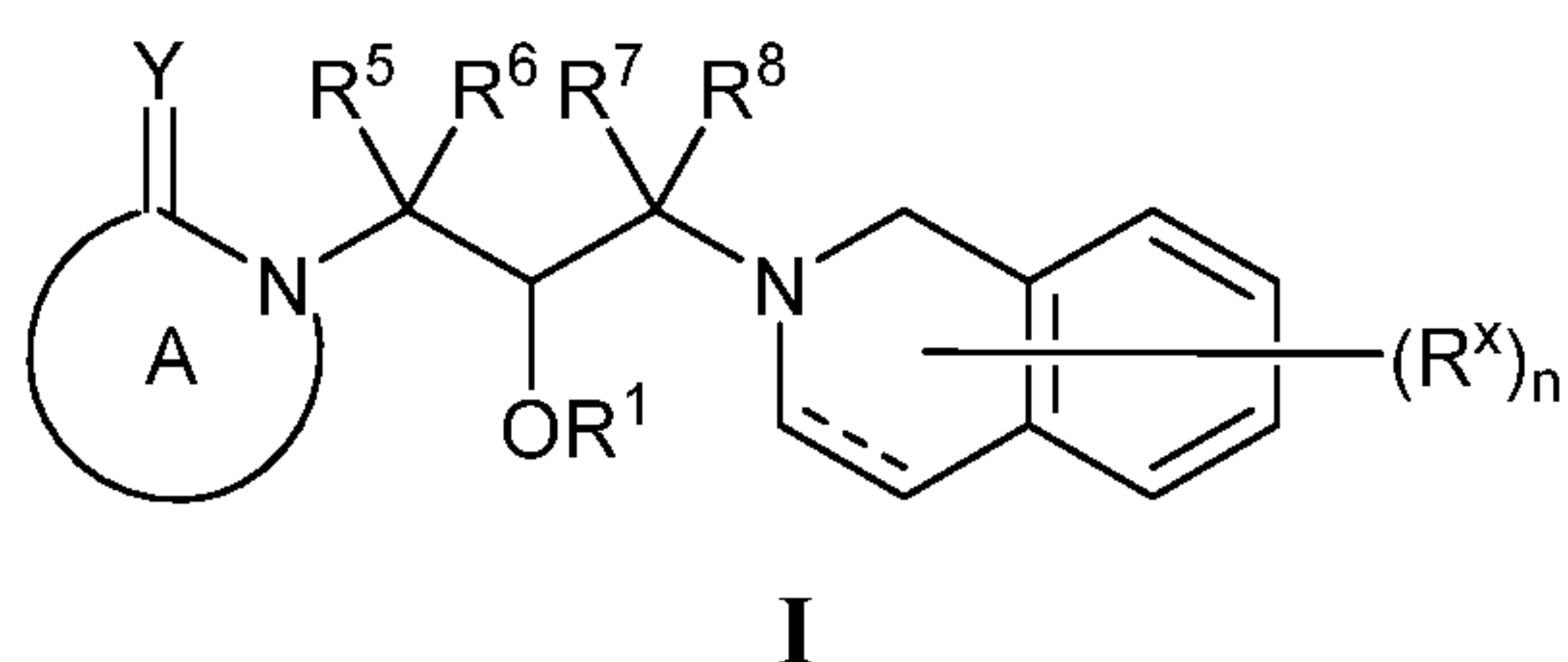
[0006] PRMT5 is an attractive target for modulation given its role in the regulation of diverse biological processes. It has now been found that compounds described herein, and pharmaceutically acceptable salts and compositions thereof, are effective as inhibitors of PRMT5.

[0007] Such compounds have the general Formula (A):



or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R¹, R⁵, R⁶, R⁷, R⁸, R^x, R¹², R¹³, and n are as defined herein.

[0008] In some embodiments, the inhibitors of PRMT5 have the general Formula (I):



or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R¹, R⁵, R⁶, R⁷, R⁸, R^x, and n are as defined herein.

[0009] In some embodiments, pharmaceutical compositions are provided which comprise a compound described herein (*e.g.*, a compound of Formula (A), *e.g.*, Formula (I)), or a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[0010] In certain embodiments, compounds described herein inhibit activity of PRMT5. In certain embodiments, methods of inhibiting PRMT5 are provided which comprise contacting PRMT5 with an effective amount of a compound of Formula (A), *e.g.*, Formula (I), or a pharmaceutically acceptable salt thereof. The PRMT5 may be purified or crude, and may be present in a cell, tissue, or a subject. Thus, such methods encompass inhibition of PRMT5 activity both *in vitro* and *in vivo*. In certain embodiments, the PRMT5 is wild-type PRMT5. In certain embodiments, the PRMT5 is overexpressed. In certain embodiments, the PRMT5 is a mutant. In certain embodiments, the PRMT5 is in a cell. In certain embodiments, the PRMT5 is in an animal, *e.g.*, a human. In some embodiments, the PRMT5

is in a subject that is susceptible to normal levels of PRMT5 activity due to one or more mutations associated with a PRMT5 substrate. In some embodiments, the PRMT5 is in a subject known or identified as having abnormal PRMT5 activity (*e.g.*, overexpression). In some embodiments, a provided compound is selective for PRMT5 over other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective relative to one or more other methyltransferases.

[0011] In certain embodiments, methods of altering gene expression in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (A), *e.g.*, Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, cell is in an animal, *e.g.*, a human.

[0012] In certain embodiments, methods of altering transcription in a cell are provided which comprise contacting a cell with an effective amount of a compound of Formula (A), *e.g.*, Formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human.

[0013] In some embodiments, methods of treating a PRMT5-mediated disorder are provided which comprise administering to a subject suffering from a PRMT5-mediated disorder an effective amount of a compound described herein (*e.g.*, a compound of Formula (A), *e.g.*, Formula (I)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof. In certain embodiments, the PRMT5-mediated disorder is a proliferative disorder, a metabolic disorder, or a blood disorder. In certain embodiments, compounds described herein are useful for treating cancer. In certain embodiments, compounds described herein are useful for treating hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer. In certain embodiments, compounds described herein are useful for treating a hemoglobinopathy. In certain embodiments, compounds described herein are useful for treating sickle cell anemia. In certain embodiments, compounds described herein are useful for treating diabetes or obesity. In certain embodiments, a provided compound is useful in treating inflammatory and autoimmune disease.

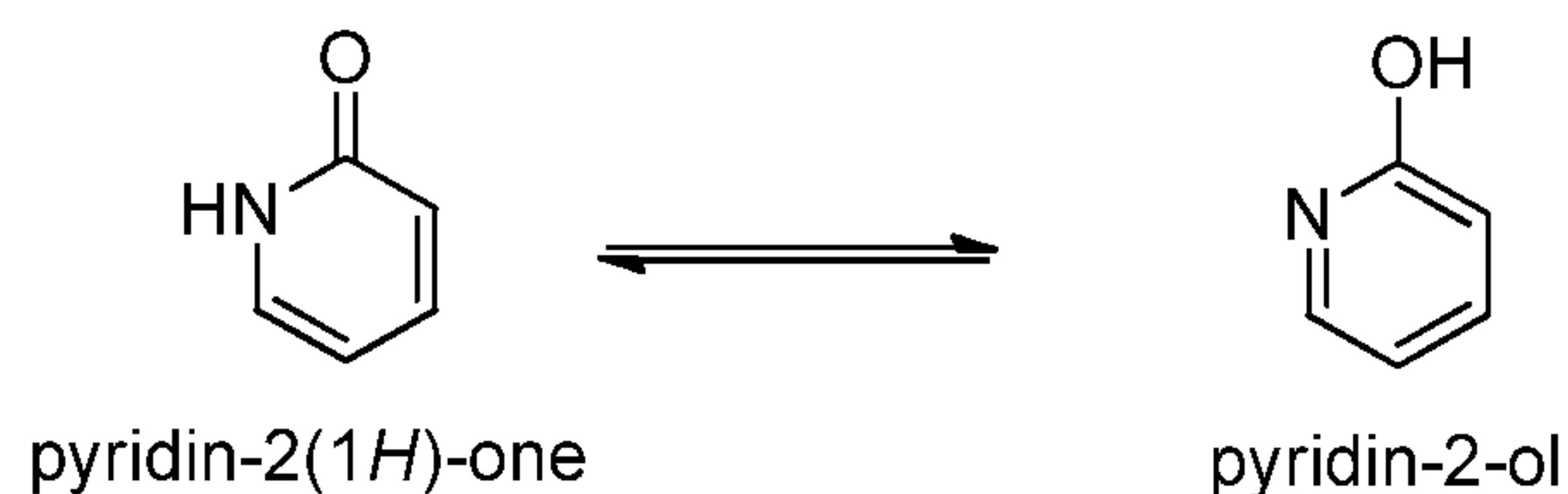
[0014] Compounds described herein are also useful for the study of PRMT5 in biological and pathological phenomena, the study of intracellular signal transduction pathways mediated by PRMT5, and the comparative evaluation of new PRMT5 inhibitors.

[0015] This application refers to various issued patent, published patent applications, journal articles, and other publications, all of which are incorporated herein by reference.

[0016] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, *Handbook of Chemistry and Physics*, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, *Organic Chemistry*, University Science Books, Sausalito, 1999; Smith and March, *March's Advanced Organic Chemistry*, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, *Comprehensive Organic Transformations*, VCH Publishers, Inc., New York, 1989; and Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0017] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, *e.g.*, enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques *et al.*, *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen *et al.*, *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972). The present disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0018] It is to be understood that the compounds of the present invention may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the present invention, and the naming of any compound described herein does not exclude any tautomer form.



[0019] Unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, replacement of ^{19}F with ^{18}F , or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of the disclosure. Such compounds are useful, for example, as analytical tools or probes in biological assays.

[0020] The term “aliphatic,” as used herein, includes both saturated and unsaturated, nonaromatic, straight chain (*i.e.*, unbranched), branched, acyclic, and cyclic (*i.e.*, carbocyclic) hydrocarbons. In some embodiments, an aliphatic group is optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, “aliphatic” is intended herein to include alkyl, alkenyl, alkynyl, cycloalkyl, and cycloalkenyl moieties.

[0021] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example “ C_{1-6} alkyl” is intended to encompass, C_1 , C_2 , C_3 , C_4 , C_5 , C_6 , C_{1-6} , C_{1-5} , C_{1-4} , C_{1-3} , C_{1-2} , C_{2-6} , C_{2-5} , C_{2-4} , C_{2-3} , C_{3-6} , C_{3-5} , C_{3-4} , C_{4-6} , C_{4-5} , and C_{5-6} alkyl.

[0022] “Alkyl” refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms (“ C_{1-20} alkyl”). In some embodiments, an alkyl group has 1 to 10 carbon atoms (“ C_{1-10} alkyl”). In some embodiments, an alkyl group has 1 to 9 carbon atoms (“ C_{1-9} alkyl”). In some embodiments, an alkyl group has 1 to 8 carbon atoms (“ C_{1-8} alkyl”). In some embodiments, an alkyl group has 1 to 7 carbon atoms (“ C_{1-7} alkyl”). In some embodiments, an alkyl group has 1 to 6 carbon atoms (“ C_{1-6} alkyl”). In some embodiments, an alkyl group has 1 to 5 carbon atoms (“ C_{1-5} alkyl”). In some embodiments, an alkyl group has 1 to 4 carbon atoms (“ C_{1-4} alkyl”). In some embodiments, an alkyl group has 1 to 3 carbon atoms (“ C_{1-3} alkyl”). In some embodiments, an alkyl group has 1 to 2 carbon atoms (“ C_{1-2} alkyl”). In some embodiments, an alkyl group has 1 carbon atom (“ C_1 alkyl”). In some embodiments, an alkyl group has 2 to 6 carbon atoms (“ C_{2-6} alkyl”). Examples of C_{1-6} alkyl groups include methyl (C_1), ethyl (C_2), n-propyl (C_3), isopropyl (C_3), n-butyl (C_4), tert-butyl (C_4), sec-butyl (C_4), iso-butyl (C_4), n-pentyl (C_5), 3-pentanyl (C_5), amyl (C_5), neopentyl (C_5), 3-methyl-2-butanyl (C_5), tertiary amyl (C_5), and n-hexyl (C_6). Additional examples of alkyl groups include n-heptyl (C_7), n-octyl (C_8) and the

like. In certain embodiments, each instance of an alkyl group is independently optionally substituted, *e.g.*, unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents. In certain embodiments, the alkyl group is unsubstituted C₁₋₁₀ alkyl (*e.g.*, -CH₃). In certain embodiments, the alkyl group is substituted C₁₋₁₀ alkyl.

[0023] In some embodiments, an alkyl group is substituted with one or more halogens. “Perhaloalkyl” is a substituted alkyl group as defined herein wherein all of the hydrogen atoms are independently replaced by a halogen, *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, the alkyl moiety has 1 to 8 carbon atoms (“C₁₋₈ perhaloalkyl”). In some embodiments, the alkyl moiety has 1 to 6 carbon atoms (“C₁₋₆ perhaloalkyl”). In some embodiments, the alkyl moiety has 1 to 4 carbon atoms (“C₁₋₄ perhaloalkyl”). In some embodiments, the alkyl moiety has 1 to 3 carbon atoms (“C₁₋₃ perhaloalkyl”). In some embodiments, the alkyl moiety has 1 to 2 carbon atoms (“C₁₋₂ perhaloalkyl”). In some embodiments, all of the hydrogen atoms are replaced with fluoro. In some embodiments, all of the hydrogen atoms are replaced with chloro. Examples of perhaloalkyl groups include -CF₃, -CF₂CF₃, -CF₂CF₂CF₃, -CCl₃, -CFCl₂, -CF₂Cl, and the like.

[0024] “Alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon double bonds, and no triple bonds (“C₂₋₂₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkenyl”). In some embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In some embodiments, an alkenyl group has 2 to 8 carbon atoms (“C₂₋₈ alkenyl”). In some embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In some embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In some embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In some embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In some embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In some embodiments, an alkenyl group has 2 carbon atoms (“C₂ alkenyl”). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C₂₋₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), and the like. In certain embodiments, each instance of an alkenyl group is independently optionally substituted, *e.g.*, unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents. In certain

embodiments, the alkenyl group is unsubstituted C₂₋₁₀ alkenyl. In certain embodiments, the alkenyl group is substituted C₂₋₁₀ alkenyl.

[0025] “Alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon triple bonds, and optionally one or more double bonds (“C₂₋₂₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkynyl”). In some embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In some embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In some embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In some embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In some embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In some embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In some embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In some embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptynyl (C₇), octyny (C₈), and the like. In certain embodiments, each instance of an alkynyl group is independently optionally substituted, *e.g.*, unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one or more substituents. In certain embodiments, the alkynyl group is unsubstituted C₂₋₁₀ alkynyl. In certain embodiments, the alkynyl group is substituted C₂₋₁₀ alkynyl.

[0026] “Carbocyclyl” or “carbocyclic” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 14 ring carbon atoms (“C₃₋₁₄ carbocyclyl”) and zero heteroatoms in the non-aromatic ring system. In some embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In some embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl groups include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl groups

include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl groups include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like. As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or is a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic carbocyclyl”) and can be saturated or can be partially unsaturated. “Carbocyclyl” also includes ring systems wherein the carbocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups wherein the point of attachment is on the carbocyclyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the carbocyclic ring system. In certain embodiments, each instance of a carbocyclyl group is independently optionally substituted, *e.g.*, unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C₃₋₁₀ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C₃₋₁₀ carbocyclyl.

[0027] In some embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 14 ring carbon atoms (“C₃₋₁₄ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 10 ring carbon atoms (“C₃₋₁₀ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 8 ring carbon atoms (“C₃₋₈ cycloalkyl”). In some embodiments, a cycloalkyl group has 3 to 6 ring carbon atoms (“C₃₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 6 ring carbon atoms (“C₅₋₆ cycloalkyl”). In some embodiments, a cycloalkyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ cycloalkyl”). Examples of C₅₋₆ cycloalkyl groups include cyclopentyl (C₅) and cyclohexyl (C₆). Examples of C₃₋₆ cycloalkyl groups include the aforementioned C₅₋₆ cycloalkyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ cycloalkyl groups include the aforementioned C₃₋₆ cycloalkyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). In certain embodiments, each instance of a cycloalkyl group is independently unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more substituents. In certain embodiments, the cycloalkyl group is unsubstituted C₃₋₁₀ cycloalkyl. In certain embodiments, the cycloalkyl group is substituted C₃₋₁₀ cycloalkyl.

[0028] “Heterocyclyl” or “heterocyclic” refers to a radical of a 3- to 14-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“3-14 membered heterocyclyl”). In certain embodiments, heterocyclyl or heterocyclic refers to a radical of a 3-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“3-10 membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. In certain embodiments, each instance of heterocyclyl is independently optionally substituted, *e.g.*, unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3-10 membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3-10 membered heterocyclyl.

[0029] In some embodiments, a heterocyclyl group is a 5-10 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5-10 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5-8 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5-8 membered heterocyclyl”). In some embodiments, a heterocyclyl group is a 5-6 membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5-6 membered heterocyclyl”). In some embodiments, the 5-6 membered heterocyclyl has 1-3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5-6 membered heterocyclyl has 1-2 ring heteroatoms independently selected from nitrogen, oxygen, and

sulfur. In some embodiments, the 5–6 membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0030] Exemplary 3–membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, and thioarenyl. Exemplary 4–membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl, and thietanyl. Exemplary 5–membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl, and pyrrolyl–2,5–dione. Exemplary 5–membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5–membered heterocyclyl groups containing three heteroatoms include, without limitation, triazolinyl, oxadiazolinyl, and thiadiazolinyl. Exemplary 6–membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridinyl, and thianyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, and dioxanyl. Exemplary 6–membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7–membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8–membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl, and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indolinyl, isoindolinyl, dihydrobenzofuranyl, dihydrobenzothieryl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and the like.

[0031] “Aryl” refers to a radical of a monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C_{6–14} aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; *e.g.*, phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; *e.g.*, naphthyl such as 1–naphthyl and 2–naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; *e.g.*, anthracyl). “Aryl” also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl

groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. In certain embodiments, each instance of an aryl group is independently optionally substituted, *e.g.*, unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents. In certain embodiments, the aryl group is unsubstituted C₆₋₁₄ aryl. In certain embodiments, the aryl group is substituted C₆₋₁₄ aryl.

[0032] “Heteroaryl” refers to a radical of a 5–14 membered monocyclic or polycyclic (*e.g.*, bicyclic or tricyclic) 4n+2 aromatic ring system (*e.g.*, having 6 or 10 π electrons shared in a cyclic array) having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–14 membered heteroaryl”). In certain embodiments, heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic 4n+2 aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5–10 membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heteroaryl” includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the point of attachment is on the heteroaryl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heteroaryl ring system. “Heteroaryl” also includes ring systems wherein the heteroaryl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the aryl or heteroaryl ring, and in such instances, the number of ring members designates the number of ring members in the fused (aryl/heteroaryl) ring system. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *e.g.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

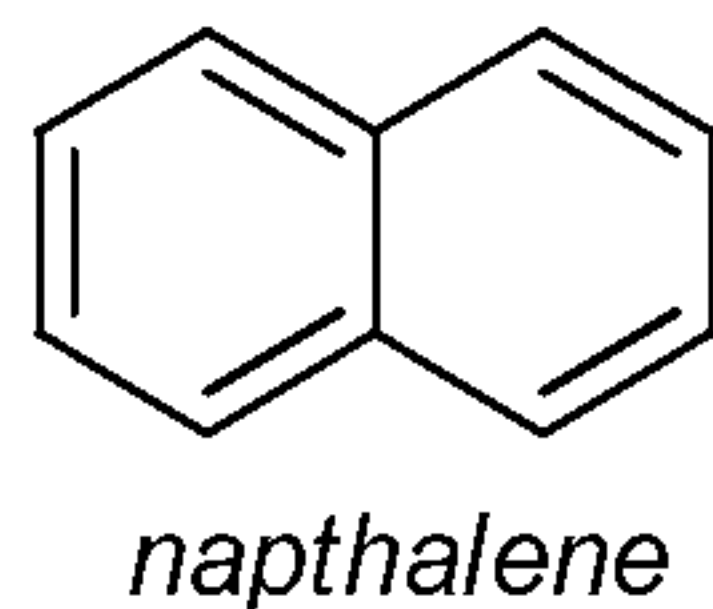
[0033] In some embodiments, a heteroaryl group is a 5–14 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–14 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–10 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided

in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–10 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–8 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–8 membered heteroaryl”). In some embodiments, a heteroaryl group is a 5–6 membered aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5–6 membered heteroaryl”). In some embodiments, the 5–6 membered heteroaryl has 1–3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1–2 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, the 5–6 membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, each instance of a heteroaryl group is independently optionally substituted, *e.g.*, unsubstituted (“unsubstituted heteroaryl”) or substituted (“substituted heteroaryl”) with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5–14 membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5–14 membered heteroaryl.

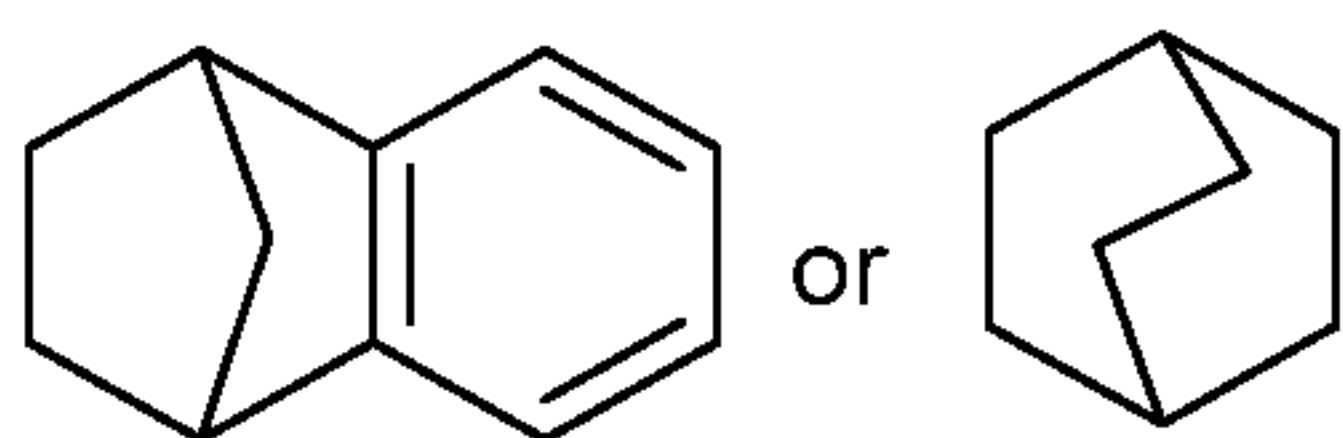
[0034] Exemplary 5-membered heteroaryl groups containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl groups containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl groups containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl groups containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl groups containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl groups containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl groups containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl groups containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl groups include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6–

bicyclic heteroaryl groups include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

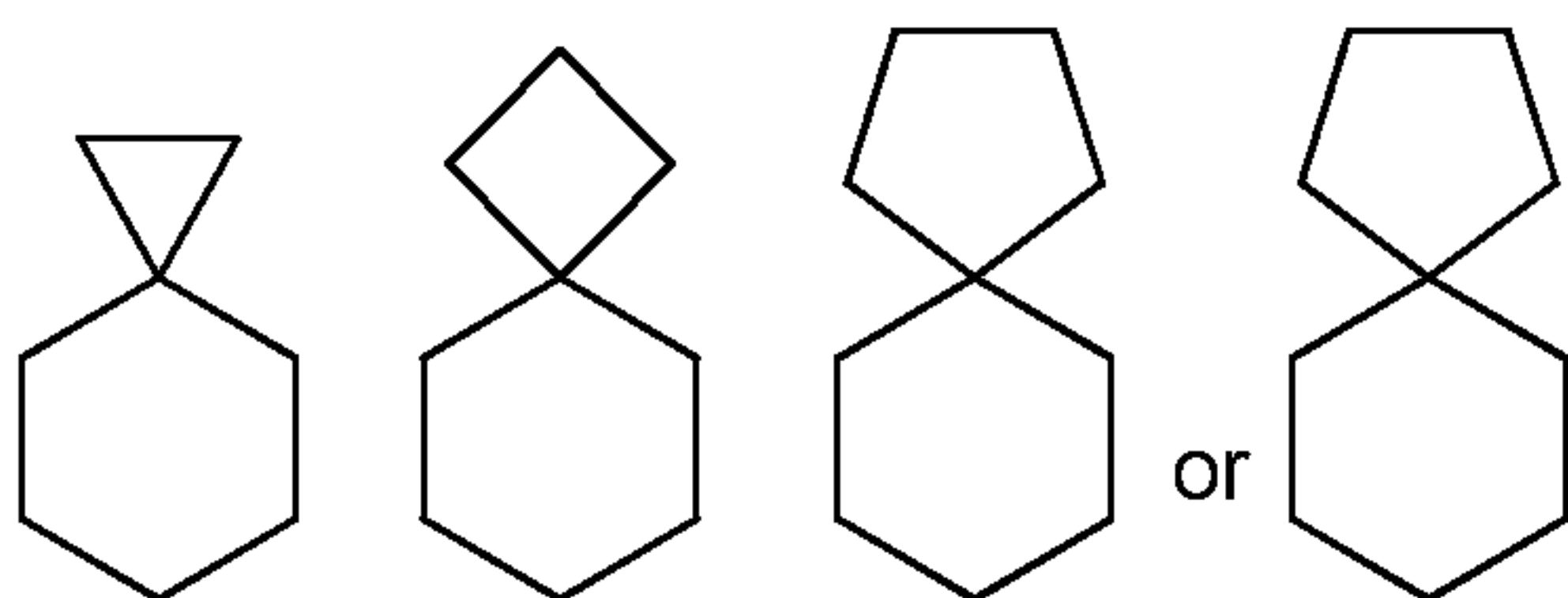
[0035] “Fused” or “ortho-fused” are used interchangeably herein, and refer to two rings that have two atoms and one bond in common, e.g.,



[0036] “Bridged” refers to a ring system containing (1) a bridgehead atom or group of atoms which connect two or more non-adjacent positions of the same ring; or (2) a bridgehead atom or group of atoms which connect two or more positions of different rings of a ring system and does not thereby form an ortho-fused ring, e.g.,



[0037] “Spiro” or “Spiro-fused” refers to a group of atoms which connect to the same atom of a carbocyclic or heterocyclic ring system (geminal attachment), thereby forming a ring, e.g.,



Spiro-fusion at a bridgehead atom is also contemplated.

[0038] “Partially unsaturated” refers to a group that includes at least one double or triple bond. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aromatic groups (*e.g.*, aryl or heteroaryl groups) as herein defined. Likewise, “saturated” refers to a group that does not contain a double or triple bond, *i.e.*, contains all single bonds.

[0039] In some embodiments, aliphatic, alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl groups, as defined herein, are optionally substituted (*e.g.*, “substituted” or “unsubstituted” aliphatic, “substituted” or “unsubstituted” alkyl, “substituted” or “unsubstituted” alkenyl, “substituted” or “unsubstituted” alkynyl, “substituted” or “unsubstituted” carbocyclyl, “substituted” or “unsubstituted” heterocyclyl, “substituted” or “unsubstituted” aryl or “substituted” or “unsubstituted” heteroaryl group). In general, the term “substituted”, whether preceded by the term “optionally” or not, means that at least one

hydrogen present on a group (*e.g.*, a carbon or nitrogen atom) is replaced with a permissible substituent, *e.g.*, a substituent which upon substitution results in a stable compound, *e.g.*, a compound which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, or other reaction. Unless otherwise indicated, a “substituted” group has a substituent at one or more substitutable positions of the group, and when more than one position in any given structure is substituted, the substituent is either the same or different at each position. The term “substituted” is contemplated to include substitution with all permissible substituents of organic compounds, including any of the substituents described herein that results in the formation of a stable compound. The present disclosure contemplates any and all such combinations in order to arrive at a stable compound. For purposes of this disclosure, heteroatoms such as nitrogen may have hydrogen substituents and/or any suitable substituent as described herein which satisfy the valencies of the heteroatoms and results in the formation of a stable moiety.

[0040] Exemplary carbon atom substituents include, but are not limited to, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}_3$, $-\text{SO}_2\text{H}$, $-\text{SO}_3\text{H}$, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{ON}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_2$, $-\text{N}(\text{R}^{\text{bb}})_3^+\text{X}^-$, $-\text{N}(\text{OR}^{\text{cc}})\text{R}^{\text{bb}}$, $-\text{SH}$, $-\text{SR}^{\text{aa}}$, $-\text{SSR}^{\text{cc}}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{CO}_2\text{H}$, $-\text{CHO}$, $-\text{C}(\text{OR}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OCO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{CO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{C}(=\text{O})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OC}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{C}(=\text{NR}^{\text{bb}})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{NR}^{\text{bb}}\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{OR}^{\text{aa}}$, $-\text{OSO}_2\text{R}^{\text{aa}}$, $-\text{S}(=\text{O})\text{R}^{\text{aa}}$, $-\text{OS}(=\text{O})\text{R}^{\text{aa}}$, $-\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{OSi}(\text{R}^{\text{aa}})_3$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{bb}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{S})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{OC}(=\text{O})\text{SR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{OR}^{\text{aa}}$, $-\text{SC}(=\text{O})\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{OP}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{OP}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{OP}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, $-\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{OP}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{NR}^{\text{bb}}\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3$, $-\text{OP}(\text{R}^{\text{cc}})_2$, $-\text{OP}(\text{R}^{\text{cc}})_3$, $-\text{B}(\text{R}^{\text{aa}})_2$, $-\text{B}(\text{OR}^{\text{cc}})_2$, $-\text{BR}^{\text{aa}}(\text{OR}^{\text{cc}})$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

or two geminal hydrogens on a carbon atom are replaced with the group $=\text{O}$, $=\text{S}$, $=\text{NN}(\text{R}^{\text{bb}})_2$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{R}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{C}(=\text{O})\text{OR}^{\text{aa}}$, $=\text{NNR}^{\text{bb}}\text{S}(=\text{O})_2\text{R}^{\text{aa}}$, $=\text{NR}^{\text{bb}}$, or $=\text{NOR}^{\text{cc}}$;

each instance of R^{aa} is, independently, selected from C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{aa} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl,

carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{bb} is, independently, selected from hydrogen, $-OH$, $-OR^{aa}$, $-N(R^{cc})_2$, $-CN$, $-C(=O)R^{aa}$, $-C(=O)N(R^{cc})_2$, $-CO_2R^{aa}$, $-SO_2R^{aa}$, $-C(=NR^{cc})OR^{aa}$, $-C(=NR^{cc})N(R^{cc})_2$, $-SO_2N(R^{cc})_2$, $-SO_2R^{cc}$, $-SO_2OR^{cc}$, $-SOR^{aa}$, $-C(=S)N(R^{cc})_2$, $-C(=O)SR^{cc}$, $-C(=S)SR^{cc}$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)_2N(R^{cc})_2$, $-P(=O)(NR^{cc})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{bb} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{cc} is, independently, selected from hydrogen, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups;

each instance of R^{dd} is, independently, selected from halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OR^{ee}$, $-ON(R^{ff})_2$, $-N(R^{ff})_2$, $-N(R^{ff})_3^+X^-$, $-N(OR^{ee})R^{ff}$, $-SH$, $-SR^{ee}$, $-SSR^{ee}$, $-C(=O)R^{ee}$, $-CO_2H$, $-CO_2R^{ee}$, $-OC(=O)R^{ee}$, $-OCO_2R^{ee}$, $-C(=O)N(R^{ff})_2$, $-OC(=O)N(R^{ff})_2$, $-NR^{ff}C(=O)R^{ee}$, $-NR^{ff}CO_2R^{ee}$, $-NR^{ff}C(=O)N(R^{ff})_2$, $-C(=NR^{ff})OR^{ee}$, $-OC(=NR^{ff})R^{ee}$, $-OC(=NR^{ff})OR^{ee}$, $-C(=NR^{ff})N(R^{ff})_2$, $-OC(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}C(=NR^{ff})N(R^{ff})_2$, $-NR^{ff}SO_2R^{ee}$, $-SO_2N(R^{ff})_2$, $-SO_2R^{ee}$, $-SO_2OR^{ee}$, $-OSO_2R^{ee}$, $-S(=O)R^{ee}$, $-Si(R^{ee})_3$, $-OSi(R^{ee})_3$, $-C(=S)N(R^{ff})_2$, $-C(=O)SR^{ee}$, $-C(=S)SR^{ee}$, $-SC(=S)SR^{ee}$, $-P(=O)_2R^{ee}$, $-P(=O)(R^{ee})_2$, $-OP(=O)(R^{ee})_2$, $-OP(=O)(OR^{ee})_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl, 5–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups, or two geminal R^{dd} substituents can be joined to form $=O$ or $=S$;

each instance of R^{ee} is, independently, selected from C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, and 3–10 membered heteroaryl, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups;

each instance of R^{ff} is, independently, selected from hydrogen, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, 3–10 membered heterocyclyl, C_{6-10} aryl and 5–10 membered heteroaryl, or two R^{ff} groups are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{gg} groups; and

each instance of R^{gg} is, independently, halogen, $-CN$, $-NO_2$, $-N_3$, $-SO_2H$, $-SO_3H$, $-OH$, $-OC_{1-6}$ alkyl, $-ON(C_{1-6}$ alkyl) $_2$, $-N(C_{1-6}$ alkyl) $_2$, $-N(C_{1-6}$ alkyl) $_3^+X^-$, $-NH(C_{1-6}$ alkyl) $_2^+X^-$, $-NH_2(C_{1-6}$ alkyl) $^+X^-$, $-NH_3^+X^-$, $-N(OC_{1-6}$ alkyl)(C_{1-6} alkyl), $-N(OH)(C_{1-6}$ alkyl), $-NH(OH)$, $-SH$, $-SC_{1-6}$ alkyl, $-SS(C_{1-6}$ alkyl), $-C(=O)(C_{1-6}$ alkyl), $-CO_2H$, $-CO_2(C_{1-6}$ alkyl), $-OC(=O)(C_{1-6}$ alkyl), $-OCO_2(C_{1-6}$ alkyl), $-C(=O)NH_2$, $-C(=O)N(C_{1-6}$ alkyl) $_2$, $-OC(=O)NH(C_{1-6}$ alkyl), $-NHC(=O)(C_{1-6}$ alkyl), $-N(C_{1-6}$ alkyl) $C(=O)(C_{1-6}$ alkyl), $-NHCO_2(C_{1-6}$ alkyl), $-NHC(=O)N(C_{1-6}$ alkyl) $_2$, $-NHC(=O)NH(C_{1-6}$ alkyl), $-NHC(=O)NH_2$, $-C(=NH)O(C_{1-6}$ alkyl), $-OC(=NH)(C_{1-6}$ alkyl), $-OC(=NH)OC_{1-6}$ alkyl, $-C(=NH)N(C_{1-6}$ alkyl) $_2$, $-C(=NH)NH(C_{1-6}$ alkyl), $-C(=NH)NH_2$, $-OC(=NH)N(C_{1-6}$ alkyl) $_2$, $-OC(NH)NH(C_{1-6}$ alkyl), $-OC(NH)NH_2$, $-NHC(NH)N(C_{1-6}$ alkyl) $_2$, $-NHC(=NH)NH_2$, $-NHSO_2(C_{1-6}$ alkyl), $-SO_2N(C_{1-6}$ alkyl) $_2$, $-SO_2NH(C_{1-6}$ alkyl), $-SO_2NH_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2OC_{1-6}$ alkyl, $-OSO_2C_{1-6}$ alkyl, $-SOC_{1-6}$ alkyl, $-Si(C_{1-6}$ alkyl) $_3$, $-OSi(C_{1-6}$ alkyl) $_3$, $-C(=S)N(C_{1-6}$ alkyl) $_2$, $-C(=S)NH(C_{1-6}$ alkyl), $-C(=S)NH_2$, $-C(=O)S(C_{1-6}$ alkyl), $-C(=S)SC_{1-6}$ alkyl, $-SC(=S)SC_{1-6}$ alkyl, $-P(=O)_2(C_{1-6}$ alkyl), $-P(=O)(C_{1-6}$ alkyl) $_2$, $-OP(=O)(C_{1-6}$ alkyl) $_2$, $-OP(=O)(OC_{1-6}$ alkyl) $_2$, C_{1-6} alkyl, C_{1-6} perhaloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-10} carbocyclyl, C_{6-10} aryl, 3–10 membered heterocyclyl, 5–10 membered heteroaryl; or two geminal R^{gg} substituents can be joined to form $=O$ or $=S$; wherein X^- is a counterion.

[0041] A “counterion” or “anionic counterion” is a negatively charged group associated with a cationic quaternary amino group in order to maintain electronic neutrality. Exemplary counterions include halide ions (*e.g.*, F^- , Cl^- , Br^- , I^-), NO_3^- , ClO_4^- , OH^- , $H_2PO_4^-$, HSO_4^- , sulfonate ions (*e.g.*, methanesulfonate, trifluoromethanesulfonate, *p*-toluenesulfonate, benzenesulfonate, 10-camphor sulfonate, naphthalene-2-sulfonate, naphthalene-1-sulfonic acid-5-sulfonate, ethan-1-sulfonic acid-2-sulfonate, and the like), and carboxylate ions (*e.g.*, acetate, ethanoate, propanoate, benzoate, glycerate, lactate, tartrate, glycolate, and the like).

[0042] “Halo” or “halogen” refers to fluorine (fluoro, $-F$), chlorine (chloro, $-Cl$), bromine (bromo, $-Br$), or iodine (iodo, $-I$).

[0043] Nitrogen atoms can be substituted or unsubstituted as valency permits, and include primary, secondary, tertiary, and quarternary nitrogen atoms. Exemplary nitrogen atom substituents include, but are not limited to, hydrogen, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CN}$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{bb}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$, $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{P}(=\text{O})(\text{NR}^{\text{cc}})_2$, C_{1-10} alkyl, C_{1-10} perhaloalkyl, C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl, or two R^{cc} groups attached to a nitrogen atom are joined to form a 3–14 membered heterocyclyl or 5–14 membered heteroaryl ring, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa} , R^{bb} , R^{cc} and R^{dd} are as defined above.

[0044] In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group). Nitrogen protecting groups include, but are not limited to, $-\text{OH}$, $-\text{OR}^{\text{aa}}$, $-\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$, $-\text{C}(=\text{O})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{CO}_2\text{R}^{\text{aa}}$, $-\text{SO}_2\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{R}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{OR}^{\text{aa}}$, $-\text{C}(=\text{NR}^{\text{cc}})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{N}(\text{R}^{\text{cc}})_2$, $-\text{SO}_2\text{R}^{\text{cc}}$, $-\text{SO}_2\text{OR}^{\text{cc}}$, $-\text{SOR}^{\text{aa}}$, $-\text{C}(=\text{S})\text{N}(\text{R}^{\text{cc}})_2$, $-\text{C}(=\text{O})\text{SR}^{\text{cc}}$, $-\text{C}(=\text{S})\text{SR}^{\text{cc}}$, C_{1-10} alkyl (*e.g.*, aralkyl, heteroaralkyl), C_{2-10} alkenyl, C_{2-10} alkynyl, C_{3-10} carbocyclyl, 3–14 membered heterocyclyl, C_{6-14} aryl, and 5–14 membered heteroaryl groups, wherein each alkyl, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aralkyl, aryl, and heteroaryl is independently substituted with 0, 1, 2, 3, 4, or 5 R^{dd} groups, and wherein R^{aa} , R^{bb} , R^{cc} , and R^{dd} are as defined herein. Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0045] Amide nitrogen protecting groups (*e.g.*, $-\text{C}(=\text{O})\text{R}^{\text{aa}}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, *N*-benzoylphenylalanyl derivative, benzamide, *p*-phenylbenzamide, *o*-nitrophenylacetamide, *o*-nitrophenoxyacetamide, acetoacetamide, (*N'*-dithiobenzyloxyacylamino)acetamide, 3-(*p*-hydroxyphenyl)propanamide, 3-(*o*-nitrophenyl)propanamide, 2-methyl-2-(*o*-nitrophenoxy)propanamide, 2-methyl-2-(*o*-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, *o*-nitrocinnamide, *N*-acetylmethionine, *o*-nitrobenzamide, and *o*-(benzoyloxymethyl)benzamide.

[0046] Carbamate nitrogen protecting groups (*e.g.*, $-\text{C}(=\text{O})\text{OR}^{\text{aa}}$) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl carbamate, 2,7-di-*t*-butyl-[9-(10,10-dioxo-10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamantyl)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-*t*-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenyl)ethyl carbamate (Bpoc), 1-(3,5-di-*t*-butylphenyl)-1-methylethyl carbamate (*t*-Bumeoc), 2-(2'- and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(*N,N*-dicyclohexylcarboxamido)ethyl carbamate, *t*-butyl carbamate (BOC), 1-adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, *N*-hydroxypiperidinyl carbamate, alkylidithio carbamate, benzyl carbamate (Cbz), *p*-methoxybenzyl carbamate (Moz), *p*-nitrobenzyl carbamate, *p*-bromobenzyl carbamate, *p*-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (MsZ), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonylethyl carbamate, 2-(*p*-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, *m*-chloro-*p*-acyloxybenzyl carbamate, *p*-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), *m*-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, *o*-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(*o*-nitrophenyl)methyl carbamate, *t*-amyl carbamate, *S*-benzyl thiocarbamate, *p*-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, *p*-decyloxybenzyl carbamate, 2,2-dimethoxyacetylvinyl carbamate, *o*-(*N,N*-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(*N,N*-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, *p*-(*p*'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(*p*-phenylazophenyl)ethyl

carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, *p*-(phenylazo)benzyl carbamate, 2,4,6-tri-*t*-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[0047] Sulfonamide nitrogen protecting groups (*e.g.*, $-S(=O)_2R^{aa}$) include, but are not limited to, *p*-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β -trimethylsilylethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzyisulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[0048] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, *N'*-*p*-toluenesulfonylaminoacyl derivative, *N'*-phenylaminothioacyl derivative, *N*-benzoylphenylalanyl derivative, *N*-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, *N*-phthalimide, *N*-dithiasuccinimide (Dts), *N*-2,3-diphenylmaleimide, *N*-2,5-dimethylpyrrole, *N*-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, *N*-methylamine, *N*-allylamine, *N*-[2-(trimethylsilyl)ethoxy]methylamine (SEM), *N*-3-acetoxypyrrolamine, *N*-(1-isopropyl-4-nitro-2-oxo-3-pyrroline-3-yl)amine, quaternary ammonium salts, *N*-benzylamine, *N*-di(4-methoxyphenyl)methylamine, *N*-5-dibenzosuberonylamine, *N*-triphenylmethylamine (Tr), *N*-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), *N*-9-phenylfluorenylamine (PhF), *N*-2,7-dichloro-9-fluorenylmethylethylamine, *N*-ferrocenylmethylamino (Fcm), *N*-2-picolylamino *N'*-oxide, *N*-1,1-dimethylthiomethylethylamine, *N*-benzylideneamine, *N*-*p*-methoxybenzylideneamine, *N*-diphenylmethylethylamine, *N*-[(2-pyridyl)mesityl]methylethylamine, *N*-(*N'*,*N'*-dimethylaminomethylethyl)amine, *N,N'*-isopropylidenediamine, *N*-*p*-nitrobenzylideneamine, *N*-salicylideneamine, *N*-5-chlorosalicylideneamine, *N*-(5-chloro-2-hydroxyphenyl)phenylmethylethylamine, *N*-cyclohexylideneamine, *N*-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, *N*-borane derivative, *N*-diphenylborinic acid derivative, *N*-[phenyl(pentaacylchromium- or tungsten)acyl]amine, *N*-copper chelate, *N*-zinc chelate, *N*-nitroamine, *N*-nitrosoamine, amine *N*-oxide, diphenylphosphinamide (Dpp),

dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, *o*-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys).

[0049] In certain embodiments, the substituent present on an oxygen atom is an oxygen protecting group (also referred to as a hydroxyl protecting group). Oxygen protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-Si(R^{aa})_3$, $-P(R^{cc})_2$, $-P(R^{cc})_3$, $-P(=O)_2R^{aa}$, $-P(=O)(R^{aa})_2$, $-P(=O)(OR^{cc})_2$, $-P(=O)_2N(R^{bb})_2$, and $-P(=O)(NR^{bb})_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein. Oxygen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

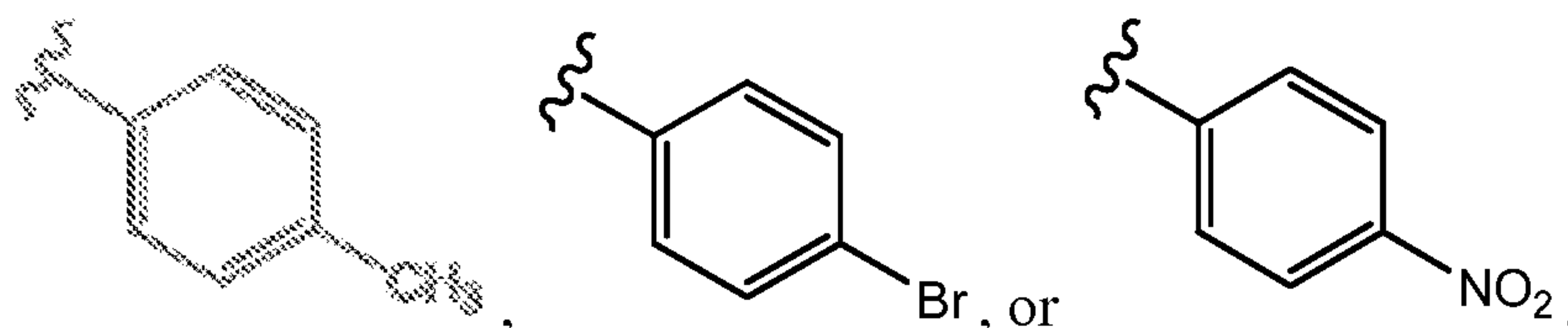
[0050] Exemplary oxygen protecting groups include, but are not limited to, methyl, methoxymethyl (MOM), methylthiomethyl (MTM), *t*-butylthiomethyl, (phenyldimethylsilyl)methoxymethyl (SMOM), benzyloxymethyl (BOM), *p*-methoxybenzyloxymethyl (PMBM), (4-methoxyphenoxy)methyl (*p*-AOM), guaiacolmethyl (GUM), *t*-butoxymethyl, 4-pentenylloxymethyl (POM), siloxymethyl, 2-methoxyethoxymethyl (MEM), 2,2,2-trichloroethoxymethyl, bis(2-chloroethoxy)methyl, 2-(trimethylsilyl)ethoxymethyl (SEMOR), tetrahydropyranyl (THP), 3-bromotetrahydropyranyl, tetrahydrothiopyranyl, 1-methoxycyclohexyl, 4-methoxytetrahydropyranyl (MTHP), 4-methoxytetrahydrothiopyranyl, 4-methoxytetrahydrothiopyranyl S,S-dioxide, 1-[(2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl (CTMP), 1,4-dioxan-2-yl, tetrahydrofuranyl, tetrahydrothiofuranyl, 2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl, 1-ethoxyethyl, 1-(2-chloroethoxy)ethyl, 1-methyl-1-methoxyethyl, 1-methyl-1-benzyloxyethyl, 1-methyl-1-benzyloxy-2-fluoroethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, 2-(phenylselenyl)ethyl, *t*-butyl, allyl, *p*-chlorophenyl, *p*-methoxyphenyl, 2,4-dinitrophenyl, benzyl (Bn), *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *o*-nitrobenzyl, *p*-nitrobenzyl, *p*-halobenzyl, 2,6-dichlorobenzyl, *p*-cyanobenzyl, *p*-phenylbenzyl, 2-picolyl, 4-picolyl, 3-methyl-2-picolyl *N*-oxido, diphenylmethyl, *p,p'*-dinitrobenzhydryl, 5-dibenzosuberyl, triphenylmethyl, α -naphthyldiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, di(*p*-methoxyphenyl)phenylmethyl, tri(*p*-methoxyphenyl)methyl, 4-(4'-

bromophenacyloxyphenyl)diphenylmethyl, 4,4',4''-tris(4,5-dichlorophthalimidophenyl)methyl, 4,4',4''-tris(levulinoyloxyphenyl)methyl, 4,4',4''-tris(benzoyloxyphenyl)methyl, 3-(imidazol-1-yl)bis(4',4''-dimethoxyphenyl)methyl, 1,1-bis(4-methoxyphenyl)-1'-pyrenylmethyl, 9-anthryl, 9-(9-phenyl)xanthenyl, 9-(9-phenyl-10-oxo)anthryl, 1,3-benzodisulfuran-2-yl, benzisothiazolyl S,S-dioxido, trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyl (TIPS), dimethylisopropylsilyl (IPDMS), diethylisopropylsilyl (DEIPS), dimethylhexylsilyl, *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), tribenzylsilyl, tri-*p*-xylylsilyl, triphenylsilyl, diphenylmethylsilyl (DPMS), *t*-butylmethoxyphenylsilyl (TBMPS), formate, benzoylformate, acetate, chloroacetate, dichloroacetate, trichloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, phenoxyacetate, *p*-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate (levulinate), 4,4-(ethylenedithio)pentanoate (levulinoyldithioacetal), pivaloate, adamantoate, crotonate, 4-methoxycrotonate, benzoate, *p*-phenylbenzoate, 2,4,6-trimethylbenzoate (mesitoate), *t*-butyl carbonate (BOC), alkyl methyl carbonate, 9-fluorenylmethyl carbonate (Fmoc), alkyl ethyl carbonate, alkyl 2,2,2-trichloroethyl carbonate (Troc), 2-(trimethylsilyl)ethyl carbonate (TMSEC), 2-(phenylsulfonyl) ethyl carbonate (Psec), 2-(triphenylphosphonio) ethyl carbonate (Peoc), alkyl isobutyl carbonate, alkyl vinyl carbonate, alkyl allyl carbonate, alkyl *p*-nitrophenyl carbonate, alkyl benzyl carbonate, alkyl *p*-methoxybenzyl carbonate, alkyl 3,4-dimethoxybenzyl carbonate, alkyl *o*-nitrobenzyl carbonate, alkyl *p*-nitrobenzyl carbonate, alkyl *S*-benzyl thiocarbonate, 4-ethoxy-1-naphthyl carbonate, methyl dithiocarbonate, 2-iodobenzoate, 4-azidobutyrate, 4-nitro-4-methylpentanoate, *o*-(dibromomethyl)benzoate, 2-formylbenzenesulfonate, 2-(methylthiomethoxy)ethyl, 4-(methylthiomethoxy)butyrate, 2-(methylthiomethoxymethyl)benzoate, 2,6-dichloro-4-methylphenoxyacetate, 2,6-dichloro-4-(1,1,3,3-tetramethylbutyl)phenoxyacetate, 2,4-bis(1,1-dimethylpropyl)phenoxyacetate, chlorodiphenylacetate, isobutyrate, monosuccinoate, (*E*)-2-methyl-2-butenate, *o*-(methoxyacyl)benzoate, α -naphthoate, nitrate, alkyl *N,N,N',N'*-tetramethylphosphorodiamidate, alkyl *N*-phenylcarbamate, borate, dimethylphosphinothioyl, alkyl 2,4-dinitrophenylsulfenate, sulfate, methanesulfonate (mesylate), benzylsulfonate, and tosylate (Ts).

[0051] In certain embodiments, the substituent present on a sulfur atom is a sulfur protecting group (also referred to as a thiol protecting group). Sulfur protecting groups include, but are not limited to, $-R^{aa}$, $-N(R^{bb})_2$, $-C(=O)SR^{aa}$, $-C(=O)R^{aa}$, $-CO_2R^{aa}$, $-C(=O)N(R^{bb})_2$, $-C(=NR^{bb})R^{aa}$, $-C(=NR^{bb})OR^{aa}$, $-C(=NR^{bb})N(R^{bb})_2$, $-S(=O)R^{aa}$, $-SO_2R^{aa}$, $-$

$\text{Si}(\text{R}^{\text{aa}})_3$, $-\text{P}(\text{R}^{\text{cc}})_2$, $-\text{P}(\text{R}^{\text{cc}})_3$, $-\text{P}(=\text{O})_2\text{R}^{\text{aa}}$, $-\text{P}(=\text{O})(\text{R}^{\text{aa}})_2$, $-\text{P}(=\text{O})(\text{OR}^{\text{cc}})_2$, $-\text{P}(=\text{O})_2\text{N}(\text{R}^{\text{bb}})_2$, and $-\text{P}(=\text{O})(\text{NR}^{\text{bb}})_2$, wherein R^{aa} , R^{bb} , and R^{cc} are as defined herein. Sulfur protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[0052] As used herein, a “leaving group”, or “LG”, is a term understood in the art to refer to a molecular fragment that departs with a pair of electrons upon heterolytic bond cleavage, wherein the molecular fragment is an anion or neutral molecule. See, for example, Smith, March *Advanced Organic Chemistry* 6th ed. (501–502). Examples of suitable leaving groups include, but are not limited to, halides (such as chloride, bromide, or iodide), alkoxycarbonyloxy, aryloxy, carbonyloxy, alkanesulfonyloxy, arenesulfonyloxy, alkyl-carbonyloxy (e.g., acetoxy), arylcarbonyloxy, aryloxy, methoxy, N,O-dimethylhydroxylamino, pixyl, haloformates, $-\text{NO}_2$, trialkylammonium, and arylodonium salts. In some embodiments, the leaving group is a sulfonic acid ester. In some embodiments, the sulfonic acid ester comprises the formula $-\text{OSO}_2\text{R}^{\text{LG1}}$ wherein R^{LG1} is selected from the group consisting alkyl optionally, alkenyl optionally substituted, heteroalkyl optionally substituted, aryl optionally substituted, heteroaryl optionally substituted, arylalkyl optionally substituted, and heterarylalkyl optionally substituted. In some embodiments, R^{LG1} is substituted or unsubstituted $\text{C}_1\text{--C}_6$ alkyl. In some embodiments, R^{LG1} is methyl. In some embodiments, R^{LG1} is $-\text{CF}_3$. In some embodiments, R^{LG1} is substituted or unsubstituted aryl. In some embodiments, R^{LG1} is substituted or unsubstituted phenyl. In some embodiments R^{LG1} is:



[0053] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The present disclosure is not intended to be limited in any manner by the above exemplary listing of substituents.

[0054] “Pharmaceutically acceptable salt” refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and other animals without undue toxicity, irritation, allergic response, and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, Berge *et al.* describe pharmaceutically acceptable salts in

detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds describe herein include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, *p*-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, quaternary salts.

[0055] A “subject” to which administration is contemplated includes, but is not limited to, humans (*e.g.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.*, infant, child, adolescent) or adult subject (*e.g.*, young adult, middle-aged adult or senior adult)) and/or other non-human animals, for example, non-human mammals (*e.g.*, primates (*e.g.*, cynomolgus monkeys, rhesus monkeys); commercially relevant mammals such as cattle, pigs, horses, sheep, goats, cats, and/or dogs), birds (*e.g.*, commercially relevant birds such as chickens, ducks, geese, and/or turkeys), rodents (*e.g.*, rats and/or mice), reptiles, amphibians, and fish. In certain embodiments, the non-human animal is a mammal. The non-human animal may be a male or female at any stage of development. A non-human animal may be a transgenic animal.

[0056] “Condition,” “disease,” and “disorder” are used interchangeably herein.

[0057] “Treat,” “treating” and “treatment” encompasses an action that occurs while a subject is suffering from a condition which reduces the severity of the condition or retards or slows the progression of the condition (“therapeutic treatment”). “Treat,” “treating” and “treatment” also encompasses an action that occurs before a subject begins to suffer from the

condition and which inhibits or reduces the severity of the condition (“prophylactic treatment”).

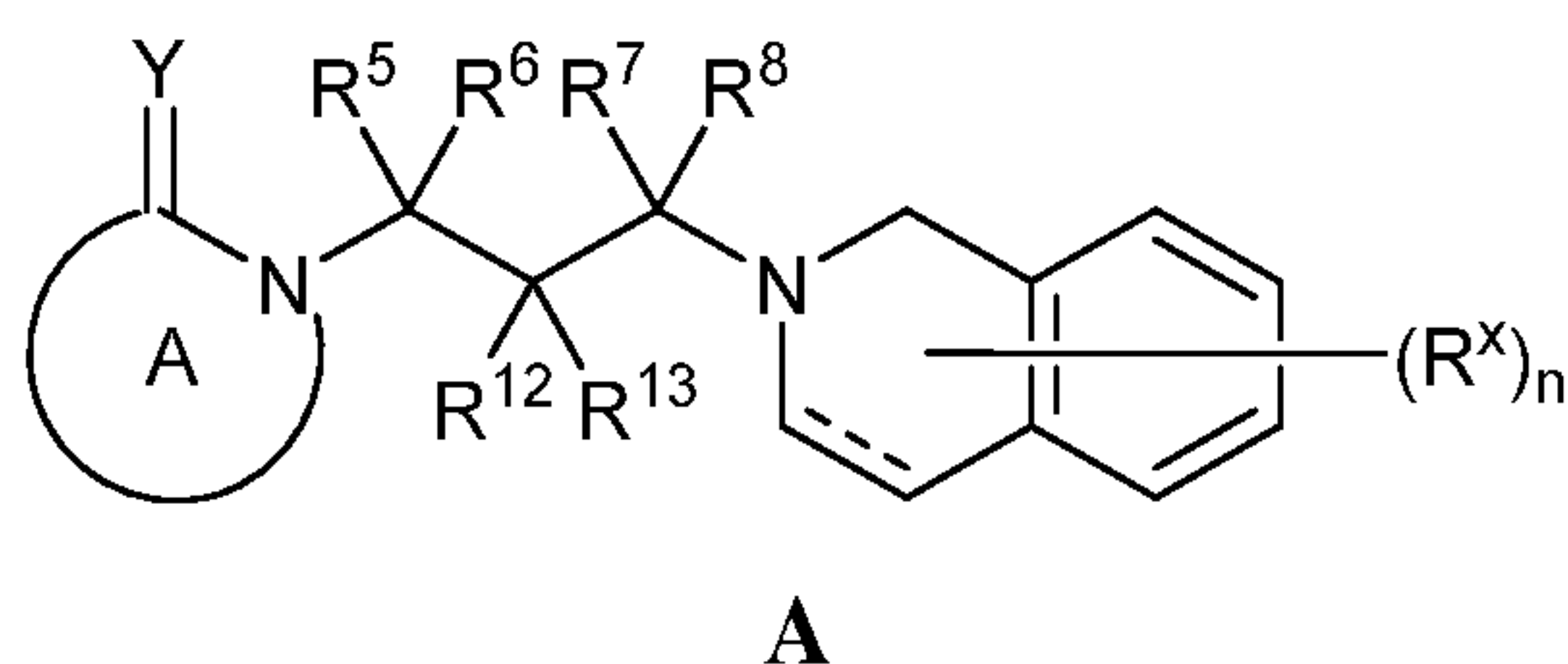
[0058] An “effective amount” of a compound refers to an amount sufficient to elicit the desired biological response, *e.g.*, treat the condition. As will be appreciated by those of ordinary skill in this art, the effective amount of a compound described herein may vary depending on such factors as the desired biological endpoint, the pharmacokinetics of the compound, the condition being treated, the mode of administration, and the age and health of the subject. An effective amount encompasses therapeutic and prophylactic treatment.

[0059] A “therapeutically effective amount” of a compound is an amount sufficient to provide a therapeutic benefit in the treatment of a condition or to delay or minimize one or more symptoms associated with the condition. A therapeutically effective amount of a compound means an amount of therapeutic agent, alone or in combination with other therapies, which provides a therapeutic benefit in the treatment of the condition. The term “therapeutically effective amount” can encompass an amount that improves overall therapy, reduces or avoids symptoms or causes of the condition, or enhances the therapeutic efficacy of another therapeutic agent.

[0060] A “prophylactically effective amount” of a compound is an amount sufficient to prevent a condition, or one or more symptoms associated with the condition or prevent its recurrence. A prophylactically effective amount of a compound means an amount of a therapeutic agent, alone or in combination with other agents, which provides a prophylactic benefit in the prevention of the condition. The term “prophylactically effective amount” can encompass an amount that improves overall prophylaxis or enhances the prophylactic efficacy of another prophylactic agent.

[0061] As used herein, the term “methyltransferase” represents transferase class enzymes that are able to transfer a methyl group from a donor molecule to an acceptor molecule, *e.g.*, an amino acid residue of a protein or a nucleic base of a DNA molecule. Methyltransferases typically use a reactive methyl group bound to sulfur in S-adenosyl methionine (SAM) as the methyl donor. In some embodiments, a methyltransferase described herein is a protein methyltransferase. In some embodiments, a methyltransferase described herein is a histone methyltransferase. Histone methyltransferases (HMT) are histone-modifying enzymes, (including histone-lysine N-methyltransferase and histone-arginine N-methyltransferase), that catalyze the transfer of one or more methyl groups to lysine and arginine residues of histone proteins. In certain embodiments, a methyltransferase described herein is a histone-arginine N-methyltransferase.

[0062] As generally described above, provided herein are compounds useful as PRMT5 inhibitors. In some embodiments, the present disclosure provides a compound of Formula (A):



or a pharmaceutically acceptable salt thereof,
wherein

===== represents a single or double bond;

R^{12} is hydrogen, halogen, or optionally substituted C_{1-3} alkyl;

R^{13} is hydrogen, halogen, optionally substituted C_{1-3} alkyl, $-NR^{A1}R^{A2}$, or $-OR^1$;

R^{A1} and R^{A2} are each independently hydrogen, optionally substituted C_{1-3} alkyl, a nitrogen protecting group, or R^{A1} and R^{A2} are taken together with the intervening nitrogen atom to form an optionally substituted 3-6 membered heterocyclic ring;

Ring A is an optionally substituted, 5- to 12-membered, monocyclic or bicyclic, heterocyclyl or heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^1 is hydrogen, R^Z , or $-C(O)R^Z$, wherein R^Z is optionally substituted C_{1-6} alkyl;

Y is O or S;

R^5 , R^6 , R^7 , and R^8 are each independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, -OR', and $-N(R'')_2$;

R' is hydrogen or optionally substituted aliphatic;

each R'' is independently hydrogen or optionally substituted aliphatic, or two R'' are taken together with their intervening atoms to form a heterocyclic ring; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits.

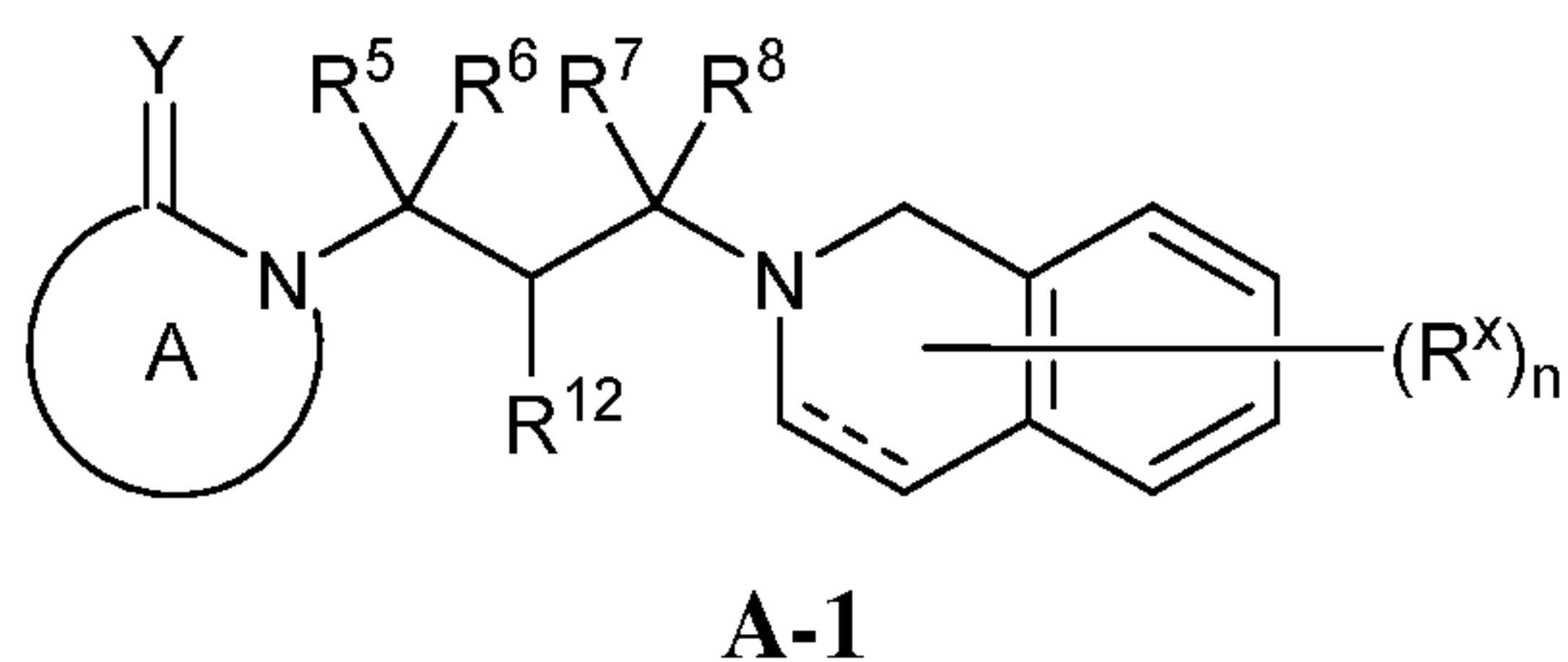
[0063] In some embodiments, the carbon attached to R^{12} has (*S*)-stereochemistry. In some embodiments, the carbon attached to R^{12} has (*R*)-stereochemistry. In some embodiments, the carbon attached to R^{13} has (*S*)-stereochemistry. In some embodiments, the carbon attached to R^{13} has (*R*)-stereochemistry. In some embodiments, R^{12} is hydrogen. In some embodiments, R^{13} is hydrogen. In some embodiments, both R^{12} and R^{13} are hydrogen. In some

embodiments, R^{12} is optionally substituted C_{1-3} alkyl. In some embodiments, R^{13} is optionally substituted C_{1-3} alkyl. In some embodiments, both R^{12} and R^{13} are optionally substituted C_{1-3} alkyl. In some embodiments, R^{12} is halogen *e.g.*, fluoro, bromo, chloro, or iodo, provided that R^{13} is not $-OR^1$. In some embodiments, R^{13} is halogen *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, both R^{12} and R^{13} are halogen *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, R^{12} is halogen *e.g.*, fluoro, bromo, chloro, or iodo and R^{13} is optionally substituted C_{1-3} alkyl. In some embodiments, R^{12} is optionally substituted C_{1-3} alkyl and R^{13} is halogen *e.g.*, fluoro, bromo, chloro, or iodo. In some embodiments, R^{13} is $-OR^1$. In some embodiments, R^{12} is optionally substituted C_{1-3} alkyl and R^{13} is $-OR^1$. In some embodiments, R^{12} is hydrogen and R^{13} is $-OR^1$. In some embodiments, R^{12} is hydrogen and R^{13} optionally substituted C_{1-3} alkyl. In some embodiments, R^{12} is optionally substituted C_{1-3} alkyl and R^{13} is hydrogen. In some embodiments, R^{12} is halogen *e.g.*, fluoro, bromo, chloro, or iodo and R^{13} is hydrogen. In some embodiments, R^{12} is hydrogen and R^{13} is halogen *e.g.*, fluoro, bromo, chloro, or iodo.

[0064] As generally defined above, R^{12} is hydrogen, halogen, or optionally substituted C_{1-3} alkyl. In certain embodiments, R^{12} is hydrogen. In certain embodiments, R^{12} is optionally substituted C_{1-3} alkyl, *e.g.*, optionally substituted with halogen. In certain embodiments, R^{12} is optionally substituted C_1 alkyl, *e.g.*, methyl or trifluoromethyl. In certain embodiments, R^{12} is optionally substituted C_2 alkyl, *e.g.*, ethyl. In certain embodiments, R^{12} is optionally substituted C_3 alkyl, *e.g.*, propyl. In certain embodiments, R^{12} is fluoro, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is chloro, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is bromo, provided that R^{13} is not $-OR^1$. In certain embodiments, R^{12} is iodo, provided that R^{13} is not $-OR^1$.

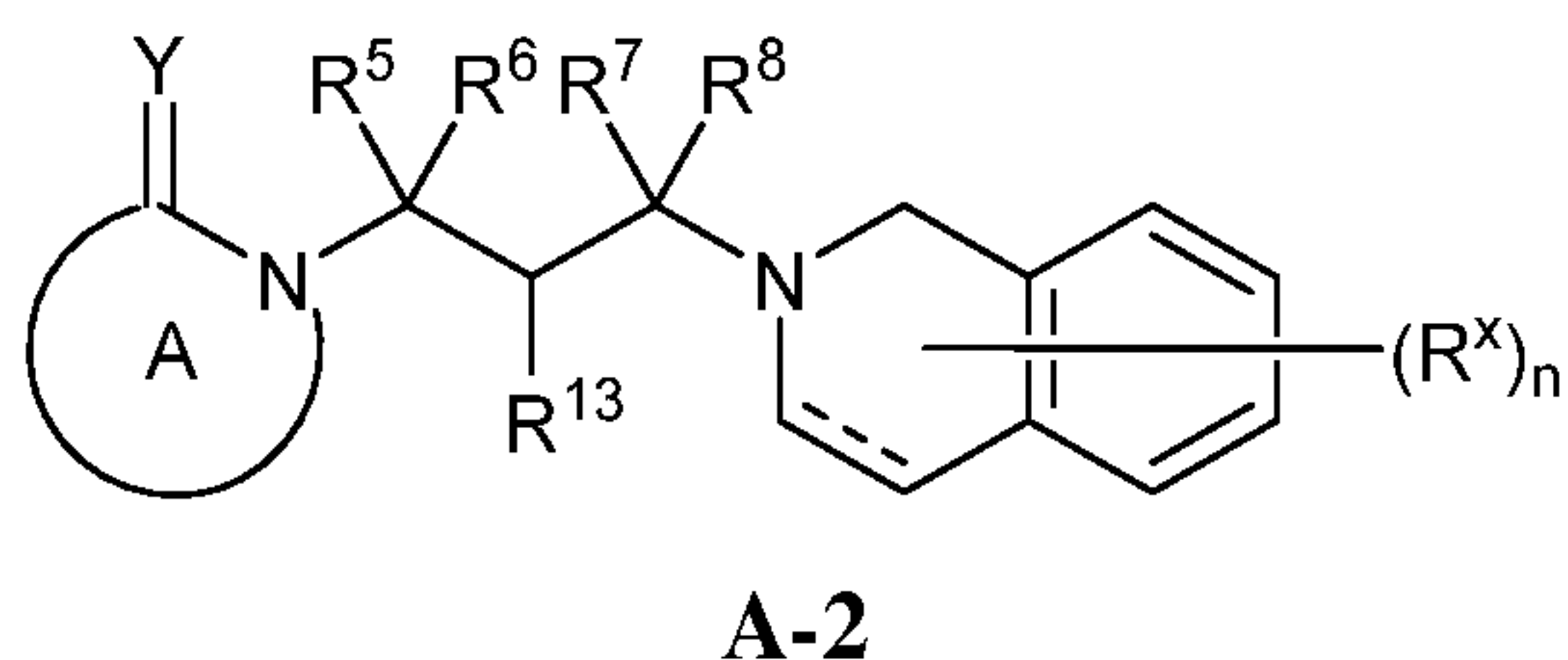
[0065] As generally defined above, R^{13} is hydrogen, halogen, optionally substituted C_{1-3} alkyl, $-NR^{A1}R^{A2}$ or $-OR^1$. In certain embodiments, R^{13} is hydrogen. In certain embodiments, R^{13} is optionally substituted C_{1-3} alkyl, *e.g.*, optionally substituted with halogen. In certain embodiments, R^{13} is optionally substituted C_1 alkyl, *e.g.*, methyl or trifluoromethyl. In certain embodiments, R^{13} is optionally substituted C_2 alkyl, *e.g.*, ethyl. In certain embodiments, R^{13} is optionally substituted C_3 alkyl, *e.g.*, propyl. In certain embodiments, R^{13} is fluoro. In certain embodiments, R^{13} is chloro. In certain embodiments, R^{13} is bromo. In certain embodiments, R^{13} is iodo.

[0066] For example, in some embodiments of Formula (A), wherein R^{13} is hydrogen, the present disclosure provides a compound of Formula (A-1):



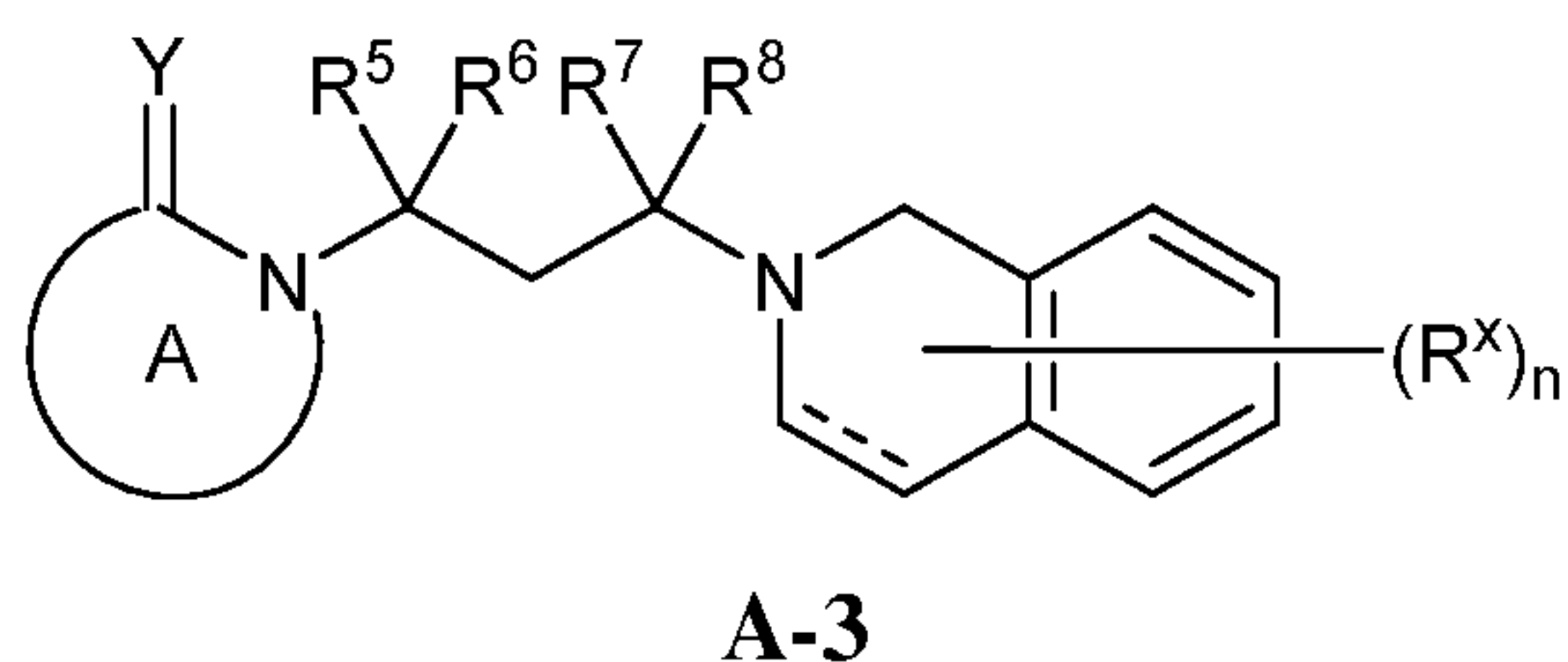
or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R^5 , R^6 , R^7 , R^8 , R^x , R^{12} , and n are as described herein.

[0067] In some embodiments of Formula (A), wherein R^{12} is hydrogen, the present disclosure provides a compound of Formula (A-2):



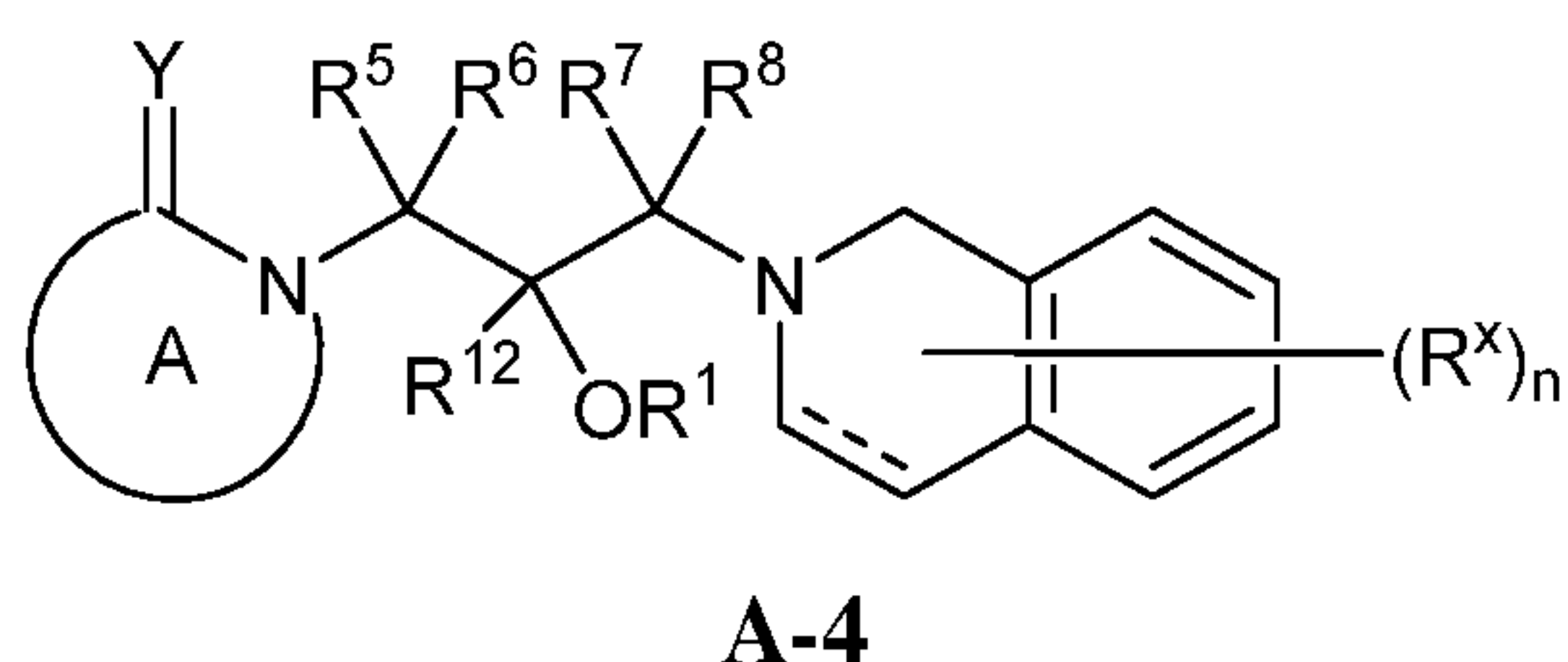
or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R^5 , R^6 , R^7 , R^8 , R^x , R^{13} , and n are as described herein.

[0068] In some embodiments of Formula (A), wherein both R^{12} and R^{13} are hydrogen, the present disclosure provides a compound of Formula (A-3):



or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R^5 , R^6 , R^7 , R^8 , R^x , and n are as described herein.

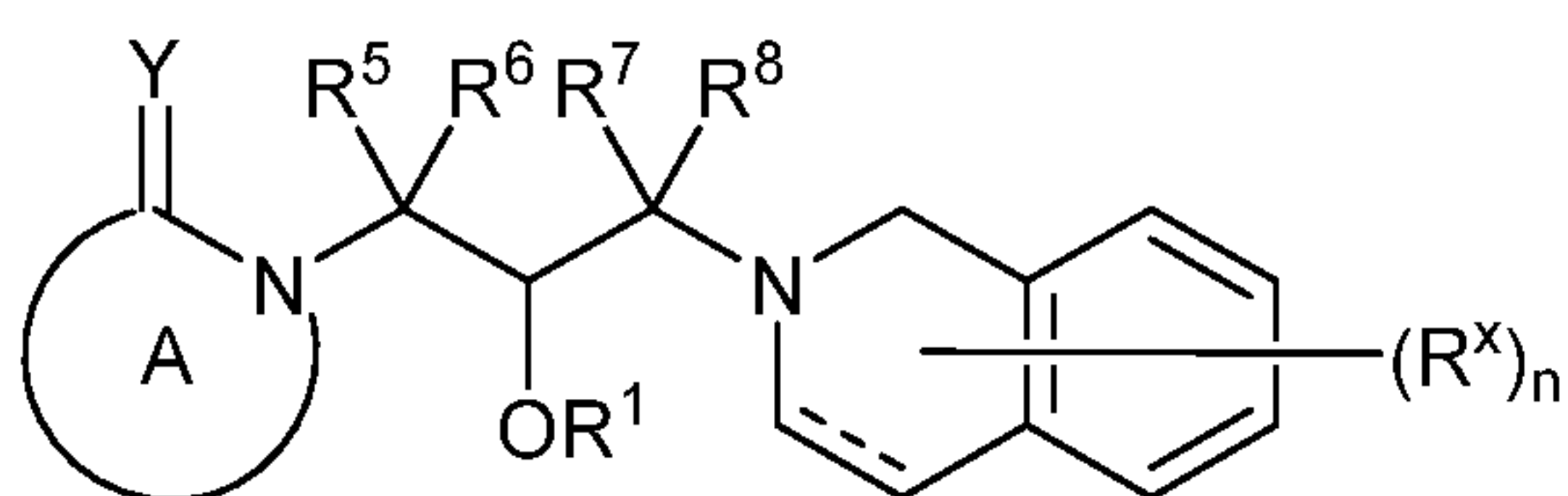
[0069] In some embodiments of Formula (A), wherein R^{13} is $-OR^1$, the present disclosure provides a compound of Formula (A-4):



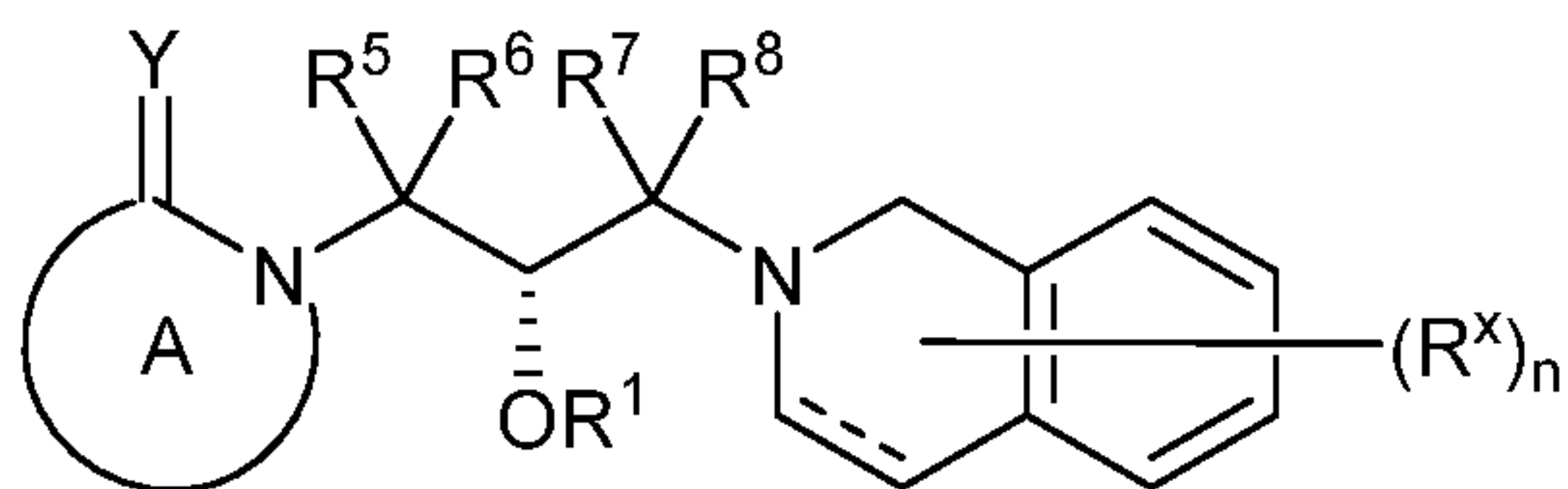
or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R^1 , R^5 , R^6 , R^7 , R^8 , R^x , R^{12} , and n are as described herein.

[illegible]

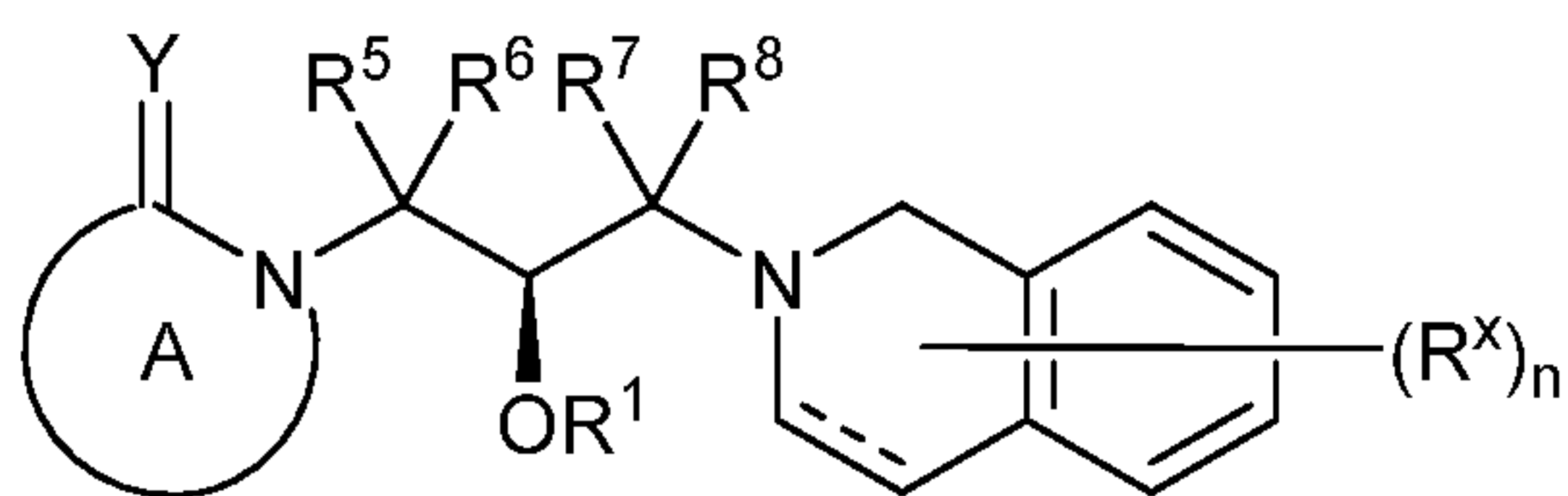
[0071] In some embodiments, the present disclosure provides a compound of Formula (I):



[0072] In certain embodiments, a provided compound is of Formula **(I-a)**:

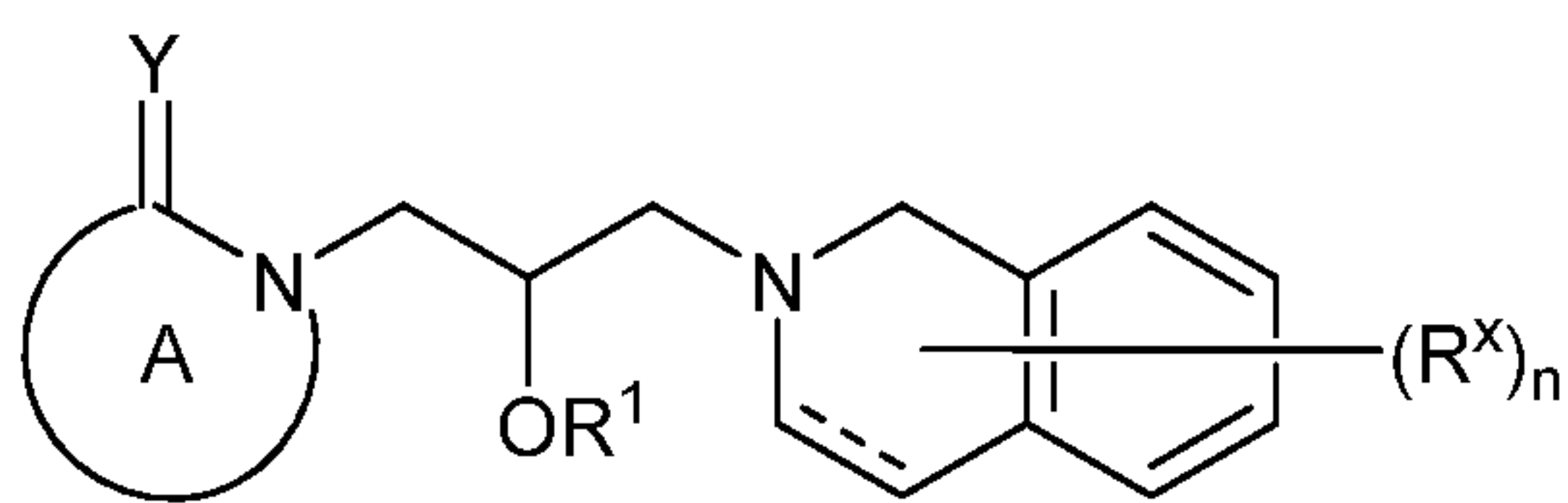


[0073] In certain embodiments, a provided compound is of Formula **(I-b)**:



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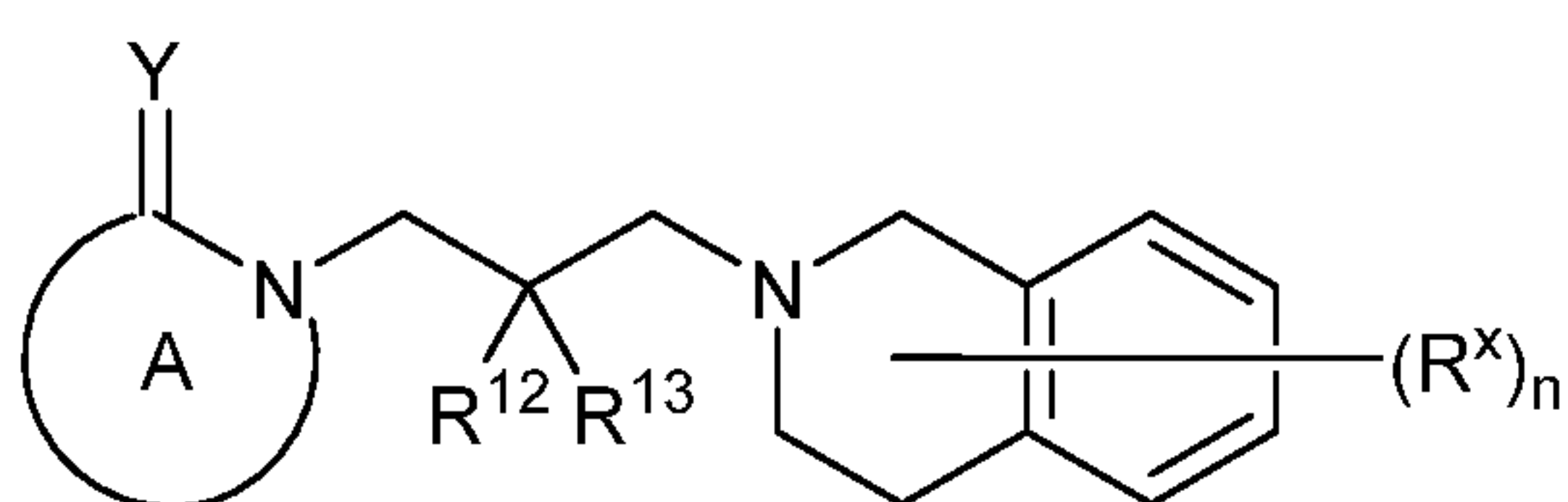
[0074] In certain embodiments, a provided compound is of Formula (**I-c**):



I-c

or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R¹, R^x, and n are as described herein.

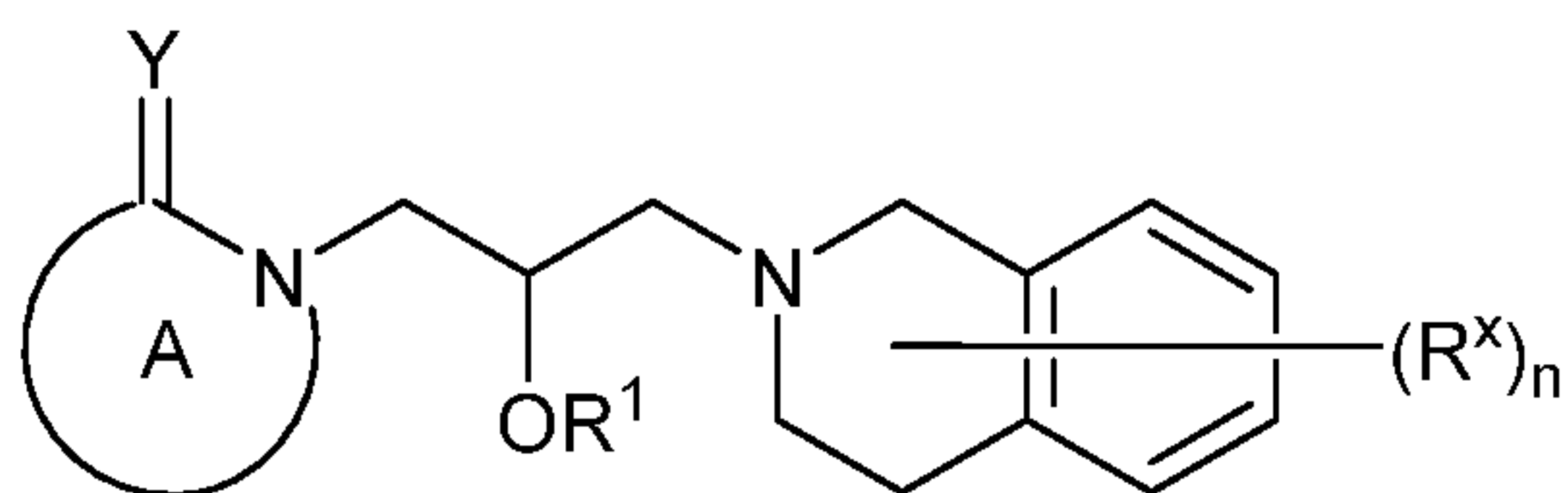
[0075] In some embodiments of Formula (A), the present disclosure provides a compound of Formula (**A-6**):



A-6

or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R^x, R¹², R¹³, and n are as described herein.

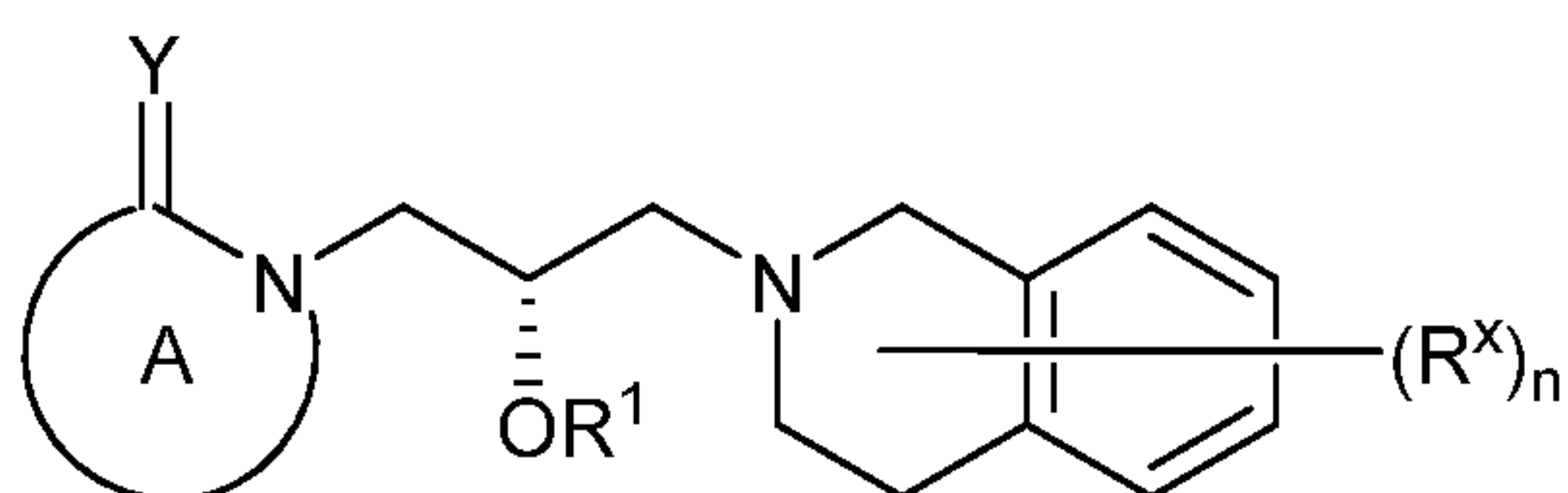
[0076] In certain embodiments, a provided compound is of Formula (**I'**):



I'

or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R¹, R^x, and n are as described herein.

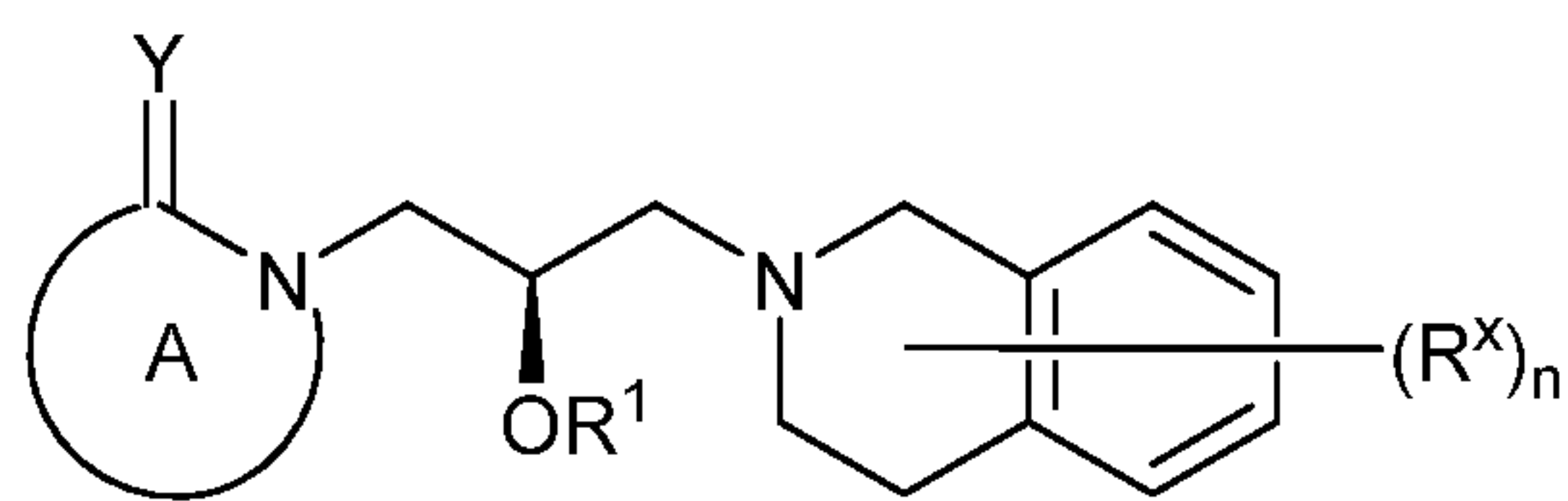
[0077] In certain embodiments, a provided compound is of Formula (**I'-a**):



I'-a

or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R¹, R^x, and n are as described herein.

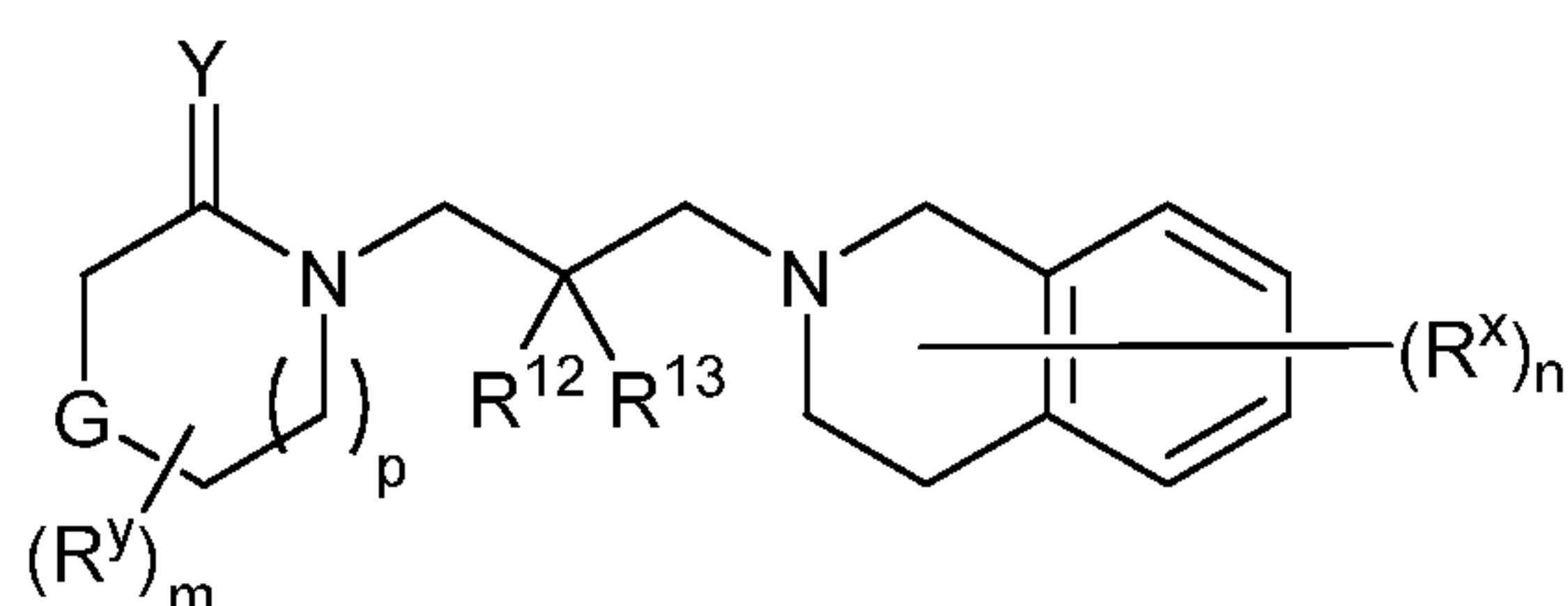
[0078] In certain embodiments, a provided compound is of Formula (I'-b):



I'-b

or a pharmaceutically acceptable salt thereof, wherein Ring A, Y, R¹, R^x, and n are as described herein.

[0079] In some embodiments of Formula (A), the present disclosure provides a compound of Formula (A-7):



(A-7)

or a pharmaceutically acceptable salt thereof, wherein Y, R^x, and n are as described herein,

G is NR², CR³R⁴, O or S;

R¹² is hydrogen, halogen, or optionally substituted C₁₋₃alkyl;

R¹³ is hydrogen, halogen, optionally substituted C₁₋₃alkyl, -NR^{A1}R^{A2}, or -OR¹;

R^{A1} and R^{A2} are independently hydrogen, optionally substituted C₁₋₃ alkyl, a nitrogen protecting group, or R^{A1} and R^{A2} are taken together with the intervening nitrogen atom to form an optionally substituted 3-6 membered heterocyclic ring;

R¹ is hydrogen, R^z, or -C(O)R^z, wherein R^z is optionally substituted C₁₋₆ alkyl;

R² is selected from the group consisting of optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -C(O)R^A, -C(O)OR^A, -C(O)SR^A, -C(O)N(R^B)₂, -C(=NR^B)R^A, -C(=NR^B)N(R^B)₂, -C(=S)R^A, -C(=S)N(R^B)₂, -S(=O)R^A, -SO₂R^A, and -SO₂N(R^B)₂;

R³ is selected from the group consisting of hydrogen, halo, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -N(R^B)₂, -SR^A, -C(=O)R^A, -C(O)OR^A, -C(O)SR^A, -C(O)N(R^B)₂, -C(O)N(R^B)N(R^B)₂, -OC(O)R^A, -OC(O)N(R^B)₂, -NR^BC(O)R^A, -NR^BC(O)N(R^B)₂, -NR^BC(O)N(R^B)N(R^B)₂, -NR^BC(O)OR^A, -SC(O)R^A, -C(=NR^B)R^A, -

$C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

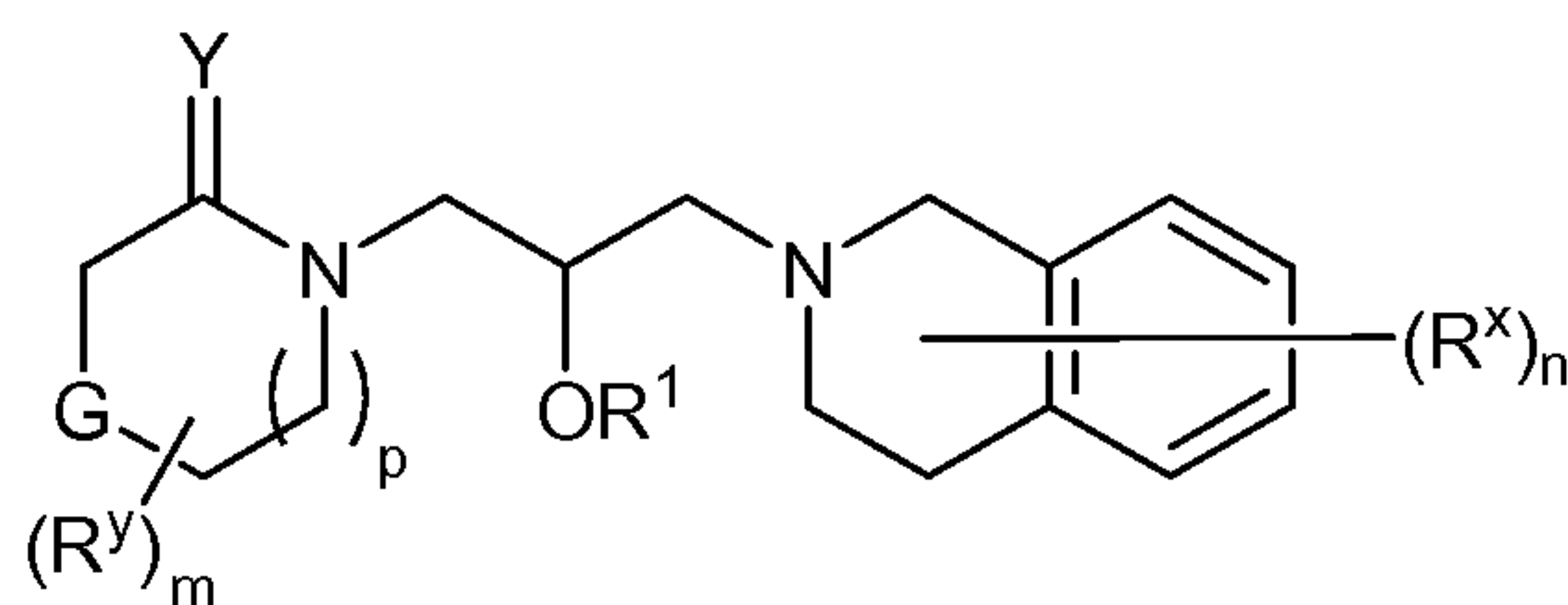
R^4 is selected from the group consisting of hydrogen, halo, and optionally substituted aliphatic;

each R^y is independently selected from the group consisting of halo, $-CN$, $-NO_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, $-SR^A$, $-C(=O)R^A$, $-C(O)OR^A$, $-C(O)SR^A$, $-C(O)N(R^B)_2$, $-C(O)N(R^B)N(R^B)_2$, $-OC(O)R^A$, $-OC(O)N(R^B)_2$, $-NR^BC(O)R^A$, $-NR^BC(O)N(R^B)_2$, $-NR^BC(O)N(R^B)N(R^B)_2$, $-NR^BC(O)OR^A$, $-SC(O)R^A$, $-C(=NR^B)R^A$, $-C(=NNR^B)R^A$, $-C(=NOR^A)R^A$, $-C(=NR^B)N(R^B)_2$, $-NR^BC(=NR^B)R^B$, $-C(=S)R^A$, $-C(=S)N(R^B)_2$, $-NR^BC(=S)R^A$, $-S(O)R^A$, $-OS(O)_2R^A$, $-SO_2R^A$, $-NR^BSO_2R^A$, and $-SO_2N(R^B)_2$, or two adjacent R^y groups may be taken together with their intervening atoms to form a saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

p is 0, 1, or 2; and

m is 0, 1, 2, 3, or 4.

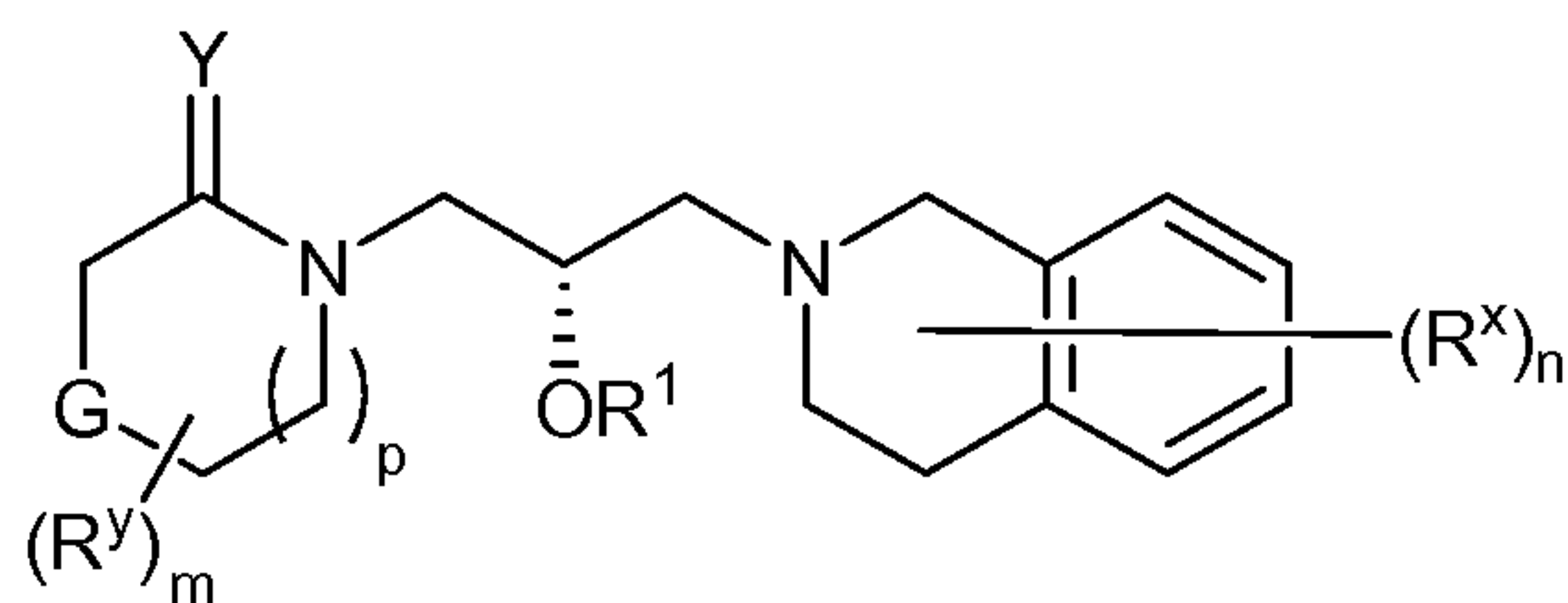
[0080] In certain embodiments, a provided compound is of Formula (II):



II

or a pharmaceutically acceptable salt thereof, wherein R^1 , G, Y, R^y , m, p, R^x , and n are as described herein.

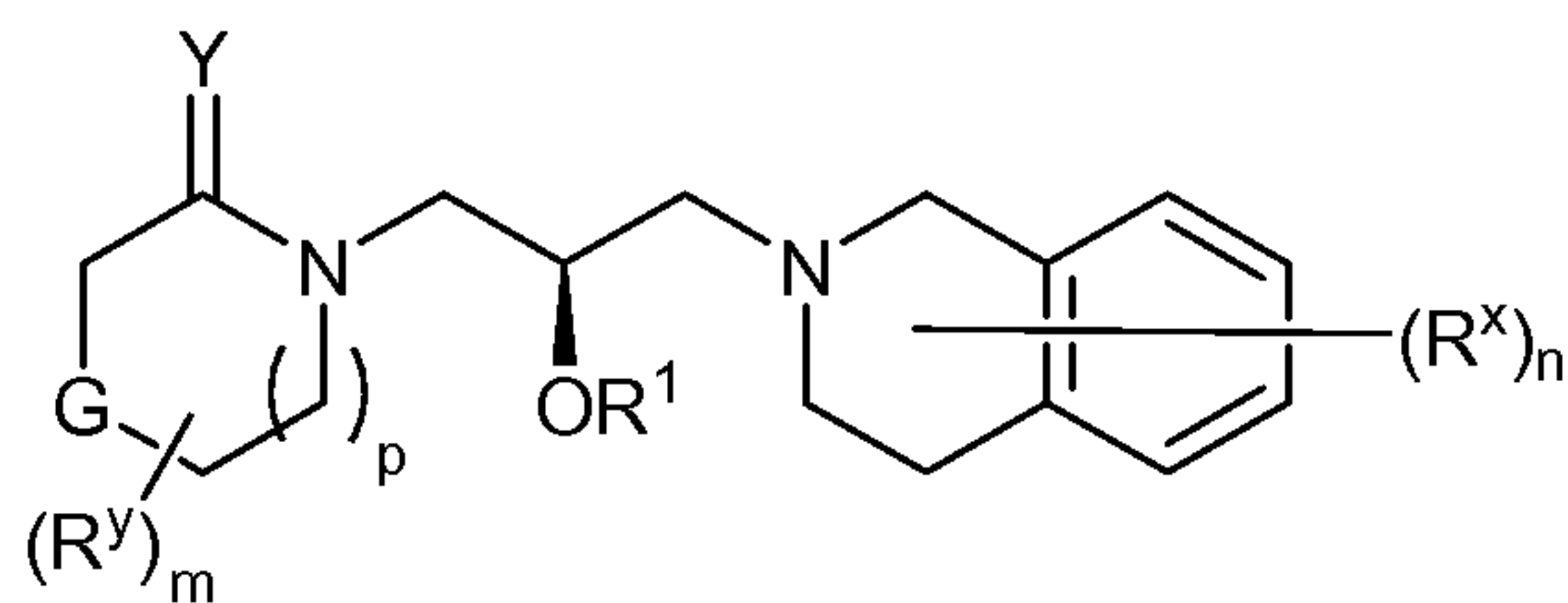
[0081] In certain embodiments, a provided compound is of Formula (II-a):



II-a

or a pharmaceutically acceptable salt thereof, wherein R^1 , G, Y, R^y , m, p, R^x , and n are as described herein.

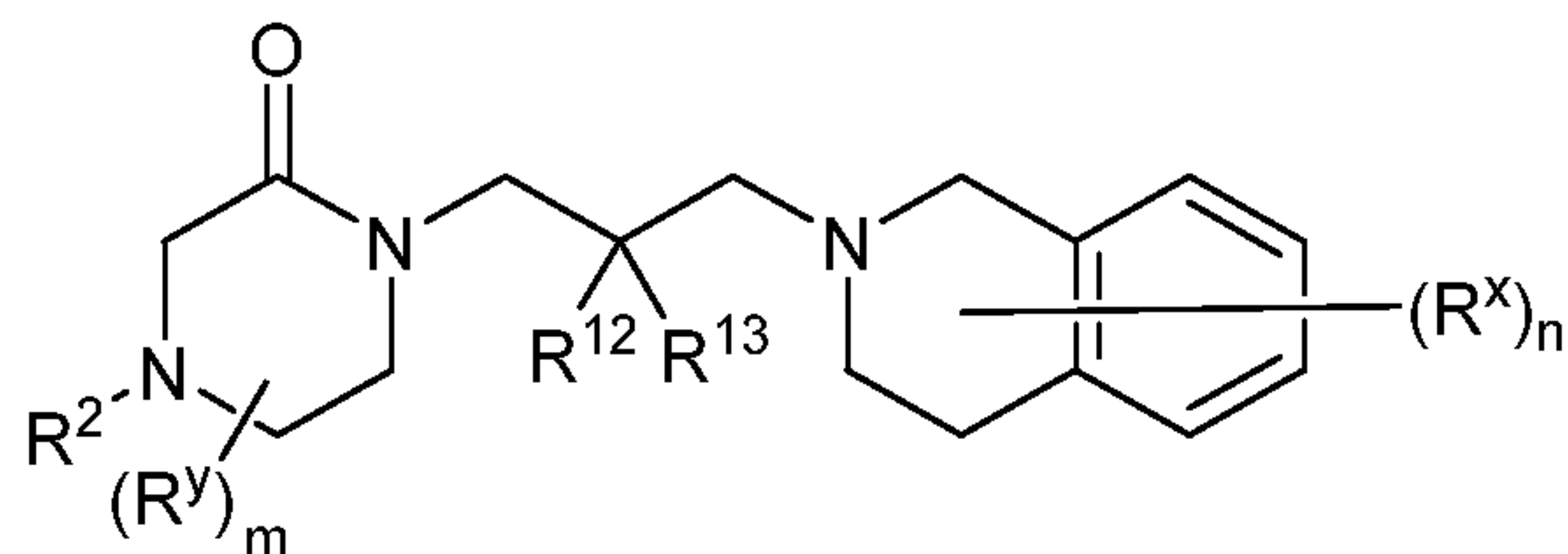
[0082] In certain embodiments, a provided compound is of Formula (II-b):



II-b

or a pharmaceutically acceptable salt thereof, wherein R^1 , G, Y, R^y , m, p, R^x , and n are as described herein.

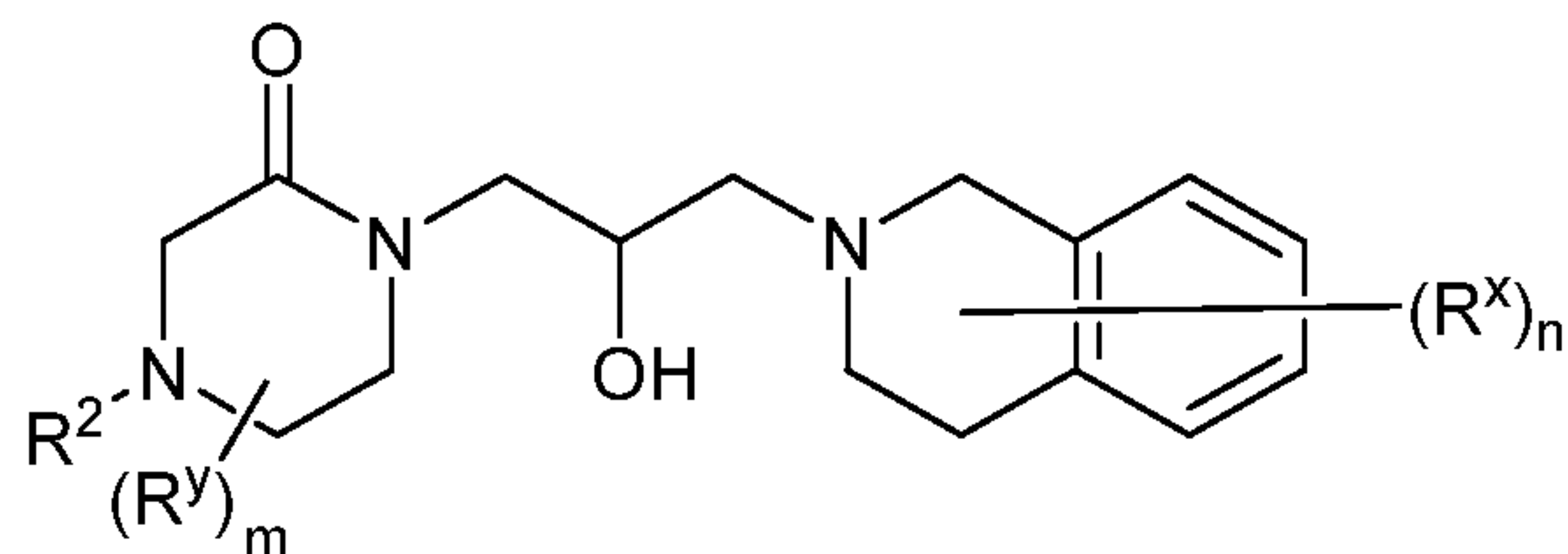
[0083] In certain embodiments, a provided compound is of Formula (A-8):



A-8

or a pharmaceutically acceptable salt thereof, wherein R^2 , R^y , m, R^x , R^{12} , R^{13} , and n are as described herein.

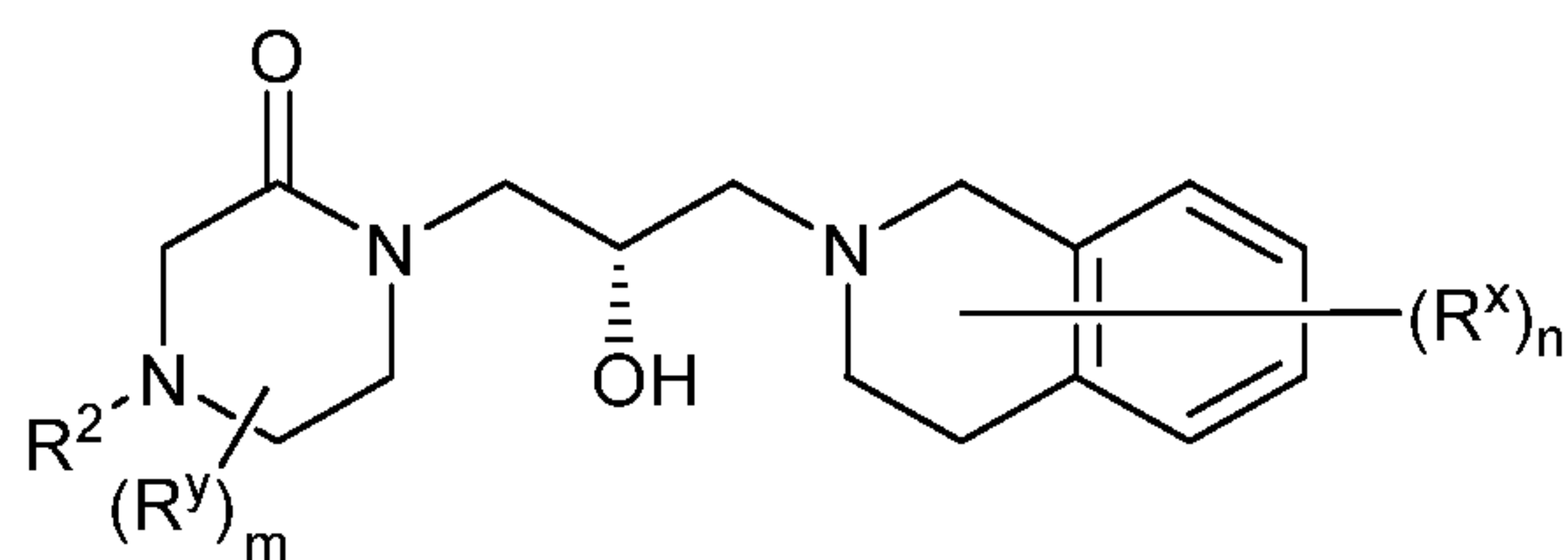
[0084] In certain embodiments, a provided compound is of Formula (III):



III

or a pharmaceutically acceptable salt thereof, wherein R^2 , R^y , m, R^x , and n are as described herein.

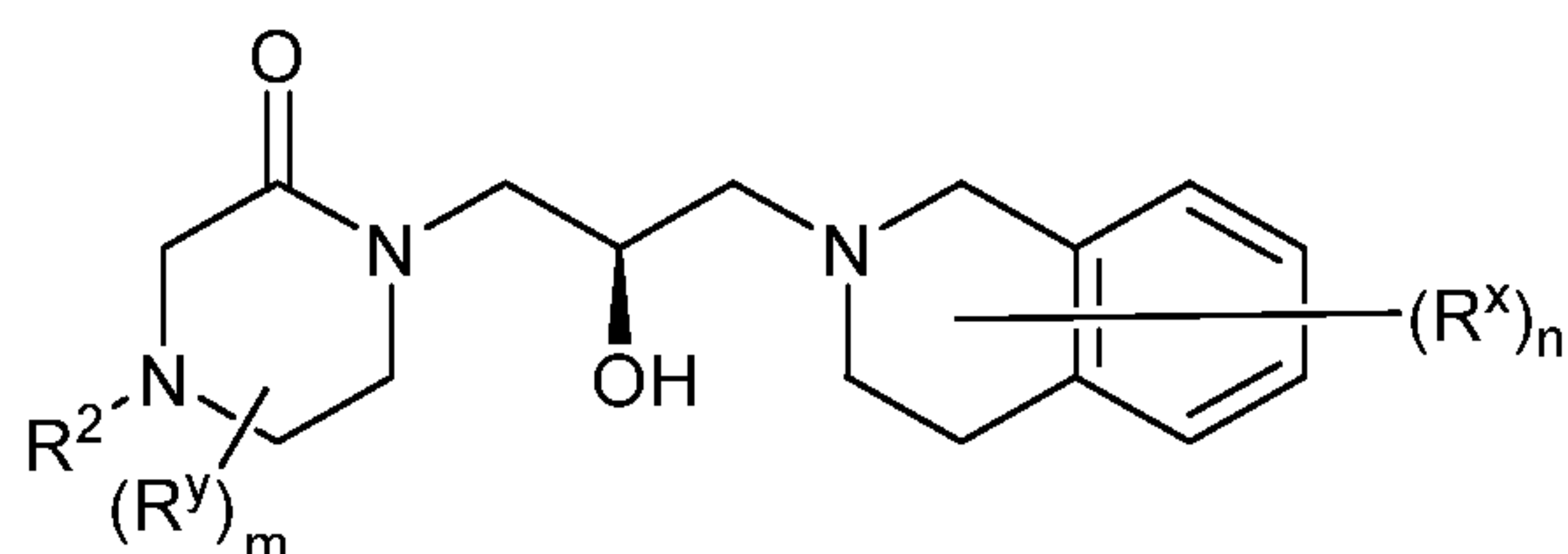
[0085] In certain embodiments, a provided compound is of Formula (III-a):



III-a

or a pharmaceutically acceptable salt thereof, wherein R^2 , R^y , m , R^x , and n are as described herein.

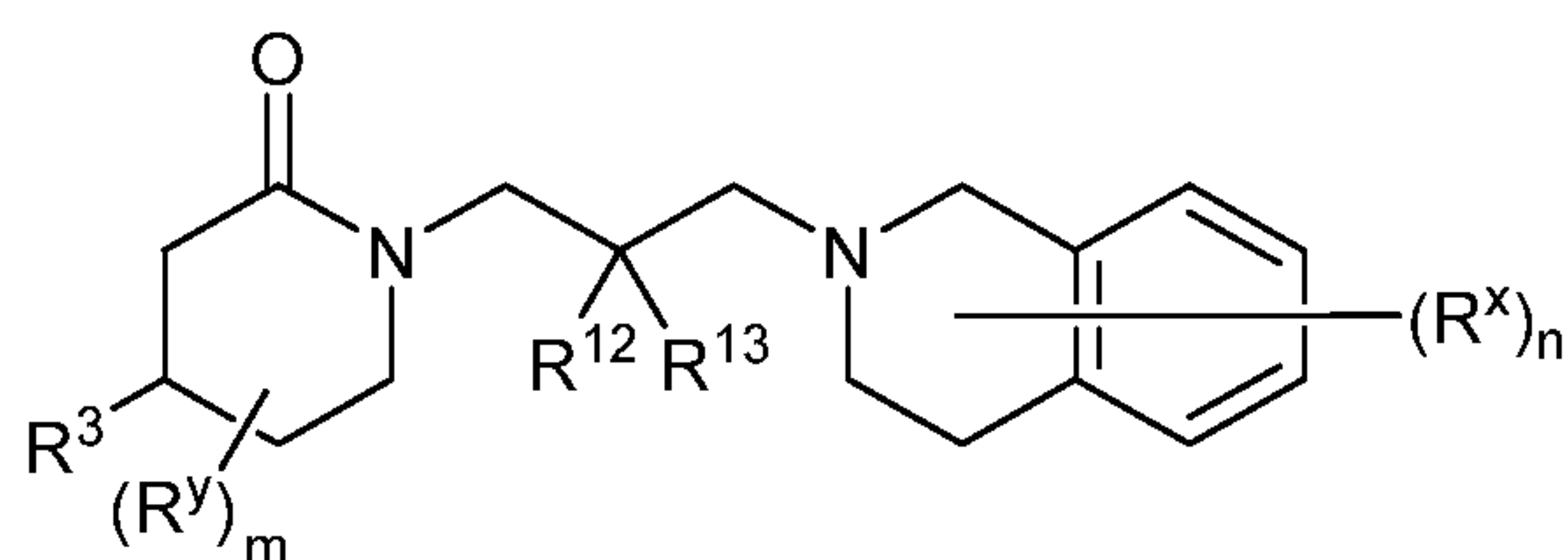
[0086] In certain embodiments, a provided compound is of Formula (III-b):



III-b

or a pharmaceutically acceptable salt thereof, wherein R^2 , R^y , m , R^x , and n are as described herein.

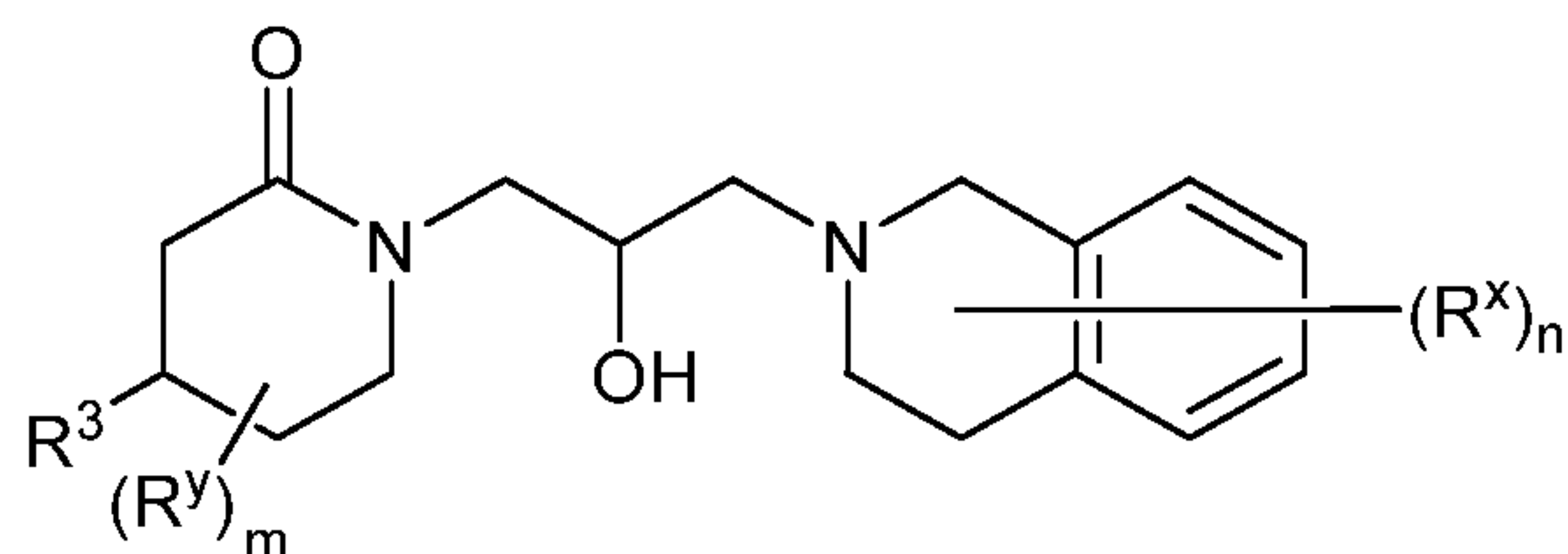
[0087] In certain embodiments, a provided compound is of Formula (A-9):



A-9

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^y , m , R^x , R^{12} , R^{13} , and n are as described herein.

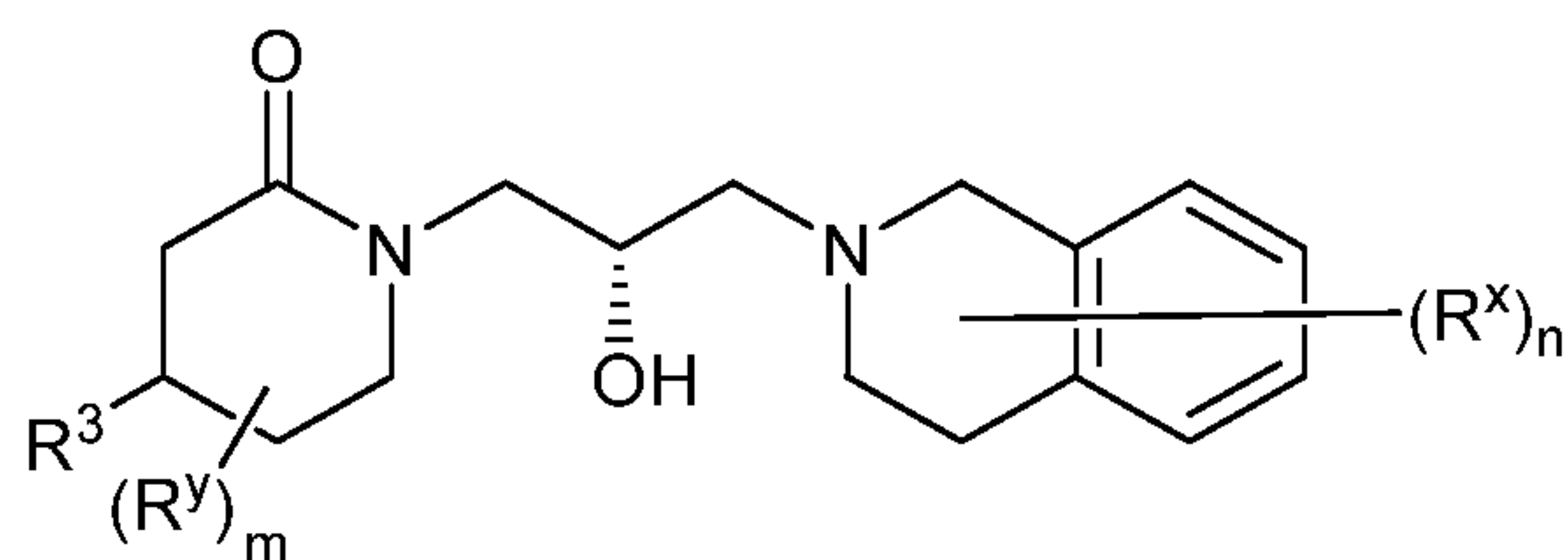
[0088] In certain embodiments, a provided compound is of Formula (IV):



IV

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^y , m , R^x , and n are as described herein.

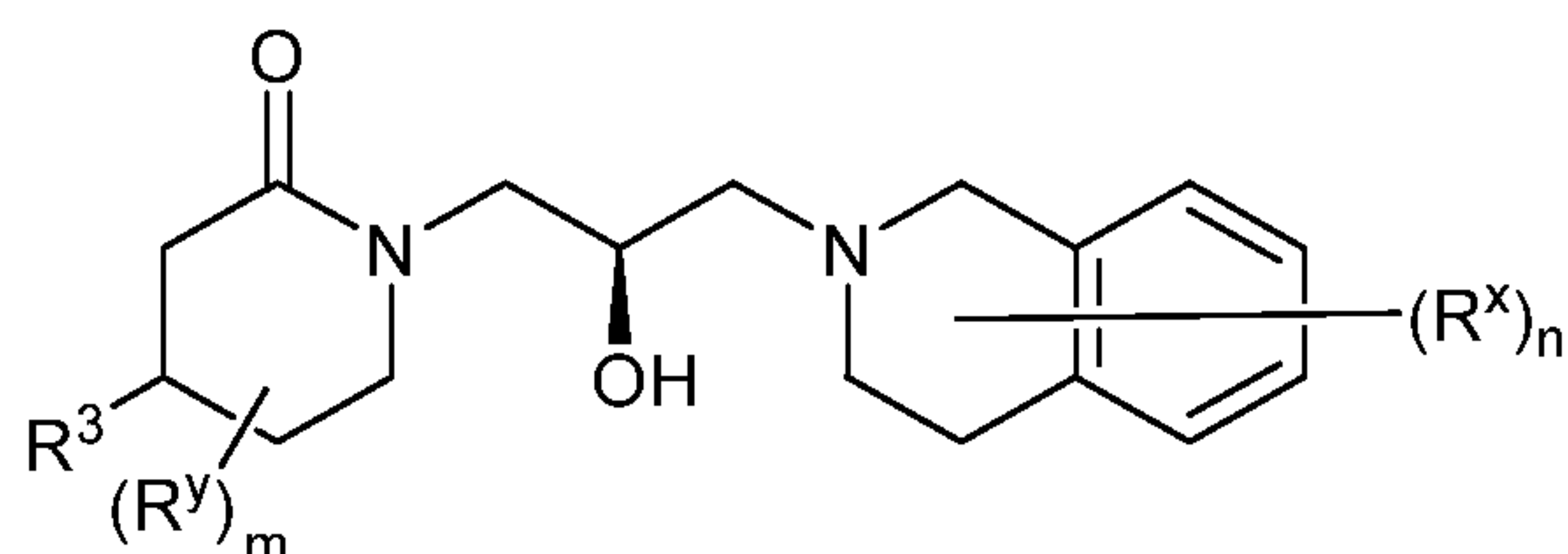
[0089] In certain embodiments, a provided compound is of Formula (IV-a):



IV-a

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^y , m , R^x , and n are as described herein.

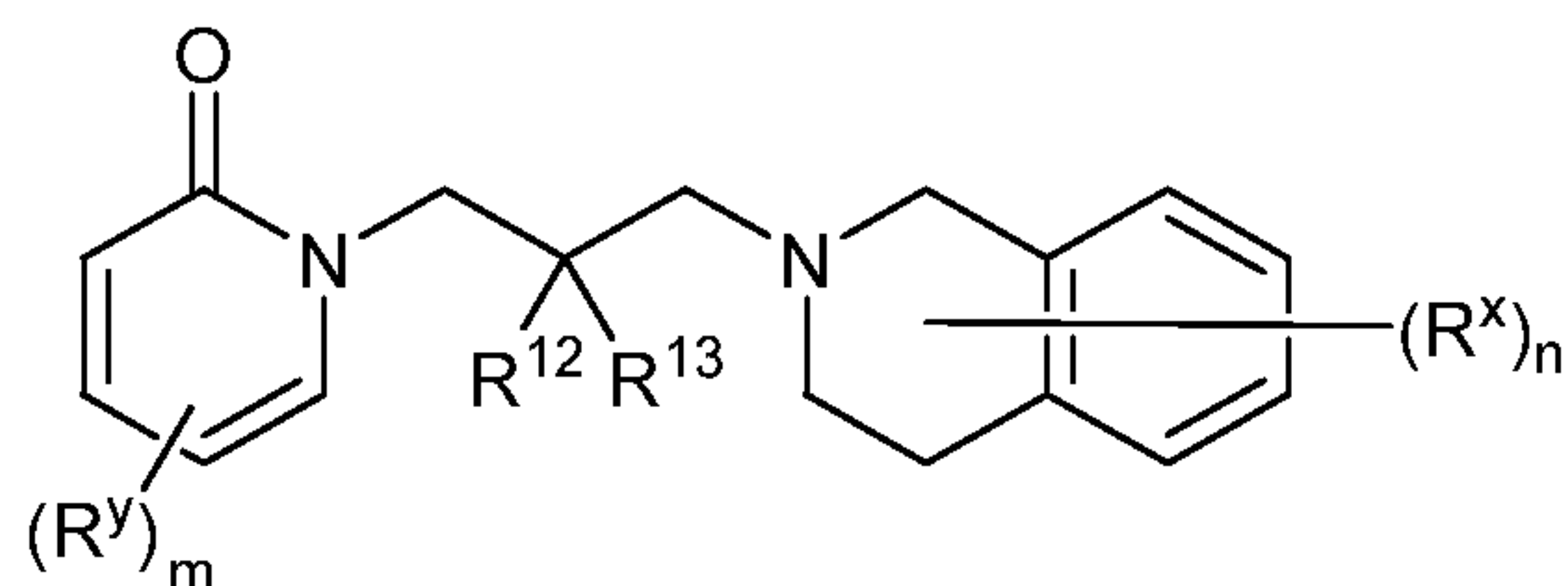
[0090] In certain embodiments, a provided compound is of Formula (IV-b):



IV-b

or a pharmaceutically acceptable salt thereof, wherein R^3 , R^y , m , R^x , and n are as described herein.

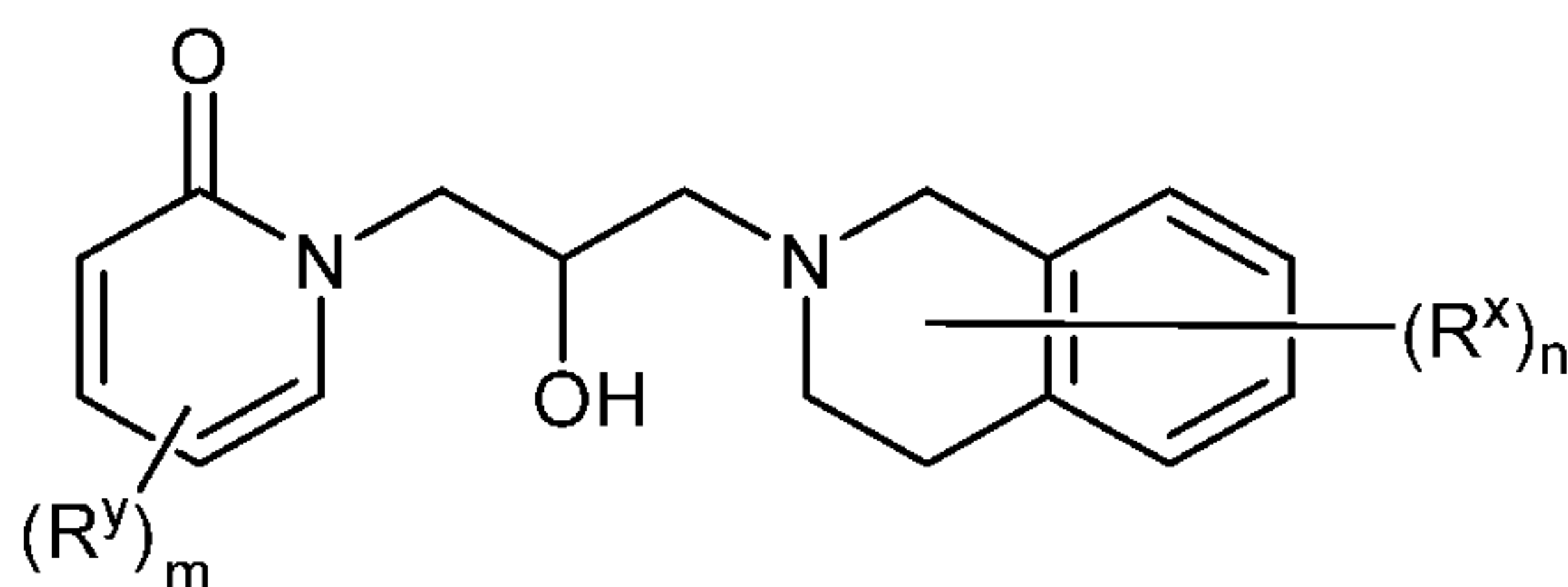
[0091] In certain embodiments, a provided compound is of Formula (A-10):



A-10

or a pharmaceutically acceptable salt thereof, wherein R^y , m , R^x , R^{12} , R^{13} , and n are as described herein.

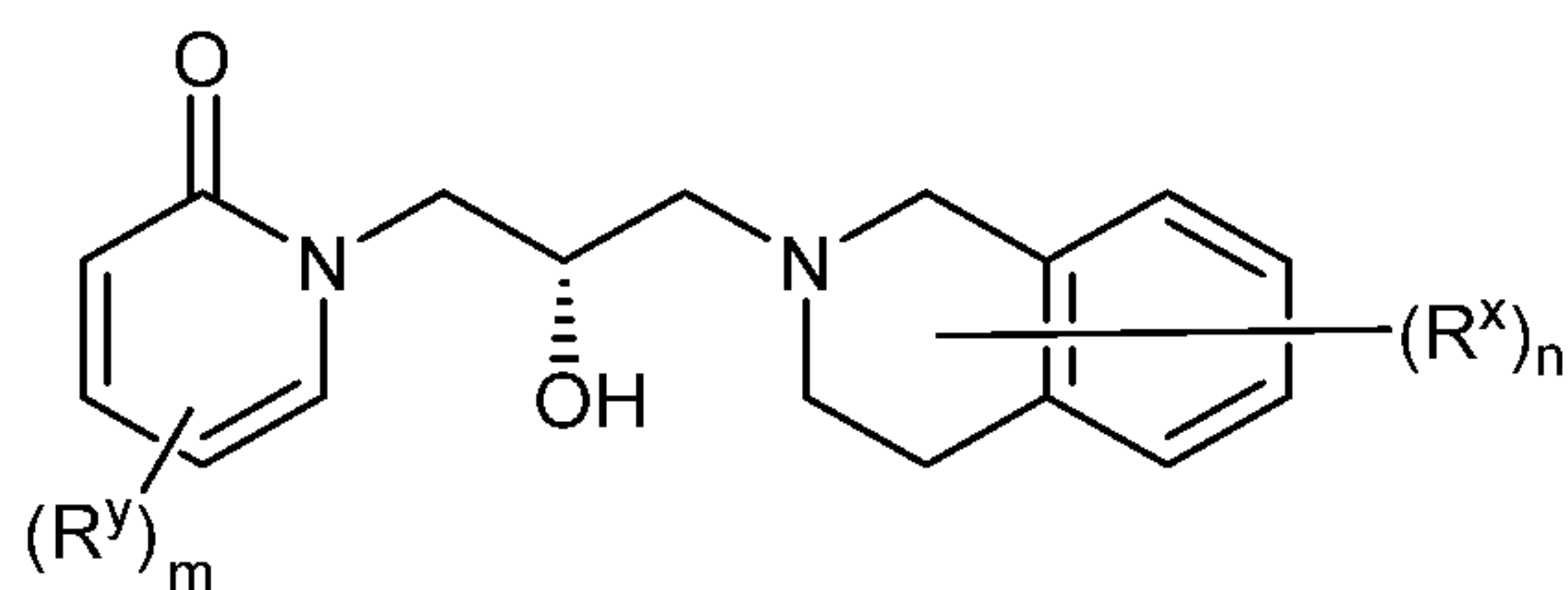
[0092] In certain embodiments, a provided compound is of Formula (V):



V

or a pharmaceutically acceptable salt thereof, wherein R^y , m , R^x , and n are as described herein.

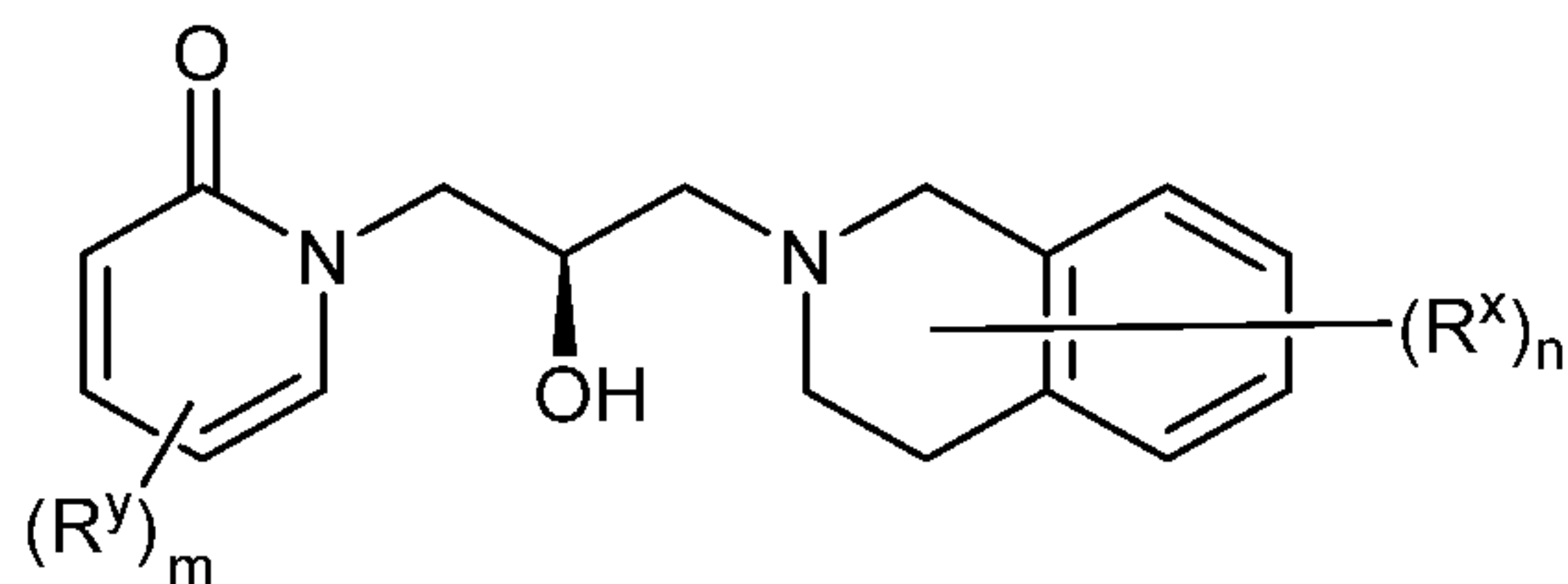
[0093] In certain embodiments, a provided compound is of Formula (V-a):



V-a

or a pharmaceutically acceptable salt thereof, wherein R^y , m , R^x , and n are as described herein.

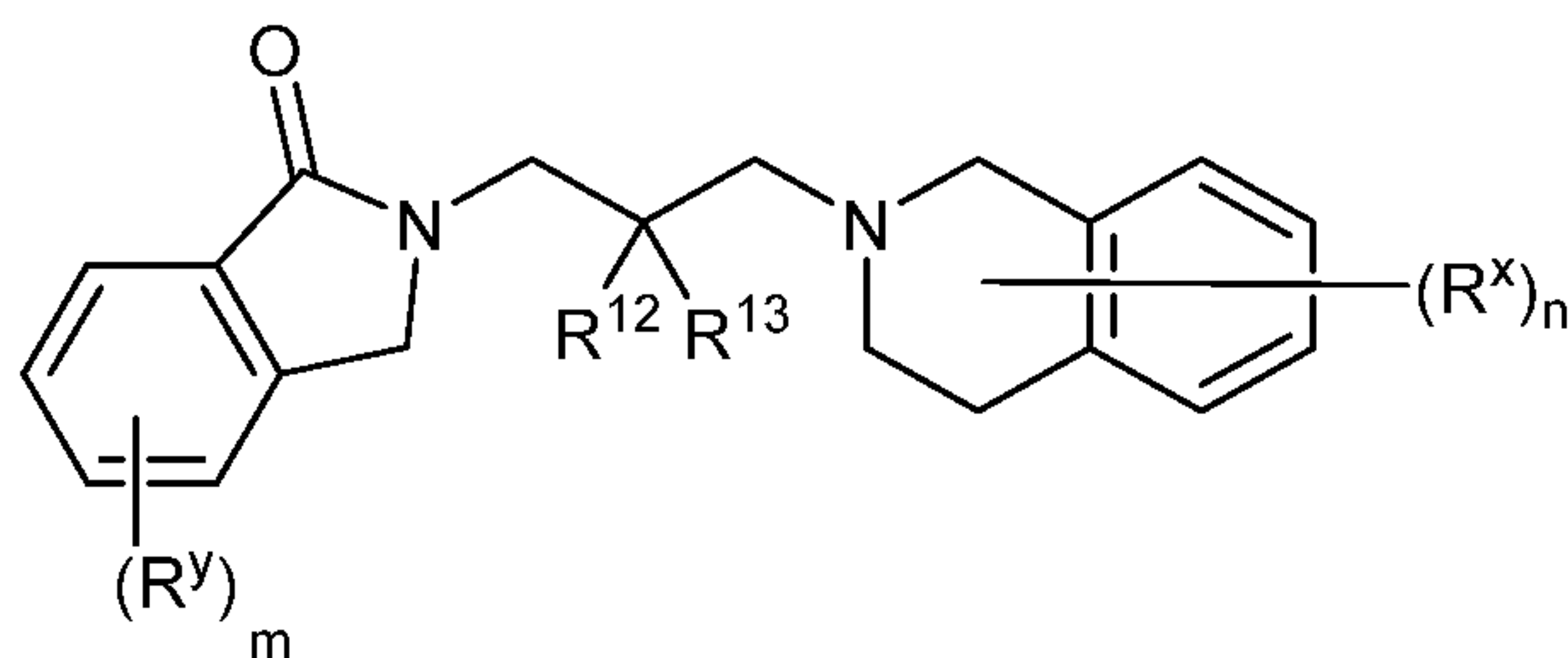
[0094] In certain embodiments, a provided compound is of Formula (V-b):



V-b

or a pharmaceutically acceptable salt thereof, wherein R^y , m , R^x , and n are as described herein.

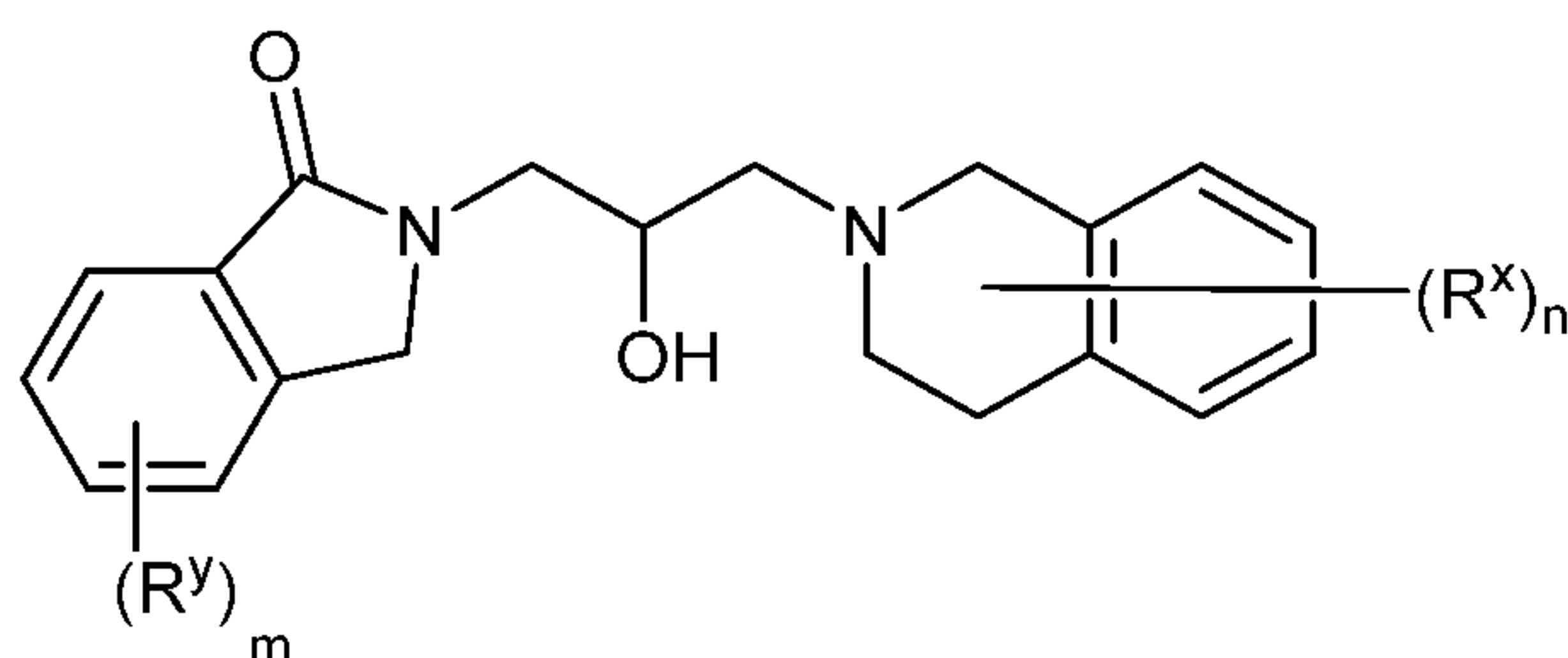
[0095] In certain embodiments, a provided compound is of Formula (A-11):



A-11

or a pharmaceutically acceptable salt thereof, wherein R^y , m , R^x , R^{12} , R^{13} and n are as described herein.

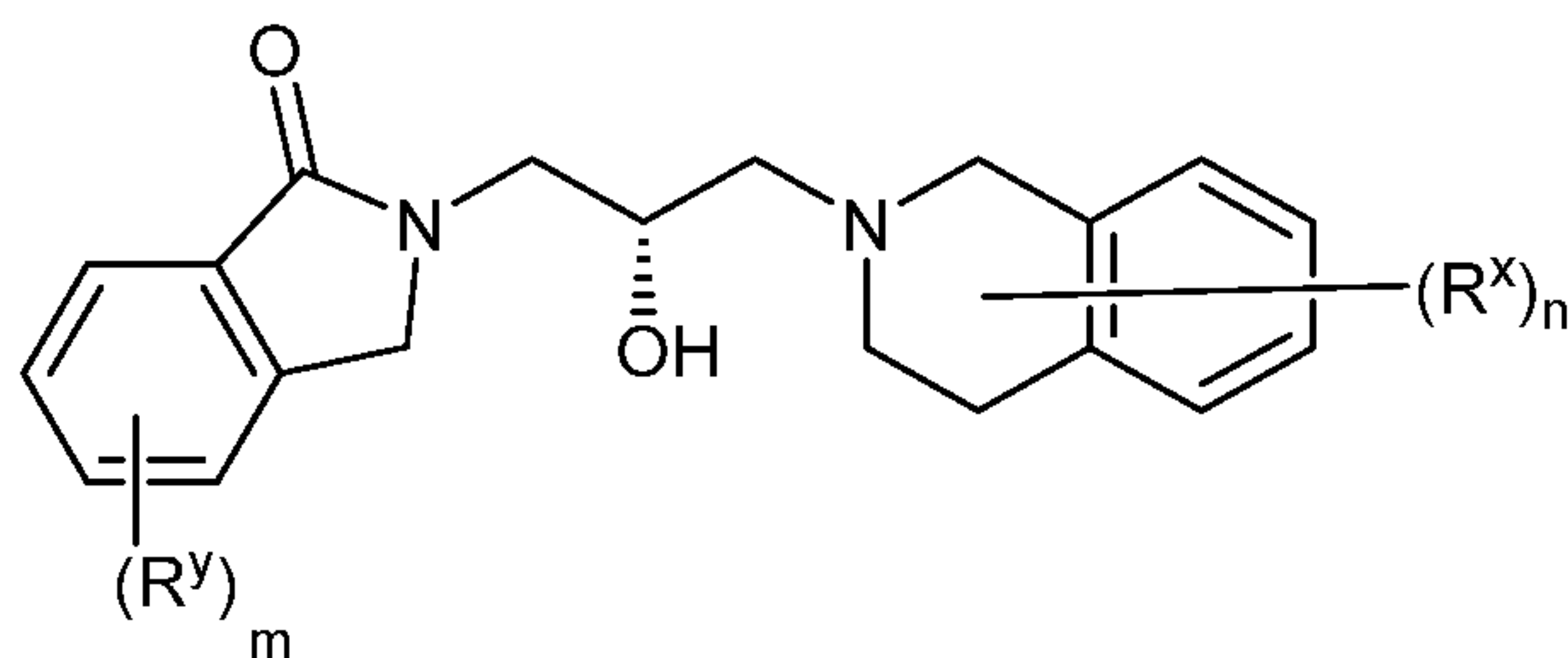
[0096] In certain embodiments, a provided compound is of Formula (VI):



VI

or a pharmaceutically acceptable salt thereof, wherein R^y , m , R^x , and n are as described herein.

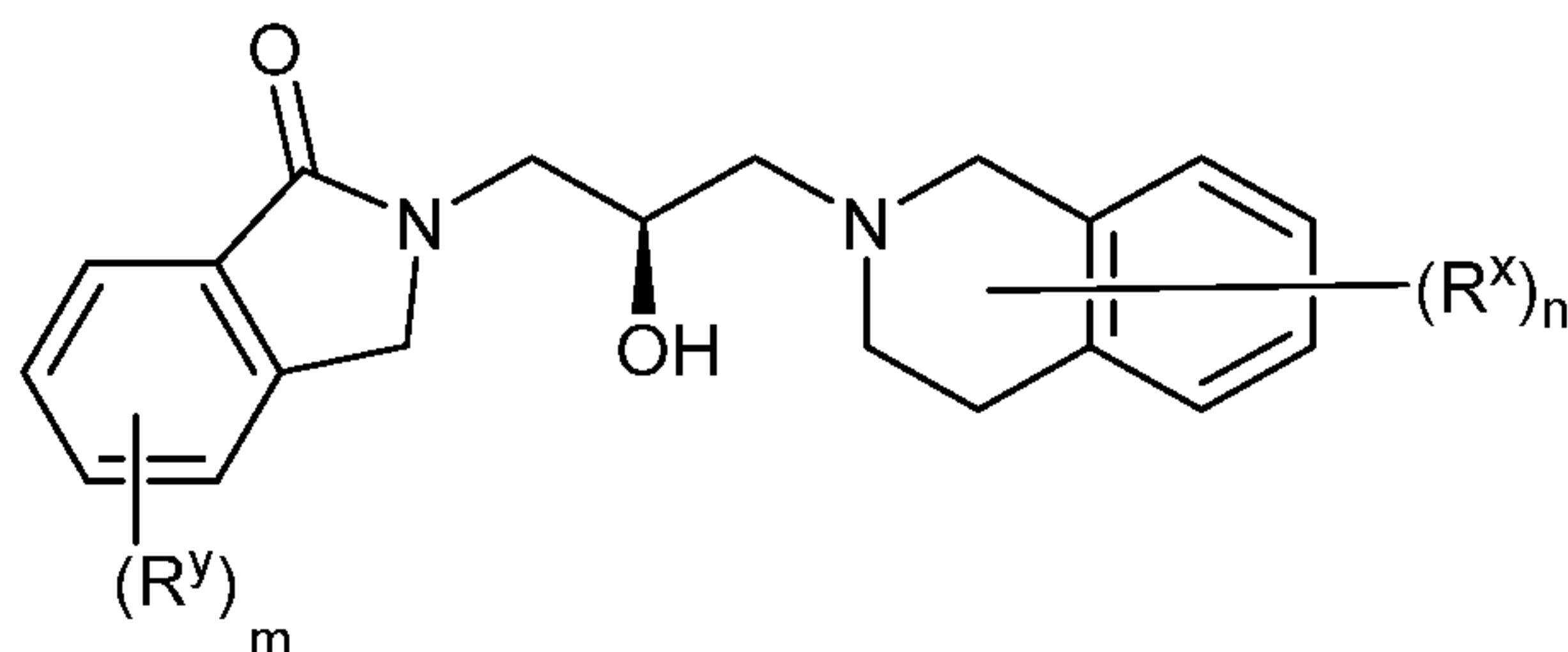
[0097] In certain embodiments, a provided compound is of Formula (VI-a):



VI-a

or a pharmaceutically acceptable salt thereof, wherein R^y , m , R^x , and n are as described herein.

[0098] In certain embodiments, a provided compound is of Formula (VI-b):



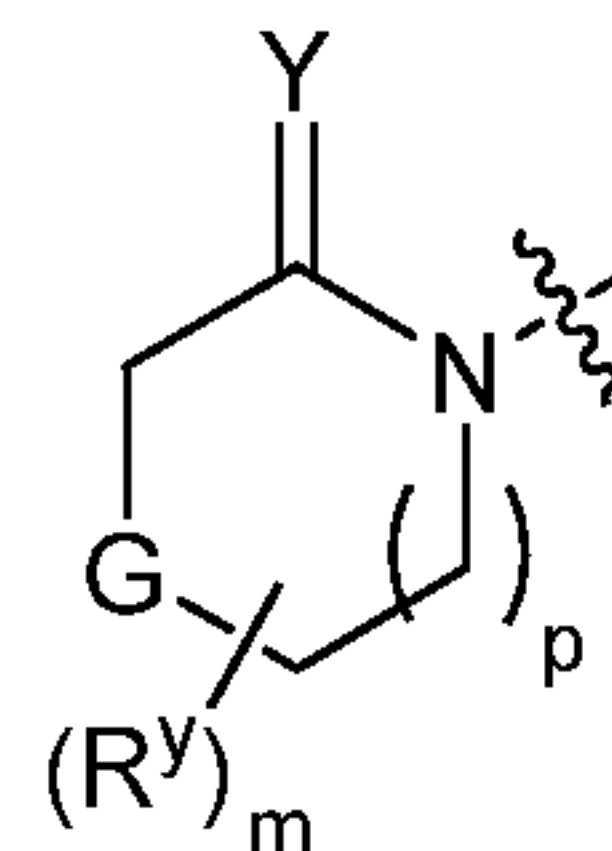
VI-b

or a pharmaceutically acceptable salt thereof, wherein R^y , m , R^x , and n are as described herein.

[0099] In some embodiments, represents a single bond. In some embodiments, represents a double bond.

[00100] As defined generally above, Ring A is an optionally substituted, 5- to 12-membered, monocyclic or bicyclic, heterocyclyl or heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. One of ordinary skill in the art will understand that Ring A comprises an amide or thioamide. In certain embodiments, Ring A is an optionally substituted, 5- to 6-membered, monocyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring A is an optionally substituted, 5- to 7-membered, monocyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring A is an optionally substituted, 8- to 10-membered, bicyclic heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, Ring A is an optionally substituted, 8- to 12-membered, bicyclic heterocyclyl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain

embodiments, Ring A is an optionally substituted piperidinone. In certain embodiments, Ring A is an optionally substituted pyridinone. In certain embodiments, Ring A is an optionally substituted piperazinone. In certain embodiments, Ring A is an optionally substituted isoindolinone. In certain embodiments, Ring A is an optionally substituted 2H-



benzo[b][1,4]oxazin-3(4H)-one. In some embodiments, Ring A is , wherein G, Y, R^y, m, and p are as described herein.

[00101] In certain embodiments, Y is O. In certain embodiments, Y is S.

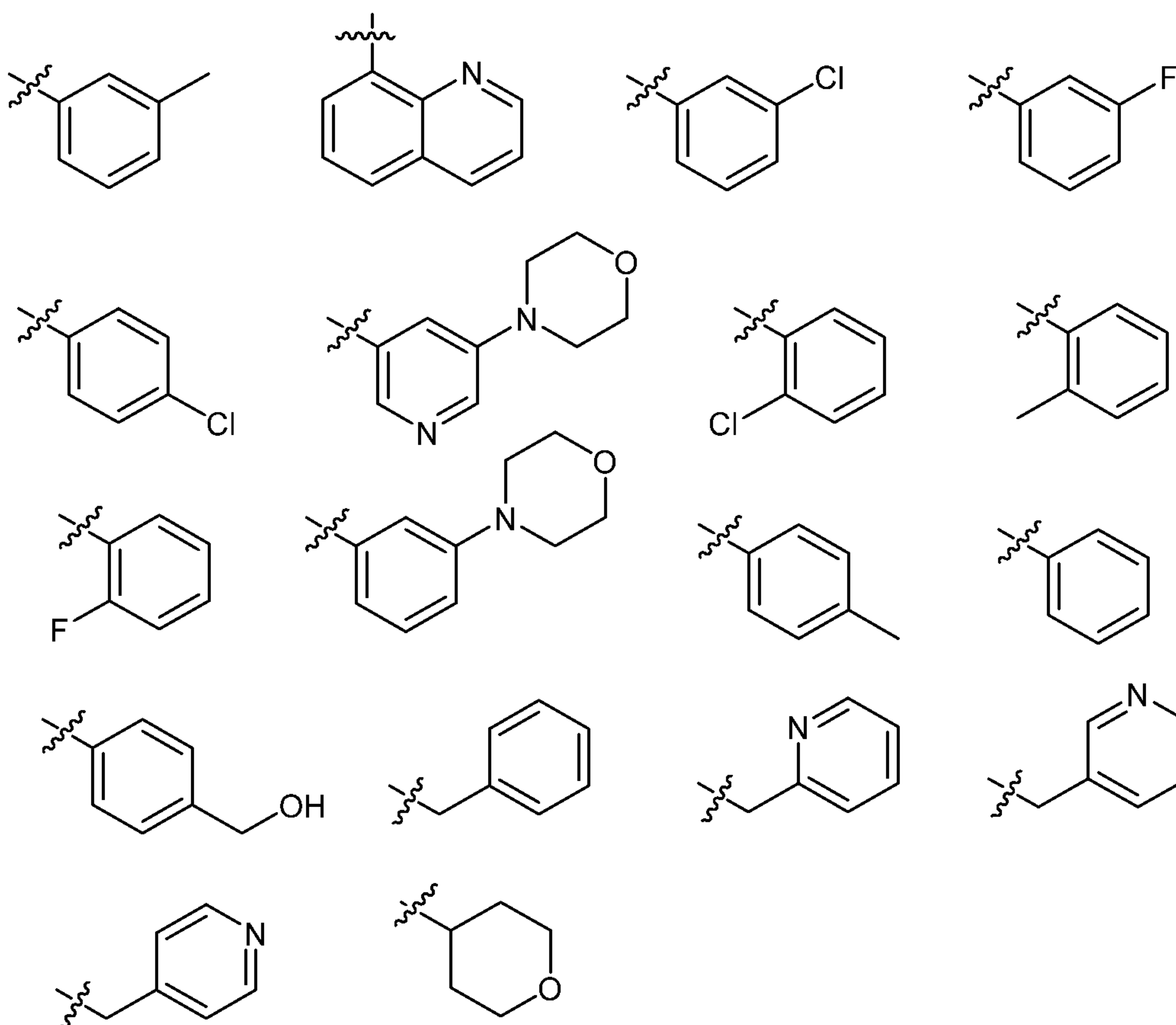
[00102] As defined generally above, R¹ is hydrogen, R^z, or -C(O)R^z, wherein R^z is optionally substituted C₁₋₆ alkyl. In certain embodiments, R¹ is hydrogen. In some embodiments, R¹ is optionally substituted C₁₋₆ alkyl. In certain embodiments, R¹ is unsubstituted C₁₋₆ alkyl. In certain embodiments, R¹ is methyl, ethyl, or propyl. In some embodiments, R¹ is -C(O)R^z, wherein R^z is optionally substituted C₁₋₆ alkyl. In certain embodiments, R¹ is -C(O)R^z, wherein R^z is unsubstituted C₁₋₆ alkyl. In certain embodiments, R¹ is acetyl.

[00103] As defined generally above, G is NR², CR³R⁴, O or S. In certain embodiments, G is NR². In certain embodiments, G is CR³R⁴. In certain embodiments, G is O. In certain embodiments, G is S.

[00104] As defined generally above, R² is selected from the group consisting of optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -C(O)R^A, -C(O)OR^A, -C(O)SR^A, -C(O)N(R^B)₂, -C(=NR^B)R^A, -C(=NR^B)N(R^B)₂, -C(=S)R^A, -C(=S)N(R^B)₂, -S(=O)R^A, -SO₂R^A, and -SO₂N(R^B)₂. In some embodiments, R² is optionally substituted aryl. In certain embodiments, R² is optionally substituted phenyl. In certain embodiments, R² is unsubstituted phenyl. In certain embodiments, R² is halophenyl. In certain embodiments, R² is fluorophenyl. In certain embodiments, R² is chlorophenyl. In some embodiments, R² is phenyl substituted with optionally substituted C₁₋₆ alkyl. In some embodiments, R² is phenyl substituted with optionally substituted C₁₋₃ alkyl. In certain embodiments, R² is phenyl substituted with methyl. In certain embodiments, R² is phenyl substituted with -CH₂OH. In some embodiments, R² is phenyl substituted with a heterocyclic ring. In certain embodiments, R² is phenyl substituted with morpholinyl. In certain embodiments, R² is

phenyl substituted with tetrahydropyranyl. In some embodiments, R^2 is optionally substituted heteroaryl. In certain embodiments, R^2 is optionally substituted quinoline. In certain embodiments, R^2 is unsubstituted quinoline. In certain embodiments, R^2 is substituted quinoline. In certain embodiments, R^2 is optionally substituted pyridine. In certain embodiments, R^2 is pyridine substituted with a heterocyclic ring. In some embodiments, R^2 is optionally substituted aliphatic. In certain embodiments, R^2 is unsubstituted aliphatic. In certain embodiments, R^2 is $-\text{CH}_2\text{-aryl}$. In certain embodiments, R^2 is benzyl. In certain embodiments, R^2 is $-\text{CH}_2\text{-heteroaryl}$. In certain embodiments, R^2 is $-\text{CH}_2\text{-pyridyl}$. In some embodiments, R^2 is $-\text{C}(=\text{O})\text{R}^A$. In certain embodiments, R^2 is $-\text{C}(=\text{O})\text{R}^A$, wherein R^A is optionally substituted aliphatic. In certain embodiments, R^2 is acetyl. In certain embodiments, R^2 is $-\text{SO}_2\text{R}^A$. In certain embodiments, R^2 is $-\text{SO}_2\text{R}^A$, wherein R^A is optionally substituted aliphatic. In certain embodiments, R^2 is $-\text{SO}_2\text{CH}_3$.

[00105] In certain embodiments, R^2 is selected from the group consisting of:



[00106] As defined generally above, R^3 is selected from the group consisting of hydrogen, halo, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-\text{OR}^A$, $-\text{N}(\text{R}^B)_2$, $-\text{SR}^A$, $-\text{C}(=\text{O})\text{R}^A$, $-\text{C}(\text{O})\text{OR}^A$, $-\text{C}(\text{O})\text{SR}^A$, $-\text{C}(\text{O})\text{N}(\text{R}^B)_2$, $-\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)_2$, -

OC(O)R^A, -OC(O)N(R^B)₂, -NR^BC(O)R^A, -NR^BC(O)N(R^B)₂, -NR^BC(O)N(R^B)N(R^B)₂, -NR^BC(O)OR^A, -SC(O)R^A, -C(=NR^B)R^A, -C(=NNR^B)R^A, -C(=NOR^A)R^A, -C(=NR^B)N(R^B)₂, -NR^BC(=NR^B)R^B, -C(=S)R^A, -C(=S)N(R^B)₂, -NR^BC(=S)R^A, -S(O)R^A, -OS(O)₂R^A, -SO₂R^A, -NR^BSO₂R^A, and -SO₂N(R^B)₂. In some embodiments, R³ is selected from the group consisting of hydrogen, halo, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -N(R^B)₂, -SR^A, -C(O)R^A, -C(O)OR^A, -C(O)SR^A, -C(O)N(R^B)₂, -OC(O)R^A, -NR^BC(=O)R^A, -NR^BC(=O)N(R^B)₂, -SC(=O)R^A, -C(=NR^B)R^A, -C(=NR^B)N(R^B)₂, -NR^BC(=NR^B)R^B, -C(=S)R^A, -C(=S)N(R^B)₂, -NR^BC(=S)R^A, -S(=O)R^A, -SO₂R^A, -NR^BSO₂R^A, and -SO₂N(R^B)₂.

[00107] In certain embodiments, R³ is hydrogen. In some embodiments, R³ is not hydrogen. In some embodiments, R³ is halo. In certain embodiments, R³ is fluoro. In some embodiments, R³ is optionally substituted aliphatic. In certain embodiments, R³ is optionally substituted C₁₋₆ aliphatic. In certain embodiments, R³ is optionally substituted C₁₋₆ alkyl. In certain embodiments, R³ is substituted C₁₋₆ alkyl. In certain embodiments, R³ is -CF₃, -CHF₂, or -CH₂F. In certain embodiments, R³ is unsubstituted C₁₋₆ alkyl. In certain embodiments, R³ is methyl, ethyl, or propyl. In some embodiments, R³ is -CN or -NO₂. In some embodiments, R³ is optionally substituted carbocyclyl, optionally substituted phenyl, optionally substituted heterocyclyl, or optionally substituted heteroaryl. In some embodiments, R³ is -OR^A, -N(R^B)₂, -SR^A, -C(=O)R^A, -C(O)OR^A, -C(O)SR^A, -C(O)N(R^B)₂, -OC(O)R^A, -NR^BC(O)R^A, -NR^BC(O)N(R^B)₂, -SC(O)R^A, -C(=NR^B)R^A, -C(=NR^B)N(R^B)₂, -NR^BC(=NR^B)R^B, -C(=S)R^A, -C(=S)N(R^B)₂, -NR^BC(=S)R^A, -S(O)R^A, -SO₂R^A, -NR^BSO₂R^A, or -SO₂N(R^B)₂. In some embodiments, R³ is optionally substituted aryl. In certain embodiments, R³ is optionally substituted phenyl. In certain embodiments, R³ is unsubstituted phenyl. In certain embodiments, R³ is halophenyl. In certain embodiments, R³ is fluorophenyl. In certain embodiments, R³ is chlorophenyl. In some embodiments, R³ is phenyl substituted with optionally substituted C₁₋₆ alkyl. In some embodiments, R³ is phenyl substituted with optionally substituted C₁₋₃ alkyl. In certain embodiments, R³ is phenyl substituted with methyl. In certain embodiments, R³ is phenyl substituted with -CH₂OH. In some embodiments, R³ is phenyl substituted with a heterocyclic ring. In certain embodiments, R³ is phenyl substituted with morpholinyl. In certain embodiments, R³ is phenyl substituted with tetrahydropyranyl. In some embodiments, R³ is optionally substituted heteroaryl. In certain embodiments, R³ is optionally substituted quinoline. In certain embodiments, R³ is unsubstituted quinoline. In certain embodiments, R³ is substituted

quinoline. In certain embodiments, R^3 is optionally substituted pyridine. In certain embodiments, R^3 is pyridine substituted with a heterocyclic ring. In some embodiments, R^3 is optionally substituted aliphatic. In certain embodiments, R^3 is unsubstituted aliphatic. In certain embodiments, R^3 is $-\text{CH}_2\text{-aryl}$. In certain embodiments, R^3 is benzyl. In certain embodiments, R^3 is $-\text{CH}_2\text{-heteroaryl}$. In certain embodiments, R^3 is $-\text{CH}_2\text{-pyridyl}$.

[00108] As defined generally above, R^4 is selected from the group consisting of hydrogen, halo, and optionally substituted aliphatic. In certain embodiments, R^4 is hydrogen. In some embodiments, R^4 is not hydrogen. In some embodiments, R^4 is halo. In certain embodiments, R^4 is fluoro. In some embodiments, R^4 is optionally substituted aliphatic. In certain embodiments, R^4 is optionally substituted C_{1-6} aliphatic. In certain embodiments, R^4 is optionally substituted C_{1-6} alkyl. In certain embodiments, R^4 is substituted C_{1-6} alkyl. In certain embodiments, R^4 is unsubstituted C_{1-6} alkyl. In certain embodiments, R^4 is methyl, ethyl, or propyl.

[00109] As defined generally above, R^5 , R^6 , R^7 , and R^8 are each independently hydrogen, halo, or optionally substituted aliphatic. In some embodiments, R^5 , R^6 , R^7 , and R^8 are hydrogen. In some embodiments, R^6 , R^7 , and R^8 are hydrogen, and R^5 is optionally substituted aliphatic. In some embodiments, R^6 , R^7 , and R^8 are hydrogen, and R^5 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^6 , R^7 , and R^8 are hydrogen, and R^5 is optionally substituted C_{1-3} aliphatic. In some embodiments, R^6 , R^7 , and R^8 are hydrogen, and R^5 is methyl. In some embodiments, R^6 , R^7 , and R^5 are hydrogen, and R^8 is optionally substituted aliphatic. In some embodiments, R^6 , R^7 , and R^5 are hydrogen, and R^8 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^6 , R^7 , and R^5 are hydrogen, and R^8 is optionally substituted C_{1-3} aliphatic. In some embodiments, R^6 , R^7 , and R^5 are hydrogen, and R^8 is methyl. In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is halo. In certain embodiments, R^5 is fluoro. In some embodiments, R^5 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^5 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^5 is methyl. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is halo. In certain embodiments, R^6 is fluoro. In some embodiments, R^6 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^6 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^6 is methyl. In some embodiments, R^7 is hydrogen. In some embodiments, R^7 is halo. In certain embodiments, R^7 is fluoro. In some embodiments, R^7 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^7 is optionally substituted C_{1-3} alkyl. In certain embodiments, R^7 is methyl. In some embodiments, R^8 is hydrogen. In some embodiments, R^8 is halo. In certain embodiments, R^8 is fluoro. In some embodiments, R^8 is

optionally substituted C₁₋₆ aliphatic. In some embodiments, R⁸ is optionally substituted C₁₋₃ alkyl. In certain embodiments, R⁸ is methyl.

[00110] As defined generally above, p is 0, 1, or 2. In certain embodiments, p is 0. In certain embodiments, p is 1. In certain embodiments, p is 2.

[00111] As defined generally above, each R^y is independently selected from the group consisting of halo, -CN, -NO₂, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, -OR^A, -N(R^B)₂, -SR^A, -C(=O)R^A, -C(O)OR^A, -C(O)SR^A, -C(O)N(R^B)₂, -C(O)N(R^B)N(R^B)₂, -OC(O)R^A, -OC(O)N(R^B)₂, -NR^BC(O)R^A, -NR^BC(O)N(R^B)₂, -NR^BC(O)N(R^B)N(R^B)₂, -NR^BC(O)OR^A, -SC(O)R^A, -C(=NR^B)R^A, -C(=NNR^B)R^A, -C(=NOR^A)R^A, -C(=NR^B)N(R^B)₂, -NR^BC(=NR^B)R^B, -C(=S)R^A, -C(=S)N(R^B)₂, -NR^BC(=S)R^A, -S(O)R^A, -OS(O)₂R^A, -SO₂R^A, -NR^BSO₂R^A, and -SO₂N(R^B)₂, wherein R^A and R^B are described herein.

[00112] In some embodiments, at least one R^y is halo. In certain embodiments, at least one R^y is fluoro. In certain embodiments, at least one R^y is chloro. In some embodiments, at least one R^y is -CN. In some embodiments, at least one R^y is -OR^A, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is -OR^A, wherein R^A is unsubstituted C₁₋₆ alkyl. In certain embodiments, at least one R^y is methoxy, ethoxy, or propoxy. In certain embodiments, at least one R^y is methoxy. In some embodiments, at least one R^y is -OR^A, wherein R^A is substituted C₁₋₆ alkyl. In certain embodiments, at least one R^y is -OCH₂CH₂N(CH₃)₂. In some embodiments, at least one R^y is -OR^A, wherein R^A is optionally substituted heterocyclyl. In some embodiments, at least one R^y is -OR^A, wherein R^A is an optionally substituted 4- to 7-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, at least one R^y is -OR^A, wherein R^A is oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl. In some embodiments, at least one R^y is -N(R^B)₂. In some embodiments, at least one R^y is -N(R^B)₂, wherein each R^B is independently hydrogen or C₁₋₆ alkyl. In some embodiments, at least one R^y is -NHR^B. In some embodiments, at least one R^y is -N(C₁₋₆ alkyl)₂, -NH(C₁₋₆ alkyl), or -NH₂. In certain embodiments, at least one R^y is -NH₂. In certain embodiments, at least one R^y is -NHCH₃. In certain embodiments, at least one R^y is -N(CH₃)₂. In some embodiments, at least one R^y is -N(R^B)₂ or -NHR^B, wherein at least one R^B is optionally substituted heterocyclyl. In some embodiments, at least one R^y is -N(R^B)₂ or -NHR^B, wherein at least one R^B is an optionally substituted 4- to 7-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In some embodiments, at least one

R^y is $-N(R^B)_2$ or $-NHR^B$, wherein at least one R^B is oxetanyl, tetrahydropyranyl, or tetrahydrofuranlyl. In some embodiments, at least one R^y is $-N(R^B)_2$ or $-NHR^B$, wherein at least one R^B is optionally substituted piperidinyl or optionally substituted piperazinyl.

[00113] In some embodiments, at least one R^y is optionally substituted aliphatic. In certain embodiments, at least one R^y is substituted aliphatic. In certain embodiments, at least one R^y is unsubstituted aliphatic. In some embodiments, at least one R^y is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is unsubstituted C_{1-6} alkyl. In certain embodiments, at least one R^y is substituted C_{1-6} alkyl. In certain embodiments, at least one R^y is methyl, ethyl, or propyl. In certain embodiments, at least one R^y is methyl. In certain embodiments, at least one R^y is $-CF_3$, CHF_2 , or CH_2F . In certain embodiments, at least one R^y is C_{1-6} alkyl substituted with aryl, heteroaryl, or heterocyclyl. In certain embodiments, at least one R^y is benzyl. In certain embodiments, at least one R^y is $-(C_{1-6} \text{ alkyl})\text{-aryl}$. In certain embodiments, at least one R^y is $-(C_{1-6} \text{ alkyl})\text{-heteroaryl}$. In certain embodiments, at least one R^y is $-(C_{1-6} \text{ alkyl})\text{-heterocyclyl}$. In certain embodiments, at least one R^y is $-CH_2\text{-aryl}$. In certain embodiments, at least one R^y is $-CH_2\text{-heteroaryl}$. In certain embodiments, at least one R^y is $-CH_2\text{-heterocyclyl}$.

[00114] In some embodiments, at least one R^y is $-C(O)N(R^B)_2$. In certain embodiments, at least one R^y is $-C(O)NHR^B$. In certain embodiments, at least one R^y is $-C(O)NH_2$. In certain embodiments, at least one R^y is $-C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is $-C(O)N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted morpholinyl.

[00115] In some embodiments, at least one R^y is $-SO_2N(R^B)_2$. In certain embodiments, at least one R^y is $-SO_2NHR^B$. In certain embodiments, at least one R^y is $-SO_2NH_2$. In certain embodiments, at least one R^y is $-SO_2N(R^B)_2$, wherein neither R^B is hydrogen. In certain embodiments, at least one R^y is $-SO_2NH(C_{1-6} \text{ alkyl})$ or $-SO_2N(C_{1-6} \text{ alkyl})_2$. In certain embodiments, at least one R^y is $-SO_2N(CH_3)_2$. In certain embodiments, at least one R^y is $-SO_2N(R^B)_2$, wherein the R^B groups are taken together with their intervening atoms to form an optionally substituted 5- to 6-membered heterocyclyl. In certain embodiments, at least one R^y is $-SO_2\text{-morpholinyl}$. In certain embodiments, at least one R^y is $-SO_2\text{-piperidinyl}$, $-SO_2\text{-piperazinyl}$, or $-SO_2\text{-piperidinyl}$.

[00116] In some embodiments, at least one R^y is $-SO_2R^A$. In some embodiments, at least one R^y is $-SO_2R^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is $-SO_2(C_{1-6} \text{ alkyl})$. In some embodiments, at least one R^y is $-SO_2CH_3$. In some

embodiments, at least one R^y is $-C(O)R^A$. In some embodiments, at least one R^y is $-C(O)R^A$, wherein R^A is optionally substituted aliphatic. In some embodiments, at least one R^y is $-C(O)(C_{1-6} \text{ alkyl})$. In some embodiments, at least one R^y is $-C(O)CH_3$.

[00117] In some embodiments, at least one R^y is $-N(R^B)C(O)R^A$. In certain embodiments, at least one R^y is $-NHC(O)R^A$. In certain embodiments, at least one R^y is $-NHC(O)(C_{1-6} \text{ alkyl})$. In certain embodiments, at least one R^y is $-NHC(O)CH_3$.

[00118] In some embodiments, at least one R^y is $-N(R^B)SO_2R^A$. In some embodiments, at least one R^y is $-NHSO_2R^A$. In some embodiments, at least one R^y is $-N(C_{1-6} \text{ alkyl})SO_2R^A$. In certain embodiments, at least one R^y is $-NHSO_2(C_{1-6} \text{ alkyl})$ or $-N(C_{1-6} \text{ alkyl})SO_2(C_{1-6} \text{ alkyl})$. In certain embodiments, at least one R^y is $-NHSO_2CH_3$. In certain embodiments, at least one R^y is $-N(CH_3)SO_2CH_3$.

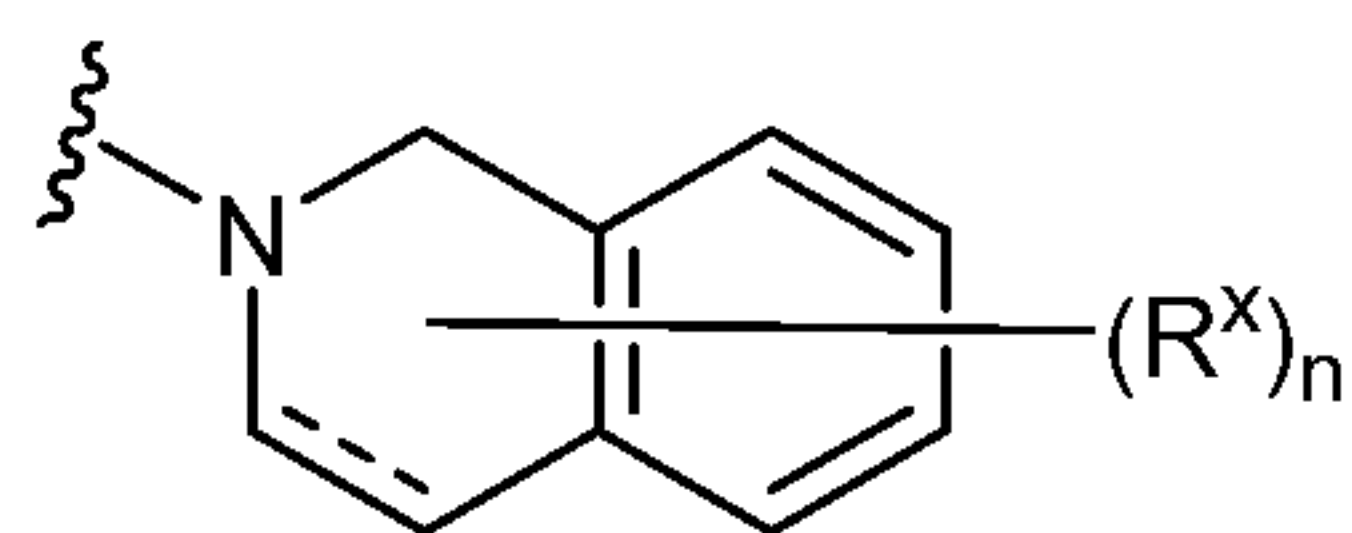
[00119] In some embodiments, at least one R^y is optionally substituted heterocyclyl, optionally substituted carbocyclyl, optionally substituted aryl, or optionally substituted heteroaryl. In certain embodiments, at least one R^y is an optionally substituted 5- to 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted pyrrolidinyl. In certain embodiments, at least one R^y is pyrrolidinyl, hydroxypyrrolidinyl, or methylpyrrolidinyl. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted piperidinyl. In certain embodiments, at least one R^y is an optionally substituted 6-membered heterocyclyl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is optionally substituted piperidinyl, optionally substituted piperazinyl, or optionally substituted morpholinyl. In certain embodiments, at least one R^y is morpholinyl, tetrahydropyranyl, piperidinyl, methylpiperidinyl, piperazinyl, methylpiperazinyl, acetylpiperazinyl, methylsulfonylpiperazinyl, aziridinyl, or methylaziridinyl. In some embodiments, at least one R^y is an optionally substituted 5- to 6-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least

one R^y is an optionally substituted 5-membered heteroaryl having one heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 5-membered heteroaryl having two heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, at least one R^y is an optionally substituted 6-membered heteroaryl having 1-3 nitrogens. In certain embodiments, at least one R^y is an optionally substituted pyrazolyl. In certain embodiments, at least one R^y is an optionally substituted imidazolyl. In certain embodiments, at least one R^y is an optionally substituted pyridyl. In certain embodiments, at least one R^y is an optionally substituted pyrimidyl. In certain embodiments, at least one R^y is pyrazolyl, methylpyrazolyl, imidazolyl, or methylimidazolyl.

[00120] In some embodiments, R^y is $-OR^A$. In some embodiments, R^y is $-OR^A$, wherein R^A is optionally substituted heterocyclyl. In some embodiments, R^y is $-OR^A$, wherein R^A is optionally substituted heteroaryl. In some embodiments, R^y is $-OR^A$, wherein R^A is optionally substituted cycloalkyl. In some embodiments, R^y is $-N(R^B)_2$. In some embodiments, R^y is $-NHR^B$. In some embodiments, R^y is $-NHR^B$, wherein R^B is optionally substituted heterocyclyl. In some embodiments, R^y is $-NHR^B$, wherein R^B is optionally substituted heteroaryl. In some embodiments, R^y is $-NHR^B$, wherein R^B is optionally substituted cycloalkyl. In some embodiments, R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heterocyclyl, and the other R^B is C_{1-4} alkyl. In some embodiments, R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted heteroaryl, and the other R^B is C_{1-4} alkyl. In some embodiments, R^y is $-N(R^B)_2$, wherein one R^B is optionally substituted cycloalkyl, and the other R^B is C_{1-4} alkyl.

[00121] As defined generally above, each R^x is independently selected from the group consisting of halo, $-CN$, optionally substituted aliphatic, $-OR'$, and $-N(R'')_2$. In certain embodiments, at least one R^x is halo. In certain embodiments, at least one R^x is fluoro. In certain embodiments, at least one R^x is $-CN$. In certain embodiments, at least one R^x is optionally substituted aliphatic. In certain embodiments, at least one R^x is optionally substituted C_{1-6} alkyl. In certain embodiments, at least one R^x is methyl. In certain embodiments, at least one R^x is $-CF_3$. In certain embodiments, at least one R^x is $-OR'$ or $-N(R'')_2$. In certain embodiments, R^x is not $-OR'$ or $-N(R'')_2$. In certain embodiments, at least one R^x is $-OCH_3$. In certain embodiments, R^x is not $-OCH_3$.

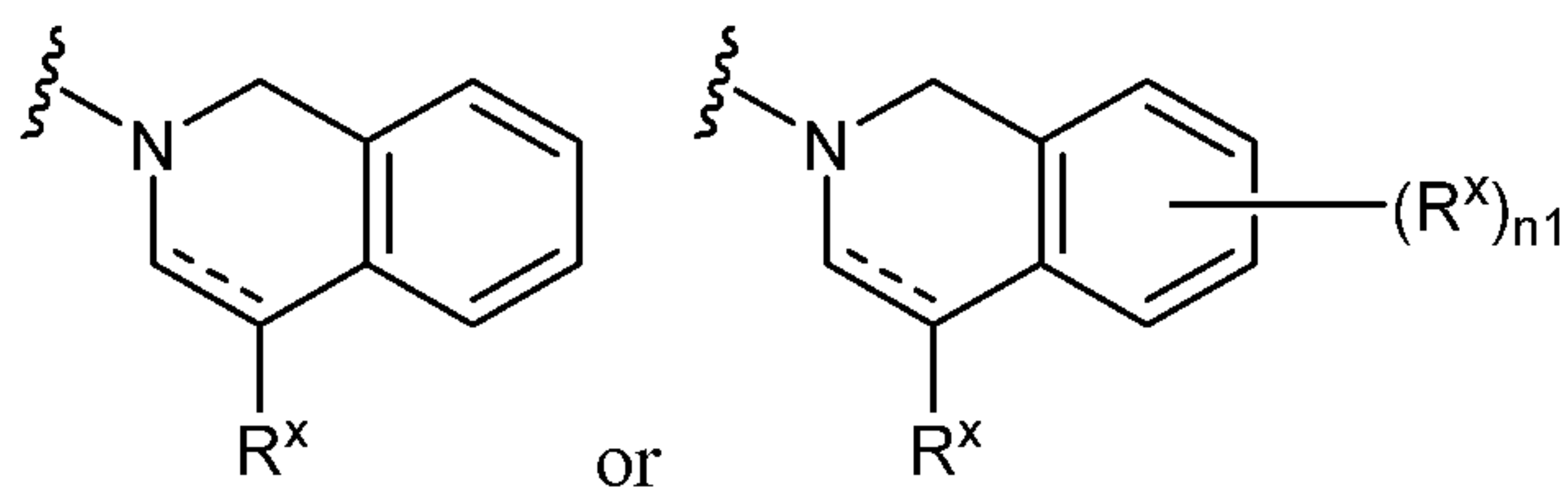
[00122] As is generally understood from the above disclosure, the ring system:



is a fused bicyclic ring system, *i.e.*, a phenyl ring fused to a nitrogen containing ring, wherein the point of attachment to the parent moiety is on the nitrogen, and wherein the fused bicyclic system is optionally substituted with $(R^x)_n$, wherein n and R^x are as defined herein. As is generally understood, each of the atoms of the phenyl ring and the nitrogen-containing ring can be independently optionally substituted with R^x , as valency permits.

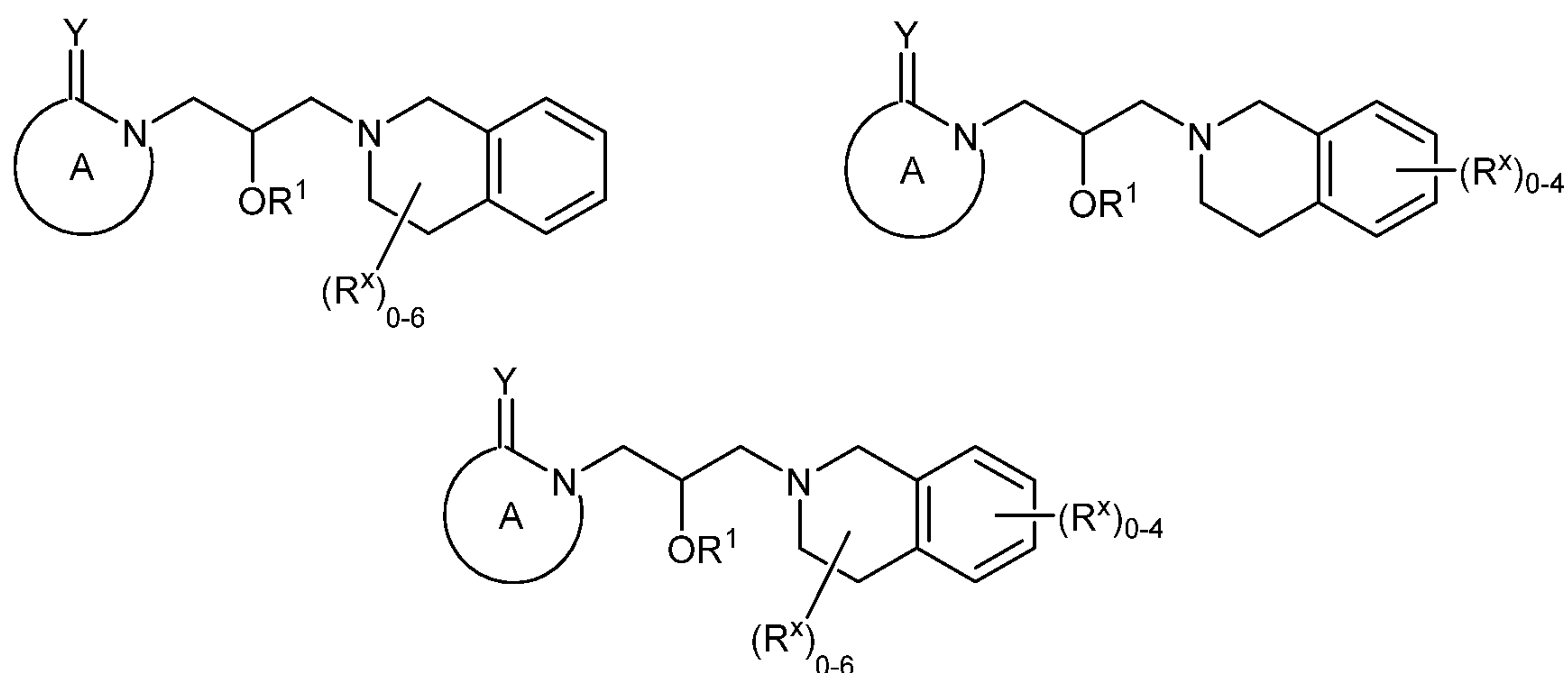
[00123] In certain embodiments, the fused bicyclic ring system is optionally substituted with one or more R^x , with the proviso that when the nitrogen-containing ring is substituted at one of the positions alpha to the nitrogen, R^x is not $-C(=O)R^{x1}$, wherein R^{x1} is optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-OR^A$, $-N(R^B)_2$, or $-SR^A$, wherein R^A and R^B are as generally defined herein. In certain embodiments, the nitrogen-containing ring does not comprise an R^x substituent. In certain embodiments, only atoms of the phenyl ring are optionally substituted with one or more R^x .

[00124] In certain embodiments, the nitrogen-containing ring is optionally substituted and the fused bicyclic ring system is of the formula:

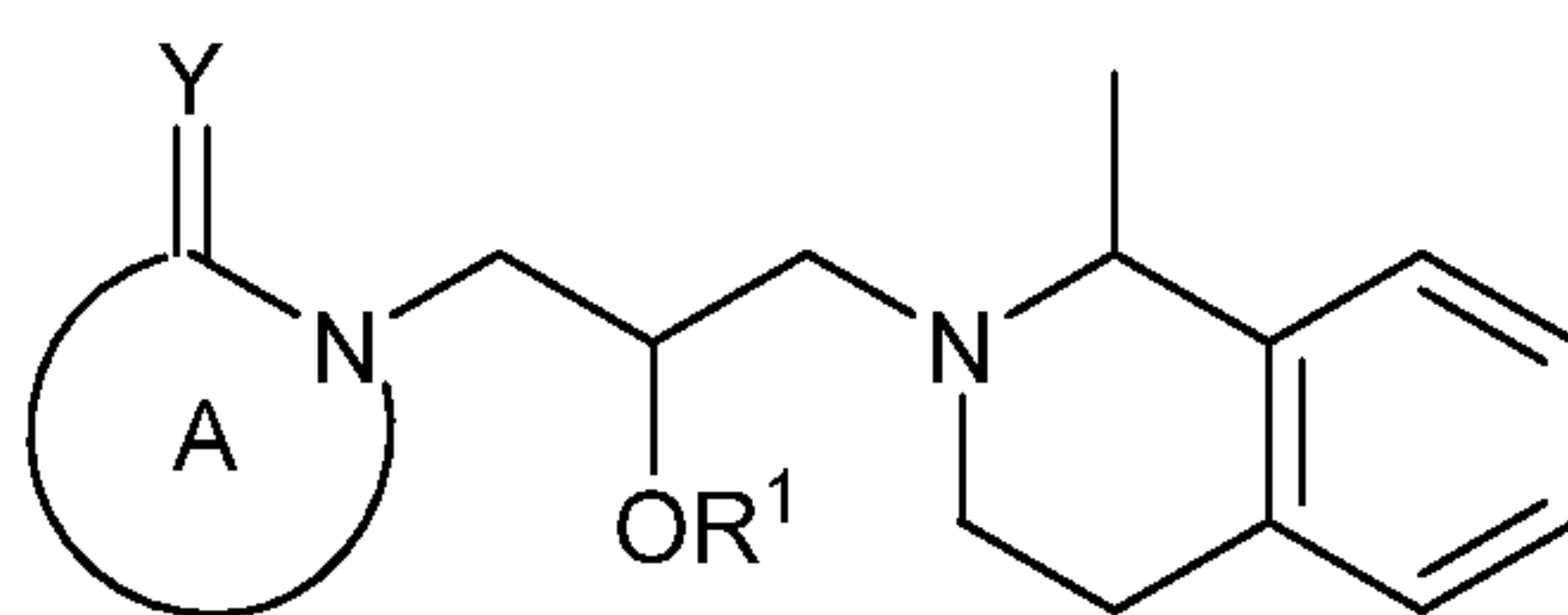


wherein R^x is as defined above, and n is 0, 1, 2, 3, or 4.

[00125] Thus, one of ordinary skill in the art will appreciate that an R^x group can be attached anywhere on the tetrahydroisoquinoline or dihydroisoquinoline ring. In certain embodiments, an R^x group is attached to the benzene portion of the tetrahydroisoquinoline or dihydroisoquinoline ring. In certain embodiments, an R^x group is attached to the tetrahydropyridine or dihydropyridine portion of the tetrahydroisoquinoline or dihydroisoquinoline ring. In certain embodiments, R^x groups are attached to both the benzene portion and the tetrahydropyridine (or dihydropyridine) portion of the tetrahydroisoquinoline (or dihydroisoquinoline) ring. See, for example, the structures shown below:



[00126] In certain embodiments, a provided compound is of Formula (VII):



VII

or a pharmaceutically acceptable salt thereof.

[00127] As defined generally above, n_1 is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10. In certain embodiments, n is 0. In certain embodiments, n is 1. In certain embodiments, n is 2.

[00128] As generally defined above, R^{A1} and R^{A2} are independently hydrogen, substituted or unsubstituted C_{1-3} alkyl, substituted or unsubstituted acyl, or a nitrogen protecting group. In some embodiments, R^{A1} is hydrogen. In some embodiments, R^{A1} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is methyl, ethyl, *n*-propyl, or isopropyl. In some embodiments, R^{A1} is substituted C_{1-3} alkyl. In some embodiments, R^{A1} is $-CF_3$, $-CHF_2$, $-CH_2F$, or $-CH(CF_3)CH_3$. In some embodiments, R^{A1} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is acetyl. In some embodiments, R^{A1} is a nitrogen protecting group. In some embodiments, R^{A1} is CH_3SO_2- . In some embodiments, R^{A2} is hydrogen. In some embodiments, R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A2} is unsubstituted C_{1-3} alkyl. In some embodiments, R^{A2} is methyl, ethyl, *n*-propyl, or isopropyl. In some embodiments, R^{A2} is substituted C_{1-3} alkyl. In some embodiments, R^{A2} is $-CF_3$, $-CHF_2$, $-CH_2F$, or $-CH(CF_3)CH_3$. In some embodiments, R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A2} is acetyl. In some embodiments, R^{A2} is a nitrogen protecting group. In some embodiments, R^{A2} is CH_3SO_2- . In some embodiments, R^{A1} is hydrogen, and R^{A2} is hydrogen. In some embodiments, R^{A1} is hydrogen, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl.

₃ alkyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is methyl, ethyl, n-propyl, or isopropyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is -CF₃, -CHF₂, -CH₂F, or -CH(CF₃)CH₃. In some embodiments, R^{A1} is hydrogen, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is acetyl. In some embodiments, R^{A1} is hydrogen, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is hydrogen and R^{A2} is CH₃SO₂-. In some embodiments, R^{A1} is substituted or unsubstituted C₁₋₃ alkyl, and R^{A2} is substituted or unsubstituted C₁₋₃ alkyl. In some embodiments, R^{A1} is substituted or unsubstituted C₁₋₃ alkyl, and R^{A2} is methyl. In some embodiments, R^{A1} is substituted or unsubstituted C₁₋₃ alkyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is substituted or unsubstituted C₁₋₃ alkyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is substituted or unsubstituted C₁₋₃ alkyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is substituted or unsubstituted C₁₋₃ alkyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is substituted or unsubstituted C₁₋₃ alkyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is methyl, and R^{A2} is substituted or unsubstituted C₁₋₃ alkyl. In some embodiments, R^{A1} is methyl, and R^{A2} is methyl. In some embodiments, R^{A1} is methyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is methyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is methyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is methyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is methyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is ethyl, and R^{A2} is substituted or unsubstituted C₁₋₃ alkyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is methyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is ethyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is n-propyl, and R^{A2} is substituted or unsubstituted C₁₋₃ alkyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is methyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is ethyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is n-propyl and R^{A2} is isopropyl. In some embodiments, R^{A1} is n-propyl, and R^{A2} is substituted or unsubstituted acyl. In some embodiments, R^{A1} is n-propyl and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is isopropyl and R^{A2} is substituted or unsubstituted C₁₋₃ alkyl. In some embodiments, R^{A1} is isopropyl and R^{A2} is methyl. In some embodiments, R^{A1} is isopropyl and R^{A2} is ethyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is n-propyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is isopropyl. In some embodiments, R^{A1} is isopropyl, and R^{A2} is substituted or unsubstituted acyl. In some

embodiments, R^{A1} is isopropyl, and R^{A2} is a nitrogen protecting group. In some embodiments, R^{A1} is substituted or unsubstituted acyl, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is substituted or unsubstituted C_{1-3} alkyl. In some embodiments, R^{A1} is a nitrogen protecting group and R^{A2} is methyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is ethyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is n-propyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is isopropyl. In some embodiments, R^{A1} is a nitrogen protecting group, and R^{A2} is a nitrogen protecting group.

[00129] As generally defined above, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted 3-6 membered heterocyclic ring. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted azetidine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted pyrrolidine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted piperidine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted piperazine. In certain embodiments, R^{A1} and R^{A2} can be taken together with the intervening nitrogen atom to form a substituted or unsubstituted morpholine.

[00130] In some embodiments, *e.g.* for Formula (A), Formula (I), or any subgenera thereof, the provided compound is of a free base form. In some embodiments, *e.g.* for Formula (A), Formula (I), or any subgenera thereof, the provided compound is in the form of a pharmaceutically acceptable salt as generally defined herein. In some embodiments, the provided compound is a hydrochloride salt thereof. In some embodiments, the provided compound is a tartrate salt thereof. In some embodiments, the provided compound is a monotartrate salt thereof. In some embodiments, the provided compound is a bitartrate salt thereof.

[00131] In certain embodiments, a provided compound is a compound listed in Table 1A, or a pharmaceutically acceptable salt thereof.

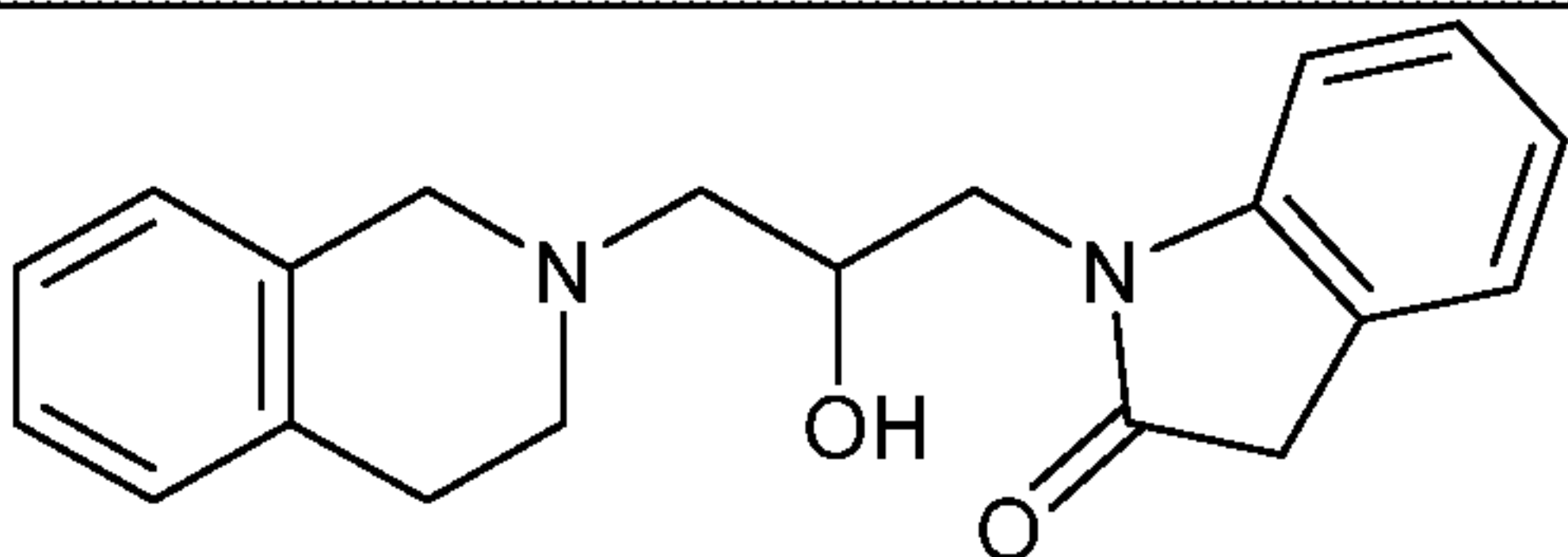
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
1		322.1681	323.1

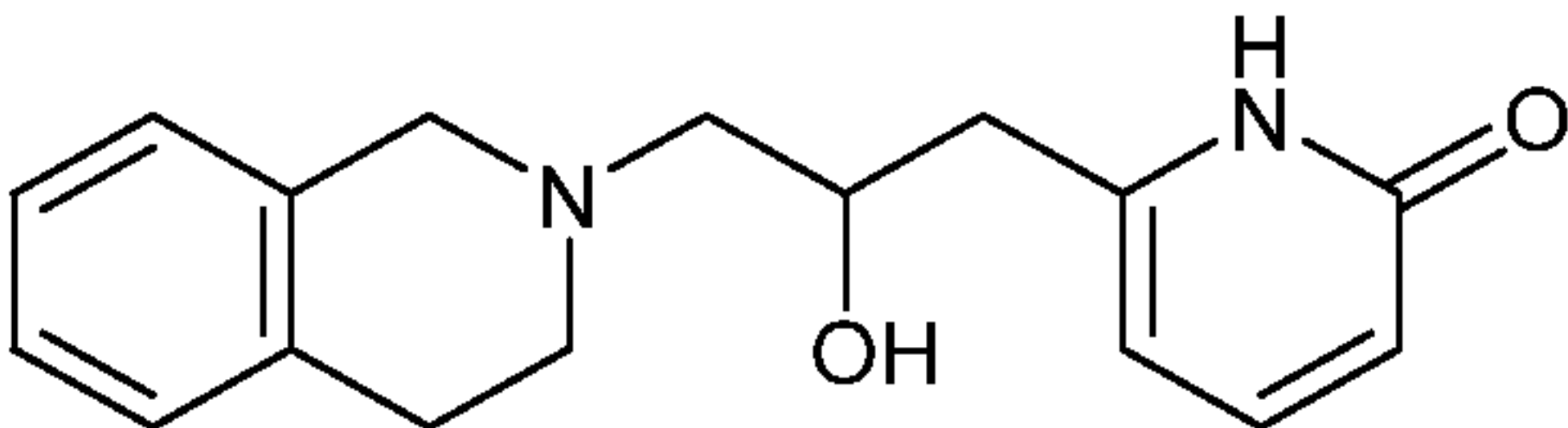
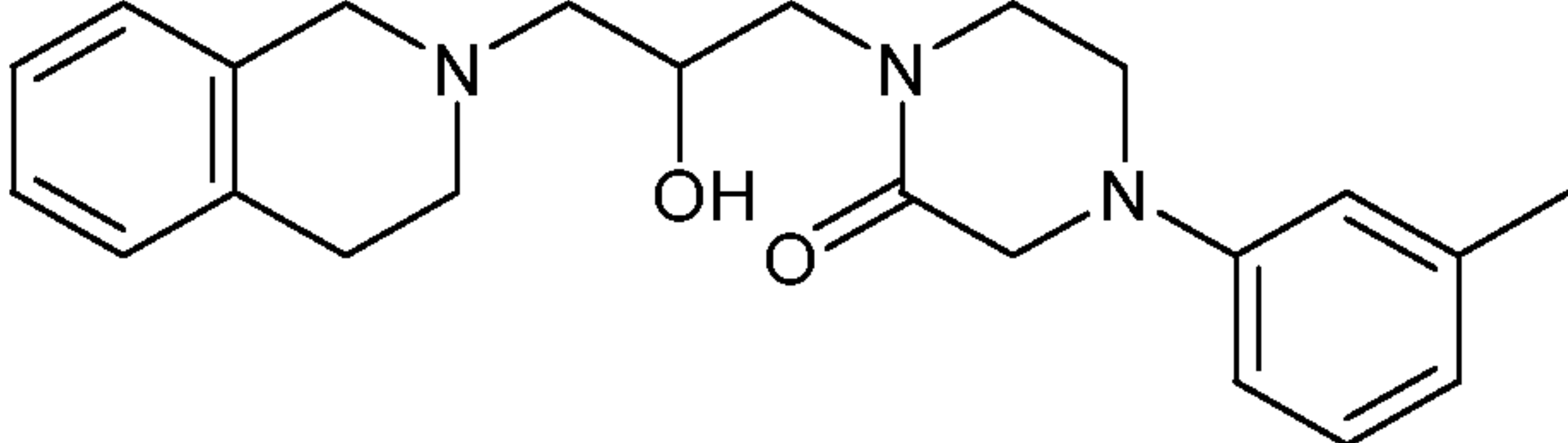
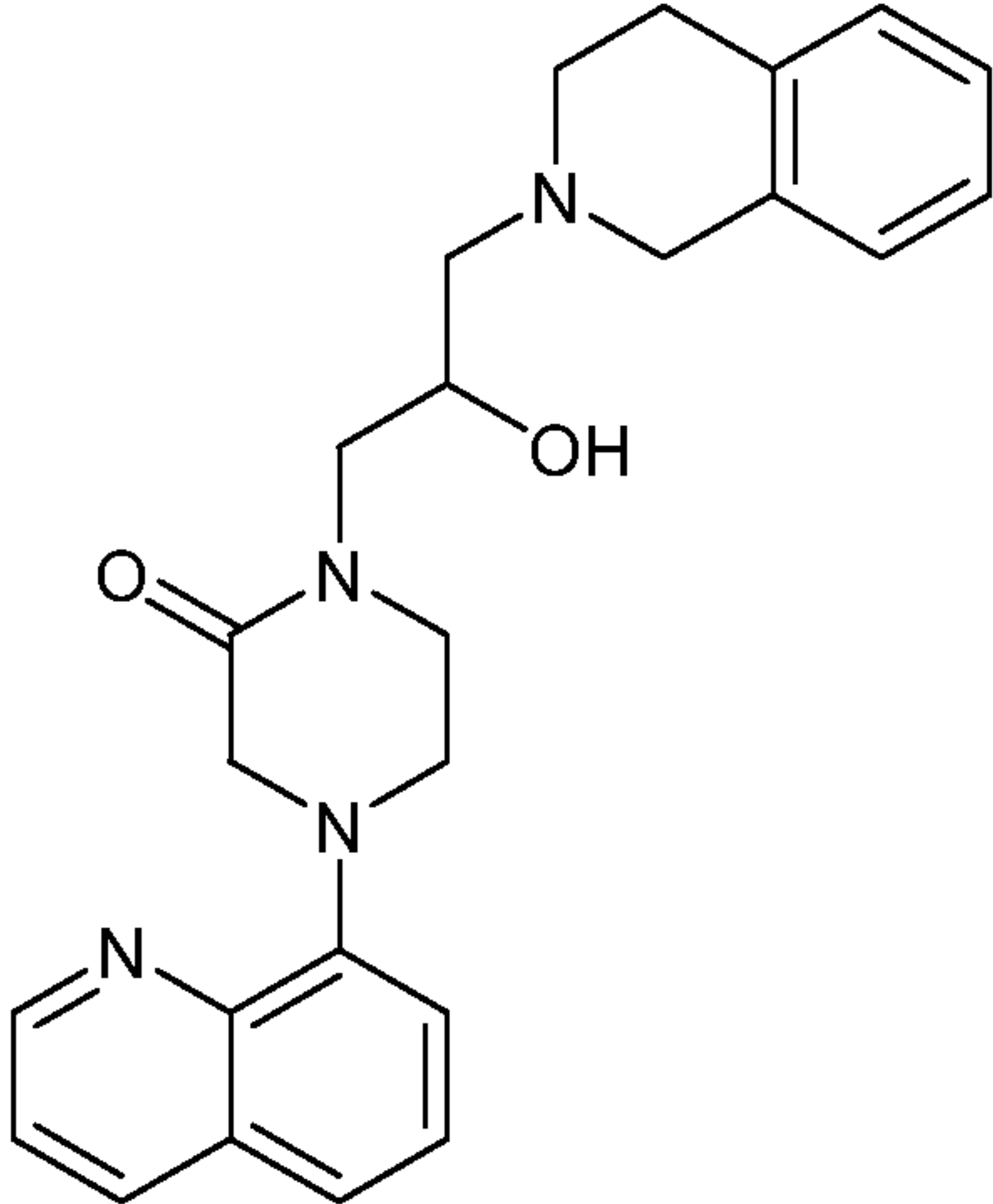
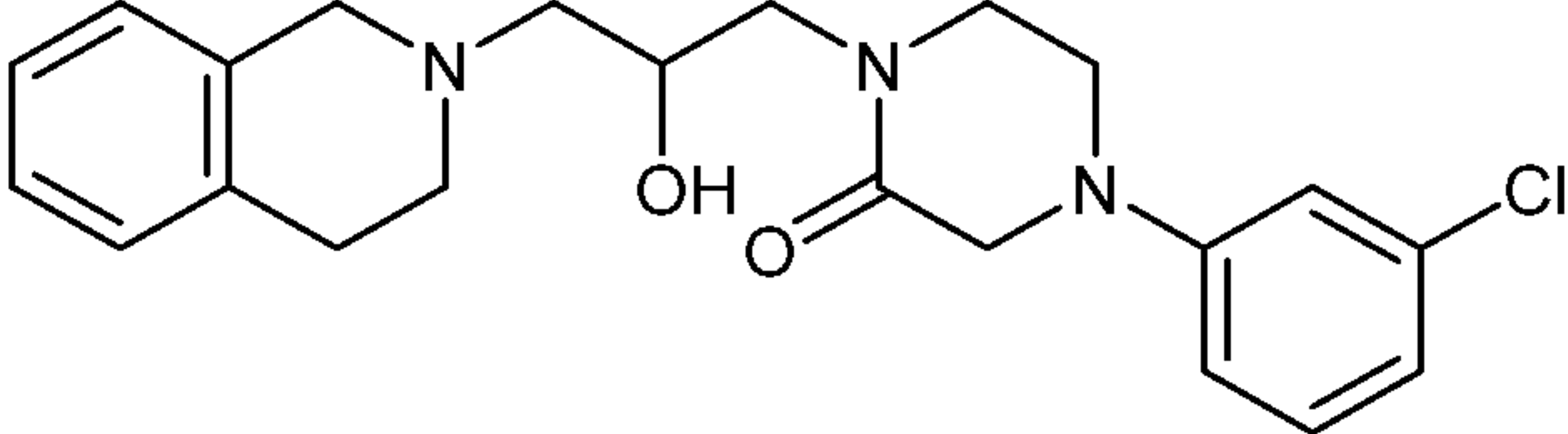
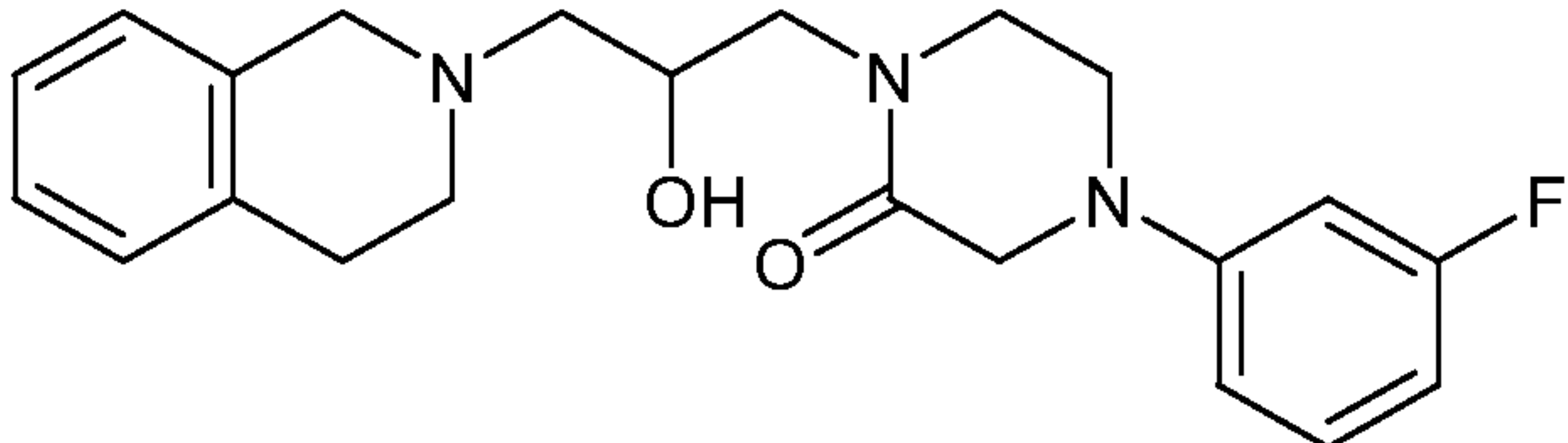
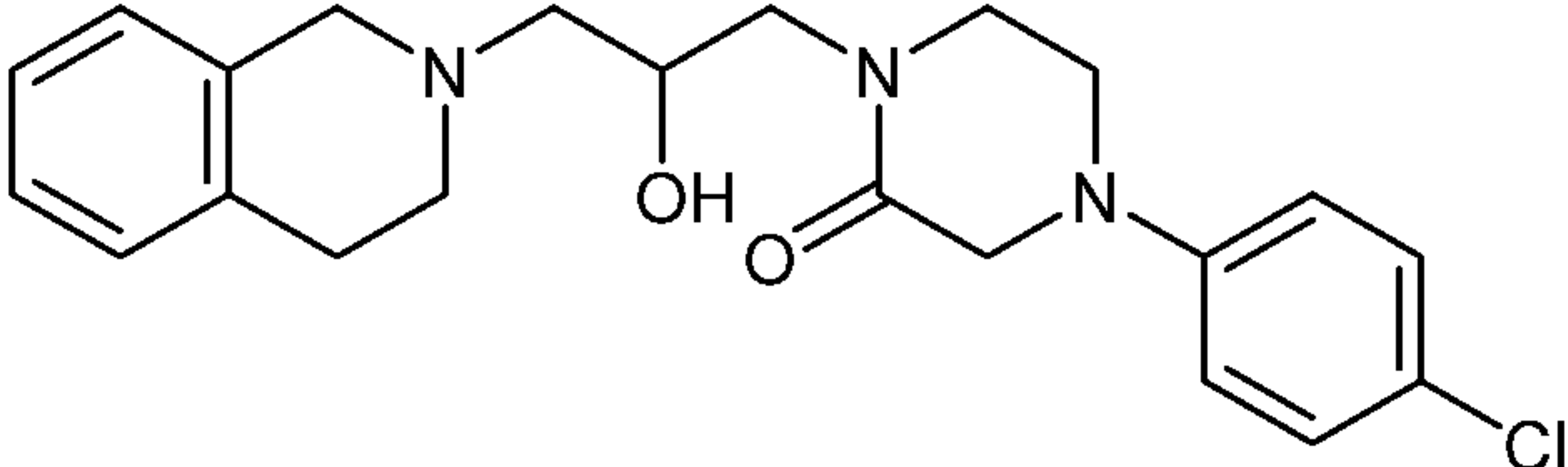
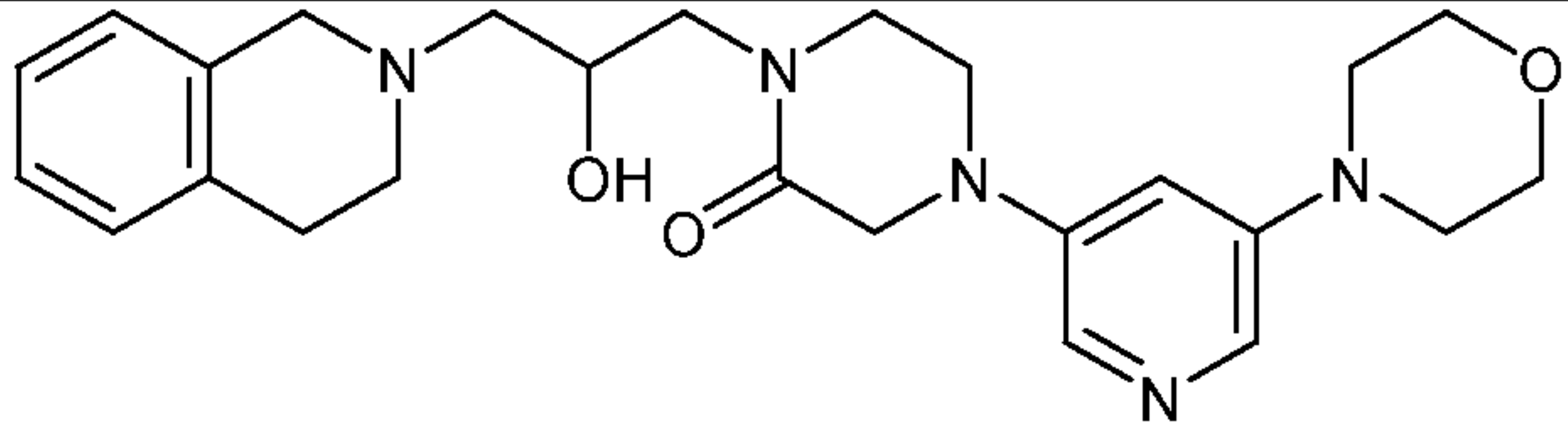
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
2		284.1525	285.1
3		379.226	380.2
4		416.2212	417.2
5		399.1714	400.1
6		383.2009	384.2
7		399.1714	400.1
8		451.2583	452.3

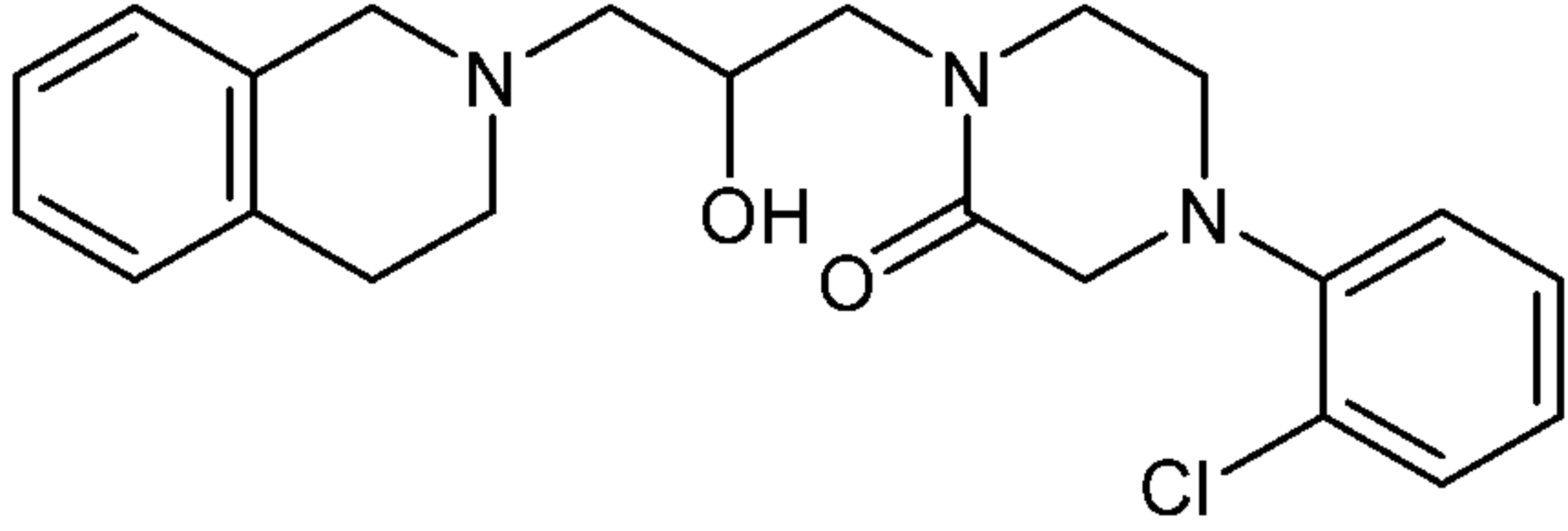
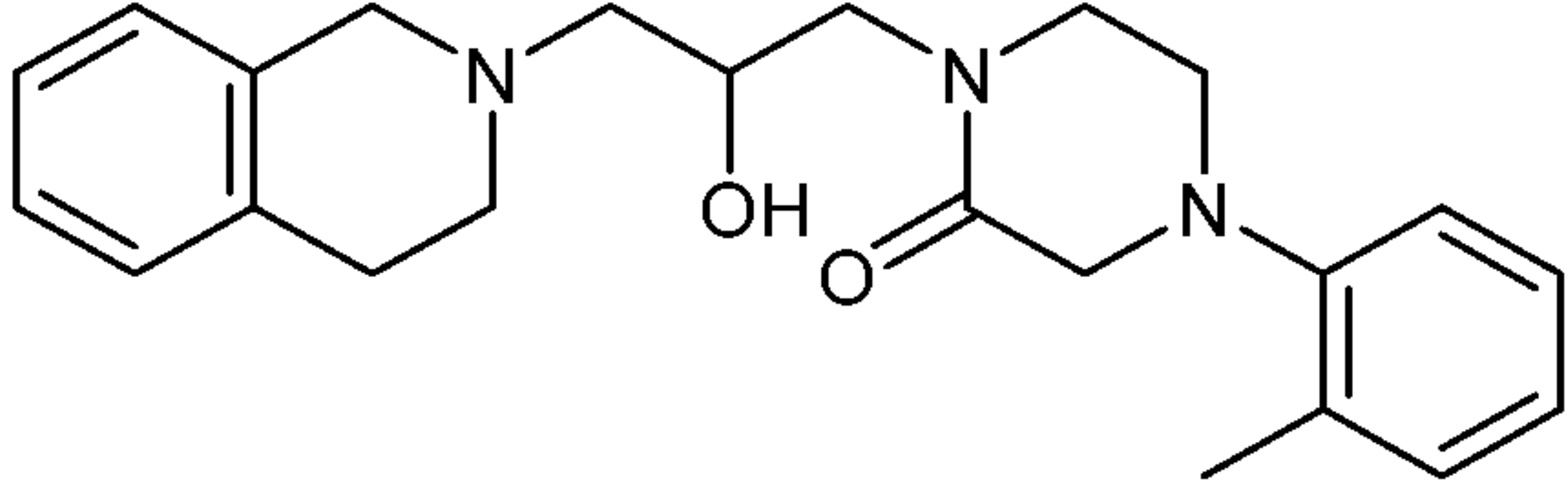
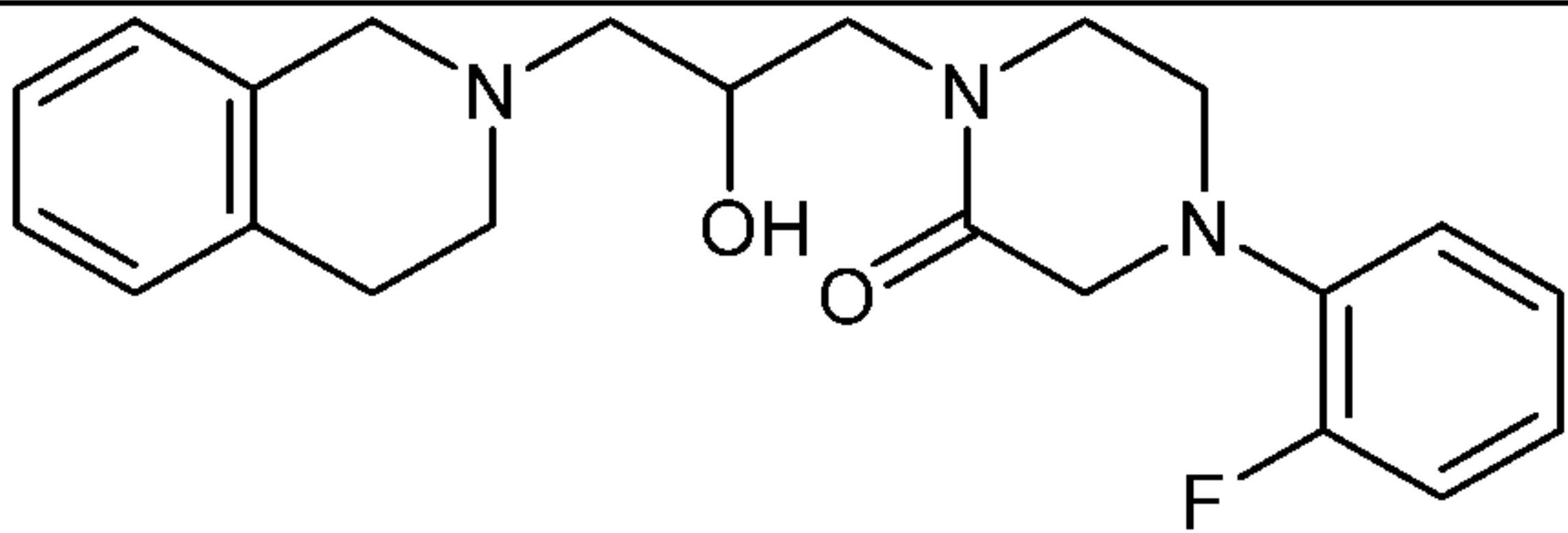
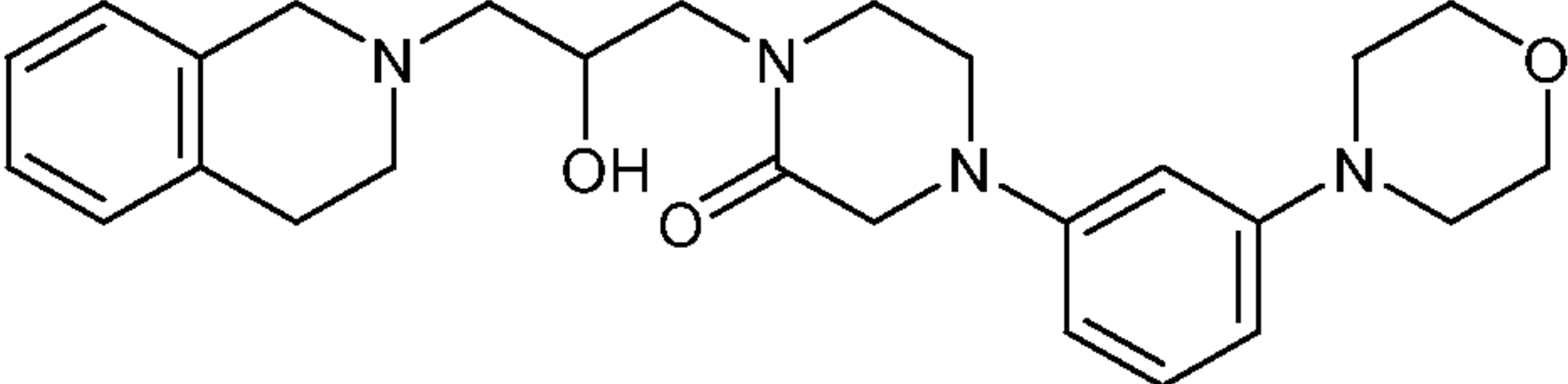
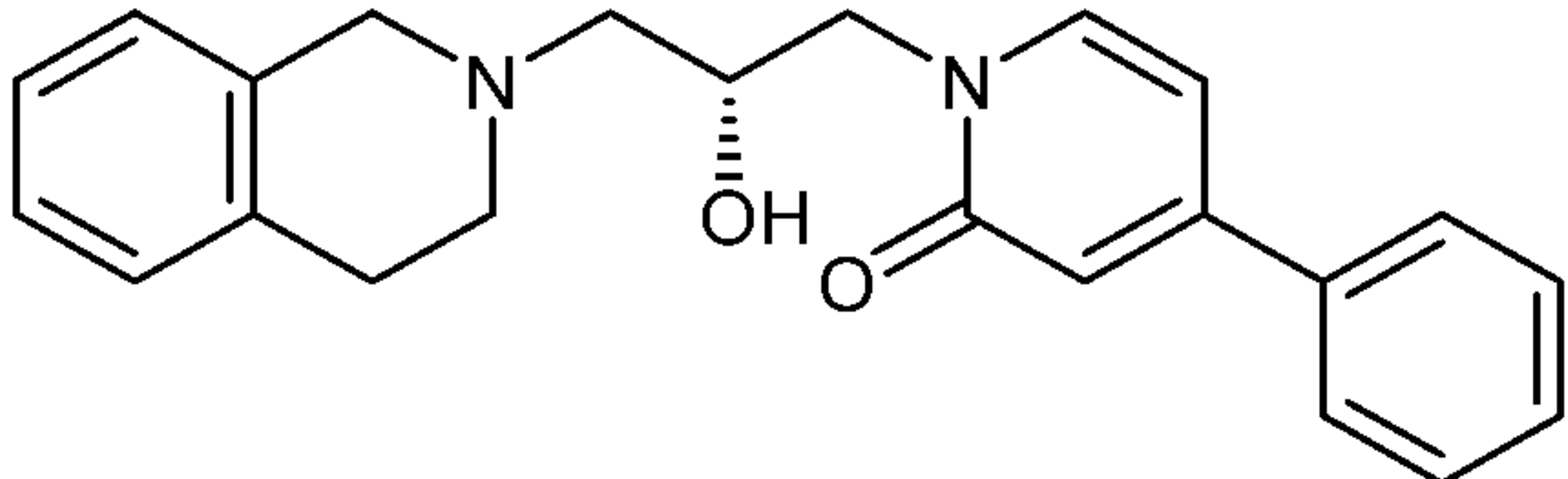
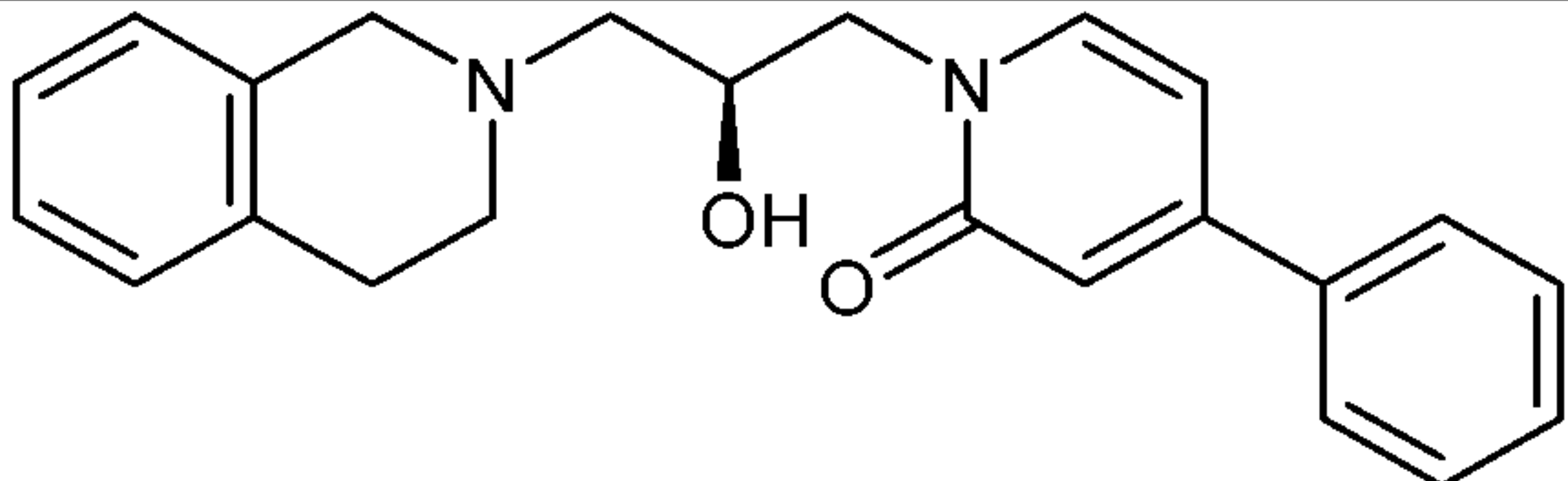
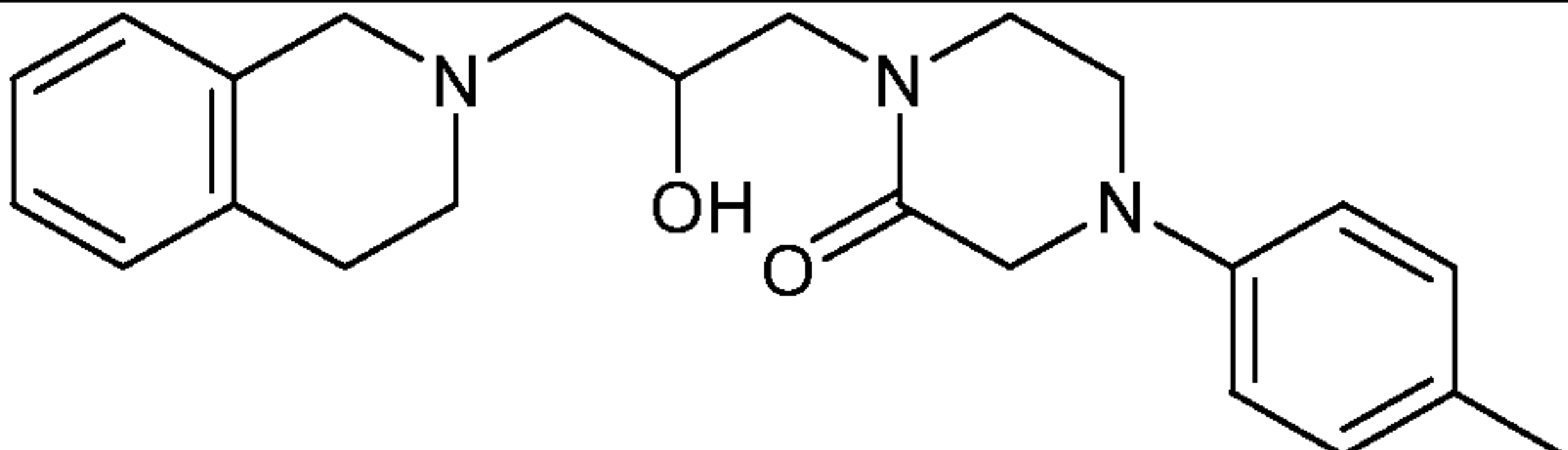
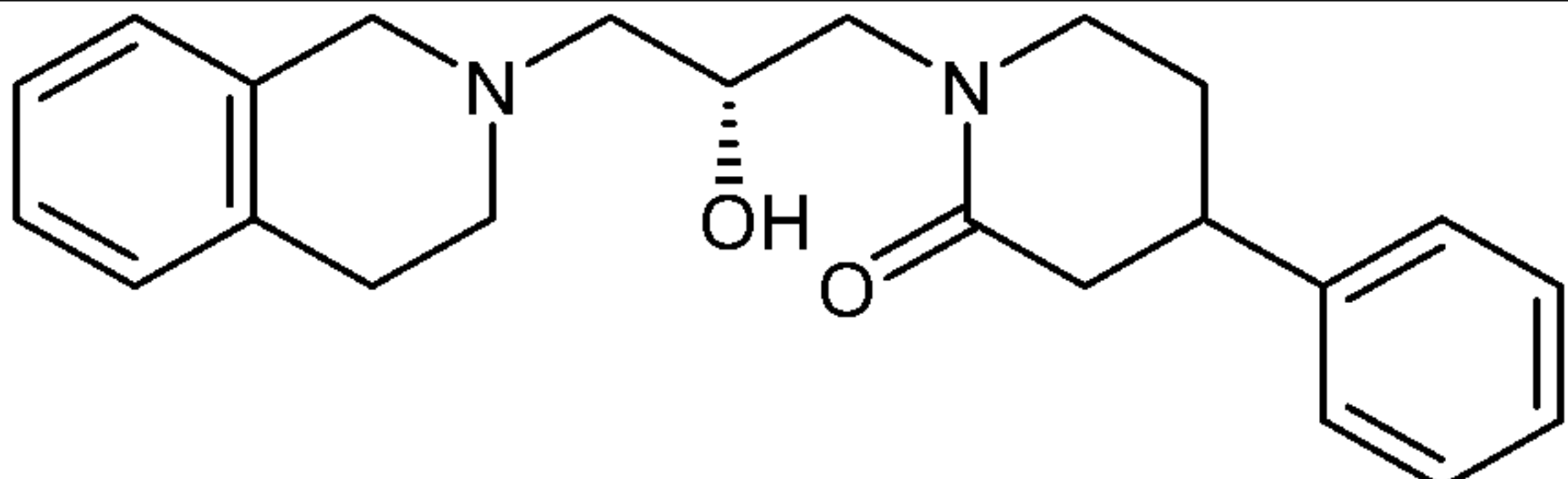
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
9		399.1714	400.1
10		379.226	380.2
11		383.2009	384.2
12		450.2631	451.2
13		360.1838	361.2
14		360.1838	361.2
15		379.226	380.2
16		364.2151	365.2

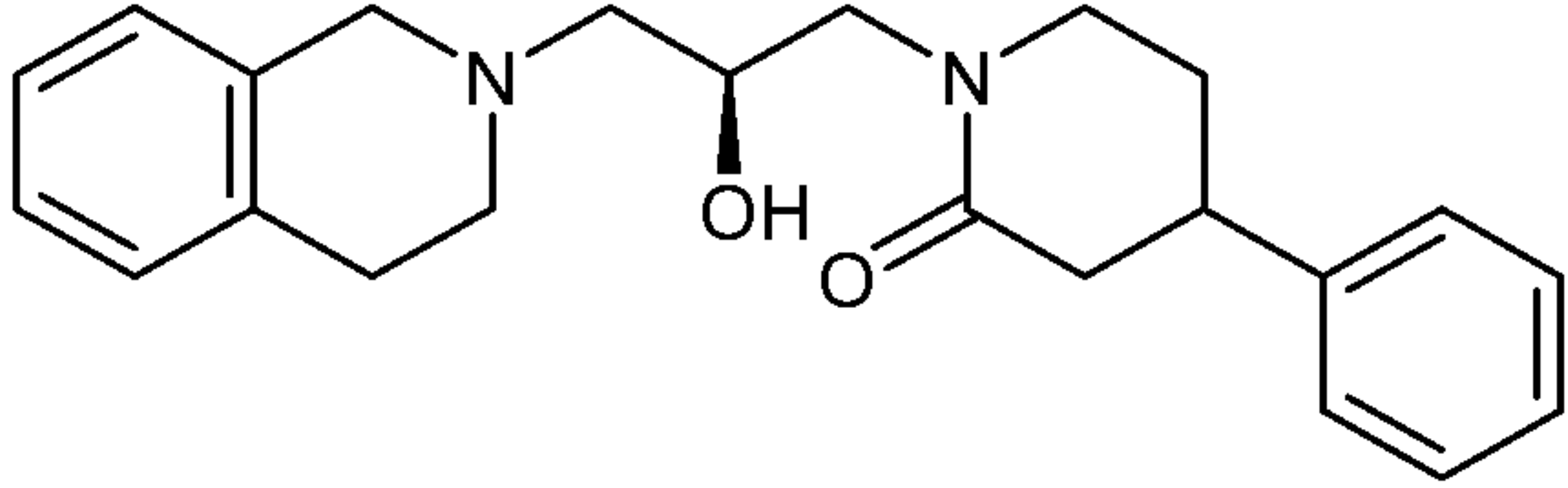
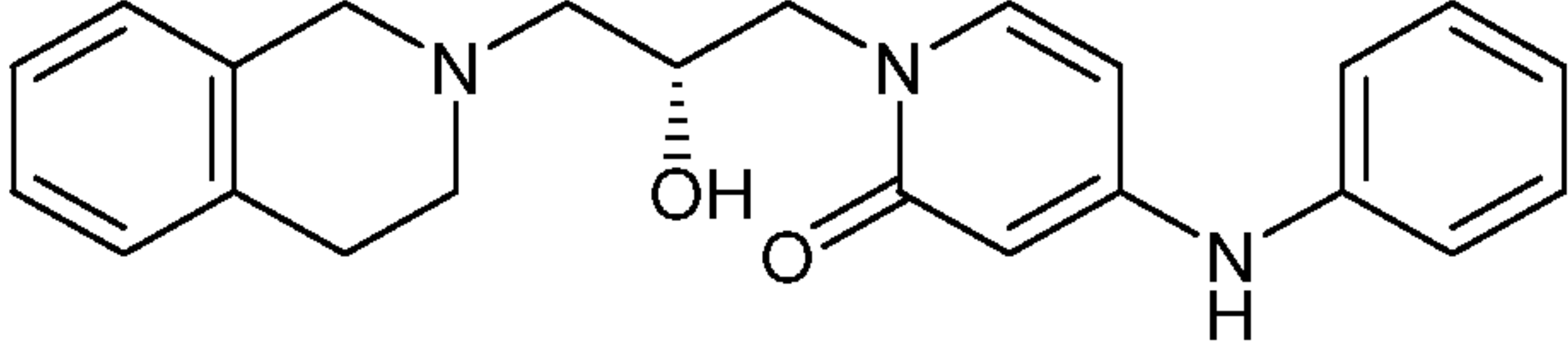
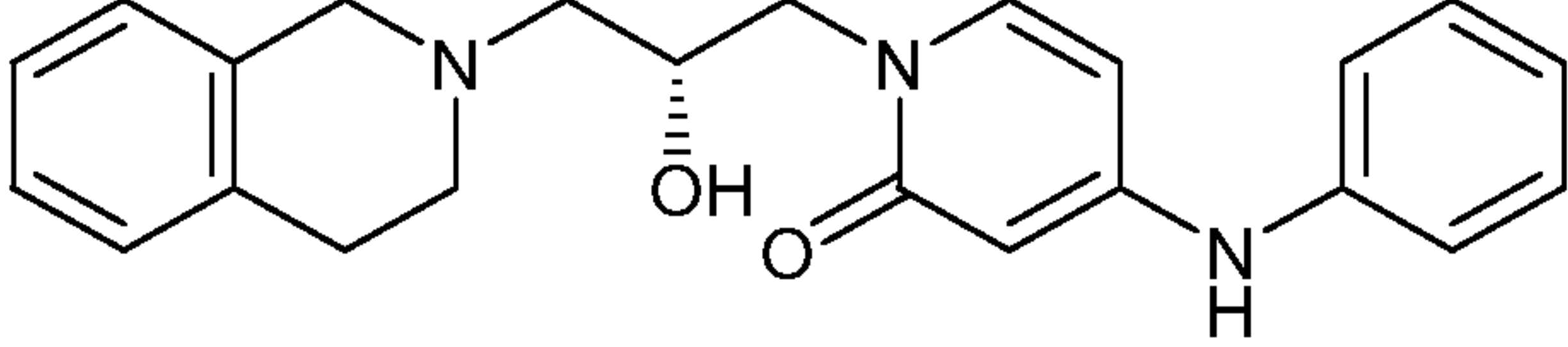
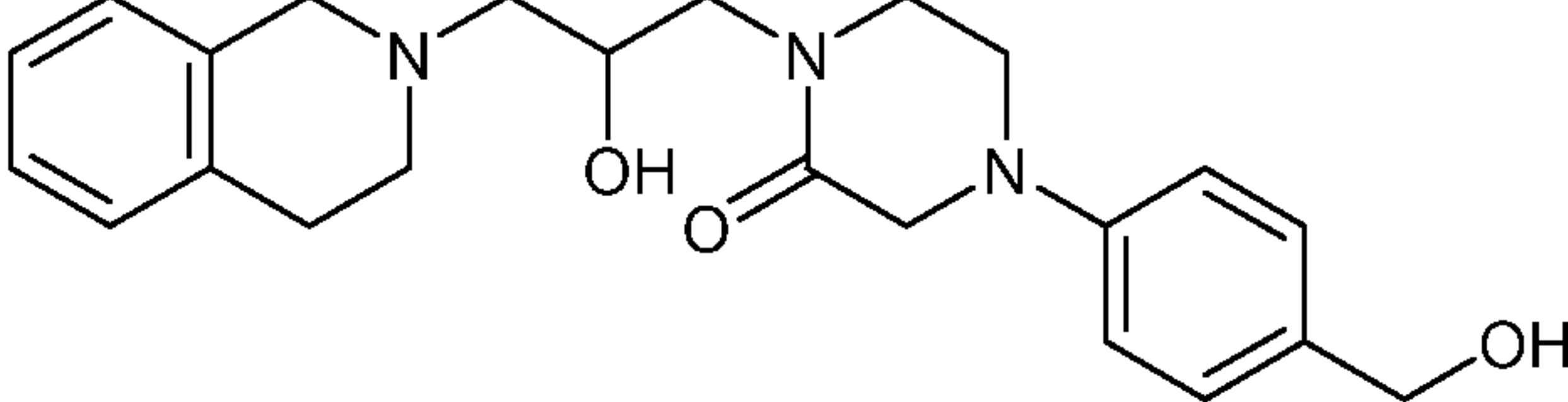
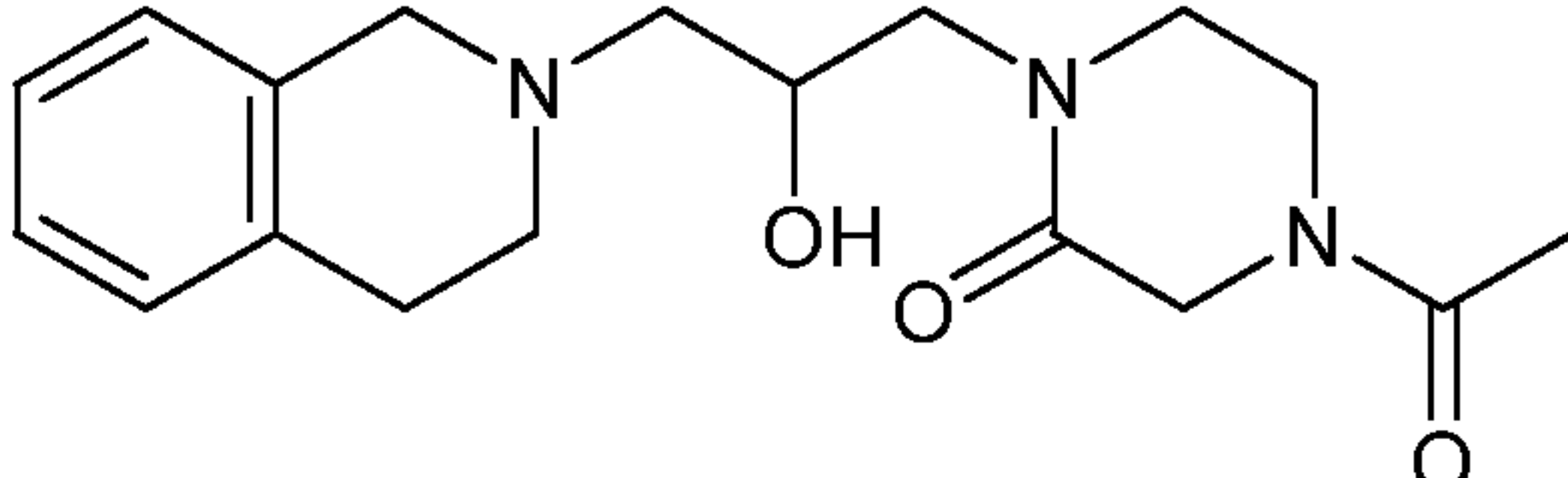
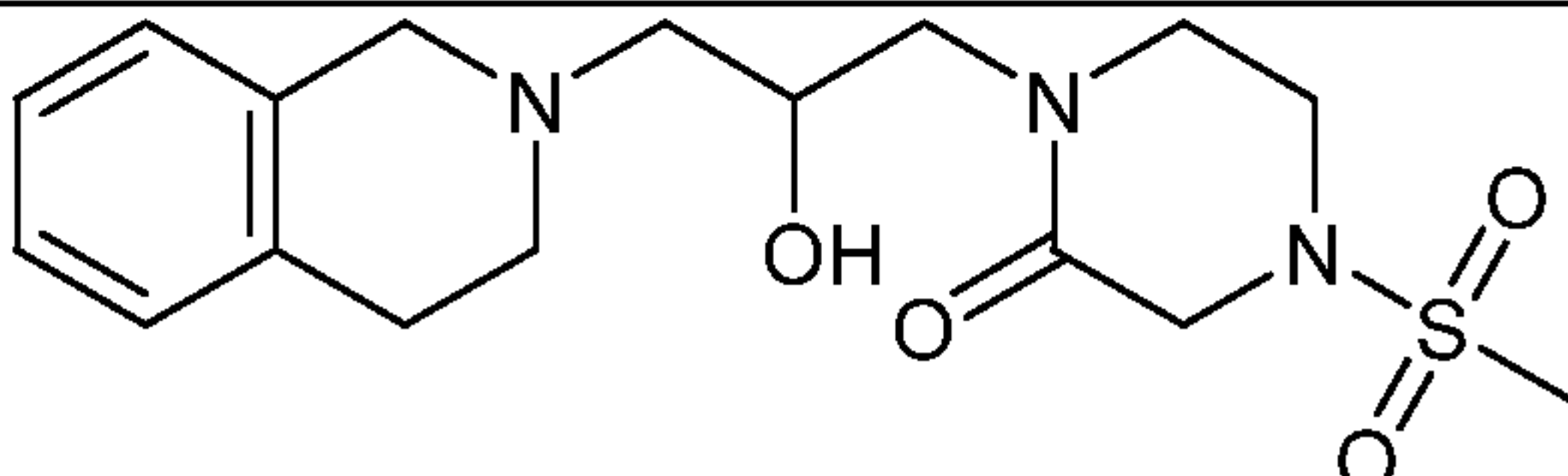
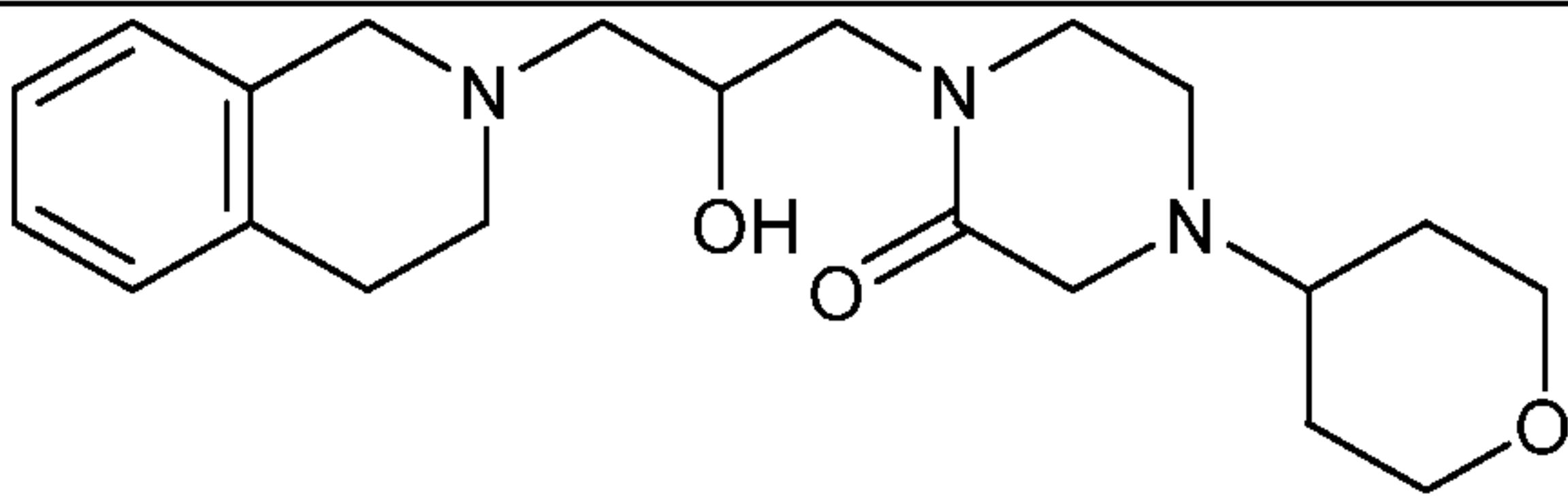
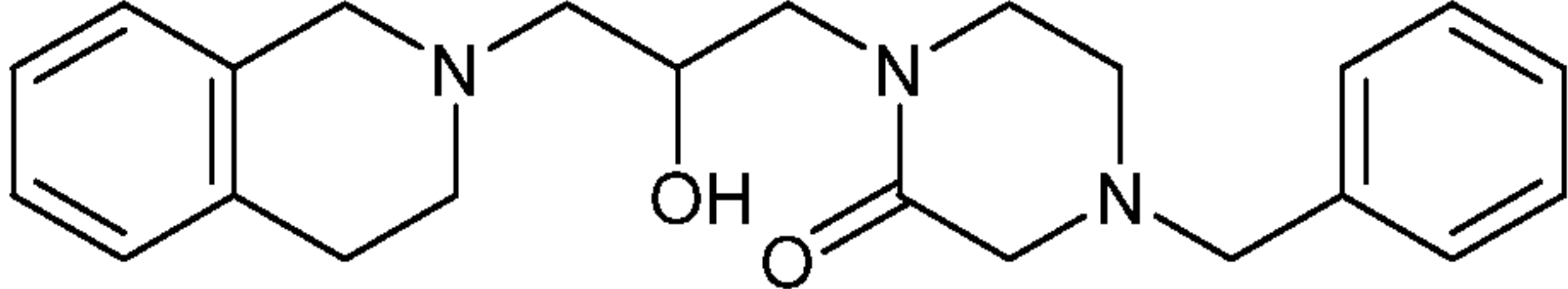
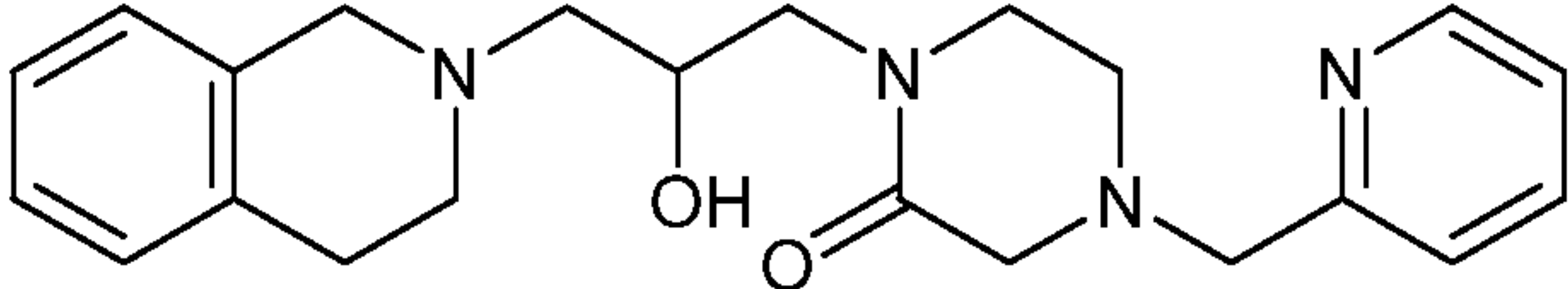
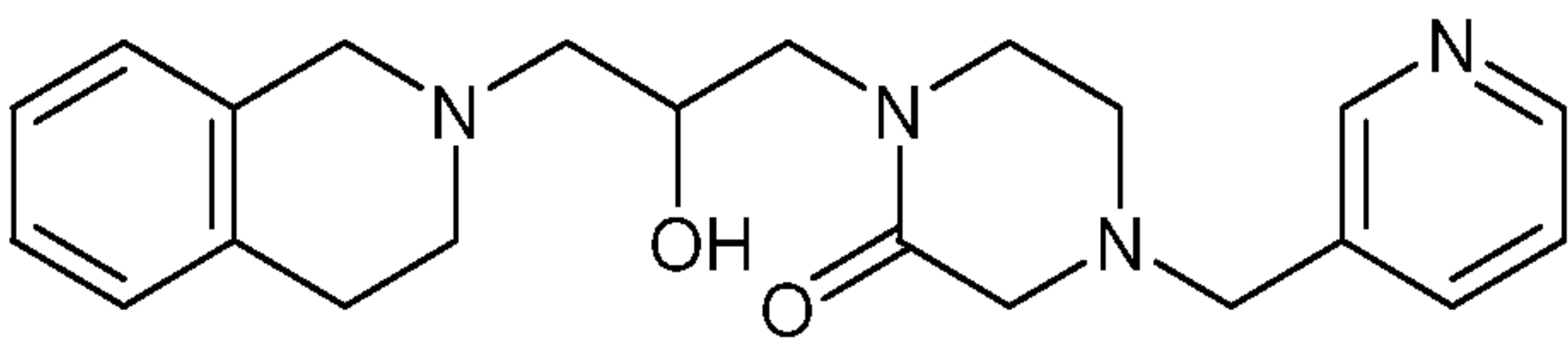
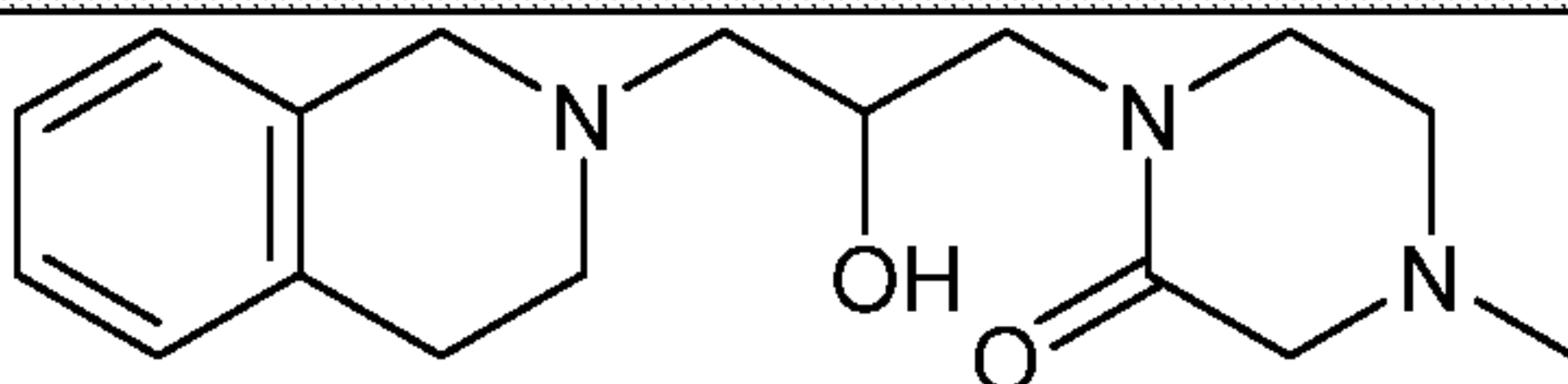
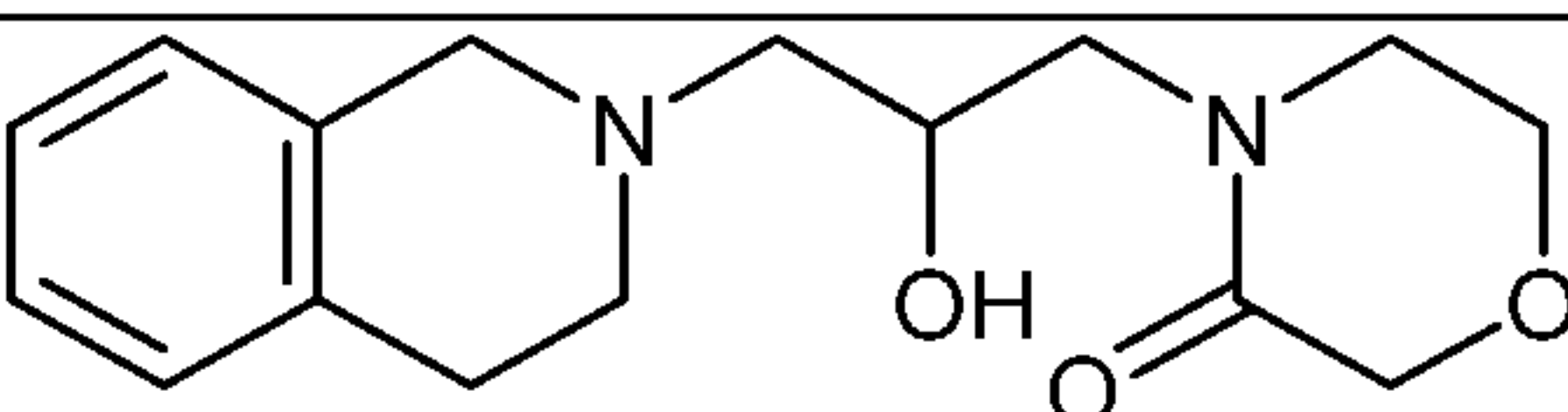
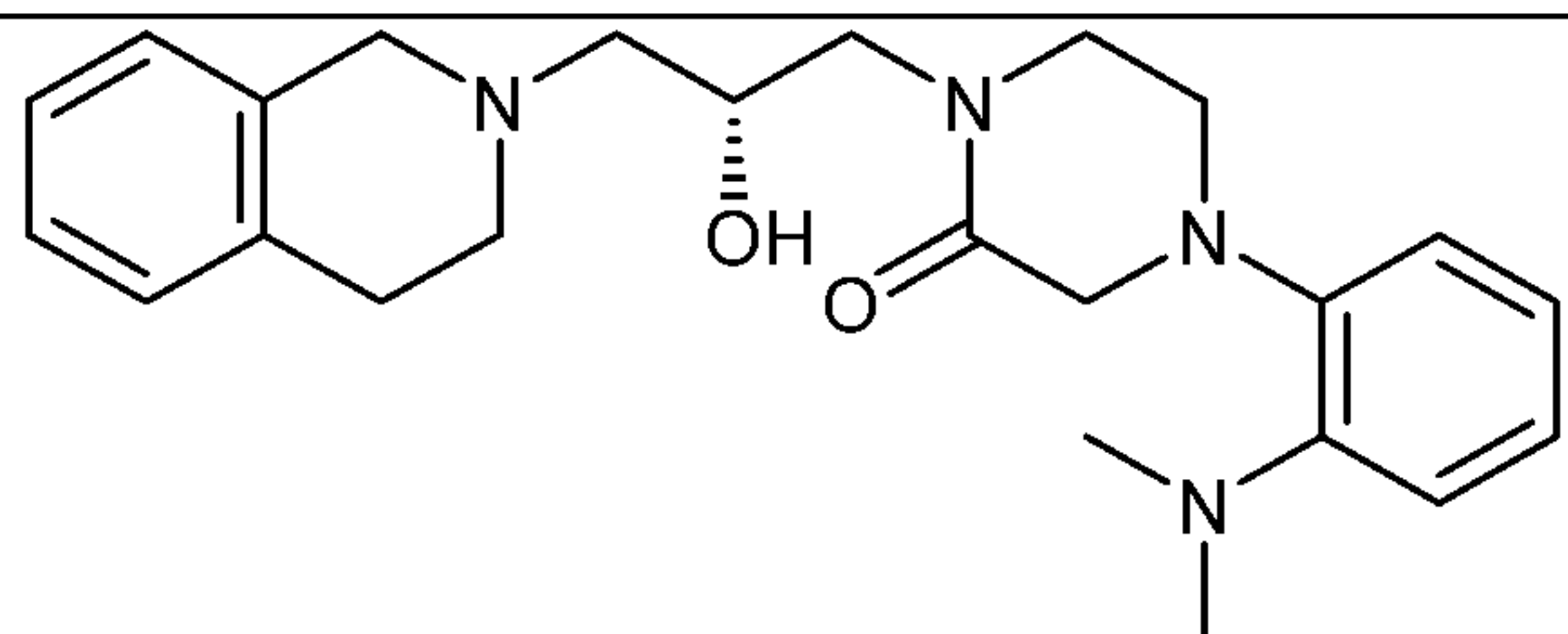
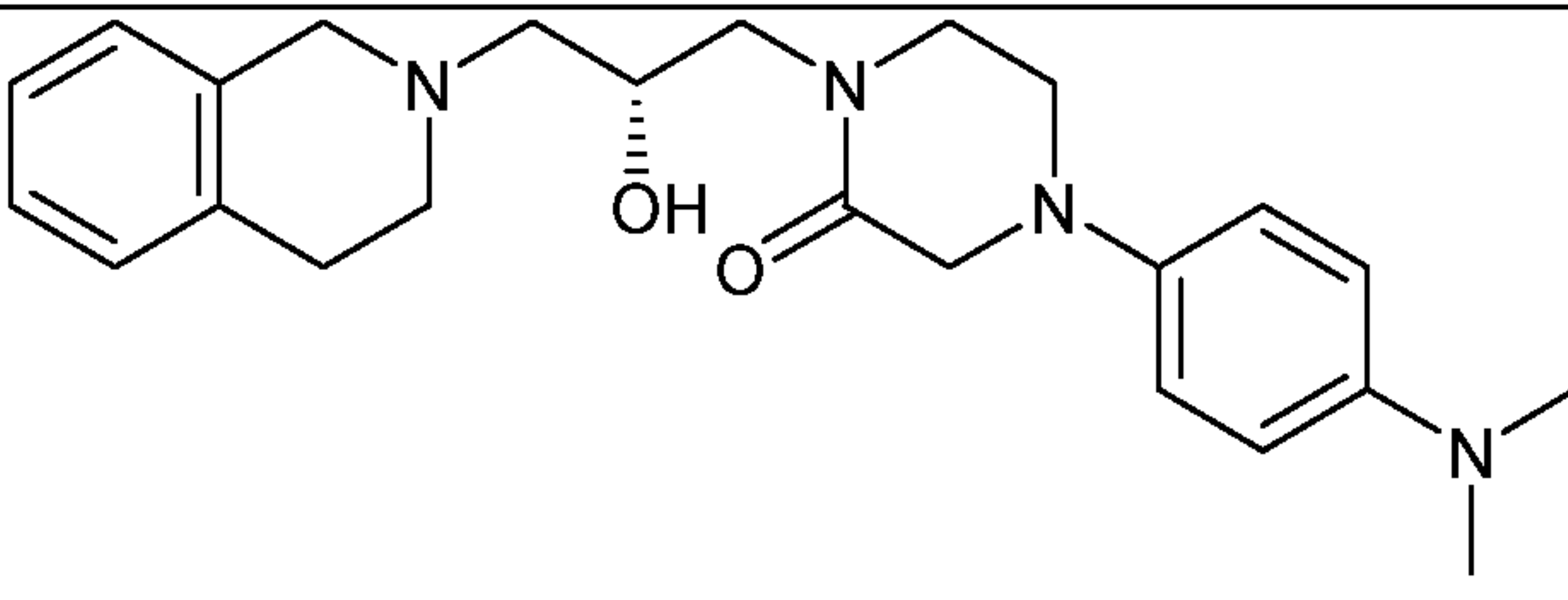
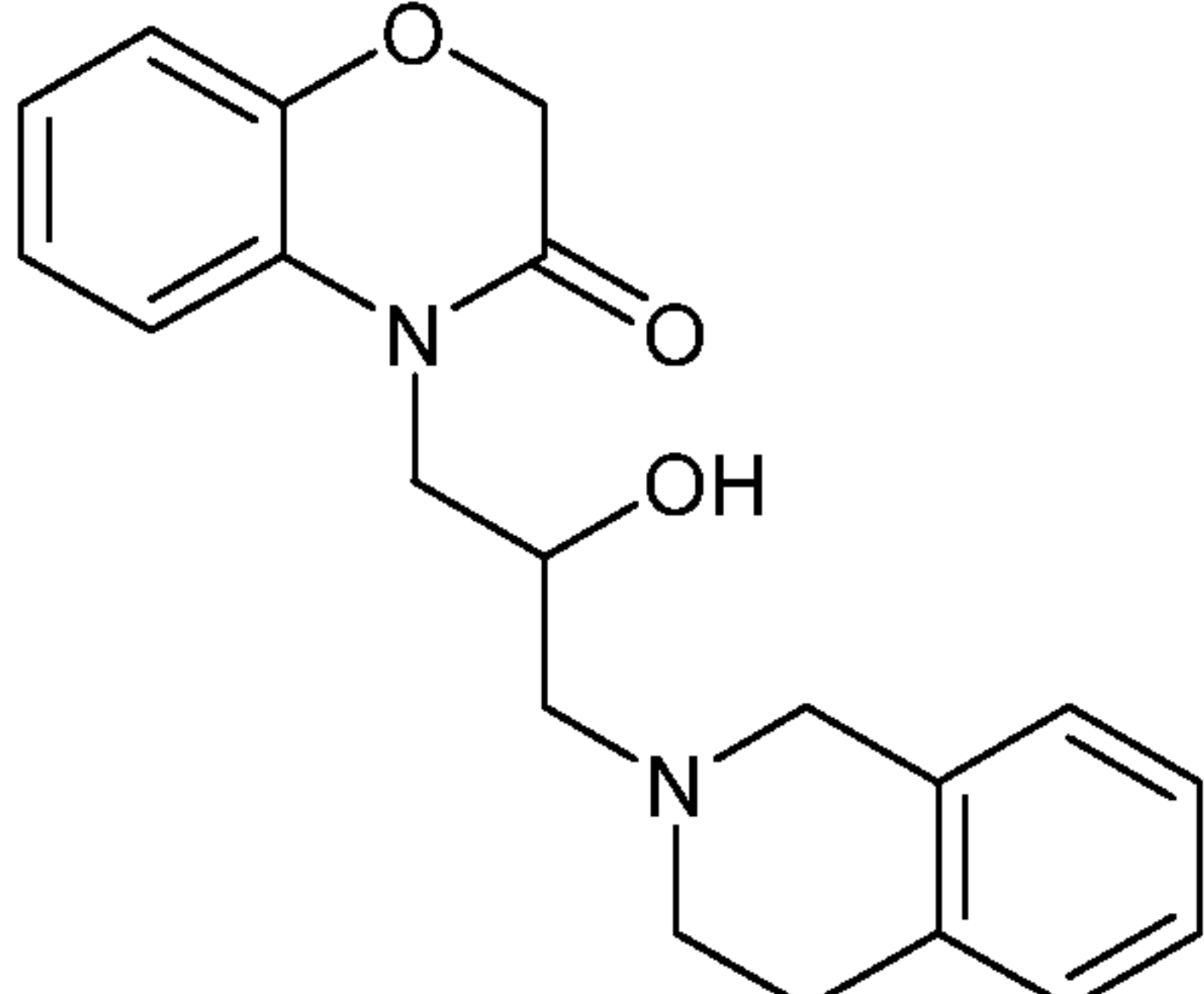
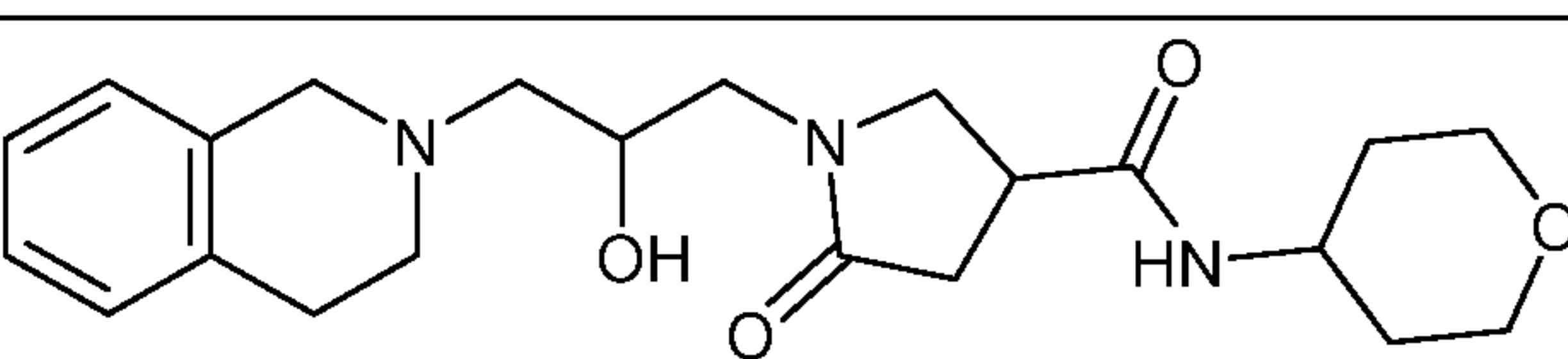
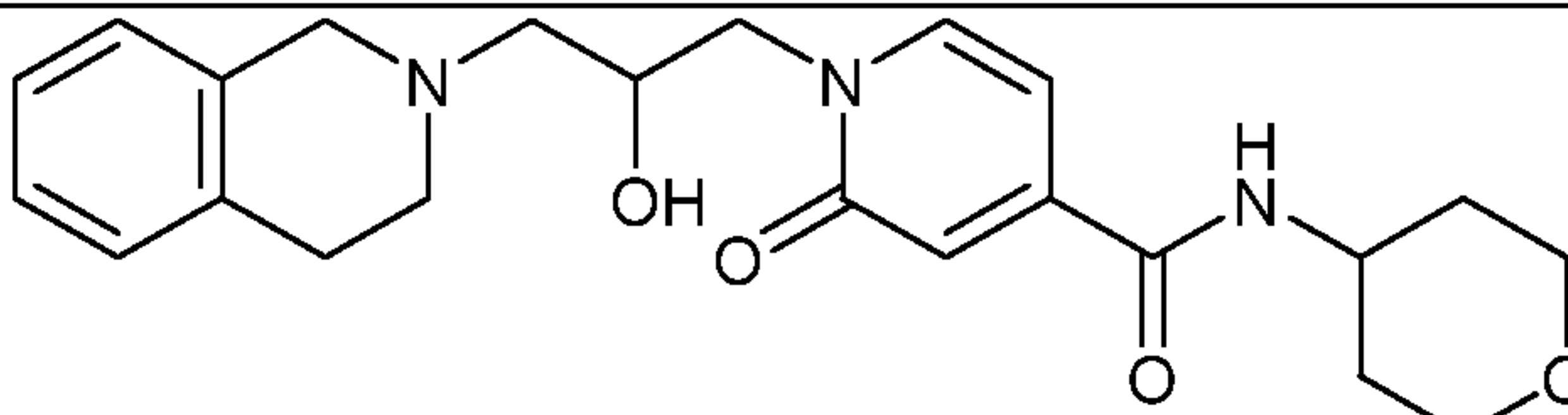
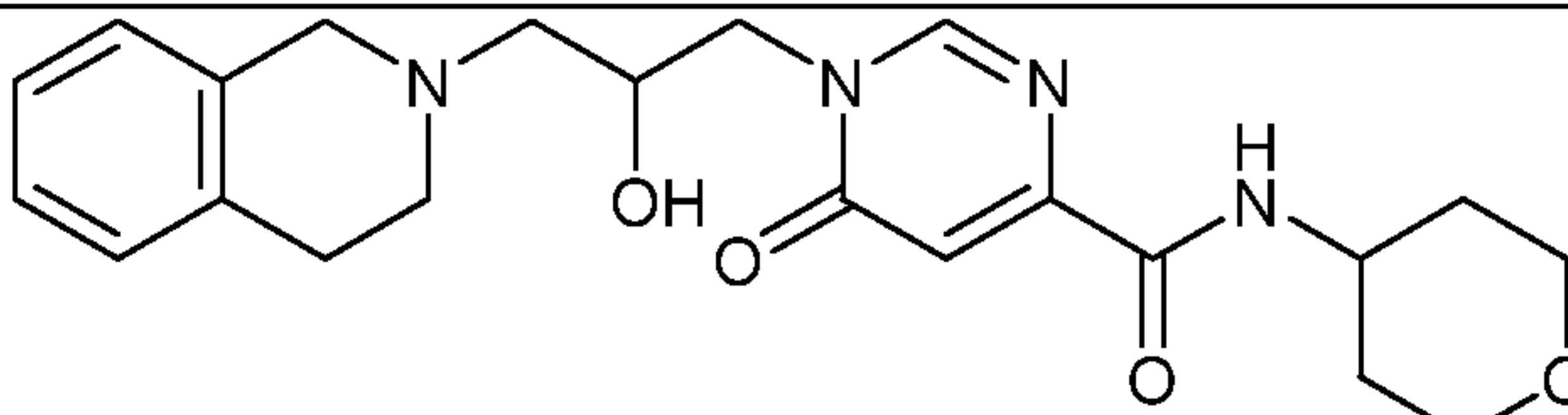
Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
17		364.2151	365.2
18		375.1947	376.2
19		375.1947	376.2
20		395.2209	396.2
21		331.1896	332.1
22		367.1566	368.1
23		373.2365	374.2
24		379.226	380.1
25		380.2212	381.2
26		380.2212	381.1

Table 1A. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
27		303.1947	304.1
28		290.163	291.1
29		408.2525	409.3
30		408.2525	407.2
31		338.163	339.2
32		401.2315	402.2
33		411.2158	412.1
34		412.2111	413.1

[00132] In certain embodiments, a provided compound is a compound listed in Table 1B, or a pharmaceutically acceptable salt thereof.

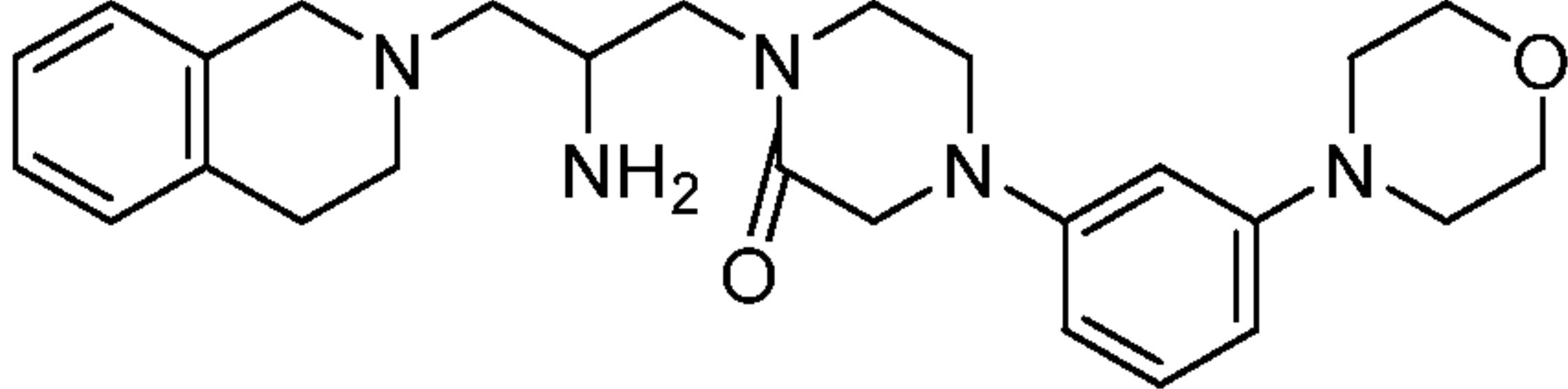
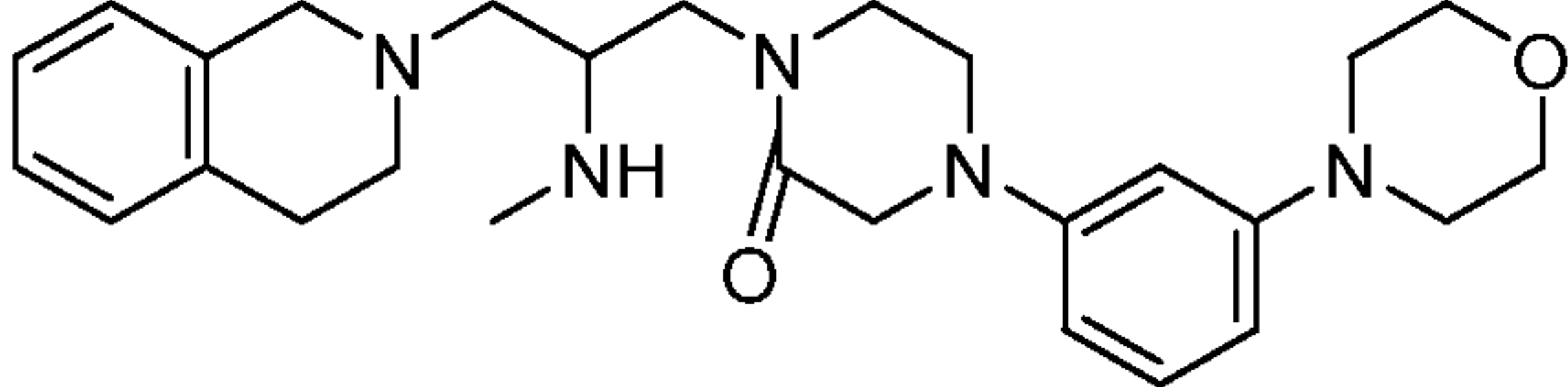
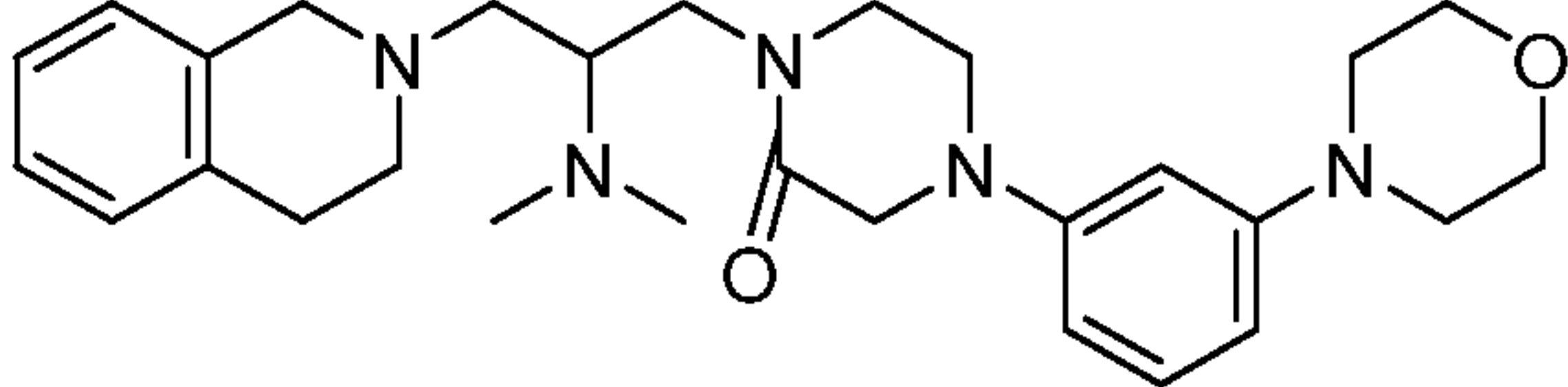
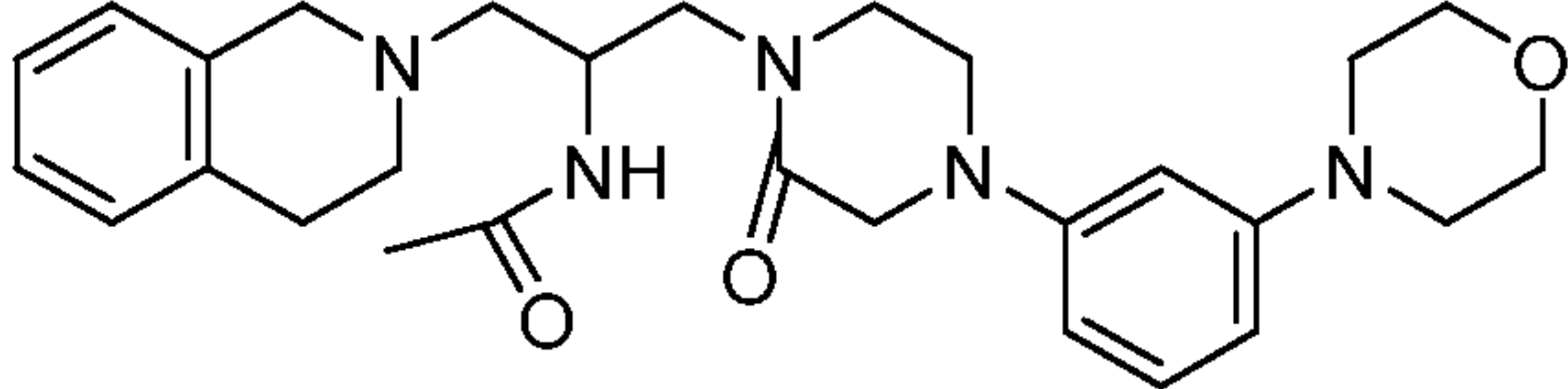
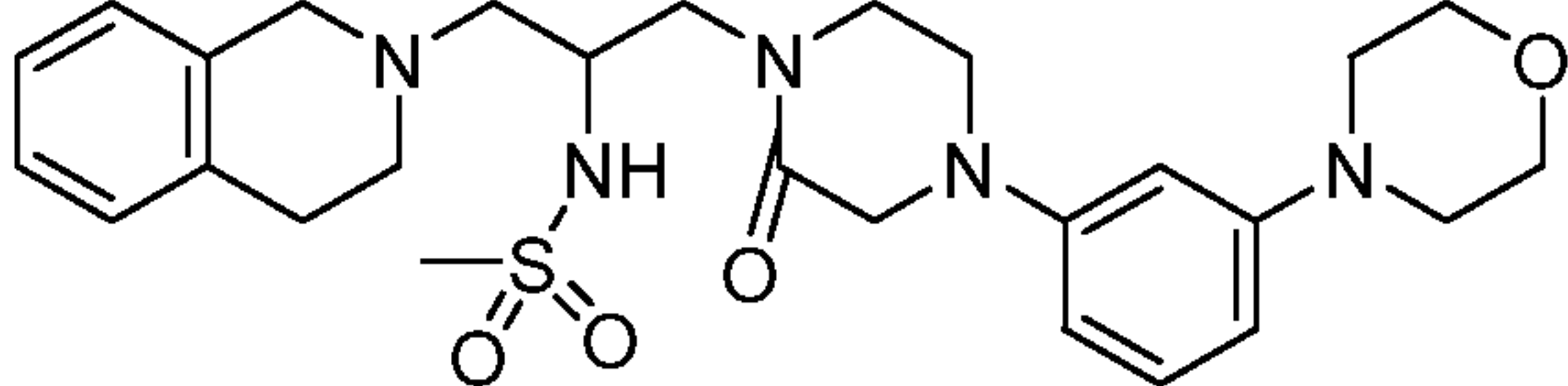
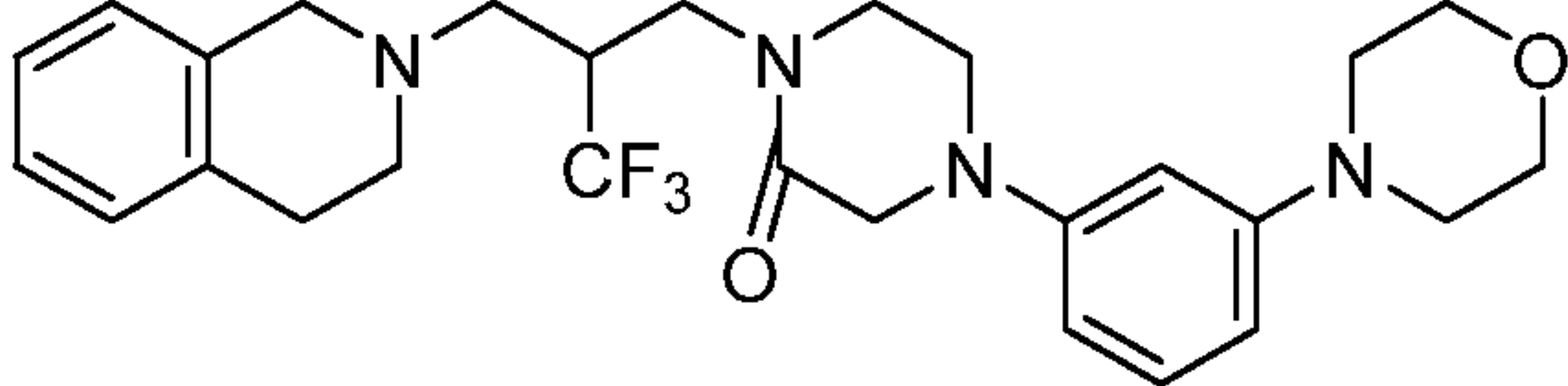
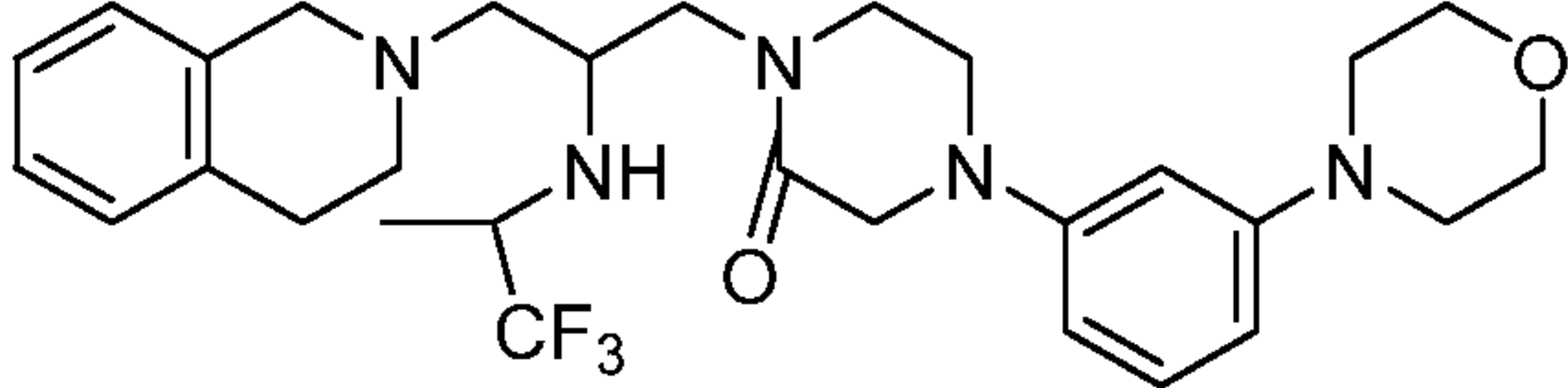
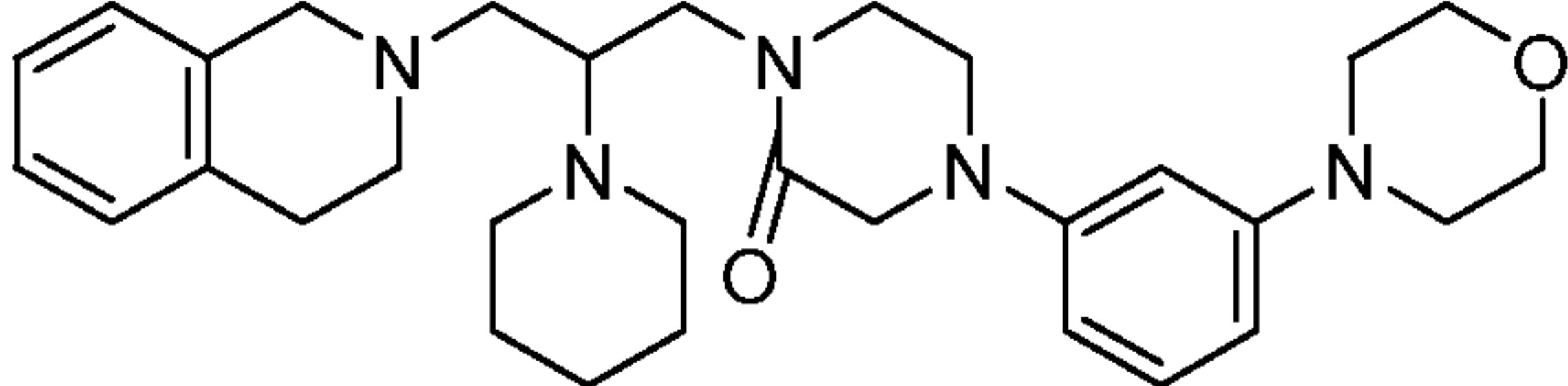
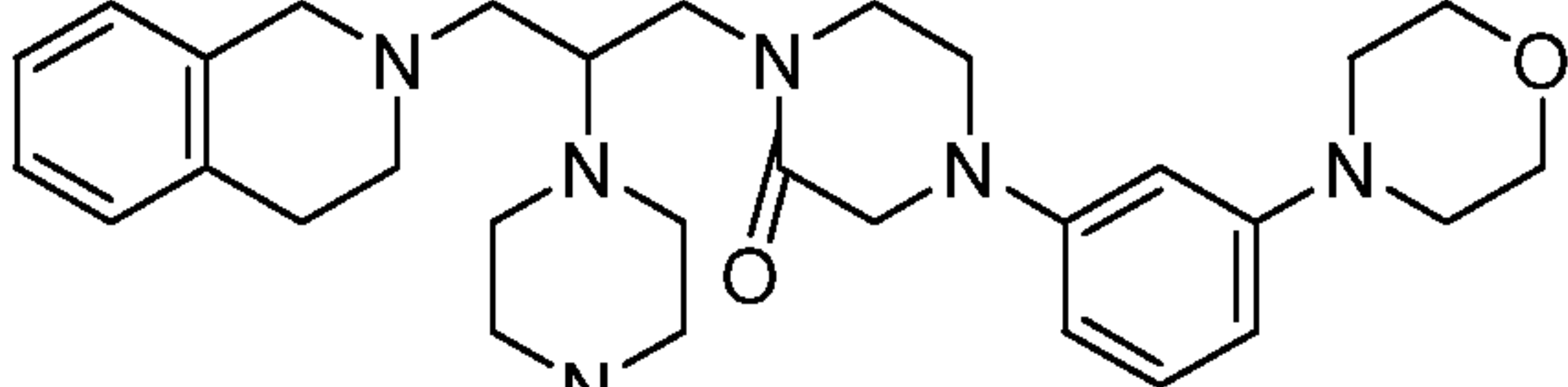
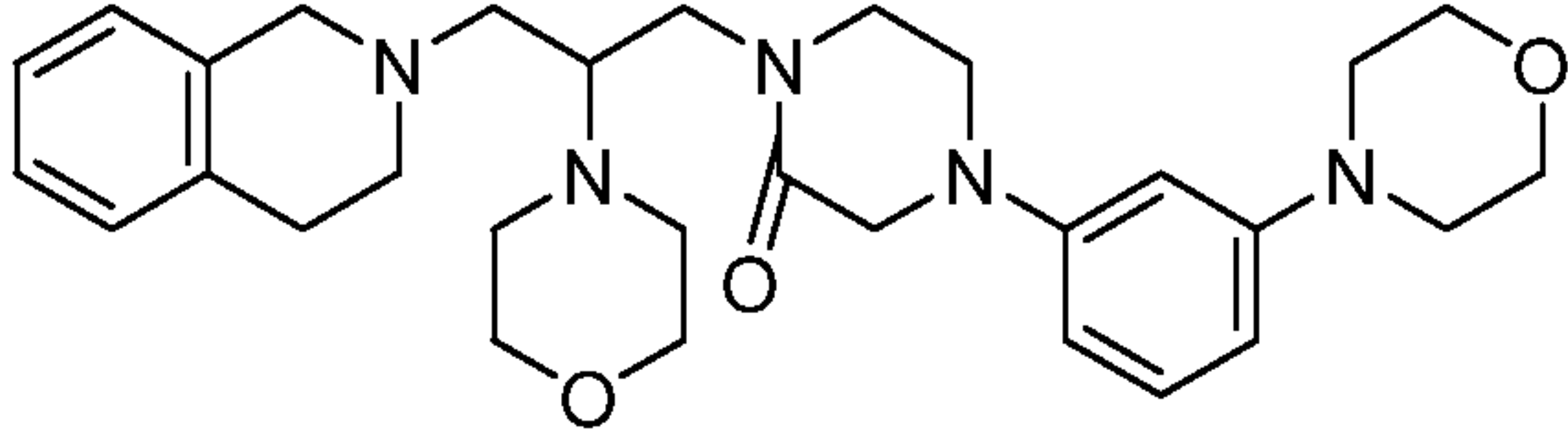
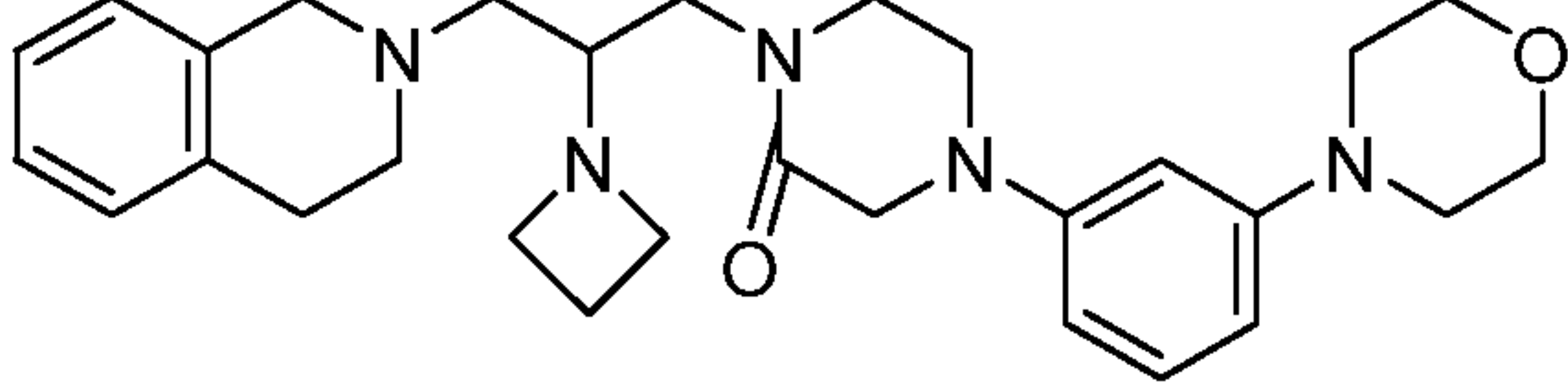
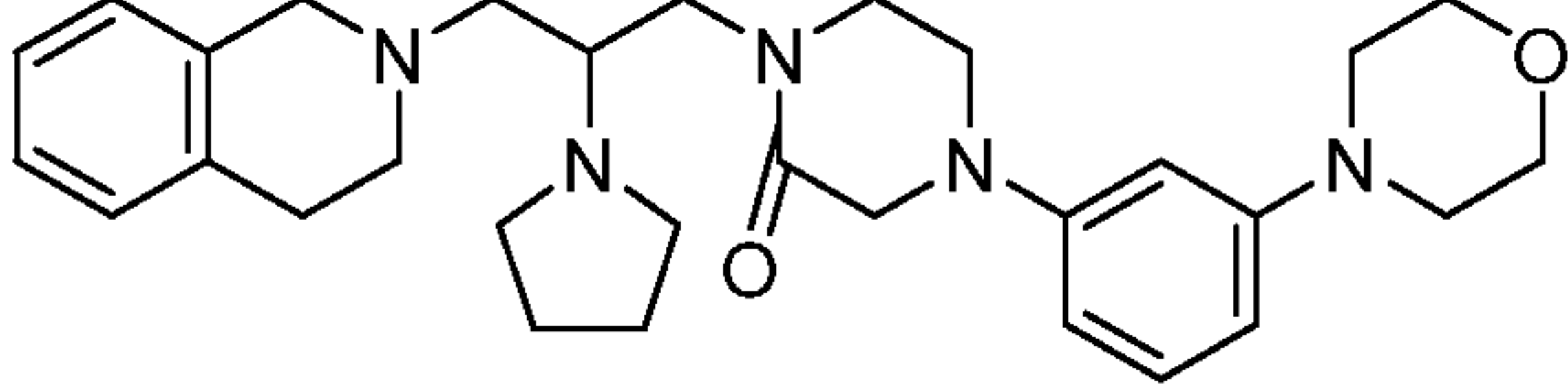
Table 1B. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
35		449.2791	--
36		463.2947	--
37		477.3104	--
38		491.2896	--
39		527.2566	--
40		502.2556	--
41		545.2978	--
42		517.3417	--
43		518.3369	--

Table 1B. Exemplary Compounds			
Cmpd No	Structure	Exact Mass	LCMS m/z (M+H)
44		519.3209	--
45		489.3104	--
46		503.3260	--

[00133] In certain embodiments, a provided compound inhibits PRMT5. In certain embodiments, a provided compound inhibits wild-type PRMT5. In certain embodiments, a provided compound inhibits a mutant PRMT5. In certain embodiments, a provided compound inhibits PRMT5, *e.g.*, as measured in an assay described herein. In certain embodiments, the PRMT5 is from a human. In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 10 μM . In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 1 μM . In certain embodiments, a provided compound inhibits PRMT5 at an IC_{50} less than or equal to 0.1 μM . In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 10 μM . In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 1 μM . In certain embodiments, a provided compound inhibits PRMT5 in a cell at an EC_{50} less than or equal to 0.1 μM . In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 10 μM . In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 1 μM . In certain embodiments, a provided compound inhibits cell proliferation at an EC_{50} less than or equal to 0.1 μM . In some embodiments, a provided compound is selective for PRMT5 over other methyltransferases. In certain embodiments, a provided compound is at least about 10-fold selective, at least about 20-fold selective, at least about 30-fold selective, at least about 40-fold selective, at least about 50-fold selective, at least about 60-fold selective, at least about 70-fold selective, at least about 80-fold selective, at least about 90-fold selective, or at least about 100-fold selective for PRMT5 relative to one or more other methyltransferases.

[00134] It will be understood by one of ordinary skill in the art that the PRMT5 can be wild-type PRMT5, or any mutant or variant of PRMT5.

[00135] In some embodiments embodiment, the mutant or variant of PRMT5 contains one or more mutations (e.g., conservative substitutions). In some embodiments, provided herein is a PRMT5 point mutant. In some embodiments, the PRMT point mutant has an amino acid sequence that a degree of homology to the amino acid sequence of SEQ ID NO: 1 of at least about 80%, e.g., at least about 85%, at least about 90%, at least about 95% , or at least about 97%. Further provided is a protein that has a degree of homology to the amino acid sequence of SEQ ID NO: 2 of at least about 80%, e.g., at least about 85%, at least about 90%, at least about 95% , or at least about 97%.

[00136] In certain embodiments, the PRMT5 is isoform A (GenBank accession no. NP006100) (SEQ ID NO.:1):

```
MAAMAVGGAG GSRVSSGRDL NCVPEIADTL GAVAKQGFDF LCMPVFHPRF
KREFIQEPAK NRPGPQTRSD LLLSGRDWNT LIVGKLSPWI RPDSKVEKIR
RNSEAAMLQE LNFGAYLGLP AFLPLLNQED NTNLARVLTN HIHTGHHSSM
FWMRVPLVAP EDLRDDIEN APTTHTEEYS GEEKTWMWWH NFRTLCDYSK
RIAAVALEIGA DLPSNHVIDR WLGEPIKAAI LPTSIFLTNK KGFPVLSKMH
QRLIFRLLKL EVQFIITGTN HHSEKEFC SY LQYLEYLSQN RPPPNAYELF
AKGYEDYLQS PLQPLMDNLE SQT YE VF EK D PIKYSQYQQA IYKCLLD RVP
EEEKDTNVQV LMVLGAGRGP LVNASLRAAK QADRRIKLYA VEKNPNAVVT
LENWQFE EWG SQVT VSSDM REWVAPEKAD IIVSELLGSF ADNELSPECL
DGAQHFLKDD GVSIPGEYTS FLAPISSSKL YNEVRACREK DRDPEAQFEM
PYVVRLHNFH QLSAPQPCFT FSHPNRDPMI DNNRYCTLEF PVEVNTVLHG
FAGYFETVLY QDITLSIRPE THSPGMFSWF PILEFPIKQPI TVREGQTICV
RFWRCSNSKK VWEWAVTAP VCSAIHNPTG RSYTIGL
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[00137] In certain embodiments, the PRMT5 is isoform B (GenBank accession no. NP001034708) (SEQ ID NO.:2)

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MRGPN SGTEK GRLVIPEKQG FDFLCMPVFH PRFKREFIQE PAKNRPGPQT
RSDLLLSGRD WNTLIVGKLS PWIRPDSKVE KIRRNSEAAM LQELNFGAYL
GLPAFLLPLN QEDNTNLARV LTNHIHTGHH SSMFWMRVPL VAPEDLRDDI
IENAPTTHTE EYSGEEKTWM WWHNFRTLCD YSKRIAAVALE IGADLPSNHV
IDRWLGEPK AAILPTSIFL TNKKGFPVLS KMHQRLIFRL LKLEVQFIIT
GTNHHSEKEF CSYLQYLEYL SQNRPPPNAY ELFAKGYEDY LQSPLQPLMD
NLESQTYEVF EKDPIKYSQY QQAIYKCLLD RVPEEEKDTN VQVLMVLGAG
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RGPLVNASLR AAKQADRRIK LYAVEKNPNA VVTLENWQFE EWGSQVTVVS
SDMREWVAPE KADIIVSELL GSFADNELSP ECLDGAQHFL KDDGVSSIPGE
YTSFLAPISS SKLYNEVRAC REKDRDPEAQ FEMPYVVRLH NFHQLSAPQP
CFTFSHPNRD PMIDNNRYCT LEFPVEVNTV LHGFAGYFET VLYQDITLSI
RPETHSPGMF SWFPILFPIK QPITVREGQT ICVRFWRCSN SKKVWYEWAV
TAPVCSAIHN PTGRSYTIGL

[00138] In certain embodiments, the PRMT5 is transcript variant 1 (GenBank accession no. NM_006109).

[00139] The present disclosure provides pharmaceutical compositions comprising a compound described herein, *e.g.*, a compound of Formula (A), *e.g.*, Formula (I), or a pharmaceutically acceptable salt thereof, as described herein, and optionally a pharmaceutically acceptable excipient. It will be understood by one of ordinary skill in the art that the compounds described herein, or salts thereof, may be present in various forms, such as amorphous, hydrates, solvates, or polymorphs. In certain embodiments, a provided composition comprises two or more compounds described herein. In certain embodiments, a compound described herein, or a pharmaceutically acceptable salt thereof, is provided in an effective amount in the pharmaceutical composition. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is an amount effective for inhibiting PRMT5. In certain embodiments, the effective amount is an amount effective for treating a PRMT5-mediated disorder. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the effective amount is an amount effective to prevent a PRMT5-mediated disorder.

[00140] In certain embodiments, the provided pharmaceutical compositions comprise a compound described herein, *e.g.*, a compound of Formula (A), *e.g.*, Formula (I), or any subgenera thereof, and optionally a pharmaceutically acceptable excipient, wherein the compound is of a free base form. In certain embodiments, the provided pharmaceutical compositions comprise a compound described herein, *e.g.*, a compound of Formula (A), *e.g.*, Formula (I), or any subgenera thereof, and optionally a pharmaceutically acceptable excipient, wherein the compound is in the form of a pharmaceutically acceptable salt as generally defined herein. In certain embodiments, the provided pharmaceutical compositions comprise a hydrochloride salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a tartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions

comprise a monotartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a bitartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a monotartrate salt and a bitartrate salt of a compound described herein and optionally a pharmaceutically acceptable excipient. In certain embodiments, the provided pharmaceutical compositions comprise a compound described herein in a form of free base, and a pharmaceutically acceptable salt thereof, and optionally a pharmaceutically acceptable excipient.

[00141] Pharmaceutically acceptable excipients include any and all solvents, diluents, or other liquid vehicles, dispersions, suspension aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants, and the like, as suited to the particular dosage form desired. General considerations in formulation and/or manufacture of pharmaceutical compositions agents can be found, for example, in *Remington's Pharmaceutical Sciences*, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980), and *Remington: The Science and Practice of Pharmacy*, 21st Edition (Lippincott Williams & Wilkins, 2005).

[00142] Pharmaceutical compositions described herein can be prepared by any method known in the art of pharmacology. In general, such preparatory methods include the steps of bringing a compound described herein (the "active ingredient") into association with a carrier and/or one or more other accessory ingredients, and then, if necessary and/or desirable, shaping and/or packaging the product into a desired single- or multi-dose unit.

[00143] Pharmaceutical compositions can be prepared, packaged, and/or sold in bulk, as a single unit dose, and/or as a plurality of single unit doses. As used herein, a "unit dose" is discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient. The amount of the active ingredient is generally equal to the dosage of the active ingredient which would be administered to a subject and/or a convenient fraction of such a dosage such as, for example, one-half or one-third of such a dosage.

[00144] Relative amounts of the active ingredient, the pharmaceutically acceptable excipient, and/or any additional ingredients in a pharmaceutical composition of the present disclosure will vary, depending upon the identity, size, and/or condition of the subject treated and further depending upon the route by which the composition is to be administered. By way of example, the composition may comprise between 0.1% and 100% (w/w) active ingredient.

[00145] Pharmaceutically acceptable excipients used in the manufacture of provided pharmaceutical compositions include inert diluents, dispersing and/or granulating agents, surface active agents and/or emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, and/or oils. Excipients such as cocoa butter and suppository waxes, coloring agents, coating agents, sweetening, flavoring, and perfuming agents may also be present in the composition.

[00146] Exemplary diluents include calcium carbonate, sodium carbonate, calcium phosphate, dicalcium phosphate, calcium sulfate, calcium hydrogen phosphate, sodium phosphate lactose, sucrose, cellulose, microcrystalline cellulose, kaolin, mannitol, sorbitol, inositol, sodium chloride, dry starch, cornstarch, powdered sugar, and mixtures thereof.

[00147] Exemplary granulating and/or dispersing agents include potato starch, corn starch, tapioca starch, sodium starch glycolate, clays, alginic acid, guar gum, citrus pulp, agar, bentonite, cellulose and wood products, natural sponge, cation–exchange resins, calcium carbonate, silicates, sodium carbonate, cross–linked poly(vinyl–pyrrolidone) (crospovidone), sodium carboxymethyl starch (sodium starch glycolate), carboxymethyl cellulose, cross–linked sodium carboxymethyl cellulose (croscarmellose), methylcellulose, pregelatinized starch (starch 1500), microcrystalline starch, water insoluble starch, calcium carboxymethyl cellulose, magnesium aluminum silicate (Veegum), sodium lauryl sulfate, quaternary ammonium compounds, and mixtures thereof.

[00148] Exemplary surface active agents and/or emulsifiers include natural emulsifiers (*e.g.*, acacia, agar, alginic acid, sodium alginate, tragacanth, chondrux, cholesterol, xanthan, pectin, gelatin, egg yolk, casein, wool fat, cholesterol, wax, and lecithin), colloidal clays (*e.g.*, bentonite (aluminum silicate) and Veegum (magnesium aluminum silicate)), long chain amino acid derivatives, high molecular weight alcohols (*e.g.*, stearyl alcohol, cetyl alcohol, oleyl alcohol, triacetin monostearate, ethylene glycol distearate, glyceryl monostearate, and propylene glycol monostearate, polyvinyl alcohol), carbomers (*e.g.*, carboxy polymethylene, polyacrylic acid, acrylic acid polymer, and carboxyvinyl polymer), carrageenan, cellulosic derivatives (*e.g.*, carboxymethylcellulose sodium, powdered cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose), sorbitan fatty acid esters (*e.g.*, polyoxyethylene sorbitan monolaurate (Tween 20), polyoxyethylene sorbitan (Tween 60), polyoxyethylene sorbitan monooleate (Tween 80), sorbitan monopalmitate (Span 40), sorbitan monostearate (Span 60], sorbitan tristearate (Span 65), glyceryl monooleate, sorbitan monooleate (Span 80)), polyoxyethylene esters (*e.g.*, polyoxyethylene monostearate (Myrj 45), polyoxyethylene hydrogenated castor oil,

polyethoxylated castor oil, polyoxymethylene stearate, and Solutol), sucrose fatty acid esters, polyethylene glycol fatty acid esters (*e.g.*, Cremophor™), polyoxyethylene ethers, (*e.g.*, polyoxyethylene lauryl ether (Brij 30)), poly(vinyl-pyrrolidone), diethylene glycol monolaurate, triethanolamine oleate, sodium oleate, potassium oleate, ethyl oleate, oleic acid, ethyl laurate, sodium lauryl sulfate, Pluronic F68, Poloxamer 188, cetrimonium bromide, cetylpyridinium chloride, benzalkonium chloride, docusate sodium, and/or mixtures thereof.

[00149] Exemplary binding agents include starch (*e.g.*, cornstarch and starch paste), gelatin, sugars (*e.g.*, sucrose, glucose, dextrose, dextrin, molasses, lactose, lactitol, mannitol, *etc.*), natural and synthetic gums (*e.g.*, acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, cellulose acetate, poly(vinyl-pyrrolidone), magnesium aluminum silicate (Veegum), and larch arabogalactan), alginates, polyethylene oxide, polyethylene glycol, inorganic calcium salts, silicic acid, polymethacrylates, waxes, water, alcohol, and/or mixtures thereof.

[00150] Exemplary preservatives include antioxidants, chelating agents, antimicrobial preservatives, antifungal preservatives, alcohol preservatives, acidic preservatives, and other preservatives.

[00151] Exemplary antioxidants include alpha tocopherol, ascorbic acid, acorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, monothioglycerol, potassium metabisulfite, propionic acid, propyl gallate, sodium ascorbate, sodium bisulfite, sodium metabisulfite, and sodium sulfite.

[00152] Exemplary chelating agents include ethylenediaminetetraacetic acid (EDTA) and salts and hydrates thereof (*e.g.*, sodium edetate, disodium edetate, trisodium edetate, calcium disodium edetate, dipotassium edetate, and the like), citric acid and salts and hydrates thereof (*e.g.*, citric acid monohydrate), fumaric acid and salts and hydrates thereof, malic acid and salts and hydrates thereof, phosphoric acid and salts and hydrates thereof, and tartaric acid and salts and hydrates thereof. Exemplary antimicrobial preservatives include benzalkonium chloride, benzethonium chloride, benzyl alcohol, bronopol, cetrimide, cetylpyridinium chloride, chlorhexidine, chlorobutanol, chlorocresol, chloroxylenol, cresol, ethyl alcohol, glycerin, hexetidine, imidurea, phenol, phenoxyethanol, phenylethyl alcohol, phenylmercuric nitrate, propylene glycol, and thimerosal.

[00153] Exemplary antifungal preservatives include butyl paraben, methyl paraben, ethyl paraben, propyl paraben, benzoic acid, hydroxybenzoic acid, potassium benzoate, potassium sorbate, sodium benzoate, sodium propionate, and sorbic acid.

[00154] Exemplary alcohol preservatives include ethanol, polyethylene glycol, phenol, phenolic compounds, bisphenol, chlorobutanol, hydroxybenzoate, and phenylethyl alcohol. Exemplary acidic preservatives include vitamin A, vitamin C, vitamin E, beta-carotene, citric acid, acetic acid, dehydroacetic acid, ascorbic acid, sorbic acid, and phytic acid.

[00155] Other preservatives include tocopherol, tocopherol acetate, deteroxime mesylate, cetrimide, butylated hydroxyanisol (BHA), butylated hydroxytoluene (BHT), ethylenediamine, sodium lauryl sulfate (SLS), sodium lauryl ether sulfate (SLES), sodium bisulfite, sodium metabisulfite, potassium sulfite, potassium metabisulfite, Glydant Plus, Phenonip, methylparaben, Germall 115, Germaben II, Neolone, Kathon, and Euxyl. In certain embodiments, the preservative is an anti-oxidant. In other embodiments, the preservative is a chelating agent.

[00156] Exemplary buffering agents include citrate buffer solutions, acetate buffer solutions, phosphate buffer solutions, ammonium chloride, calcium carbonate, calcium chloride, calcium citrate, calcium gluconate, calcium gluceptate, calcium gluconate, D-gluconic acid, calcium glycerophosphate, calcium lactate, propanoic acid, calcium levulinate, pentanoic acid, dibasic calcium phosphate, phosphoric acid, tribasic calcium phosphate, calcium hydroxide phosphate, potassium acetate, potassium chloride, potassium gluconate, potassium mixtures, dibasic potassium phosphate, monobasic potassium phosphate, potassium phosphate mixtures, sodium acetate, sodium bicarbonate, sodium chloride, sodium citrate, sodium lactate, dibasic sodium phosphate, monobasic sodium phosphate, sodium phosphate mixtures, tromethamine, magnesium hydroxide, aluminum hydroxide, alginic acid, pyrogen-free water, isotonic saline, Ringer's solution, ethyl alcohol, and mixtures thereof.

[00157] Exemplary lubricating agents include magnesium stearate, calcium stearate, stearic acid, silica, talc, malt, glyceryl behenate, hydrogenated vegetable oils, polyethylene glycol, sodium benzoate, sodium acetate, sodium chloride, leucine, magnesium lauryl sulfate, sodium lauryl sulfate, and mixtures thereof.

[00158] Exemplary natural oils include almond, apricot kernel, avocado, babassu, bergamot, black current seed, borage, cade, camomile, canola, caraway, carnauba, castor, cinnamon, cocoa butter, coconut, cod liver, coffee, corn, cotton seed, emu, eucalyptus, evening primrose, fish, flaxseed, geraniol, gourd, grape seed, hazel nut, hyssop, isopropyl myristate, jojoba, kukui nut, lavandin, lavender, lemon, litsea cubeba, macademia nut,

mallow, mango seed, meadowfoam seed, mink, nutmeg, olive, orange, orange roughy, palm, palm kernel, peach kernel, peanut, poppy seed, pumpkin seed, rapeseed, rice bran, rosemary, safflower, sandalwood, sasquana, savoury, sea buckthorn, sesame, shea butter, silicone, soybean, sunflower, tea tree, thistle, tsubaki, vetiver, walnut, and wheat germ oils.

Exemplary synthetic oils include, but are not limited to, butyl stearate, caprylic triglyceride, capric triglyceride, cyclomethicone, diethyl sebacate, dimethicone 360, isopropyl myristate, mineral oil, octyldodecanol, oleyl alcohol, silicone oil, and mixtures thereof.

[00159] Liquid dosage forms for oral and parenteral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredients, the liquid dosage forms may comprise inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (*e.g.*, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents. In certain embodiments for parenteral administration, the compounds described herein are mixed with solubilizing agents such as Cremophor™, alcohols, oils, modified oils, glycols, polysorbates, cyclodextrins, polymers, and mixtures thereof.

[00160] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00161] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00162] In order to prolong the effect of a drug, it is often desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This can be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

[00163] Compositions for rectal or vaginal administration are typically suppositories which can be prepared by mixing the compounds described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active ingredient.

[00164] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active ingredient is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may comprise buffering agents.

[00165] Solid compositions of a similar type can be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. Solid compositions of a similar type can be employed as

fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00166] The active ingredient can be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active ingredient can be admixed with at least one inert diluent such as sucrose, lactose, or starch. Such dosage forms may comprise, as is normal practice, additional substances other than inert diluents, *e.g.*, tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets, and pills, the dosage forms may comprise buffering agents. They may optionally comprise opacifying agents and can be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

[00167] Dosage forms for topical and/or transdermal administration of a provided compound may include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants and/or patches. Generally, the active ingredient is admixed under sterile conditions with a pharmaceutically acceptable carrier and/or any desired preservatives and/or buffers as can be required. Additionally, the present disclosure encompasses the use of transdermal patches, which often have the added advantage of providing controlled delivery of an active ingredient to the body. Such dosage forms can be prepared, for example, by dissolving and/or dispensing the active ingredient in the proper medium. Alternatively or additionally, the rate can be controlled by either providing a rate controlling membrane and/or by dispersing the active ingredient in a polymer matrix and/or gel.

[00168] Suitable devices for use in delivering intradermal pharmaceutical compositions described herein include short needle devices such as those described in U.S. Patents 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions can be administered by devices which limit the effective penetration length of a needle into the skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof. Jet injection devices which deliver liquid vaccines to the dermis via a liquid jet injector and/or via a needle which pierces the stratum corneum and produces a jet which reaches the dermis are suitable. Jet injection devices are described, for example, in U.S. Patents 5,480,381; 5,599,302; 5,334,144;

5,993,412; 5,649,912; 5,569,189; 5,704,911; 5,383,851; 5,893,397; 5,466,220; 5,339,163; 5,312,335; 5,503,627; 5,064,413; 5,520,639; 4,596,556; 4,790,824; 4,941,880; 4,940,460; and PCT publications WO 97/37705 and WO 97/13537. Ballistic powder/particle delivery devices which use compressed gas to accelerate vaccine in powder form through the outer layers of the skin to the dermis are suitable. Alternatively or additionally, conventional syringes can be used in the classical mantoux method of intradermal administration.

[00169] Formulations suitable for topical administration include, but are not limited to, liquid and/or semi liquid preparations such as liniments, lotions, oil in water and/or water in oil emulsions such as creams, ointments and/or pastes, and/or solutions and/or suspensions. Topically-administrable formulations may, for example, comprise from about 1% to about 10% (w/w) active ingredient, although the concentration of the active ingredient can be as high as the solubility limit of the active ingredient in the solvent. Formulations for topical administration may further comprise one or more of the additional ingredients described herein.

[00170] A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation suitable for pulmonary administration via the buccal cavity. Such a formulation may comprise dry particles which comprise the active ingredient and which have a diameter in the range from about 0.5 to about 7 nanometers or from about 1 to about 6 nanometers. Such compositions are conveniently in the form of dry powders for administration using a device comprising a dry powder reservoir to which a stream of propellant can be directed to disperse the powder and/or using a self propelling solvent/powder dispensing container such as a device comprising the active ingredient dissolved and/or suspended in a low-boiling propellant in a sealed container. Such powders comprise particles wherein at least 98% of the particles by weight have a diameter greater than 0.5 nanometers and at least 95% of the particles by number have a diameter less than 7 nanometers. Alternatively, at least 95% of the particles by weight have a diameter greater than 1 nanometer and at least 90% of the particles by number have a diameter less than 6 nanometers. Dry powder compositions may include a solid fine powder diluent such as sugar and are conveniently provided in a unit dose form.

[00171] Low boiling propellants generally include liquid propellants having a boiling point of below 65 °F at atmospheric pressure. Generally the propellant may constitute 50 to 99.9% (w/w) of the composition, and the active ingredient may constitute 0.1 to 20% (w/w) of the composition. The propellant may further comprise additional ingredients such as a liquid

non-ionic and/or solid anionic surfactant and/or a solid diluent (which may have a particle size of the same order as particles comprising the active ingredient).

[00172] Pharmaceutical compositions formulated for pulmonary delivery may provide the active ingredient in the form of droplets of a solution and/or suspension. Such formulations can be prepared, packaged, and/or sold as aqueous and/or dilute alcoholic solutions and/or suspensions, optionally sterile, comprising the active ingredient, and may conveniently be administered using any nebulization and/or atomization device. Such formulations may further comprise one or more additional ingredients including, but not limited to, a flavoring agent such as saccharin sodium, a volatile oil, a buffering agent, a surface active agent, and/or a preservative such as methylhydroxybenzoate. The droplets provided by this route of administration may have an average diameter in the range from about 0.1 to about 200 nanometers.

[00173] Formulations described herein as being useful for pulmonary delivery are useful for intranasal delivery of a pharmaceutical composition. Another formulation suitable for intranasal administration is a coarse powder comprising the active ingredient and having an average particle from about 0.2 to 500 micrometers. Such a formulation is administered by rapid inhalation through the nasal passage from a container of the powder held close to the nares.

[00174] Formulations for nasal administration may, for example, comprise from about as little as 0.1% (w/w) and as much as 100% (w/w) of the active ingredient, and may comprise one or more of the additional ingredients described herein. A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for buccal administration. Such formulations may, for example, be in the form of tablets and/or lozenges made using conventional methods, and may contain, for example, 0.1 to 20% (w/w) active ingredient, the balance comprising an orally dissolvable and/or degradable composition and, optionally, one or more of the additional ingredients described herein. Alternately, formulations for buccal administration may comprise a powder and/or an aerosolized and/or atomized solution and/or suspension comprising the active ingredient. Such powdered, aerosolized, and/or atomized formulations, when dispersed, may have an average particle and/or droplet size in the range from about 0.1 to about 200 nanometers, and may further comprise one or more of the additional ingredients described herein.

[00175] A provided pharmaceutical composition can be prepared, packaged, and/or sold in a formulation for ophthalmic administration. Such formulations may, for example, be in the form of eye drops including, for example, a 0.1/1.0% (w/w) solution and/or suspension of the

active ingredient in an aqueous or oily liquid carrier. Such drops may further comprise buffering agents, salts, and/or one or more other of the additional ingredients described herein. Other ophthalmically-administrable formulations which are useful include those which comprise the active ingredient in microcrystalline form and/or in a liposomal preparation. Ear drops and/or eye drops are contemplated as being within the scope of this disclosure.

[00176] Although the descriptions of pharmaceutical compositions provided herein are principally directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood by the skilled artisan that such compositions are generally suitable for administration to animals of all sorts. Modification of pharmaceutical compositions suitable for administration to humans in order to render the compositions suitable for administration to various animals is well understood, and the ordinarily skilled veterinary pharmacologist can design and/or perform such modification with ordinary experimentation.

[00177] Compounds provided herein are typically formulated in dosage unit form for ease of administration and uniformity of dosage. It will be understood, however, that the total daily usage of provided compositions will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including the disease, disorder, or condition being treated and the severity of the disorder; the activity of the specific active ingredient employed; the specific composition employed; the age, body weight, general health, sex and diet of the subject; the time of administration, route of administration, and rate of excretion of the specific active ingredient employed; the duration of the treatment; drugs used in combination or coincidental with the specific active ingredient employed; and like factors well known in the medical arts.

[00178] The compounds and compositions provided herein can be administered by any route, including enteral (*e.g.*, oral), parenteral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, subcutaneous, intraventricular, transdermal, interdermal, rectal, intravaginal, intraperitoneal, topical (as by powders, ointments, creams, and/or drops), mucosal, nasal, bucal, sublingual; by intratracheal instillation, bronchial instillation, and/or inhalation; and/or as an oral spray, nasal spray, and/or aerosol. Specifically contemplated routes are oral administration, intravenous administration (*e.g.*, systemic intravenous injection), regional administration via blood and/or lymph supply, and/or direct administration to an affected site. In general the most appropriate route of administration will

depend upon a variety of factors including the nature of the agent (*e.g.*, its stability in the environment of the gastrointestinal tract), and/or the condition of the subject (*e.g.*, whether the subject is able to tolerate oral administration).

[00179] The exact amount of a compound required to achieve an effective amount will vary from subject to subject, depending, for example, on species, age, and general condition of a subject, severity of the side effects or disorder, identity of the particular compound(s), mode of administration, and the like. The desired dosage can be delivered three times a day, two times a day, once a day, every other day, every third day, every week, every two weeks, every three weeks, or every four weeks. In certain embodiments, the desired dosage can be delivered using multiple administrations (*e.g.*, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, or more administrations).

[00180] In certain embodiments, an effective amount of a compound for administration one or more times a day to a 70 kg adult human may comprise about 0.0001 mg to about 3000 mg, about 0.0001 mg to about 2000 mg, about 0.0001 mg to about 1000 mg, about 0.001 mg to about 1000 mg, about 0.01 mg to about 1000 mg, about 0.1 mg to about 1000 mg, about 1 mg to about 1000 mg, about 1 mg to about 100 mg, about 10 mg to about 1000 mg, or about 100 mg to about 1000 mg, of a compound per unit dosage form.

[00181] In certain embodiments, a compound described herein may be administered at dosage levels sufficient to deliver from about 0.001 mg/kg to about 1000 mg/kg, from about 0.01 mg/kg to about mg/kg, from about 0.1 mg/kg to about 40 mg/kg, from about 0.5 mg/kg to about 30 mg/kg, from about 0.01 mg/kg to about 10 mg/kg, from about 0.1 mg/kg to about 10 mg/kg, or from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00182] In some embodiments, a compound described herein is administered one or more times per day, for multiple days. In some embodiments, the dosing regimen is continued for days, weeks, months, or years.

[00183] It will be appreciated that dose ranges as described herein provide guidance for the administration of provided pharmaceutical compositions to an adult. The amount to be administered to, for example, a child or an adolescent can be determined by a medical practitioner or person skilled in the art and can be lower or the same as that administered to an adult.

[00184] It will be also appreciated that a compound or composition, as described herein, can be administered in combination with one or more additional therapeutically active agents. In certain embodiments, a compound or composition provided herein is administered in

combination with one or more additional therapeutically active agents that improve its bioavailability, reduce and/or modify its metabolism, inhibit its excretion, and/or modify its distribution within the body. It will also be appreciated that the therapy employed may achieve a desired effect for the same disorder, and/or it may achieve different effects.

[00185] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional therapeutically active agents. In certain embodiments, the additional therapeutically active agent is a compound of Formula (A), *e.g.*, Formula (I). In certain embodiments, the additional therapeutically active agent is not a compound of Formula (A), *e.g.*, Formula (I). In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. It will further be appreciated that the additional therapeutically active agent utilized in this combination can be administered together in a single composition or administered separately in different compositions. The particular combination to employ in a regimen will take into account compatibility of a provided compound with the additional therapeutically active agent and/or the desired therapeutic effect to be achieved. In general, it is expected that additional therapeutically active agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

[00186] Exemplary additional therapeutically active agents include, but are not limited to, small organic molecules such as drug compounds (*e.g.*, compounds approved by the U.S. Food and Drug Administration as provided in the Code of Federal Regulations (CFR)), peptides, proteins, carbohydrates, monosaccharides, oligosaccharides, polysaccharides, nucleoproteins, mucoproteins, lipoproteins, synthetic polypeptides or proteins, small molecules linked to proteins, glycoproteins, steroids, nucleic acids, DNAs, RNAs, nucleotides, nucleosides, oligonucleotides, antisense oligonucleotides, lipids, hormones, vitamins, and cells.

[00187] Also encompassed by the present disclosure are kits (*e.g.*, pharmaceutical packs). The kits provided may comprise a provided pharmaceutical composition or compound and a container (*e.g.*, a vial, ampule, bottle, syringe, and/or dispenser package, or other suitable container). In some embodiments, provided kits may optionally further include a second container comprising a pharmaceutical excipient for dilution or suspension of a provided pharmaceutical composition or compound. In some embodiments, a provided pharmaceutical composition or compound provided in the container and the second container are combined

to form one unit dosage form. In some embodiments, a provided kits further includes instructions for use.

[00188] Compounds and compositions described herein are generally useful for the inhibition of PRMT5. In some embodiments, methods of treating PRMT5-mediated disorder in a subject are provided which comprise administering an effective amount of a compound described herein (*e.g.*, a compound of Formula (A), *e.g.*, Formula (I)), or a pharmaceutically acceptable salt thereof), to a subject in need of treatment. In certain embodiments, the effective amount is a therapeutically effective amount. In certain embodiments, the effective amount is a prophylactically effective amount. In certain embodiments, the subject is suffering from a PRMT5-mediated disorder. In certain embodiments, the subject is susceptible to a PRMT5-mediated disorder.

[00189] As used herein, the term “PRMT5-mediated disorder” means any disease, disorder, or other pathological condition in which PRMT5 is known to play a role. Accordingly, in some embodiments, the present disclosure relates to treating or lessening the severity of one or more diseases in which PRMT5 is known to play a role.

[00190] In some embodiments, the present disclosure provides a method of inhibiting PRMT5 comprising contacting PRMT5 with an effective amount of a compound described herein (*e.g.*, a compound of Formula (A), *e.g.*, Formula (I)), or a pharmaceutically acceptable salt thereof. The PRMT5 may be purified or crude, and may be present in a cell, tissue, or subject. Thus, such methods encompass both inhibition of *in vitro* and *in vivo* PRMT5 activity. In certain embodiments, the method is an *in vitro* method, *e.g.*, such as an assay method. It will be understood by one of ordinary skill in the art that inhibition of PRMT5 does not necessarily require that all of the PRMT5 be occupied by an inhibitor at once. Exemplary levels of inhibition of PRMT5 include at least 10% inhibition, about 10% to about 25% inhibition, about 25% to about 50% inhibition, about 50% to about 75% inhibition, at least 50% inhibition, at least 75% inhibition, about 80% inhibition, about 90% inhibition, and greater than 90% inhibition.

[00191] In some embodiments, provided is a method of inhibiting PRMT5 activity in a subject in need thereof comprising administering to the subject an effective amount of a compound described herein (*e.g.*, a compound of Formula (A), *e.g.*, Formula (I)), or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[00192] In certain embodiments, provided is a method of altering gene expression in a cell which comprises contacting a cell with an effective amount of a compound of Formula (A), *e.g.*, Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the

cell in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human. In certain embodiments, the cell is in a subject in need of treatment.

[00193] In certain embodiments, provided is a method of altering transcription in a cell which comprises contacting a cell with an effective amount of a compound of Formula (A), *e.g.*, Formula (I), or a pharmaceutically acceptable salt thereof. In certain embodiments, the cell is in culture *in vitro*. In certain embodiments, the cell is in an animal, *e.g.*, a human. In certain embodiments, the cell is in a subject in need of treatment.

[00194] In certain embodiments, a method is provided of selecting a therapy for a subject having a disease associated with PRMT5-mediated disorder or mutation comprising the steps of determining the presence of PRMT5-mediated disorder or gene mutation in the PRMT5 gene or and selecting, based on the presence of PRMT5-mediated disorder a gene mutation in the PRMT5 gene a therapy that includes the administration of a provided compound. In certain embodiments, the disease is cancer.

[00195] In certain embodiments, a method of treatment is provided for a subject in need thereof comprising the steps of determining the presence of PRMT5-mediated disorder or a gene mutation in the PRMT5 gene and treating the subject in need thereof, based on the presence of a PRMT5-mediated disorder or gene mutation in the PRMT5 gene with a therapy that includes the administration of a provided compound. In certain embodiments, the subject is a cancer patient.

[00196] In some embodiments, a provided compound is useful in treating a proliferative disorder, such as cancer, a benign neoplasm, an autoimmune disease, or an inflammatory disease. For example, while not being bound to any particular mechanism, PRMT5 has been shown to be involved in cyclin D1 dysregulated cancers. Increased PRMT5 activity mediates key events associated with cyclin D1-dependent neoplastic growth including CUL4 repression, CDT1 overexpression, and DNA re-replication. Further, human cancers harboring mutations in Fbx4, the cyclin D1 E3 ligase, exhibit nuclear cyclin D1 accumulation and increased PRMT5 activity. See, *e.g.*, Aggarwal *et al.*, *Cancer Cell*. (2010) 18(4):329-40. Additionally, PRMT5 has also been implicated in accelerating cell cycle progression through G1 phase and modulating regulators of G1; for example, PRMT5 may upregulate cyclin-dependent kinase (CDK) 4, CDK6, and cyclins D1, D2 and E1. Moreover, PRMT5 may activate phosphoinositide 3-kinase (PI3K)/AKT signaling. See, *e.g.*, Wei *et al.*, *Cancer Sci*. (2012) 103(9):1640-50. PRMT5 has been reported to play a role in apoptosis through methylation of E2F-1. See, *e.g.*, Cho *et al.*, *EMBO J*. (2012) 31:1785-1797; Zheng *et al.*, *Mol. Cell*. (2013) 52:37-51. PRMT5 has been reported to be an essential regulator of splicing and

affect the alternative splicing of ‘sensor’ mRNAs that can then lead to defects in downstream events such as apoptosis. See, *e.g.*, Bezzi *et al.*, *Genes Dev.* (2013) 27:1903-1916. PRMT5 has been reported to play a role in the RAS-ERK pathway. See, *e.g.*, Andrew-Perez *et al.*, *Sci Signal.* (2011) Sep 13;4(190)ra58 doi: 10.1126/scisignal.2001936. PRMT5 has been reported to affect C/EBP β target genes through interaction with the Mediator complex and hence affect cellular differentiation and inflammatory response. See, *e.g.*, Tsutsui *et al.*, *J. Biol. Chem.* (2013) 288:20955-20965. PRMT5 has been shown to methylate HOXA9 essential for ELAM expression during the EC inflammatory response. See, *e.g.*, Bandyopadhyay *et al.*, *Mol. Cell. Biol.* (2012) 32:1202-1203. Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating the following non-limiting list of cancers: breast cancer, esophageal cancer, bladder cancer, lung cancer, hematopoietic cancer, lymphoma, medulloblastoma, rectum adenocarcinoma, colon adenocarcinoma, gastric cancer, pancreatic cancer, liver cancer, adenoid cystic carcinoma, lung adenocarcinoma, head and neck squamous cell carcinoma, brain tumors, hepatocellular carcinoma, renal cell carcinoma, melanoma, oligodendroglioma, ovarian clear cell carcinoma, and ovarian serous cystadenocarcinoma. See, *e.g.*, Pal *et al.*, *EMBO J.* (2007) 26:3558-3569 (mantle cell lymphoma); Wang *et al.*, *Mol. Cell Biol.* (2008) 28:6262-77 (chronic lymphocytic leukemia (CLL)); and Tae *et al.*, *Nucleic Acids Res.* (2011) 39:5424-5438.

[00197] In some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating prostate cancer and lung cancer, in which PRMT5 has been shown to play a role. See, *e.g.*, Gu *et al.*, *PLoS One* 2012;7(8):e44033; Gu *et al.*, *Biochem. J.* (2012) 446:235–241. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of cancer. In some embodiments, a provided compound is administered in combination with other compounds, drugs, or therapeutics to treat cancer.

[00198] In some embodiments, compounds described herein are useful for treating a cancer including, but not limited to, acoustic neuroma, adenocarcinoma, adrenal gland cancer, anal cancer, angiosarcoma (*e.g.*, lymphangiosarcoma, lymphangioendotheliosarcoma, hemangiosarcoma), appendix cancer, benign monoclonal gammopathy, biliary cancer (*e.g.*, cholangiocarcinoma), bladder cancer, breast cancer (*e.g.*, adenocarcinoma of the breast, papillary carcinoma of the breast, mammary cancer, medullary carcinoma of the breast), brain cancer (*e.g.*, meningioma; glioma, *e.g.*, astrocytoma, oligodendroglioma; medulloblastoma), bronchus cancer, carcinoid tumor, cervical cancer (*e.g.*, cervical adenocarcinoma), choriocarcinoma, chordoma, craniopharyngioma, colorectal cancer (*e.g.*,

colon cancer, rectal cancer, colorectal adenocarcinoma), epithelial carcinoma, ependymoma, endotheliosarcoma (*e.g.*, Kaposi's sarcoma, multiple idiopathic hemorrhagic sarcoma), endometrial cancer (*e.g.*, uterine cancer, uterine sarcoma), esophageal cancer (*e.g.*, adenocarcinoma of the esophagus, Barrett's adenocarcinoma), Ewing sarcoma, eye cancer (*e.g.*, intraocular melanoma, retinoblastoma), familial hypereosinophilia, gall bladder cancer, gastric cancer (*e.g.*, stomach adenocarcinoma), gastrointestinal stromal tumor (GIST), head and neck cancer (*e.g.*, head and neck squamous cell carcinoma, oral cancer (*e.g.*, oral squamous cell carcinoma (OSCC), throat cancer (*e.g.*, laryngeal cancer, pharyngeal cancer, nasopharyngeal cancer, oropharyngeal cancer))), hematopoietic cancers (*e.g.*, leukemia such as acute lymphocytic leukemia (ALL) (*e.g.*, B-cell ALL, T-cell ALL), acute myelocytic leukemia (AML) (*e.g.*, B-cell AML, T-cell AML), chronic myelocytic leukemia (CML) (*e.g.*, B-cell CML, T-cell CML), and chronic lymphocytic leukemia (CLL) (*e.g.*, B-cell CLL, T-cell CLL); lymphoma such as Hodgkin lymphoma (HL) (*e.g.*, B-cell HL, T-cell HL) and non-Hodgkin lymphoma (NHL) (*e.g.*, B-cell NHL such as diffuse large cell lymphoma (DLCL) (*e.g.*, diffuse large B-cell lymphoma (DLBCL)), follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma (MCL), marginal zone B-cell lymphomas (*e.g.*, mucosa-associated lymphoid tissue (MALT) lymphomas, nodal marginal zone B-cell lymphoma, splenic marginal zone B-cell lymphoma), primary mediastinal B-cell lymphoma, Burkitt lymphoma, lymphoplasmacytic lymphoma (*i.e.*, "Waldenström's macroglobulinemia"), hairy cell leukemia (HCL), immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma and primary central nervous system (CNS) lymphoma; and T-cell NHL such as precursor T-lymphoblastic lymphoma/leukemia, peripheral T-cell lymphoma (PTCL) (*e.g.*, cutaneous T-cell lymphoma (CTCL) (*e.g.*, mycosis fungoides, Sezary syndrome), angioimmunoblastic T-cell lymphoma, extranodal natural killer T-cell lymphoma, enteropathy type T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, anaplastic large cell lymphoma); a mixture of one or more leukemia/lymphoma as described above; and multiple myeloma (MM)), heavy chain disease (*e.g.*, alpha chain disease, gamma chain disease, mu chain disease), hemangioblastoma, inflammatory myofibroblastic tumors, immunocytic amyloidosis, kidney cancer (*e.g.*, nephroblastoma *a.k.a.* Wilms' tumor, renal cell carcinoma), liver cancer (*e.g.*, hepatocellular cancer (HCC), malignant hepatoma), lung cancer (*e.g.*, bronchogenic carcinoma, small cell lung cancer (SCLC), non-small cell lung cancer (NSCLC), adenocarcinoma of the lung), leiomyosarcoma (LMS), mastocytosis (*e.g.*, systemic mastocytosis), myelodysplastic syndrome (MDS), mesothelioma, myeloproliferative disorder (MPD) (*e.g.*, polycythemia

Vera (PV), essential thrombocytosis (ET), agnogenic myeloid metaplasia (AMM) *a.k.a.* myelofibrosis (MF), chronic idiopathic myelofibrosis, chronic myelocytic leukemia (CML), chronic neutrophilic leukemia (CNL), hypereosinophilic syndrome (HES)), neuroblastoma, neurofibroma (*e.g.*, neurofibromatosis (NF) type 1 or type 2, schwannomatosis), neuroendocrine cancer (*e.g.*, gastroenteropancreatic neuroendocrine tumor (GEP-NET), carcinoid tumor), osteosarcoma, ovarian cancer (*e.g.*, cystadenocarcinoma, ovarian embryonal carcinoma, ovarian adenocarcinoma), papillary adenocarcinoma, pancreatic cancer (*e.g.*, pancreatic adenocarcinoma, intraductal papillary mucinous neoplasm (IPMN), Islet cell tumors), penile cancer (*e.g.*, Paget's disease of the penis and scrotum), pinealoma, primitive neuroectodermal tumor (PNT), prostate cancer (*e.g.*, prostate adenocarcinoma), rectal cancer, rhabdomyosarcoma, salivary gland cancer, skin cancer (*e.g.*, squamous cell carcinoma (SCC), keratoacanthoma (KA), melanoma, basal cell carcinoma (BCC)), small bowel cancer (*e.g.*, appendix cancer), soft tissue sarcoma (*e.g.*, malignant fibrous histiocytoma (MFH), liposarcoma, malignant peripheral nerve sheath tumor (MPNST), chondrosarcoma, fibrosarcoma, myxosarcoma), sebaceous gland carcinoma, sweat gland carcinoma, synovioma, testicular cancer (*e.g.*, seminoma, testicular embryonal carcinoma), thyroid cancer (*e.g.*, papillary carcinoma of the thyroid, papillary thyroid carcinoma (PTC), medullary thyroid cancer), urethral cancer, vaginal cancer, and vulvar cancer (*e.g.*, Paget's disease of the vulva).

[00199] In some embodiments, a provided compound is useful in treating a metabolic disorder, such as diabetes or obesity. For example, while not being bound to any particular mechanism, a role for PRMT5 has been recognized in adipogenesis. Inhibition of PRMT5 expression in multiple cell culture models for adipogenesis prevented the activation of adipogenic genes, while overexpression of PRMT5 enhanced adipogenic gene expression and differentiation. See, *e.g.*, LeBlanc *et al.*, *Mol Endocrinol.* (2012) 26:583-597. Additionally, it has been shown that adipogenesis plays a pivotal role in the etiology and progression of diabetes and obesity. See, *e.g.*, Camp *et al.*, *Trends Mol Med.* (2002) 8:442-447. Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating diabetes and/or obesity.

[00200] In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, diabetes. In some embodiments, the diabetes is Type 1 diabetes. In some embodiments, the diabetes is Type 2 diabetes. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, obesity. In some embodiments, a provided compound is

useful to help a subject lose weight. In some embodiments, a provided compound could be used in combination with other compounds, drugs, or therapeutics, such as metformin and insulin, to treat diabetes and/or obesity.

[00201] In some embodiments, a provided compound is useful in treating a blood disorder, *e.g.*, a hemoglobinopathy, such as sickle cell disease or β -thalassemia. For example, while not being bound to any particular mechanism, PRMT5 is a known repressor of γ -globin gene expression, and increased fetal γ -globin (HbF) levels in adulthood are associated with symptomatic amelioration in sickle cell disease and β -thalassemia. See, *e.g.*, Xu *et al.*, *Haematologica*. (2012) 97:1632-1640; Rank *et al.* *Blood*. (2010) 116:1585-1592. Thus in some embodiments, the inhibition of PRMT5 by a provided compound is useful in treating a blood disorder, such as a hemoglobinopathy such as sickle cell disease or β -thalassemia.

[00202] In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, sickle cell disease. In some embodiments, a provided compound is useful to delay the onset of, slow the progression of, or ameliorate the symptoms of, β -thalassemia. In some embodiments, a provided compound could be used in combination with other compounds, drugs, or therapeutics, to treat a hemoglobinopathy such as sickle cell disease or β -thalassemia.

[00203] In some embodiments, a provided compound is useful in treating inflammatory and autoimmune disease. PRMT5 is reported to activate NF κ B signaling pathway through the methylation of p65. PRMT5 is reported to interact with Death receptor 4 and Death receptor 5 contributing to TRAIL-induced activation of inhibitor of κ B kinase (IKK) and nuclear factor- κ B (NF- κ B). See, *e.g.*, Tanaka *et al.*, *Mol. Cancer. Res.* (2009) 7:557-569.; Wei *et al.*, *Proc. Nat'l. Acad. Sci. USA* (2013) 110:13516-21.

[00204] The term “inflammatory disease” refers to those diseases, disorders or conditions that are characterized by signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and/or loss of function (functio laesa, which can be partial or complete, temporary or permanent. Inflammation takes on many forms and includes, but is not limited to, acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse, disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing,

seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative inflammation.

[00205] Exemplary inflammatory diseases include, but are not limited to, inflammation associated with acne, anemia (*e.g.*, aplastic anemia, haemolytic autoimmune anaemia), asthma, arteritis (*e.g.*, polyarteritis, temporal arteritis, periarteritis nodosa, Takayasu's arteritis), arthritis (*e.g.*, crystalline arthritis, osteoarthritis, psoriatic arthritis, gouty arthritis, reactive arthritis, rheumatoid arthritis and Reiter's arthritis), ankylosing spondylitis, amylosis, amyotrophic lateral sclerosis, autoimmune diseases, allergies or allergic reactions, atherosclerosis, bronchitis, bursitis, chronic prostatitis, conjunctivitis, Chagas disease, chronic obstructive pulmonary disease, dermatomyositis, diverticulitis, diabetes (*e.g.*, type I diabetes mellitus, type 2 diabetes mellitus), a skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), endometriosis, Guillain-Barre syndrome, infection, ischaemic heart disease, Kawasaki disease, glomerulonephritis, gingivitis, hypersensitivity, headaches (*e.g.*, migraine headaches, tension headaches), ileus (*e.g.*, postoperative ileus and ileus during sepsis), idiopathic thrombocytopenic purpura, interstitial cystitis (painful bladder syndrome), gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), lupus, multiple sclerosis, morphea, myasthenia gravis, myocardial ischemia, nephrotic syndrome, pemphigus vulgaris, pernicious anaemia, peptic ulcers, polymyositis, primary biliary cirrhosis, neuroinflammation associated with brain disorders (*e.g.*, Parkinson's disease, Huntington's disease, and Alzheimer's disease), prostatitis, chronic inflammation associated with cranial radiation injury, pelvic inflammatory disease, reperfusion injury, regional enteritis, rheumatic fever, systemic lupus erythematosus, scleroderma, scleroderma, sarcoidosis, spondyloarthropathies, Sjogren's syndrome, thyroiditis, transplantation rejection, tendonitis, trauma or injury (*e.g.*, frostbite, chemical irritants, toxins, scarring, burns, physical injury), vasculitis, vitiligo and Wegener's granulomatosis.

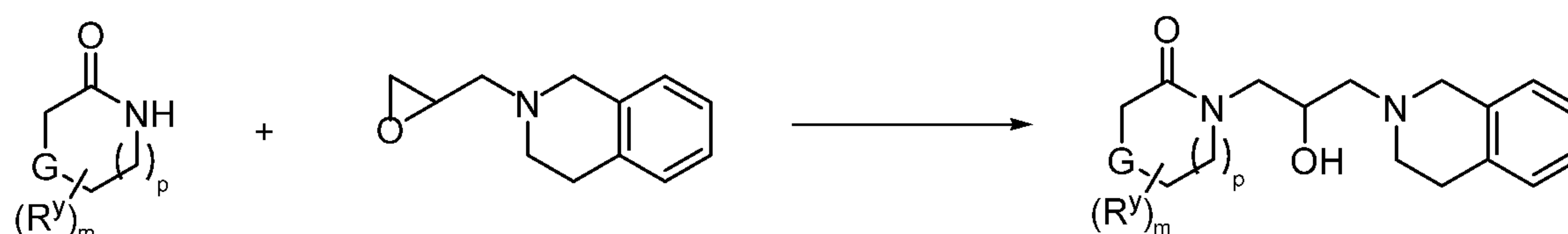
[00206] In certain embodiments, the inflammatory disease is an acute inflammatory disease (*e.g.*, for example, inflammation resulting from infection). In certain embodiments, the inflammatory disease is a chronic inflammatory disease (*e.g.*, conditions resulting from

asthma, arthritis and inflammatory bowel disease). The compounds may also be useful in treating inflammation associated with trauma and non-inflammatory myalgia. The compounds may also be useful in treating inflammation associated with cancer.

[00207] Exemplary autoimmune diseases, include, but are not limited to, arthritis (including rheumatoid arthritis, spondyloarthropathies, gouty arthritis, degenerative joint diseases such as osteoarthritis, systemic lupus erythematosus, Sjogren's syndrome, ankylosing spondylitis, undifferentiated spondylitis, Behcet's disease, haemolytic autoimmune anaemias, multiple sclerosis, amyotrophic lateral sclerosis, amylosis, acute painful shoulder, psoriatic, and juvenile arthritis), asthma, atherosclerosis, osteoporosis, bronchitis, tendonitis, bursitis, skin condition (*e.g.*, psoriasis, eczema, burns, dermatitis, pruritus (itch)), enuresis, eosinophilic disease, gastrointestinal disorder (*e.g.*, selected from peptic ulcers, regional enteritis, diverticulitis, gastrointestinal bleeding, eosinophilic gastrointestinal disorders (*e.g.*, eosinophilic esophagitis, eosinophilic gastritis, eosinophilic gastroenteritis, eosinophilic colitis), gastritis, diarrhea, gastroesophageal reflux disease (GORD, or its synonym GERD), inflammatory bowel disease (IBD) (*e.g.*, Crohn's disease, ulcerative colitis, collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, Behcet's syndrome, indeterminate colitis) and inflammatory bowel syndrome (IBS)), and disorders ameliorated by a gastroprokinetic agent (*e.g.*, ileus, postoperative ileus and ileus during sepsis; gastroesophageal reflux disease (GORD, or its synonym GERD); eosinophilic esophagitis, gastroparesis such as diabetic gastroparesis; food intolerances and food allergies and other functional bowel disorders, such as non-ulcerative dyspepsia (NUD) and non-cardiac chest pain (NCCP, including costo-chondritis)).

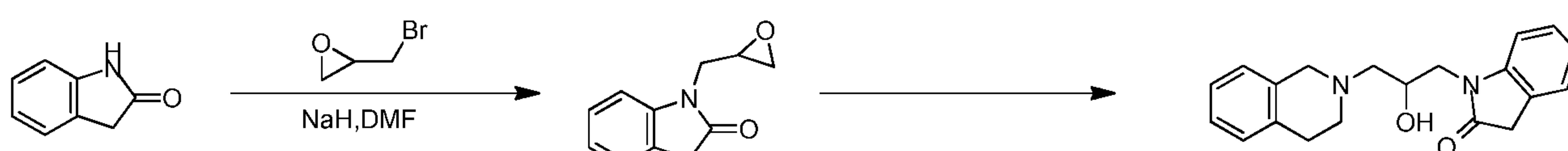
[00208] In some embodiments, a provided compound is useful in somatic cell reprogramming, such as reprogramming somatic cells into stem cells. See, *e.g.*, Nagamatsu *et al.*, *J Biol Chem.* (2011) 286:10641-10648. In some embodiments, a provided compound is useful in germ cell development, and are thus envisioned useful in the areas of reproductive technology and regenerative medicine. See, *e.g.*, Ancelin *et al.*, *Nat. Cell. Biol.* (2006) 8:623-630.

[00209] In some embodiments, compounds described herein can prepared using methods shown in general Scheme 1, which describes ring opening of a chiral or racemic epoxide group to form the amino alcohol moiety linker. Further substitution of the tetrahydroisoquinoline ring and/or the G-containing ring can be carried out before or after the coupling reaction.

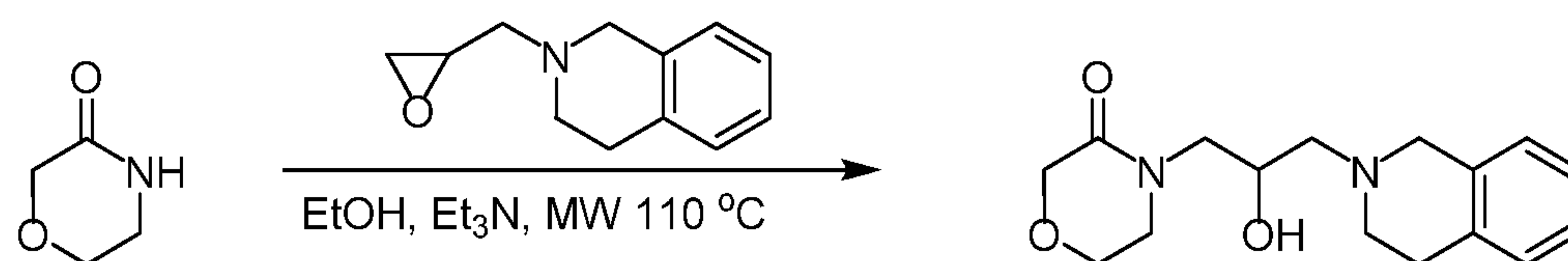


Scheme 1

[00210] In some embodiments, epoxide opening can be performed in the final step as shown in exemplary Schemes 2 and 3.

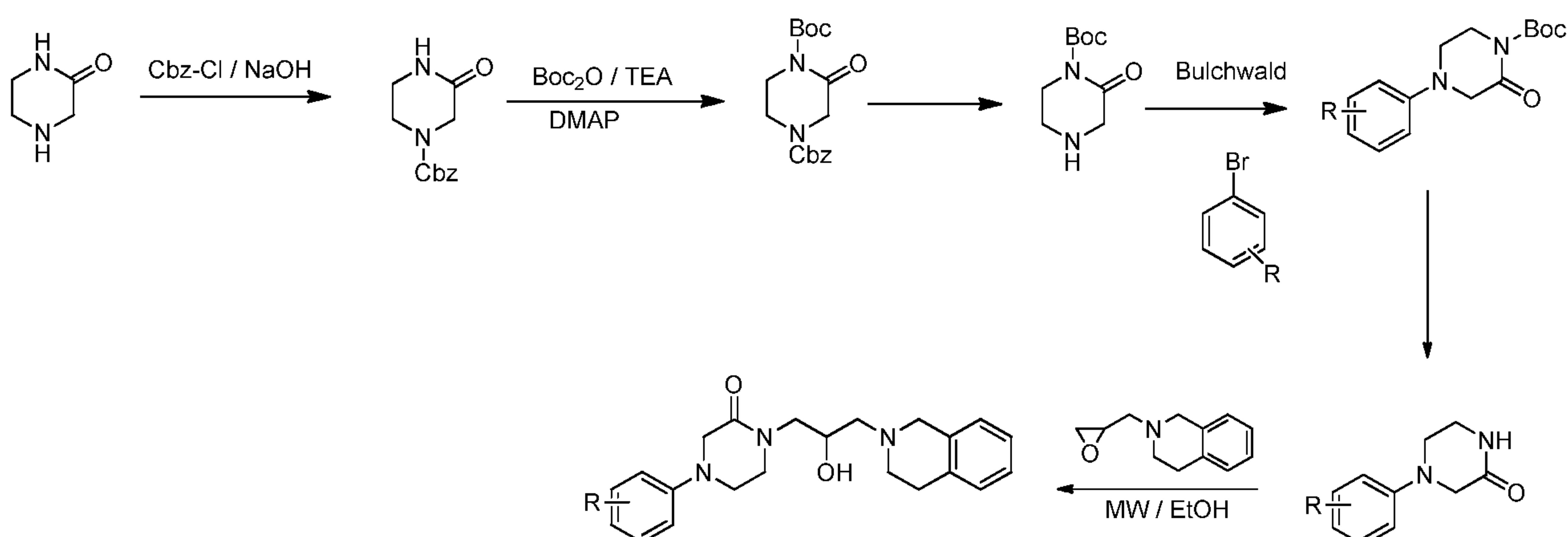


Scheme 2

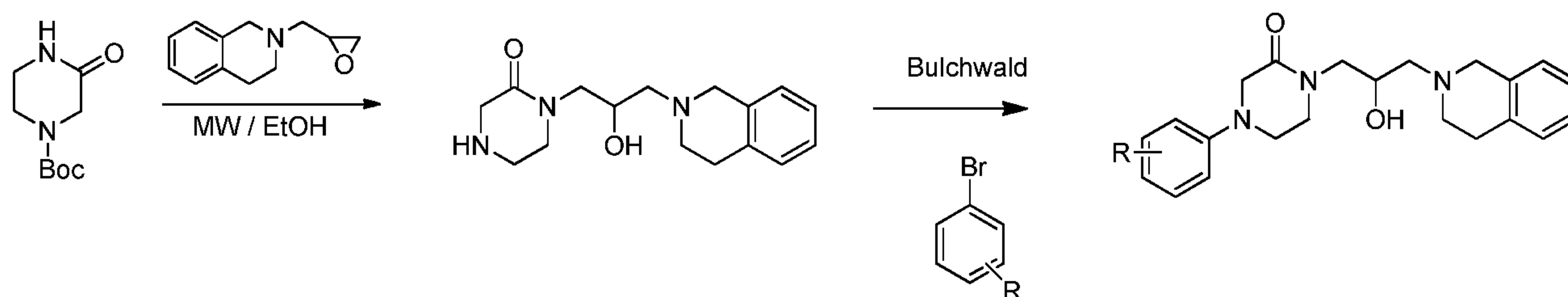


Scheme 3

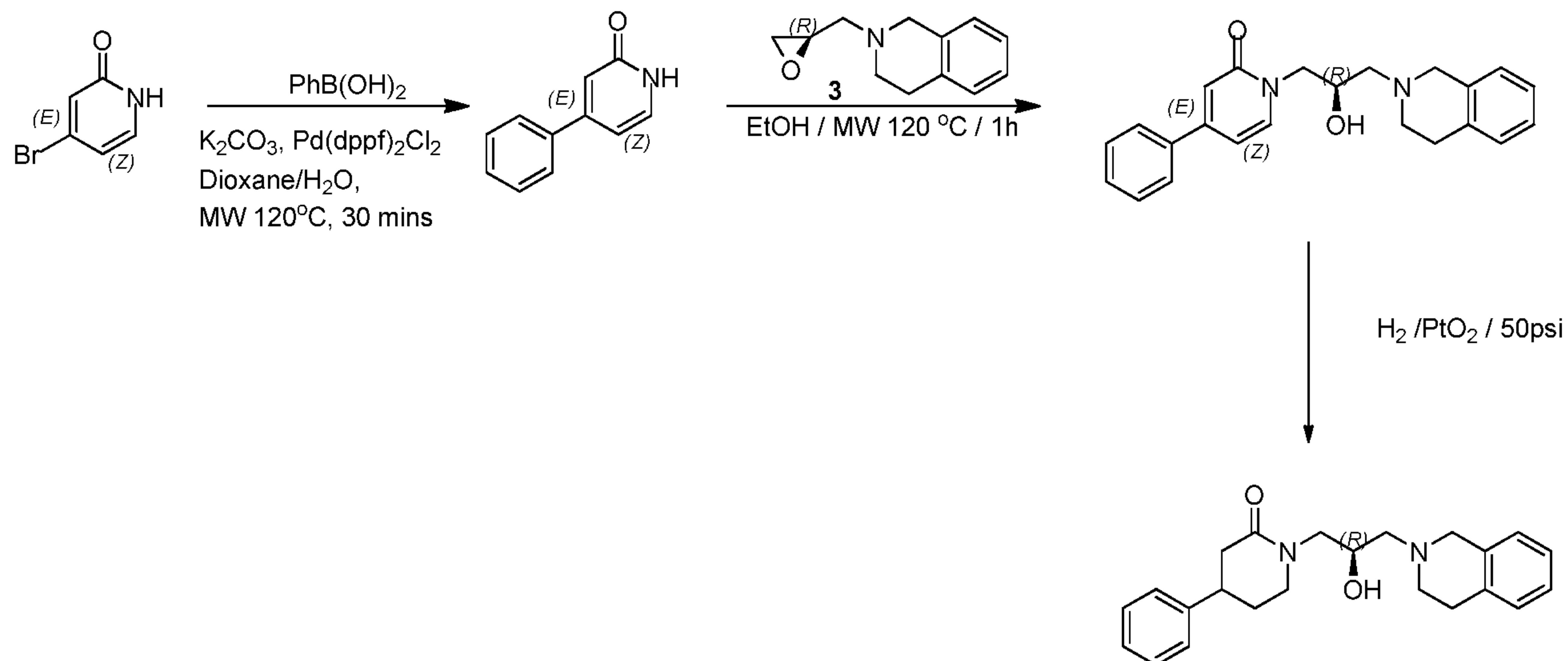
[00211] In some embodiments, an amide coupling step can be used to provide a key intermediate for further synthesis, as shown in exemplary Schemes 4-6.



Scheme 4

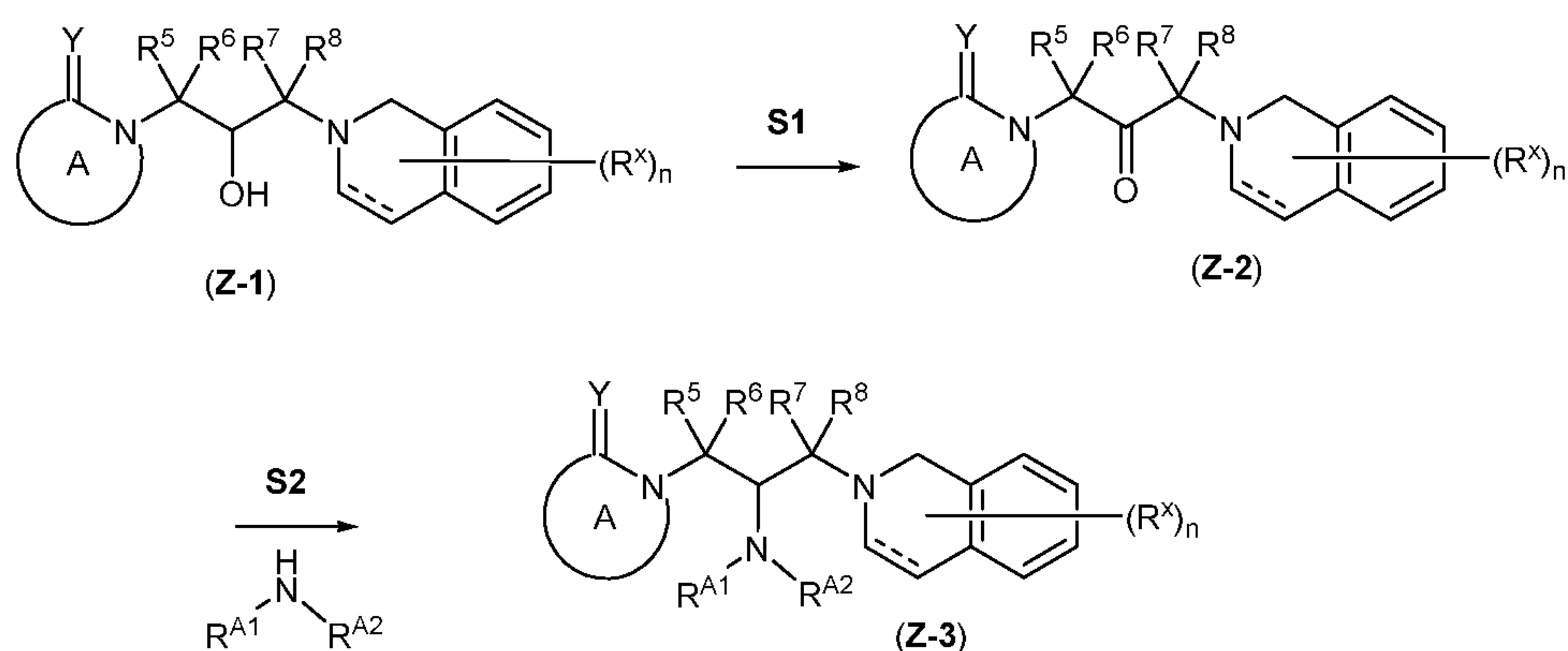


Scheme 5



Scheme 6

[00212] In some embodiments of the compounds described herein, R^{12} or R^{13} is an amine. A non-limiting example of the synthetic sequence used to prepare such analogs is provided herein (see Scheme 7). In this example, an alcohol of Formula (**Z-1**) is oxidized under suitable conditions **S1** to affect transformation into an intermediate ketone of Formula (**Z-2**). A ketone of Formula (**Z-2**) can be contacted with a primary or secondary amine under suitable conditions **S2** to affect a reductive amination which can afford an amino compound of Formula (**Z-3**).



Scheme 7

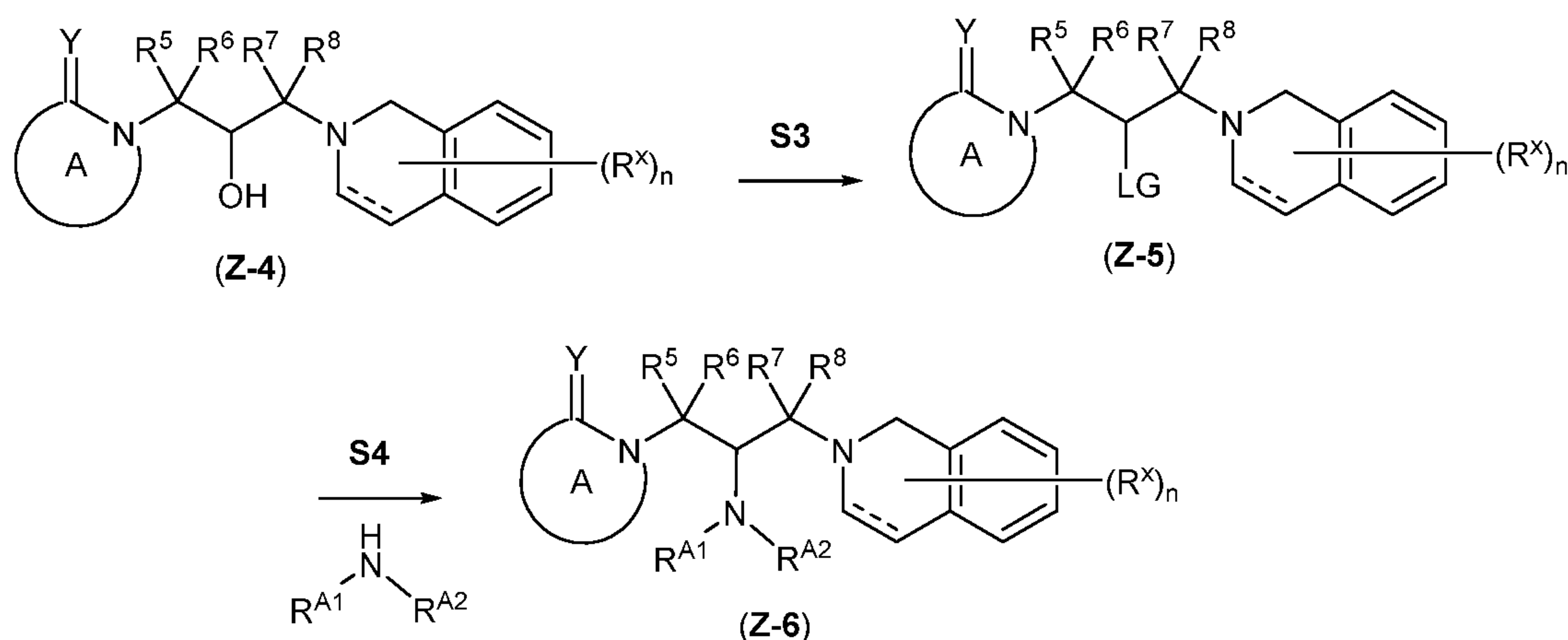
[00213] In some embodiments, the oxidation reaction **S1** is carried out directly with a stoichiometric oxidant. In some embodiments, the stoichiometric oxidant is pyridinium chlorochromate. In some embodiments, the stoichiometric oxidant is pyridinium dichromate. In some embodiments, the stoichiometric oxidant is Dess-Martin periodinane. In some embodiments, the stoichiometric oxidant is prepared *in situ*. In some embodiments, the stoichiometric oxidant is prepared *in situ* using sulfur trioxide pyridine complex and dimethylsulfoxide. In some embodiments, the stoichiometric oxidant is prepared *in situ* using oxallyl chloride and dimethylsulfoxide. In some embodiments, the stoichiometric oxidant is prepared *in situ* using a carbodiimide and dimethylsulfoxide. In some embodiments, the stoichiometric oxidant is prepared *in situ* using *N*-chlorosuccinimide and dimethylsulfide. In some embodiments, the oxidation reaction **S1** is catalyzed. In some embodiments, the catalyst is (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl. In some embodiments, the catalyst is a ruthenium complex. In some embodiments, the catalyst is a palladium complex. In some embodiments, the catalyst is a copper complex. For examples of standard methods and conditions for alcohol oxidation, see Epstein *et al.*, *Chem. Rev.* (1967) 67(3):247-260 and B.M. Trost ed. "Comprehensive Organic Synthesis", (1991), Vol. 7, p 281-305.

[00214] In some embodiments, both the oxidation step **S1** and reductive amination step **S2** occur in one pot. In some embodiments, both the oxidation step **S1** and the reductive amination step **S2** are carried out using the same catalyst. In some embodiments, the catalyst is a rhodium complex. In some embodiments, the catalyst is a ruthenium complex. In some embodiments, the catalyst is an iridium complex.

[00215] In some embodiments, the reductive amination reaction **S2** is carried out using a borohydride. In some embodiments, the reductive amination reaction **S2** is carried out using sodium borohydride. In some embodiments, the reductive amination reaction **S2** is carried out using sodium cyanoborohydride. In some embodiments, the reductive amination reaction **S2** is carried out using sodium triacetoxyborohydride. In some embodiments, the reductive amination reaction **S2** is carried out using a borane. In some embodiments, the reductive amination reaction **S2** is carried out using a silyl hydride. In some embodiments, the reductive amination reaction **S2** is carried out using hydrogen. In some embodiments, the reductive amination reaction **S2** is carried out in two steps, by first contacting a ketone of (**Z-2**) with an amine to form an intermediate imine, and then reducing the intermediate imine under sufficient conditions to afford a compound of Formula (**Z-3**). In some embodiments, the reaction conditions **S2** comprise addition of a protic acid. In some embodiments, the reaction conditions **S2** comprise addition of an aprotic acid. In some embodiments, the

reaction conditions **S2** comprise *in situ* formation of the reducing agent. In some embodiments, the reaction conditions **S2** comprise a catalyst. In some embodiments, the reaction conditions **S2** comprise a transition metal catalyst. In some embodiments, the reaction conditions **S2** comprise a palladium or nickel catalyst. In some embodiments, the reductive amination reaction **S2** is stereoselective. In some embodiments, the stereoselective reductive amination reaction **S2** is carried out in the presence of a chiral catalyst. For examples of standard methods and conditions for reductive aminations, see Gomez *et al.*, *Adv. Synth. Catal.* (2002) 344(10):1037-1057 and Abdel-Magid *et al.*, *J. Org. Chem.* (1996), 61:3849.

[00216] An alternative non-limiting synthetic sequence leading to the aforementioned amine analogs is described herein (see Scheme 8). The hydroxyl moiety of a compound of Formula (**Z-4**) can be transformed into a leaving group under sufficient conditions **S3** to afford a compound of Formula (**Z-5**). The leaving group of a compound of Formula (**Z-5**) can be displaced with an amine under suitable conditions **S4** to produce an amino compound of Formula (**Z-6**).



Scheme 8

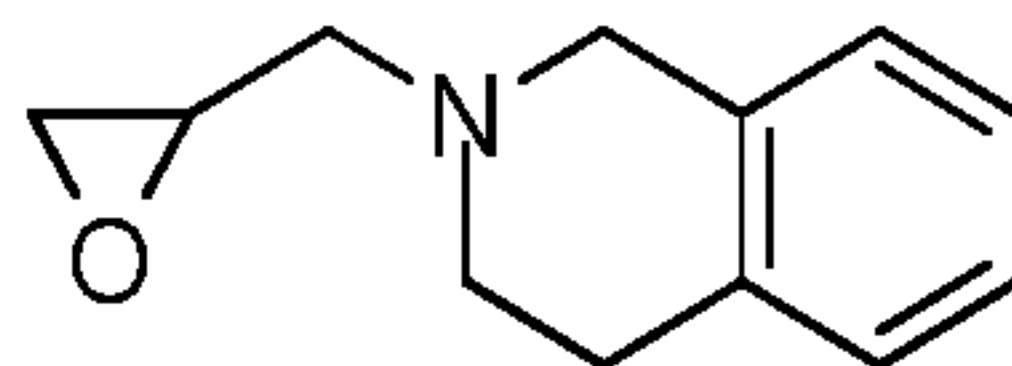
[00217] In some embodiments, LG of Formula (**Z-5**) is a halide. In some embodiments, LG of Formula (**Z-5**) is bromine. In some embodiments, LG of Formula (**Z-5**) is iodine. In some embodiments, LG of Formula (**Z-5**) is a substituted or unsubstituted alkyl sulfonate. In some embodiments, LG of Formula (**Z-5**) is a substituted or unsubstituted aryl sulfonate. In some embodiments, LG of Formula (**Z-5**) is methyl sulfonate. In some embodiments, LG of Formula (**A-5**) is trifluoromethane sulfonate. In some embodiments, LG of Formula (**Z-5**) is a toluene sulfonate. In some embodiments, LG of Formula (**Z-5**) is a nitrobenzene sulfonate. In some embodiments, when LG of Formula (**Z-5**) is halide, conditions **S3** comprise a phosphoryl halide. In some embodiments, when LG of Formula (**Z-5**) is halide, conditions

S3 comprise a sulfonyl halide. In some embodiments, when LG of Formula (**Z-5**) is sulfonate, conditions **S3** comprise a sulfonyl halide. In some embodiments, when LG of Formula (**Z-5**) is sulfonate, conditions **S3** comprise a sulfonyl anhydride. For examples of standard methods and conditions for organohalide or sulfonate ester synthesis, see Lautens *et al.*, *Synthesis* (2011) 2:342-346 or Marcotullio *et al.*, *Synthesis* (2006) 16:2760-2766.

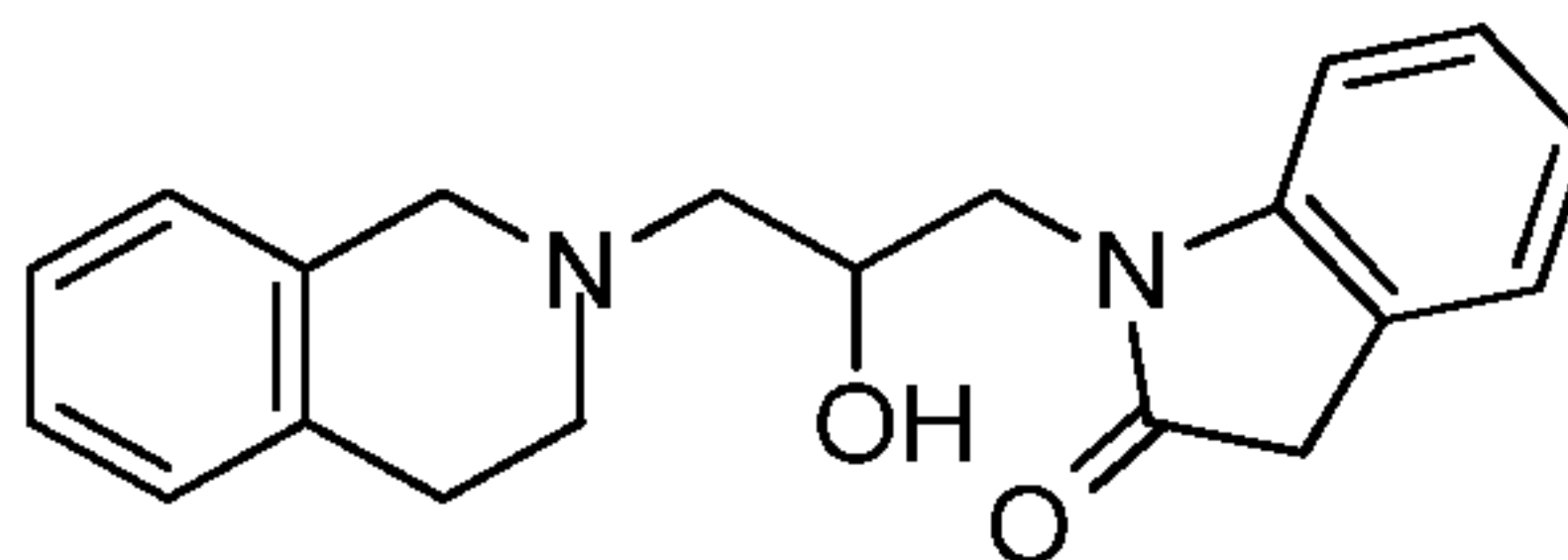
[00218] In some embodiments, conditions **S4** are neutral. In some embodiments, conditions **S4** comprise addition of a base. In certain embodiments of conditions **S4**, the base is either inorganic or organic. In certain embodiments of conditions **S4**, the base is inorganic. In certain embodiments of conditions **S4**, the base is organic. In certain embodiments of conditions **S4**, the base is a metal acetate, alkoxide, amide, amidine, carbonate, hydroxide, phenoxide, or phosphate. In certain embodiments of conditions **S4**, the base is sodium, potassium, or caesium carbonate. In certain embodiments of conditions **S4**, the base is sodium, potassium, or caesium bicarbonate. In certain embodiments of conditions **S4**, the base is 1,1,3,3-tetramethylguanidine, 1,4-diazabicyclo[2.2.2]octane, 1,8-bis(dimethylamino)naphthalene, 1,8-diazabicycloundec-7-ene, ammonia, diisopropylamine, imidazole, N,N-diisopropylethylamine, piperidine, pyridine, pyrrolidine, or triethylamine. In some embodiments of conditions **S4**, the solvent is a polar protic solvent. In some embodiments of conditions **S4**, the solvent is a polar aprotic solvent. In some embodiments of conditions **S4**, the reaction is performed in the absence of solvent. In some embodiments, conditions **S4** comprise a catalyst. In some embodiments of conditions **S4**, the catalyst is an iodide salt. In some embodiments, both step **S3** and the displacement step **S4** occur in one pot. In some embodiments, the hydroxyl moiety of a compound of Formula (**Z-4**) is converted into a leaving group *in situ*. In some embodiments, the hydroxyl moiety of a compound of Formula (**Z-4**) is converted into a leaving group *in situ* using an azodicarboxylate and an aryl or alkyl phosphine. For examples of standard methods and conditions for amine syntheses through alkylation reactions, see Salvatore *et. al*, *Tetrahedron* (2001) 57:7785-7811.

Examples

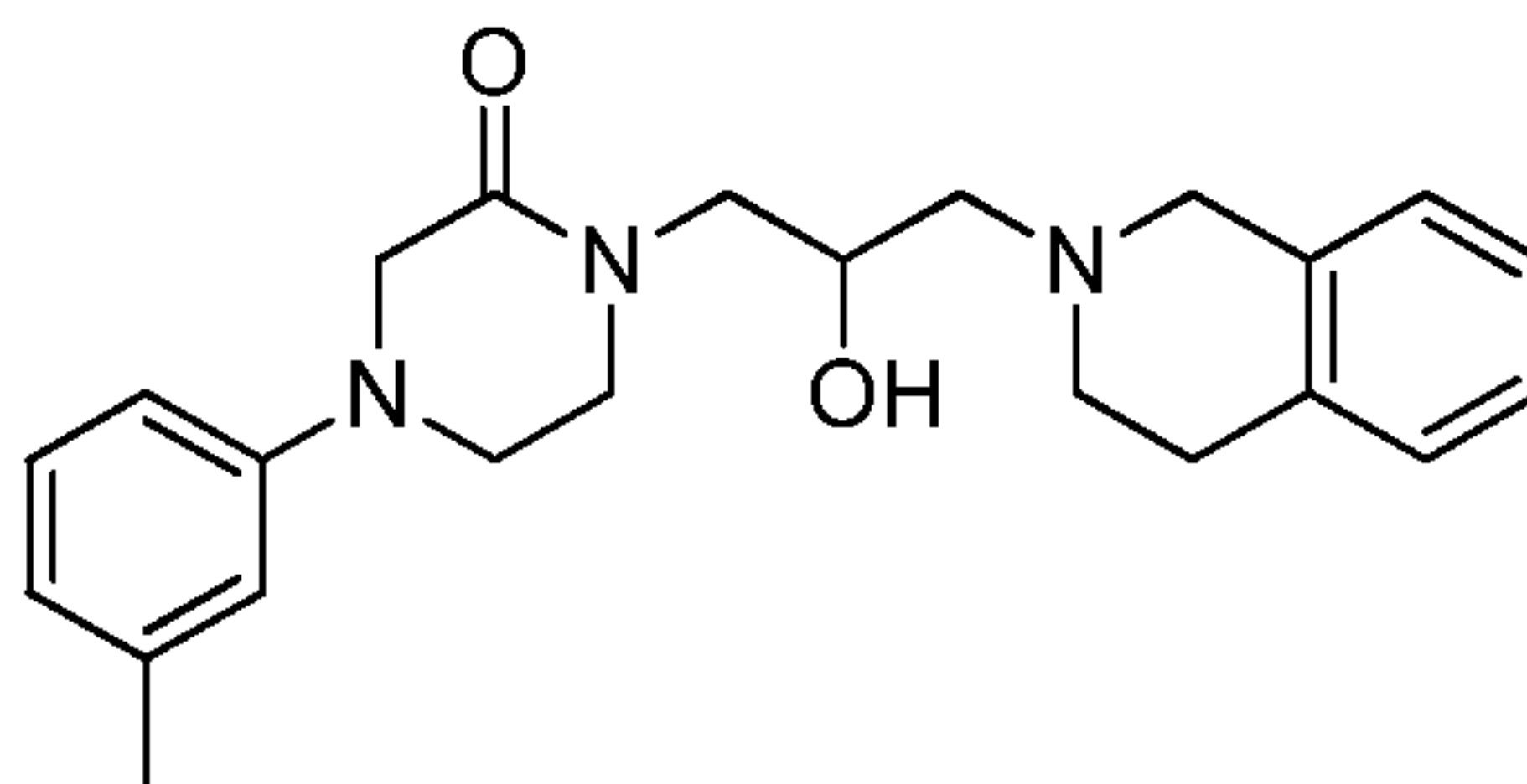
[00219] In order that the invention described herein may be more fully understood, the following examples are set forth. It should be understood that these examples are for illustrative purposes only and are not to be construed as limiting this invention in any manner.

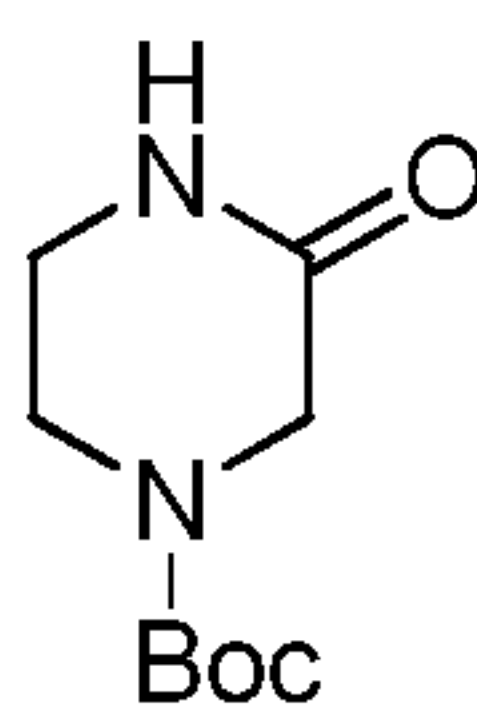
*Synthetic Methods***Intermediate Synthesis****2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline**

[00220] To a solution of 1,2,3,4-tetrahydroisoquinoline (15g, 0.11mol) in MeCN (100 mL) was added K_2CO_3 (30.7 g, 0.23 mol) at 0 °C. 2-(bromomethyl)oxirane (17g, 0.12 mol) was added to the reaction after 1 h. The solution was stirred at 22 °C for 16 h at which time the solids were filtered and washed with MeCN. The solution was concentrated and the residue was used in the next step without further purification (17 g, Yield 78%). LCMS (m/z): 190.1 (M+1).

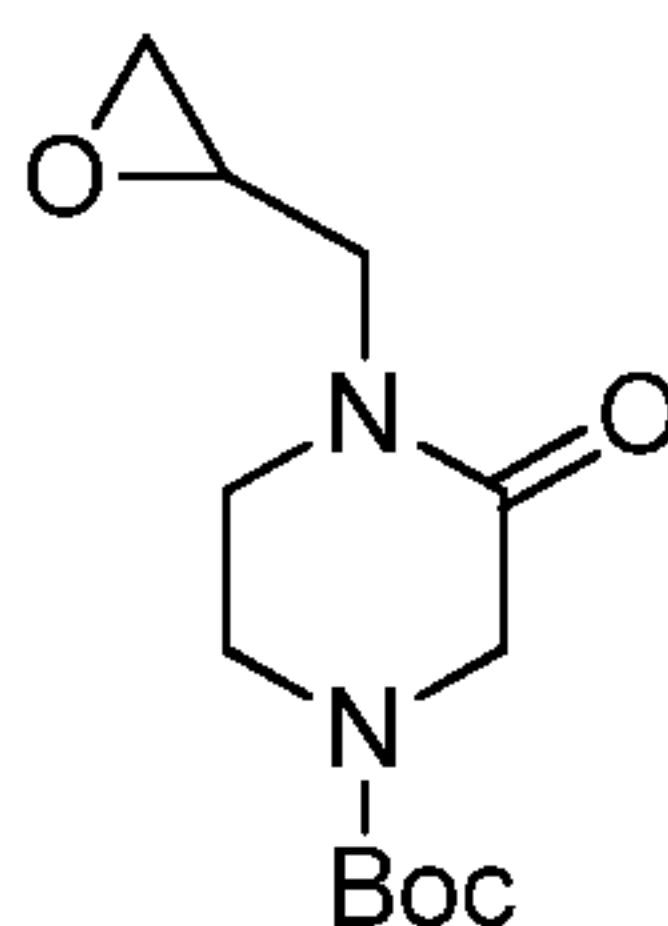
Compound 1**1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)indolin-2-one**

[00221] To a solution of indolin-2-one (50.0 mg, 0.378 mmol) in ethanol (5 mL) was added 2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (85.0 mg, 0.451 mmol). The mixture was heated under microwave conditions at 120 °C for 0.5 h, concentrated and purified by preparative HPLC purification. (40.0 mg, yield 33.0%) MS (ESI⁺) e/z: 323.1 [M+1]⁺. ¹H NMR (MeOD, 400 MHz), δ ppm: 7.30 - 7.23 (m, 2H), 7.14 - 7.07 (m, 4H), 7.06 (d, $J=7.5$ Hz, 1H), 7.01 (t, $J=5.8$ Hz, 1H), 4.94 (d, $J=7.8$ Hz, 2H), 4.31 - 4.18 (m, 1H), 3.97 - 3.86 (m, 1H), 3.82 - 3.72 (m, 1H), 3.71 - 3.64 (m, 2H), 2.90 - 2.73 (m, 4H), 2.73 - 2.59 (m, 2H).

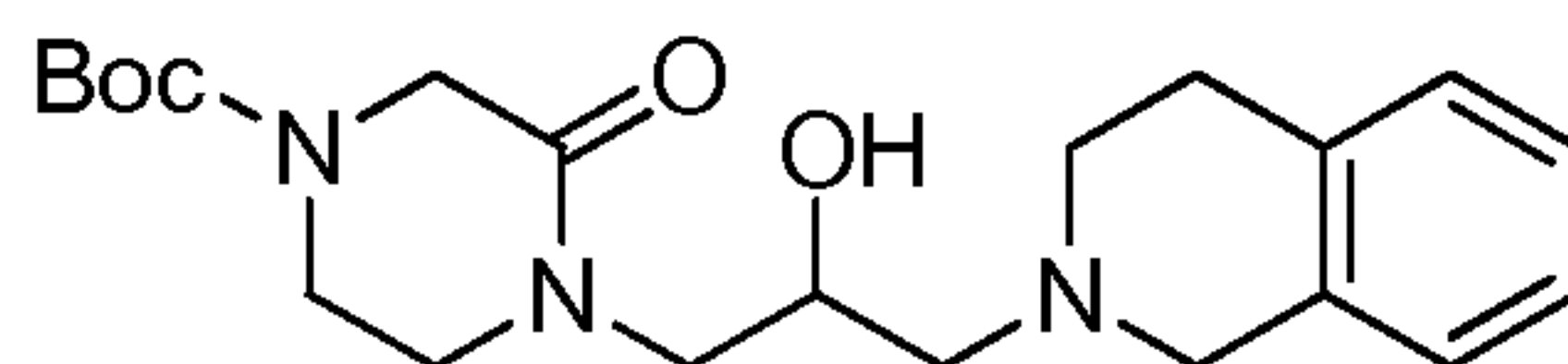
Compound 3**1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(m-tolyl)piperazin-2-one**

Step 1: *tert*-butyl 3-oxopiperazine-1-carboxylate

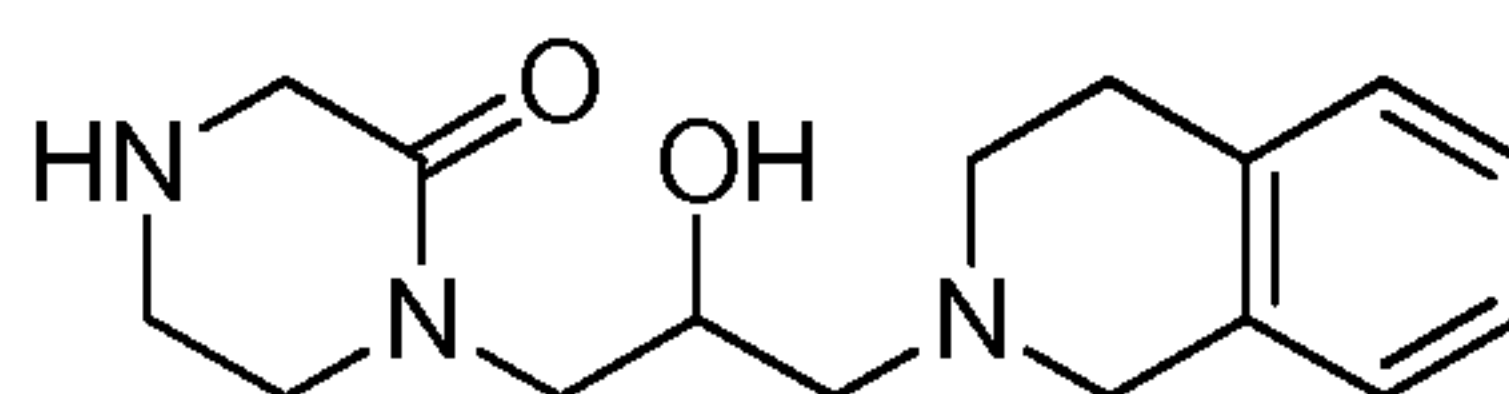
[00222] Piperazin-2-one (10 g, 0.1 mol), Et₃N (20.2g, 0.2 mmol) and DCM (100 mL) were combined and cooled to 0 °C. To the solution was added Boc₂O (26.1 g, 0.12 mol) in DCM (250 ml), and the resulting mixture was warmed to room temperature and stirred for 12 h. The reaction mixture was concentrated and dissolved in ethyl acetate, washed with 1 N HCl, brine, dried over sodium sulfate, filtered and concentrated. The crude product was used without further purification. (19.5 g, yield 97.5%).

Step 2: *tert*-butyl 4-(oxiran-2-ylmethyl)-3-oxopiperazine-1-carboxylate

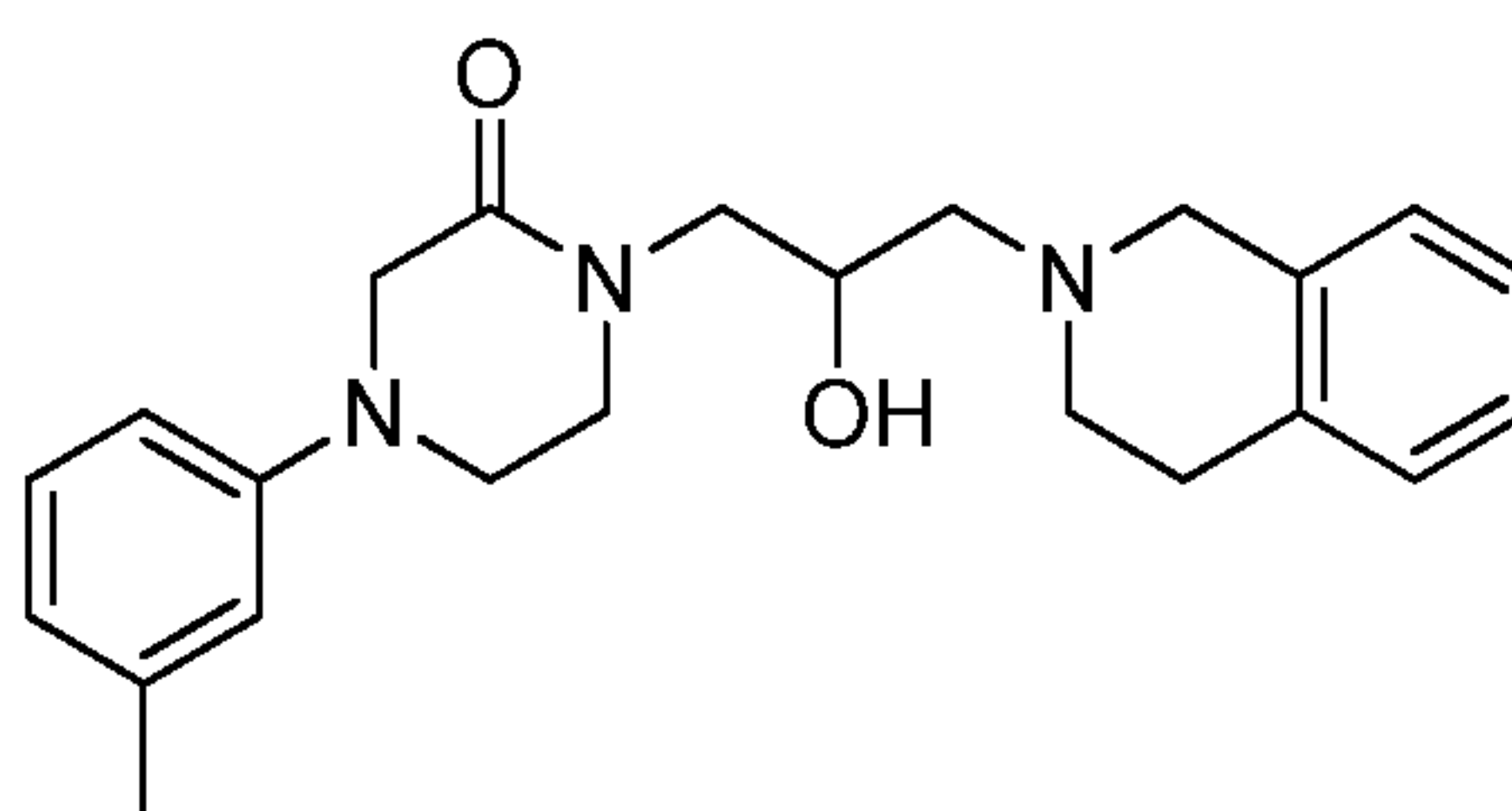
[00223] *tert*-butyl 3-oxopiperazine-1-carboxylate (400 mg, 2 mmol) was dissolved in THF (20 mL) and cooled to 0 °C. NaH (72 mg, 3 mmol) was added to the solution followed by 2-(bromomethyl)oxirane (326 mg, 2.4 mmol), and the resulting mixture was stirred at 0 °C for 16 h. The reaction mixture was quenched by addition of ice water, extracted with ethyl acetate, washed with brine, dried over sodium sulfate and concentrated. The crude product was used without further purification. (400 mg, yield 78.1%).

Step 3: *tert*-butyl 4-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-oxopiperazine-1-carboxylate

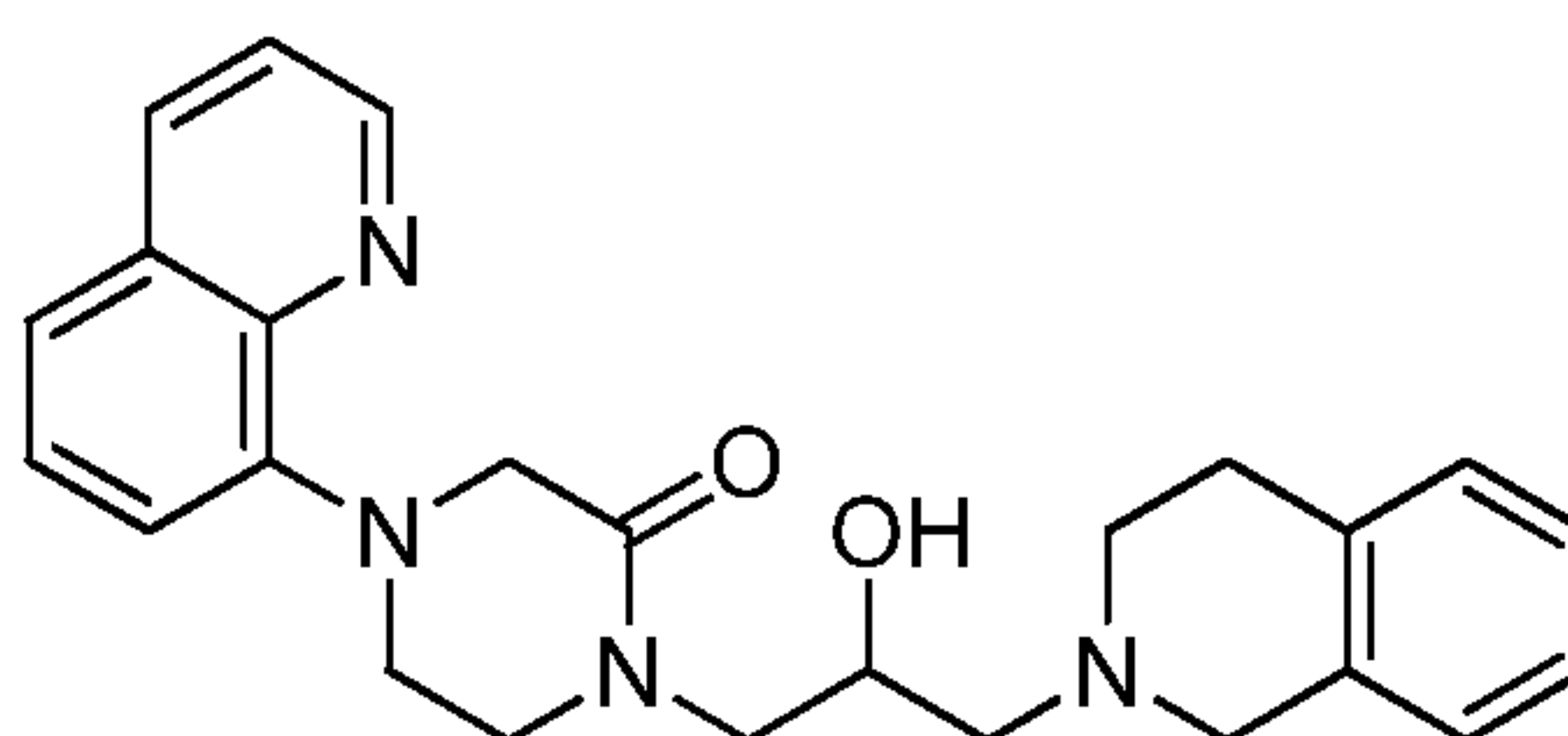
[00224] To a solution of *tert*-butyl 4-(oxiran-2-ylmethyl)-3-oxopiperazine-1-carboxylate (400 mg, 1.56 mmol) in EtOH (1 mL) was added 1,2,3,4-tetrahydroisoquinoline (207 mg, 1.56 mmol). The mixture was heated under microwave conditions at 120 °C for 0.5 h and concentrated. The crude product was used without further purification. (600 mg, yield 98%) MS (ESI⁺) *m/z*: 390.2 [M+1]⁺.

Step 4: 1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)piperazin-2-one

[00225] To a solution of *tert*-butyl 4-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-3-oxopiperazine-1-carboxylate (200 mg, 0.69 mmol) in ethyl acetate (10 mL) was added HCl/ethyl acetate (4 mL). The reaction mixture was stirred at 20 °C overnight, concentrated and used in the next step without further purification. (100 mg, yield 50%) MS (ESI⁺) *m/z*: 290.2 [M+1]⁺.

Step 5: 1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(*m*-tolyl)piperazin-2-one

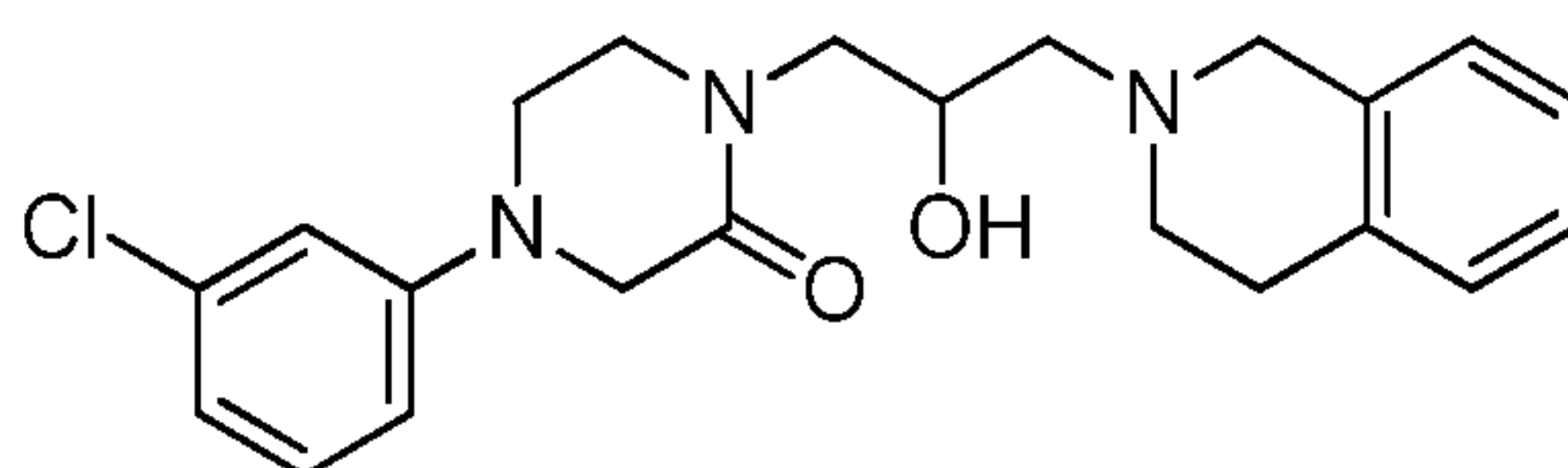
[00226] A mixture of 1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)piperazin-2-one (50 mg, 0.17 mmol), 1-iodo-3-methylbenzene (55.3 mg, 0.25 mmol), Pd₂(dba)₃ (10 mg, 0.01 mmol), Xantphos (20 mg, 0.02 mmol) and *t*-BuONa (30 mg, 0.3 mmol) were placed in the three-neck reactor with a condenser and magnetic stirring bar, the system was degassed 3 times (N₂) and dioxane (10 mL) was added. The mixture was heated at reflux for 16 h, cooled, filtered and concentrated. The residue was purified by preparative HPLC purification. (18.0 mg, yield 28.0%) MS (ESI⁺) *m/z*: 380.2 [M+1]⁺. ¹H NMR (MeOD, 400 MHz), δ ppm: 7.10 (br. s., 5H), 6.85 - 6.65 (m, 3H), 4.33 - 4.14 (m, 1H), 3.88 - 3.81 (m, 2H), 3.81 - 3.68 (m, 4H), 3.67 - 3.58 (m, 1H), 3.56 - 3.44 (m, 2H), 3.32 - 3.25 (m, 1H), 3.02-2.76 (m, 4H), 2.68 - 2.54 (m, 2H), 2.32 (s, 3H).

Compound 4**1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(quinolin-8-yl)piperazin-2-one**

[00227] To a solution of 1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)piperazin-2-one (100 mg, 0.35 mmol) in 10 mL of dry toluene was added 8-bromoquinoline (108 mg, 0.52 mmol), $\text{Pd}_2(\text{dba})_3$ (32 mg, 0.035 mmol), NINAP (44 mg, 0.07 mmol) and t-BuONa (101 mg, 1.05 mmol). The flask was degassed and charged with N_2 , then heated at 110 °C for 16 h. The reaction mixture was cooled, filtered, and concentrated. The residue was purified by preparative HPLC purification. (23 mg, yield 15.8%) MS (ESI^+) m/z : 417.2 $[\text{M}+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 8.96 - 8.85 (m, 1H), 8.53 - 8.39 (m, 1H), 8.38 - 8.29 (m, 1H), 7.70 - 7.62 (m, 1H), 7.62 - 7.51 (m, 2H), 7.37 - 7.24 (m, 4H), 7.24 - 7.17 (m, 1H), 4.60 - 4.52 (m, 1H), 4.52 - 4.41 (m, 2H), 4.08 - 3.98 (m, 2H), 3.87 - 3.78 (m, 2H), 3.77 - 3.69 (m, 1H), 3.69 - 3.58 (m, 4H), 3.57 - 3.49 (m, 1H), 3.42 - 3.34 (m, 1H), 3.32 - 3.27 (m, 1H), 3.27 - 3.13 (m, 2H).

Compound 5

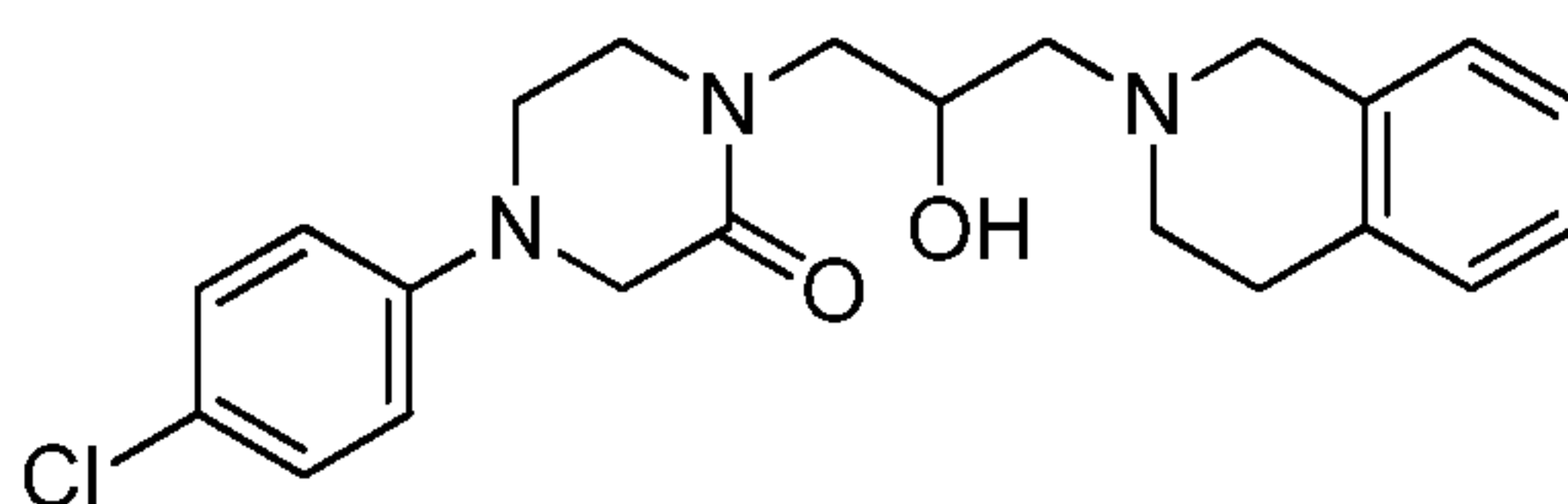
4-(3-chlorophenyl)-1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)piperazin-2-one



[00228] Compound **5** was synthesized in by a procedure analogous to that employed for compound **3**. (5.3 mg, yield 7.8%) MS (ESI^+) m/z : 400.1 $[\text{M}+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.26 - 7.21 (m, 1H), 7.16 - 7.07 (m, 3H), 7.07 - 7.01 (m, 1H), 6.95 - 6.89 (m, 1H), 6.89 - 6.78 (m, 2H), 4.26 - 4.19 (m, 1H), 3.92 - 3.85 (m, 2H), 3.83 - 3.70 (m, 4H), 3.69 - 3.62 (m, 1H), 3.59 - 3.51 (m, 2H), 3.32 - 3.24 (m, 1H), 2.97 - 2.90 (m, 2H), 2.89 - 2.80 (m, 2H), 2.66 - 2.56 (m, 2H).

Compound 7

4-(4-chlorophenyl)-1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)piperazin-2-one

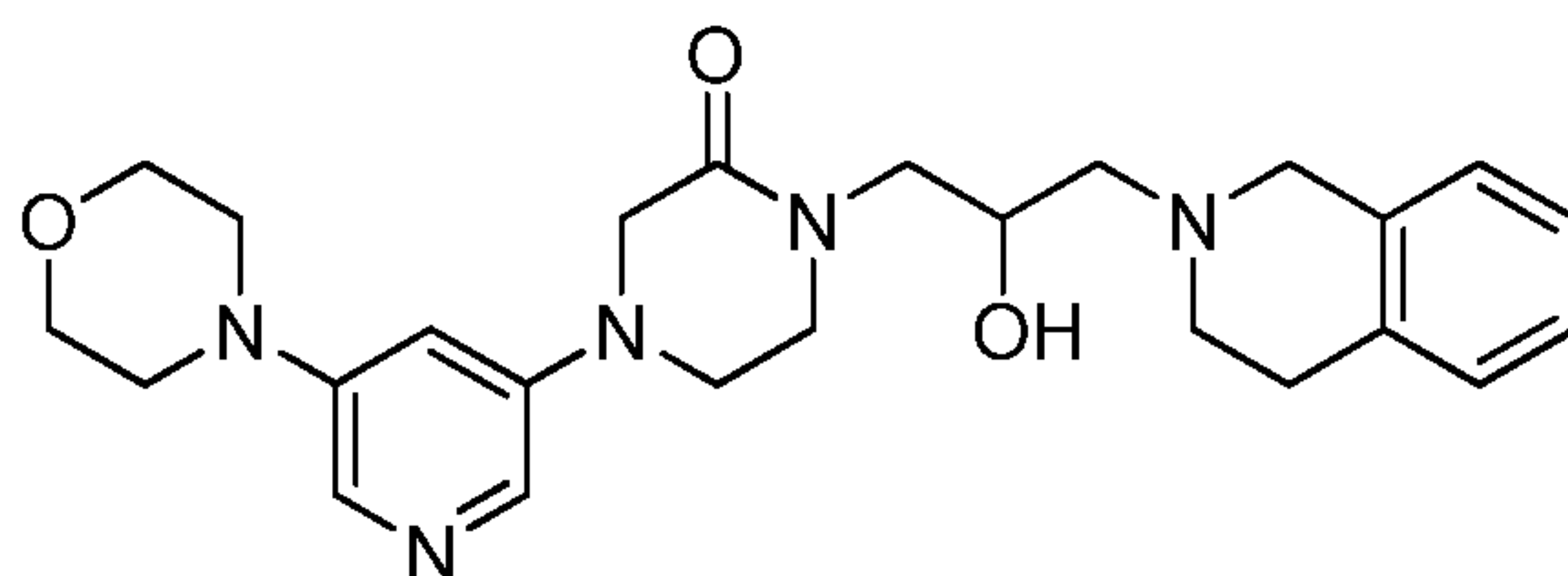


[00229] Compound **7** was synthesized in by a procedure analogous to that employed for compound **3**. (14.6 mg, yield 21.5%) MS (ESI^+) m/z : 400.1 $[\text{M}+1]^+$. ^1H NMR (MeOD, 400

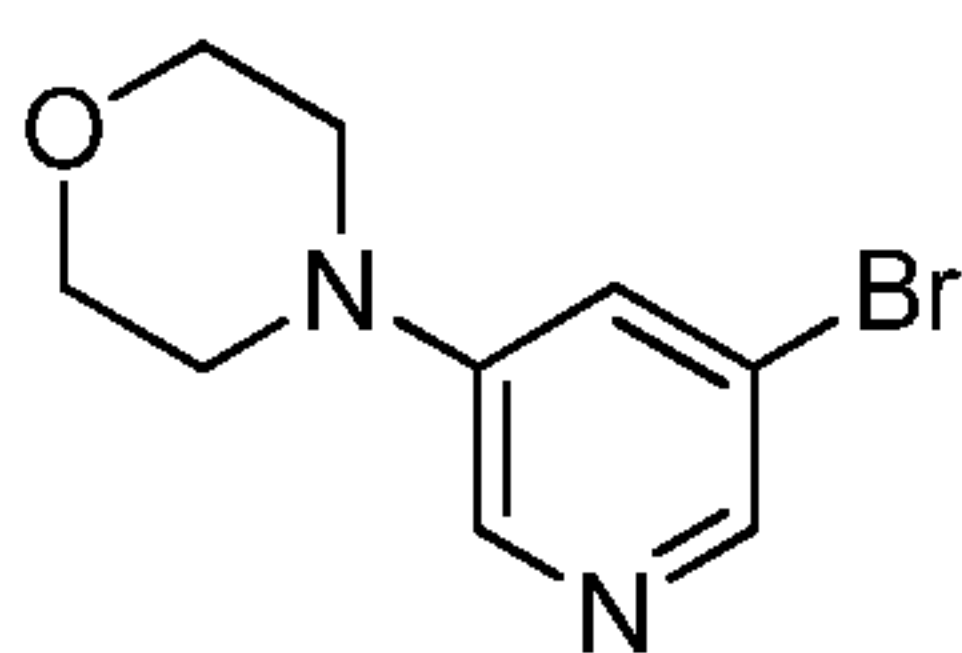
MHz), δ ppm: 7.28 - 7.16 (m, 2H), 7.16-6.98 (m, 4H), 6.95 - 6.85 (m, 2H), 4.25 - 4.16 (m, 1H), 3.90 - 3.81 (m, 2H), 3.81 - 3.68 (m, 4H), 3.67 - 3.58 (m, 1H), 3.55 - 3.45 (m, 2H), 2.97 - 2.87 (m, 2H), 2.86 - 2.75 (m, 2H), 2.66 - 2.52 (m, 2H).

Compound 8

1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(5-morpholinopyridin-3-yl)piperazin-2-one



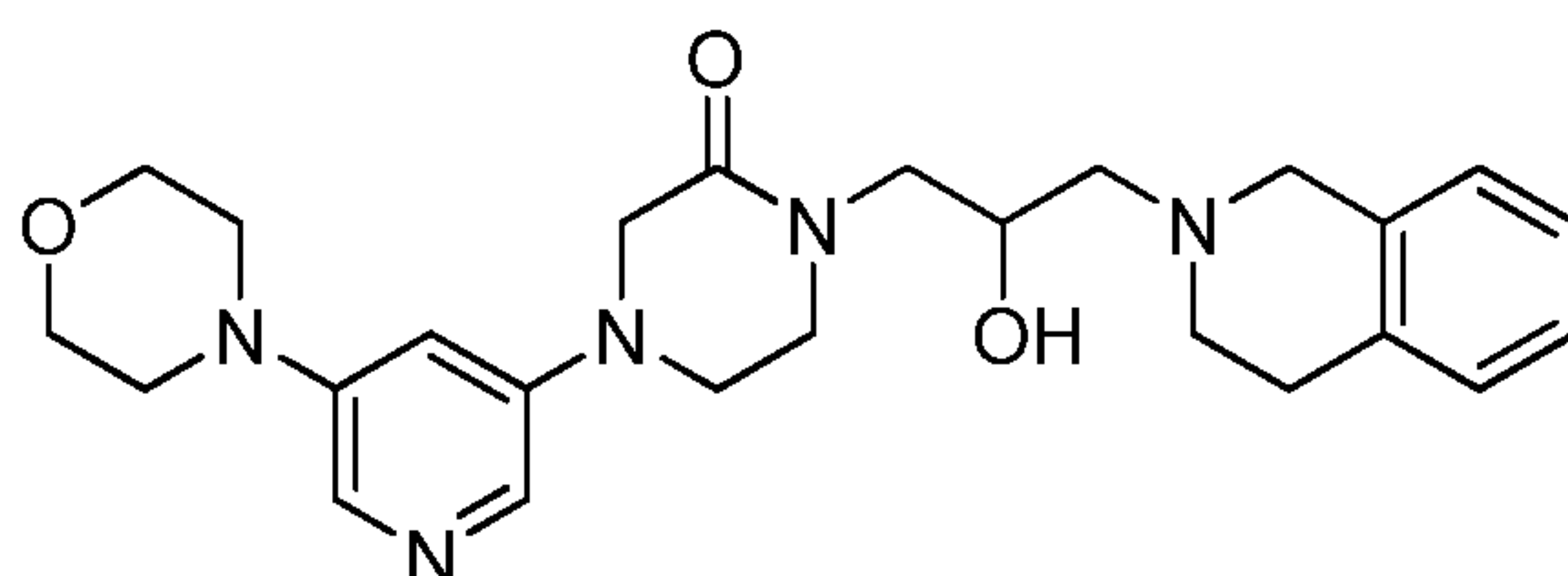
Step 1: 4-(5-bromopyridin-3-yl)morpholine



[00230] To a solution of morpholine (3.67 g, 4.23 mmol), NMP (2 mL) and toluene (4 mL) was added 3,5-dibromopyridine (1.00 g, 4.20 mmol) and the mixture was heated under microwave conditions at 180 °C for 1 h. The solution was partitioned between DCM and water, the organic layer was washed with water, brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by column chromatography eluting with (EtOAc: PE= 1:5). (200 mg, yield 19.5%) MS (ESI⁺) m/z : 243.0 [M+1]⁺LCMS.

[00231]

Step 2: 1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(5-morpholinopyridin-3-yl)piperazin-2-one

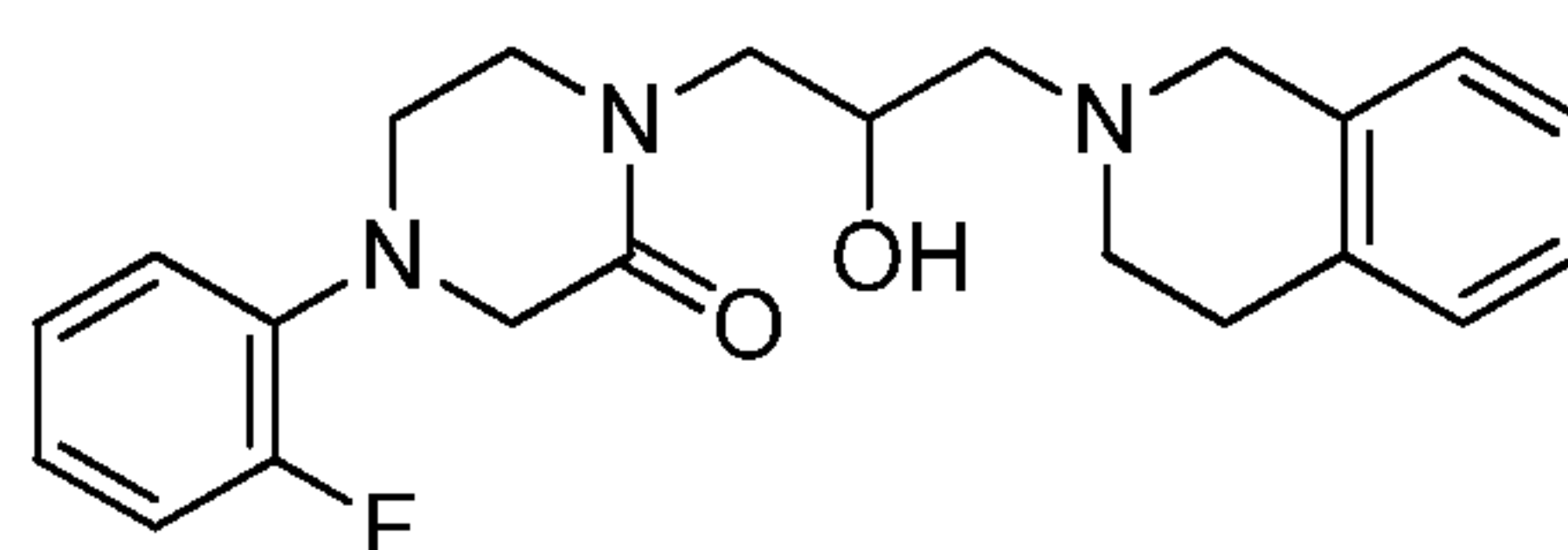


[00232] A solution of 4-(5-bromopyridin-3-yl)morpholine (100 mg, 0.413 mmol), 1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)piperazin-2-one (119 mg, 0.413 mmol), X-phos (20 mg, 0.042 mmol), Pd(dba)₂ (10 mg, 0.017 mmol) and NaOtBu (59.0 mg, 0.615 mmol) in dioxane (5 mL) was heated at 120 °C 1 h under microwave conditions. The crude

reaction mixture was filtered, concentrated, and purified by preparative HPLC purification. (6.10 mg, yield 3.3%) ^1H NMR (MeOD, 400 MHz), δ ppm: 7.76 (d, $J=2.3$ Hz, 1H), 7.72 (d, $J=2.0$ Hz, 1H), 7.17 - 7.07 (m, 3H), 7.07 - 7.01 (m, 1H), 6.89 - 6.80 (m, 1H), 4.28 - 4.18 (m, 1H), 3.93 (s, 2H), 3.89 - 3.82 (m, 4H), 3.82 - 3.72 (m, 4H), 3.71 - 3.63 (m, 1H), 3.59 (t, $J=1.0$ Hz, 2H), 3.32 - 3.28 (m, 1H), 3.27 - 3.16 (m, 4H), 2.99 - 2.90 (m, 2H), 2.90 - 2.81 (m, 2H), 2.68 - 2.58 (m, 2H).

Compound 11

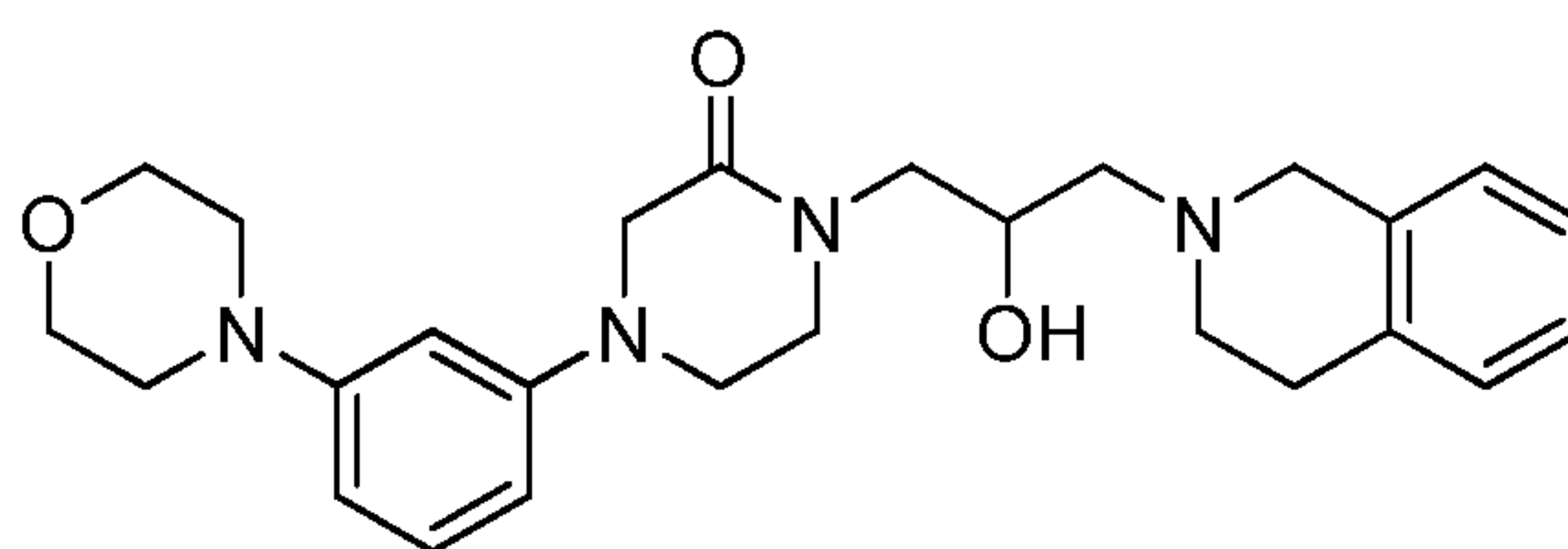
1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(2-fluorophenyl)piperazin-2-one



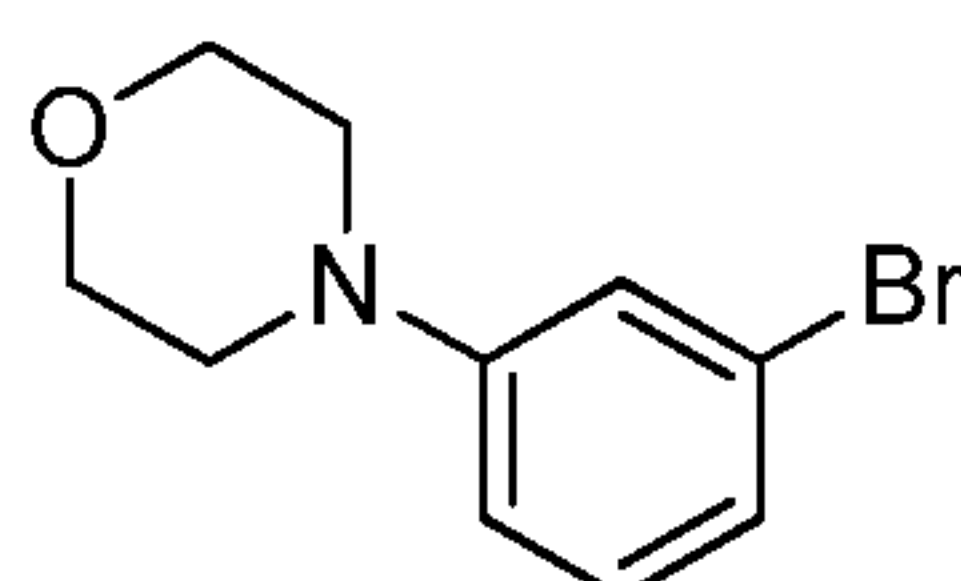
[00233] Compound **11** was synthesized in by a procedure analogous to that employed for compound **3**. (15.7 mg, yield 24.1%) MS (ESI⁺) m/z : 384.2[M+1]⁺. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.14 – 6.98 (m, 8H), 4.27 - 4.18 (m, 1H), 3.81 - 3.68 (m, 6H), 3.65 - 3.57 (m, 1H), 3.43 - 3.36 (m, 2H), 3.30 - 3.22 (m, 1H), 2.95 - 2.88 (m, 2H), 2.87 - 2.80 (m, 2H), 2.64 - 2.53 (m, 2H).

Compound 12

1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(3-morpholinophenyl)piperazin-2-one



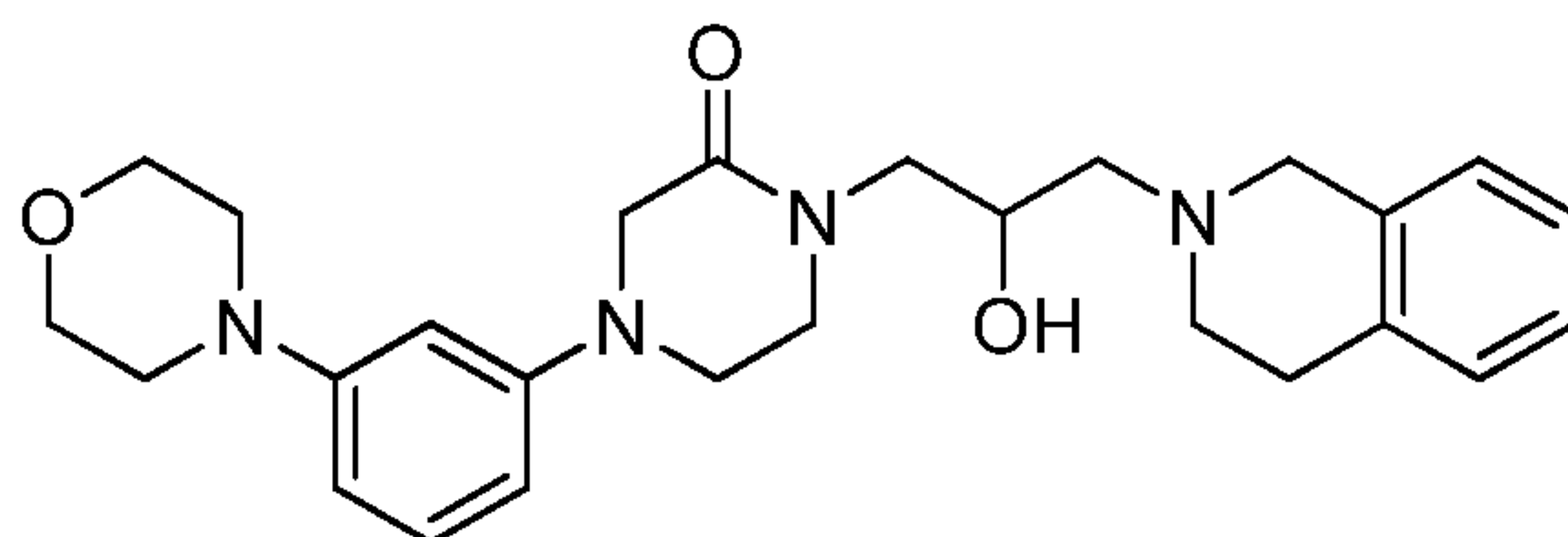
Step 1: 4-(3-bromophenyl)morpholine



[00234] To a solution of 3-bromoaniline (1.00 g, 5.81 mmol) in anhydrous DMF (20 mL) was added 1-bromo-2-(2-bromoethoxy)ethane (1.62 g, 6.18 mmol) and DIPEA (2.25 g, 17.4 mmol). The solution was heated to 100 °C for 16 h, cooled and concentrated. The residue

was purified by preparative HPLC purification. (230 mg, yield 16.4%) MS (ESI⁺) *m/z*: 242.0 [M+1]⁺.

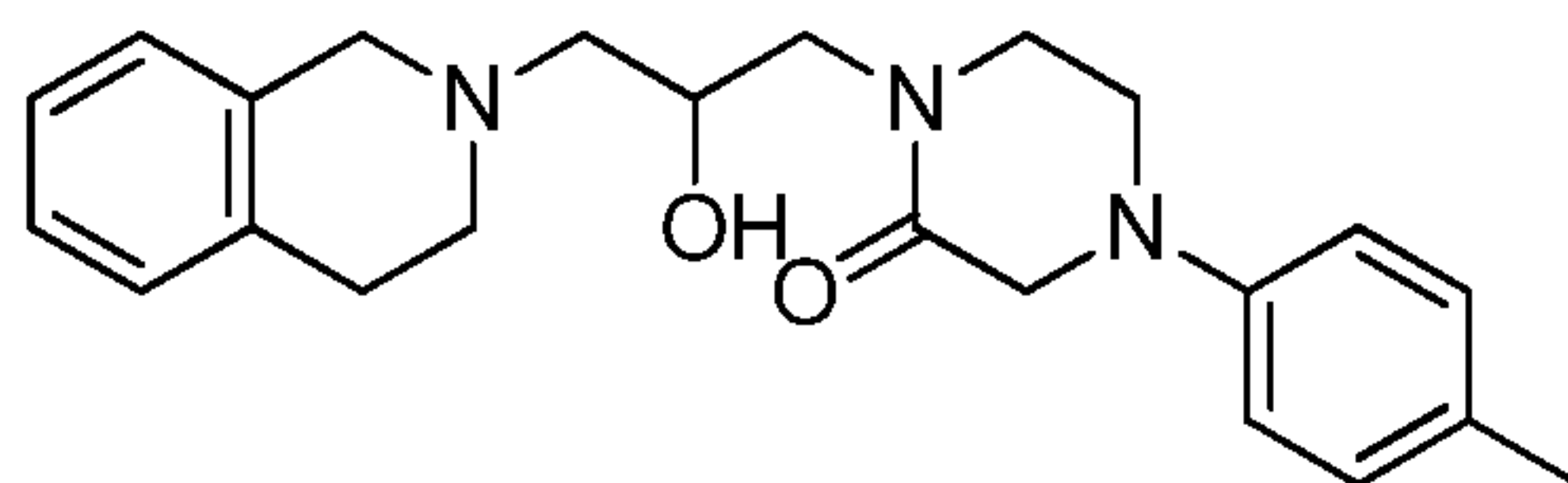
Step 2: 1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(3-morpholinophenyl)piperazin-2-one



[00235] 4-(3-bromophenyl)morpholine (100 mg, 0.413 mmol), 1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)piperazin-2-one (119 mg, 0.413 mmol), Xphos (20 mg, 0.042 mmol), Pd(dba)₂ (10 mg, 0.017 mmol) and NaOtBu (59.0 mg, 0.615 mmol) and dioxane (5 mL) were combined in a three-neck flask with a condenser and magnetic stirring bar, the system was degassed (N₂) and dioxane (10 mL) was added. The reaction mixture was heated at 100 °C for 16 h, filtered and concentrated. The residue was purified by preparative HPLC purification. (3.2 mg, yield 1.7%). ¹H NMR (MeOD, 400 MHz), δ ppm: 7.21 - 7.15 (m, 1H), 7.15 - 7.07 (m, 3H), 7.07 - 7.00 (m, 1H), 6.58 - 6.45 (m, 3H), 4.22 (br. s., 1H), 3.86 - 3.82 (m, 6H), 3.78 - 3.69 (m, 4H), 3.68 - 3.59 (m, 1H), 3.56 - 3.46 (m, 2H), 3.31 - 3.26 (m, 1H), 3.16 - 3.12 (m, 4H), 2.98 - 2.90 (m, 2H), 2.90 - 2.78 (m, 2H), 2.60 (d, J=6.0 Hz, 2H).

Compound 15

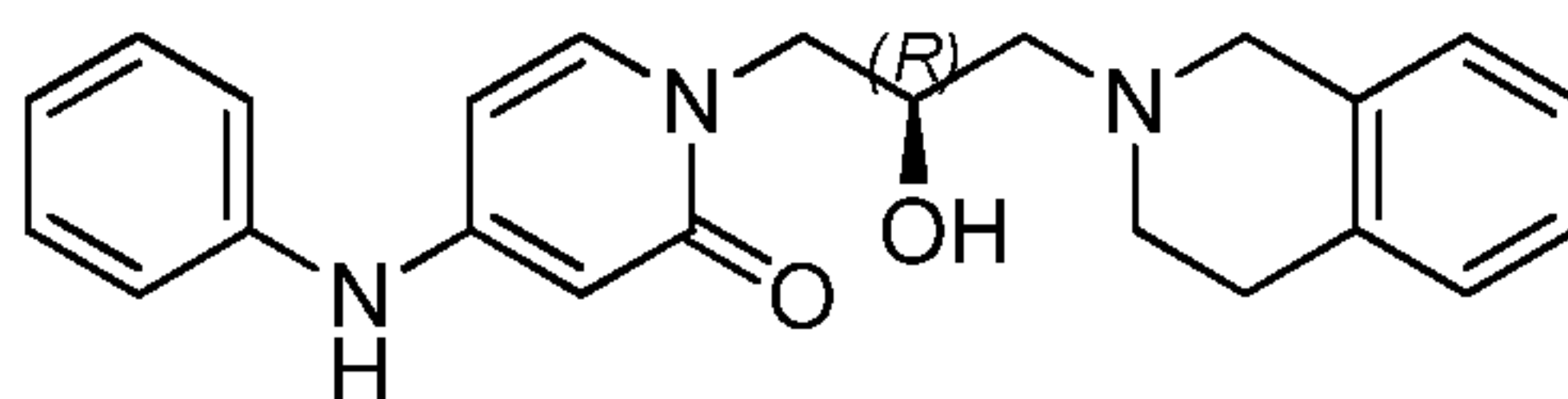
1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(p-tolyl)piperazin-2-one



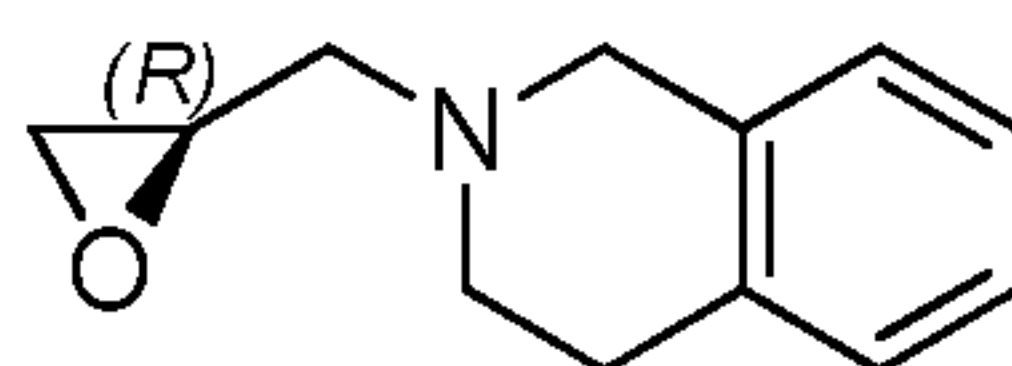
[00236] Compound **15** was synthesized in by a procedure analogous to that employed for compound **3**. (14.9 mg, yield 23.1%) MS (ESI⁺) *m/z*: 380.2 [M+1]⁺. ¹H NMR (MeOD, 400 MHz), δ ppm: 7.14- 6.98 (m, 6H), 6.89 - 6.80 (m, 2H), 4.26 - 4.13 (m, 1H), 3.84 - 3.65 (m, 6H), 3.65 - 3.55 (m, 1H), 3.49 - 3.38 (m, 2H),) 3.30 - 3.20 (m, 1H), 2.96 - 2.86 (m, 2H), 2.86 - 2.76 (m, 2H), 2.64 - 2.53 (m, 2H), 2.24 (s, 3H).

Compound 19

(R)-1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(phenylamino)pyridin-2(1H)-one

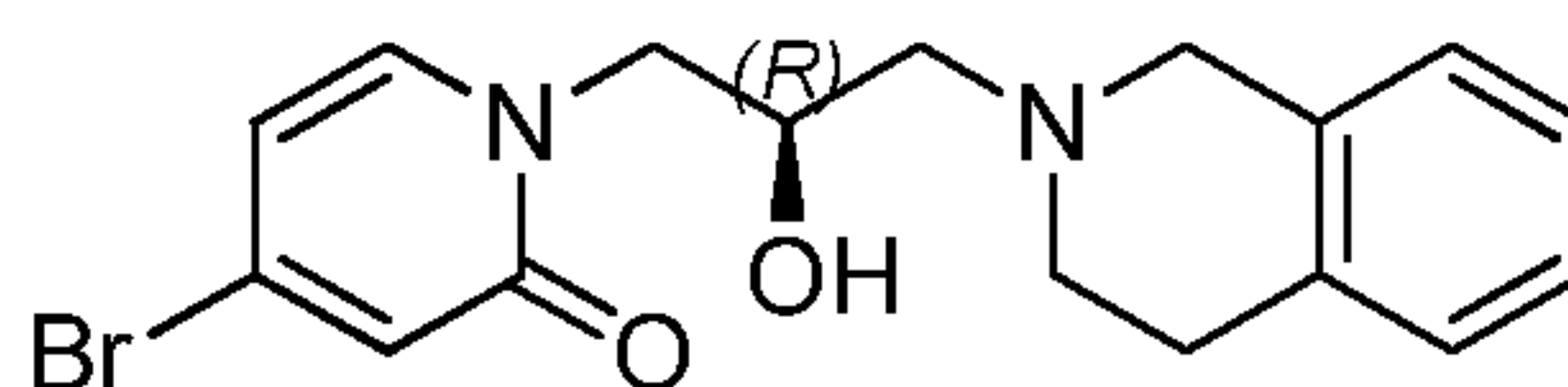


Step 1: (R)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline



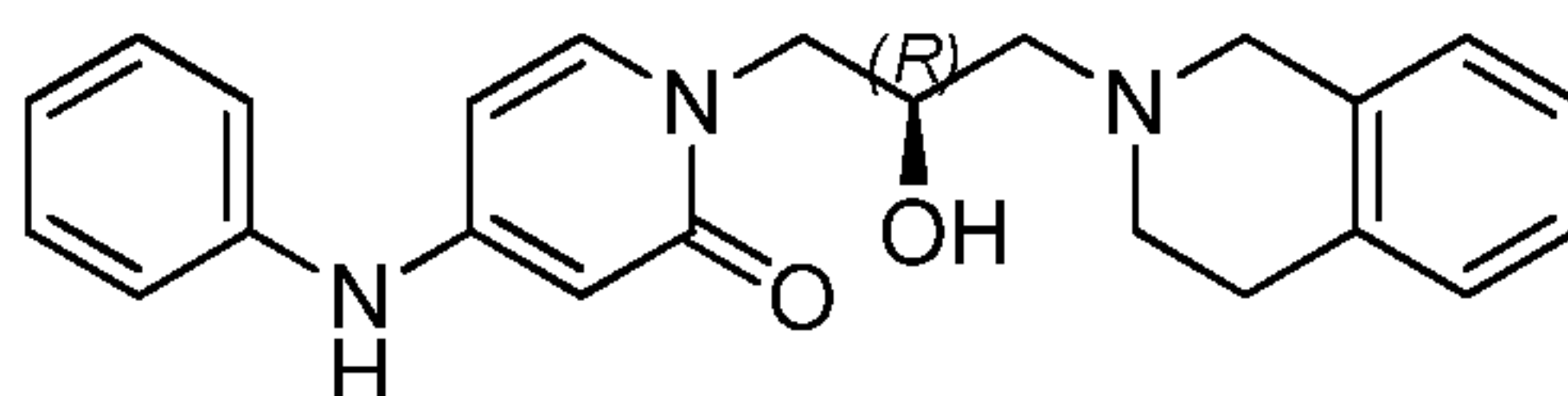
[00237] A solution of 1,2,3,4-tetrahydroisoquinoline (10 g, 0.15 mol) in THF (100 mL) was cooled to 0 °C and potassium fluoride (22 g, 0.3 mol) was added. After 1 h, (R)-oxiran-2-ylmethyl 3-nitrobenzenesulfonate (21.4 g, 0.17 mol) was added; the mixture was warmed to 25 °C and stirred for 16 h. The solution was filtered, washed with THF and concentrated. The crude product was used in next step without further purification. (15 g, yield 53%) MS (ESI⁺) *m/z*: 190.1 [M+1]⁺.

Step 2: (R)-4-bromo-1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)pyridin-2(1H)-one



[00238] To a solution of 4-bromopyridin-2(1H)-one (1 g, 5.747 mmol) in EtOH (3 mL) was added (R)-2-(oxiran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (1.087 g, 5.747 mmol). The mixture was heated under microwave conditions at 120 °C for 0.5 h and concentrated. The crude product was purified by column chromatography eluting with DCM / MeOH (10:1). (475 mg, yield 22.8%) MS (ESI⁺) *m/z*: 363.1 [M+1]⁺.

Step 3: (R)-1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-4-(phenylamino)pyridin-2(1H)-one

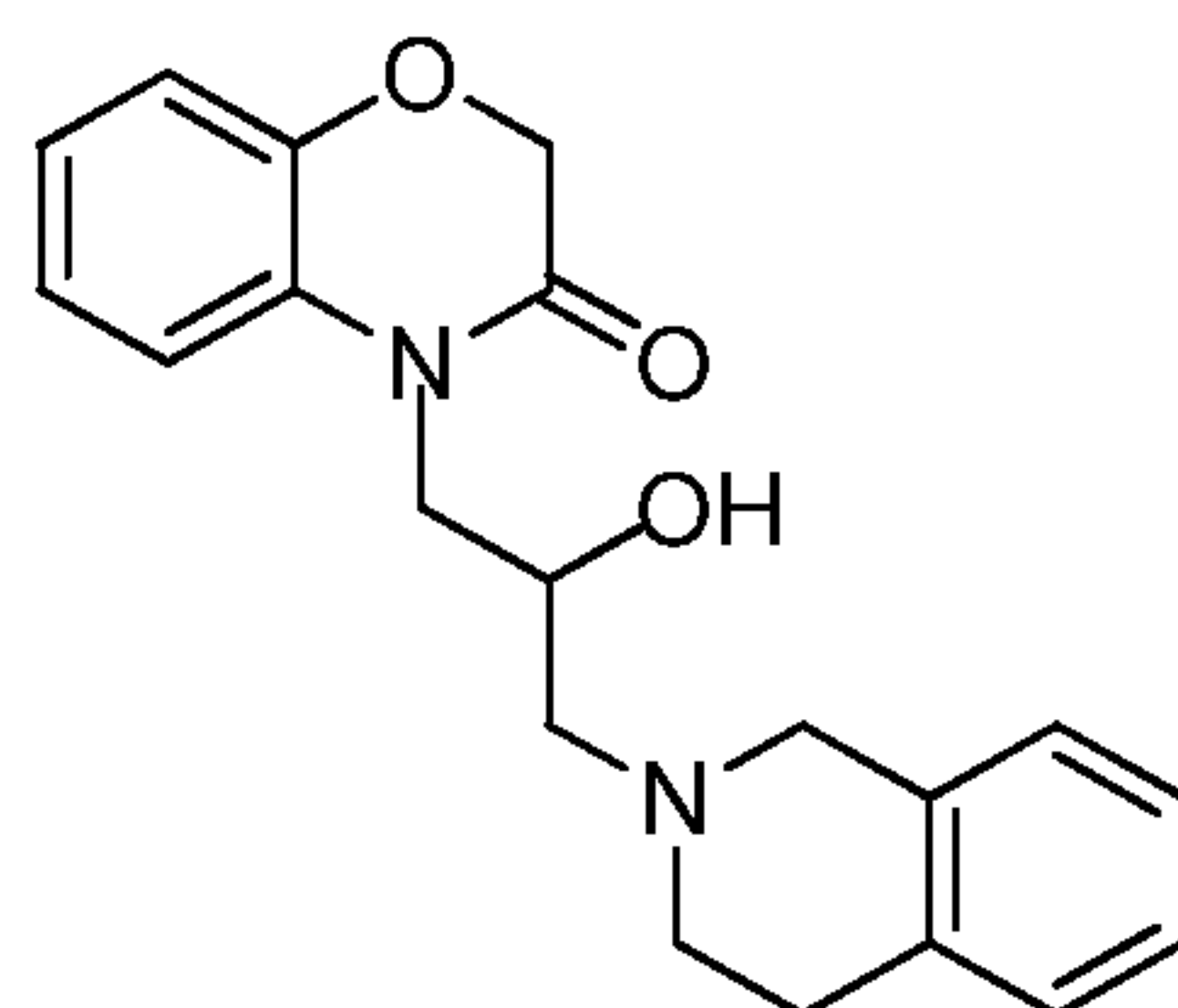


[00239] To a solution of (R)-4-bromo-1-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)pyridin-2(1H)-one (200 mg, 0.551 mmol) in anhydrous toluene (5 mL) was

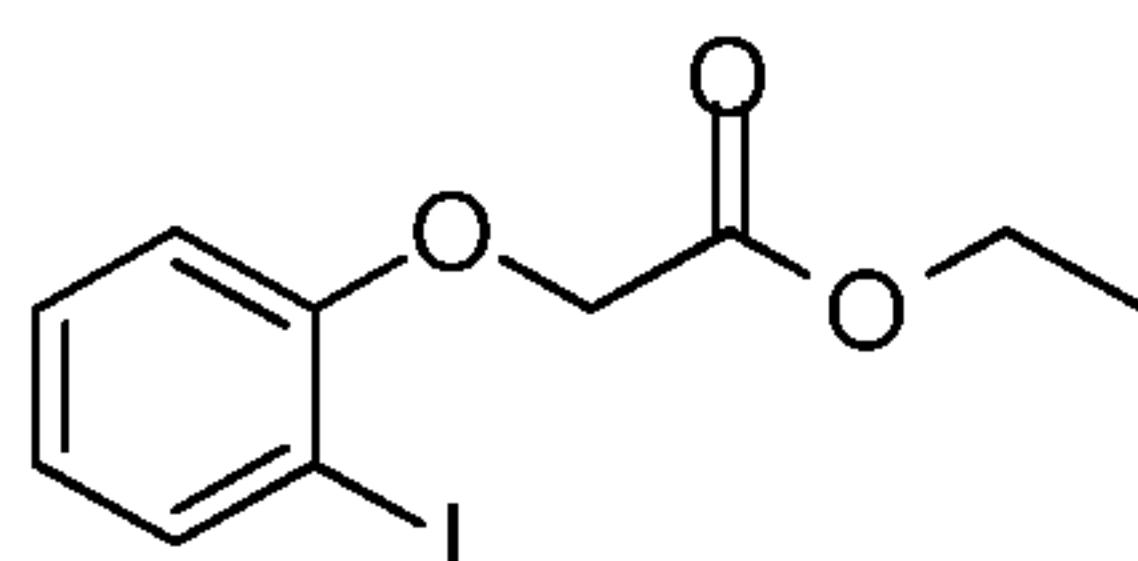
added aniline (51 mg, 0.551 mmol), xantphos (20 mg), $\text{Pd}_2(\text{dba})_3$ (20 mg) and t-BuOK (123 mg, 1.102 mmol). The mixture was heated under microwave conditions at 140 °C for 1 h, filtered and concentrated. The crude product was purified by preparative HPLC purification. (18 mg, yield 8.7%) MS (ESI^+) m/z : 376.1 $[\text{M}+1]^+$. ^1H NMR (MeOD, 400 MHz), δ ppm: 7.45 - 7.35 (m, 3H), 7.24 - 7.18 (m, 2H), 7.17 - 7.08 (m, 4H), 7.07 - 7.02 (m, 1H), 6.11 (dd, $J=2.6$, 7.5 Hz, 1H), 5.99 (d, $J=2.5$ Hz, 1H), 4.33 (dd, $J=3.3$, 13.4 Hz, 1H), 4.27 - 4.15 (m, 1H), 3.73 (s, 2H), 3.63 (dd, $J=8.0$, 13.6 Hz, 1H), 2.96 - 2.89 (m, 2H), 2.88 - 2.82 (m, 2H), 2.66 - 2.58 (m, 2H).

Compound 31

4-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2H-benzo[b][1,4]oxazin-3(4H)-one

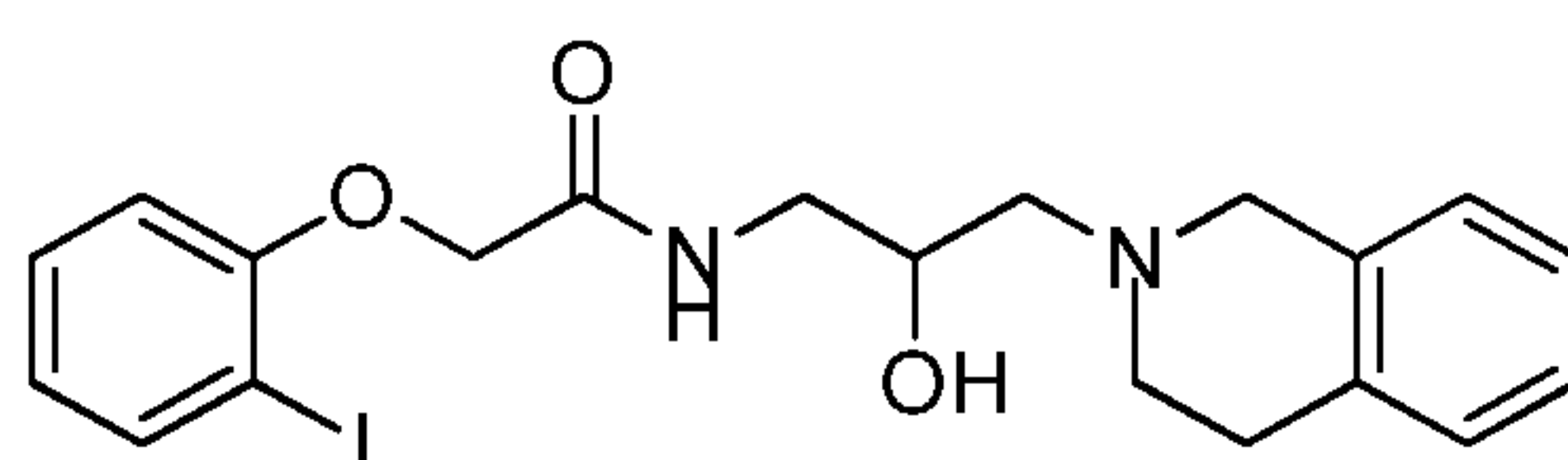


Step 1: ethyl 2-(2-iodophenoxy)acetate



[00240] To a solution of 2-iodophenol (1g, 4.55 mmol) in CH_3CN (20 mL) was added K_2CO_3 (0.93g, 6.83 mmol) and ethyl 2-bromoacetate (0.835g, 5.0 mmol). The reaction mixture was stirred at reflux for 2 h, cooled to room temperature, extracted with EtOAc, washed with brine, dried over sodium sulfate and concentrated. The crude product was used in the next step without further purification. (1.1 g, yield 79%) MS (ESI^+) m/z : 307.1 $[\text{M}+1]^+$.

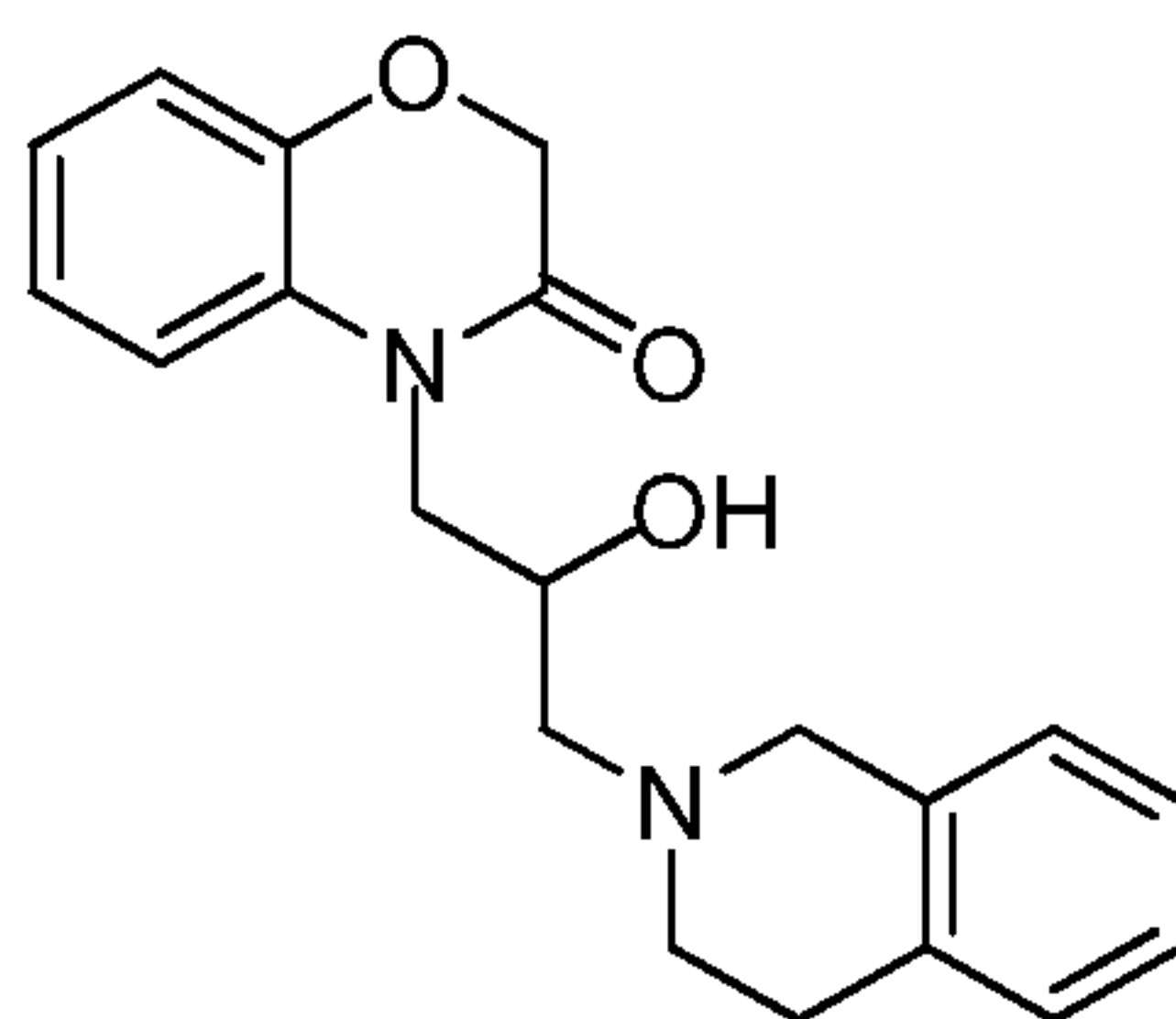
Step 2: N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2-(2-iodophenoxy)acetamide



[00241] To a solution of ethyl 2-(2-iodophenoxy)acetate (900 mg, 2.94 mmol) in EtOH (3

mL) was added 1-amino-3-(3,4-dihydroisoquinolin-2(1H)-yl)propan-2-ol (677 mg, 3.24 mmol). The reaction mixture was heated under microwave conditions at 80 °C for 3 h, cooled and concentrated. The crude product was used in the next step without further purification. (1.3 g, yield 95%) MS (ESI⁺) *m/z*: 467.1 [M+1]⁺. ¹H NMR (MeOD, 400MHz), δ ppm: 7.80 (dd, *J*=1.0, 7.8 Hz, 1H), 7.41 - 7.30 (m, 1H), 7.15 - 7.05 (m, 3H), 7.05 - 6.99 (m, 1H), 6.96 (d, *J*=8.0 Hz, 1H), 6.87 - 6.76 (m, 1H), 4.66 - 4.53 (m, 2H), 4.06 (quin, *J*=5.9 Hz, 1H), 3.77 - 3.63 (m, 2H), 3.58 (dd, *J*=4.5, 13.6 Hz, 1H), 3.38 (dd, *J*=6.4, 13.7 Hz, 1H), 2.98 - 2.86 (m, 2H), 2.86 - 2.76 (m, 2H), 2.66 - 2.57 (m, 2H).

Step 3: 4-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2H-benzo[b][1,4]oxazin-3(4H)-one



[00242] To a solution of N-(3-(3,4-dihydroisoquinolin-2(1H)-yl)-2-hydroxypropyl)-2- (2-iodophenoxy)acetamide (100 mg, 0.215 mmol) in dioxane (5 mL) was added Cs₂CO₃ (139 mg, 0.429 mmol), BINAP (13.3 mg, 0.0215 mmol) and Pd₂(dba)₃ (8.0 mg, 0.0215 mmol). The reaction mixture was heated at 120 °C for 16 h, cooled to room temperature, filtered, and concentrated. The crude produce was purified by preparative HPLC purification. (23.6 mg, yield 32.5%) MS (ESI⁺) *m/z*: 339.2 [M+1]⁺. ¹H NMR (MeOD, 400MHz), δ ppm: 7.41 - 7.32 (m, 1H), 7.15 - 7.06 (m, 3H), 7.06 - 6.94 (m, 4H), 4.67 - 4.50 (m, 2H), 4.29 - 4.13 (m, 2H), 4.07 - 3.94 (m, 1H), 3.77 - 3.64 (m, 2H), 2.95 - 2.83 (m, 3H), 2.83 - 2.76 (m, 1H), 2.73 - 2.62 (m, 2H).

LC-MS conditions

Method A (LCMS-B (0-60AB_ELSD_2MIN))

[00243] Experiments performed on an Agilent 1200 HPLC (with a PDA detector and a ELSD detector) with Agilent 6100 MSD mass spectrometer using ESI as ionization source using an Xtimate TM-C18 30*2.1mm column and a 0.8ml/minute flow rate. Acquire Time: 2 min, Wavelength: UV220, Oven Temp.: 50 °C. The solvent system was a gradient starting

with 100% water containing 0.038%TFA (solvent A) and 0% acetonitrile containing 0.02%TFA (solvent B), followed by a gradient up to 40% solvent A and 60% solvent B over the next 0.9 minutes . This was maintained for 0.6minutes before returning to 100% solvent A over the next 0.5 minute. Total run time was 2 min.

Method B (LCMS-C(10-80_AB))

[00244] Experiments performed on an SHIMADZU 20A HPLC (with a PDA detector) with SHIMADZU 2010EV MSD mass spectrometer using ESI as ionization source using an Xtimate TM-C18 30*2.1mm column and a 1.2ml/minute flow rate. The solvent system was a gradient starting with 90% water containing 0.038%TFA (solvent A) and 10% acetonitrile containing 0.02%TFA (solvent B), followed by a gradient up to 20% solvent A and 80% solvent B over the next 0.9 minutes . This was maintained for 0.6minutes before returning to 90% solvent A and 10% solvent B over the next 0.5 minute. Total run time was 2 min.

Method C (LCMS-E(5-95AB_220&254nm))

[00245] Experiments performed on an SHIMADZU 20A HPLC (with a PDA detector) with SHIMADZU 2010EV MSD mass spectrometer using ESI as ionization source using an Merk RP-18e 2*25mm column and a 1.5ml/minute flow rate. The solvent system was a gradient starting with 95% water containing 0.038%TFA (solvent A) and 5% acetonitrile containing 0.02%TFA (solvent B), followed by a gradient up to 5% solvent A and 95% solvent B over the next 0.7 minutes . This was maintained for 0.4minutes before returning to 95% solvent A and 5% solvent B over the next 0.4 minute. Total run time was 1.5 min.

Method D (LCMS-A(0-30_AB))

[00246] Experiments performed on an SHIMADZU 20A HPLC (with a PDA detector) with SHIMADZU 2010EV MSD mass spectrometer using ESI as ionization source using an Xtimate TM-C18 30*2.1mm column and a 1.2ml/minute flow rate. The solvent system was a gradient starting with 100% water containing 0.038%TFA (solvent A) and 0% acetonitrile containing 0.02%TFA (solvent B), followed by a gradient up to 70% solvent A and 30% solvent B over the next 0.9 minutes . This was maintained for 0.6minutes before returning to 100% solvent A over the next 0.5 minute. Total run time was 2 min.

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General HPLC conditions (Acidic)

Mobile phase A: 4L H₂O\1.5ml TFA; Mobile phase B: 4L ACN\0.75ml TFA

Column: HPLC-D: Innovation C18 UPLC Column 2.1X30mm, 2.6um

HPLC-E: Xtimate C18 2.1*30mm*3um

HPLC-H: Innovation C18 UPLC Column 2.1X30mm, 2.6um

Column temperature: 50 °C; Wavelength: 220nm&254nm&215nm

General HPLC conditions (Basic)

Mobile phase A: 4L H₂O\2ml NH₄OH; Mobile phase B: Acetonitrile

Column: HPLC-B: XBridge C18 2.1*50mm,5um

HPLC-C: Xbridge shield RP18 2.1*50mm,5u

Column temperature: 30 °C; Wavelength : 220nm&254nm&215nm

General HPLC conditions (Neutral)

Mobile phase A: H₂O; Mobile phase B: Acetonitrile

Column: HPLC-B: XBridge C18 2.1*50mm,5um

HPLC-C: Xbridge shield RP18 2.1*50mm, 5um

Column temperature: 30 °C; Wavelength : 220nm&254nm&215nm

Method A (0-30AB_6MIN)

Flow Rate: 0.8ml/min

Gradient : 0%B to 30%B in 4.2min, holding 30%B for 1min, 30%B to 0%B in 0.01min, holding 0%B for 1.09min and then end.

Method B (0-60AB_6MIN)

Flow Rate: 0.8ml/min

Gradient : 0%B to 60%B in 4.2min, holding 60%B for 1min, 60%B to 0%B in 0.01min, holding 0%B for 1.09min and then end.

Method C (10-80AB_6MIN)

Flow Rate: 0.8ml/min

Gradient : 10%B to 80%B in 4.2min, holding 80%B for 1min, 80%B to 10%B in 0.01min, holding 10%B for 1.09min and then end.

Chiral HPLC conditions :

Method A (OJ-H) :

Column: Chiralcel OJ-H 250×4.6mm I.D., 5µm

Mobile phase: A/B=90/10, A:Hexane with 0.1%DEA ,B: Ethanol

Flow rate: 0.5mL/min

Wavelength: 220nm

Method B (OD-H):

Column: Chiralcel OD-H 250×4.6mm I.D., 5µm

Mobile phase: A/B=90/10, A: Hexane with 0.1%DEA ,B: Ethanol

Flow rate: 0.5mL/min

Wavelength: 220nm

Method C (AD-H):

Column: Chiralpak AD-H 250×4.6mm I.D., 5µm

Mobile phase: A/B=90/10, A: Hexane with 0.1%DEA, B: Ethanol

Flow rate: 0.5mL/min

Wavelength: 220nm

Method D (AS-H):

Column: Chiralpak OJ-H 250×4.6mm I.D., 5µm

Mobile phase: A/B=90/10, A: Hexane with 0.1%DEA, B: Ethanol

Flow rate: 0.5mL/min

Wavelength: 220nm

*Biological Assays***PRMT5 Biochemical Assay**

[00247] General Materials. S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), bicine, KCl, Tween20, dimethylsulfoxide (DMSO), bovine skin gelatin (BSG), and Tris(2-carboxyethyl)phosphine hydrochloride solution (TCEP) were purchased from Sigma-Aldrich at the highest level of purity possible. ³H-SAM was purchase from American Radiolabeled Chemicals with a specific activity of 80 Ci/mmol. 384-well streptavidin Flashplates were purchased from PerkinElmer.

[00248] Substrates. Peptide representative of human histone H4 residues 1-15 was synthesized with a C-terminal linker-affinity tag motif and a C-terminal amide cap by 21st Century Biochemicals. The peptide was high high-performance liquid chromatography (HPLC) purified to greater than 95% purity and confirmed by liquid chromatography mass spectrometry (LC-MS). The sequence was Ac-SGRGKGGKGLGKGGA[K-Biot]-amide (SEQ ID NO.:3).

[00249] Molecular Biology: Full-length human PRMT5 (NM_006109.3) transcript variant 1 clone was amplified from a fetal brain cDNA library, incorporating flanking 5' sequence encoding a FLAG tag (MDYKDDDDK) (SEQ ID NO.:4) fused directly to Ala 2 of PRMT5. Full-length human MEP50 (NM_024102) clone was amplified from a human testis cDNA library incorporating a 5' sequence encoding a 6-histidine tag (MHHHHHH) (SEQ ID NO.:5) fused directly to Arg 2 of MEP50. The amplified genes were subcloned into pENTR/D/TEV (Life Technologies) and subsequently transferred by GatewayTM attL x attR recombination to pDEST8 baculovirus expression vector (Life Technologies).

[00250] Protein Expression. Recombinant baculovirus and Baculovirus-Infected Insect Cells (BIIC) were generated according to Bac-to-Bac kit instructions (Life Technologies) and Wasilko, 2006, respectively. Protein over-expression was accomplished by infecting exponentially growing *Spodoptera frugiperda* (SF9) cell culture at 1.2X10⁶ cell/ml with a 5000 fold dilution of BIIC stock. Infections were carried out at 27°C for 72 hours, harvested by centrifugation, and stored at -80°C for purification.

[00251] Protein Purification. Expressed full-length human Flag-PRMT5/6His-MeP50 protein complex was purified from cell paste by NiNTA agarose affinity chromatography after a five hour equilibration of the resin with buffer containing 50mM Tris-HCL, pH 8.0, 25 mM NaCl, and 1mM TCEP at 4°C, to minimize the adsorption of tubulin impurity by the resin. Flag-PRMT5/6His-MeP50 was eluted with 300mM Imidazole in the same buffer. The

purity of recovered protein was 87%. Reference: Wasilko, D.J. and S.E. Lee: “TIPS: titerless infected-cells preservation and scale-up” Bioprocess J., 5 (2006), pp. 29–32.

[00252] Predicted Translations:

Flag-PRMT5 (SEQ ID NO.:6)

MDYKDDDDKA AMAVGGAGGS RVSSGRDLNC VPEIADTLGA VAKQGFDFLC MPVFHPRFKR
 EFIQEPAKNR PGPQTRSDLL LSGRDWNTLI VGKLSPWIRP DSKVEKIRRN SEAAMLQELN
 FGAYLGLPAF LLPLNQEDNT NLARVLTNHI HTGHHSSMFW MRVPLVAPED LRDDIIENAP
 TTHTEEYSGE EKTWMWWHNF RTLCDYSKRI AVALEIGADL PSNHVIDRWL GEPIKAAILP
 TSIFLTNKKG FVLSKMHQR LIFRLLKLEV QFIITGTNHH SEKEFCSYLQ YLEYLSQNRP
 PPNAYELFAK GYEDYLQSPL QPLMDNLESQ TYEVFEKDPI KYSQYQQAIY KCLLDRVPEE
 EKDTNVQVLM VLGAGRGPLV NASLRAAKQA DRRIKLYAVE KNPNAVVTLE NWQFEEWGSQ
 VTVVSSDMRE WVAPEKADII VSELLGSFAD NELSPECLDG AQHFLKDDGV SIPGEYTSFL
 APISSSKLYN EVRACREKDR DPEAQFEMPY VVRLHNFHQL SAPQPCFTFS HPNRDPMIDN
 NRYCTLEFPV EVNTVLHGFA GYFETVLYQD ITLSIRPETH SPGMFSWFPI LFPIKQPITV
 REGQTICVRF WRCSNSKKVW YEWAVTAPVC SAIHNPTGRS YTIG L

6His-MEP50 (SEQ ID NO.:7)

MHHHHHHRKE TPPPLVPPAA REWNLPNAP ACMERQLEAA RYRSDGALLL GASSLSGRCW
 AGSLWLFKDP CAAPNEGFCF AGVQTEAGVA DLTWVGGERGI LVASDSGAVE LWELDENETL
 IVSKFCKYEH DDIIVSTVSVL SSGTQAVSGS KDICIKVWDL AQQVVLSSYR AHAAQVTCVA
 ASPHKDSVFL SCSEDNRILL WDTRCPKPAS QIGCSAPGYL PTSLAWHPQQ SEVFVFGDEN
 GTVSLVDTKS TSCVLSSAVH SQCVTGLVFS PHSVPFLASL SEDCSLAVLD SSLSELFERSQ
 AHRDFVRDAT WSPLNHSLLT TVGWDHQVVH HVVPTEPLPA PGPASVTE

[00253] General Procedure for PRMT5/MEP50 Enzyme Assays on Peptide

Substrates. The assays were all performed in a buffer consisting of 20mM Bicine (pH=7.6), 1mM TCEP, 0.005% BSG, and 0.002% Tween20, prepared on the day of use. Compounds in 100% DMSO (1ul) were spotted into a polypropylene 384-well V-bottom plates (Greiner) using a Platemate Plus outfitted with a 384-channel head (Thermo Scientific). DMSO (1ul) was added to Columns 11, 12, 23, 24, rows A-H for the maximum signal control and 1ul of SAH, a known product and inhibitor of PRMT5/MEP50, was added to columns 11, 12, 23, 24, rows I-P for the minimum signal control. A cocktail (40ul) containing the PRMT5/MEP50 enzyme and the peptide was added by Multidrop Combi (Thermo-Fisher). The compounds were allowed to incubate with PRMT5/MEP50 for 30 min at 25 degrees Celsius, then a cocktail (10ul) containing ³H-SAM was added to initiate the reaction (final

volume = 51ul). The final concentrations of the components were as follows: PRMT5/MEP50 was 4nM, ^3H -SAM was 75nM, peptide was 40nM, SAH in the minimum signal control wells was 100uM, and the DMSO concentration was 1%. The assays were stopped by the addition of non-radioactive SAM (10ul) to a final concentration of 600uM, which dilutes the ^3H -SAM to a level where its incorporation into the peptide substrate is no longer detectable. 50ul of the reaction in the 384-well polypropylene plate was then transferred to a 384-well Flashplate and the biotinylated peptides were allowed to bind to the streptavidin surface for at least 1 hour before being washed three times with 0.1% Tween20 in a Biotek ELx405 plate washer. The plates were then read in a PerkinElmer TopCount plate reader to measure the quantity of ^3H -labeled peptide bound to the Flashplate surface, measured as disintegrations per minute (dpm) or alternatively, referred to as counts per minute (cpm).

% inhibition calculation

$$\% inh = 100 - \left(\frac{dpm_{cmpd} - dpm_{min}}{dpm_{max} - dpm_{min}} \right) \times 100$$

Where dpm = disintegrations per minute, cmpd = signal in assay well, and min and max are the respective minimum and maximum signal controls.

Four-parameter IC50 fit

$$Y = Bottom + \frac{(Top - Bottom)}{\left(1 + \left(\frac{X}{IC_{50}} \right)^{Hill\ Coefficient} \right)}$$

Where top and bottom are the normally allowed to float, but may be fixed at 100 or 0 respectively in a 3-parameter fit. The Hill Coefficient normally allowed to float but may also be fixed at 1 in a 3-parameter fit. Y is the % inhibition and X is the compound concentration.

Z-138 Methylation Assay

[00254] Z-138 suspension cells were purchased from ATCC (American Type Culture Collection, Manassas, VA). RPMI/Glutamax medium, penicillin-streptomycin, heat inactivated fetal bovine serum, and D-PBS were purchased from Life Technologies, Grand Island, NY, USA. Odyssey blocking buffer, 800CW goat anti-rabbit IgG (H+L) antibody, and

Licor Odyssey infrared scanner were purchased from Licor Biosciences, Lincoln, NE, USA. Symmetric di-methyl arginine antibody was purchased from EMD Millipore, Billerica, MA, USA. 16% Paraformaldehyde was purchased from Electron Microscopy Sciences, Hatfield, PA, USA.

[00255] Z-138 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) and cultured at 37 °C under 5% CO₂.

[00256] Cell Treatment, In Cell Western (ICW) for detection of Symmetric di-Methyl Arginine and DNA content. Z-138 cells were seeded in assay medium at a concentration of 50,000 cells per mL to a 384-well cell culture plate with 50 µL per well. Compound (100 nL) from 384 well source plates was added directly to 384 well cell plate. Plates were incubated at 37°C, 5% CO₂ for 96 hours. After four days of incubation, 40 µL of cells from incubated plates were added to poly-D-lysine coated 384 well culture plates (BD Biosciences 356697). Plates were incubated at room temperature for 30 minutes then incubated at 37°C, 5% CO₂ for 5 hours. After the incubation, 40 µL per well of 8% paraformaldehyde in PBS (16% paraformaldehyde was diluted to 8% in PBS) was added to each plate and incubated for 30 minutes. Plates were transferred to a Biotek 405 plate washer and washed 5 times with 100 µL per well of wash buffer (1X PBS with 0.1% Triton X-100 (v/v)). Next 30 µL per well of Odyssey blocking buffer were added to each plate and incubated 1 hour at room temperature. Blocking buffer was removed and 20 µL per well of primary antibody was added (symmetric di-methyl arginine diluted 1:100 in Odyssey buffer with 0.1% Tween 20 (v/v)) and plates were incubated overnight (16 hours) at 4°C. Plates were washed 5 times with 100 µL per well of wash buffer. Next 20 µL per well of secondary antibody was added (1:200 800CW goat anti-rabbit IgG (H+L) antibody, 1:1000 DRAQ5 (Biostatus limited) in Odyssey buffer with 0.1% Tween 20 (v/v)) and incubated for 1 hour at room temperature. The plates were washed 5 times with 100 µL per well wash buffer then 1 time with 100 µL per well of water. Plates were allowed to dry at room temperature then imaged on the Licor Odyssey machine which measures integrated intensity at 700nm and 800nm wavelengths. Both 700 and 800 channels were scanned.

[00257] Calculations: First, the ratio for each well was determined by:

$$\left(\frac{\text{symmetric di-methyl Arginine 800nm value}}{\text{DRAQ5 700nm value}} \right)$$

[00258] Each plate included fourteen control wells of DMSO only treatment (minimum inhibition) as well as fourteen control wells for maximum inhibition treated with 3 µM of a

reference compound (Background wells). The average of the ratio values for each control type was calculated and used to determine the percent inhibition for each test well in the plate. Reference compound was serially diluted three-fold in DMSO for a total of nine test concentrations, beginning at 3 μ M. Percent inhibition was determined and IC₅₀ curves were generated using triplicate wells per concentration of compound.

Percent Inhibition = 100-

$$\left(\frac{(\text{Individual Test Sample Ratio}) - (\text{Background Avg Ratio})}{(\text{Minimum Inhibition Ratio}) - (\text{Background Average Ratio})} \right) * 100$$

Z-138 Proliferation Assay

[00259] Z-138 suspension cells were purchased from ATCC (American Type Culture Collection, Manassas, VA). RPMI/Glutamax medium, penicillin-streptomycin, heat inactivated fetal bovine serum were purchased from Life Technologies, Grand Island, NY, USA. V-bottom polypropylene 384-well plates were purchased from Greiner Bio-One, Monroe, NC, USA. Cell culture 384-well white opaque plates were purchased from Perkin Elmer, Waltham, MA, USA. Cell-Titer Glo[®] was purchased from Promega Corporation, Madison, WI, USA. SpectraMax M5 plate reader was purchased from Molecular Devices LLC, Sunnyvale, CA, USA.

[00260] Z-138 suspension cells were maintained in growth medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and cultured at 37°C under 5% CO₂. Under assay conditions, cells were incubated in assay medium (RPMI 1640 supplemented with 10% v/v heat inactivated fetal bovine serum and 100 units/mL penicillin-streptomycin) at 37°C under 5% CO₂.

[00261] For the assessment of the effect of compounds on the proliferation of the Z-138 cell line, exponentially growing cells were plated in 384-well white opaque plates at a density of 10,000 cells/ml in a final volume of 50 μ l of assay medium. A compound source plate was prepared by performing triplicate nine-point 3-fold serial dilutions in DMSO, beginning at 10 mM (final top concentration of compound in the assay was 20 μ M and the DMSO was 0.2%). A 100 nL aliquot from the compound stock plate was added to its respective well in the cell plate. The 100% inhibition control consisted of cells treated with 200 nM final concentration of staurosporine and the 0% inhibition control consisted of DMSO treated cells. After addition of compounds, assay plates were incubated for 5 days at 37°C, 5% CO₂, relative

humidity > 90%.

Cell viability was measured by quantitation of ATP present in the cell cultures, adding 35 μ l of Cell Titer Glo[®] reagent to the cell plates. Luminescence was read in the SpectraMax M5 microplate reader. The concentration of compound inhibiting cell viability by 50% was determined using a 4-parametric fit of the normalized dose response curves.

[00262] Results for certain compounds described herein are shown in **Table 2**.

Table 2. Biological Assay Results			
Cmpd No	Biochemical IC₅₀	ICW EC₅₀	Proliferation EC₅₀
1	B	B	**
2	D	--	--
3	D	--	--
4	A	B	C
5	A	C	--
6	A	B	**
7	A	B	D
8	A	B	C
9	B	B	D
10	--	E	--
11	--	E	--
12	A	A	C
13	--	E	--
14	--	E	--
15	B	B	**
16	C	--	--
17	C	--	--
18	C	--	--
19	B	B	**
20	B	C	--
21	C	--	--
22	C	--	--
23	C	--	--
24	C	--	--
25	C	--	--

Table 2. Biological Assay Results			
Cmpd No	Biochemical IC₅₀	ICW EC₅₀	Proliferation EC₅₀
26	C	--	--
27	E	--	--
28	C	--	--
29	B	B	D
30	C	--	--
31	B	B	**
32	*	--	--
33	B	C	**
34	C	--	--

For **Table 2**, “A” indicates an IC₅₀ or EC₅₀ < 0.100 μM, “B” indicates an IC₅₀ or EC₅₀ of 0.101 – 1.000 μM, “C” indicates an IC₅₀ or EC₅₀ of 1.001 – 10.000 μM, “D” indicates an IC₅₀ or EC₅₀ of 10.001 – 50 μM, and “E” indicates an IC₅₀ or EC₅₀ > 50 μM. “--” indicates no data. “*” indicates an IC₅₀ or EC₅₀ > 10 μM. “**” indicates an IC₅₀ or EC₅₀ > 20 μM.

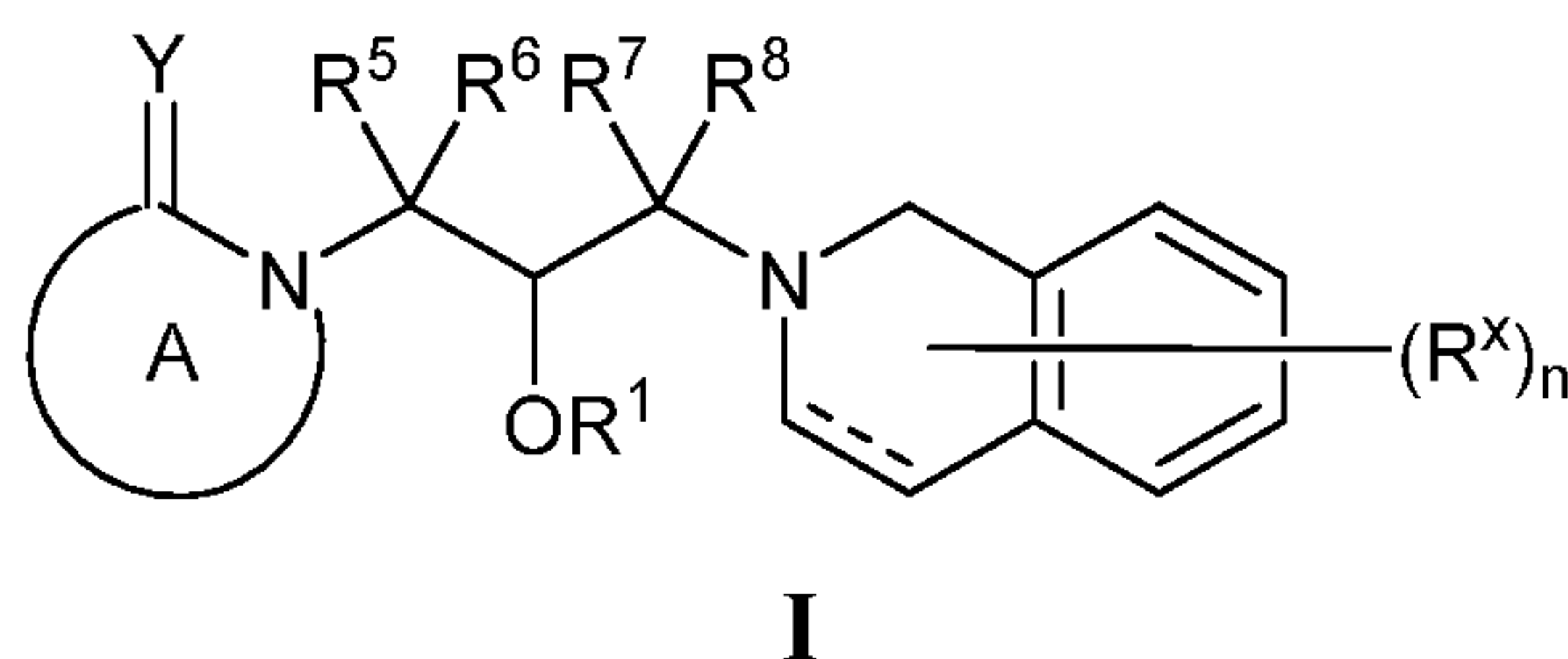
Other Embodiments

[00263] The foregoing has been a description of certain non-limiting embodiments of the invention. Those of ordinary skill in the art will appreciate that various changes and modifications to this description may be made without departing from the spirit or scope of the present invention, as defined in the following claims.

What is claimed is:

Claims

1. A compound of Formula (I):



or a pharmaceutically acceptable salt thereof,
wherein

===== represents a single or double bond;

Ring A is an optionally substituted, 5- to 12-membered, monocyclic or bicyclic, heterocyclyl or heteroaryl having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

R^1 is hydrogen, R^Z , or $-C(O)R^Z$, wherein R^Z is optionally substituted C_{1-6} alkyl;

Y is O or S;

R^5 , R^6 , R^7 , and R^8 are independently hydrogen, halo, or optionally substituted aliphatic;

each R^x is independently selected from the group consisting of halo, -CN, optionally substituted aliphatic, -OR', and $-N(R'')_2$;

R' is hydrogen or optionally substituted aliphatic;

each R'' is independently hydrogen or optionally substituted aliphatic, or two R'' are taken together with their intervening atoms to form a heterocyclic ring; and

n is 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10, as valency permits;

wherein, and unless otherwise specified,

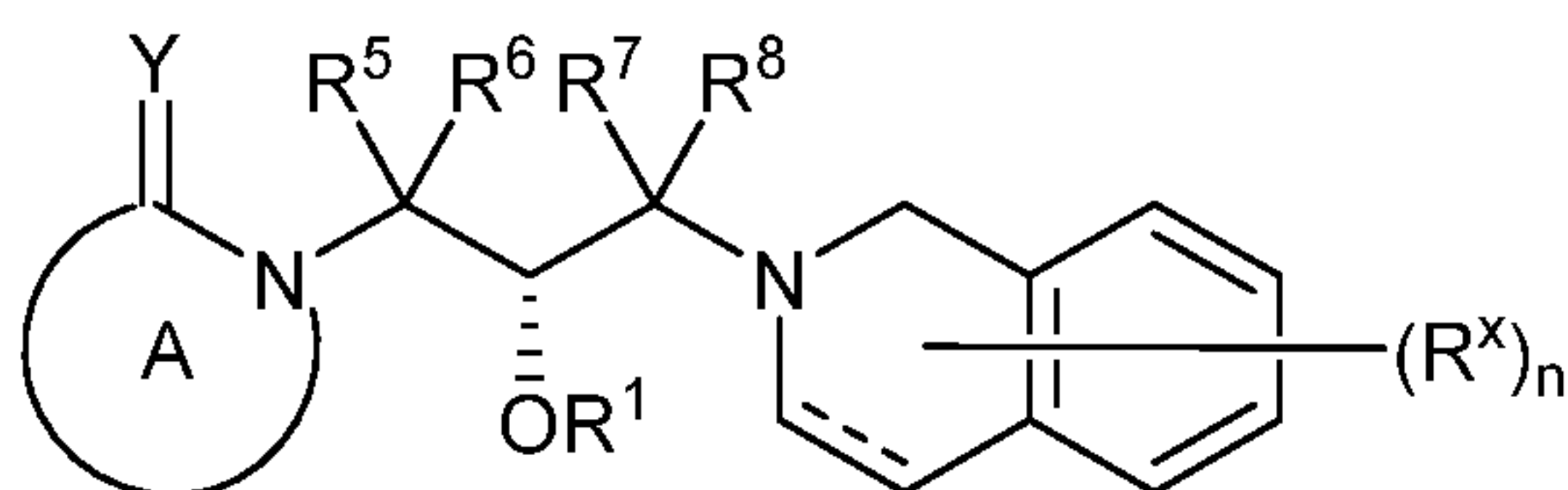
heterocyclyl or heterocyclic refers to a radical of a 3–10 membered non–aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur;

carbocyclyl or carbocyclic refers to a radical of a non–aromatic cyclic hydrocarbon group having from 3 to 10 ring carbon atoms and zero heteroatoms in the non–aromatic ring system;

aryl refers to a radical of a monocyclic or polycyclic aromatic ring system having 6–14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system; and

heteroaryl refers to a radical of a 5–10 membered monocyclic or bicyclic aromatic ring system having ring carbon atoms and 1–4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur.

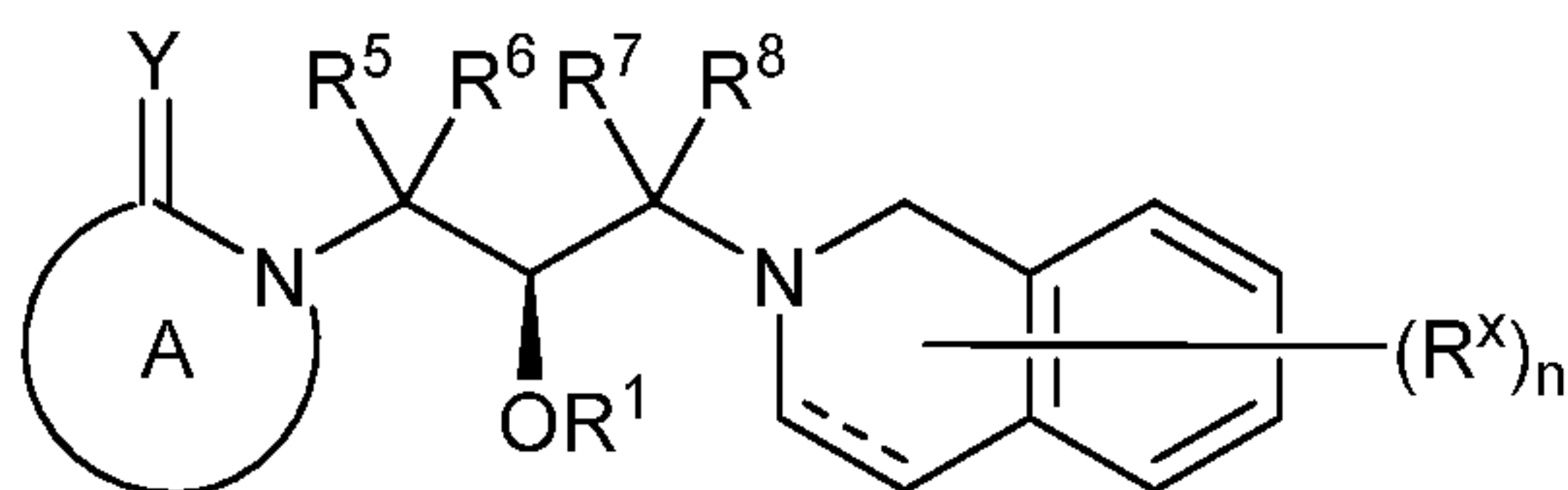
2. The compound of claim 1, wherein the compound is of Formula (**I-a**):



I-a

or a pharmaceutically acceptable salt thereof.

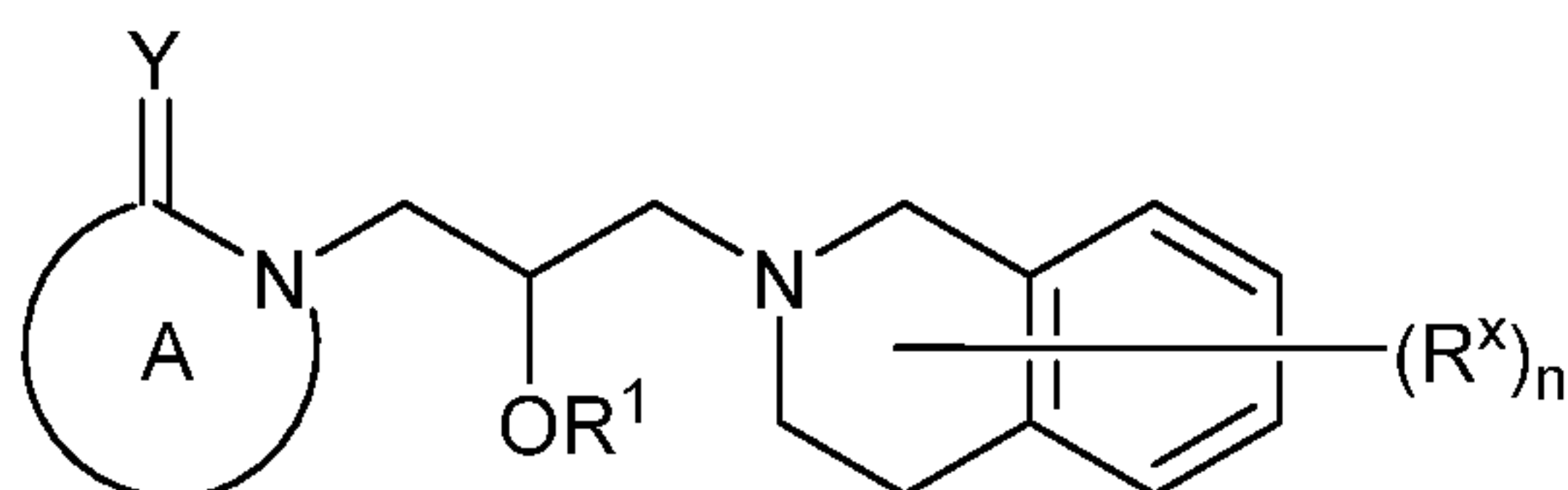
3. The compound of claim 1, wherein the compound is of Formula (**I-b**):



I-b

or a pharmaceutically acceptable salt thereof.

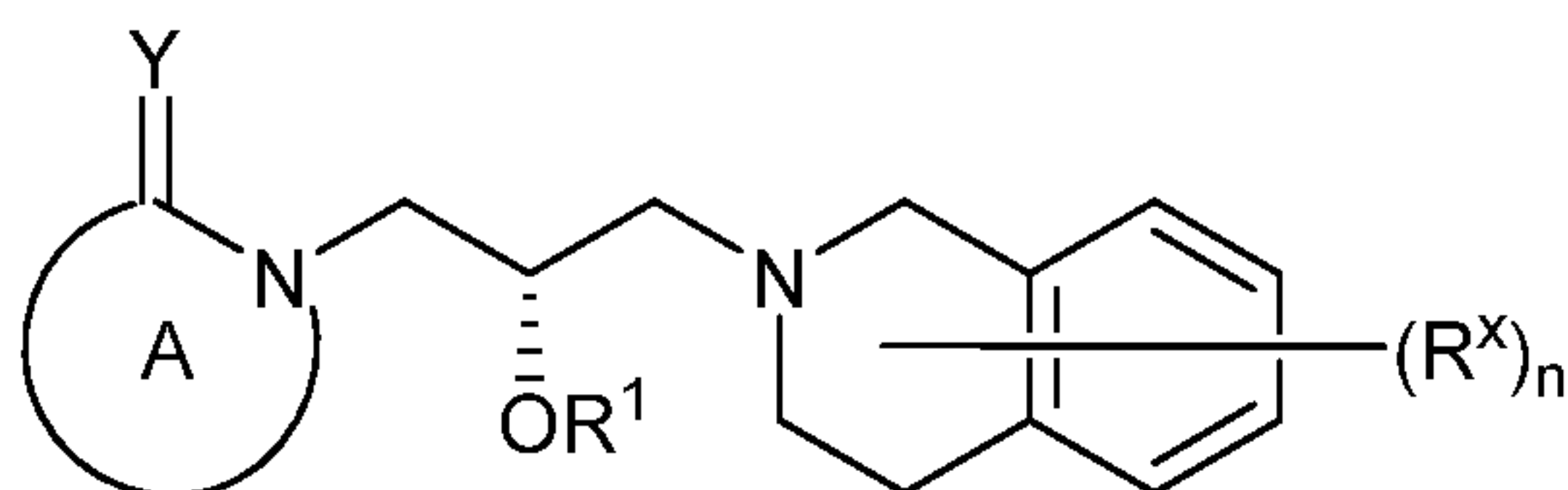
4. The compound of claim 1, wherein the compound is of Formula (**I'**):



I'

or a pharmaceutically acceptable salt thereof.

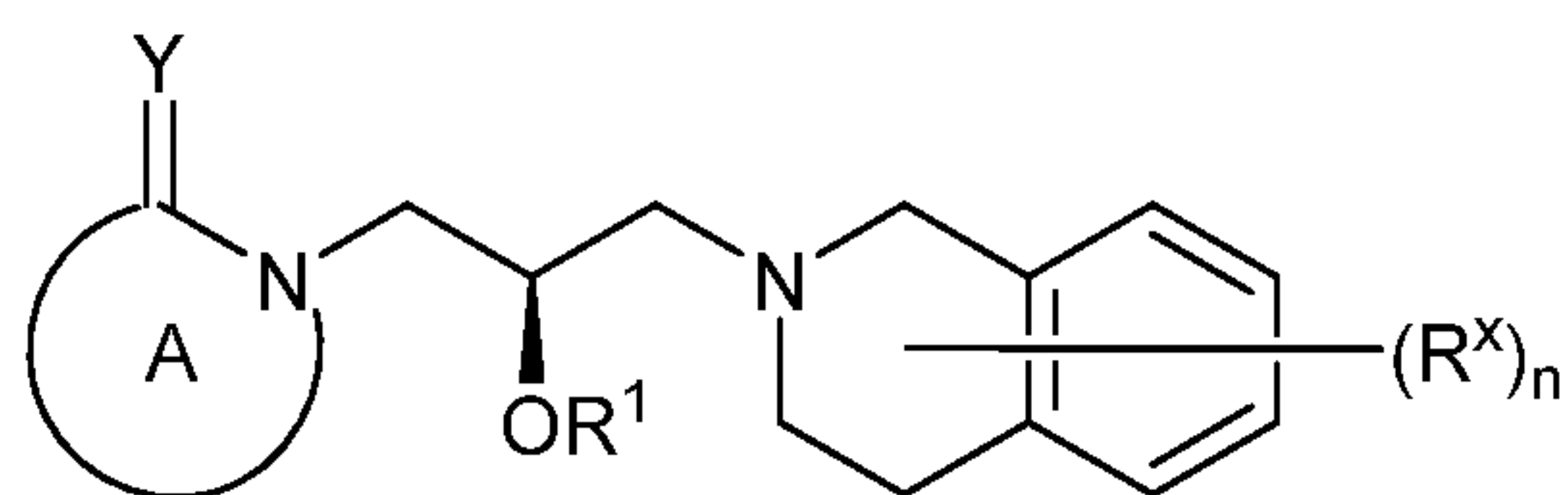
5. The compound of claim 4, wherein the compound is of Formula (**I'-a**):



I'-a

or a pharmaceutically acceptable salt thereof.

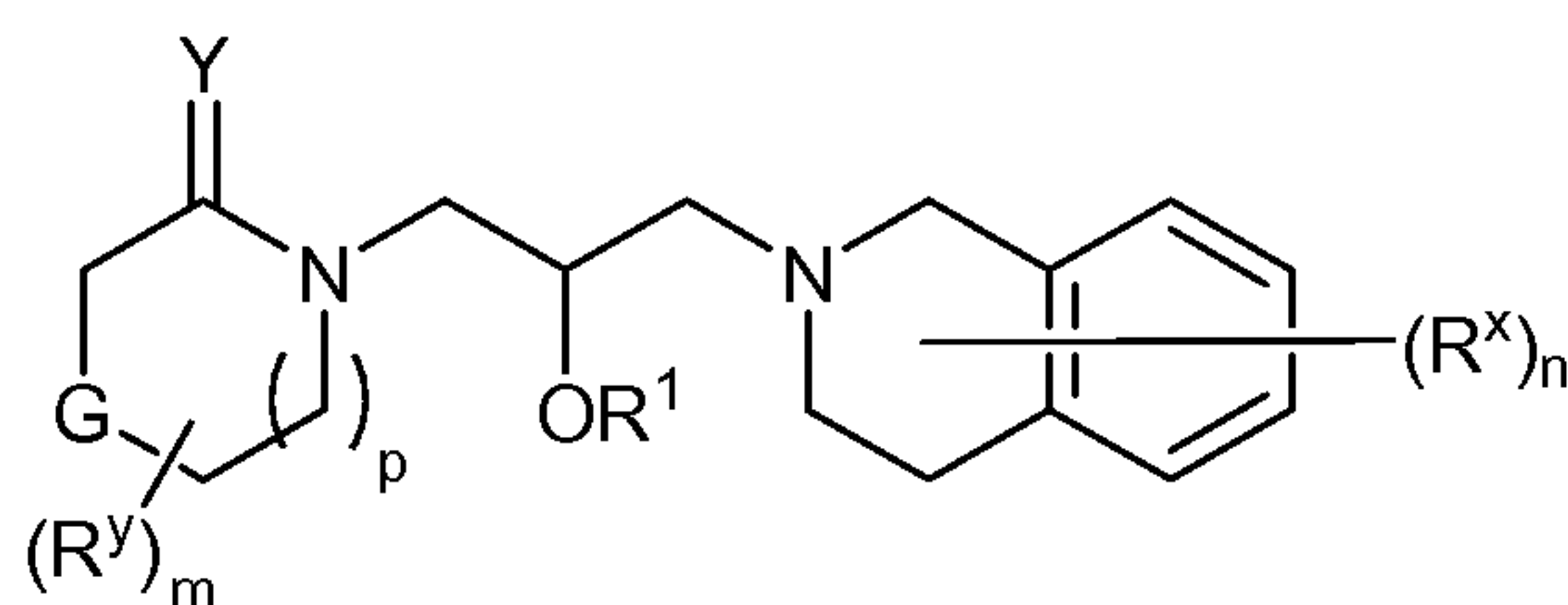
6. The compound of claim 4, wherein the compound is of Formula (I'-b):



I'-b

or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, wherein the compound is of Formula (II):



II

or a pharmaceutically acceptable salt thereof,

wherein

G is NR^2 , CR^3R^4 , O or S;

R^2 is selected from the group consisting of optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-\text{C}(\text{O})\text{R}^A$, $-\text{C}(\text{O})\text{OR}^A$, $-\text{C}(\text{O})\text{SR}^A$, $-\text{C}(\text{O})\text{N}(\text{R}^B)_2$, $-\text{C}(=\text{NR}^B)\text{R}^A$, $-\text{C}(=\text{NR}^B)\text{N}(\text{R}^B)_2$, $-\text{C}(=\text{S})\text{R}^A$, $-\text{C}(=\text{S})\text{N}(\text{R}^B)_2$, $-\text{S}(=\text{O})\text{R}^A$, $-\text{SO}_2\text{R}^A$, and $-\text{SO}_2\text{N}(\text{R}^B)_2$;

R^3 is selected from the group consisting of hydrogen, halo, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-\text{OR}^A$, $-\text{N}(\text{R}^B)_2$, $-\text{SR}^A$, $-\text{C}(=\text{O})\text{R}^A$, $-\text{C}(\text{O})\text{OR}^A$, $-\text{C}(\text{O})\text{SR}^A$, $-\text{C}(\text{O})\text{N}(\text{R}^B)_2$, $-\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)_2$, $-\text{OC}(\text{O})\text{R}^A$, $-\text{OC}(\text{O})\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(\text{O})\text{R}^A$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(\text{O})\text{OR}^A$, $-\text{SC}(\text{O})\text{R}^A$, $-\text{C}(=\text{NR}^B)\text{R}^A$, $-\text{C}(=\text{NNR}^B)\text{R}^A$, $-\text{C}(=\text{NOR}^A)\text{R}^A$, $-\text{C}(=\text{NR}^B)\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(=\text{NR}^B)\text{R}^B$, $-\text{C}(=\text{S})\text{R}^A$, $-\text{C}(=\text{S})\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(=\text{S})\text{R}^A$, $-\text{S}(\text{O})\text{R}^A$, $-\text{OS}(\text{O})_2\text{R}^A$, $-\text{SO}_2\text{R}^A$, $-\text{NR}^B\text{SO}_2\text{R}^A$, and $-\text{SO}_2\text{N}(\text{R}^B)_2$;

each R^A is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl, optionally substituted aryl, and optionally substituted heteroaryl;

each R^B is independently selected from the group consisting of hydrogen, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted heterocyclyl,

optionally substituted aryl, and optionally substituted heteroaryl, or two R^B groups are taken together with their intervening atoms to form an optionally substituted heterocyclic ring;

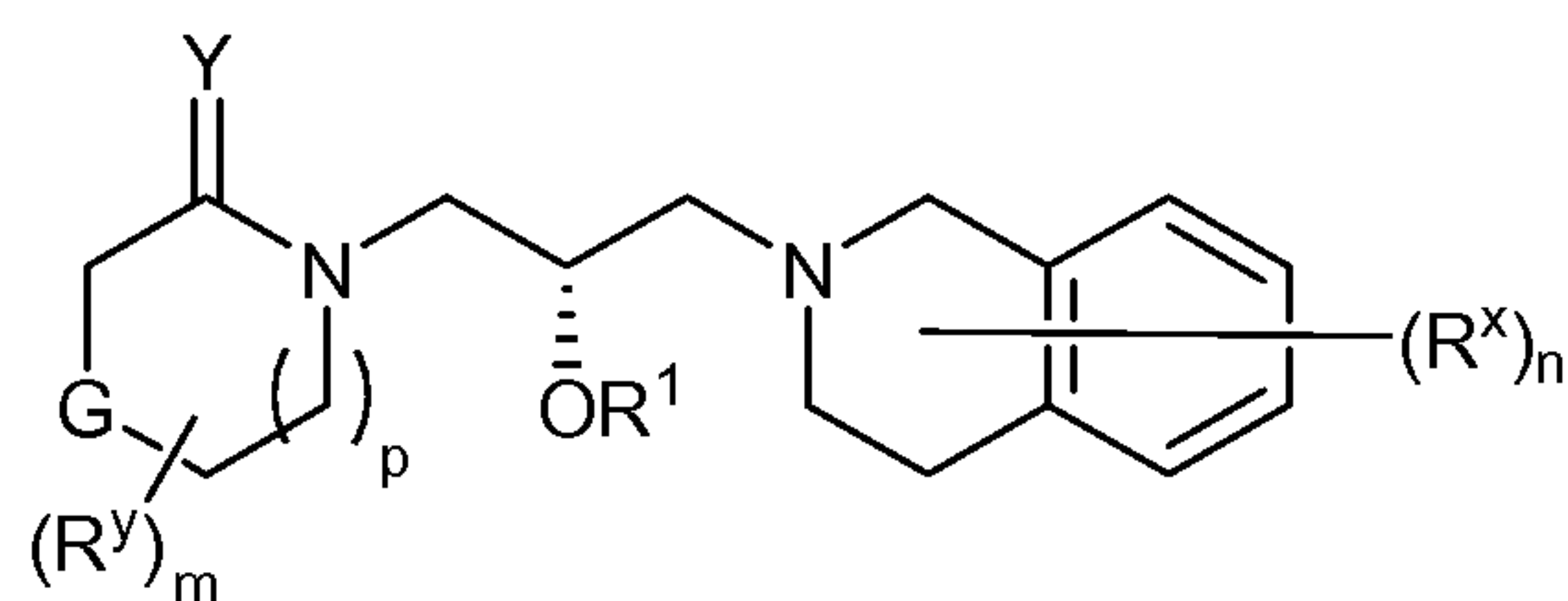
R^4 is selected from the group consisting of hydrogen, halo, or optionally substituted aliphatic;

each R^y is independently selected from the group consisting of halo, $-\text{CN}$, $-\text{NO}_2$, optionally substituted aliphatic, optionally substituted carbocyclyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, $-\text{OR}^A$, $-\text{N}(\text{R}^B)_2$, $-\text{SR}^A$, $-\text{C}(=\text{O})\text{R}^A$, $-\text{C}(\text{O})\text{OR}^A$, $-\text{C}(\text{O})\text{SR}^A$, $-\text{C}(\text{O})\text{N}(\text{R}^B)_2$, $-\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)_2$, $-\text{OC}(\text{O})\text{R}^A$, $-\text{OC}(\text{O})\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(\text{O})\text{R}^A$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(\text{O})\text{N}(\text{R}^B)\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(\text{O})\text{OR}^A$, $-\text{SC}(\text{O})\text{R}^A$, $-\text{C}(=\text{NR}^B)\text{R}^A$, $-\text{C}(=\text{NNR}^B)\text{R}^A$, $-\text{C}(=\text{NOR}^A)\text{R}^A$, $-\text{C}(=\text{NR}^B)\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(=\text{NR}^B)\text{R}^B$, $-\text{C}(=\text{S})\text{R}^A$, $-\text{C}(=\text{S})\text{N}(\text{R}^B)_2$, $-\text{NR}^B\text{C}(=\text{S})\text{R}^A$, $-\text{S}(\text{O})\text{R}^A$, $-\text{OS}(\text{O})_2\text{R}^A$, $-\text{SO}_2\text{R}^A$, $-\text{NR}^B\text{SO}_2\text{R}^A$, and $-\text{SO}_2\text{N}(\text{R}^B)_2$, or two adjacent R^y groups may be taken together with their intervening atoms to form a saturated, partially unsaturated, or aromatic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

p is 0, 1, or 2; and

m is 0, 1, 2, 3, or 4.

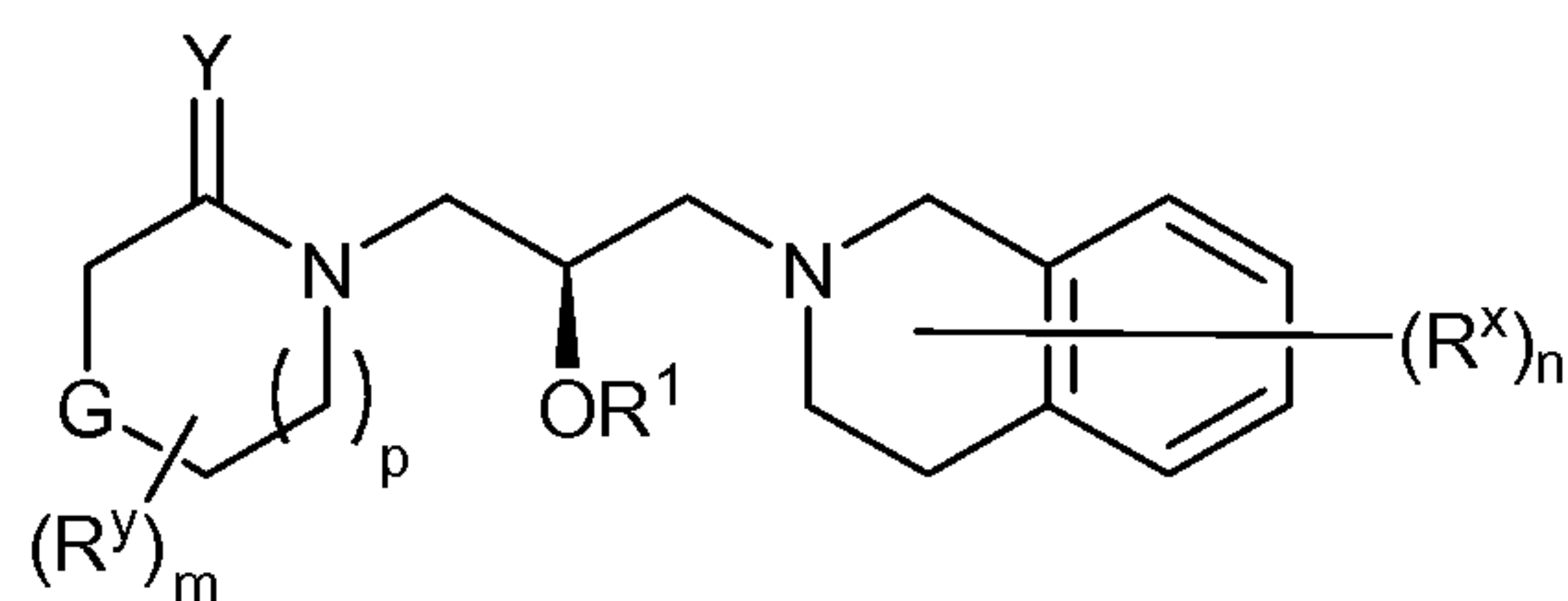
8. The compound of claim 7, wherein the compound is of Formula (II-a):



II-a

or a pharmaceutically acceptable salt thereof.

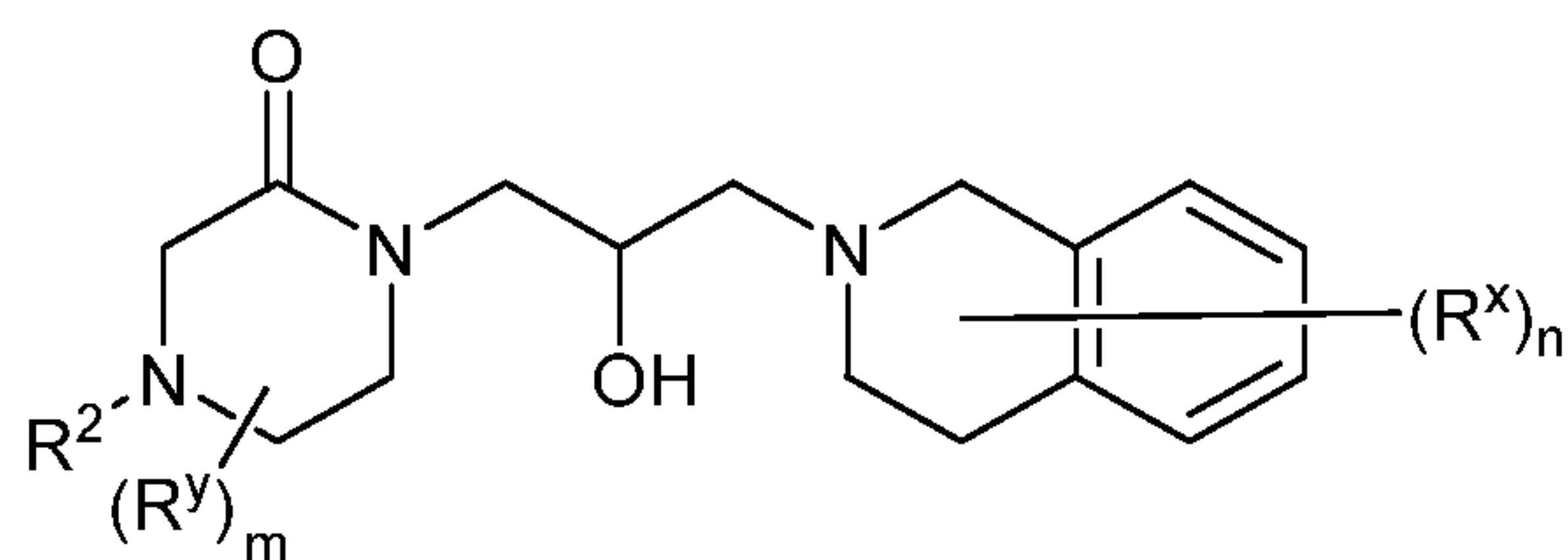
9. The compound of claim 7, wherein the compound is of Formula (II-b):



II-b

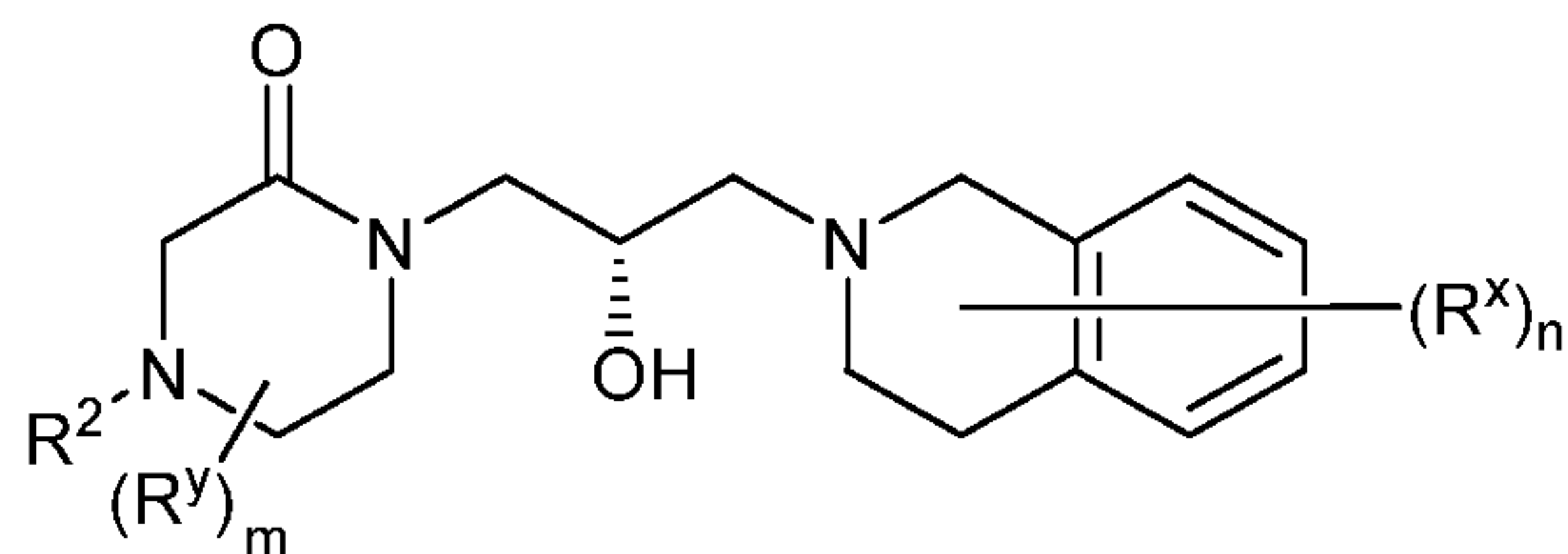
or a pharmaceutically acceptable salt thereof.

10. The compound of claim 7, wherein the compound is of Formula (III):

**III**

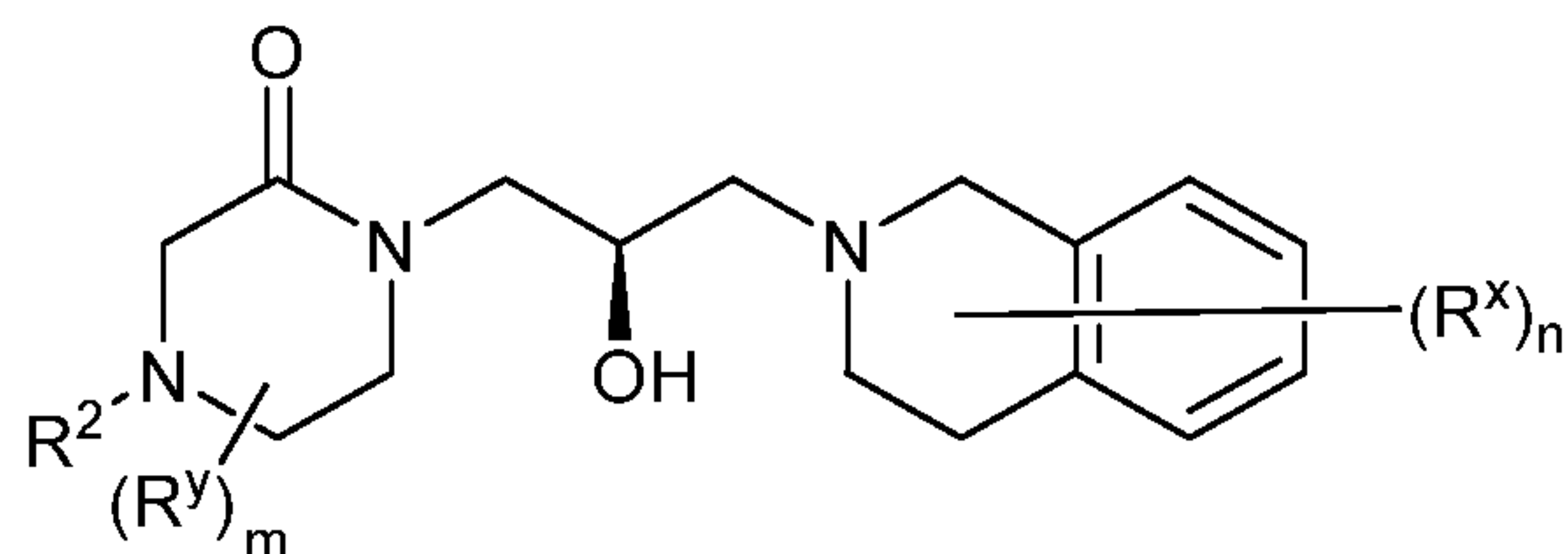
or a pharmaceutically acceptable salt thereof.

11. The compound of claim 10, wherein the compound is of Formula (III-a):

**III-a**

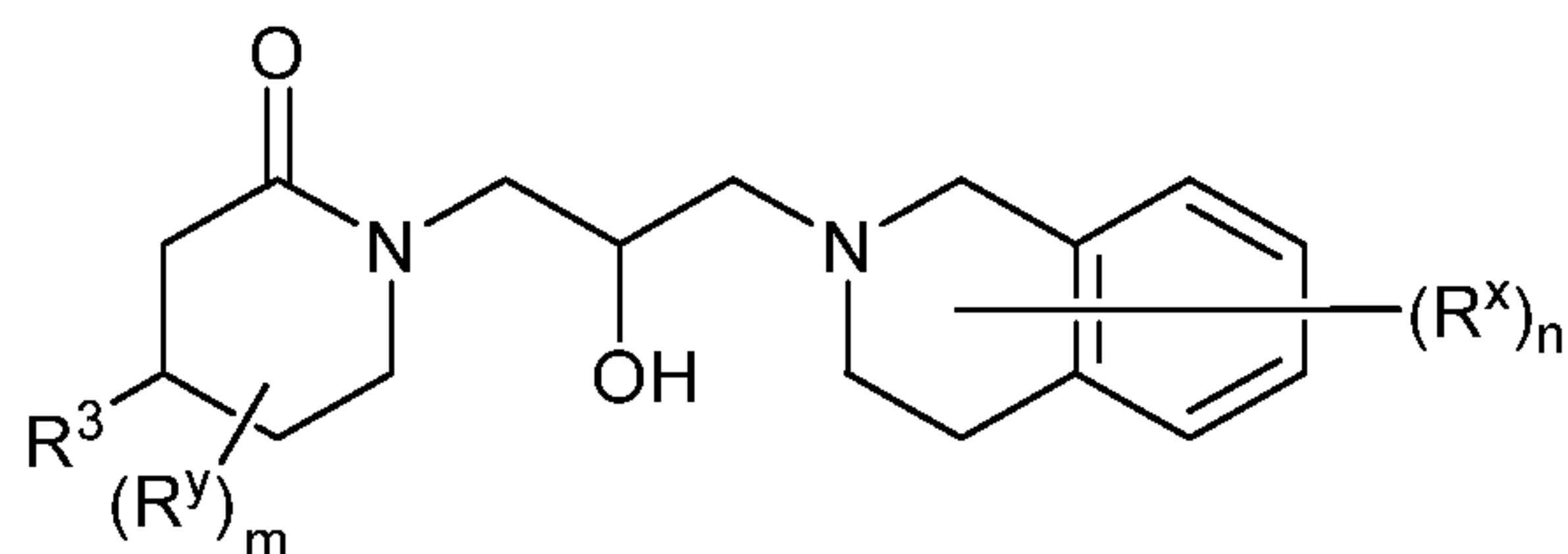
or a pharmaceutically acceptable salt thereof.

12. The compound of claim 10, wherein the compound is of Formula (III-b):

**III-b**

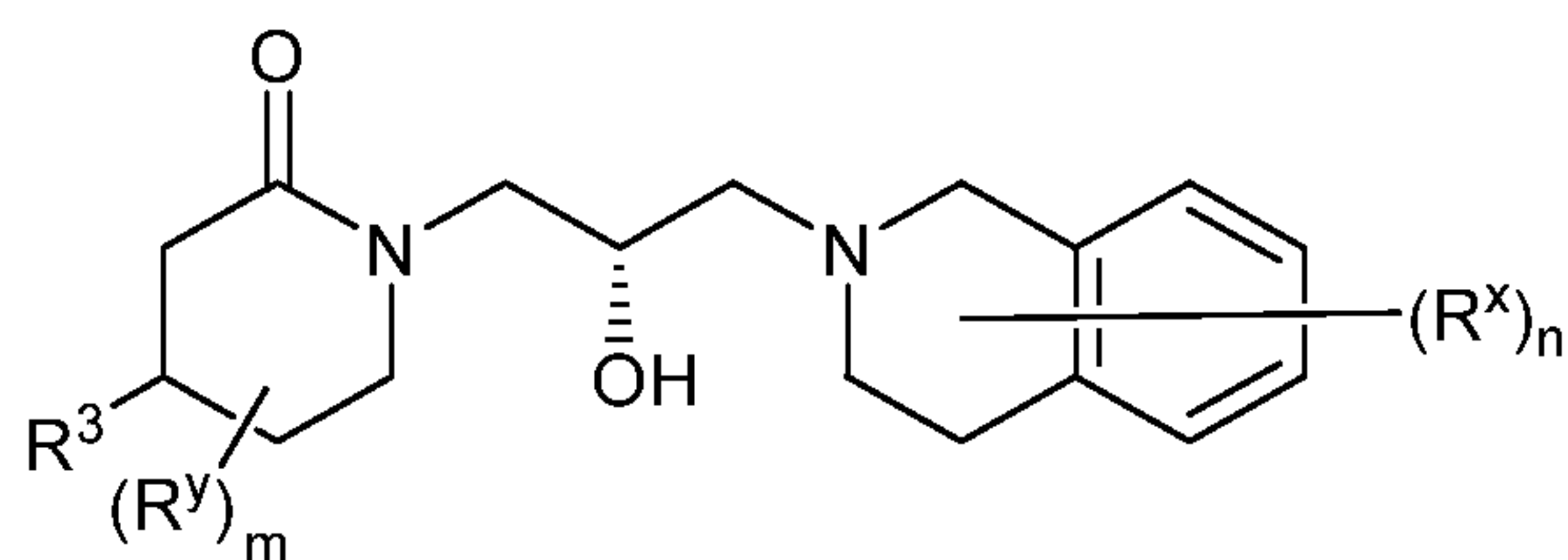
or a pharmaceutically acceptable salt thereof.

13. The compound of claim 7, wherein the compound is of Formula (IV):

**IV**

or a pharmaceutically acceptable salt thereof.

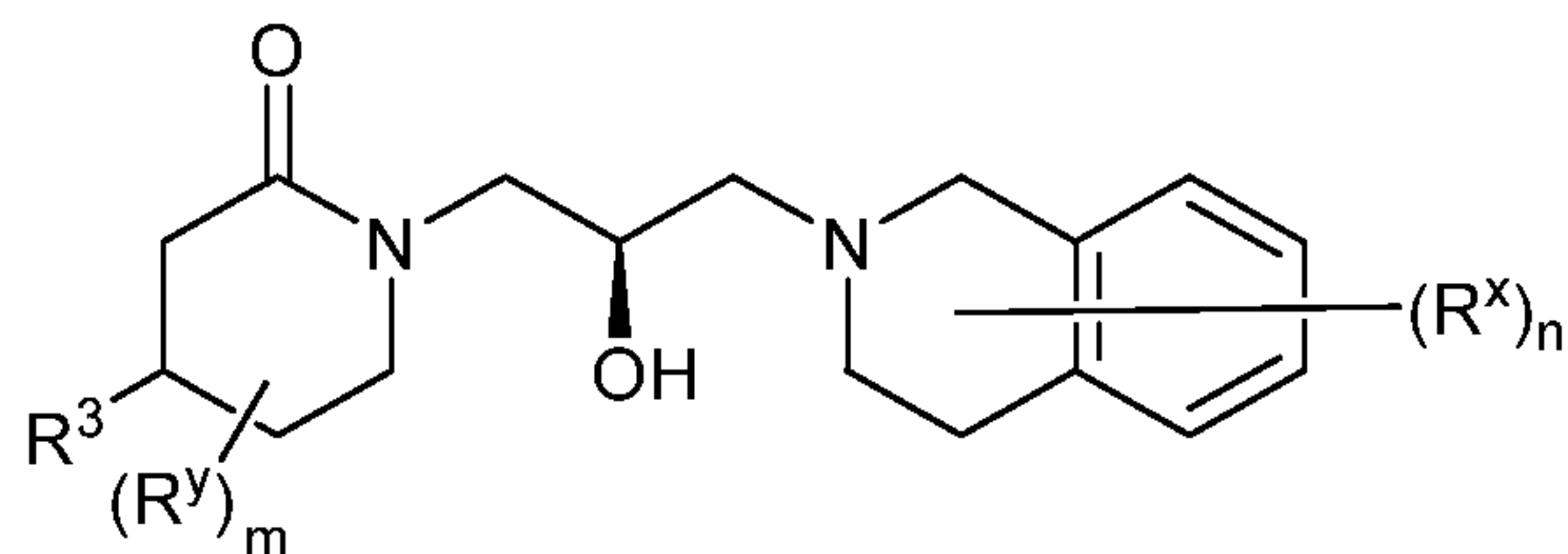
14. The compound of claim 13, wherein the compound is of Formula (IV-a):



IV-a

or a pharmaceutically acceptable salt thereof.

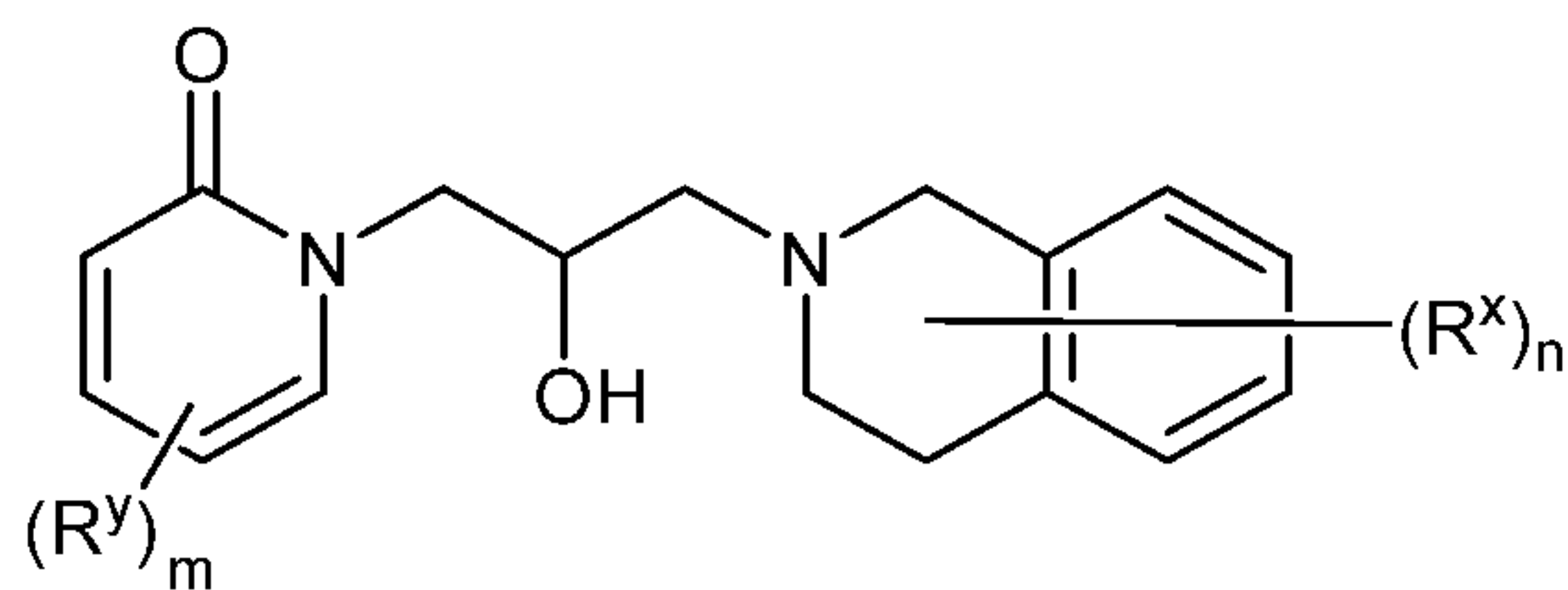
15. The compound of claim 13, wherein the compound is of Formula (IV-b):



IV-b

or a pharmaceutically acceptable salt thereof.

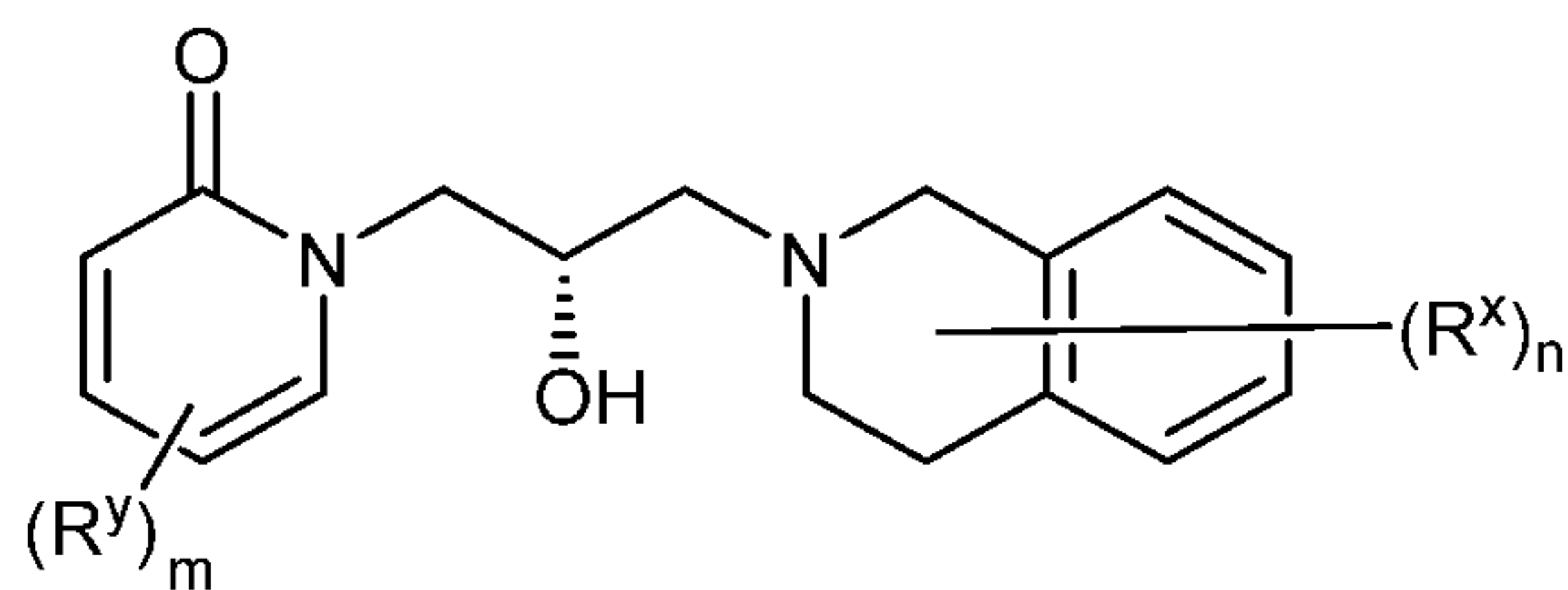
16. The compound of claim 1, wherein the compound is of Formula (V):



V

or a pharmaceutically acceptable salt thereof.

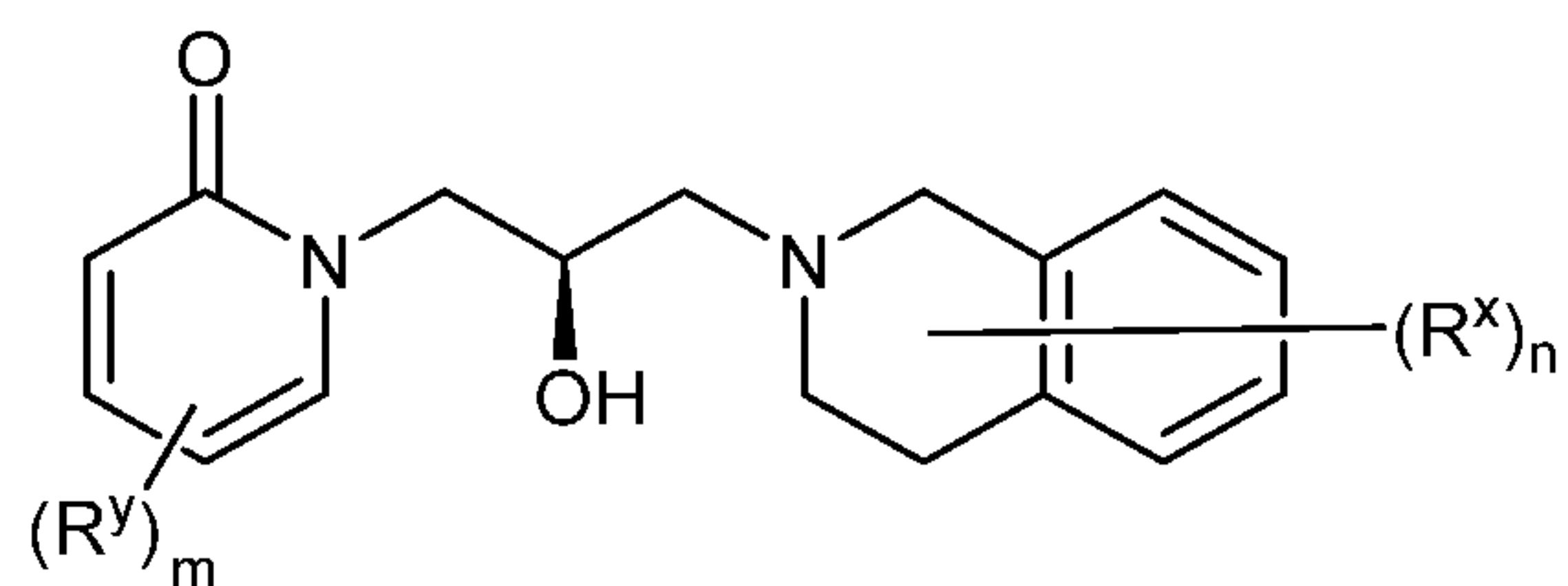
17. The compound of claim 16, wherein the compound is of Formula (V-a):



V-a

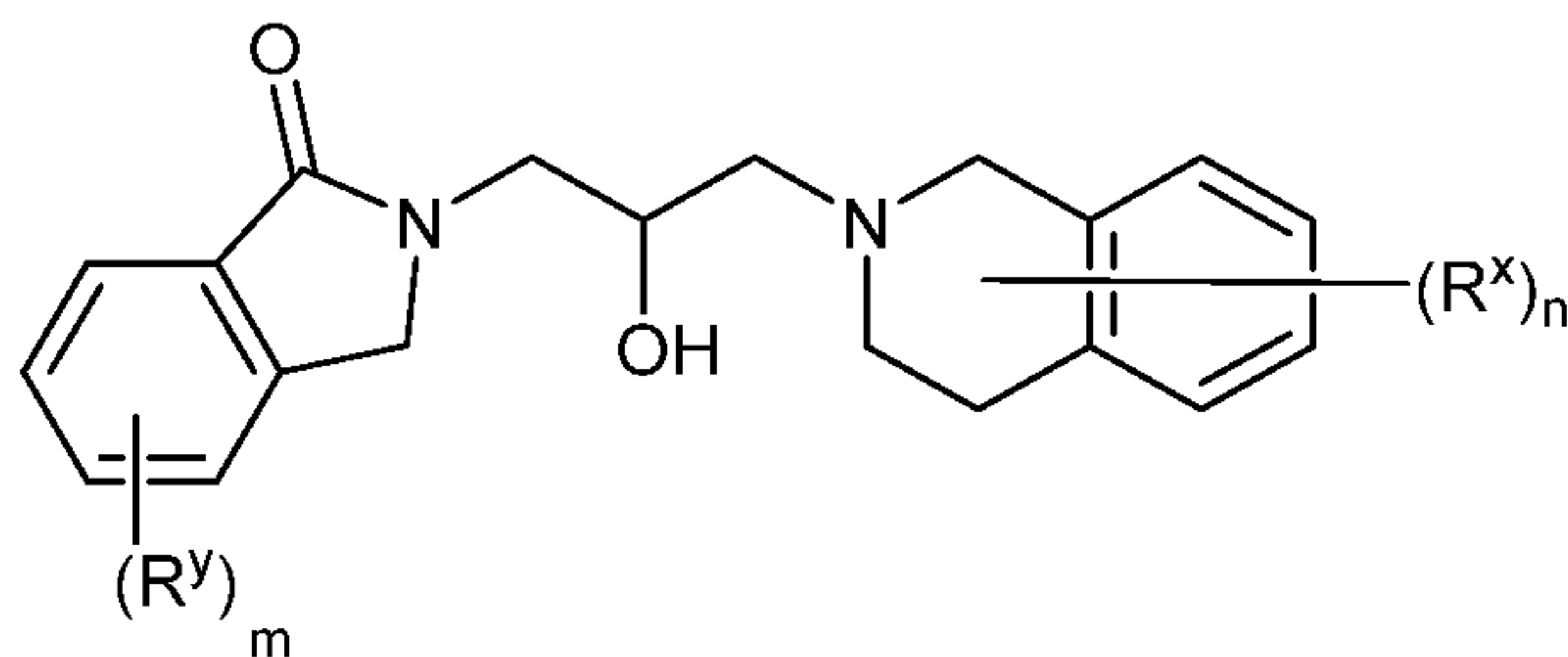
or a pharmaceutically acceptable salt thereof.

18. The compound of claim 16, wherein the compound is of Formula (**V-b**):

**V-b**

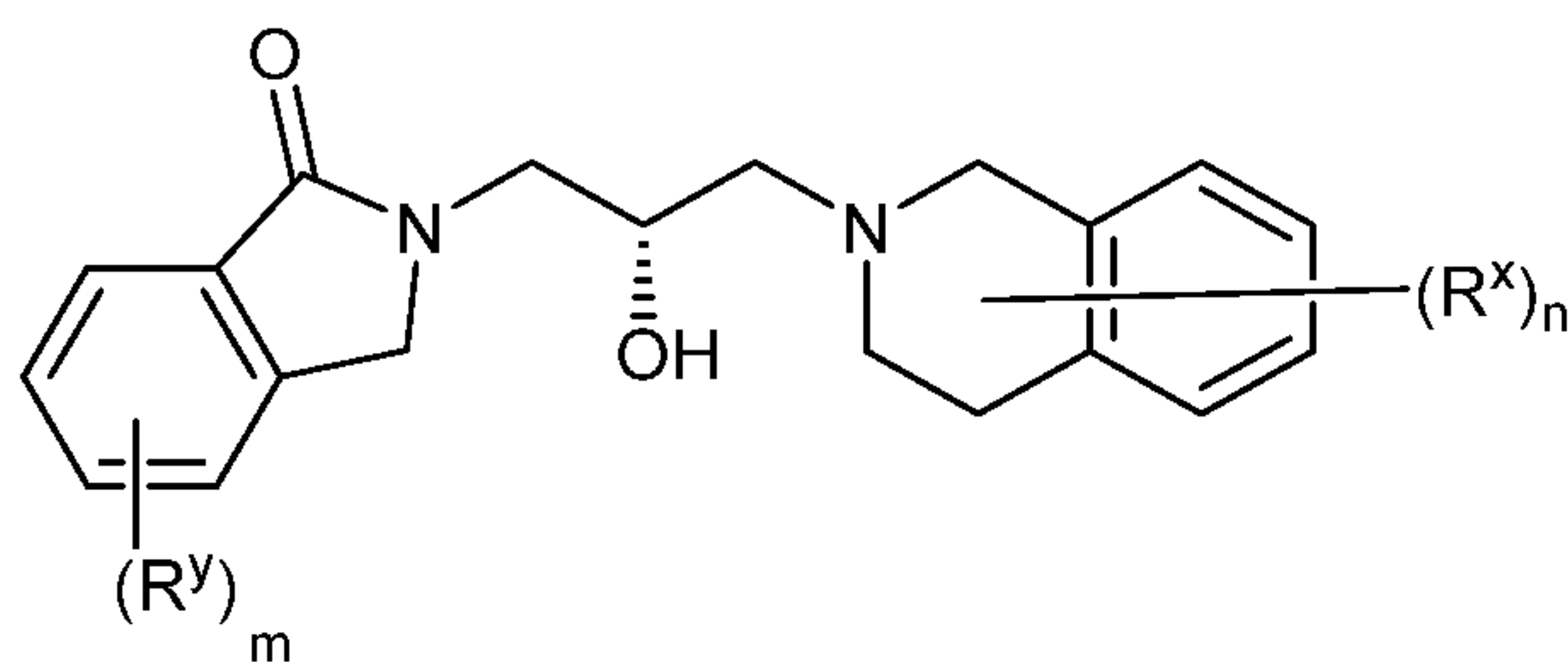
or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, wherein the compound is of Formula (**VI**):

**VI**

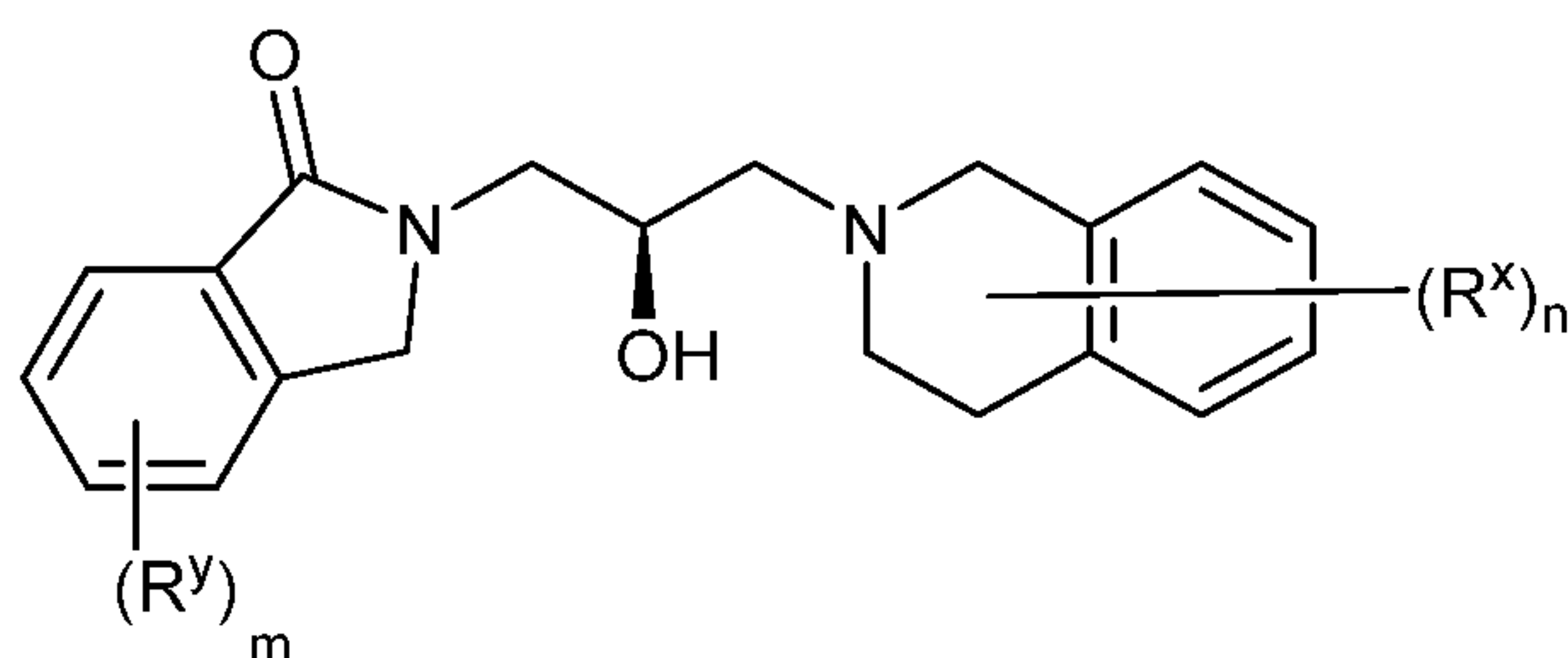
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 19, wherein the compound is of Formula (**VI-a**):

**VI-a**

or a pharmaceutically acceptable salt thereof.

21. The compound of claim 19, wherein the compound is of Formula (**VI-b**):

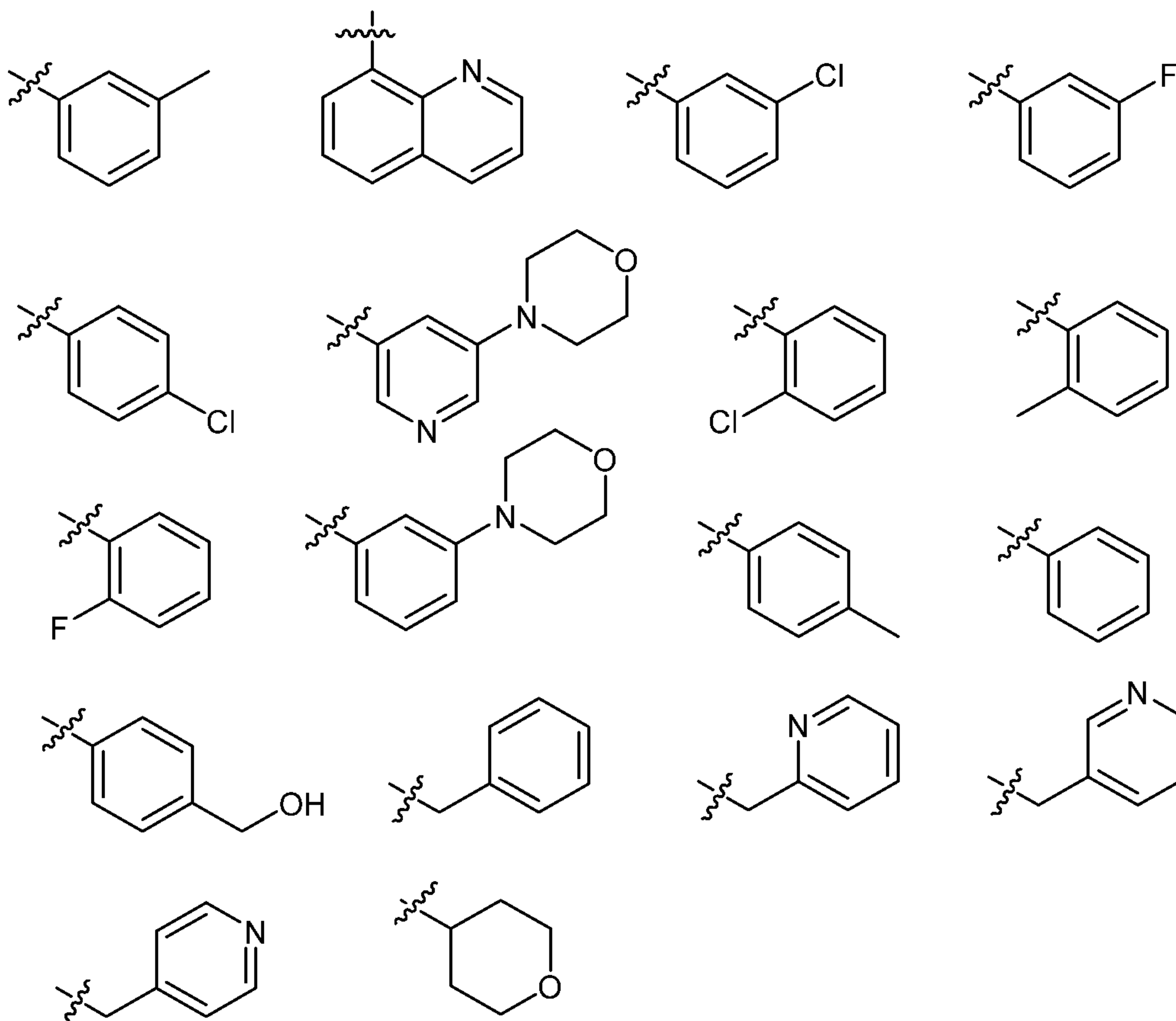
**VI-b**

or a pharmaceutically acceptable salt thereof.

22. The compound of any one of claims 1-9, wherein R^1 is hydrogen.
23. The compound of any one of claims 1-22, wherein n is 0.
24. The compound of any one of claims 1-22, wherein n is 1.
25. The compound of any one of claims 1-22, wherein n is 2.
26. The compound of any one of claims 1-9 and 22-25, wherein Y is O.
27. The compound of any one of claims 7-9 and 22-25, wherein p is 1.
28. The compound of any one of claims 7-27, wherein m is 0.
29. The compound of any one of claims 7-27, wherein m is 1.
30. The compound of any one of claims 7-27, wherein m is 2.
31. The compound of any one of claims 7-9 and 22-30, wherein G is NR^2 .
32. The compound of claim 31, wherein R^2 is optionally substituted aryl.
33. The compound of claim 32, wherein R^2 is optionally substituted phenyl.
34. The compound of claim 33, wherein R^2 is unsubstituted phenyl.
35. The compound of claim 33, wherein R^2 is halophenyl.
36. The compound of claim 33, wherein R^2 is fluorophenyl.
37. The compound of claim 33, wherein R^2 is chlorophenyl.

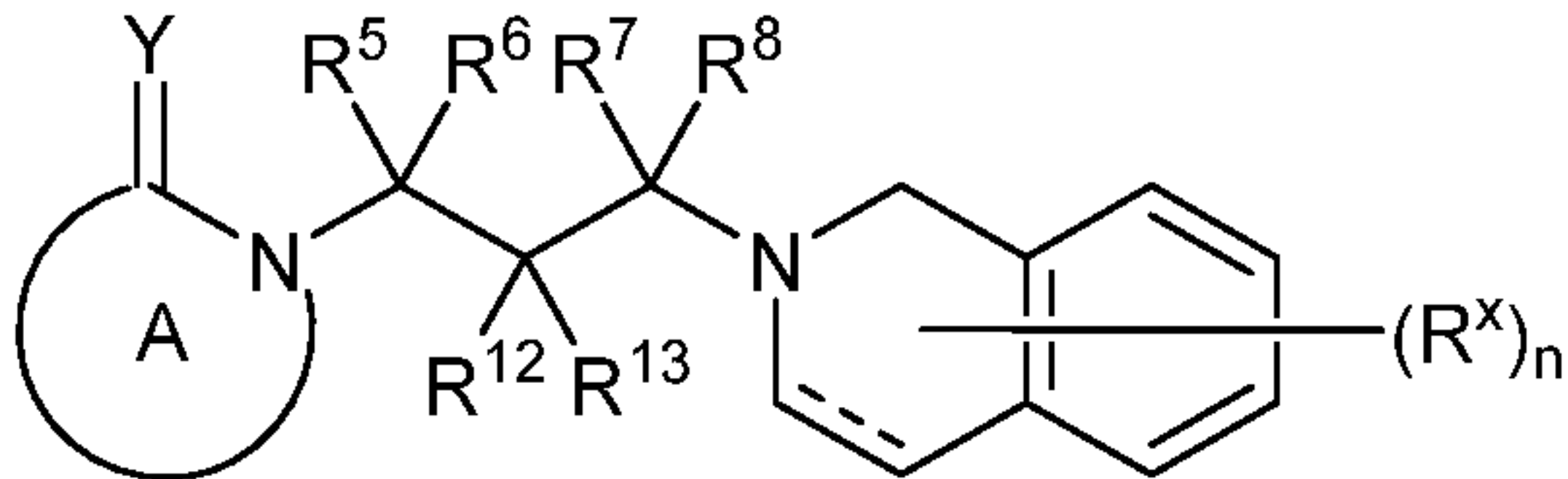
38. The compound of claim 33, wherein R^2 is phenyl substituted with optionally substituted C_{1-6} alkyl.
39. The compound of claim 38, wherein R^2 is phenyl substituted with optionally substituted C_{1-3} alkyl.
40. The compound of claim 39, wherein R^2 is phenyl substituted with methyl.
41. The compound of claim 39, wherein R^2 is phenyl substituted with $-CH_2OH$.
42. The compound of claim 33, wherein R^2 is phenyl substituted with a heterocyclic ring.
43. The compound of claim 42, wherein R^2 is phenyl substituted with morpholinyl.
44. The compound of claim 43, wherein R^2 is phenyl substituted with tetrahydropyranyl.
45. The compound of claim 31, wherein R^2 is optionally substituted heteroaryl.
46. The compound of claim 45, wherein R^2 is optionally substituted quinoline.
47. The compound of claim 45, wherein R^2 is optionally substituted pyridine.
48. The compound of claim 47, wherein R^2 is pyridine substituted with a heterocyclic ring.
49. The compound of claim 31, wherein R^2 is optionally substituted aliphatic.
50. The compound of claim 49, wherein R^2 is unsubstituted aliphatic.
51. The compound of claim 49, wherein R^2 is $-CH_2$ -aryl.
52. The compound of claim 51, wherein R^2 is benzyl.
53. The compound of claim 49, wherein R^2 is $-CH_2$ -heteroaryl.

54. The compound of claim 53, wherein R^2 is $-\text{CH}_2\text{-pyridyl}$.
55. The compound of claim 31, wherein R^2 is $-\text{C}(=\text{O})\text{R}^A$.
56. The compound of claim 55, wherein R^A is optionally substituted aliphatic.
57. The compound of claim 56, wherein R^2 is acetyl.
58. The compound of claim 31, wherein R^2 is $-\text{SO}_2\text{R}^A$.
59. The compound of claim 58, wherein R^A is optionally substituted aliphatic.
60. The compound of claim 59, wherein R^2 is $-\text{SO}_2\text{CH}_3$.
61. The compound of claim 31, wherein R^2 is selected from the group consisting of:



62. The compound of any one of claims 7-9 and 22-30, wherein G is CR³R⁴.
63. The compound of claim 62, wherein R⁴ is hydrogen.
64. The compound of claim 62 or 63, wherein R³ is optionally substituted aryl.
65. The compound of any one of claims 7-9 and 22-30, wherein G is O.
66. The compound of claim 64 or 65, wherein m is 0.
67. The compound of any one of claims 64-66, wherein n is 0.
68. The compound of claim 1, wherein the compound is selected from the group consisting of the compounds in Table 1A.
69. A pharmaceutical composition comprising a compound of any one of claims 1-68 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient
70. A kit or packaged pharmaceutical comprising a compound of any one of claims 1-68 or a pharmaceutically acceptable salt thereof, and instructions for use thereof.
71. A method of inhibiting PRMT5 comprising contacting a cell with an effective amount of a compound of any one of claims 1-68 or a pharmaceutically acceptable salt thereof.
72. A method of altering gene expression comprising contacting a cell with an effective amount of a compound of any one of claims 1-68 or a pharmaceutically acceptable salt thereof.
73. A method of altering transcription comprising contacting a cell with an effective amount of a compound of any one of claims 1-68 or a pharmaceutically acceptable salt thereof.
74. The method of any one of claims 71-73, wherein the cell is *in vitro*.

75. The method of any one of claims 71-73, wherein the cell is in a subject.
76. A method of treating a PRMT5-mediated disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-68, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 69.
77. The method of claim 76, wherein the disorder is a proliferative disorder.
78. The method of claim 77, wherein the disorder is cancer.
79. The method of claim 78, wherein the cancer is hematopoietic cancer, lung cancer, prostate cancer, melanoma, or pancreatic cancer.
80. The method of claim 76, wherein the disorder is a metabolic disorder.
81. The method of claim 80, wherein the metabolic disorder is diabetes.
82. The method of claim 80, wherein the metabolic disorder is obesity.
83. The method of claim 76, wherein the disorder is a blood disorder.
84. The method of claim 83, wherein the disorder is a hemoglobinopathy.
85. The method of claim 84, wherein the disorder is sickle cell anemia.
86. The method of claim 84, wherein the disorder is β -thalassemia.



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