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(54) **Title:** (PIPERIDIN-3-YL)(NAPHTHALEN-2-YL)METHANONE DERIVATIVES AND RELATED COMPOUNDS AS INHIBITORS OF THE HISTONE DEMETHYLASE KDM2B FOR THE TREATMENT OF CANCER

(57) **Abstract:** The present invention relates to (piperidin-3-yl)(naphthalen-2-yl) methanone derivatives and related compounds as inhibitors of one or more histone demethylases, such as KDM2b. The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and discloses methods of using said compositions in the treatment of cancer, such as lung cancer, leukemia or lymphoma.



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**(PIPERIDIN-3-YL)(NAPHTHALEN-2-YL)METHANONE DERIVATIVES AND
RELATED COMPOUNDS AS INHIBITORS OF
THE HISTONE DEMETHYLASE KDM2B FOR THE TREATMENT OF CANCER**

PRIORITY OF INVENTION

This application claims priority from United States Provisional Patent Application
5 Number 62/101,927, filed January 9, 2015, which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

Compounds useful as inhibitors of histone demethylases, such as KDM2b are provided.

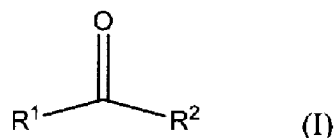
BACKGROUND

10 Packaging the 3 billion nucleotides of the human genome into the nucleus of a cell requires tremendous compaction. To accomplish this feat, DNA in our chromosomes is wrapped around spools of proteins called histones to form dense repeating protein/DNA polymers known as chromatin. Far from serving as mere packaging modules, chromatin
15 templates form the basis of a newly appreciated and fundamentally important set of gene control mechanisms termed epigenetic regulation. By conferring a wide range of specific chemical modifications to histones and DNA, epigenetic regulators modulate the structure, function, and accessibility of our genome, thereby exerting a tremendous impact on gene expression. Hundreds of epigenetic effectors have recently been identified, many of which are chromatin-
20 binding or chromatin-modifying enzymes. Significantly, an increasing number of these enzymes have been associated with a variety of disorders such as cancer. Thus, therapeutic agents directed against this emerging class of gene regulatory enzymes promise new approaches to the treatment of human diseases.

There is currently a need for compounds that inhibit of KDM2 demethylases for treating hyperproliferative diseases.

25 **SUMMARY OF THE INVENTION**

One aspect provides a compound of formula (I):



or a salt thereof, wherein:

30 R^1 is:

a) a carbon-linked piperidine ring that is substituted on the piperidine ring nitrogen with a group R^x and that is optionally further substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo; or

b) a carbon-linked piperazine ring that is substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo;

each R^b is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, and C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, aryl, and C_{2-6} alkynyl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-N(R^c)_2$, $-CN$, $-C(O)-N(R^c)_2$, $-S(O)-N(R^c)_2$, $-S(O)_2-N(R^c)_2$, $-O-R^c$, $-S-R^c$, $-O-C(O)-R^c$, $-C(O)-R^c$, $-C(O)-OR^c$, $-S(O)-R^c$, $-S(O)_2-R^c$, $-N(R^c)-C(O)-R^c$, $-N(R^c)-S(O)-R^c$, $-N(R^c)-C(O)-$

$N(R^c)_2$, and $-N(R^c)-S(O)_2-R^c$; or two R^b are taken together with the nitrogen to which they are attached to form a pyrrolidino, piperidino, or piperazino ring;

each R^c is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo, amino, hydroxy, and C_{1-6} alkoxy; or two R^c are taken together with the nitrogen to which they are attached to form a heterocyclyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo and C_{1-3} alkyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo and halo;

R^x is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle is optionally substituted with one or more groups independently selected from the group consisting of halo, $-CN$, C_{1-3} alkoxy, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and C_{3-8} carbocycle that is optionally substituted with one or more groups independently selected from the group consisting of halo and C_{1-3} alkyl;

R^2 is a 5-10 membered heteroaryl or a 6-12 membered aryl, which 5-10 membered heteroaryl, and 6-12 membered aryl is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo;

each R^d is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, and C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, aryl, and C_{2-6} alkynyl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-N(R^e)_2$, $-CN$, $-C(O)-N(R^e)_2$, $-S(O)-N(R^e)_2$, $-S(O)_2-N(R^e)_2$, $-O-R^e$, $-S-R^e$, $-O-C(O)-R^e$, $-C(O)-R^e$, $-C(O)-OR^e$, $-S(O)-R^e$, $-S(O)_2-R^e$, $-N(R^e)-C(O)-R^e$, $-N(R^e)-S(O)-R^e$, $-N(R^e)-C(O)-$

$N(R^c)_2$, and $-N(R^c)-S(O)_2-R^c$; or two R^d are taken together with the nitrogen to which they are attached to form a pyrrolidino, piperidino, or piperazino ring; and

each R^e is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo, amino, hydroxy, and C_{1-6} alkoxy; or two R^e are taken together with the nitrogen to which they are attached to form a heterocyclyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo and C_{1-3} alkyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo and halo;

provided that when R^2 is 6-methoxy-2-naphthyl, then R^1 is not 1-(cyclopropylmethyl)piperidin-3-yl, 1-(cyclobutyl)piperidin-3-yl, 1-(cyclopentyl)piperidin-3-yl, or 1-(tetrahydropyranyl)piperidin-3-yl; and

provided that when R^2 is phenyl, naphthyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl, 2-methyl-6-quinolyl, 1,5-benzodioxepin-7-yl, benzo[b]thien-7-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1H-1-(*tert*-butoxycarbonyl)-4-bromo-indol-2-yl, 1H-1-(*tert*-butoxycarbonyl)-4-cyano-indol-2-yl, 3,4-dihydroxyphenyl, 3-methoxy-4-hydroxyphenyl, 3,4-dimethoxyphenyl, 3-methoxycarbonyl-4-hydroxyphenyl, 4-hydroxyphenyl, or 2-hydroxyphenyl, then R^1 is not optionally substituted piperizine-2-yl.

Another aspect includes a composition, comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

Another aspect includes a method of treating a disease associated with KDM2b activity, comprising administering an therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, to a patient in need thereof.

Another aspect includes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in therapy.

Another aspect includes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in treating a disease associated with KDM2b activity.

Another aspect includes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease associated with KDM2b activity.

Another aspect includes a method of increasing the efficacy of a cancer treatment comprising a cancer therapy agent, comprising administering to a patient (a) an effective amount

of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and (b) an effective amount of the cancer therapy agent.

Another aspect includes a method of treating an individual with cancer who has an increased likelihood of developing resistance to a cancer therapy agent comprising administering
5 to the individual (a) an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and (b) an effective amount of the cancer therapy agent.

Another aspect includes a method of treating cancer in a mammal in need thereof, comprising administering to the mammal, a compound of formula (I), or a pharmaceutically acceptable salt thereof.

10 Another aspect includes a method of inducing differentiation of a cancer stem/progenitor cell(s) in a mammal in need thereof, comprising administering to the mammal, an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Another aspect includes a method of reducing activity of a cancer stem/progenitor cell(s) in a mammal in need thereof, comprising administering to the mammal, an effective amount of a
15 compound of formula (I), or a pharmaceutically acceptable salt thereof.

Another aspect includes a method of depleting a cancer stem/progenitor cell in a mammal in need thereof, comprising administering to the mammal, an effective amount a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Another aspect includes a method of decreasing cancer initiation in a mammal in need
20 thereof, comprising administering to the mammal, an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

Another aspect includes a compound of formula (I), or a pharmaceutically acceptable salt thereof for the therapeutic or prophylactic treatment of cancer.

Another aspect includes a compound of formula (I), or a pharmaceutically acceptable salt
25 thereof for inducing differentiation of a cancer stem/progenitor cell(s).

Another aspect includes a compound of formula (I), or a pharmaceutically acceptable salt thereof for reducing activity of a cancer stem/progenitor cell(s).

Another aspect includes a compound of formula (I), or a pharmaceutically acceptable salt thereof for depleting a cancer stem/progenitor cell.

30 Another aspect includes a compound of formula (I), or a pharmaceutically acceptable salt thereof for decreasing cancer initiation.

Another aspect includes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof to prepare a medicament for treating cancer in a mammal.

Another aspect includes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof to prepare a medicament for inducing differentiation of a cancer stem/progenitor cell(s) in a mammal.

5 Another aspect includes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof to prepare a medicament for reducing activity of a cancer stem/progenitor cell(s) in a mammal.

Another aspect includes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof to prepare a medicament for depleting a cancer stem/progenitor cell in a mammal.

10 Another aspect includes the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof to prepare a medicament for decreasing cancer initiation in a mammal.

Another aspect includes a method of treating cancer in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

15 Another aspect includes a method of inducing differentiation of a cancer stem/progenitor cell(s) in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

Another aspect includes a method of reducing activity of a cancer stem/progenitor cell(s) in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

20 Another aspect includes a method of depleting a cancer stem/progenitor cell population in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

Another aspect includes a method of decreasing cancer initiation in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

25 Another aspect includes a processes and synthetic intermediates that are useful for preparing a compound of formula (I), or a salt thereof.

Another aspect includes compounds for the study of histone demethylases, such as KDM2b, the study of intracellular signal transduction pathways mediated by such histone demethylases, and the comparative evaluation of modulators of these demethylases.

30 DETAILED DESCRIPTION

Definitions

Definitions of specific functional groups and chemical terms are described in more detail below. 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 *Organic Chemistry*, Thomas Sorrell, 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; Carruthers, *Some Modern Methods of Organic Synthesis*, 3rd Edition, Cambridge University Press, Cambridge, 1987; the entire contents of each of which are incorporated herein by reference.

Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are included.

Additionally, 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 including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ¹³C- or ¹⁴C-enriched carbon are included. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents.

Where a particular enantiomer is preferred, it may, in some embodiments be provided substantially free of the corresponding enantiomer, and may also be referred to as "optically enriched." "Optically-enriched," as used herein, means that the compound is made up of a significantly greater proportion of one enantiomer. In certain embodiments the compound is made up of at least about 90% by weight of a preferred enantiomer. In other embodiments the compound is made up of at least about 95%, 98%, or 99% by weight of a preferred enantiomer. Preferred enantiomers may be isolated from racemic mixtures by any method known to those skilled in the art, including chiral high pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts or 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, E.L. *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); Wilen, S.H. *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.L. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

The term “a compound as described herein” includes the compounds described in the Examples herein and salts and free-bases thereof, as well as compounds of formula (I) and salts thereof.

The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

As used herein a “direct bond” or “covalent bond” refers to a single, double or triple bond. In certain embodiments, a “direct bond” or “covalent bond” refers to a single bond.

The terms “halo” and “halogen” as used herein refer to an atom selected from fluorine (fluoro, -F), chlorine (chloro, -Cl), bromine (bromo, -Br), and iodine (iodo, -I).

The term “aliphatic” or “aliphatic group”, as used herein, denotes a hydrocarbon moiety that may be straight-chain (i.e., unbranched), branched, or cyclic (including fused, bridging, and spiro-fused polycyclic) and may be completely saturated or may contain one or more units of unsaturation, but which is not aromatic. Unless otherwise specified, aliphatic groups contain 1–6 carbon atoms. In some embodiments, aliphatic groups contain 1–4 carbon atoms, and in yet other embodiments aliphatic groups contain 1–3 carbon atoms. Suitable aliphatic groups include, but are not limited to, linear or branched, alkyl, alkenyl, and alkynyl groups, and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

The term “unsaturated”, as used herein, means that a moiety has one or more units of unsaturation.

The terms “cycloaliphatic”, “carbocycle”, “carbocyclyl”, “carbocyclo”, or “carbocyclic”, used alone or as part of a larger moiety, refer to a saturated or partially unsaturated cyclic aliphatic monocyclic, bicyclic, or spiro ring systems, as described herein, having from 3 to 10 members, wherein the aliphatic ring system is optionally substituted as described herein. Cycloaliphatic groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, and cyclooctadienyl. In some embodiments, the cycloalkyl has 3–6 carbons. Also included within the scope of the term “cycloaliphatic”, “carbocycle”, “carbocyclyl”, “carbocyclo”, or “carbocyclic”, as it is used herein, is a group in which an “cycloaliphatic”, “carbocycle”, “carbocyclyl”, “carbocyclo”, or “carbocyclic” is fused to one or more aryl, heterocyclyl, or heteroaryl rings, wherein the point of attachment is a carbon of the “cycloaliphatic”, “carbocycle”, “carbocyclyl”, “carbocyclo”, or “carbocyclic” ring.

The term “alkyl,” as used herein, refers to a monovalent saturated, straight- or branched-chain hydrocarbon radical derived from an aliphatic moiety containing between one and six carbon atoms by removal of a single hydrogen atom. In some embodiments, alkyl contains 1–5 carbon atoms. In another embodiment, alkyl contains 1–4 carbon atoms. In still other
5 embodiments, alkyl contains 1–3 carbon atoms. In yet another embodiment, alkyl contains 1–2 carbons. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, sec-pentyl, iso-pentyl, tert-butyl, n-pentyl, neopentyl, n-hexyl, sec-hexyl, n-heptyl, n-octyl, n-decyl, n-undecyl, dodecyl, and the like.

The term “alkenyl,” as used herein, denotes a monovalent group derived from a straight-
10 or branched-chain aliphatic moiety having at least one carbon-carbon double bond by the removal of a single hydrogen atom. In certain embodiments, alkenyl contains 2–6 carbon atoms. In certain embodiments, alkenyl contains 2–5 carbon atoms. In some embodiments, alkenyl contains 2–4 carbon atoms. In another embodiment, alkenyl contains 2–3 carbon atoms. Alkenyl groups include, for example, ethenyl (“vinyl”), propenyl (“allyl”), butenyl, 1-methyl-
15 2-buten-1-yl, and the like.

The term “alkynyl,” as used herein, refers to a monovalent group derived from a straight- or branched-chain aliphatic moiety having at least one carbon-carbon triple bond by the removal of a single hydrogen atom. In certain embodiments, alkynyl contains 2–6 carbon atoms. In certain embodiments, alkynyl contains 2–5 carbon atoms. In some embodiments,
20 alkynyl contains 2–4 carbon atoms. In another embodiment, alkynyl contains 2–3 carbon atoms. Representative alkynyl groups include, but are not limited to, ethynyl, 2-propynyl (“propargyl”), 1-propynyl, and the like.

The term “aryl” used alone or as part of a larger moiety as in “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, refers to monocyclic and bicyclic ring systems having a total of 6, 7, 8, 9, 10,
25 11, or 12 ring members, wherein at least one ring in the system is aromatic. The term “aryl” may be used interchangeably with the term “aryl ring”. In certain embodiments, “aryl” refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term “aryl”, as it is used herein, is a group in which an aromatic carbon ring is fused to one or
30 more cycloaliphatic, heterocyclyl, or heteroaryl rings, wherein the point of attachment is a carbon of the aromatic carbon ring.

The terms “heteroaryl” and “heteroar-”, used alone or as part of a larger moiety, e.g., “heteroaralkyl”, or “heteroaralkoxy”, refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition

to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indoliziny, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, wherein the point of attachment is a carbon of the heteroaromatic ring.

Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalyl, 4*H*-quinoliziny, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be mono- or bicyclic.

As used herein, the terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably and refer to a stable 3- to 8-membered monocyclic or 7-10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl), or ⁺NR (as in *N*-substituted pyrrolidinyl).

A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle", "heterocyclyl", "heterocyclyl ring", "heterocyclic group", "heterocyclic moiety", and "heterocyclic radical", are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, 2-azabicyclo[2.2.1]heptanyl, octahydroindolyl, or tetrahydroquinolinyl, where the radical or point of attachment is any atom in the heterocyclyl ringsystem. A heterocyclyl group may be mono-

or bicyclic. The term “heterocyclylalkyl” refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

As used herein, the term “partially unsaturated” refers to a ring moiety that includes at least one double or triple bond between ring atoms but is not aromatic. The term “partially unsaturated” is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

The term “alkylene” refers to a bivalent alkyl group. An “alkylene chain” is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

As used herein, the term “inhibitor” refers to a compound that binds to and inhibits a KDM2b enzyme with measurable affinity and activity. In certain embodiments, an inhibitor has an IC_{50} and/or binding constant of less about 50 μM , less than about 1 μM , less than about 500 nM, less than about 100 nM, or less than about 10 nM.

The terms “measurable affinity” and “measurably inhibit,” as used herein, refer to a measurable reduction in activity of a KDM2b enzyme between: (i) a sample comprising a compound as described herein and such KDM2b enzyme, and (ii) an equivalent sample comprising such KDM2b enzyme, in the absence of said compound.

“Pharmaceutically acceptable salts” include both acid and base addition salts. “Pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, carbonic acid, phosphoric acid and the like, and organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes of organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, gluconic acid, lactic acid, pyruvic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, aspartic acid, ascorbic acid, glutamic acid, anthranilic acid, benzoic acid, cinnamic acid, mandelic acid, embonic acid, phenylacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

“Pharmaceutically acceptable base addition salts” include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly base addition salts are the ammonium,

potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases includes salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, tromethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly organic non-toxic bases are isopropylamine, diethylamine, ethanolamine, tromethamine, dicyclohexylamine, choline, and caffeine.

The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

A "solvate" refers to an association or complex of one or more solvent molecules and a compound or pharmaceutically acceptable salt thereof as described herein. Examples of solvents include water, isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid and ethanolamine. The term "hydrate" refers to the complex where the solvent molecule is water.

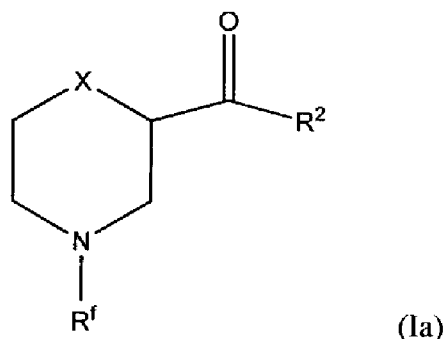
"Therapeutically effective amount" refers to an amount of a compound or pharmaceutically acceptable salt thereof as described herein that (i) treats the particular disease, condition or disorder, (ii) attenuates, ameliorates or eliminates one or more symptoms of the particular disease, condition, or disorder, or (iii) prevents or delays the onset of one or more symptoms of the particular disease, condition or disorder described herein. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. For cancer therapy, efficacy can, for example, be measured by assessing the time to disease progression (TTP) and/or determining the response rate (RR). In the case of immunological disorders, the therapeutic effective amount is an amount sufficient to decrease or alleviate an allergic disorder, the symptoms of an autoimmune and/or inflammatory disease, or the symptoms of an acute inflammatory reaction (e.g. asthma). In some embodiments, a therapeutically effective amount is an amount of a chemical entity

described herein sufficient to significantly decrease the activity or number of drug tolerant or drug tolerant persisting cancer cells.

“Treatment” (and variations such as “treat” or “treating”) refers to clinical intervention in an attempt to alter the natural course of the individual or cell being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include one or more of preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, stabilized (*i.e.*, not worsening) state of disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, prolonging survival as compared to expected survival if not receiving treatment and remission or improved prognosis. In certain embodiments, a compound as described herein is used to delay development of a disease or disorder or to slow the progression of a disease or disorder. Those individuals in need of treatment include those already with the condition or disorder as well as those prone to have the condition or disorder, (for example, through a genetic mutation or aberrant expression of a gene or protein) or those in which the condition or disorder is to be prevented.

Exemplary Values

In one embodiment the compound is a compound of formula (Ia):



or a salt thereof, wherein:

X is CR^gR^h or NR^k ;

each R^f is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, and $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-$

$S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo;

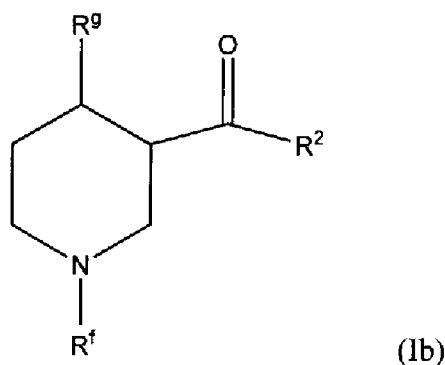
each R^g is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$,
 5 $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$,
 $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$;
 wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle,
 aryl, and heteroaryl is optionally substituted with one or more groups independently selected
 10 from the group consisting of halo, $-NO_2-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$,
 $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-$
 $S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with
 one or more groups independently selected from halo;

each R^h is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl,
 C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, and halo, wherein each
 15 C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and
 heteroaryl is optionally substituted with one or more groups independently selected from the
 group consisting of halo, $-NO_2-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$,
 $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$,
 $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or
 20 more groups independently selected from halo; and

each R^k is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl,
 C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl, wherein each C_{1-}
 6 alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl
 is optionally substituted with one or more groups independently selected from the group
 25 consisting of halo, $-NO_2-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$,
 $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-$
 $C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more
 groups independently selected from halo.

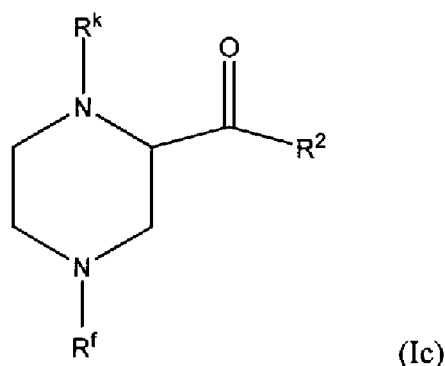
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In one embodiment the compound is a compound of formula (Ib):



or a salt thereof.

In one embodiment the compound is a compound of formula (Ic):

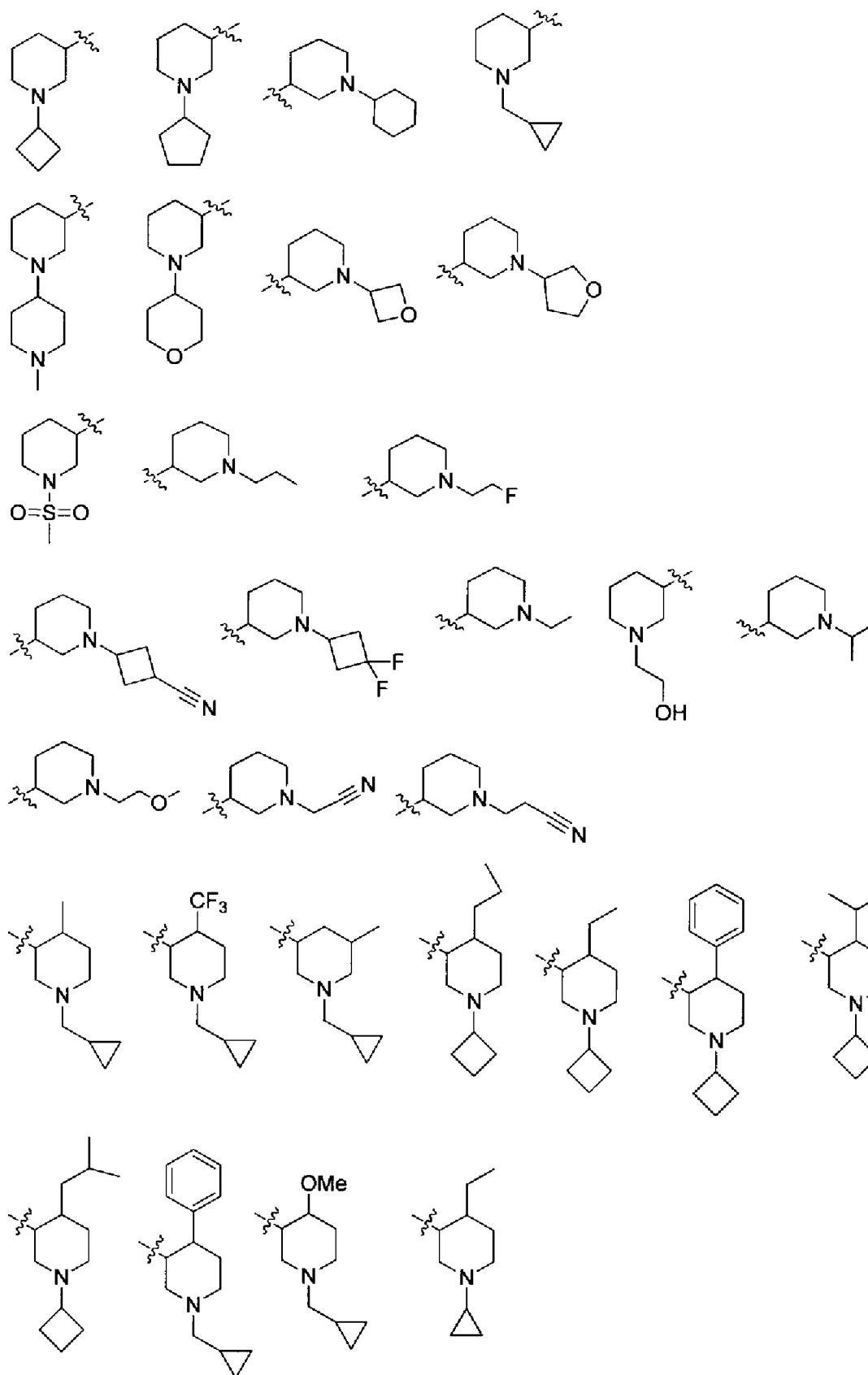


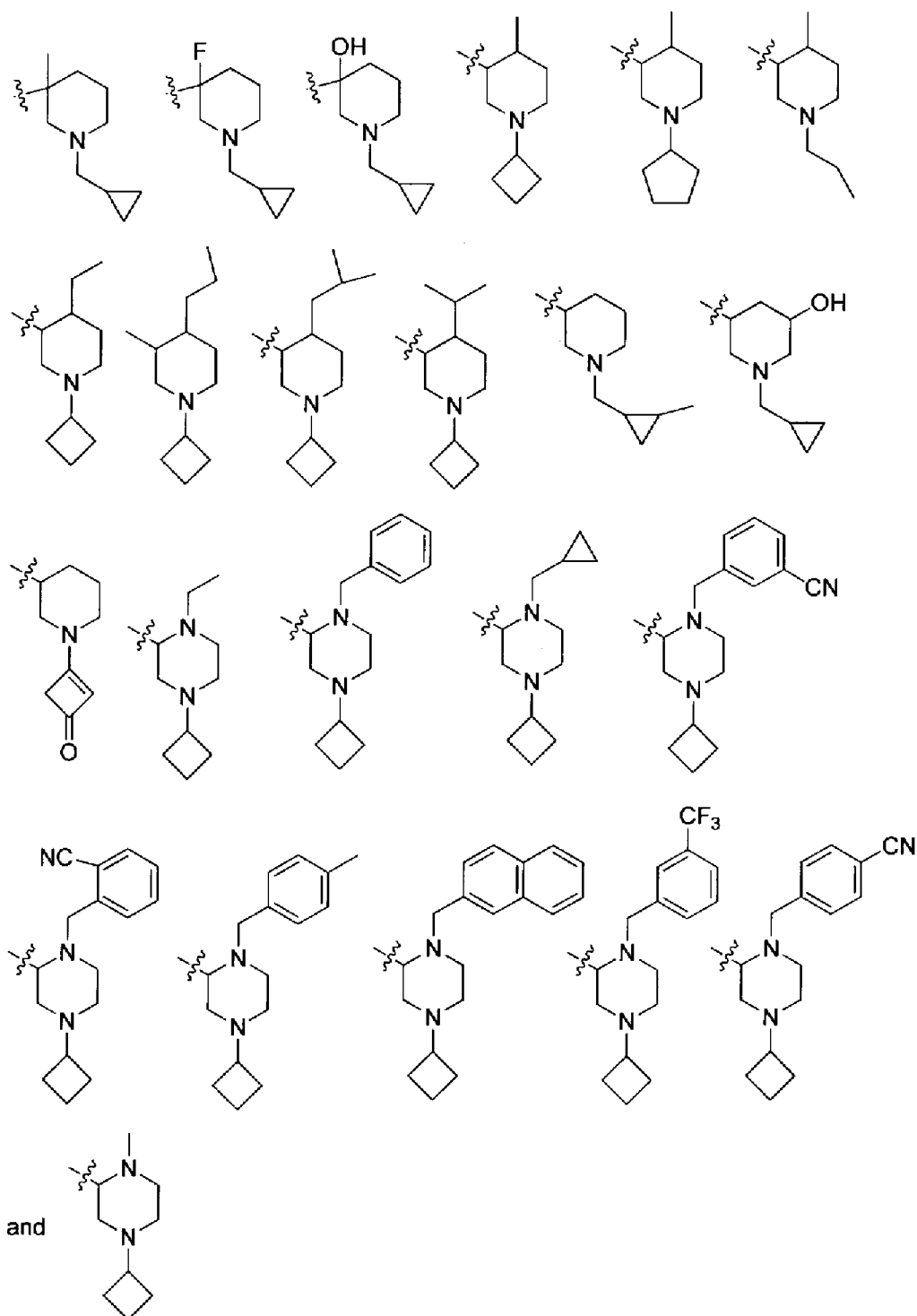
or a salt thereof.

In one embodiment when R^2 is 2-naphthyl or 6-methoxy-2-naphthyl, then R^1 is not optionally substituted piperidin-3-yl.

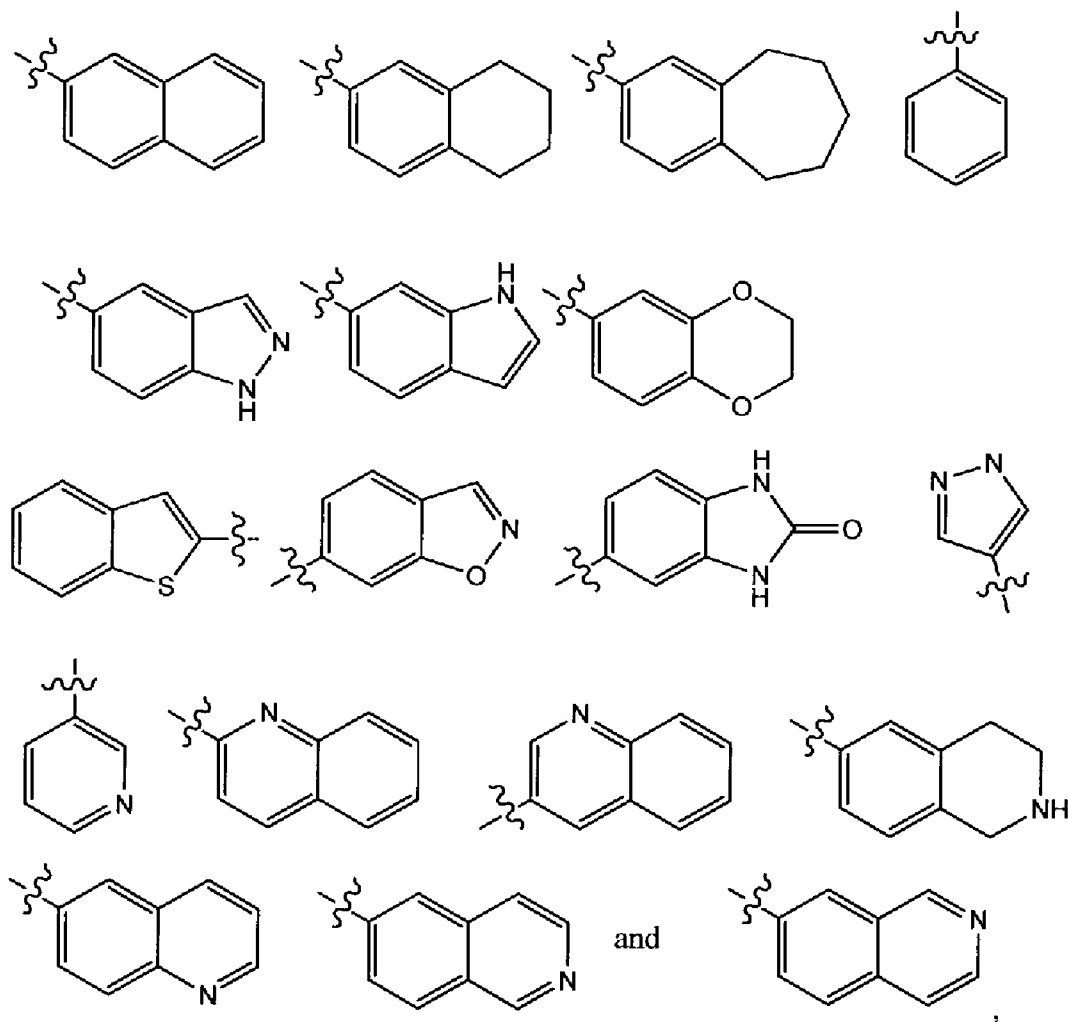
In one embodiment R^2 is a ring selected from the group consisting of naphthyl, tetralinyl, phenyl, benzisoxazolyl, benzo[7]annulenyl, 1,4-benzodioxinyl, benzimidazolyl-2-one, indolyl, indazolyl, thiophenyl, pyridyl, quinolyl, tetrahydroquinolyl, isoquinolyl, tetrahydroisoquinolyl, and pyrazolyl; which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

In one embodiment R^1 is selected from the group consisting of:





In one embodiment R^2 is a ring selected from the group consisting of:



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which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

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In one embodiment R^2 is a naphthyl ring that is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

$C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

In one embodiment R^2 is a naphthyl ring that is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, carbocycle, aryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

In one embodiment R^2 is a phenyl ring that is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

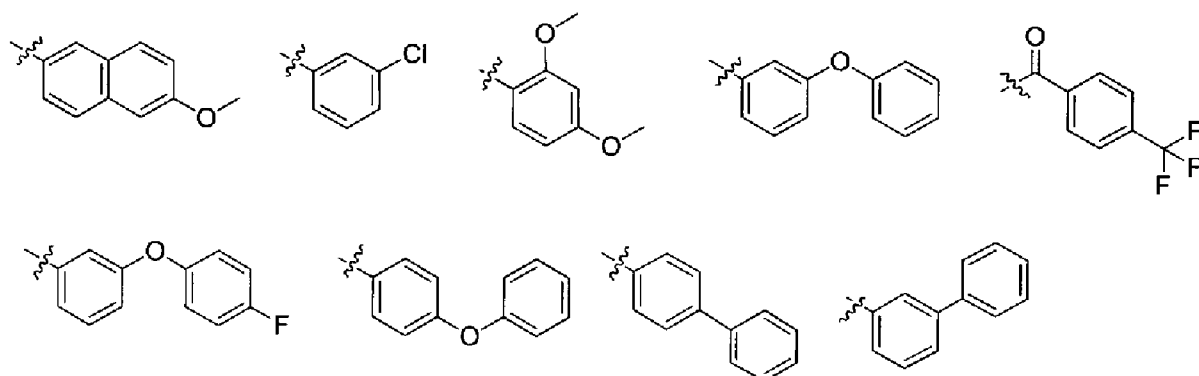
In one embodiment R^2 is a phenyl ring that is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, carbocycle, aryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently

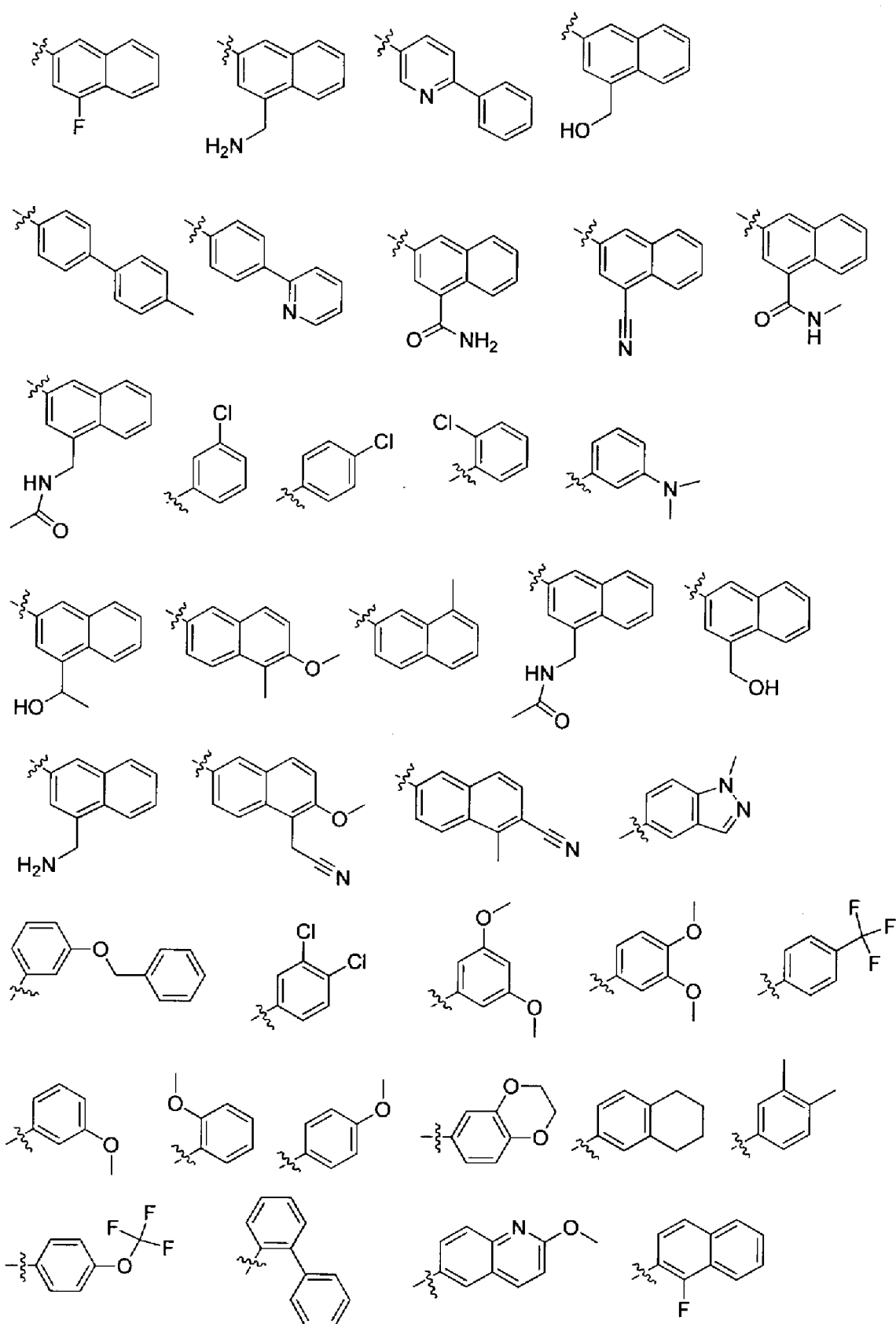
selected from the group consisting of halo, $-\text{NO}_2-\text{N}(\text{R}^d)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^d)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^d)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^d)_2$, $-\text{O}-\text{R}^d$, $-\text{S}-\text{R}^d$, $-\text{O}-\text{C}(\text{O})-\text{R}^d$, $-\text{C}(\text{O})-\text{R}^d$, $-\text{C}(\text{O})-\text{OR}^d$, $-\text{S}(\text{O})-\text{R}^d$, $-\text{S}(\text{O})_2-\text{R}^d$, $-\text{N}(\text{R}^d)-\text{C}(\text{O})-\text{R}^d$, $-\text{N}(\text{R}^d)-\text{S}(\text{O})-\text{R}^d$, $-\text{N}(\text{R}^d)-\text{C}(\text{O})-\text{N}(\text{R}^d)_2$, $-\text{N}(\text{R}^d)-\text{S}(\text{O})_2-\text{R}^d$, and $\text{C}_{1-6}\text{alkyl}$ that is optionally substituted with one or more groups independently selected from halo.

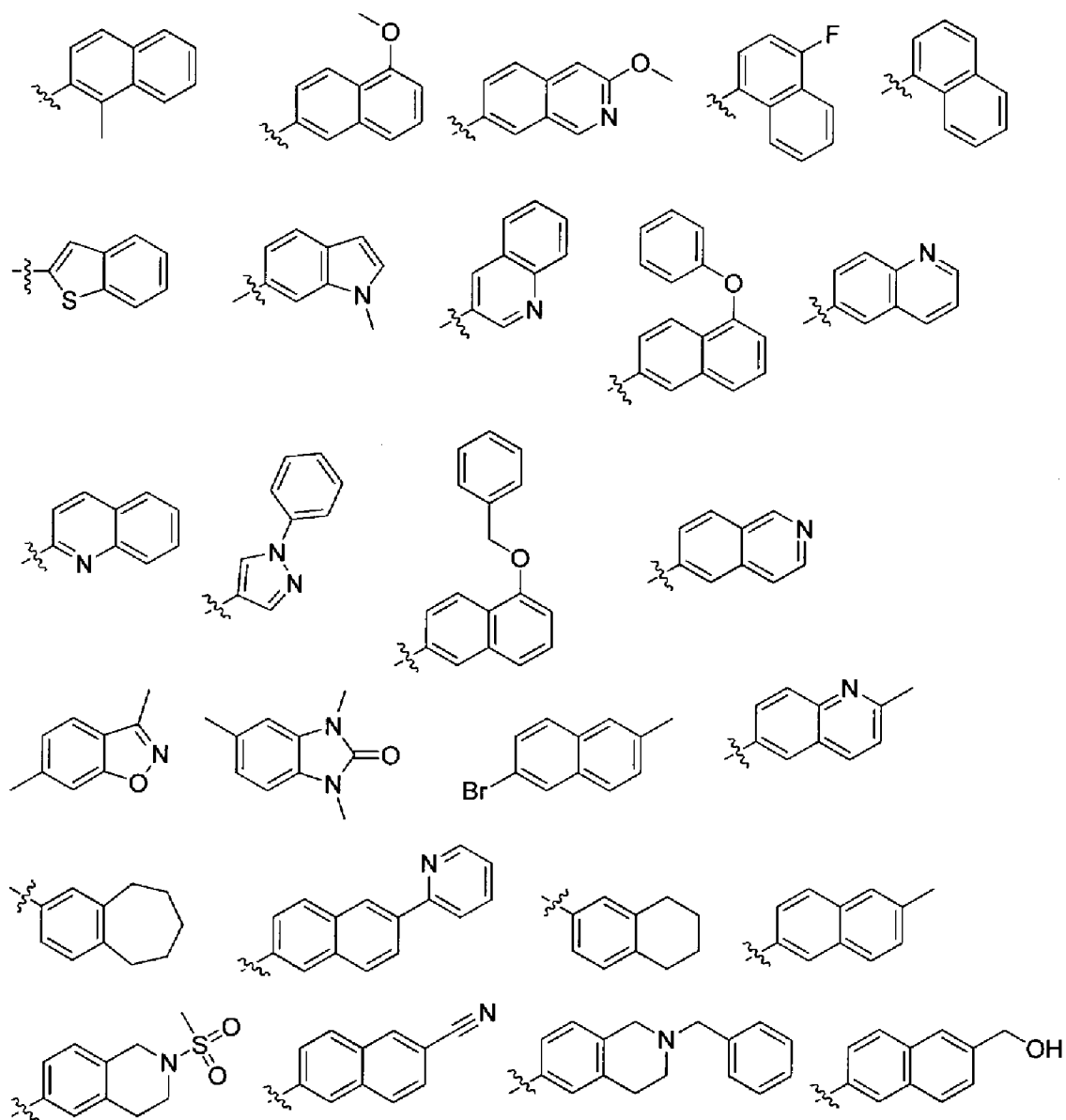
In one embodiment R^2 is a quinolyl or isoquinolyl ring, which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

In one embodiment R^2 is a quinolyl or isoquinolyl ring, which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, carbocycle, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

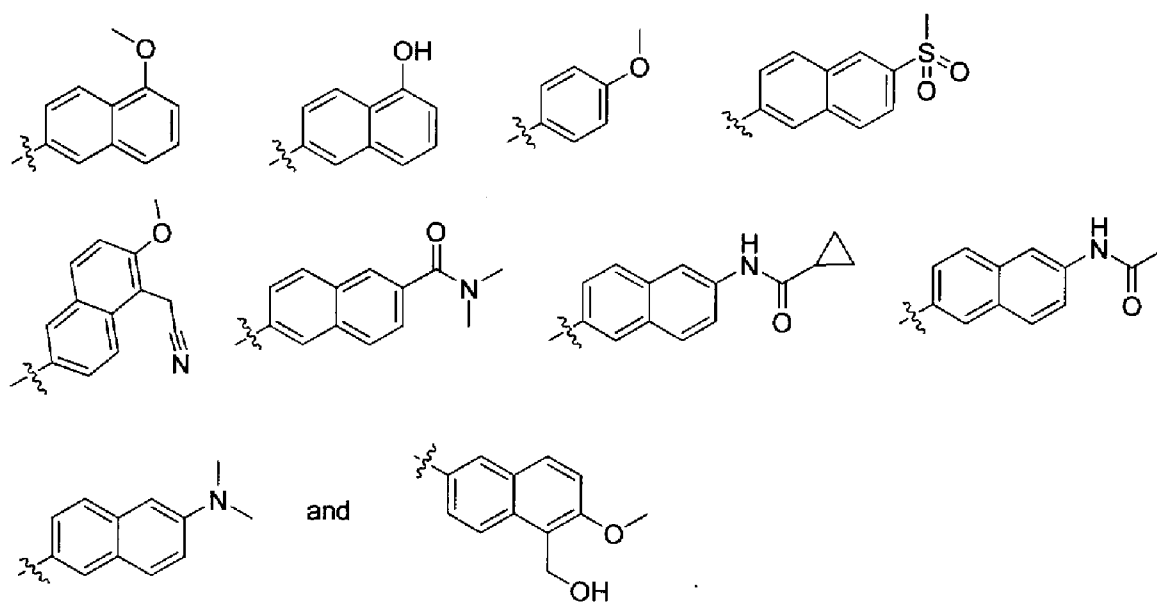
In one embodiment R^2 is selected from the group consisting of:







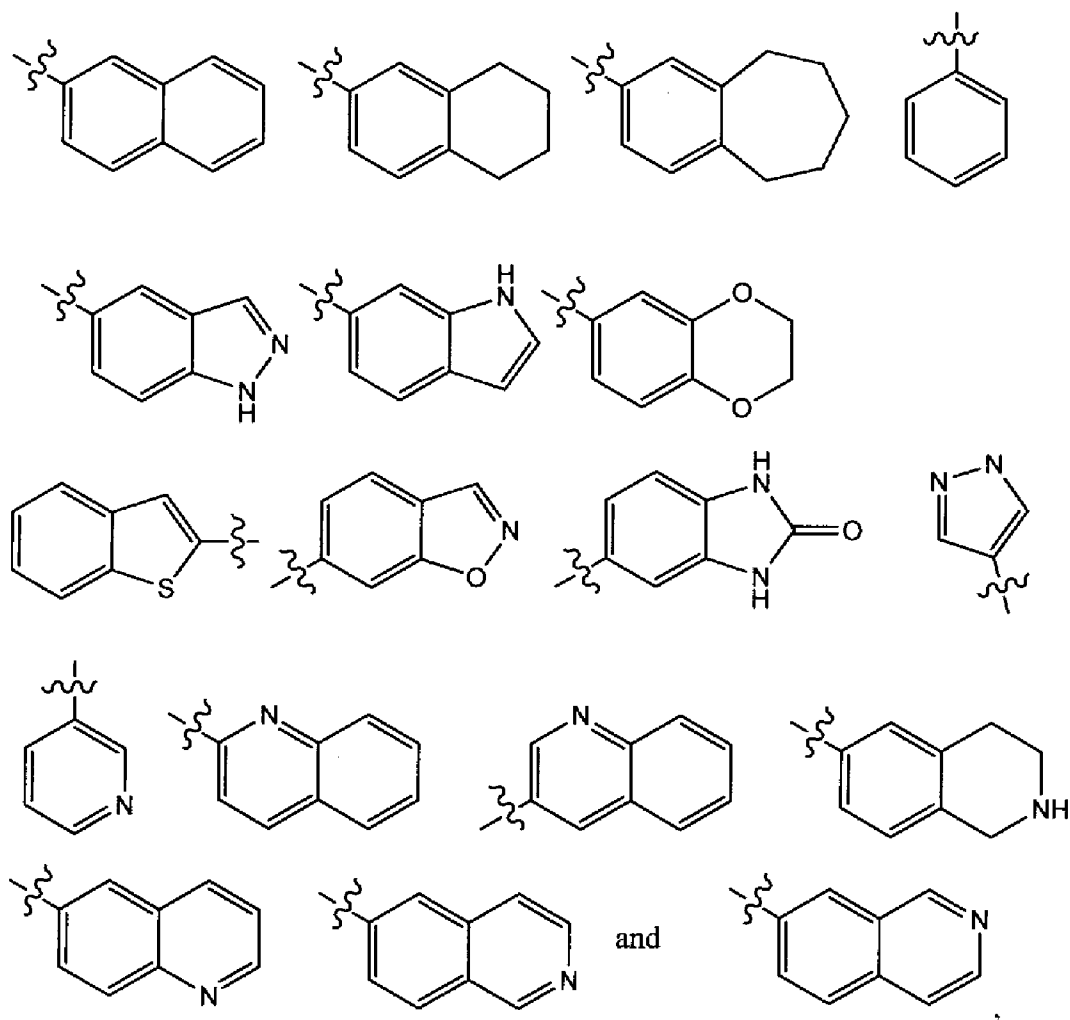
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In one embodiment: R^1 is a carbon-linked piperidine ring that is substituted on the piperidine ring nitrogen with a group R^x and that is optionally further substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl,

- 5 C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected
- 10 from the group consisting of halo, $-NO_2-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo; and

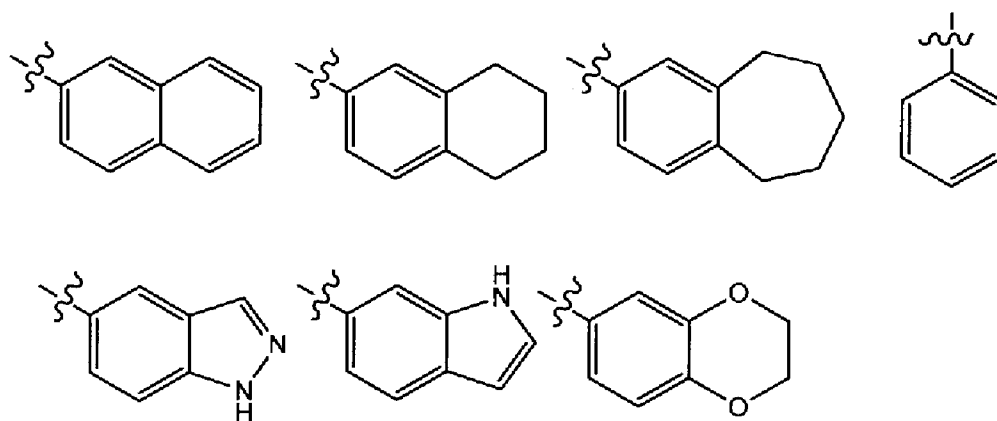
R^2 is a ring selected from the group consisting of:

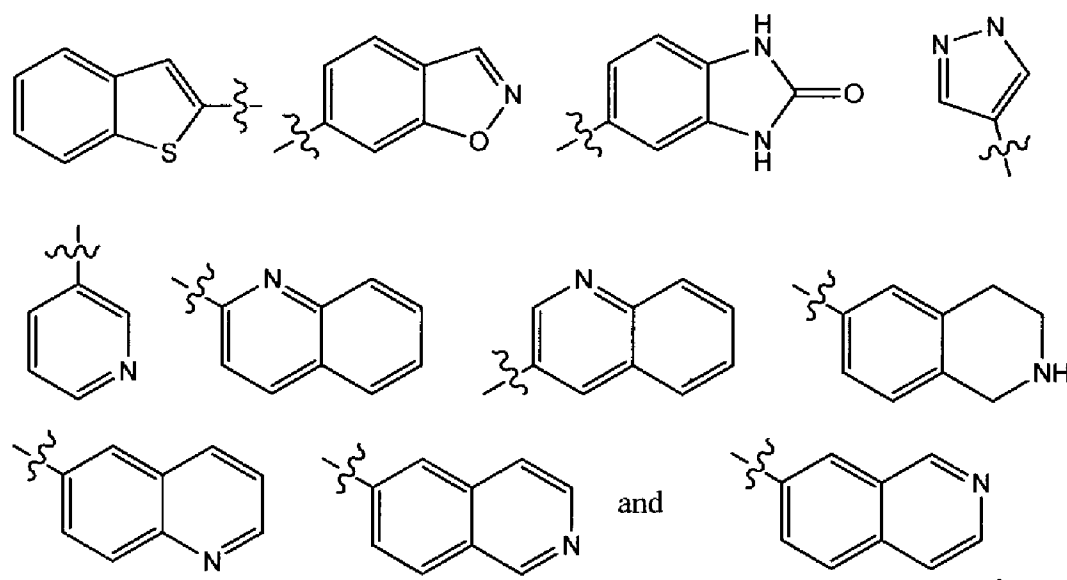


which ring is optionally substituted with one or more groups independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, -NO₂, -N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, and -N(R^d)-S(O)₂-R^d; wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -NO₂, -N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, -N(R^d)-S(O)₂-R^d, and C₁₋₆alkyl that is optionally substituted with one or more groups independently selected from halo.

In one embodiment: R¹ is a carbon-linked piperazine ring that is substituted with one or more groups independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, -NO₂, -N(R^b)₂, -CN, -C(O)-N(R^b)₂, -S(O)-N(R^b)₂, -S(O)₂-N(R^b)₂, -O-R^b, -S-R^b, -O-C(O)-R^b, -C(O)-R^b, -C(O)-OR^b, -S(O)-R^b, -S(O)₂-R^b, -N(R^b)-C(O)-R^b, -N(R^b)-S(O)-R^b, -N(R^b)-C(O)-N(R^b)₂, and -N(R^b)-S(O)₂-R^b; wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -NO₂, -N(R^b)₂, -CN, -C(O)-N(R^b)₂, -S(O)-N(R^b)₂, -S(O)₂-N(R^b)₂, -O-R^b, -S-R^b, -O-C(O)-R^b, -C(O)-R^b, -C(O)-OR^b, -S(O)-R^b, -S(O)₂-R^b, -N(R^b)-C(O)-R^b, -N(R^b)-S(O)-R^b, -N(R^b)-C(O)-N(R^b)₂, -N(R^b)-S(O)₂-R^b, and C₁₋₆alkyl that is optionally substituted with one or more groups independently selected from halo; and

R² is a ring selected from the group consisting of:



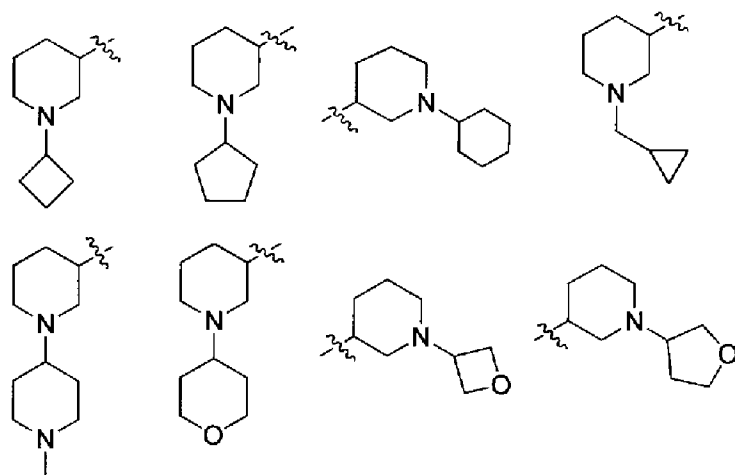


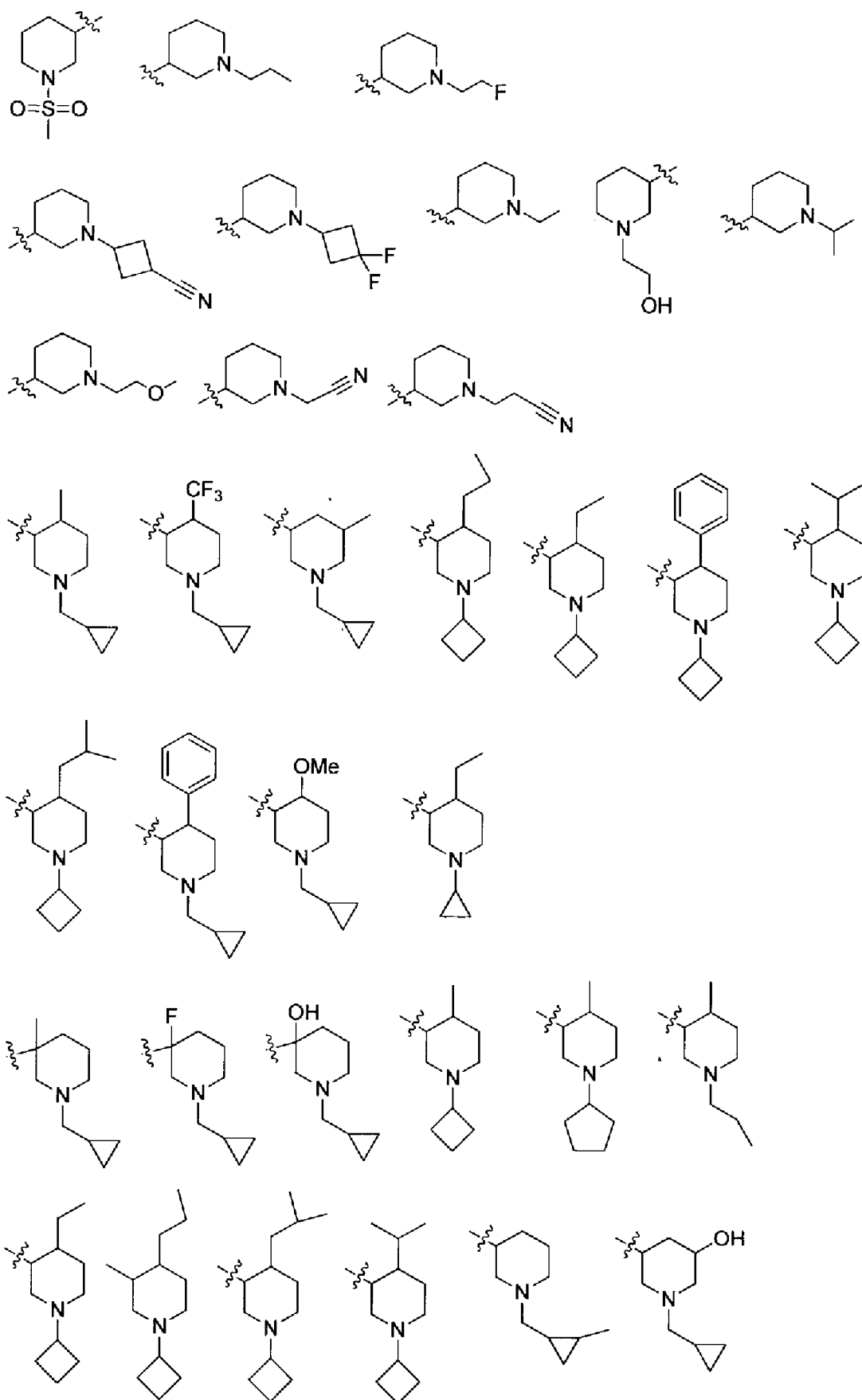
which ring is optionally substituted with one or more groups independently selected from the

- 5 group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently
- 10 selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

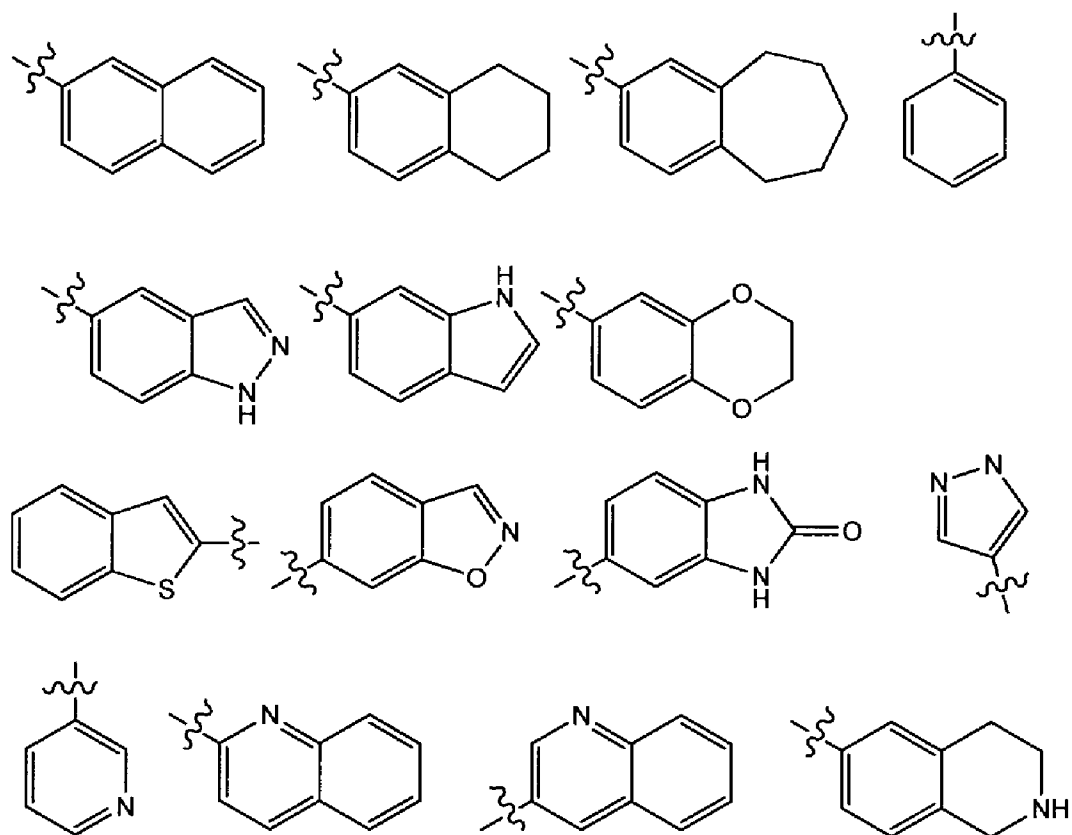
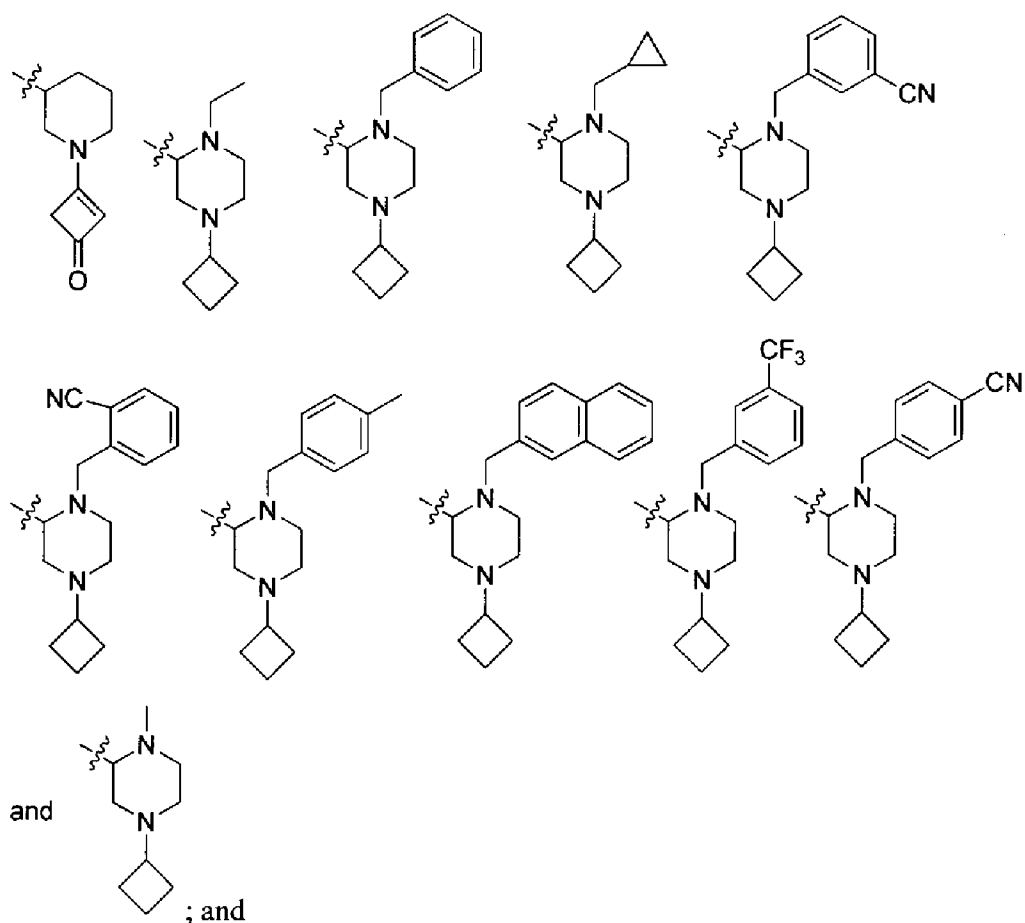
In one embodiment: R^1 is selected from the group consisting of:

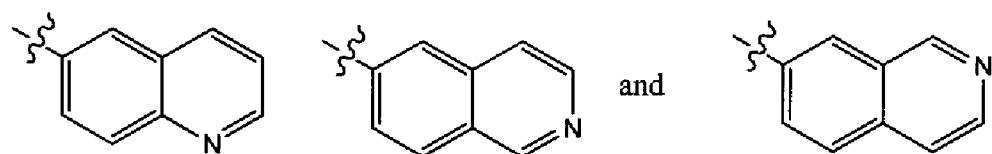
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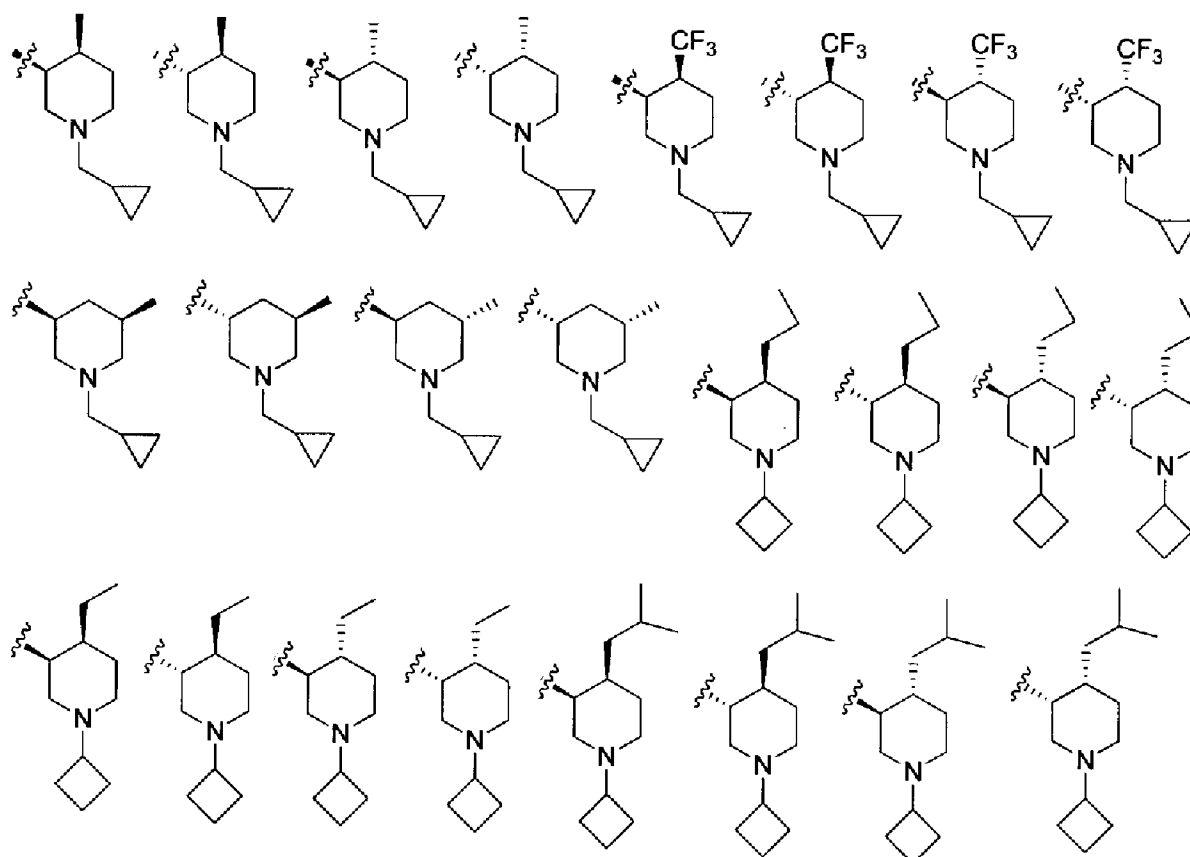
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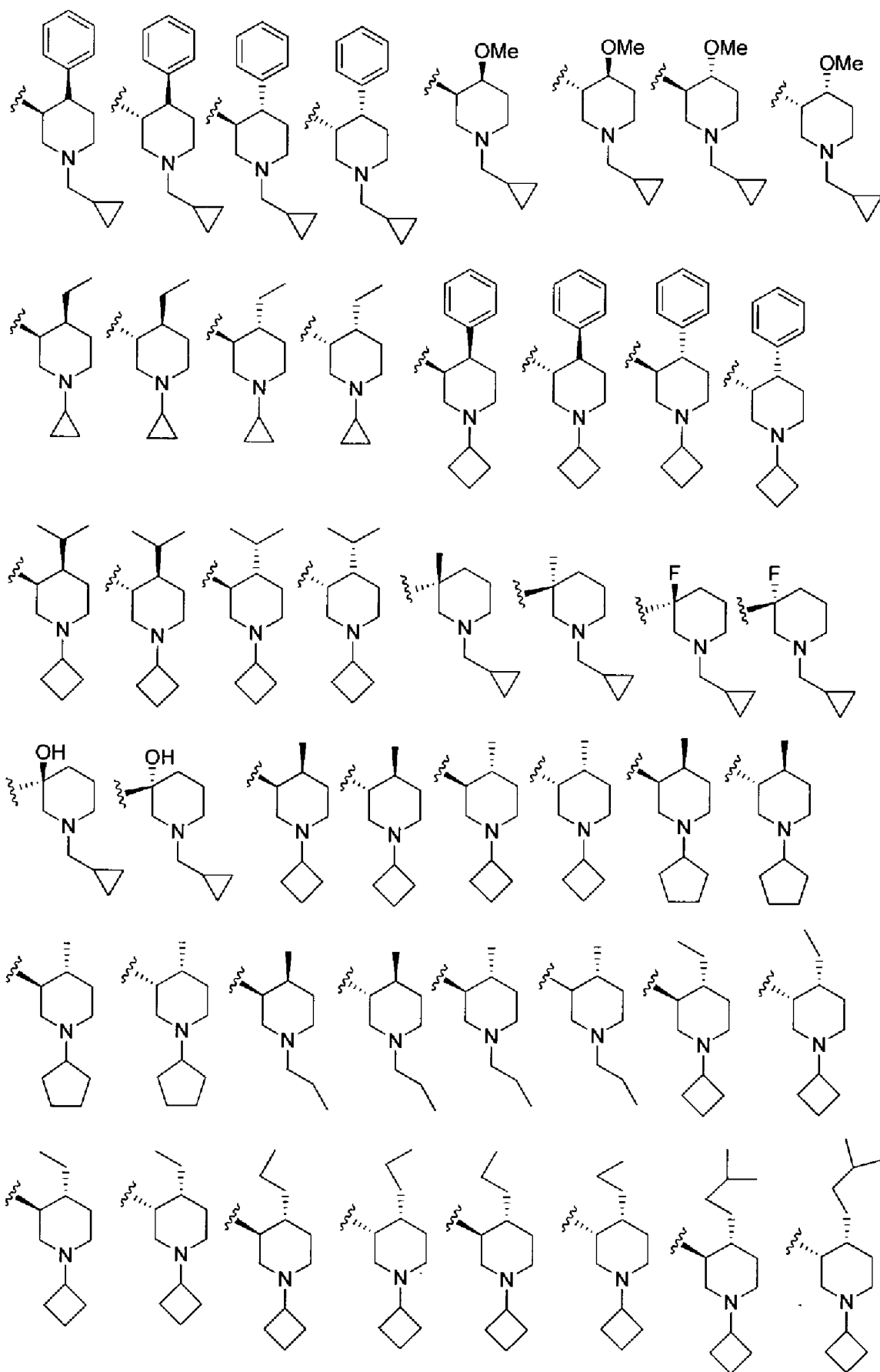


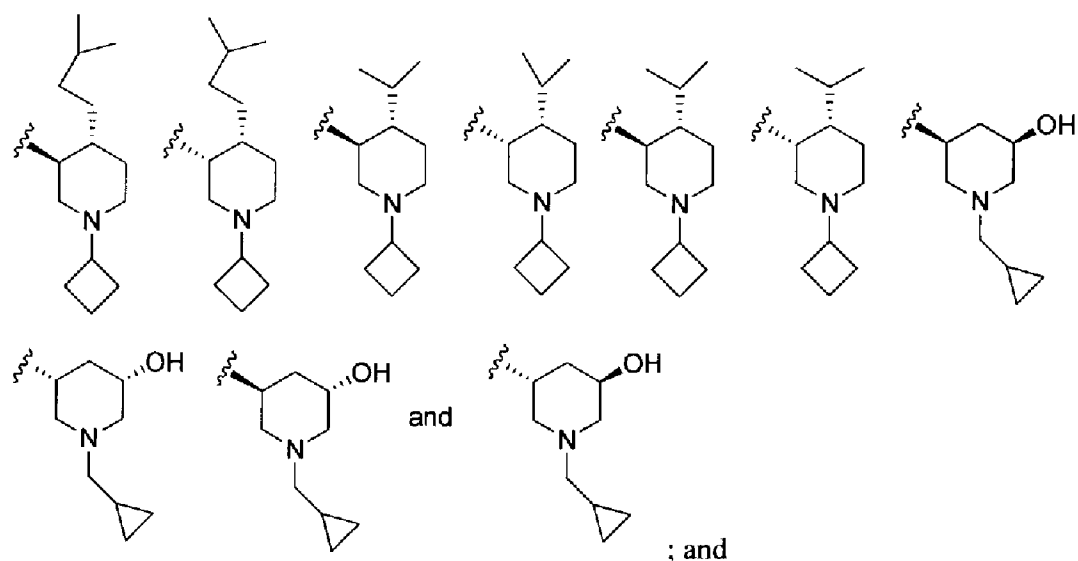


which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

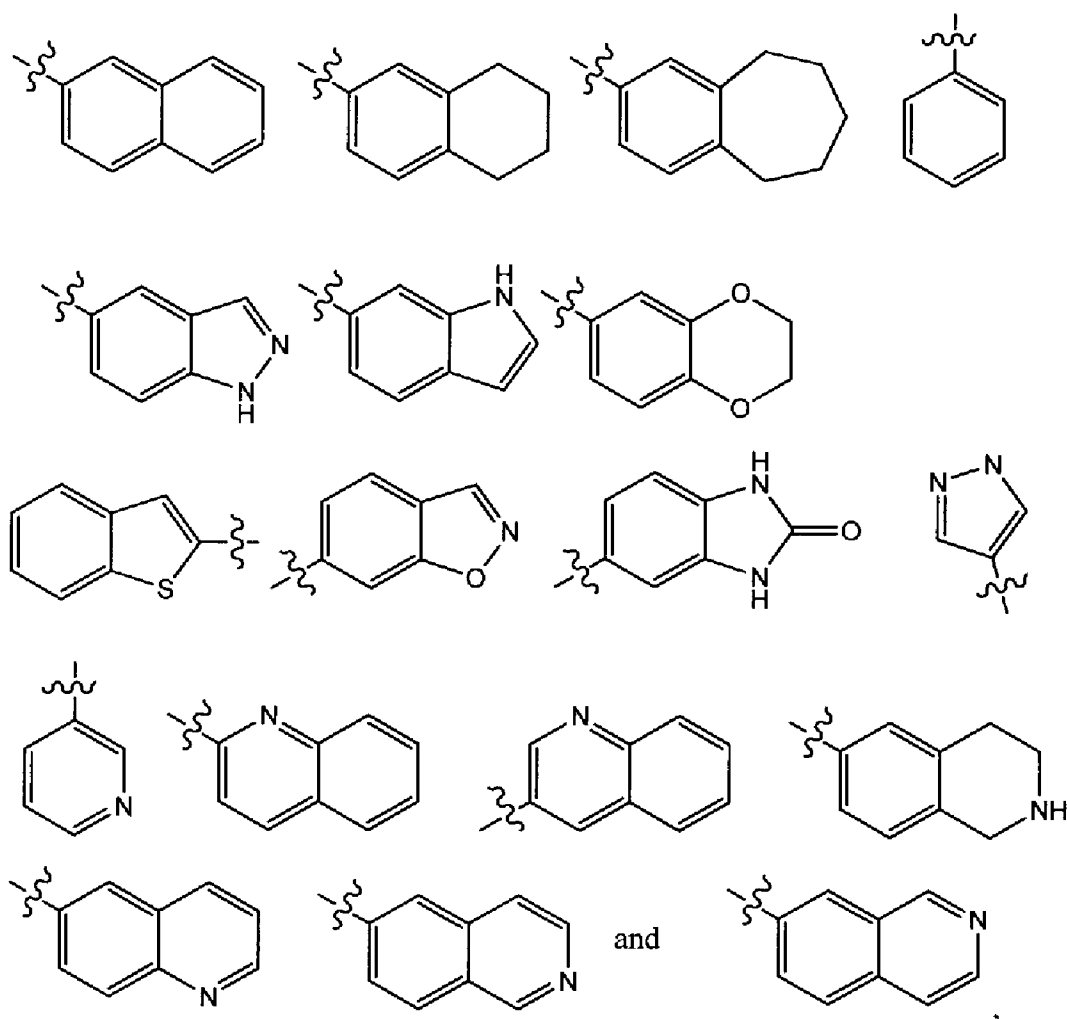
In one embodiment: R^1 is selected from the group consisting of:







R^2 is a ring selected from the group consisting of:

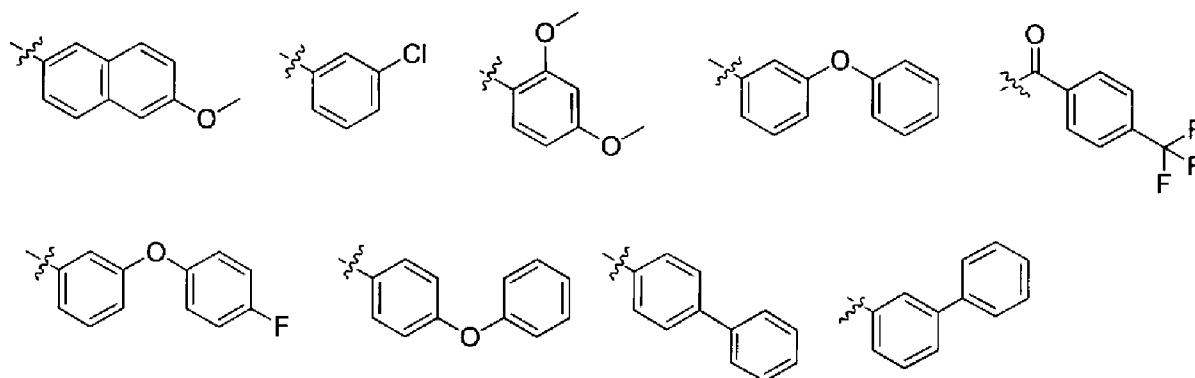


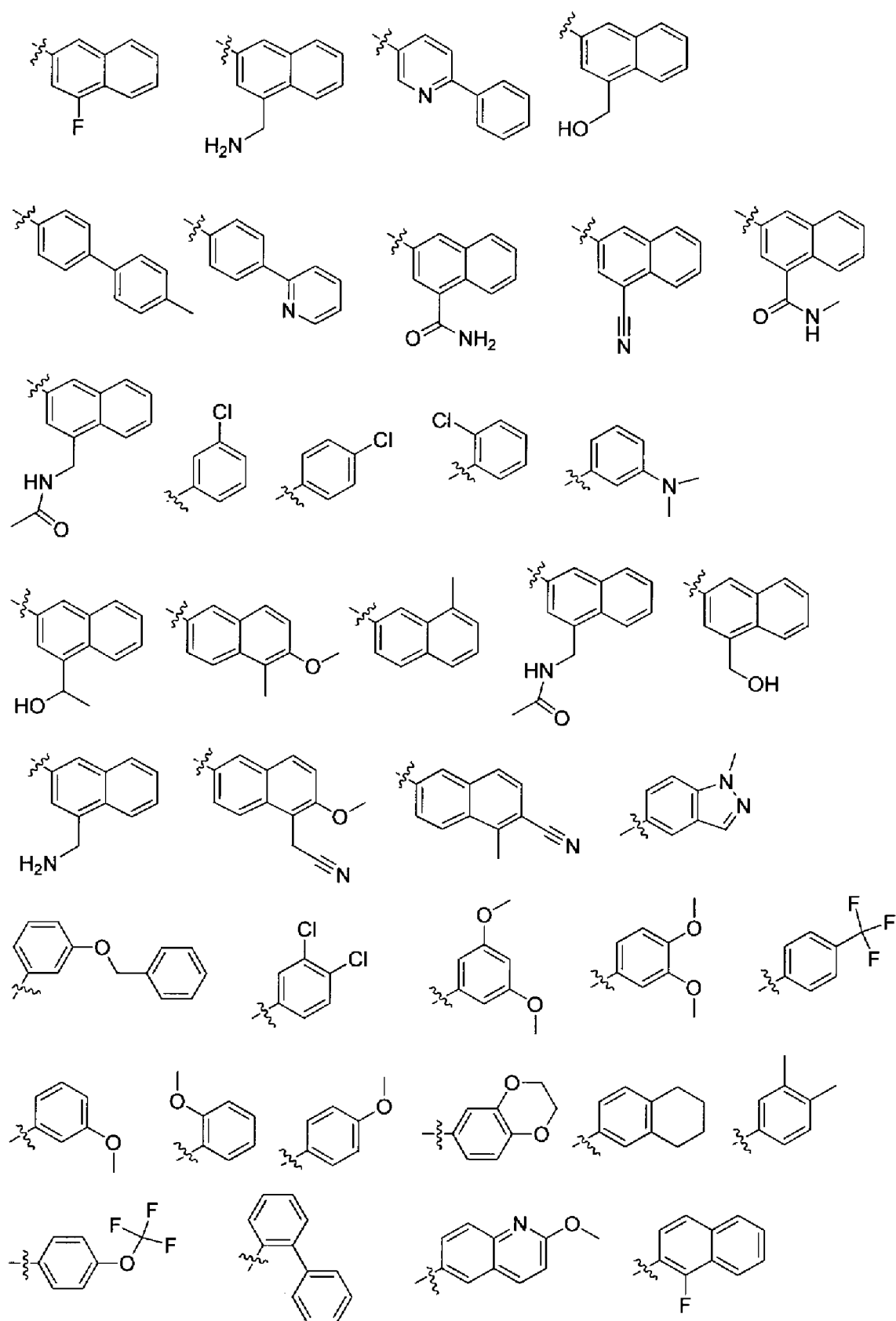
which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-$

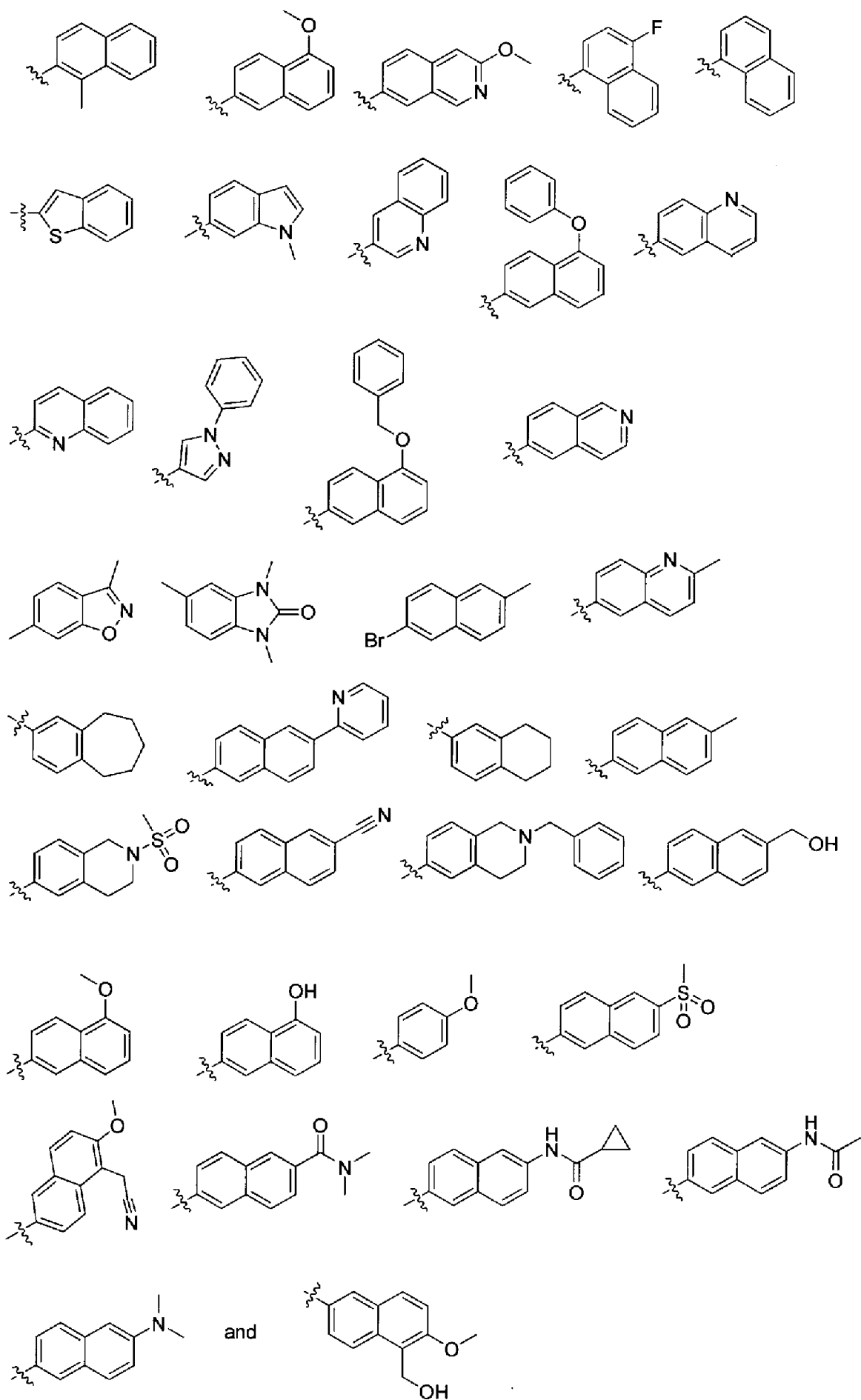
R^d , $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

In one embodiment: R^1 is a carbon-linked piperidine ring that is substituted on the piperidine ring nitrogen with a group R^x and that is optionally further substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo; and

R^2 is selected from the group consisting of:

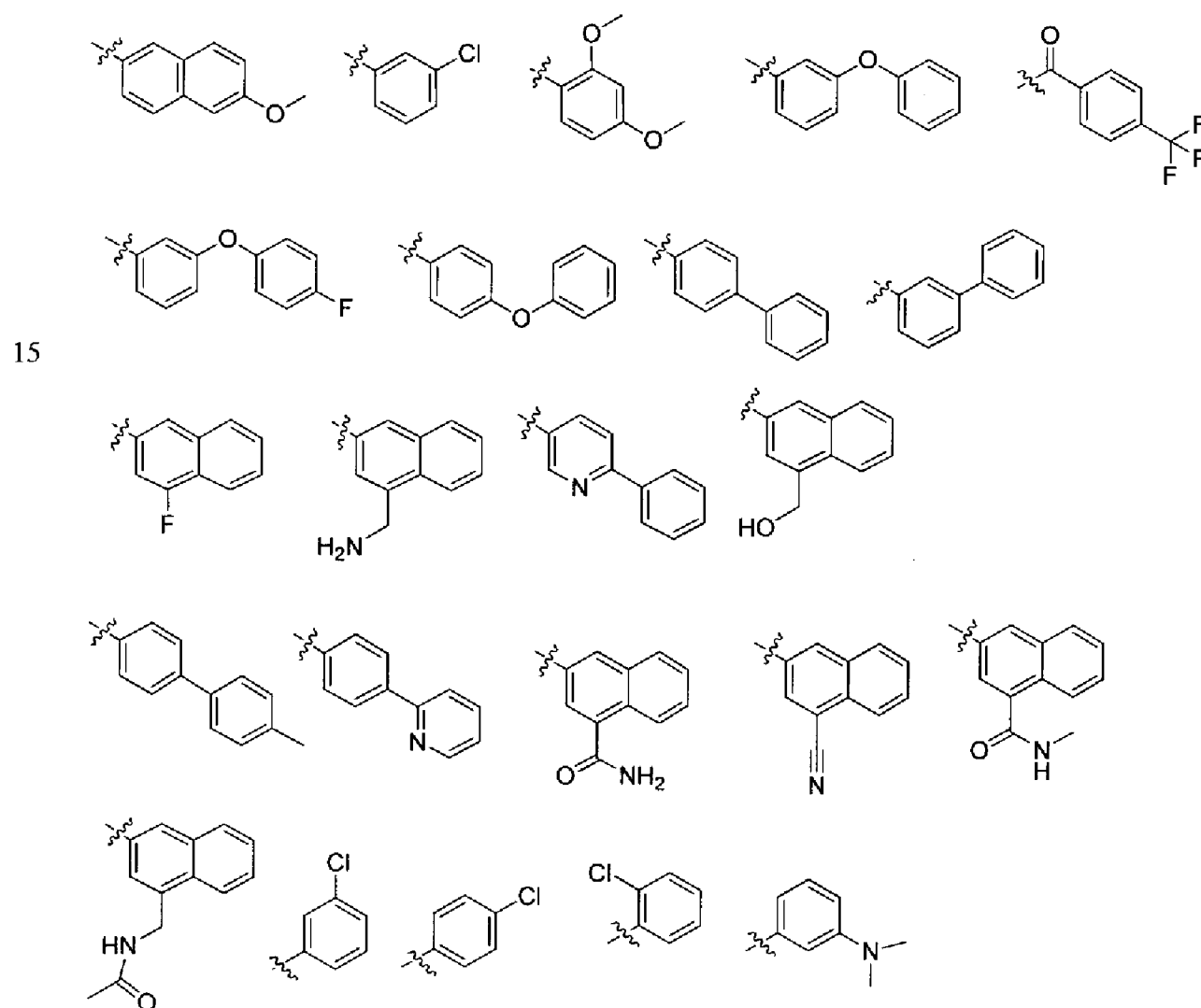


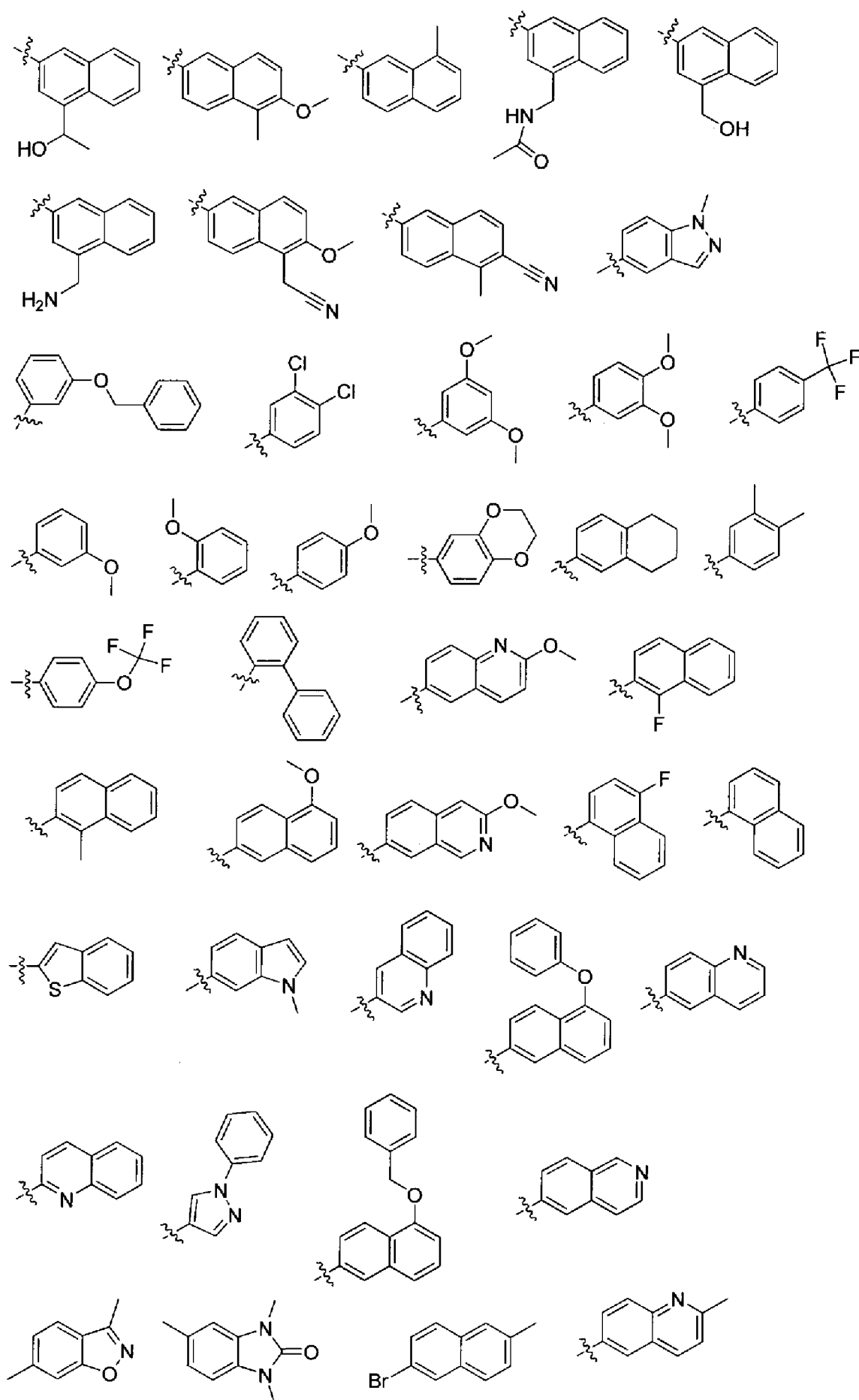


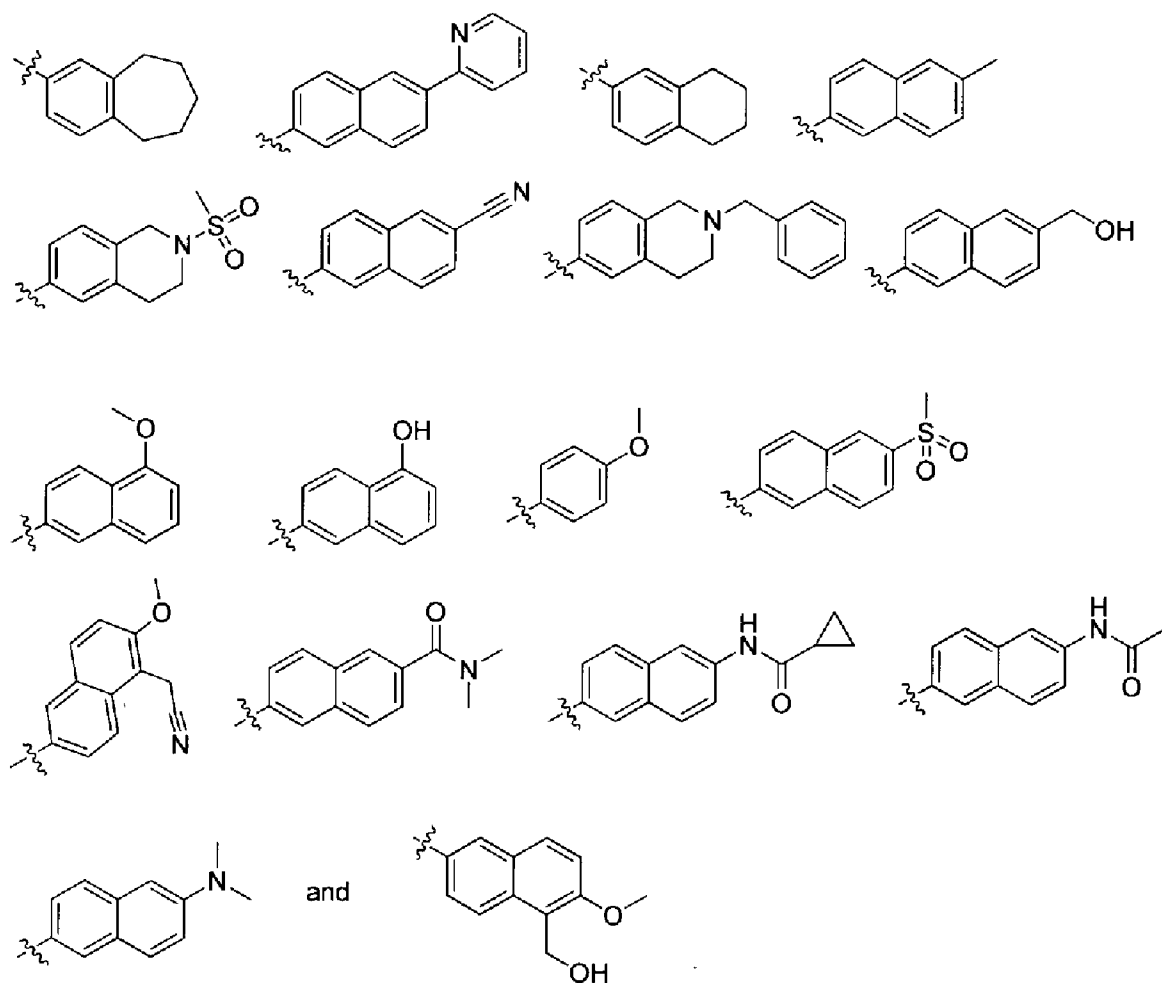


In one embodiment: R^1 is a carbon-linked piperazine ring that is substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo; and

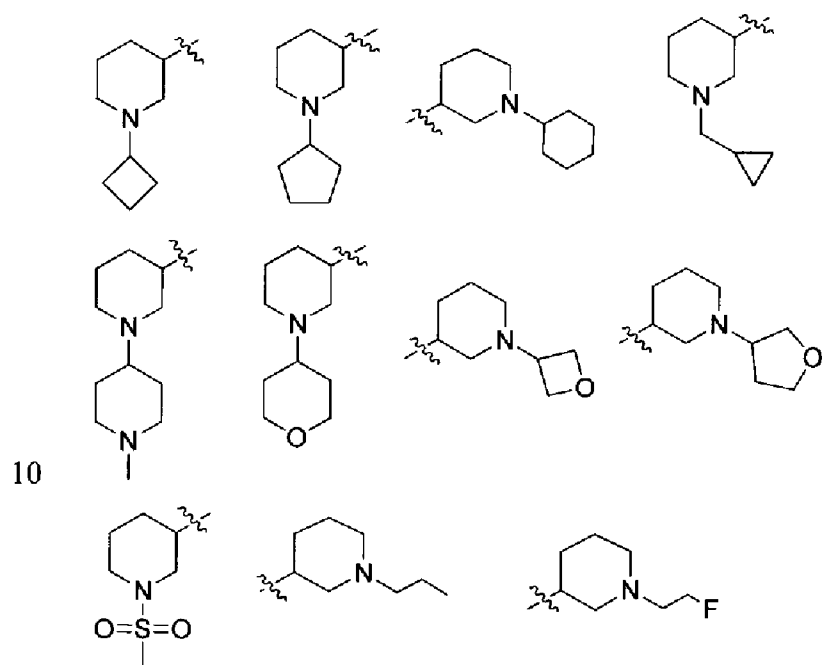
R^2 is selected from the group consisting of:

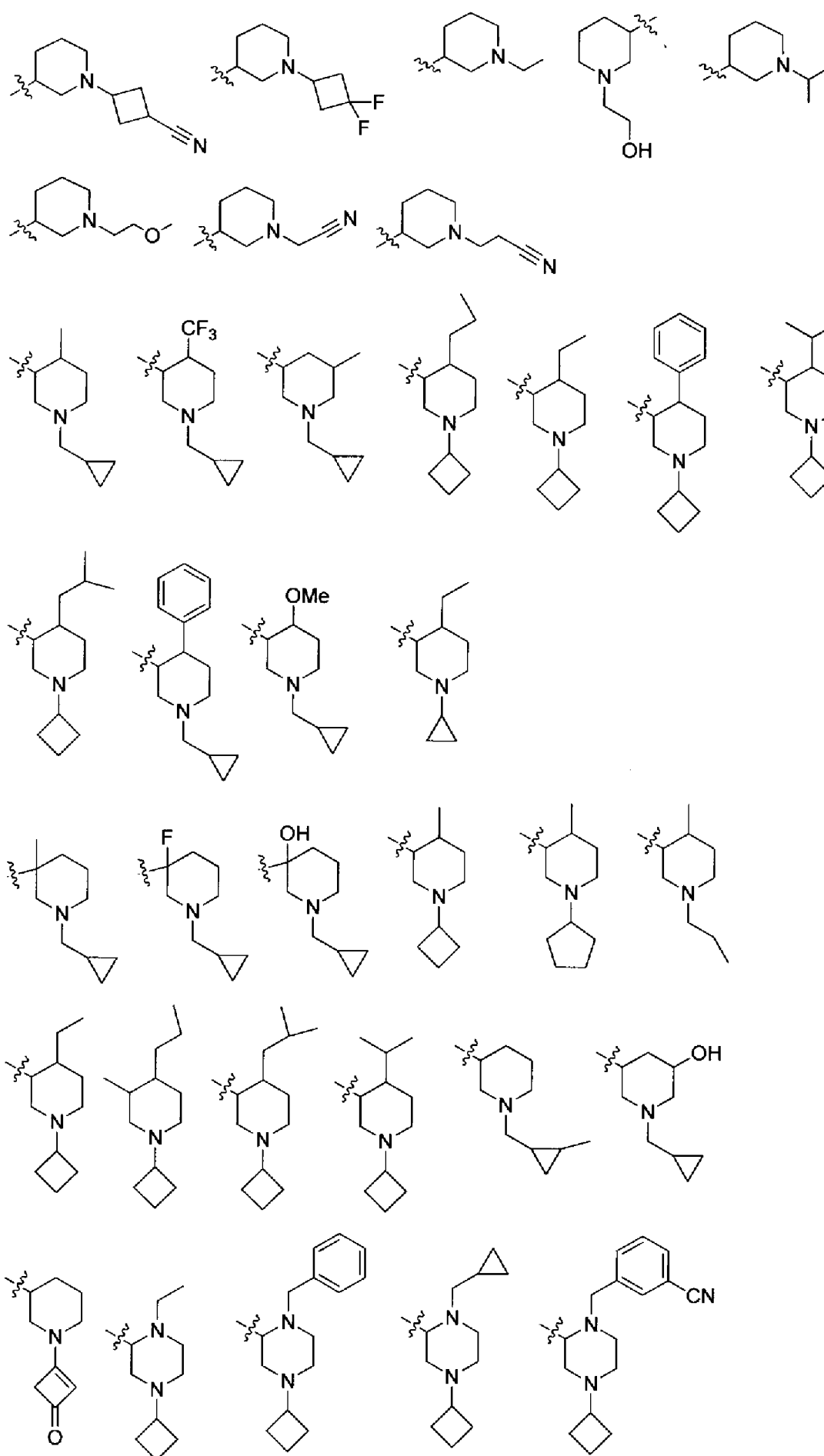


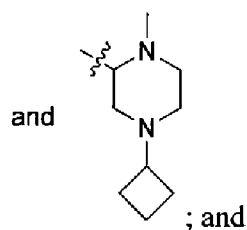
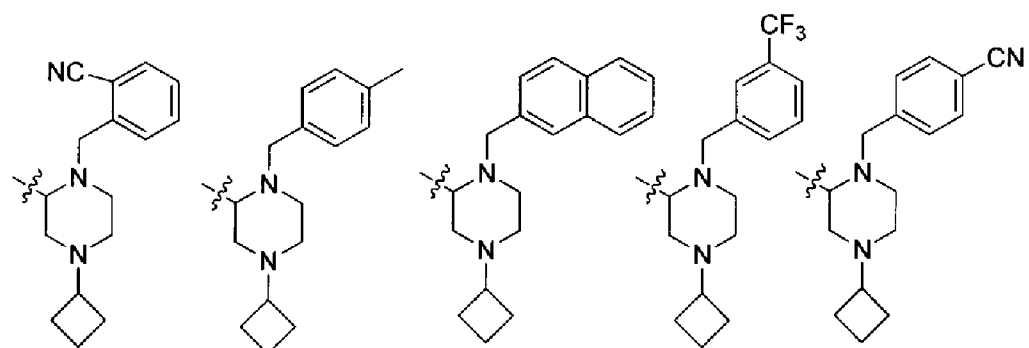




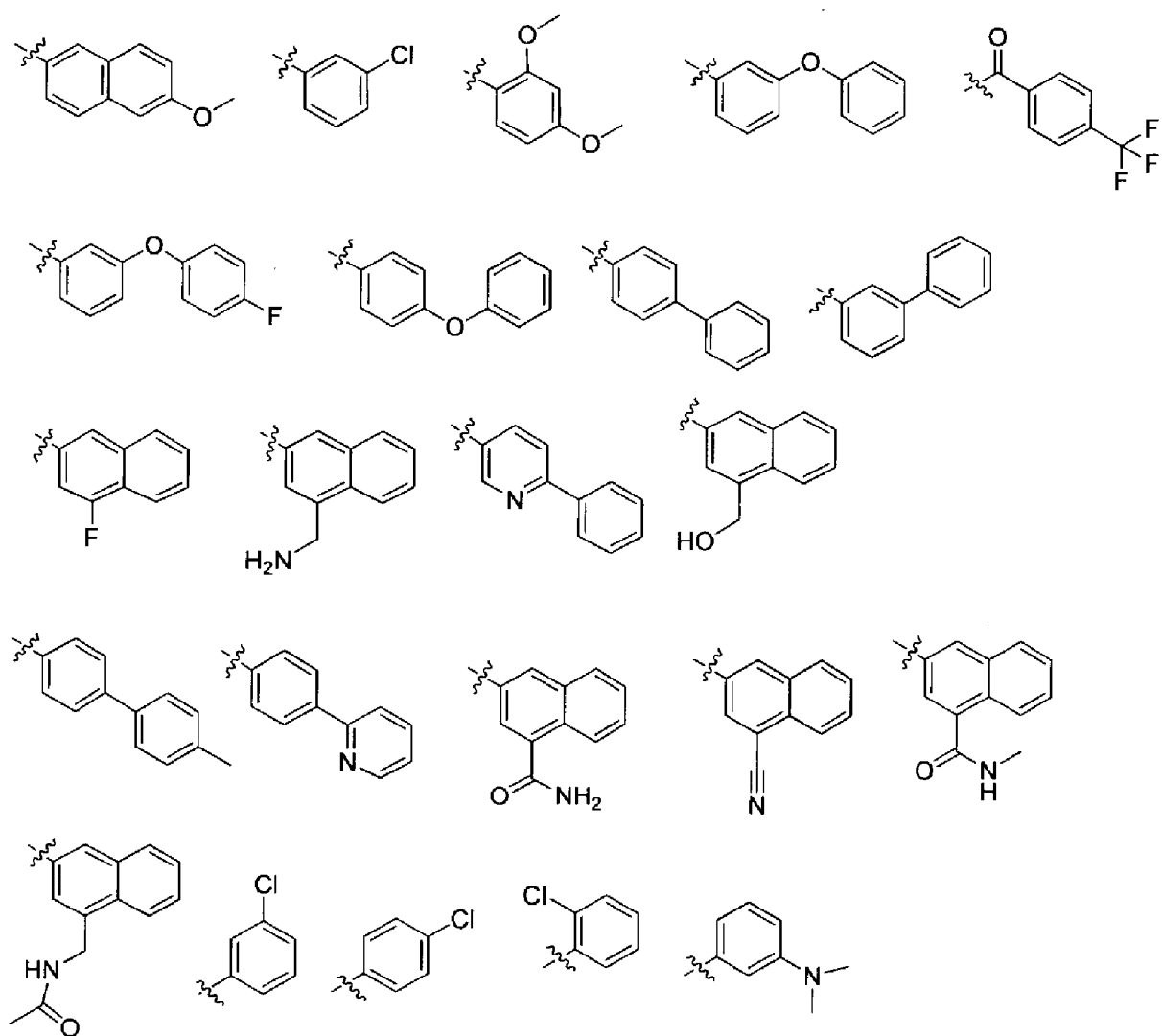
In one embodiment: R^1 is selected from the group consisting of:

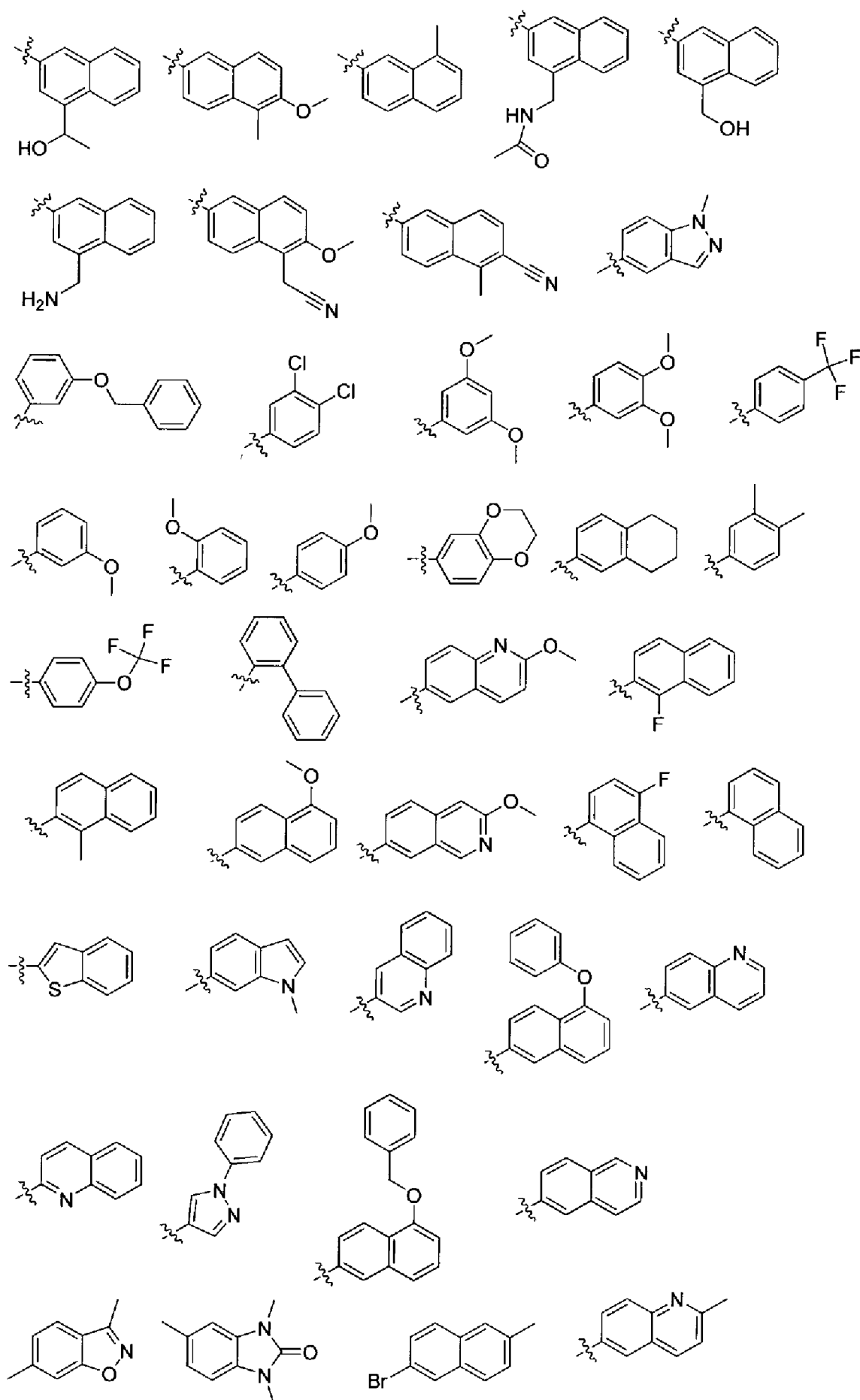


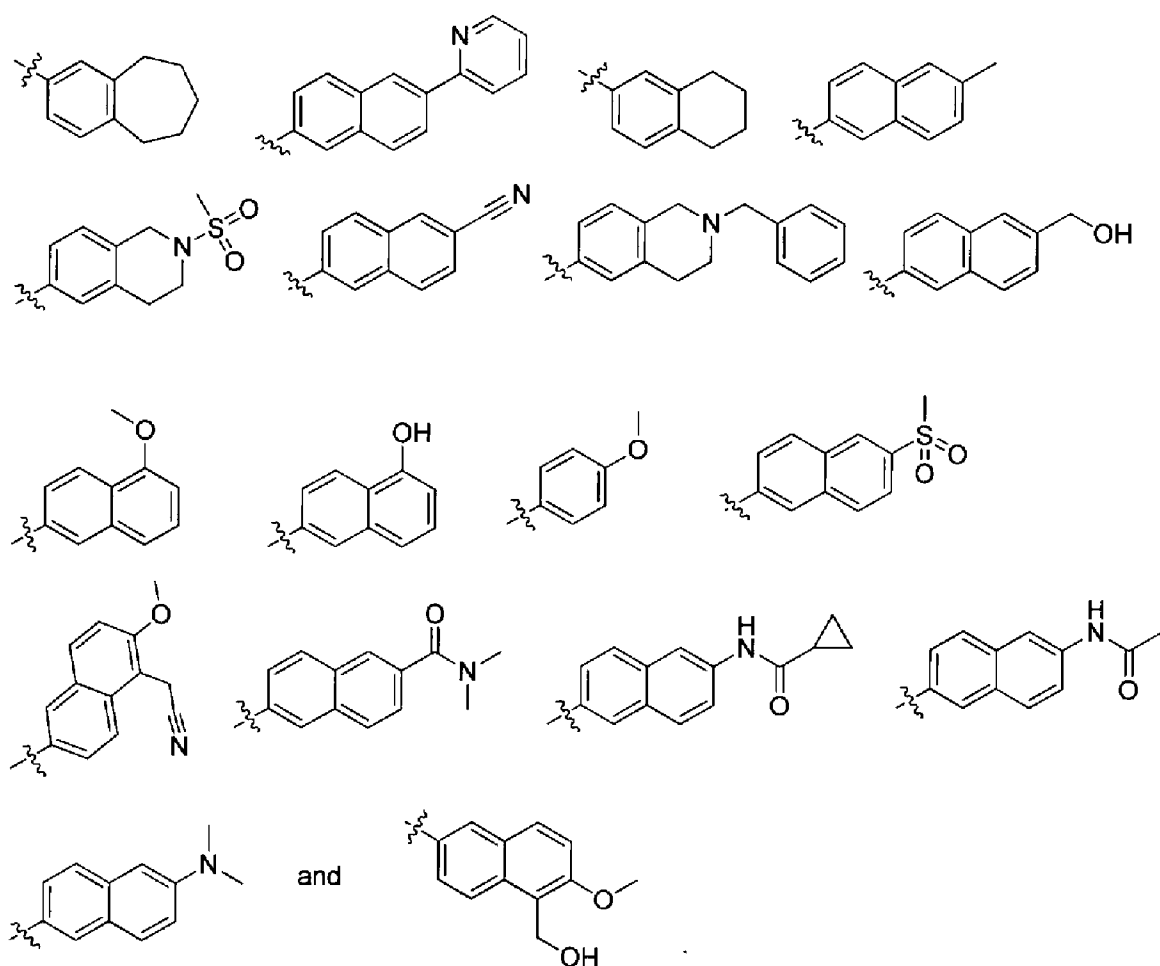




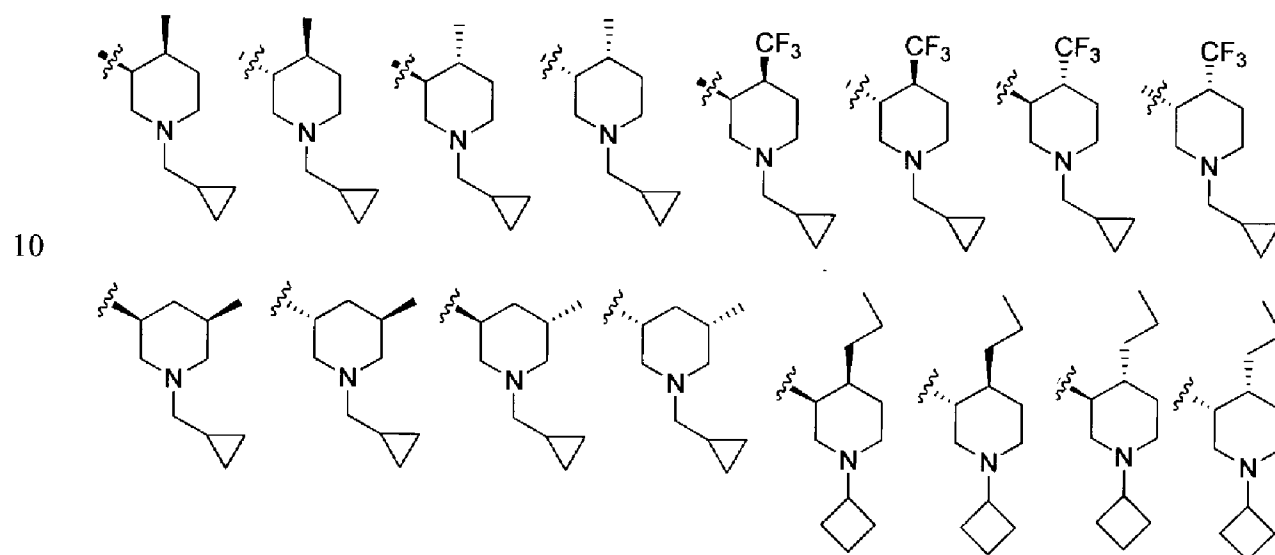
R^2 is selected from the group consisting of:

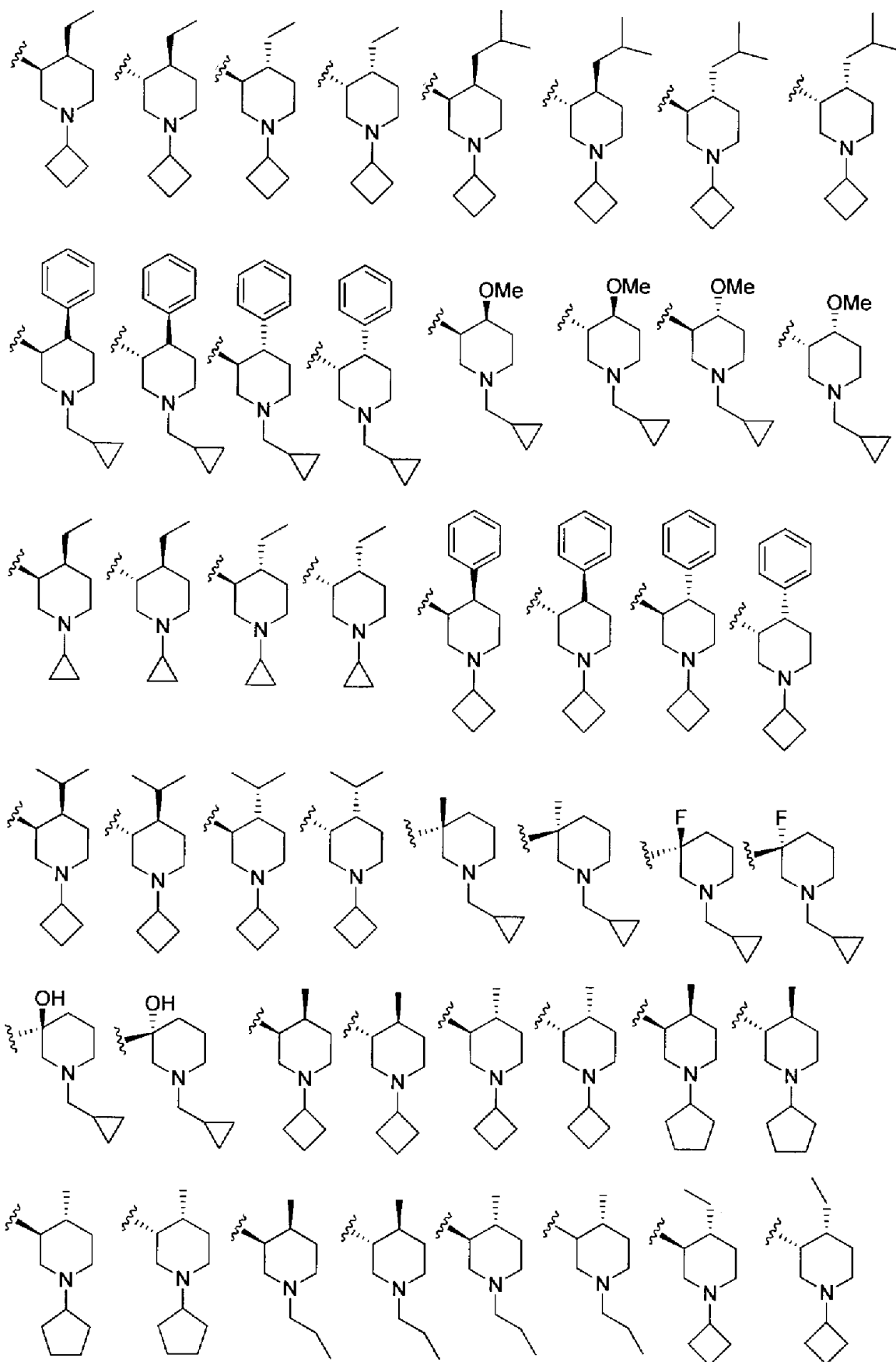


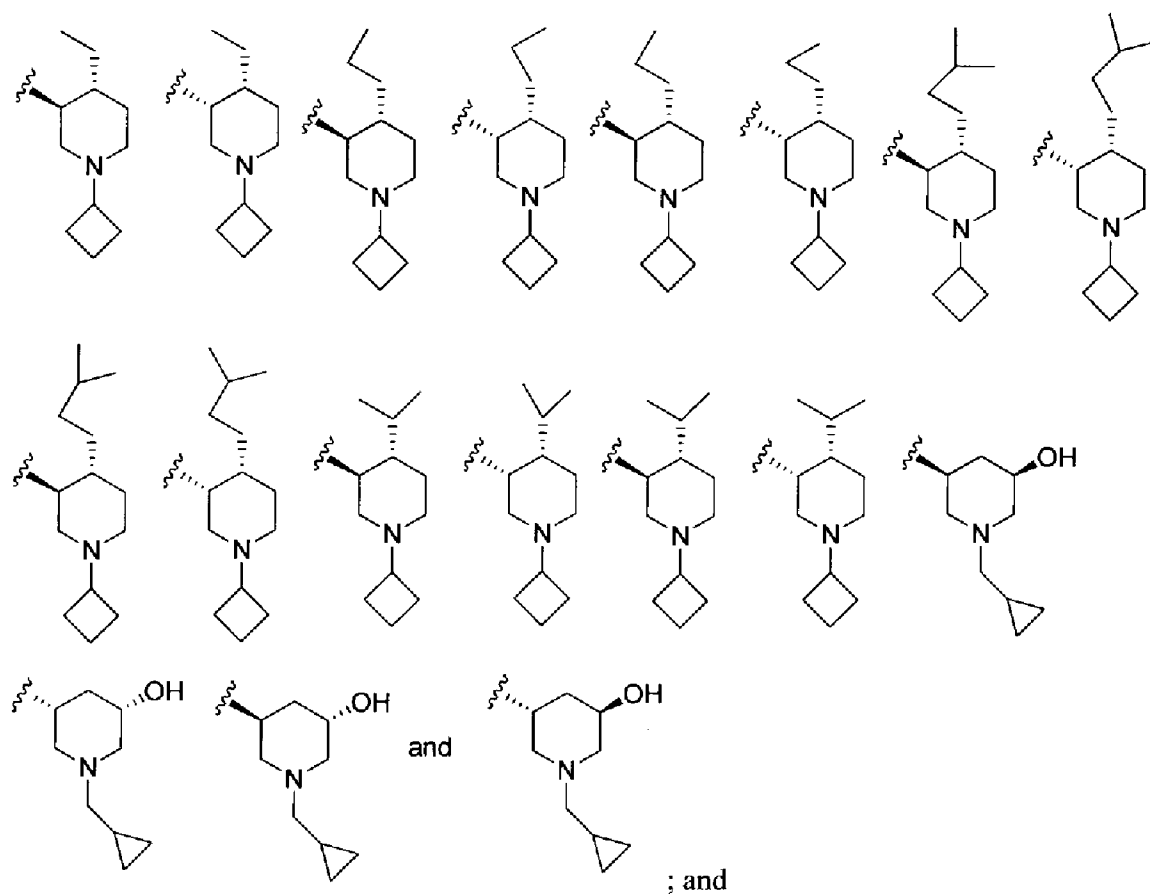




In one embodiment: R^1 is selected from the group consisting of:

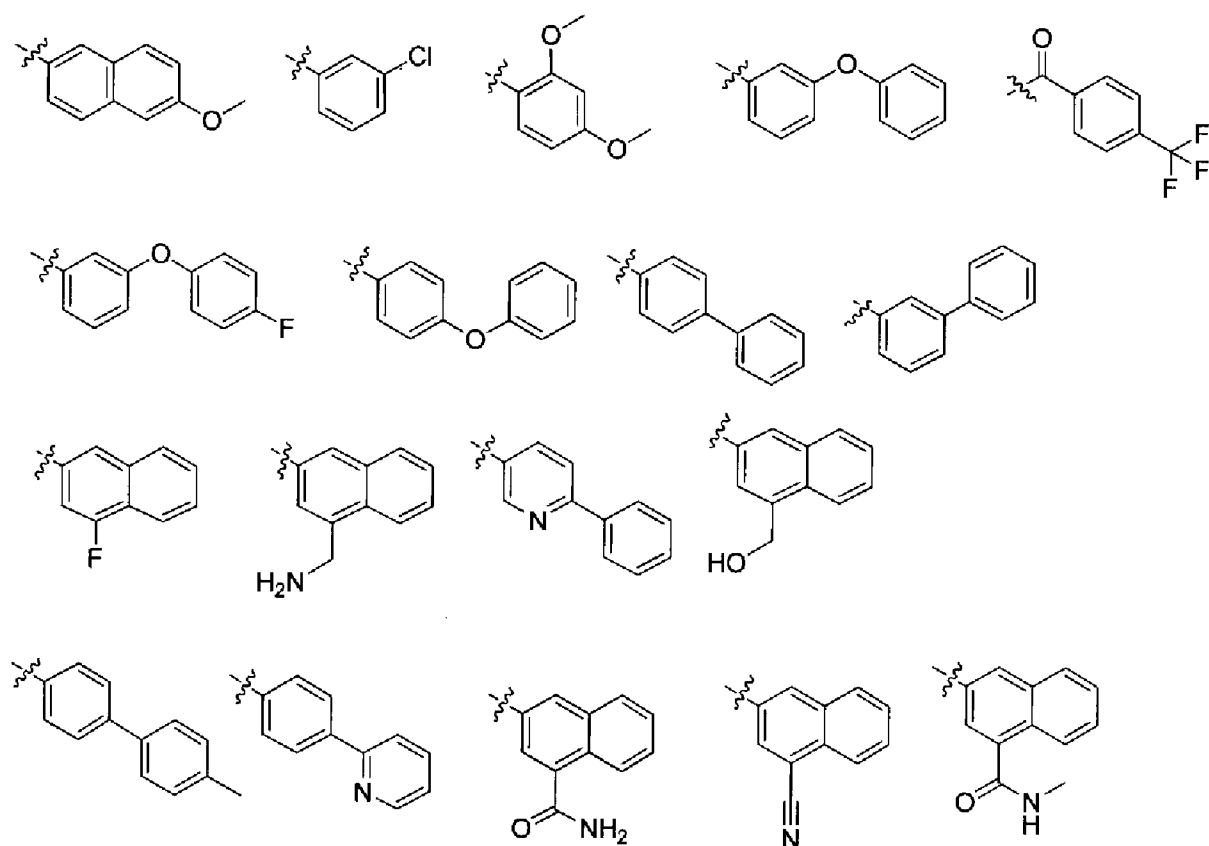


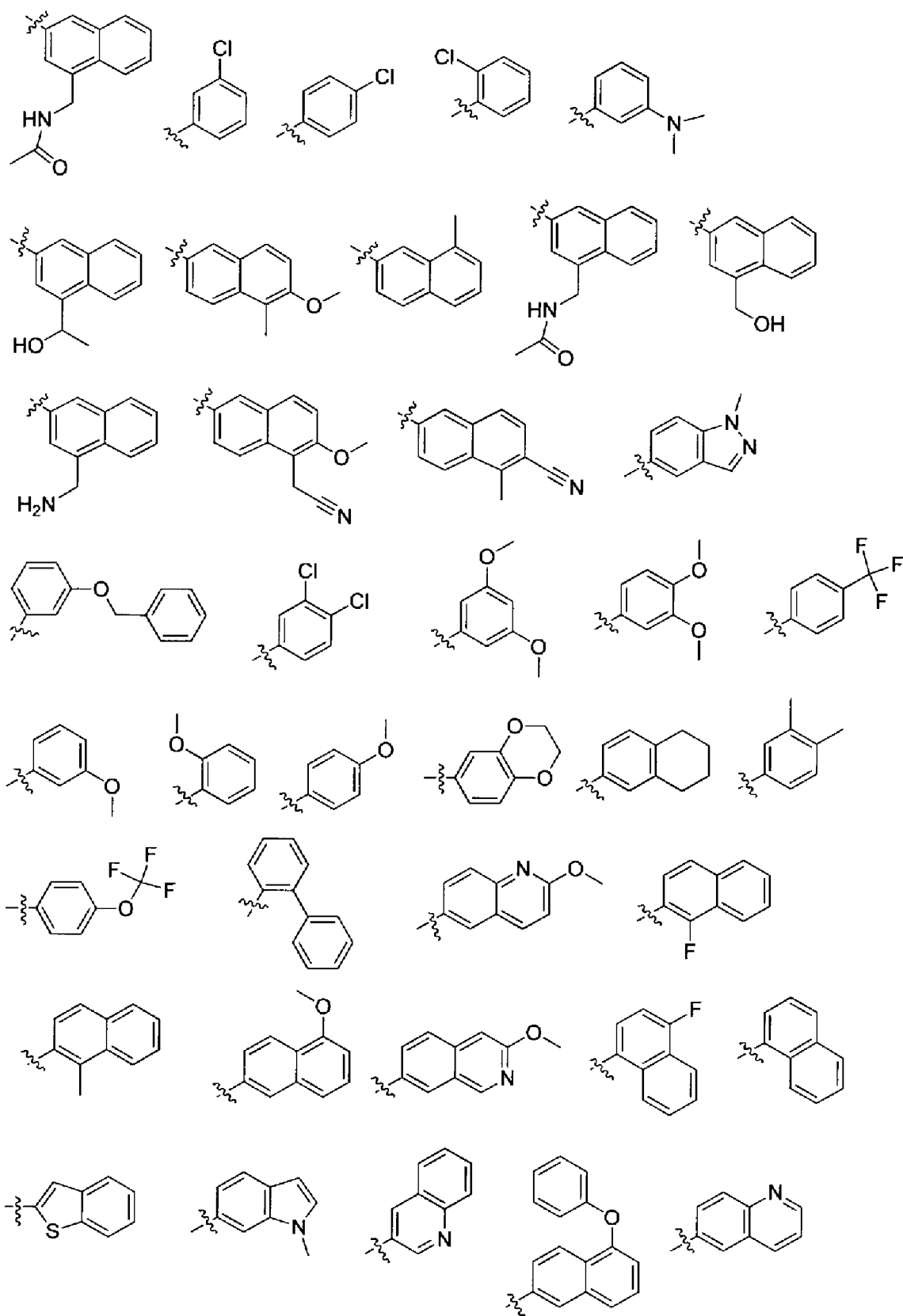




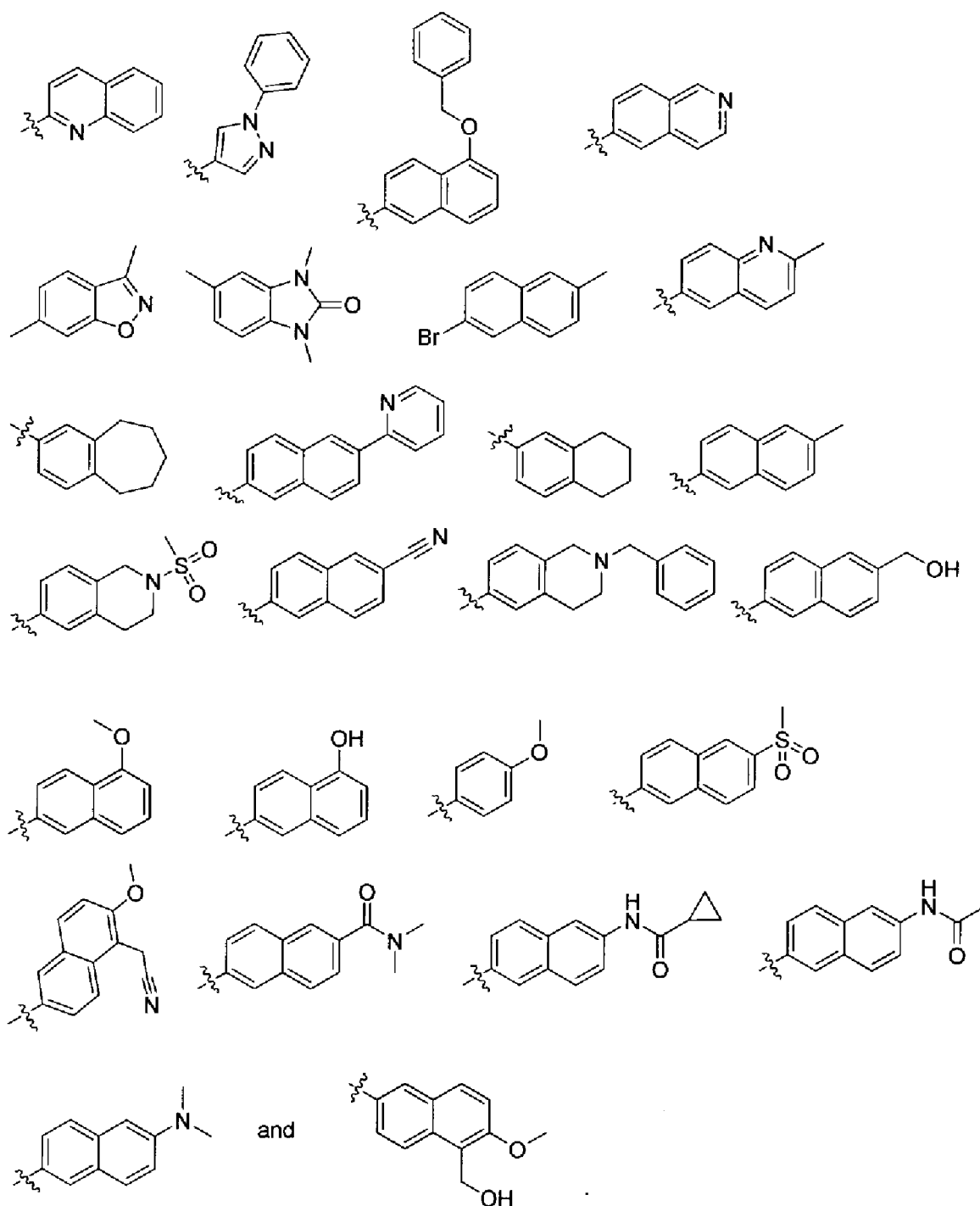
R^2 is selected from the group consisting of:

5

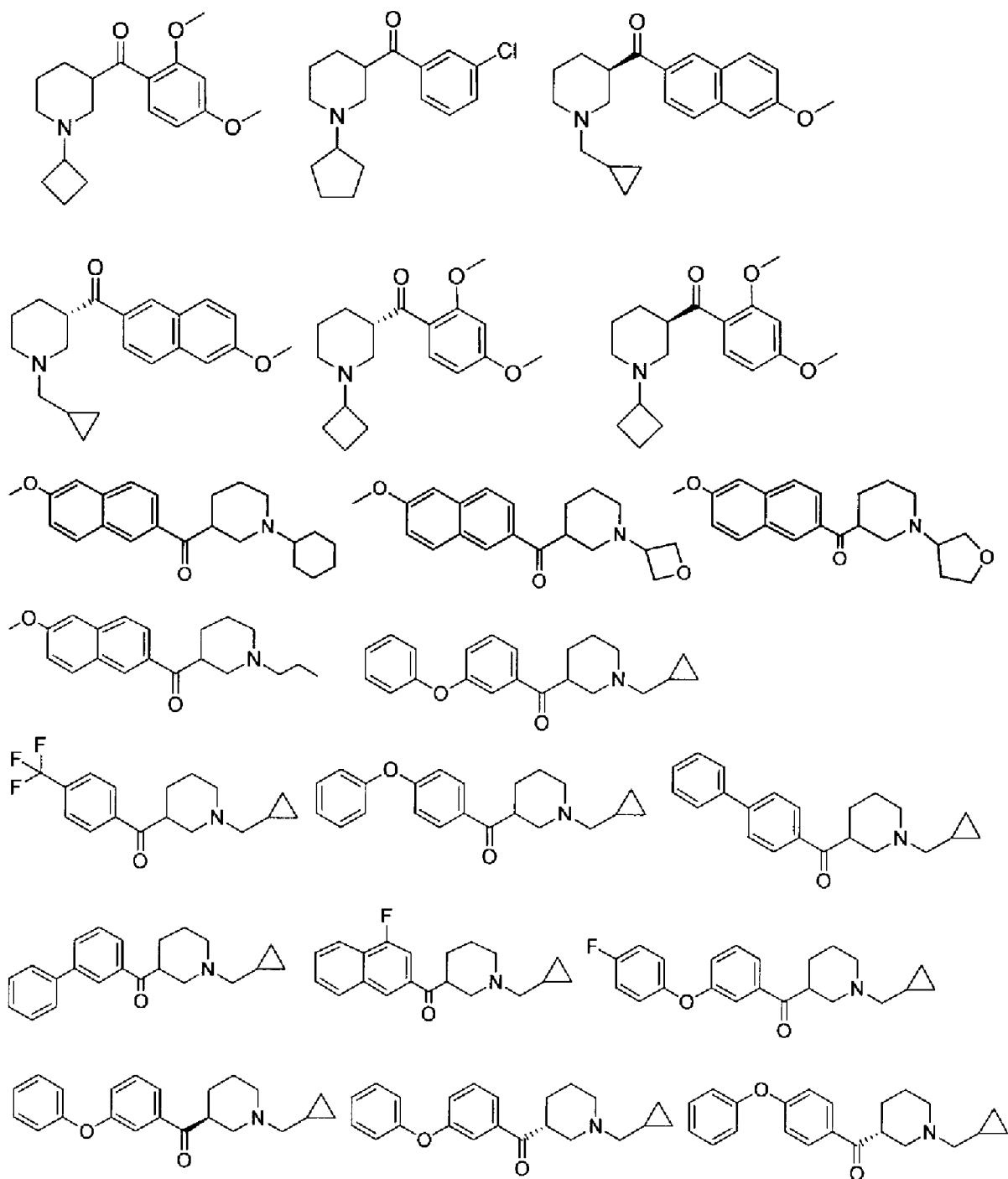


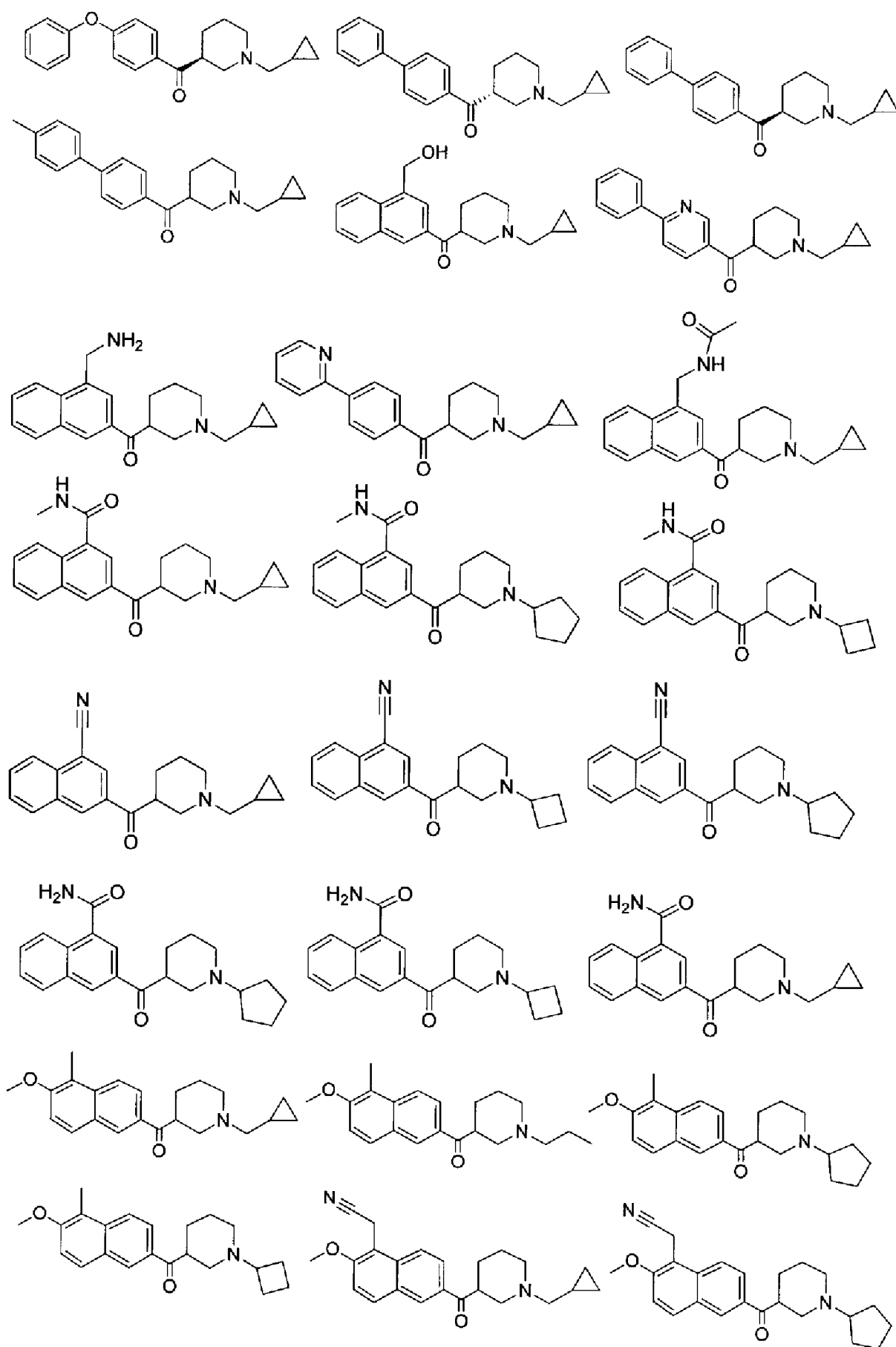


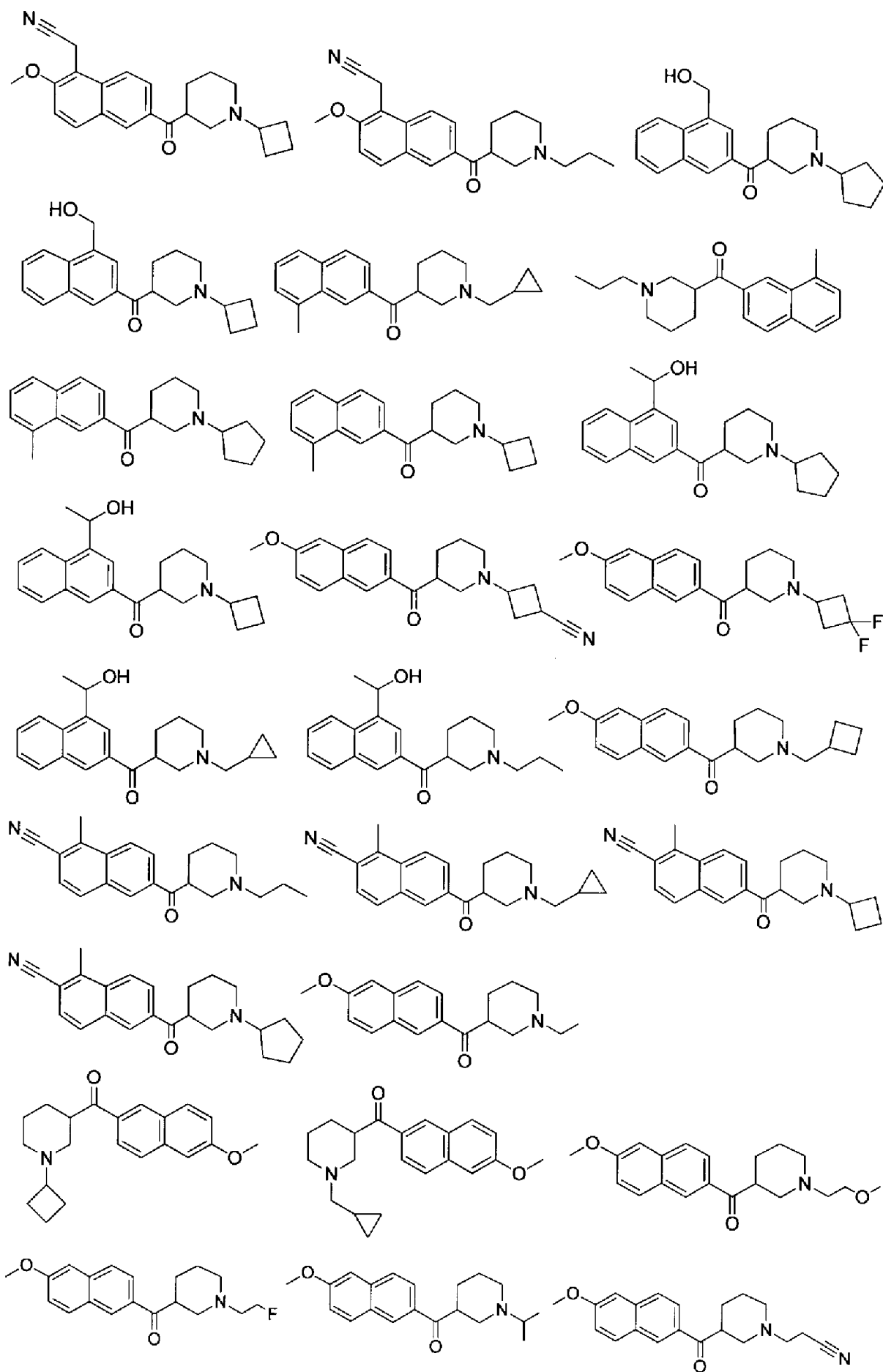
5

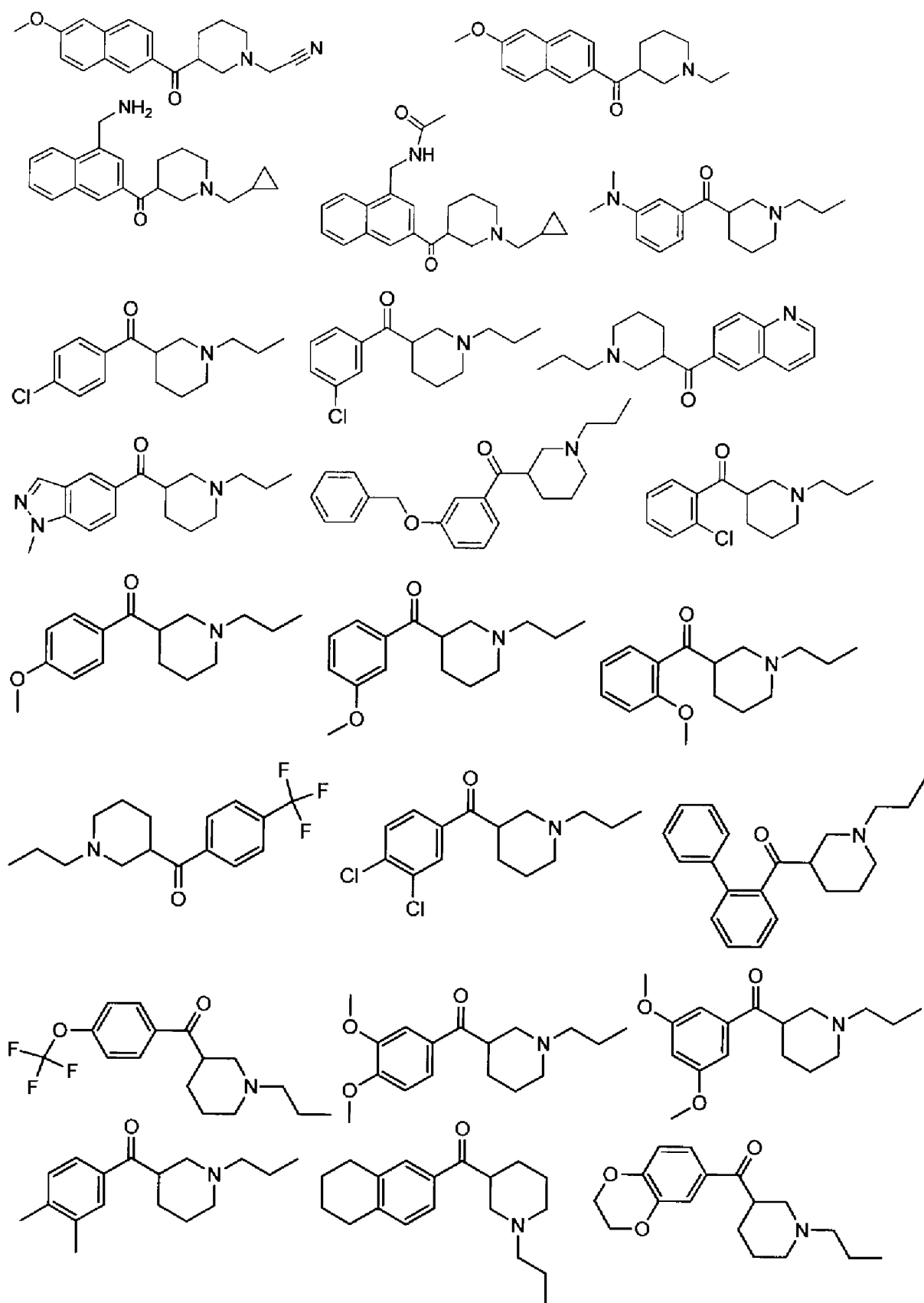


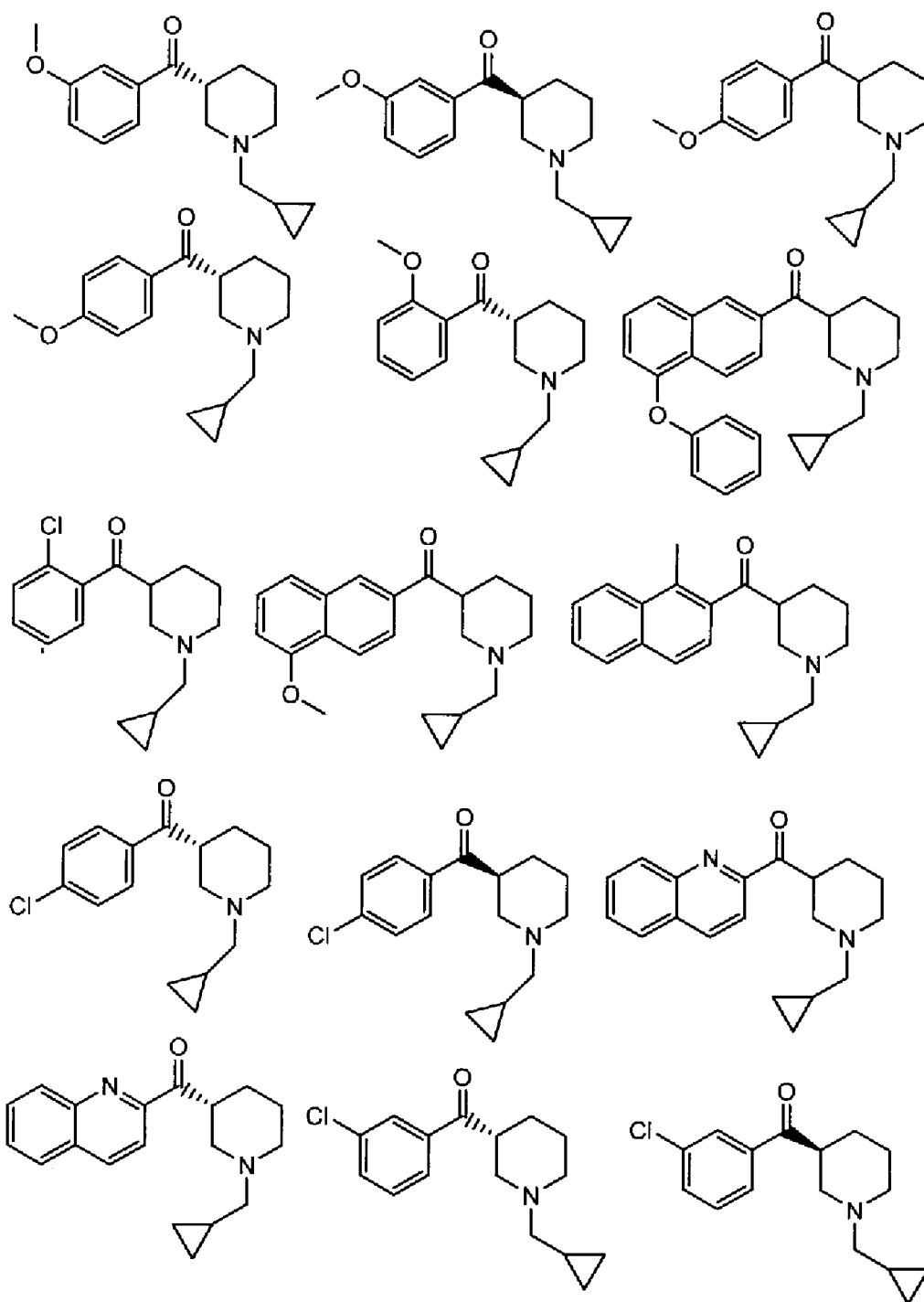
In one embodiment the compound is selected from the group consisting of:

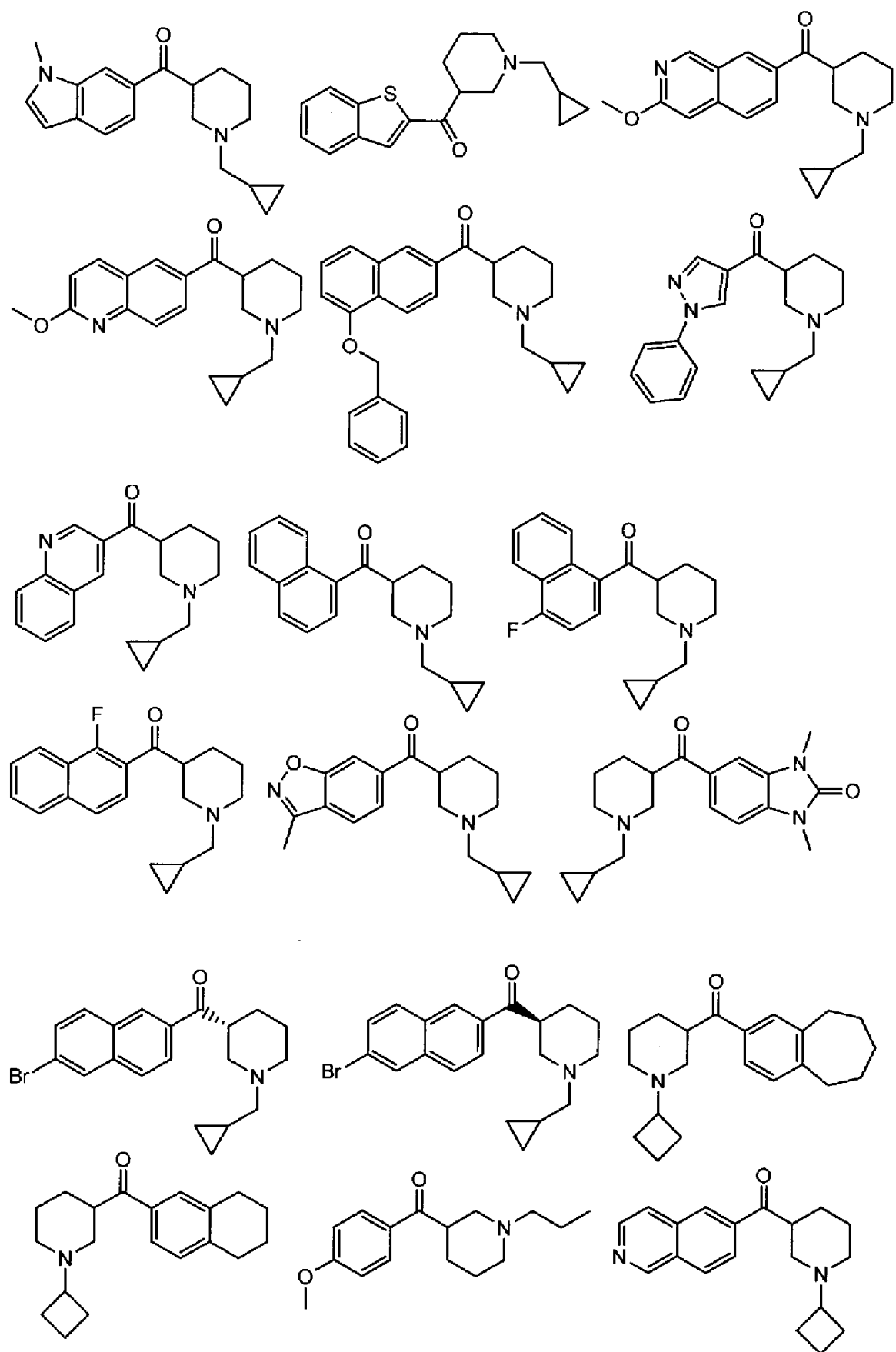


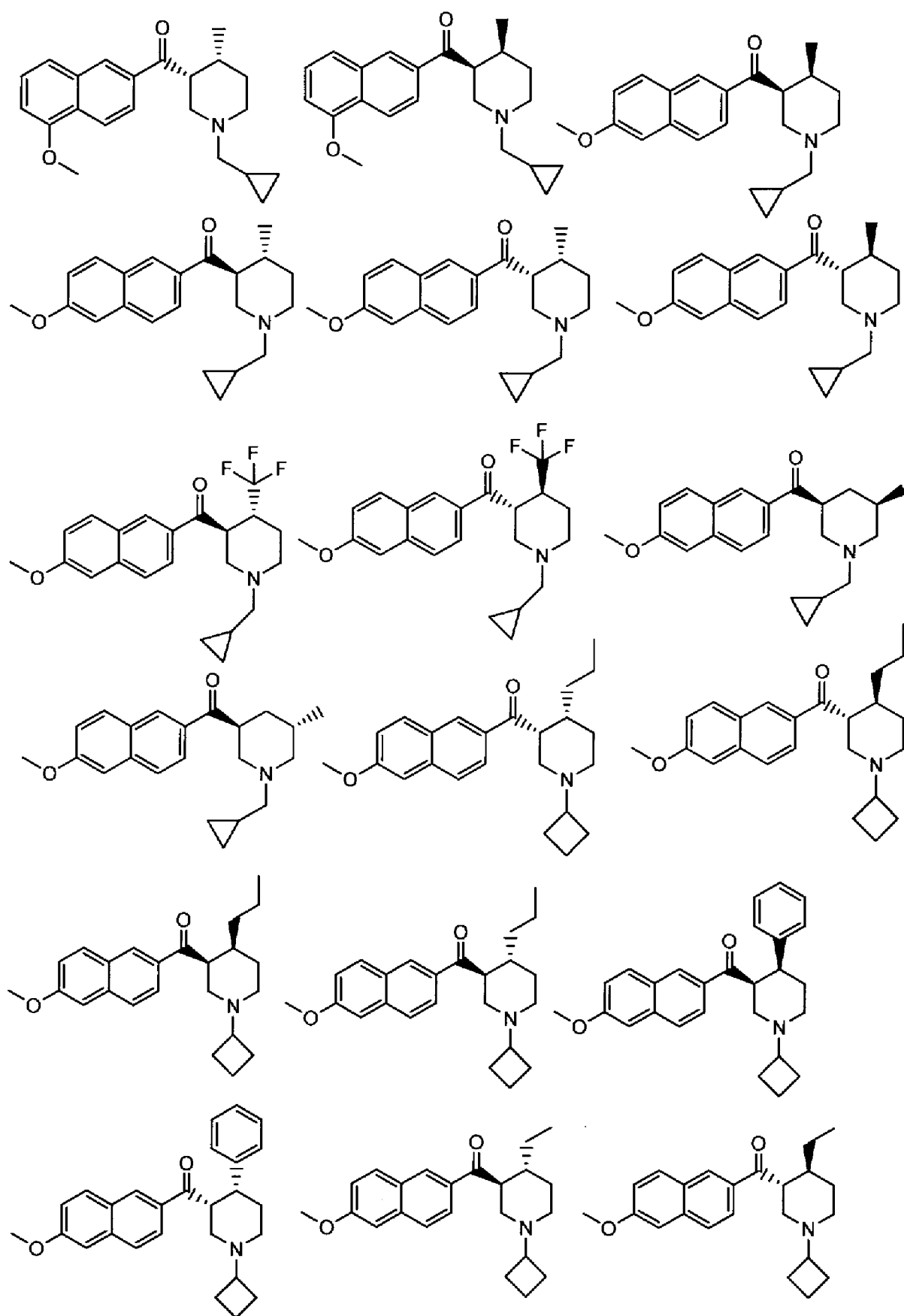


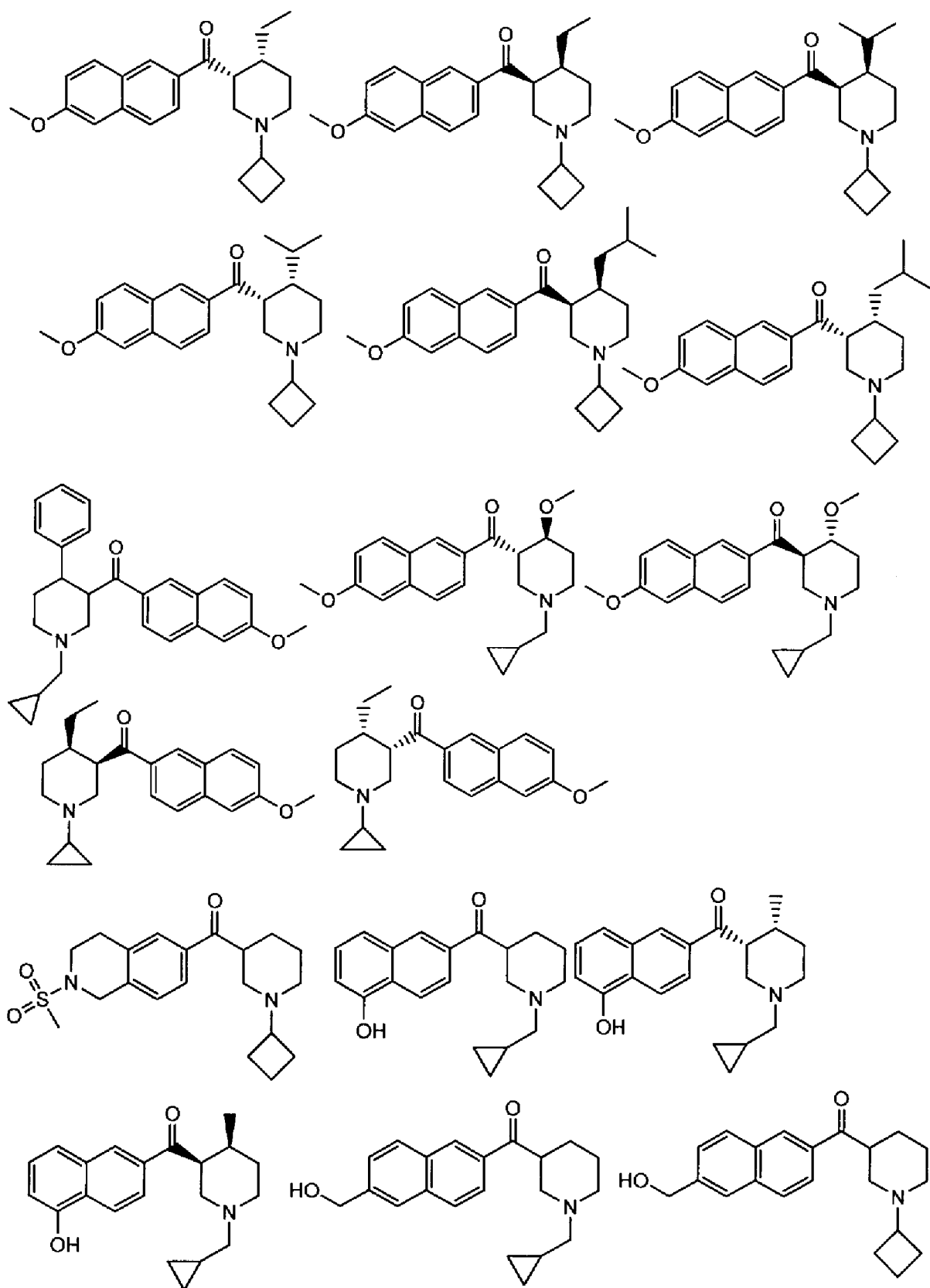


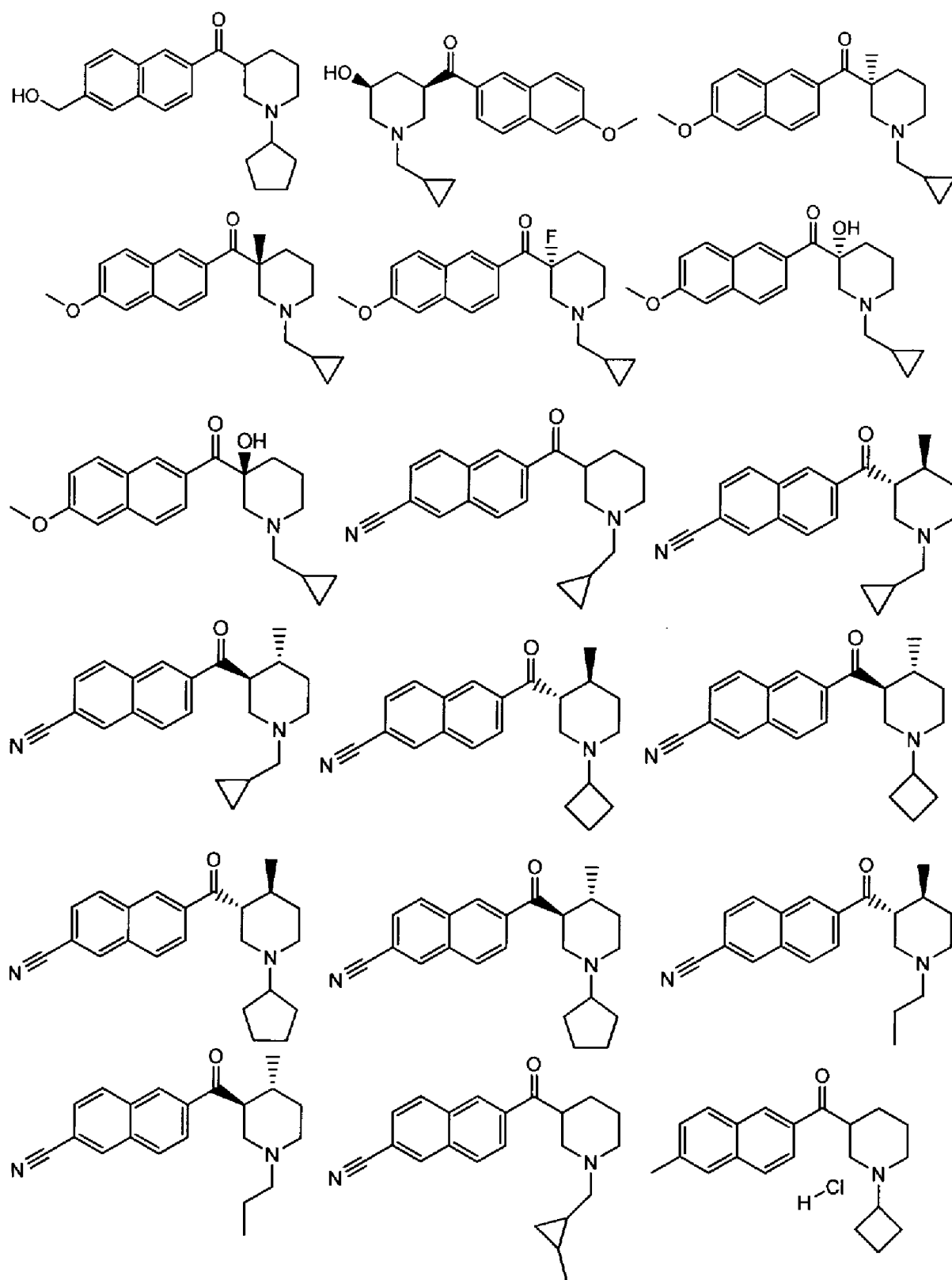


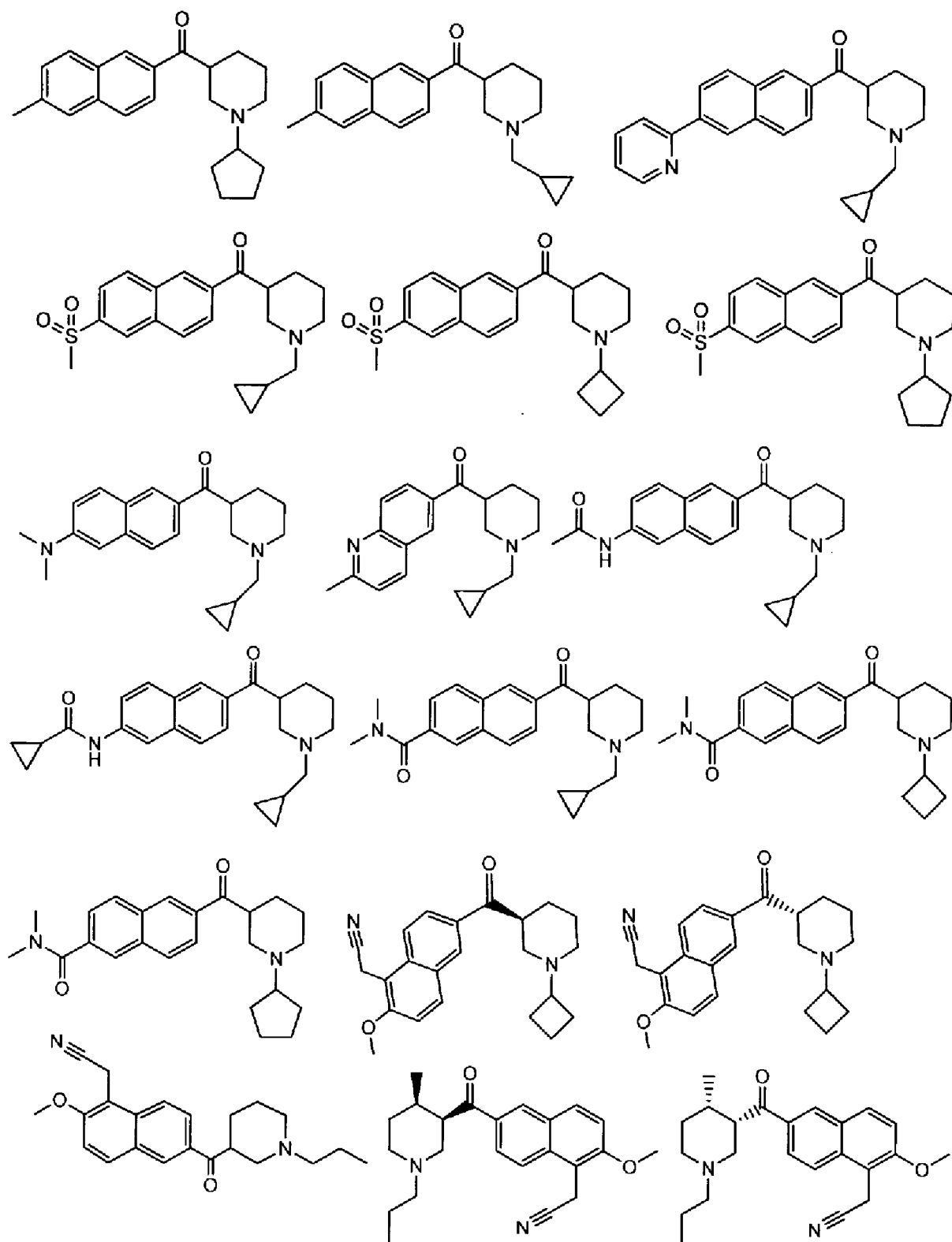


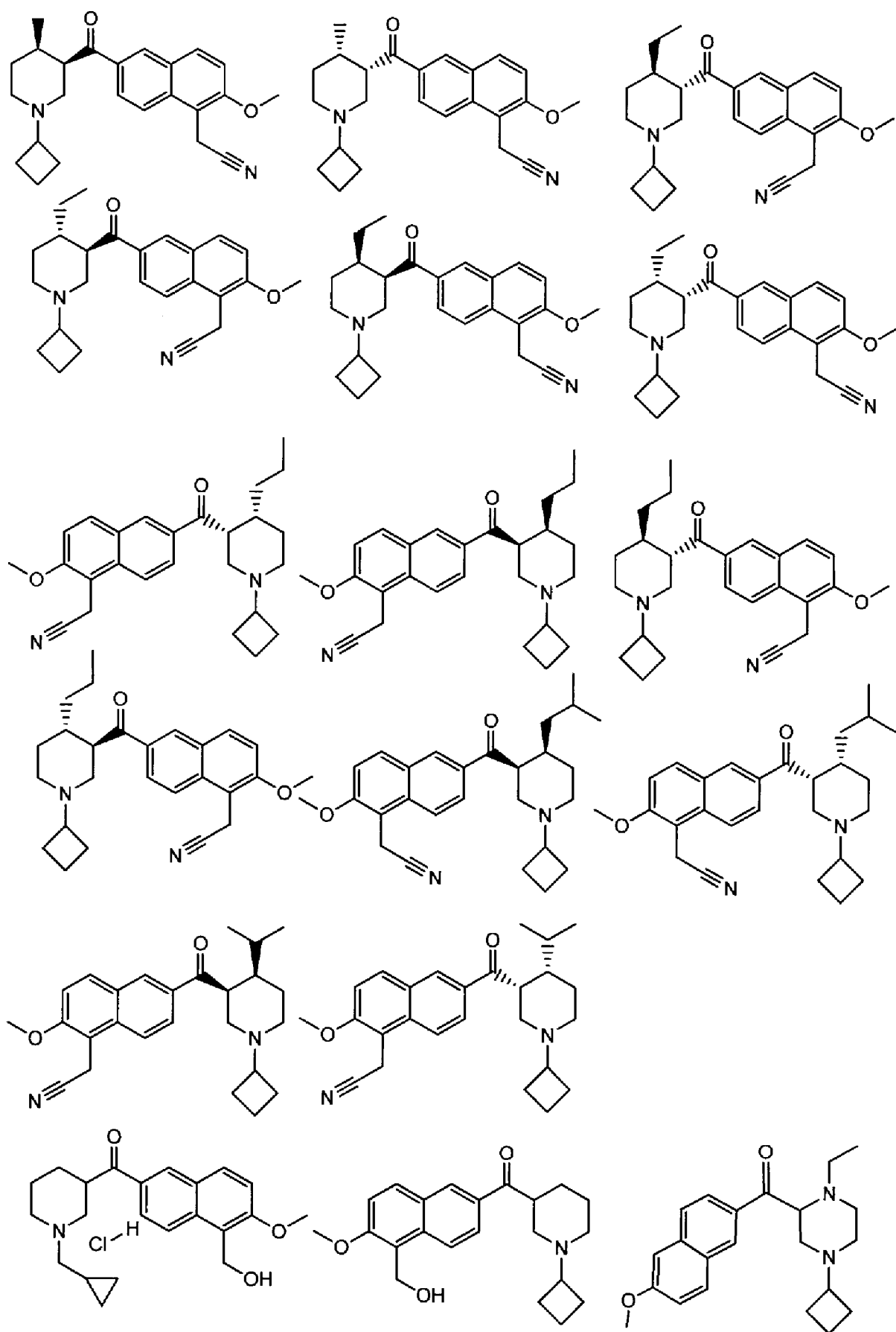


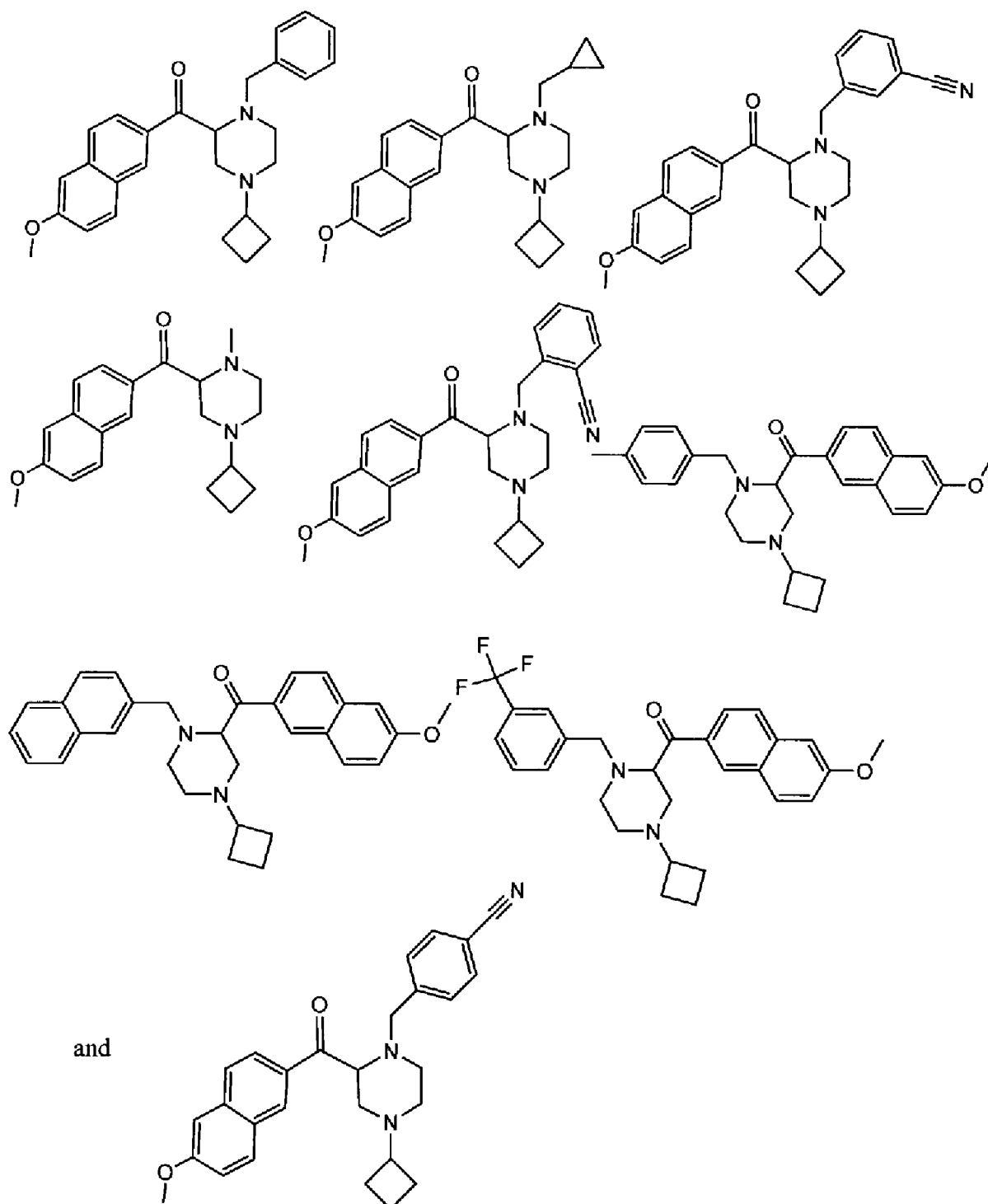












and salts thereof.

Uses, Formulation and Administration

5 *Pharmaceutically acceptable compositions*

Another aspect includes a pharmaceutical composition comprising a compound as described herein or a pharmaceutically acceptable salt thereof. In one embodiment, the composition further comprises a pharmaceutically acceptable carrier, adjuvant, or vehicle. In another embodiment, the composition further comprises an amount of the compound effective to

measurably inhibit KDM2b. In certain embodiments, the composition is formulated for administration to a patient in need thereof certain embodiments.

The term "patient" or "individual" as used herein, refers to an animal, such as a mammal, such as a human. In one embodiment, patient or individual refers to a human.

5 The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer
10 substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-
15 polyoxypropylene-block polymers, polyethylene glycol and wool fat.

Compositions comprising a compound as described herein may be administered orally, parenterally, by inhalation spray, topically, transdermally, rectally, nasally, buccally, sublingually, vaginally, intraperitoneal, intrapulmonary, intradermal, epidural or via an
20 implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques.

In one embodiment, the composition comprising a compound as described herein is formulated as a solid dosage form for oral administration. Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In certain embodiments,
25 the solid oral dosage form comprising a compound as described herein further comprises one or more of (i) an inert, pharmaceutically acceptable excipient or carrier, such as sodium citrate or dicalcium phosphate, and (ii) filler or extender such as starches, lactose, sucrose, glucose, mannitol, or silicic acid, (iii) binders such as carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose or acacia, (iv) humectants such as glycerol, (v) disintegrating
30 agent such as agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates or sodium carbonate, (vi) solution retarding agents such as paraffin, (vii) absorption accelerators such as quaternary ammonium salts, (viii) a wetting agent such as cetyl alcohol or glycerol monostearate, (ix) absorbent such as kaolin or bentonite clay, and (x) lubricant such as talc, calcium stearate, magnesium stearate, polyethylene glycols or sodium lauryl sulfate. In certain

embodiments, the solid oral dosage form is formulated as capsules, tablets or pills. In certain embodiments, the solid oral dosage form further comprises buffering agents. In certain embodiments, such compositions for solid oral dosage forms may be formulated as fillers in soft and hard-filled gelatin capsules comprising one or more excipients such as lactose or milk sugar, polyethylene glycols and the like.

In certain embodiments, tablets, dragees, capsules, pills and granules of the compositions comprising a compound as described herein optionally comprise coatings or shells such as enteric coatings. They may optionally comprise opacifying agents and can also 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 include polymeric substances and waxes, which may also 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.

In another embodiment, a composition comprises micro-encapsulated compound as described herein, and optionally, further comprises one or more excipients.

In another embodiment, compositions comprise liquid dosage formulations comprising a compound as described herein for oral administration, and optionally further comprise one or more of pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In certain embodiments, the liquid dosage form optionally, further comprise one or more of an inert diluent such as water or other solvent, a solubilizing agent, and an emulsifier such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols or fatty acid esters of sorbitan, and mixtures thereof. In certain embodiments, liquid oral compositions optionally further comprise one or more adjuvant, such as a wetting agent, a suspending agent, a sweetening agent, a flavoring agent and a perfuming agent.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also 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 may 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.

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.

In order to prolong the effect of a compound as described herein, it may be desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

In certain embodiments, the composition for rectal or vaginal administration are formulated as suppositories which can be prepared by mixing a compound as described herein with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax, for example those which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the compound.

Example dosage forms for topical or transdermal administration of a compound as described herein include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The compound as described herein is admixed under sterile conditions with a pharmaceutically acceptable carrier, and optionally preservatives or buffers. Additional formulation examples include an ophthalmic formulation, ear drops, eye drops, transdermal patches. Transdermal dosage forms can be made by dissolving or dispensing the compound as described herein in medium, for example ethanol or dimethylsulfoxide. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

Nasal aerosol or inhalation formulations of a compound as described herein may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

5 In certain embodiments, pharmaceutical compositions may be administered with or without food. In certain embodiments, pharmaceutically acceptable compositions are administered without food. In certain embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

10 Specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, the judgment of the treating physician, and the severity of the particular disease being treated. The amount of a compound as described herein in the composition will also depend upon the particular compound in the composition.

15 In one embodiment, the therapeutically effective amount of the compound of the invention administered parenterally per dose will be in the range of about 0.01-100 mg/kg, alternatively about 0.1 to 20 mg/kg of patient body weight per day, with the typical initial range of compound used being 0.3 to 15 mg/kg/day. In another embodiment, oral unit dosage forms, such as tablets and capsules, contain from about 5 to about 100 mg of the compound of the invention.

20 An example tablet oral dosage form comprises about 2 mg, 5 mg, 25 mg, 50 mg, 100 mg, 250 mg or 500 mg of a compound as described herein, and further comprises about 95-30 mg anhydrous lactose, about 5-40 mg sodium croscarmellose, about 5-30 mg polyvinylpyrrolidone (PVP) K30 and about 1-10 mg magnesium stearate. The process of formulating the tablet comprises mixing the powdered ingredients together and further mixing with a solution of the PVP. The resulting composition can be dried, granulated, mixed with the magnesium stearate and compressed to tablet form using conventional equipment. An example of an aerosol formulation can be prepared by dissolving about 2-500 mg of a compound as described herein, in a suitable buffer solution, e.g. a phosphate buffer, and adding a tonicifier, e.g. a salt such sodium chloride, if desired. The solution may be filtered, e.g. using a 0.2 micron filter, to
30 remove impurities and contaminants.

Uses of Compounds and Pharmaceutically Acceptable Compositions

Another aspect includes the use of a compound as described herein for the inhibition of KDM2b. Compounds as described herein may also be used to inhibit the removal of methyl marks on histone lysine residues, including inhibiting the removal of methyl marks from mono-,

di- or tri-methylation of histones H1, H2A, H2B, H3 and H4, such as H3K36 (including for example the KDM2b substrate H3K36me2), thereby altering interactions of these histone proteins with DNA and/or other proteins, and altering certain subsequent genetic or protein expression. Compounds as described herein may also be used to inhibit KDM2b and reduce the activity of a cancer stem/progenitor cell population and/or deplete a cancer stem/progenitor cell population.

In certain embodiments, the binding or inhibition activity of a compound as described herein may be determined by running a competition experiment where the compound is incubated with the KDM2b enzyme bound to known radioligands. Detailed conditions for assaying a compound as an inhibitor of KDM2b or a mutant thereof are set forth in the Examples below.

In certain embodiments, detection of KDM2b activity is achieved with *in vitro* assays, which can be either direct binding (non-catalytic) or enzymatic (catalytic) assays. Types of substrates that are used in such assays may include: short synthetic peptides corresponding to a number of residues from the N-terminus of histone sequences comprising the target lysine residue, single recombinant histone polypeptides, histone octamers reconstituted with recombinant histone proteins, and reconstituted nucleosomes (using reconstituted octamers and specific recombinant DNA fragments). The reconstituted nucleosomes may be mononucleosomes or oligonucleosomes.

Another aspect includes a method of treating or preventing a disease responsive to the inhibition of KDM2b activity in a patient. The method includes administering a therapeutically effective amount of a compound as described hereinto a patient in need thereof.

Another aspect includes the use of a compound as described herein, in therapy. Another aspect includes the use of a pharmaceutical composition comprising a compound as described herein, in therapy.

Another aspect includes the use of a compound as described herein, in treating a disease associated with KDM2b activity. Another aspect includes the use of a pharmaceutical composition comprising a compound as described herein, in treating a disease associated with KDM2b activity.

Another aspect includes the use of a compound as described herein, in the manufacture of a medicament for the treatment of a disease associated with KDM2b activity. Another aspect includes the use of a pharmaceutical composition comprising a compound as described herein, in the manufacture of a medicament for the treatment of a disease associated with KDM2b activity.

In certain embodiments, the disease or condition is a hyperproliferative disease, cancer, stroke, diabetes, hepatomegaly, cardiovascular disease, multiple sclerosis, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease, asthma, allergic disorders, inflammation, neurological disorders, a hormone-related disease, conditions associated with organ transplantation, immunodeficiency disorders, destructive bone disorders, proliferative disorders, infectious diseases, conditions associated with cell death, thrombin-induced platelet aggregation, liver disease, pathologic immune conditions involving T cell activation, CNS disorders or a myeloproliferative disorder.

In certain embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

Another aspect includes a method for treating, ameliorating or preventing cancer, drug-resistant cancer or another proliferative disorder by administration of an effective amount of a compound as described herein to a mammal, for example a human, in need of such treatment. In certain embodiments, the disease to be treated is cancer.

Examples of cancers that may be treated using the compounds and methods described herein include, but are not limited to, adrenal cancer, acinic cell carcinoma, acoustic neuroma, acral lentiginous melanoma, acrospiroma, acute eosinophilic leukemia, acute erythroid leukemia, acute lymphoblastic leukemia, acute megakaryoblastic leukemia, acute monocytic leukemia, acute promyelocytic leukemia, adenocarcinoma, adenoid cystic carcinoma, adenoma, adenomatoid odontogenic tumor, adenosquamous carcinoma, adipose tissue neoplasm, adrenocortical carcinoma, adult T-cell leukemia/lymphoma, aggressive NK-cell leukemia, AIDS-related lymphoma, alveolar rhabdomyosarcoma, alveolar soft part sarcoma, ameloblastic fibroma, anaplastic large cell lymphoma, anaplastic thyroid cancer, androgen dependent cancer, angioimmunoblastic T-cell lymphoma, angiomyolipoma, angiosarcoma, astrocytoma, atypical teratoid rhabdoid tumor, B-cell chronic lymphocytic leukemia, B-cell lymphoma, basal cell carcinoma, biliary tract cancer, bladder cancer, blastoma, bone cancer, Brenner tumor, Brown tumor, Burkitt's lymphoma, breast cancer (e.g., triple negative-breast cancer), brain cancer, carcinoma, carcinoma in situ, carcinosarcoma, cartilage tumor, cementoma, myeloid sarcoma, chondroma, chordoma, choriocarcinoma, choroid plexus papilloma, clear-cell sarcoma of the

kidney, craniopharyngioma, cutaneous T-cell lymphoma, cervical cancer, colorectal cancer, Degos disease, desmoplastic small round cell tumor, diffuse large B-cell lymphoma, dysembryoplastic neuroepithelial tumor, dysgerminoma, embryonal carcinoma, endocrine gland neoplasm, endodermal sinus tumor, enteropathy-associated T-cell lymphoma, esophageal cancer, fetus in fetu, fibroma, fibrosarcoma, follicular lymphoma, follicular thyroid cancer, 5 ganglioneuroma, gastrointestinal cancer, germ cell tumor, gestational choriocarcinoma, giant cell fibroblastoma, giant cell tumor of the bone, glial tumor, glioblastoma multiforme, glioma, gliomatosis cerebri, glucagonoma, gonadoblastoma, granulosa cell tumor, gynandroblastoma, gallbladder cancer, gastric cancer, hemangioblastoma, head and neck cancer, 10 hemangiopericytoma, hematological malignancy, hepatoblastoma, hepatosplenic T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, invasive lobular carcinoma, intestinal cancer, kidney cancer, laryngeal cancer, lentigo maligna, leukemia, leydig cell tumor, liposarcoma, lung cancer, lymphangioma, lymphangiosarcoma, lymphoepithelioma, lymphoma, acute lymphocytic leukemia (e.g., T-cell or B-cell), acute myelogenous leukemia, chronic 15 lymphocytic leukemia, liver cancer, small cell lung cancer, non-small cell lung cancer, MALT lymphoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, malignant triton tumor, mantle cell lymphoma, marginal zone B-cell lymphoma, mast cell leukemia, mediastinal germ cell tumor, medullary carcinoma of the breast, medullary thyroid cancer, medulloblastoma, melanoma, meningioma, merkel cell cancer, mesothelioma, metastatic 20 urothelial carcinoma, mixed Mullerian tumor, mucinous tumor, multiple myeloma, muscle tissue neoplasm, acute myeloid leukemia, chronic myeloid leukemia, mycosis fungoides, myxoid liposarcoma, myxoma, myxosarcoma, nasopharyngeal carcinoma, neurinoma, neuroblastoma, neurofibroma, neuroma, nodular melanoma, ocular cancer, oligoastrocytoma, oligodendroglioma, oncocytoma, optic nerve sheath meningioma, optic nerve tumor, oral cancer, 25 osteosarcoma, ovarian cancer, Pancoast tumor, papillary thyroid cancer, paraganglioma, pinealoblastoma, pineocytoma, pituicytoma, pituitary adenoma, pituitary tumor, plasmacytoma, polyembryoma, precursor T-lymphoblastic lymphoma, primary central nervous system lymphoma, primary effusion lymphoma, preimary peritoneal cancer, prostate cancer, pancreatic cancer, pharyngeal cancer, pseudomyxoma peritonei, renal cell carcinoma, renal medullary 30 carcinoma, retinoblastoma, rhabdomyoma, rhabdomyosarcoma, Richter's transformation, rectal cancer, sarcoma, Schwannomatosis, seminoma, Sertoli cell tumor, sex cord-gonadal stromal tumor, signet ring cell carcinoma, skin cancer, small blue round cell tumors, small cell carcinoma, soft tissue sarcoma, somatostatinoma, soot wart, spinal tumor, splenic marginal zone lymphoma, squamous cell carcinoma, synovial sarcoma, Sezary's disease, small intestine

cancer, stomach cancer, T-cell lymphoma, testicular cancer, thecoma, thyroid cancer, transitional cell carcinoma, throat cancer, urachal cancer, urogenital cancer, urothelial carcinoma, uveal melanoma, uterine cancer, verrucous carcinoma, visual pathway glioma, vulvar cancer, vaginal cancer, Waldenstrom's macroglobulinemia, Warthin's tumor and Wilms' tumor.

Another embodiment includes a method for the treatment of benign proliferative disorders. Examples of benign proliferative disorders include, but are not limited to, benign soft tissue tumors, bone tumors, brain and spinal tumors, eyelid and orbital tumors, granuloma, lipoma, meningioma, multiple endocrine neoplasia, nasal polyps, pituitary tumors, prolactinoma, pseudotumor cerebri, seborrheic keratoses, stomach polyps, thyroid nodules, cystic neoplasms of the pancreas, hemangiomas, vocal cord nodules, polyps, and cysts, Castleman disease, chronic pilonidal disease, dermatofibroma, pilar cyst, pyogenic granuloma and juvenile polyposis syndrome.

Another embodiment includes a therapeutic method useful for modulating protein methylation, gene expression, cell proliferation, cell differentiation and/or apoptosis *in vivo* in diseases mentioned above, in particular cancer, comprising administering to a patient in need of such therapy a pharmacologically active and therapeutically effective amount of one or more of the compounds as described herein.

Another embodiment includes a method for regulating endogenous or heterologous promotor activity by contacting a cell with a compound as described herein.

Another embodiment includes the use of a compound as described herein for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis and/or amelioration of the diseases, disorders, illnesses and/or conditions as mentioned herein.

Another embodiment includes the use of a compound as described herein for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of diseases and/or disorders responsive or sensitive to the inhibition of histone demethylases, particularly those diseases mentioned above, such as e.g. cancer.

Compounds as described herein may be administered using any amount and any route of administration effective for treating or lessening the severity of the disorder. The exact amount required will vary from patient to patient, depending on the species, age, and general condition of the patient, for example the severity of the disorder, the particular compound, its mode of administration, and the like. The total daily usage of a compound as described herein by a given patient will be decided by the attending physician within the scope of sound medical judgment.

The specific effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts.

Another embodiment includes a method of inhibiting KDM2b activity in a biological sample comprising contacting said biological sample with a compound as described herein.

The term "biological sample", as used herein, includes, without limitation, a cell, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

Co-Administration of Compounds and Other Agents

The compound as described herein may be employed alone or in combination with other agents for treatment. For example, the second agent of the pharmaceutical combination formulation or dosing regimen may have complementary activities to the compound as described herein such that they do not adversely affect each other. The compounds may be administered together in a unitary pharmaceutical composition or separately. In one embodiment a compound or a pharmaceutically acceptable salt can be co-administered with a cytotoxic agent to treat proliferative diseases and cancer.

The term "co-administering" refers to either simultaneous administration, or any manner of separate sequential administration, of a compound as described herein, and a further active pharmaceutical ingredient or ingredients, including cytotoxic agents and radiation treatment. If the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Typically, any agent that has activity against a disease or condition being treated may be co-administered. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the disease involved.

In one embodiment, the treatment method includes the co-administration of a compound as described herein and at least one cytotoxic agent. The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (e.g., At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu);

chemotherapeutic agents; growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof.

Exemplary cytotoxic agents can be selected from anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, inhibitors of LDH-A; inhibitors of fatty acid biosynthesis; cell cycle signaling inhibitors; HDAC inhibitors, proteasome inhibitors; and inhibitors of cancer metabolism.

"Chemotherapeutic agent" includes chemical compounds useful in the treatment of cancer. Examples of chemotherapeutic agents include erlotinib (TARCEVA[®], Genentech/OSI Pharm.), bortezomib (VELCADE[®], Millennium Pharm.), disulfiram, epigallocatechin gallate, salinosporamide A, carfilzomib, 17-AAG(geldanamycin), radicicol, lactate dehydrogenase A (LDH-A), fulvestrant (FASLODEX[®], AstraZeneca), sunitib (SUTENT[®], Pfizer/Sugen), letrozole (FEMARA[®], Novartis), imatinib mesylate (GLEEVEC[®], Novartis), finasunate (VATALANIB[®], Novartis), oxaliplatin (ELOXATIN[®], Sanofi), 5-FU (5-fluorouracil), leucovorin, Rapamycin (Sirolimus, RAPAMUNE[®], Wyeth), Lapatinib (TYKERB[®], GSK572016, Glaxo Smith Kline), Lonafamib (SCH 66336), sorafenib (NEXAVAR[®], Bayer Labs), gefitinib (IRESSA[®], AstraZeneca), AG1478, alkylating agents such as thiotepa and CYTOXAN[®] cyclophosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylenelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylmelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including topotecan and irinotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogs); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); adrenocorticosteroids (including prednisone and prednisolone); cyproterone acetate; 5 α -reductases including finasteride and dutasteride); vorinostat, romidepsin, panobinostat, valproic acid, mocetinostat dolastatin; aldesleukin, talc

duocarmycin (including the synthetic analogs, KW-2189 and CB1-TM1); eleutherobin;
 pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil,
 chlomaphazine, chlorophosphamide, estramustine, ifosfamide, mechlorethamine,
 mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine,
 5 trofosfamide, uracil mustard; nitrosoureas such as carmustine, chlorozotocin, fotemustine,
 lomustine, nimustine, and ranimustine; antibiotics such as the enediyne antibiotics (e.g.,
 calicheamicin, especially calicheamicin γ II and calicheamicin ω II (*Angew Chem. Intl. Ed. Engl.*
1994 33:183-186); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an
 esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne
 10 antibiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins,
 cactinomycin, carabycin, caminomycin, carzinophilin, chromomycinis, dactinomycin,
 daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN[®] (doxorubicin),
 morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and
 deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as
 15 mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, porfiromycin,
 puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex,
 zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid
 analogs such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as
 fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine,
 20 azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine,
 floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol,
 mepitiothane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic
 acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic
 acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine;
 25 diaziquone; elfomithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate;
 hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins;
 mitoguazone; mitoxantrone; mopidamrol; nitraerine; pentostatin; phenamet; pirarubicin;
 losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK[®] polysaccharide
 complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran;
 30 spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes
 (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine;
 mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C");
 cyclophosphamide; thiotepa; taxoids, e.g., TAXOL (paclitaxel; Bristol-Myers Squibb Oncology,
 Princeton, N.J.), ABRAXANE[®] (Cremophor-free), albumin-engineered nanoparticle

formulations of paclitaxel (American Pharmaceutical Partners, Schaumburg, Ill.), and TAXOTERE[®] (docetaxel, doxetaxel; Sanofi-Aventis); chloranmbucil; GEMZAR[®] (gemcitabine); 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine;
 5 NAVELBINE[®] (vinorelbine); novantrone; teniposide; edatrexate; daunomycin; aminopterin; capecitabine (XELODA[®]); ibandronate; CPT-11; topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; and pharmaceutically acceptable salts, acids and derivatives of any of the above.

Chemotherapeutic agent also includes (i) anti-hormonal agents that act to regulate or
 10 inhibit hormone action on tumors such as anti-estrogens and selective estrogen receptor modulators (SERMs), including, for example, tamoxifen (including NOLVADEX[®]; tamoxifen citrate), raloxifene, droloxifene, idoxifene, 4-hydroxytamoxifen, trioxifene, keoxifene, LY117018, onapristone, and FARESTON[®] (toremifine citrate); (ii) aromatase inhibitors that inhibit the enzyme aromatase, which regulates estrogen production in the adrenal glands, such
 15 as, for example, 4(5)-imidazoles, aminoglutethimide, MEGASE[®] (megestrol acetate), AROMASIN[®] (exemestane; Pfizer), formestane, fadrozole, RIVISOR[®] (vorozole), FEMARA[®] (letrozole; Novartis), and ARIMIDEX[®] (anastrozole; AstraZeneca); (iii) anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide and goserelin; buserelin, tripterelin, medroxyprogesterone acetate, diethylstilbestrol, premarin, fluoxymesterone, all transretinoic
 20 acid, fenretinide, as well as troxacitabine (a 1,3-dioxolane nucleoside cytosine analog); (iv) protein kinase inhibitors; (v) lipid kinase inhibitors; (vi) antisense oligonucleotides, particularly those which inhibit expression of genes in signaling pathways implicated in aberrant cell proliferation, such as, for example, PKC-alpha, Ralf and H-Ras; (vii) ribozymes such as VEGF expression inhibitors (e.g., ANGIOZYME[®]) and HER2 expression inhibitors; (viii) vaccines
 25 such as gene therapy vaccines, for example, ALLOVECTIN[®], LEUVECTIN[®], and VAXID[®]; PROLEUKIN[®], rIL-2; a topoisomerase 1 inhibitor such as LURTOTECAN[®]; ABARELIX[®] rmRH; and (ix) pharmaceutically acceptable salts, acids and derivatives of any of the above.

Chemotherapeutic agent also includes antibodies such as alemtuzumab (Campath), bevacizumab (AVASTIN[®], Genentech); cetuximab (ERBITUX[®], Imclone); panitumumab
 30 (VECTIBIX[®], Amgen), rituximab (RITUXAN[®], Genentech/Biogen Idec), pertuzumab (OMNITARG[®], 2C4, Genentech), trastuzumab (HERCEPTIN[®], Genentech), tositumomab (Bexxar, Corixa), and the antibody drug conjugate, gemtuzumab ozogamicin (MYLOTARG[®], Wyeth). Additional humanized monoclonal antibodies with therapeutic potential as agents in combination with the compounds of the invention include: apolizumab, aselizumab, atlizumab,

bapineuzumab, bivatuzumab mertansine, cantuzumab mertansine, cedelizumab, certolizumab pegol, cidfusituzumab, cidtuzumab, daclizumab, eculizumab, efalizumab, epratuzumab, erlizumab, felvizumab, fontolizumab, gemtuzumab ozogamicin, inotuzumab ozogamicin, ipilimumab, labetuzumab, lintuzumab, matuzumab, mepolizumab, motavizumab, motovizumab, 5 natalizumab, nimotuzumab, nolovizumab, numavizumab, ocrelizumab, omalizumab, palivizumab, pascolizumab, pecfusituzumab, pectuzumab, pexelizumab, ralivizumab, ranibizumab, reslivizumab, reslizumab, resyvizumab, rovelizumab, ruplizumab, sibrotuzumab, sipilizumab, sontuzumab, tacatuzumab tetraxetan, tadocizumab, talizumab, tefibazumab, tocilizumab, toralizumab, tucotuzumab celmoleukin, tucusituzumab, umavizumab, 10 urtoxazumab, ustekinumab, visilizumab, and the anti-interleukin-12 (ABT-874/J695, Wyeth Research and Abbott Laboratories) which is a recombinant exclusively human-sequence, full-length IgG₁ λ antibody genetically modified to recognize interleukin-12 p40 protein.

Chemotherapeutic agent also includes "EGFR inhibitors," which refers to compounds that bind to or otherwise interact directly with EGFR and prevent or reduce its signaling activity, 15 and is alternatively referred to as an "EGFR antagonist." Examples of such agents include antibodies and small molecules that bind to EGFR. Examples of antibodies which bind to EGFR include MAb 579 (ATCC CRL HB 8506), MAb 455 (ATCC CRL HB8507), MAb 225 (ATCC CRL 8508), MAb 528 (ATCC CRL 8509) (see, US Patent No. 4,943, 533, Mendelsohn *et al.*) and variants thereof, such as chimerized 225 (C225 or Cetuximab; ERBUTIX[®]) and 20 reshaped human 225 (H225) (see, WO 96/40210, Imclone Systems Inc.); IMC-11F8, a fully human, EGFR-targeted antibody (Imclone); antibodies that bind type II mutant EGFR (US Patent No. 5,212,290); humanized and chimeric antibodies that bind EGFR as described in US Patent No. 5,891,996; and human antibodies that bind EGFR, such as ABX-EGF or Panitumumab (see WO98/50433, Abgenix/Amgen); EMD 55900 (Stragliotto *et al. Eur. J. 25 Cancer* 32A:636-640 (1996)); EMD7200 (matuzumab) a humanized EGFR antibody directed against EGFR that competes with both EGF and TGF- α for EGFR binding (EMD/Merck); human EGFR antibody, HuMax-EGFR (GenMab); fully human antibodies known as E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6. 3 and E7.6. 3 and described in US 6,235,883; MDX-447 (Medarex Inc); and mAb 806 or humanized mAb 806 (Johns *et al., J. Biol. Chem.* 279(29):30375-30384 30 (2004)). The anti-EGFR antibody may be conjugated with a cytotoxic agent, thus generating an immunoconjugate (see, *e.g.*, EP659,439A2, Merck Patent GmbH). EGFR antagonists include small molecules such as compounds described in US Patent Nos: 5,616,582, 5,457,105, 5,475,001, 5,654,307, 5,679,683, 6,084,095, 6,265,410, 6,455,534, 6,521,620, 6,596,726, 6,713,484, 5,770,599, 6,140,332, 5,866,572, 6,399,602, 6,344,459, 6,602,863, 6,391,874,

6,344,455, 5,760,041, 6,002,008, and 5,747,498, as well as the following PCT publications: WO98/14451, WO98/50038, WO99/09016, and WO99/24037. Particular small molecule EGFR antagonists include OSI-774 (CP-358774, erlotinib, TARCEVA® Genentech/OSI

Pharmaceuticals); PD 183805 (CI 1033, 2-propenamide, N-[4-[(3-chloro-4-

- 5 fluorophenyl)amino]-7-[3-(4-morpholinyl)propoxy]-6-quinazolinyl]-, dihydrochloride, Pfizer Inc.); ZD1839, gefitinib (IRESSA®) 4-(3'-Chloro-4'-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline, AstraZeneca); ZM 105180 ((6-amino-4-(3-methylphenyl-amino)-quinazoline, Zeneca); BIBX-1382 (N8-(3-chloro-4-fluoro-phenyl)-N2-(1-methyl-piperidin-4-yl)-pyrimido[5,4-d]pyrimidine-2,8-diamine, Boehringer Ingelheim); PKI-166 ((R)-
- 10 4-[4-[(1-phenylethyl)amino]-1H-pyrrolo[2,3-d]pyrimidin-6-yl]-phenol); (R)-6-(4-hydroxyphenyl)-4-[(1-phenylethyl)amino]-7H-pyrrolo[2,3-d]pyrimidine); CL-387785 (N-[4-[(3-bromophenyl)amino]-6-quinazolinyl]-2-butanamide); EKB-569 (N-[4-[(3-chloro-4-fluorophenyl)amino]-3-cyano-7-ethoxy-6-quinoliny]-4-(dimethylamino)-2-butenamide) (Wyeth); AG1478 (Pfizer); AG1571 (SU 5271; Pfizer); dual EGFR/HER2 tyrosine kinase
- 15 inhibitors such as lapatinib (TYKERB®, GSK572016 or N-[3-chloro-4-[(3-fluorophenyl)methoxy]phenyl]-6[[[2-methylsulfonyl]ethyl]amino]methyl]-2-furanyl]-4-quinazolinamine).

Chemotherapeutic agents also include "tyrosine kinase inhibitors" including the EGFR-targeted drugs noted in the preceding paragraph; small molecule HER2 tyrosine kinase inhibitor

- 20 such as TAK165 available from Takeda; CP-724,714, an oral selective inhibitor of the ErbB2 receptor tyrosine kinase (Pfizer and OSI); dual-HER inhibitors such as EKB-569 (available from Wyeth) which preferentially binds EGFR but inhibits both HER2 and EGFR-overexpressing cells; lapatinib (GSK572016; available from Glaxo-SmithKline), an oral HER2 and EGFR tyrosine kinase inhibitor; PKI-166 (available from Novartis); pan-HER inhibitors such as
- 25 canertinib (CI-1033; Pharmacia); Raf-1 inhibitors such as antisense agent ISIS-5132 available from ISIS Pharmaceuticals which inhibit Raf-1 signaling; non-HER targeted TK inhibitors such as imatinib mesylate (GLEEVEC®, available from Glaxo SmithKline); multi-targeted tyrosine kinase inhibitors such as sunitinib (SUTENT®, available from Pfizer); VEGF receptor tyrosine kinase inhibitors such as vatalanib (PTK787/ZK222584, available from Novartis/Schering AG);
- 30 MAPK extracellular regulated kinase I inhibitor CI-1040 (available from Pharmacia); quinazolines, such as PD 153035, 4-(3-chloroanilino) quinazoline; pyridopyrimidines; pyrimidopyrimidines; pyrrolopyrimidines, such as CGP 59326, CGP 60261 and CGP 62706; pyrazolopyrimidines, 4-(phenylamino)-7H-pyrrolo[2,3-d] pyrimidines; curcumin (diferuloyl methane, 4,5-bis (4-fluoroanilino)phthalimide); tyrphostines containing nitrothiophene moieties;

PD-0183805 (Warner-Lambert); antisense molecules (*e.g.* those that bind to HER-encoding nucleic acid); quinoxalines (US Patent No. 5,804,396); tryphostins (US Patent No. 5,804,396); ZD6474 (Astra Zeneca); PTK-787 (Novartis/Schering AG); pan-HER inhibitors such as CI-1033 (Pfizer); Affinitac (ISIS 3521; Isis/Lilly); imatinib mesylate (GLEEVEC®); PKI 166 (Novartis); GW2016 (Glaxo SmithKline); CI-1033 (Pfizer); EKB-569 (Wyeth); Semaxinib (Pfizer); ZD6474 (AstraZeneca); PTK-787 (Novartis/Schering AG); INC-1C11 (Imclone), rapamycin (sirolimus, RAPAMUNE®); or as described in any of the following patent publications: US Patent No. 5,804,396; WO 1999/09016 (American Cyanamid); WO 1998/43960 (American Cyanamid); WO 1997/38983 (Warner Lambert); WO 1999/06378 (Warner Lambert); WO 1999/06396 (Warner Lambert); WO 1996/30347 (Pfizer, Inc); WO 1996/33978 (Zeneca); WO 1996/3397 (Zeneca) and WO 1996/33980 (Zeneca).

Chemotherapeutic agents also include dexamethasone, interferons, colchicine, metoprine, cyclosporine, amphotericin, metronidazole, alemtuzumab, alitretinoin, allopurinol, amifostine, arsenic trioxide, asparaginase, BCG live, bevacuzimab, bexarotene, cladribine, clofarabine, darbepoetin alfa, denileukin, dexrazoxane, epoetin alfa, elotinib, filgrastim, histrelin acetate, ibritumomab, interferon alfa-2a, interferon alfa-2b, lenalidomide, levamisole, mesna, methoxsalen, nandrolone, nelarabine, nofetumomab, oprelvekin, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, plicamycin, porfimer sodium, quinacrine, rasburicase, sargramostim, temozolomide, VM-26, 6-TG, toremifene, tretinoin, ATRA, valrubicin, zoledronate, and zoledronic acid, and pharmaceutically acceptable salts thereof.

Chemotherapeutic agents also include hydrocortisone, hydrocortisone acetate, cortisone acetate, tixocortol pivalate, triamcinolone acetonide, triamcinolone alcohol, mometasone, amcinonide, budesonide, desonide, fluocinonide, fluocinolone acetonide, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, fluocortolone, hydrocortisone-17-butyrate, hydrocortisone-17-valerate, aclometasone dipropionate, betamethasone valerate, betamethasone dipropionate, prednicarbate, clobetasone-17-butyrate, clobetasol-17-propionate, fluocortolone caproate, fluocortolone pivalate and fluprednidene acetate; immune selective anti-inflammatory peptides (ImSAIDs) such as phenylalanine-glutamine-glycine (FEG) and its D-isomeric form (feG) (IMULAN BioTherapeutics, LLC); anti-rheumatic drugs such as azathioprine, ciclosporin (cyclosporine A), D-penicillamine, gold salts, hydroxychloroquine, leflunomideminocycline, sulfasalazine, tumor necrosis factor alpha (TNF α) blockers such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi), Interleukin 1 (IL-1)

blockers such as anakinra (Kineret), T cell costimulation blockers such as abatacept (Orencia), Interleukin 6 (IL-6) blockers such as tocilizumab (ACTEMERA®); Interleukin 13 (IL-13) blockers such as lebrikizumab; Interferon alpha (IFN) blockers such as Rontalizumab; Beta 7 integrin blockers such as rhuMAb Beta7; IgE pathway blockers such as Anti-M1 prime;

5 Secreted homotrimeric LTa3 and membrane bound heterotrimer LTa1/β2 blockers such as Anti-lymphotoxin alpha (LTa); radioactive isotopes (e.g., At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu); miscellaneous investigational agents such as thioplatin, PS-341, phenylbutyrate, ET-18-OCH₃, or farnesyl transferase inhibitors (L-739749, L-744832); polyphenols such as quercetin, resveratrol, piceatannol, epigallocatechine gallate,

10 theaflavins, flavanols, procyanidins, betulinic acid and derivatives thereof; autophagy inhibitors such as chloroquine; delta-9-tetrahydrocannabinol (dronabinol, MARINOL®); beta-lapachone; lapachol; colchicines; betulinic acid; acetylcamptothecin, scopollectin, and 9-aminocamptothecin); podophyllotoxin; tegafur (UFTORAL®); bexarotene (TARGRETIN®); bisphosphonates such as clodronate (for example, BONEFOS® or OSTAC®), etidronate

15 (DIDROCAL®), NE-58095, zoledronic acid/zoledronate (ZOMETA®), alendronate (FOSAMAX®), pamidronate (AREDIA®), tiludronate (SKELID®), or risedronate (ACTONEL®); and epidermal growth factor receptor (EGF-R); vaccines such as THERATOPE® vaccine; perifosine, COX-2 inhibitor (e.g. celecoxib or etoricoxib), proteasome inhibitor (e.g. PS341); CCI-779; tipifarnib (R11577); orafenib, ABT510; Bcl-2 inhibitor such as

20 oblimersen sodium (GENASENSE®); pixantrone; farnesyltransferase inhibitors such as lonafarnib (SCH 6636, SARASARTM); and pharmaceutically acceptable salts, acids or derivatives of any of the above; as well as combinations of two or more of the above such as CHOP, an abbreviation for a combined therapy of cyclophosphamide, doxorubicin, vincristine, and prednisolone; and FOLFOX, an abbreviation for a treatment regimen with oxaliplatin

25 (ELOXATINTM) combined with 5-FU and leucovorin.

Chemotherapeutic agents also include non-steroidal anti-inflammatory drugs with analgesic, antipyretic and anti-inflammatory effects. NSAIDs include non-selective inhibitors of the enzyme cyclooxygenase. Specific examples of NSAIDs include aspirin, propionic acid derivatives such as ibuprofen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin and naproxen,

30 acetic acid derivatives such as indomethacin, sulindac, etodolac, diclofenac, enolic acid derivatives such as piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam and isoxicam, fenamic acid derivatives such as mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, and COX-2 inhibitors such as celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, rofecoxib, and valdecoxib. NSAIDs can be indicated for the symptomatic relief of

conditions such as rheumatoid arthritis, osteoarthritis, inflammatory arthropathies, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, acute gout, dysmenorrhoea, metastatic bone pain, headache and migraine, postoperative pain, mild-to-moderate pain due to inflammation and tissue injury, pyrexia, ileus, and renal colic.

5 Chemotherapeutic agents also include treatments for Alzheimer's Disease such as donepezil hydrochloride and rivastigmine; treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating multiple sclerosis (MS) such as beta interferon (e.g., Avonex[®] and Rebif[®]), glatiramer acetate, and mitoxantrone; treatments for asthma such as
10 albuterol and montelukast sodium; agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophosphamide, azathioprine, and sulfasalazine; neurotrophic
15 factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic
20 agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

Additionally, chemotherapeutic agents include pharmaceutically acceptable salts, acids or derivatives of any of chemotherapeutic agents, described herein, as well as combinations of two or more of them.

25 The amount of both the compound as described herein and additional agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. In certain embodiments, compositions of this invention are formulated such that a dosage of between 0.01 - 100 mg/kg
30 body weight/day of an inventive can be administered.

The additional therapeutic agent and the compound as described herein may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions may be less than that required in a monotherapy utilizing only that therapeutic agent, or there may be fewer side effects for the patient given that a lower dose is used. In certain embodiments, in

such compositions a dosage of between 0.01 – 1,000 µg/kg body weight/day of the additional therapeutic agent can be administered.

In particular, provided herein are methods of treating cancer in an individual comprising administering to the individual (a) a compound as described herein and (b) a cytotoxic agent

(*e.g.*, targeted therapy, chemotherapy, and/or radiotherapy).

In certain embodiments of any of the methods, the cytotoxic agent is a targeted therapy. In certain embodiments, the targeted therapy is one or more of an EGFR antagonist, RAF inhibitor, and/or PI3K inhibitor.

In certain embodiments of any of the methods, the targeted therapy is an EGFR antagonist. In certain embodiments of any of the methods, the EGFR antagonist is N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine and/or a pharmaceutical acceptable salt thereof. In certain embodiments, the EGFR antagonist is N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. In certain embodiments, the EGFR antagonist is N-(4-(3-fluorobenzyloxy)-3-chlorophenyl)-6-(5-((2-(methylsulfonyl)ethylamino)methyl)furan-2-yl)quinazolin-4-amine, di4-methylbenzenesulfonate or a pharmaceutically acceptable salt thereof (*e.g.*, lapatinib).

In certain embodiments of any of the methods, targeted therapy is a RAF inhibitor. In certain embodiments, the RAF inhibitor is a BRAF inhibitor. In certain embodiments, the RAF inhibitor is a CRAF inhibitor. In certain embodiments, the BRAF inhibitor is vemurafenib. In certain embodiments, the RAF inhibitor is 3-(2-cyanopropan-2-yl)-N-(4-methyl-3-(3-methyl-4-oxo-3,4-dihydroquinazolin-6-ylamino)phenyl)benzamide or a pharmaceutically acceptable salt thereof (*e.g.*, AZ628 (CAS# 878739-06-1)).

In certain embodiments of any of the methods, the targeted therapy is a PI3K inhibitor.

In certain embodiments of any of the methods, the cytotoxic agent is chemotherapy. In certain embodiments of any of the methods, the chemotherapy is a taxane. In certain embodiments, the taxane is paclitaxel. In certain embodiments, the taxane is docetaxel.

In certain embodiments of any of the methods, the cytotoxic agent is a platinum agent. In certain embodiments, the platinum agent is carboplatin. In certain embodiments, the platinum agent is cisplatin. In certain embodiments of any of the methods, the cytotoxic agent is a taxane and a platinum agent. In certain embodiments, the taxane is paclitaxel. In certain embodiments, the taxane is docetaxel. In certain embodiments, the platinum agent is carboplatin. In certain embodiments, the platinum agent is cisplatin.

In certain embodiments of any of the methods, the cytotoxic agent is a vinca alkylid. In certain embodiments, the vinca alkylid is vinorelbine. In certain embodiments of any of the

methods, the chemotherapy is a nucleoside analog. In certain embodiments, the nucleoside analog is gemcitabine.

In certain embodiments of any of the methods, the cytotoxic agent is radiotherapy.

5 In certain embodiments of any of the methods, the compound as described herein is concomitantly administered with the cytotoxic agent (*e.g.*, targeted therapy, chemotherapy, and/or radiotherapy). In certain embodiments, the compound as described herein is administered prior to and/or concurrently with the cytotoxic agent (*e.g.*, targeted therapy, chemotherapy, and/or radiotherapy).

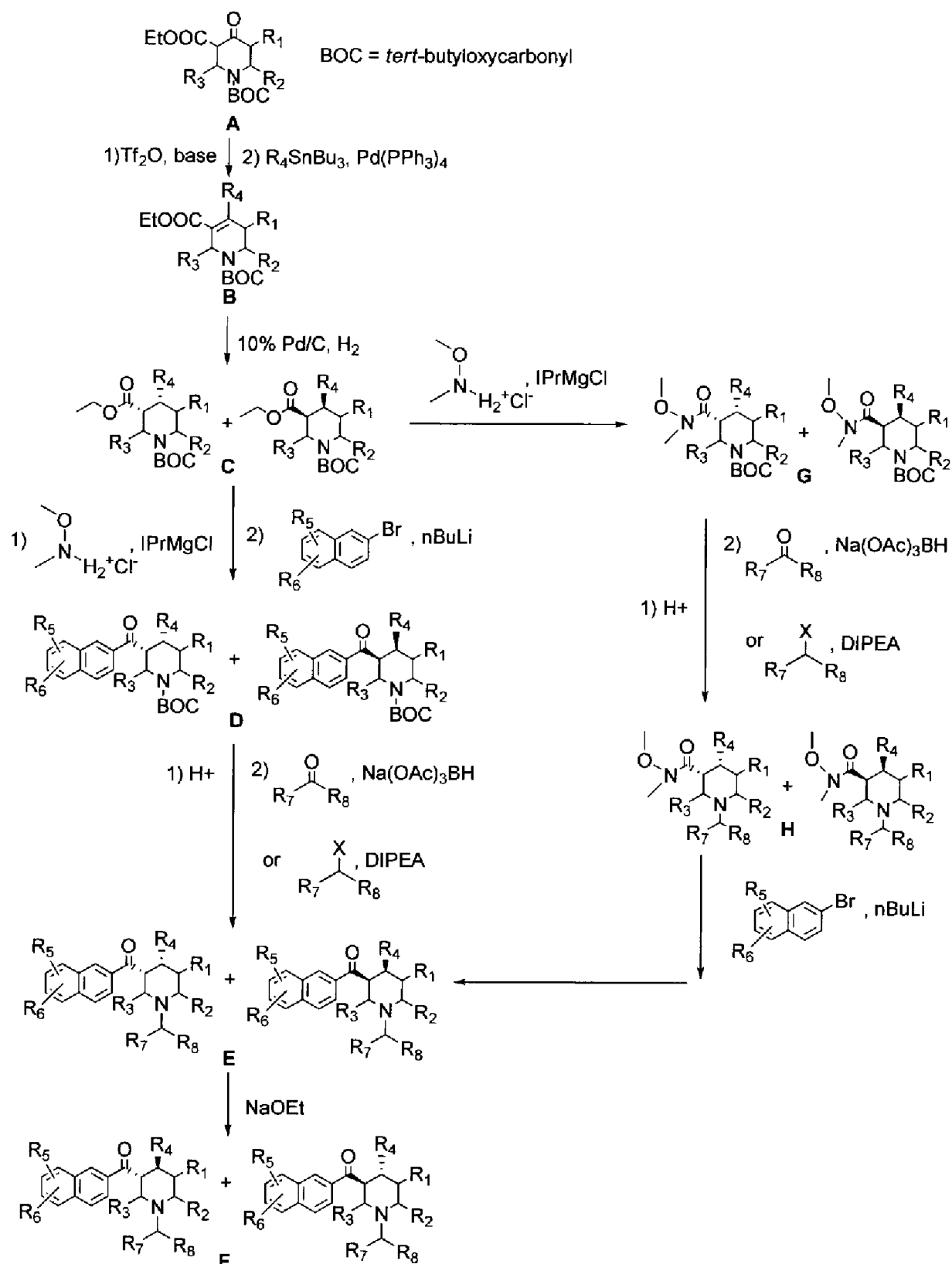
10 In certain embodiments of any of the methods, the cancer is lung cancer (*e.g.*, non-small cell lung cancer), breast cancer (*e.g.*, triple-negative breast cancer), pancreatic cancer, leukemia (*e.g.*, AML, CML, ALL (*e.g.*, T-cell or B-cell), MLL), lymphoma, bladder cancer, prostate cancer and/or seminoma. In certain embodiments, the cancer is lung. In certain embodiments, the lung cancer is NSCLC. In certain embodiments, the cancer is leukemia. In certain embodiments, the cancer is lymphoma.

15 **EXEMPLIFICATION**

As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds, the following general methods, and other methods known to one of ordinary skill in the art, can typically be applied to all
20 compounds and subclasses and species of each of these compounds, as described herein.

The general synthetic methods illustrated in Schemes 1-2 were used to prepare the compounds of the Examples as detailed below.

Generic Scheme:



Treatment of β -ketoesters as exemplified by formula A in an organic solvent such as, but not limited to, DCM with trifluoromethanesulfonic anhydride in the presence of an organic base

such as, but not limited to, diisopropylethyl amine at a temperature of -78°C can provide the corresponding vinyl-triflate. Treatment of the vinyl-triflate with a nucleophile such as, but not limited to, an alkyl stannane in the presence of a catalyst such as, but not limited to, palladium triphenylphosphine tetrakis can then provide $\square\square\square\square$ unsaturated esters as exemplified by

5 formula B. These entities can then be reduced using conditions such as, but not limited to, hydrogenation in the presence of palladium to predominantly afford the *cis*-diastereomers of the corresponding BOC-protected piperidine esters as exemplified by formula C. Both *cis* diastereomers can then be transformed into the weinreb amide by treating with *N,O*-dimethylhydroxylamine hydrochloride in the presence of isopropylmagnesium chloride in an

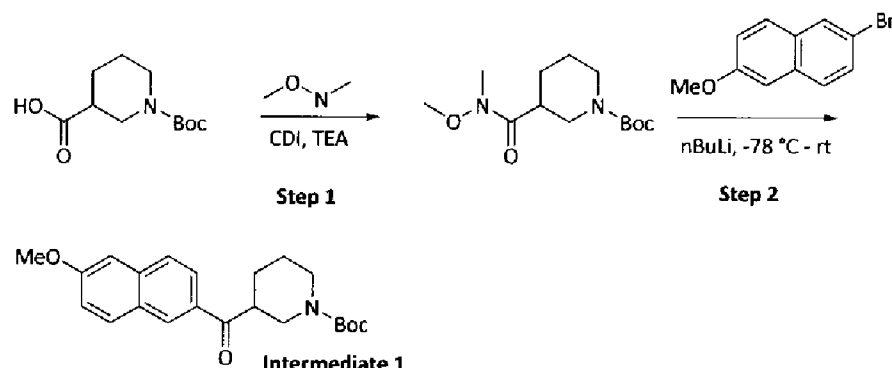
10 organic solvent such as, but not limited to, THF at a temperature between -78°C and 0°C . The weinreb amides can then be converted to the corresponding ketones as exemplified by formula D under conditions such as, but not limited to, lithium halogen exchange conditions with both commercially available and custom synthesized arylbromides. The BOC group can then be cleaved to reveal the free amine of the piperidine sub-unit by exposure to strong acid such as,

15 but not limited to, trifluoroacetic acid in an organic solvent such as, but not limited to, DCM. Next, the free amine can be treated with ketones and aldehydes in the presence of a reducing agent such as, but not limited to, sodium triacetoxyborohydride or treated with alkylhalides in the presence of an organic base such as, but not limited to, diisopropylethylamine to produce *N*-alkylated piperidine ketones as exemplified by formula E. In addition, the *cis*-enantiomers can

20 be transformed into the corresponding *trans*-enantiomers exemplified by formula F by exposure to a strong base such as , but not limited to, sodium ethoxide in an organic solvent such as, but not limited to ethanol.

Alternatively, the unsaturated esters exemplified by formula C can be converted to the corresponding weinreb amides as exemplified by formula G through previously described

25 conditions. These intermediates can then be BOC deprotected and *N*-alkylated using previously described conditions to afford the *N*-alkylated weinreb amides as exemplified H. These entities can then be converted into the corresponding aryl ketones as exemplified by formula E using previously described conditions.

Synthesis of Intermediates**Intermediate 1: *tert*-butyl 3-(6-methoxy-2-naphthoyl)piperidine-1-carboxylate**

5

Step 1:**Benzyl 3-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate**

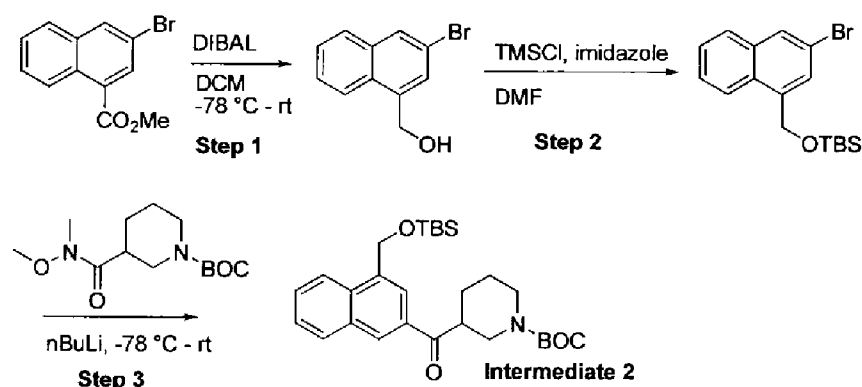
To a solution of 1-benzoyloxycarbonylpiperidine-3-carboxylic acid (10 g, 43.6 mmol) in THF (100 mL) at 0 °C was added 1,1'-carbonyldiimidazole (38.57 g, 52.3 mmol). The mixture was stirred at 0 °C for 1 h. Triethylamine (7.13 g, 69.8 mmol) was added followed by *N*-methoxymethanamine hydrochloride (6.38 g, 65.4 mmol). The mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was diluted with EtOAc, washed with 0.5 N HCl, sat. NaHCO₃, and brine. The organic layer was dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash chromatography (0-30% EtOAc/heptane) to give the title compound (11.03 g, 93% yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.28 (m, 5H), 5.20 – 5.07 (m, 2H), 4.15 (d, *J* = 34.48 Hz, 2H), 3.66 (d, *J* = 38.49 Hz, 3H), 3.16 (s, 3H), 2.94 (d, *J* = 12.21 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.79 – 1.62 (m, 2H), 1.57 (s, 2H). LCMS (ESI) *m/z* 307.2 [M+H⁺].

Step 2:***tert*-butyl 3-(6-methoxy-2-naphthoyl)piperidine-1-carboxylate**

A solution of 2-bromo-6-methoxy-naphthalene (3.56 g, 15 mmol) in THF (60 mL) was cooled to -78 °C. A solution of *n*BuLi (2.5 M in hexane, 6.0 mL, 15 mmol) was added dropwise. After stirring for 1 h at -78 °C, a solution of *tert*-butyl 3-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate (2.723 g, 10 mmol) in THF (5 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with sat. NH₄Cl, extracted with DCM (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash chromatography (0-5%

EtOAc/DCM) to give the title compound (3.36 g, 91% yield) as a pale yellow foam. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.42 (d, *J* = 1.71 Hz, 1H), 8.00 (dd, *J* = 1.82, 8.65 Hz, 1H), 7.87 (d, *J* = 8.94 Hz, 1H), 7.78 (d, *J* = 8.62 Hz, 1H), 7.21 (dd, *J* = 2.52, 8.97 Hz, 1H), 7.17 (s, 1H), 4.5-4.303 (m, 1H), 4.16-4.12 (m, 1H), 3.95 (s, 3H), 3.60 – 3.49 (m, 1H), 3.03-2.97 (m, 1H), 2.81-2.75 (m, 1H), 2.11-2.07 (m, 1H), 1.85 – 1.59 (m, 3H), 1.48 (s, 9H). LCMS (ESI) *m/z* 370.2 [M+H⁺].

Intermediate 2: *tert*-butyl 3-[4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]naphthalene-2-carbonyl]piperidine-1-carboxylate



Step 1:

(3-bromo-1-naphthyl)methanol

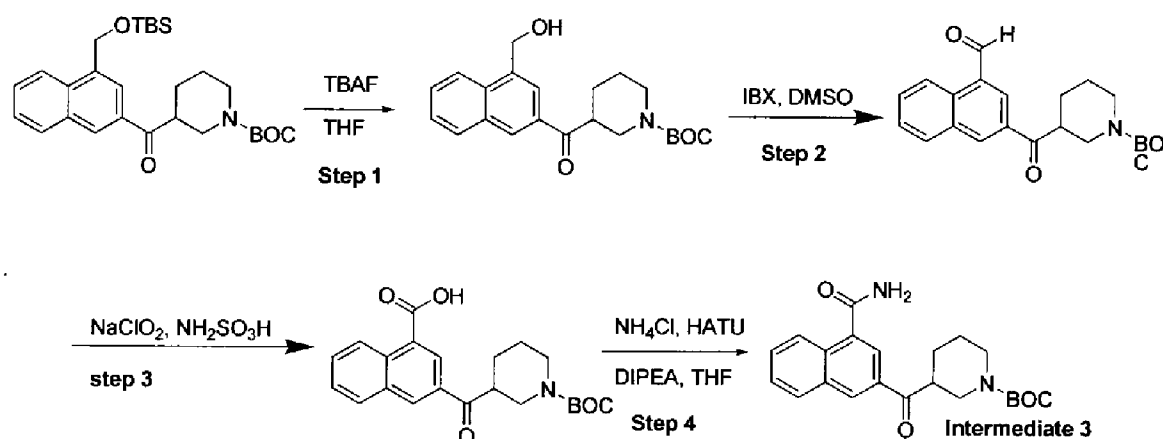
To a solution of methyl 3-bromonaphthalene-1-carboxylate (800 mg, 3.02 mmol) in DCM (12 mL) at -78 °C was added DIBAL-H (1 M in THF, 9 mL, 9 mmol) dropwise. The mixture was warmed to room temperature and stirred for 2 h. The reaction was cooled to -78°C, charged with 2 mL of methanol, warmed to room temperature, and poured into 40 mL of a 25% Rochelle's salt aqueous solution. The resulting mixture was vigorously stirred. Once the organic layer became clear, it was separated and extracted with EtOAc (3x). The combined organics were dried (Na₂SO₄), filtered and concentrated to give the title compound (715 mg, 99.9% yield) as a light yellow solid which was used directly without purification. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.05 – 8.01 (m, 1H), 7.96 (d, *J* = 2.08 Hz, 1H), 7.79-7.77 (m, 1H), 7.67 – 7.64 (m, 1H), 7.58 – 7.49 (m, 2H), 5.14 (d, *J* = 5.82 Hz, 2H), 1.78 (td, *J* = 1.28, 5.98 Hz, 1H).

Step 2:**(3-bromo-1-naphthyl)methoxy-*tert*-butyl-dimethyl-silane**

The mixture of (3-bromo-1-naphthyl)methanol (715 mg, 3.02 mmol), imidazole (514 mg, 7.545 mmol), and TMSCl (586 mg, 3.77 mmol) in DMF (15 mL) was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with sat. aqueous NaCl twice. The aqueous phase was back-extracted with EtOAc (2x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash chromatography (0-10% EtOAc/heptane) to give the title compound (971 mg, 91.6% yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 7.85 (m, 2H), 7.79 – 7.72 (m, 1H), 7.69-7.68 (m, 1H), 7.53 – 7.44 (m, 2H), 5.16 (t, *J* = 0.88 Hz, 2H), 0.97 (s, 9H), 0.15 (s, 6H).

Step 3:***tert*-butyl 3-[4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]naphthalene-2-carbonyl]piperidine-1-carboxylate**

A solution of (3-bromo-1-naphthyl)methoxy-*tert*-butyl-dimethyl-silane (719 mg, 2.0 mmol) in THF (6 mL) was cooled to -78 °C before a solution of nBuLi (2.5 M in hexane, 0.8 mL, 2.0 mmol) was added dropwise. After stirring for 1 h at -78 °C, a solution of *tert*-butyl 3-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate (364 mg, 1.34 mmol) in THF (2 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with sat. NH₄Cl and extracted with DCM (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash chromatography (0-25% EtOAc/heptane) to give the title compound (451 mg, 69.8% yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.42 (s, 1H), 8.13 (d, *J* = 1.63 Hz, 1H), 8.02 (t, *J* = 7.59 Hz, 2H), 7.63 (ddd, *J* = 1.41, 6.73, 8.28 Hz, 1H), 7.57 (t, *J* = 7.72 Hz, 1H), 5.21 (s, 2H), 4.31 (brs, 1H), 4.20 – 4.08 (m, 1H), 3.61-3.55 (m, 1H), 3.06 (brs, 1H), 2.79 (t, *J* = 12.67 Hz, 1H), 2.18 – 2.06 (m, 1H), 1.85 – 1.59 (m, 3H), 1.47 (s, 9H), 0.97 (s, 9H), 0.15 (s, 6H). LCMS (ESI) *m/z* 484.2 [M+H⁺].

Intermediate 3: *tert*-butyl 3-(4-carbamoylnaphthalene-2-carbonyl)piperidine-1-carboxylate**5 Step 1:*****tert*-butyl 3-[4-(hydroxymethyl)naphthalene-2-carbonyl]piperidine-1-carboxylate**

To a solution of *tert*-butyl 3-[4-[[*tert*-butyl(dimethyl)silyl]oxymethyl]naphthalene-2-carbonyl]piperidine-1-carboxylate (1.46 g, 3.02 mmol) in THF (15 mL) was added TBAF (1.0 M in THF, 4.5 mL). The mixture was stirred at room temperature for 1.5 h. The mixture was quenched with sat. aqueous NH_4Cl and extracted with DCM (3x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica-gel flash chromatography (0-60% EtOAc/heptane) to give the title compound (930 mg, 83.4% yield) as a yellow oil. LCMS (ESI) m/z 370.2 $[\text{M}+\text{H}^+]$.

15 Step 2:***tert*-butyl 3-(4-formylnaphthalene-2-carbonyl)piperidine-1-carboxylate**

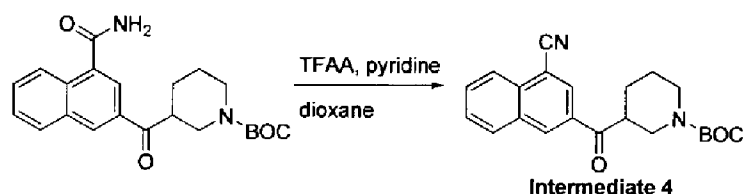
To a solution of *tert*-butyl 3-[4-(hydroxymethyl)naphthalene-2-carbonyl]piperidine-1-carboxylate (680 mg, 1.84 mmol) in DMSO (12 mL) was added 2-iodobenzoic acid (1.718 g, 2.761 mmol). The mixture was stirred at room temperature for 3 h. The mixture was diluted with EtOAc and washed with sat. NaHCO_3 (1x), water (3x). The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-25% EtOAc/heptane) to give the title compound (488 mg, 72.2% yield) as a white solid. LCMS (ESI) m/z 368.2 $[\text{M}+\text{H}^+]$.

Step 3:**3-(1-(*tert*-butoxycarbonyl)piperidine-3-carbonyl)-1-naphthoic acid**

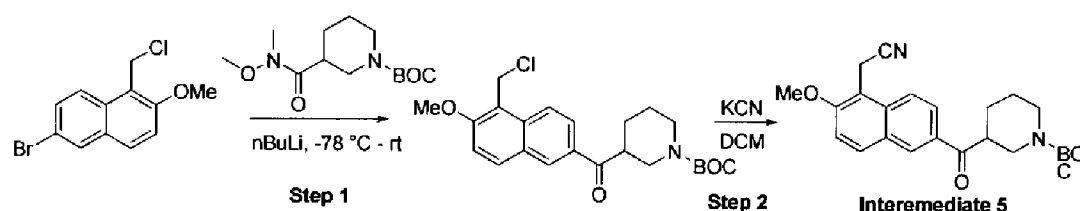
tert-butyl-3-(4-formylnaphthalene-2-carbonyl)piperidine-1-carboxylate (606 mg, 1.65 mmol) was dissolved in DCM (12 mL) and water (12 mL). Sulfamic acid (192 mg, 1.98 mmol) was added and the mixture was stirred vigorously at 0 °C for 5 min. A solution of sodium chlorite (179 mg, 1.98 mmol) in water (1 mL) was then added and the mixture was stirred at room temperature for 2 h. The mix was diluted with water and the layers were separated. The aqueous layer was extracted with DCM (2x). The combined organics were dried (Na₂SO₄), filtered and concentrated to give the title compound (679 mg, quantitative yield) as a light yellow foam. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.38 (s, 1H), 8.94 (s, 1H), 8.89 (d, *J* = 8.66 Hz, 1H), 8.55 (d, *J* = 1.77 Hz, 1H), 8.24 (d, *J* = 8.15 Hz, 1H), 7.84 – 7.76 (m, 1H), 7.71 (t, *J* = 7.47 Hz, 1H), 4.05-4.02 (m, 1H), 3.76-3.72 (m, 2H), 2.93 (t, *J* = 11.66 Hz, 1H), 2.08 – 1.90 (m, 1H), 1.84 – 1.71 (m, 1H), 1.61-1.56 (m, 2H), 1.34 (s, 9H). LCMS (ESI) *m/z* 384.2 [M+H⁺].

Step 4:***tert*-butyl 3-(4-carbamoylnaphthalene-2-carbonyl)piperidine-1-carboxylate**

A mixture of 3-(1-*tert*-butoxycarbonylpiperidine-3-carbonyl)naphthalene-1-carboxylic acid (1.252 mmol, 480 mg), NH₄Cl (335mg, 6.26 mmol), HATU (589 mg, 1.502 mmol) and DIPEA (404 mg, 3.13 mmol) in THF (5 mL) was stirred at room temperature for 16 h. The reaction was quenched with sat. NH₄Cl and extracted with EtOAc (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash chromatography (0-80% EtOAc/heptane) to give the title compound (491 mg, 99% yield) as a white solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 (s, 1H), 8.34 (d, *J* = 8.25 Hz, 1H), 8.24 – 8.15 (m, 1H), 8.09 (s, 1H), 8.06 (d, *J* = 1.66 Hz, 1H), 7.73 (ddd, *J* = 1.48, 6.85, 8.52 Hz, 1H), 7.67 (ddd, *J* = 1.44, 6.94, 8.24 Hz, 2H), 4.06-4.00 (m, 1H), 3.90-3.087 (m, 1H), 3.74-3.70 (m, 1H), 2.86 (t, *J* = 11.42 Hz, 1H), 2.04-2.01 (m, 1H), 1.75-1.73 (m, 1H), 1.61-1.57 (m, 1H), 0.86 (t, *J* = 6.74 Hz, 2H). LCMS (ESI) *m/z* 383.2 [M+H⁺].

Intermediate 4 : *tert*-butyl 3-(4-cyanonaphthalene-2-carbonyl)piperidine-1-carboxylate

To a cloudy solution of *tert*-butyl 3-(4-carbamoylnaphthalene-2-carbonyl)piperidine-1-carboxylate (292 mg, 0.764 mmol) in 1,4-dioxane (2 mL) at room temperature was added pyridine (211 mg, 2.673 mmol) followed by trifluoroacetic anhydride (353 mg, 1.68 mmol). The mixture was stirred at room temperature for 2 h. The reaction was quenched with water and extracted with EtOAc (3x). The combined organic layers were washed with 10% citric acid, brine, dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash chromatography (0-25% EtOAc/heptane) to give the title compound (228 mg, 81.9% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.75 – 8.67 (m, 1H), 8.46 (d, *J* = 1.68 Hz, 1H), 8.32 – 8.27 (m, 1H), 8.09 (d, *J* = 7.96 Hz, 1H), 7.88 – 7.80 (m, 1H), 7.73 (t, *J* = 7.57 Hz, 1H), 4.32 br(s, 1H), 4.13-4.11 (m, 1H), 3.55-3.51 (m, 1H), 3.04 (brs, 1H), 2.83 (t, *J* = 12.25 Hz, 1H), 2.10-2.07 (m, 1H), 1.84-1.72 (m, 2H), 1.68-1.64 (m, 1H), 1.48 (s, 9H). LCMS (ESI) *m/z* 365.2 [M+H⁺].

Intermediate 5: *tert*-butyl 3-[5-(cyanomethyl)-6-methoxy-naphthalene-2-carbonyl]piperidine-1-carboxylate**Step 1:*****tert*-butyl 3-[5-(chloromethyl)-6-methoxy-naphthalene-2-carbonyl]piperidine-1-carboxylate**

A solution of 6-bromo-(chloromethyl)-2-methoxynaphthalene (530 mg, 1.8 mmol) in THF (8 mL) was cooled to -78 °C before a solution of nBuLi (2.5 M in hexane, 0.86 mL, 2.16 mmol) was added dropwise. After stirring for 1 h at -78 °C, a solution of *tert*-butyl-3-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate (327 mg, 1.2 mmol) in THF (2 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h. The

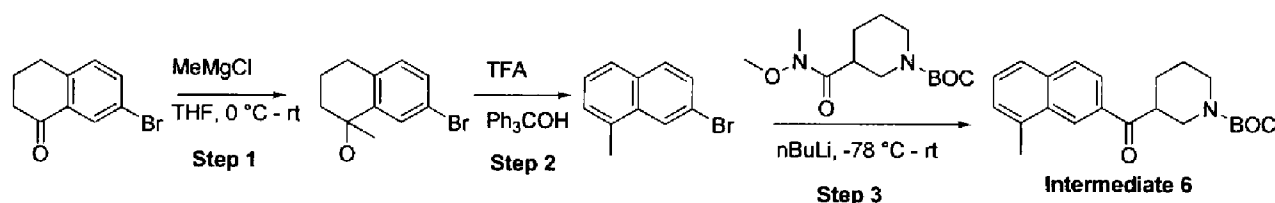
reaction was quenched with sat. NH_4Cl and extracted with DCM (3x). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-25% EtOAc/heptane) to give the title compound (380 mg, 75.8% yield) as a colorless oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 8.12 – 8.09 (m, 2H), 8.01 (d, J = 9.20 Hz, 1H), 7.35 (d, J = 9.17 Hz, 1H), 5.16 (s, 2H), 4.33 (brs, 1H), 4.16-4.13 (m, 1H), 4.05 (s, 3H), 3.60 – 3.48 (m, 1H), 3.00 (brs, 1H), 2.82-2.76 (m, 1H), 2.11-2.07 (m, 1H), 1.85 – 1.69 (m, 2H), 1.74-1.61 (m, 1H), 1.48 (s, 9H).

Step 2:

***tert*-butyl 3-[5-(cyanomethyl)-6-methoxy-naphthalene-2-carbonyl]piperidine-1-carboxylate**

To a solution of *tert*-butyl 3-[5-(chloromethyl)-6-methoxy-naphthalene-2-carbonyl]piperidine-1-carboxylate (340 mg, 0.814 mmol) and benzyltriethylammonium chloride (37 mg, 0.1623 mmol) in DCM (4 mL) was added a solution of KCN (270 mg, 4.1 mmol) in water (500 μL). The mixture was heated at 35 $^\circ\text{C}$ for 6 h. The mixture was diluted with water and extracted with DCM (3x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-50% EtOAc/heptane) to give the title compound (265 mg, 79.6% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.48 (d, J = 1.77 Hz, 1H), 8.13 (dd, J = 1.86, 8.95 Hz, 1H), 8.03 (d, J = 9.07 Hz, 1H), 7.95 (d, J = 8.96 Hz, 1H), 7.37 (d, J = 9.07 Hz, 1H), 4.34 (brs, 1H), 4.16-4.14 (, 1H), 4.12 (s, 2H), 4.06 (s, 3H), 3.56-3.52 ms, 1H), 3.01 (brs, 1H), 2.86 – 2.73 (m, 1H), 2.11-2.07 (m, 1H), 1.85 – 1.69 (m, 2H), 1.68-1.62 (m, 1H), 1.48 (s, 9H). LCMS (ESI) m/z 409.2 $[\text{M}+\text{H}^+]$.

Intermediate 6: *tert*-butyl 3-(8-methylnaphthalene-2-carbonyl)piperidine-1-carboxylate



Step 1:**7-bromo-1-methyl-1,2,3,4-tetrahydronaphthalen-1-ol**

To a solution of 7-bromotetralin-1-one (1.0 g, 4.44 mmol) in THF (20 mL) at 0 °C was added MeMgCl (3 M in THF, 5.92 mL, 17.8 mmol) dropwise. The mixture was stirred at room temperature for 2 h. The reaction was quenched with Sat. NH₄Cl and extracted with DCM (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated to a yellow oil to afford the title compound (715 mg, 99.9% yield) that was used without purification. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 2.10 Hz, 1H), 7.29 – 7.23 (m, 1H), 6.94 (dt, *J* = 1.00, 8.28 Hz, 1H), 3.77 – 3.69 (m, 1H), 2.72 (q, *J* = 6.25, 7.13 Hz, 2H), 1.95 – 1.79 (m, 4H).

Step 2:**7-bromo-1-methylnaphthalene**

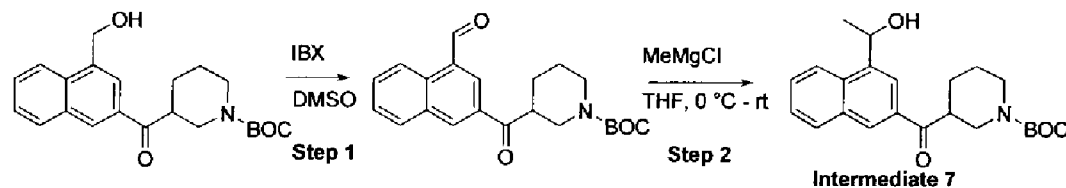
The crude product from Step 1 was combined with triphenylmethanol (1.55 g, 5.77 mmol) and TFA (2.53 g, 22.2 mmol). The resulting dark brown mixture was stirred at room temperature for 18 h. The mixture was diluted with water and extracted with DCM (3x). The combine organic layers were washed with sat. NaHCO₃, dried (Na₂SO₄), filtered and concentrated. The oily residue was treated with heptane. The precipitate was filtered off and washed with heptane. The filtrate was concentrated, and purified by silica flash chromatography (100% heptane) to give the title compound (736 mg, 75% yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.13 (d, *J* = 1.77 Hz, 1H), 7.68 (d, *J* = 8.71 Hz, 1H), 7.64 (d, *J* = 8.04 Hz, 1H), 7.53 (dd, *J* = 1.92, 8.68 Hz, 1H), 7.36 (t, *J* = 7.53 Hz, 1H), 7.33 (s, 1H), 2.63 (s, 3H).

Step 3:***tert*-butyl 3-(8-methylnaphthalene-2-carbonyl)piperidine-1-carboxylate**

A solution of 7-bromo-1-methylnaphthalene (338 mg, 1.5 mmol) in THF (5 mL) was cooled to -78°C before a solution of nBuLi (2.5 M in hexane, 0.8 mL, 2.00 mmol) was added dropwise. After stirring for 1 h at -78 °C, a solution of *tert*-butyl 3-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate (272 mg, 1.0 mmol) in THF (2 mL) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with sat. NH₄Cl and extracted with DCM (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash chromatography (0-20% EtOAc/heptane) to give the title compound (0.7414 mmol, 74.1% yield, 262 mg) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.02 (dd, *J* = 1.73, 8.56 Hz, 1H), 7.91 (d, *J* = 8.60 Hz, 1H), 7.74 (d, *J* = 8.18 Hz, 1H), 7.50 (dd, *J* = 6.99,

8.23 Hz, 1H), 7.43 – 7.37 (m, 1H), 4.15-4.10 (m, 2H), 3.96(brs, 1H), 3.61-3.57 (m, 1H), 2.79 (s, 3H), 2.83-2.79 (m, 2H), 2.15 – 2.07 (m, 1H), 1.86 – 1.69 (m, 3H), 1.48 (s, 9H). LCMS (ESI) m/z 354.2 $[M+H]^+$.

5 **Intermediate 7: *tert*-butyl 3-[4-(1-hydroxyethyl)naphthalene-2-carbonyl]piperidine-1-carboxylate**



Step 1:

***tert*-butyl 3-(4-formylnaphthalene-2-carbonyl)piperidine-1-carboxylate**

- 10 To a solution of *tert*-butyl 3-[4-(hydroxymethyl)naphthalene-2-carbonyl]piperidine-1-carboxylate (1.900 mmol, 702 mg) in DMSO (12 mL) was added 2-iodoxybenzoic acid (1.77 g, 2.851 mmol). The mixture was stirred at room temperature for 2 h. The mixture was diluted with EtOAc and washed with sat. NaHCO₃ (1x) and water (3x). The organic phase was dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash
- 15 chromatography (0-25% EtOAc/heptane) to give the title compound (708 mg, 99% yield) as a white solid. ¹H NMR (300 MHz, Chloroform-*d*) δ 10.45 (s, 1H), 9.30 (d, *J* = 8.57 Hz, 1H), 8.72 (s, 1H), 8.56 (d, *J* = 1.82 Hz, 1H), 8.09 (dd, *J* = 1.16, 8.22 Hz, 1H), 7.83 (ddd, *J* = 1.38, 6.85, 8.49 Hz, 1H), 7.69 (t, *J* = 7.68 Hz, 1H), 4.36 (brs, 1H), 4.21 – 4.07 (m, 1H), 3.63-3.59 (m, 1H), 3.06 (brs, 1H), 2.83 (t, *J* = 12.31 Hz, 1H), 2.14-2.10 (m, 1H), 1.91 – 1.59 (m, 3H), 1.48 (s, 9H).
- 20 LCMS (ESI) m/z 368.2 $[M+H]^+$.

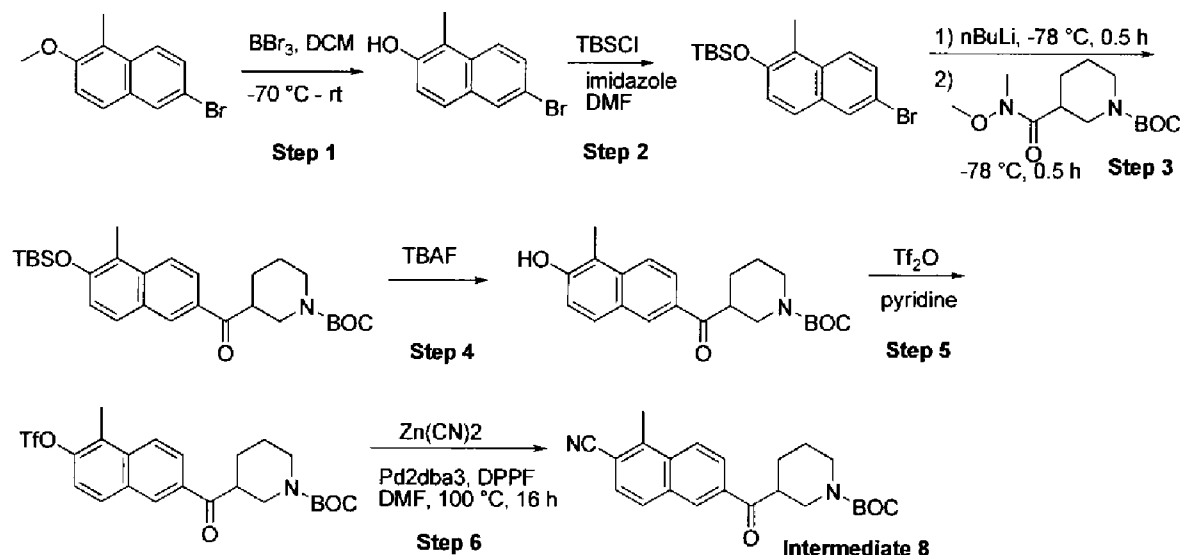
Step 2:

***tert*-butyl 3-[4-(1-hydroxyethyl)naphthalene-2-carbonyl]piperidine-1-carboxylate**

- To a solution of *tert*-butyl 3-(4-formylnaphthalene-2-carbonyl)piperidine-1-carboxylate (350 mg, 0.95 mmol) in THF (12 mL) in a salt-ice bath was added MeMgCl (3 M in THF, 0.36 mL, 1.08 mmol) dropwise. The mixture was stirred in a salt-ice bath for 5 min. The reaction was then quenched with sat. NH₄Cl at 0 °C and extracted with DCM (2x). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated to give the title compound (369 mg, 101% yield) as a white solid, which was used without purification. ¹H NMR (400 MHz, Chloroform-*d*) δ
- 25 8.41 (t, *J* = 2.17 Hz, 1H), 8.24 (s, 1H), 8.15 (td, *J* = 2.84, 6.66, 7.63 Hz, 1H), 8.02 (dd, *J* = 1.35, 8.26 Hz, 1H), 7.65 (ddd, *J* = 1.46, 6.85, 8.42 Hz, 1H), 7.57 (t, *J* = 7.55 Hz, 1H), 5.75 – 5.60 (m,
- 30

1H), 4.34 br(s, 1H), 4.15-4.11 (m, 1H), 3.62-3.58 (m, 1H), 3.00 (brs, 1H), 2.87 – 2.72 (m, 1H), 2.13-2.08 (m, 1H), 1.83-1.78 (m, 1H), 1.70 (dd, $J = 2.24, 6.50$ Hz, 3H), 1.67 – 1.60 (m, 3H), 1.48 (s, 9H). LCMS (ESI) m/z 400.2 $[M+H^+]$.

5 **Intermediate 8 : *tert*-butyl 3-(6-cyano-5-methyl-naphthalene-2-carbonyl)piperidine-1-carboxylate**



Step 1:

6-bromo-1-methyl-naphthalen-2-ol

- 10 To a solution of 6-bromo-2-methoxy-1-methyl-naphthalene (576 mg, 2.29 mmol) in DCM (5 mL) at -78°C was added BBr_3 (1 M in DCM, 2.75 mL, 2.75 mmol) dropwise. The mixture was slowly warmed to room temperature. After stirring for 1.5 h at room temperature, the reaction was quenched with ice-water and extracted with DCM (2x). The combined organics were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash
- 15 chromatography (0-25% EtOAc/heptane) to give the title compound (524 mg, 96% yield) as a white solid. ^1H NMR (400 MHz, Chloroform- d) δ 7.91 (d, $J = 2.11$ Hz, 1H), 7.78 (d, $J = 9.02$ Hz, 1H), 7.57 – 7.49 (m, 2H), 7.07 (d, $J = 8.79$ Hz, 1H), 4.92 (s, 1H), 2.51 (s, 3H). LCMS (ESI) m/z 237.0 $[M+H^+]$.

Step 2:**(6-bromo-1-methyl-2-naphthyl)oxy-*tert*-butyl-dimethyl-silane**

The mixture of 6-bromo-1-methyl-naphthalen-2-ol (613 mg, 2.58 mmol), imidazole (264 mg, 3.88 mmol), and TBSCl (482 mg, 3.1 mmol) in DMF (5 mL) was stirred at room temperature for 16 h. The mixture was diluted with EtOAc and washed with sat. NaCl twice. The aqueous phase was back-extracted with EtOAc once. The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash chromatography (0-5% EtOAc/heptane) to give the title compound (859 mg, 94.6% yield) as a white solid. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 2.08 Hz, 1H), 7.78 (d, *J* = 9.04 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.08 (d, *J* = 8.82 Hz, 1H), 2.50 (s, 3H), 1.05 (s, 9H), 0.23 (s, 6H).

Step 3:***tert*-butyl 3-[6-[*tert*-butyl(dimethyl)silyl]oxy-5-methyl-naphthalene-2-carbonyl]piperidine-1-carboxylate**

A solution of (6-bromo-1-methyl-2-naphthyl)oxy-*tert*-butyl-dimethyl-silane (1.668 mmol, 598 mg, 1.67 mmol) in THF (8 mL) was cooled to -78°C before a solution of *n*BuLi (2.5 M in hexane, 1.0 mL, 2.5 mmol) was added dropwise. After stirring for 30 min at -78 °C, a solution of *tert*-butyl 3-[methoxy(methyl)carbamoyl]piperidine-1-carboxylate (1.751 mmol, 476.8 mg) in THF (2 mL) was added dropwise. The mixture was stirred at -78°C for 30 min. The reaction was quenched with sat. NH₄Cl and extracted with DCM (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica flash chromatography (0-15% EtOAc/heptane) to give the title compound (562 mg, 69.7% yield) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 8.41 (d, *J* = 1.77 Hz, 1H), 8.02 (dd, *J* = 1.82, 8.94 Hz, 1H), 7.98 (s, 1H), 7.73 (d, *J* = 8.87 Hz, 1H), 7.13 (d, *J* = 8.85 Hz, 1H), 4.33 (s, 1H), 4.20 – 4.10 (m, 1H), 3.96 (s, 1H), 3.55 (dd, *J* = 8.91, 12.85 Hz, 1H), 2.78 (t, *J* = 12.02 Hz, 1H), 2.53 (s, 3H), 2.09 (d, *J* = 12.55 Hz, 1H), 1.83 – 1.59 (m, 4H), 1.48 (s, 9H), 1.06 (s, 9H), 0.26 (s, 6H). LCMS (ESI) *m/z* 484.2 [M+H⁺].

Step 4:***tert*-butyl 3-(6-hydroxy-5-methyl-naphthalene-2-carbonyl)piperidine-1-carboxylate**

To a solution of *tert*-butyl-3-[6-[*tert*-butyl(dimethyl)silyl]oxy-5-methyl-naphthalene-2-carbonyl]piperidine-1-carboxylate (562 mg, 1.16 mmol) in THF (12 mL) was added TBAF (1 M in THF, 2.3 mL, 2.3 mmol) dropwise. The reaction mixture was stirred at room temperature for 30 min. The mixture was quenched with sat. NH₄Cl and extracted with DCM (3x). The

combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-100% EtOAc/heptane) to give the title compound (354 mg, 82.5% yield) as a white solid. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.38 (d, J = 1.87 Hz, 1H), 8.05 – 7.98 (m, 1H), 7.94 (d, J = 9.01 Hz, 1H), 7.72 (d, J = 8.79 Hz, 1H), 7.12 (d, J = 8.79 Hz, 1H), 5.31 (brs, 1H), 4.34 (brs, 1H), 4.15-4.13 (m, 1H), 3.54 (tt, J = 3.68, 11.01 Hz, 1H), 3.01-2.99 (m, 1H), 2.79 (t, J = 12.58 Hz, 1H), 2.53 (s, 3H), 2.08 (d, J = 12.84 Hz, 1H), 1.85 – 1.71 (m, 2H), 1.71 – 1.59 (m, 1H), 1.49 (s, 9H).

Step 5:

***tert*-butyl 3-[5-methyl-6-(trifluoromethylsulfonyloxy)naphthalene-2-carbonyl]piperidine-1-carboxylate**

To a solution of *tert*-butyl 3-(6-hydroxy-5-methyl-naphthalene-2-carbonyl)piperidine-1-carboxylate (0.9367 mmol, 346 mg) in pyridine (4 mL) at 0°C was added trifluoromethanesulfonic anhydride (317 mg, 1.12 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1 h. The mix was diluted with water and extracted with EtOAc (2x). The combined organic layers were washed with 10% citric acid, brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by silica flash chromatography (0-30% EtOAc/heptane) to give the title compound (460 mg, 97.9% yield) as a colorless oil which solidified when drying in high vacuum. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.51 (s, 1H), 8.15 (d, J = 1.45 Hz, 2H), 7.93 (d, J = 9.04 Hz, 1H), 7.45 (d, J = 9.02 Hz, 1H), 4.34 (brs, 1H), 4.15-4.11 (m, 1H), 3.58-3.53 (m, 1H), 3.01 (brs, 1H), 2.81 (td, J = 2.81, 12.64, 13.25 Hz, 1H), 2.72 (s, 3H), 2.15 – 2.04 (m, 1H), 1.86 – 1.70 (m, 2H), 1.68-1.61 (m, 1H). LCMS (ESI) m/z 502 $[\text{M}+\text{H}^+]$.

Step 6:

***tert*-butyl 3-(6-cyano-5-methyl-naphthalene-2-carbonyl)piperidine-1-carboxylate**

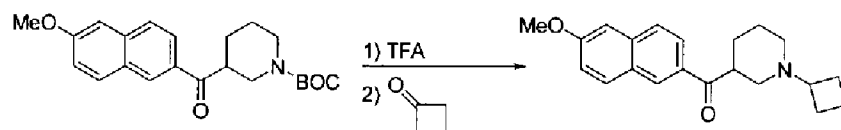
A mixture of *tert*-butyl 3-[5-methyl-6-(trifluoromethylsulfonyloxy)naphthalene-2-carbonyl]piperidine-1-carboxylate (417 mg, 0.83 mmol), ZnCN (98 mg, 0.83 mmol), Pd_2dba_3 (16mg, 0.0166 mmol) and 1,1'-bis(diphenylphosphino)ferrocene (234 mg, 0.042 mmol) in DMF (8 mL) was heated at 100 °C under N_2 for 16 h. The mixture was filtered through celite and concentrated. The crude product was purified by silica flash chromatography (0-30% EtOAc/heptane) to give the title compound (249 mg, 79% yield) as a colorless oil. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.49 (s, 1H), 8.15 (d, J = 1.54 Hz, 2H), 7.90 (d, J = 8.55 Hz, 1H), 7.61 (d, J = 8.52 Hz, 1H), 4.46 – 4.24 (m, 1H), 4.18 – 4.06 (m, 1H), 3.57 (7t, J = 3.44, 10.40 Hz,

1H), 3.11 – 2.95 (m, 1H), 2.94 (s, 3H), 2.88 – 2.78 (m, 1H), 2.16 – 2.05 (m, 1H), 1.85-1.72 (m, 2H), 1.68-1.64 (m, 1H), 1.49 (s, 9H). LCMS (ESI) m/z 379 $[M+H]^+$.

Synthesis of Final Compounds

5

Example 1 : (1-cyclobutylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone



10 To a solution of *tert*-butyl 3-(6-methoxynaphthalene-2-carbonyl)piperidine-1-carboxylate (1.666 g, 4.51 mmol) in DCM (5 mL) was added TFA (5.142 g, 45.1 mmol). The mixture was stirred at room temperature for 1 h. The mixture was concentrated to give (6-methoxynaphthalen-2-yl)(piperidin-3-yl)methanone as a colorless oil and used directly without purification.

A mixture of (6-methoxy-2-naphthyl)-(3-piperidyl)methanone (80 mg, 0.297 mmol),
 15 cyclopentanone (75 mg, 0.891 mmol), AcOH (36 mg, 0.594 mmol) and NaBH(OCH₃)₃ (99.4 mg, 0.446 mmol) in 1,2-dichloroethane (1.5 mL) was stirred at room temperature for 16 h. The reaction was quenched with 1 N NaOH and extracted with EtOAc (3x). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. The crude product was purified by preparative reverse phase HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% NH₄OH (aq))
 20 to give the title compound (57.2 mg, 57% yield) as a yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.60 (d, J = 1.47 Hz, 1H), 8.06 (d, J = 8.99 Hz, 1H), 7.94 – 7.86 (m, 2H), 7.40 (d, J = 2.57 Hz, 1H), 7.26 (dd, J = 2.56, 8.96 Hz, 1H), 3.92 (s, 3H), 3.72 (tt, J = 3.48, 10.84 Hz, 1H), 3.07 – 3.00 (m, 1H), 2.93 (m, 1H), 2.51 (m, 3H), 2.13 – 2.05 (m, 1H), 1.98 – 1.82 (m, 2H), 1.80 – 1.64 (m, 3H), 1.60 – 1.26 (m, 7H). LCMS (ESI) m/z 338 $[M+H]^+$,

25

The following compounds were prepared in a manner similar to example 1: (1-cyclobutylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone. In some cases, racemic mixtures are exemplified. In those cases where a specific enantiomer is exemplified, purification was conducted using super-fluid chromatography with the following conditions to separate
 30 *enantiomers. SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μ m particle size) at 20% MeOH w/0.1%NH₄OH; 60 mL/min, 100 bars, 40 °C.*

Example	Compound Name	¹ H NMR	(m/z) M+H
3	(3-chlorophenyl)-(1-cyclopentyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.90 (dp, <i>J</i> = 1.60, 4.87 Hz, 2H), 7.70 (ddd, <i>J</i> = 1.09, 2.17, 8.00 Hz, 1H), 7.57 (t, <i>J</i> = 8.05 Hz, 1H), 3.60 – 3.52 (m, 1H), 2.99 – 2.92 (m, 1H), 2.84 (m, 1H), 2.08 (dd, <i>J</i> = 9.99, 11.30 Hz, 1H), 1.94 (td, <i>J</i> = 3.40, 11.07 Hz, 1H), 1.84 – 1.40 (m, 10H), 1.34 (m, 3H)	292
5	(1-cyclobutyl-3-piperidyl)-(2,4-dimethoxyphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.49 (d, <i>J</i> = 8.66 Hz, 1H), 6.64 (d, <i>J</i> = 2.27 Hz, 1H), 6.59 (dd, <i>J</i> = 2.31, 8.65 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.38 – 3.31 (m, 1H), 2.83 – 2.75 (m, 1H), 2.68 – 2.58 (m, 2H), 1.97 – 1.86 (m, 2H), 1.81 – 1.54 (m, 8H), 1.54 – 1.39 (m, 1H), 1.33 – 1.18 (m, 1H)	304
6	(6-methoxy-2-naphthyl)-(1-tetrahydropyran-4-yl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (s, 1H), 8.06 (dd, <i>J</i> = 3.27, 8.92 Hz, 1H), 7.90 (p, <i>J</i> = 2.06 Hz, 2H), 7.40 (q, <i>J</i> = 2.50 Hz, 1H), 7.25 (dq, <i>J</i> = 2.32, 8.83 Hz, 1H), 3.92 (s, 3H), 3.86-3.83 (m, 2H), 3.75 – 3.63 (m, 1H), 3.29 – 3.18 (m, 3H), 3.02-2.09 (m, 1H), 2.91 - 2.88 (m, 1H), 2.36 – 2.25 (m, 1H), 2.15 - 2.09 (m, 1H), 1.89 - 1.86 (m, 1H), 1.72-1.60 (m, 4H), 1.43-1.37 (m, 3H)	354
7	[(3 <i>R</i>)-1-(cyclopropylmethyl)-3-piperidyl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (DMSO- <i>d</i> ₆) δ: 8.69 – 8.54 (m, 1H), 8.06 (d, <i>J</i> = 9.0 Hz, 1H), 7.98 – 7.83 (m, 2H), 7.40 (d, <i>J</i> = 2.5 Hz, 1H), 7.26 (dd, <i>J</i> = 9.0, 2.5 Hz, 1H), 3.92 (s, 3H), 3.82 – 3.67 (m, 1H), 3.13 – 2.93 (m, 2H), 2.29 – 2.06 (m, 3H), 2.02 – 1.83 (m, 2H), 1.78 – 1.65 (m, 2H), 1.49 – 1.29 (m, 1H), 0.90 – 0.74 (m, 1H), 0.49 – 0.36 (m, 2H), 0.10 – 0.01 (m, 2H)	324

8	[(3 <i>S</i>)-1-(cyclopropylmethyl)-3-piperidyl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (DMSO- <i>d</i> ₆) δ: 8.69 – 8.57 (m, 1H), 8.06 (d, <i>J</i> = 9.0 Hz, 1H), 7.99 – 7.85 (m, 2H), 7.40 (d, <i>J</i> = 2.5 Hz, 1H), 7.26 (dd, <i>J</i> = 9.0, 2.5 Hz, 1H), 3.92 (s, 3H), 3.82 – 3.69 (m, 1H), 3.13 – 2.93 (m, 2H), 2.31 – 2.05 (m, 3H), 2.03 – 1.83 (m, 2H), 1.78 – 1.64 (m, 2H), 1.46 – 1.30 (m, 1H), 0.88 – 0.75 (m, 1H), 0.50 – 0.35 (m, 2H), 0.12 – 0.01 (m, 2H)	324
9	[(3 <i>R</i>)-1-cyclopentyl-3-piperidyl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.60 (d, <i>J</i> = 1.45 Hz, 1H), 8.06 (d, <i>J</i> = 9.00 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.40 (d, <i>J</i> = 2.55 Hz, 1H), 7.26 (dd, <i>J</i> = 2.55, 8.94 Hz, 1H), 3.91 (s, 3H), 3.72 (tt, <i>J</i> = 3.53, 10.77 Hz, 1H), 3.08 – 3.00 (m, 1H), 2.93 (d, <i>J</i> = 11.20 Hz, 1H), 2.58 – 2.52 (m, 1H), 2.13 – 2.04 (m, 1H), 1.93 (td, <i>J</i> = 3.81, 10.93 Hz, 1H), 1.89 – 1.82 (m, 1H), 1.82 – 1.23 (m, 11H)	338
10	[(3 <i>S</i>)-1-cyclopentyl-3-piperidyl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.60 (d, <i>J</i> = 1.46 Hz, 1H), 8.06 (d, <i>J</i> = 8.93 Hz, 1H), 7.95 – 7.85 (m, 2H), 7.40 (d, <i>J</i> = 2.55 Hz, 1H), 7.26 (dd, <i>J</i> = 2.56, 8.94 Hz, 1H), 3.72 (tt, <i>J</i> = 3.49, 10.82 Hz, 1H), 3.03 (ddd, <i>J</i> = 1.82, 3.59, 11.30 Hz, 1H), 2.96 – 2.88 (m, 1H), 2.59 – 2.51 (m, 1H), 2.14 – 2.04 (m, 1H), 1.93 (td, <i>J</i> = 3.90, 10.99 Hz, 1H), 1.86 (dd, <i>J</i> = 3.43, 12.73 Hz, 1H), 1.79 – 1.25 (m, 11H).	338
11	[(3 <i>S</i>)-1-cyclobutyl-3-piperidyl]-(2,4-dimethoxyphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.49 (d, <i>J</i> = 8.55 Hz, 1H), 6.64 (d, <i>J</i> = 2.27 Hz, 1H), 6.59 (dd, <i>J</i> = 2.30, 8.64 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.39 – 3.32 (m, 1H), 2.84 – 2.75 (m, 1H), 2.69 – 2.56 (m, 2H), 1.99 – 1.86 (m, 2H), 1.81 – 1.38 (m, 9H), 1.33 – 1.19 (m, 1H)	304

12	[(3 <i>R</i>)-1-cyclobutyl-3-piperidyl]-(2,4-dimethoxyphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 7.49 (d, <i>J</i> = 8.58 Hz, 1H), 6.64 (d, <i>J</i> = 2.26 Hz, 1H), 6.59 (dd, <i>J</i> = 2.30, 8.68 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.38 – 3.31 (m, 1H), 2.84 – 2.76 (m, 1H), 2.69 – 2.58 (m, 2H), 1.97 – 1.87 (m, 2H), 1.79 – 1.41 (m, 9H), 1.32 – 1.20 (m, 1H)	304
13	(1-cyclohexyl-3-piperidyl)-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.58 (s, 1H), 8.06 (d, <i>J</i> = 9.00 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.40 (d, <i>J</i> = 2.76 Hz, 1H), 7.26 (dd, <i>J</i> = 2.59, 8.91 Hz, 1H), 3.92 (s, 3H), 3.72 – 3.61 (m, 1H), 2.95 (d, <i>J</i> = 11.17 Hz, 1H), 2.82 (d, <i>J</i> = 10.83 Hz, 1H), 2.36 (t, <i>J</i> = 10.71 Hz, 1H), 2.31-2.27 (m, 1H), 2.25 – 2.15 (m, 1H), 1.89 – 1.85 (m, 1H), 1.72 – 1.62 (m, 6H), 1.56 – 1.52 (m, 1H), 1.45 – 1.31 (m, 1H), 1.21 – 1.14 (m, 4H), 1.6-1.024 (m, 1H)	355
14	(6-methoxy-2-naphthyl)-[1-(oxetan-3-yl)-3-piperidyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.63 (s, 1H), 8.08 (dd, <i>J</i> = 2.52, 8.77 Hz, 1H), 7.97 – 7.87 (m, 2H), 7.40 (d, <i>J</i> = 2.84 Hz, 1H), 7.26 (dd, <i>J</i> = 2.58, 9.02 Hz, 1H), 4.5 – 4.492 (m, 2H), 4.45 – 4.38 (m, 2H), 3.92 (s, 3H), 3.78 – 3.72 (m, 1H), 3.42 (p, <i>J</i> = 6.31 Hz, 1H), 2.83 – 2.79 (m, 1H), 2.75 – 2.65 (m, 1H), 2.04 – 1.87 (m, 2H), 1.85 – 1.68 (m, 3H), 1.44.382 (m, 1H)	326
15	(6-methoxy-2-naphthyl)-(1-tetrahydrofuran-3-yl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.61 (d, <i>J</i> = 3.48 Hz, 1H), 8.07 (dd, <i>J</i> = 1.67, 8.97 Hz, 1H), 7.97 – 7.86 (m, 2H), 7.40 (d, <i>J</i> = 2.52 Hz, 1H), 7.26 (dd, <i>J</i> = 2.60, 8.91 Hz, 1H), 3.92 (s, 3H), 3.80 – 3.68 (m, 3H), 3.62-3.58 (m, 1H), 3.49 – 3.44 (m, 1H), 3.06 – 2.68 (m, 3H), 2.24-2.128 (m, 1H), 2.07 – 1.83 (m, 3H), 1.78 – 1.61 (m, 3H), 1.47 – 1.32 (m, 1H)	340

18	(6-methoxy-2-naphthyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.60 (d, <i>J</i> = 1.45 Hz, 1H), 8.06 (d, <i>J</i> = 9.03 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.40 (d, <i>J</i> = 2.55 Hz, 1H), 7.26 (dd, <i>J</i> = 2.54, 8.95 Hz, 1H), 3.92 (s, 3H), 3.76-3.70 (m, 1H), 3.01 – 2.94 (m, 1H), 2.89 - 2.96 (m, 1H), 2.29 (t, <i>J</i> = 7.44 Hz, 2H), 2.12 (t, <i>J</i> = 10.81 Hz, 1H), 1.99 – 1.83 (m, 2H), 1.74 - 1.68 (m, 2H), 1.50 – 1.32 (m, 3H), 0.83 (t, <i>J</i> = 7.39 Hz, 3H)	312
21	[1-(cyclopropylmethyl)-3-piperidyl]-(3-phenoxyphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 7.73 (dt, <i>J</i> = 1.20, 7.80 Hz, 1H), 7.55 (t, <i>J</i> = 7.92 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.29 (ddd, <i>J</i> = 0.97, 2.50, 8.20 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.09 – 7.03 (m, 2H), 3.52 (tt, <i>J</i> = 3.50, 10.88 Hz, 1H), 3.03 – 2.96 (m, 1H), 2.94 – 2.86 (m, 1H), 2.23 – 2.11 (m, 2H), 2.07 (t, <i>J</i> = 10.70 Hz, 1H), 1.92 (td, <i>J</i> = 3.28, 11.12 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.72 – 1.54 (m, 2H), 1.31 (qd, <i>J</i> = 4.49, 11.72 Hz, 1H), 0.81 - 0.72 (m, 1H), 0.46 – 0.35 (m, 2H), 0.05-0.01 (m, 2H)	336
22	[1-(cyclopropylmethyl)-3-piperidyl]-[4-(trifluoromethyl)phenyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.13 (d, <i>J</i> = 8.11 Hz, 2H), 7.89 (d, <i>J</i> = 8.26 Hz, 2H), 3.62 (tt, <i>J</i> = 3.55, 10.36 Hz, 1H), 3.03 - 2.98 (m, 1H), 2.90 (dt, <i>J</i> = 3.94, 11.08 Hz, 1H), 2.26 – 2.10 (m, 3H), 1.97 (td, <i>J</i> = 3.39, 11.00 Hz, 1H), 1.5 - 1.802 (m, 1H), 1.75 – 1.57 (m, 2H), 1.39-1.29 (m, 1H), 0.82 - 0.737 (m, 1H), 0.45 – 0.34 (m, 2H), 0.08 – 0.00 (m, 2H)	312

23	[1-(cyclopropylmethyl)-3-piperidyl]-(4-phenoxyphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.03 – 7.94 (m, 2H), 7.50 – 7.42 (m, 2H), 7.25 (t, <i>J</i> = 7.39 Hz, 1H), 7.16 – 7.10 (m, 2H), 7.08 – 7.00 (m, 2H), 3.54 (tt, <i>J</i> = 3.48, 10.90 Hz, 1H), 3.05 – 2.98 (m, 1H), 2.96-2.93 (m, 1H), 2.19 (qd, <i>J</i> = 6.57, 12.68 Hz, 2H), 2.07 (t, <i>J</i> = 10.81 Hz, 1H), 1.91 (td, <i>J</i> = 3.53, 11.12 Hz, 1H), 1.84-1.80 (m, 1H), 1.73 – 1.57 (m, 2H), 1.31 (qd, <i>J</i> = 4.75, 11.70 Hz, 1H), 0.83 – 0.75 (m, 1H), 0.48 – 0.36 (m, 2H), 0.09 – 0.01 (m, 2H)	336
24	[1-(cyclopropylmethyl)-3-piperidyl]-(4-phenylphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.07 – 8.00 (m, 2H), 7.87 – 7.80 (m, 2H), 7.77 – 7.72 (m, 2H), 7.55 – 7.48 (m, 2H), 7.46 – 7.40 (m, 1H), 3.62 (ddt, <i>J</i> = 3.50, 6.98, 13.90 Hz, 1H), 3.08 – 3.03 (m, 1H), 2.98-2.93 (m, 1H), 2.21 (qd, <i>J</i> = 6.56, 12.67 Hz, 2H), 2.11 (dd, <i>J</i> = 10.32, 11.27 Hz, 1H), 1.94 (td, <i>J</i> = 3.86, 10.99 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.75 – 1.60 (m, 2H), 1.40 – 1.28 (m, 1H), 0.87 – 0.75 (m, 1H), 0.48 – 0.37 (m, 2H), 0.10 – 0.01 (m, 2H)	320
25	[1-(cyclopropylmethyl)-3-piperidyl]-(3-phenylphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.15 (t, <i>J</i> = 1.79 Hz, 1H), 7.97 – 7.89 (m, 2H), 7.76 – 7.70 (m, 2H), 7.63 (t, <i>J</i> = 7.73 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.44 – 7.38 (m, 1H), 3.70 (tt, <i>J</i> = 3.53, 10.73 Hz, 1H), 3.10 – 3.02 (m, 1H), 2.95-2.92 (m, 1H), 2.27 – 2.08 (m, 3H), 1.95 (td, <i>J</i> = 4.24, 10.78 Hz, 1H), 1.87 – 1.84 (m, 1H), 1.72 – 1.65 (m, 2H), 1.43 – 1.29 (m, 1H), 0.86 – 0.73 (m, 1H), 0.47 – 0.34 (m, 2H), 0.09 – 0.01 (m, 2H)	320

26	[1-(cyclopropylmethyl)-3-piperidyl]-(4-fluoro-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.62 (t, <i>J</i> = 0.99 Hz, 1H), 8.27 (dt, <i>J</i> = 1.61, 8.12 Hz, 1H), 8.11 (dd, <i>J</i> = 1.22, 8.21 Hz, 1H), 7.77 (dddd, <i>J</i> = 1.34, 6.96, 8.21, 20.50 Hz, 2H), 7.69 (dd, <i>J</i> = 1.47, 11.60 Hz, 1H), 3.84 – 3.74 (m, 1H), 3.10 – 3.08 (m, 1H), 3.01 – 2.93 (m, 1H), 2.29 – 2.11 (m, 3H), 2.01 – 1.86 (m, 2H), 1.75–1.69 (m, 2H), 1.45 – 1.31z (m, 1H), 0.87 – 0.75 (m, 1H), 0.47 – 0.36 (m, 2H), 0.10 – 0.01 (m, 2H)	312
27	[1-(cyclopropylmethyl)-3-piperidyl]-[3-(4-fluorophenoxy)phenyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.76 – 7.69 (m, 1H), 7.54 (t, <i>J</i> = 7.92 Hz, 1H), 7.41 (dd, <i>J</i> = 1.56, 2.55 Hz, 1H), 7.31 – 7.22 (m, 3H), 7.16 – 7.08 (m, 2H), 3.52 (tt, <i>J</i> = 3.52, 10.76 Hz, 1H), 3.01–2.98 (m, 1H), 2.92–2.89 (m, 1H), 2.23 – 2.11 (m, 2H), 2.11 – 2.03 (m, 1H), 1.92 (td, <i>J</i> = 3.40, 11.12 Hz, 1H), 1.82–1.78 (m, 1H), 1.72 – 1.53 (m, 2H), 1.31 (qd, <i>J</i> = 4.55, 11.72 Hz, 1H), 0.83 – 0.70 (m, 1H), 0.47 – 0.35 (m, 2H), 0.08 – 0.01 (m, 2H)	354
28	[(3 <i>S</i>)-1-(cyclopropylmethyl)-3-piperidyl]-(3-phenoxyphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.73 (dt, <i>J</i> = 1.23, 7.77 Hz, 1H), 7.55 (t, <i>J</i> = 7.91 Hz, 1H), 7.47 – 7.38 (m, 3H), 7.28 (ddd, <i>J</i> = 0.98, 2.56, 8.20 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.10 – 7.01 (m, 2H), 3.52 (tt, <i>J</i> = 3.45, 10.62 Hz, 1H), 3.03 – 2.96 (m, 1H), 2.91–2.88 (m, 1H), 2.24 – 2.11 (m, 2H), 2.07 (t, <i>J</i> = 10.71 Hz, 1H), 1.92 (td, <i>J</i> = 3.34, 11.21 Hz, 1H), 1.82–1.78 (m, 1H), 1.73 – 1.53 (m, 2H), 1.31 (qd, <i>J</i> = 4.45, 11.60 Hz, 1H), 0.85 – 0.69 (m, 1H), 0.46 – 0.33 (m, 2H), 0.08 – 0.00 (m, 2H)	336

29	[(3 <i>R</i>)-1-(cyclopropylmethyl)-3-piperidyl]-(3-phenoxyphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.73 (dt, <i>J</i> = 1.21, 7.77 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.46 – 7.38 (m, 3H), 7.28 (ddd, <i>J</i> = 0.94, 2.49, 8.19 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.09 – 7.03 (m, 2H), 3.52 (tt, <i>J</i> = 3.56, 10.21 Hz, 1H), 3.03 – 2.95 (m, 1H), 2.91-2.88 (m, 1H), 2.23 – 2.11 (m, 2H), 2.07 (dd, <i>J</i> = 10.12, 11.29 Hz, 1H), 1.92 (td, <i>J</i> = 3.32, 11.16 Hz, 1H), 1.84 – 1.76 (m, 1H), 1.72 – 1.53 (m, 2H), 1.37 – 1.25 (m, 1H), 0.80-0.73 (m, 1H), 0.46 – 0.34 (m, 2H), 0.07 – 0.00 (m, 2H)	336
30	[(3 <i>R</i>)-1-(cyclopropylmethyl)-3-piperidyl]-(4-phenoxyphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.02 – 7.94 (m, 2H), 7.50 – 7.42 (m, 2H), 7.28 – 7.21 (m, 1H), 7.16 – 7.09 (m, 2H), 7.07 – 7.01 (m, 2H), 3.54 (tt, <i>J</i> = 3.43, 11.21 Hz, 1H), 3.05 – 2.98 (m, 1H), 2.96-2.93 (m, 1H), 2.19 (qd, <i>J</i> = 6.51, 12.62 Hz, 2H), 2.07 (t, <i>J</i> = 10.84 Hz, 1H), 1.91 (td, <i>J</i> = 3.65, 11.19 Hz, 1H), 1.84 - 1.80 (m, 1H), 1.73 – 1.57 (m, 2H), 1.31 (qd, <i>J</i> = 4.84, 11.81 Hz, 1H), 0.86 – 0.74 (m, 1H), 0.48 – 0.36 (m, 2H), 0.09 – 0.01 (m, 2H)	336
31	[(3 <i>S</i>)-1-(cyclopropylmethyl)-3-piperidyl]-(4-phenoxyphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.03 – 7.92 (m, 2H), 7.51 – 7.42 (m, 2H), 7.29 – 7.21 (m, 1H), 7.16 – 7.10 (m, 2H), 7.07 – 6.99 (m, 2H), 3.61 – 3.47 (m, 1H), 3.03-2.99 (m, 1H), 2.97 – 2.89 (m, 1H), 2.19 (qd, <i>J</i> = 6.54, 12.64 Hz, 2H), 2.07 (t, <i>J</i> = 10.83 Hz, 1H), 1.91 (td, <i>J</i> = 3.57, 11.12 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.69-1.62 (m, 2H), 1.39 – 1.24 (m, 1H), 0.82-0.78 (m, 1H), 0.49 – 0.35 (m, 2H), 0.09 – 0.01 (m, 2H)	336

32	[(3 <i>R</i>)-1-(cyclopropylmethyl)-3-piperidyl]-(4-phenylphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.07 – 8.00 (m, 2H), 7.86 – 7.80 (m, 2H), 7.77 – 7.72 (m, 2H), 7.55 – 7.47 (m, 2H), 7.47 – 7.40 (m, 1H), 3.62 (tt, <i>J</i> = 3.50, 10.43 Hz, 1H), 3.08-3.03 (m, 1H), 2.97 - 2.93 (m, 1H), 2.21 (qd, <i>J</i> = 6.51, 12.62 Hz, 2H), 2.11 (t, <i>J</i> = 10.79 Hz, 1H), 1.94 (td, <i>J</i> = 3.89, 10.99 Hz, 1H), 1.88 - 1.85 (m, 1H), 1.74 – 1.60 (m, 2H), 1.42 – 1.28 (m, 1H), 0.86 - 0.75 (m, 1H), 0.49 – 0.37 (m, 2H), 0.09 – 0.01 (m, 2H)	320
33	[(3 <i>S</i>)-1-(cyclopropylmethyl)-3-piperidyl]-(4-phenylphenyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.07 – 8.00 (m, 2H), 7.87 – 7.80 (m, 2H), 7.78 – 7.71 (m, 2H), 7.55 – 7.47 (m, 2H), 7.47 – 7.39 (m, 1H), 3.67 – 3.57 (m, 1H), 3.09 – 3.01 (m, 1H), 3.00 – 2.91 (m, 1H), 2.21 (qd, <i>J</i> = 6.54, 12.66 Hz, 2H), 2.11 (t, <i>J</i> = 10.79 Hz, 1H), 1.94 (td, <i>J</i> = 3.89, 10.98 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.75 – 1.60 (m, 2H), 1.40 – 1.28 (m, 1H), 0.86 - 0.76 (m, 1H), 0.48 – 0.36 (m, 2H), 0.10 – 0.01 (m, 2H)	320
34	[1-(cyclopropylmethyl)-3-piperidyl]-[4-(<i>p</i> -tolyl)phenyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.08 – 7.98 (m, 2H), 7.87 – 7.77 (m, 2H), 7.69 – 7.60 (m, 2H), 7.37 – 7.27 (m, 2H), 3.61 (tt, <i>J</i> = 3.46, 10.95 Hz, 1H), 3.10 – 3.01 (m, 1H), 2.97 - 2.94 (m, 1H), 2.36 (s, 3H), 2.20 (qd, <i>J</i> = 6.54, 12.65 Hz, 2H), 2.14 – 2.05 (m, 1H), 1.94 (td, <i>J</i> = 3.90, 10.99 Hz, 1H), 1.87 - 1.84 (m, 1H), 1.75 – 1.59 (m, 2H), 1.34 (qd, <i>J</i> = 5.22, 11.63 Hz, 1H), 0.83-0.79 (m, 1H), 0.50 – 0.35 (m, 2H), 0.10 – 0.01 (m, 2H)	334

35	[1-(cyclopropylmethyl)-3-piperidyl]-[4-(hydroxymethyl)-2-naphthyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.61 (s, 1H), 8.18 (dd, J = 1.38, 8.09 Hz, 1H), 8.11 (d, J = 8.45 Hz, 1H), 8.03 (d, J = 1.72 Hz, 1H), 7.71 (ddd, J = 1.48, 6.82, 8.42 Hz, 1H), 7.65 (ddd, J = 1.27, 6.80, 8.07 Hz, 1H), 5.44 (t, J = 5.44 Hz, 1H), 5.01 (d, J = 5.00 Hz, 2H), 3.9 - 3.947 (m, 1H), 2.08 - 1.93 (m, 1H), 1.85 - 1.81 (m, 2H), 1.50 - 1.45 (m, 1H), 0.98 - 0.92 (m, 1H), 0.55 - 0.51 (m, 2H), 0.21 - 0.15 (m, 2H)	324.2
36	[1-(cyclopropylmethyl)-3-piperidyl]-(6-phenyl-3-pyridyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 9.14 (d, J = 2.29 Hz, 1H), 8.33 (dd, J = 2.29, 8.34 Hz, 1H), 8.14 (dq, J = 2.11, 2.66, 8.35 Hz, 2H), 8.09 (d, J = 8.39 Hz, 1H), 7.55 - 7.41 (m, 3H), 3.61 (tt, J = 3.47, 10.39 Hz, 1H), 3.01 (dd, J = 2.99, 10.89 Hz, 1H), 2.90 - 2.86 (m, 1H), 2.25 - 2.07 (m, 3H), 1.93 (td, J = 4.08, 10.71 Hz, 1H), 1.88 - 1.78 (m, 1H), 1.72 - 1.59 (m, 2H), 1.32 (qd, J = 5.24, 11.35 Hz, 1H), 0.84 - 0.67 (m, 1H), 0.45 - 0.29 (m, 2H), 0.06 - -0.03 (m, 2H)	321
37	[4-(aminomethyl)-2-naphthyl]-[1-(cyclopropylmethyl)-3-piperidyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.57 (d, J = 1.80 Hz, 1H), 8.17 - 8.14 (m, 1H), 7.97 - 7.92 (m, 1H), 7.71 - 7.65 (m, 1H), 7.63 - 7.56 (m, 2H), 4.86 (s, 2H), 4.22 (d, J = 2.32 Hz, 2H), 3.85 - 3.71 (m, 1H), 3.09 (d, J = 9.18 Hz, 2H), 2.99 (d, J = 10.88 Hz, 2H), 2.28 - 2.12 (m, 5H), 1.72 (td, J = 4.94, 8.99, 10.27 Hz, 4H), 0.88 - 0.72 (m, 2H), 0.45 - 0.38 (m, 2H), 0.10 - 0.01 (m, 2H)	323

38	[1-(cyclopropylmethyl)-3-piperidyl]-[4-(2-pyridyl)phenyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.68 (ddd, J = 0.91, 1.88, 4.78 Hz, 1H), 8.24 – 8.17 (m, 2H), 8.06 – 7.99 (m, 3H), 7.90 (td, J = 1.84, 7.73 Hz, 1H), 7.39 (ddd, J = 1.07, 4.79, 7.49 Hz, 1H), 3.60 (tt, J = 3.52, 10.47 Hz, 1H), 3.4-3.002 (m, 1H), 2.91 (dt, J = 3.68, 10.98 Hz, 1H), 2.23 – 2.10 (m, 2H), 2.07 (t, J = 10.87 Hz, 1H), 1.90 (td, J = 3.85, 11.01 Hz, 1H), 1.85-1.81 (m, 1H), 1.72 – 1.56 (m, 2H), 1.39 – 1.23 (m, 1H), 0.79-0.73 (m, 1H), 0.45 – 0.31 (m, 2H), 0.06 – -0.04 (m, 2H)	321
39	<i>N</i> -[[3-[1-(cyclopropylmethyl)piperidine-3-carbonyl]-1-naphthyl]methyl]acetamide	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.67 – 8.62 (m, 1H), 8.42 (t, J = 5.87 Hz, 1H), 8.20 (dd, J = 1.39, 8.08 Hz, 1H), 8.16 – 8.09 (m, 1H), 7.88 (d, J = 1.71 Hz, 1H), 7.71 (ddd, J = 1.44, 6.81, 8.39 Hz, 1H), 7.65 (ddd, J = 1.18, 6.88, 8.01 Hz, 1H), 4.75 (d, J = 5.80 Hz, 2H), 3.79 (ddt, J = 3.56, 7.12, 10.86 Hz, 1H), 3.11-3.08 (m, 1H), 3.02-2.99 (m, 2H), 2.30 – 2.18 (m, 2H), 2.15 (t, J = 9.47 Hz, 1H), 2.02 – 1.90 (m, 2H), 1.89 (s, 3H), 1.76-1.70 (m, 2H), 1.45 – 1.31 (m, 1H), 0.89 – 0.75 (m, 1H), 0.47-0.38 (m, 2H), 0.11 – 0.01 (m, 2H)	365
40	3-[1-(cyclopropylmethyl)piperidine-3-carbonyl]- <i>N</i> -methyl-naphthalene-1-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.83 – 8.77 (m, 1H), 8.57 (q, J = 4.28 Hz, 1H), 8.28 – 8.19 (m, 2H), 7.99 (d, J = 1.69 Hz, 1H), 7.74 - 7.64 (m, 2H), 3.82 (tt, J = 3.45, 10.67 Hz, 1H), 3.11-3.07 (m, 1H), 2.30-2.97 (m, 1H), 2.87 (d, J = 4.57 Hz, 3H), 2.29 – 2.10 (m, 3H), 2.02 – 1.84 (m, 2H), 1.5-1.704 (m, 2H), 1.46 – 1.30 (m, 1H), 0.90 – 0.74 (m, 1H), 0.49 – 0.34 (m, 2H), 0.11 – 0.01 (m, 2H)	351

41	3-(1-cyclopentylpiperidine-3-carbonyl)-N-methyl-naphthalene-1-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.80 – 8.76 (m, 1H), 8.56 (q, <i>J</i> = 4.49 Hz, 1H), 8.23 (ddd, <i>J</i> = 1.32, 8.39, 12.62 Hz, 2H), 7.98 (d, <i>J</i> = 1.72 Hz, 1H), 7.73 - 7.64 (m, 2H), 3.80 (tt, <i>J</i> = 3.49, 10.64 Hz, 1H), 3.09 – 3.02 (m, 1H), 2.93 (d, <i>J</i> = 11.17 Hz, 1H), 2.88 - 2.86 (m, 3H), 2.60 – 2.52 (m, 1H), 2.12 (t, <i>J</i> = 10.72 Hz, 1H), 2.00 – 1.85 (m, 2H), 1.82 – 1.66 (m, 4H), 1.60 – 1.27 (m, 7H)	365
42	3-(1-cyclobutylpiperidine-3-carbonyl)-N-methyl-naphthalene-1-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.78 (t, <i>J</i> = 1.17 Hz, 1H), 8.56 (q, <i>J</i> = 4.63 Hz, 1H), 8.23 (ddd, <i>J</i> = 1.33, 8.44, 10.10 Hz, 2H), 7.98 (d, <i>J</i> = 1.72 Hz, 1H), 7.74 - 7.64 (m, 2H), 3.77 (tt, <i>J</i> = 3.53, 10.90 Hz, 1H), 2.94 – 2.88 (m, 1H), 2.87 (d, <i>J</i> = 4.58 Hz, 3H), 2.80-2.76 (m, 1H), 2.75 – 2.69 (m, 1H), 1.98 - 1.88 (m, 4H), 1.82 – 1.66 (m, 5H), 1.2-1.581 (m, 2H), 1.44 – 1.31 (m, 1H)	351
43	3-[1-(cyclopropylmethyl)piperidine-3-carbonyl]naphthalene-1-carbonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.08 – 9.02 (m, 1H), 8.55 (d, <i>J</i> = 1.69 Hz, 1H), 8.42 – 8.34 (m, 1H), 8.18 (dd, <i>J</i> = 0.99, 8.30 Hz, 1H), 7.95 (ddd, <i>J</i> = 1.27, 6.93, 8.36 Hz, 1H), 7.83 (ddd, <i>J</i> = 1.15, 6.91, 8.08 Hz, 1H), 3.82 (tt, <i>J</i> = 3.57, 10.14 Hz, 1H), 3.09-3.05 (m, 1H), 3.00 – 2.90 (m, 1H), 2.29 – 2.13 (m, 3H), 2.04 – 1.85 (m, 2H), 1.75 - 1.69 (m, 2H), 1.43 - 1.38 (m, 1H), 0.83 - 0.75 (m, 1H), 0.43 - 0.37 (m, 2H), 0.10 – 0.01 (m, 2H)	319

44	3-(1-cyclobutylpiperidine-3-carbonyl)naphthalene-1-carbonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.07 – 9.01 (m, 1H), 8.54 (d, <i>J</i> = 1.71 Hz, 1H), 8.37 (d, <i>J</i> = 8.02 Hz, 1H), 8.18 (d, <i>J</i> = 8.28 Hz, 1H), 7.95 (ddd, <i>J</i> = 1.23, 6.89, 8.27 Hz, 1H), 7.83 (ddd, <i>J</i> = 1.08, 6.89, 8.08 Hz, 1H), 3.77 (tt, <i>J</i> = 3.57, 10.59 Hz, 1H), 2.94 – 2.84 (m, 1H), 2.79 – 2.65 (m, 2H), 2.00 – 1.86 (m, 4H), 1.82 – 1.53 (m, 7H), 1.37 (qd, <i>J</i> = 4.64, 11.13 Hz, 1H)	319
45	3-(1-cyclopentylpiperidine-3-carbonyl)naphthalene-1-carbonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 9.07 – 8.99 (m, 1H), 8.53 (d, <i>J</i> = 1.70 Hz, 1H), 8.37 (d, <i>J</i> = 7.98 Hz, 1H), 8.17 (d, <i>J</i> = 8.34 Hz, 1H), 7.98 – 7.91 (m, 1H), 7.87 – 7.79 (m, 1H), 3.79 (tt, <i>J</i> = 3.48, 10.13 Hz, 1H), 3.05–3.02 (m, 1H), 2.95 – 2.84 (m, 1H), 2.56–2.51 (m, 1H), 2.15 (t, <i>J</i> = 10.60 Hz, 1H), 1.97 (td, <i>J</i> = 4.31, 10.67 Hz, 1H), 1.91–1.86 (m, 1H), 1.80 – 1.63 (m, 4H), 1.58 – 1.54 (m, 2H), 1.51 – 1.21 (m, 5H)	333
46	3-(1-cyclopentylpiperidine-3-carbonyl)naphthalene-1-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.77 (d, <i>J</i> = 1.71 Hz, 1H), 8.33 (d, <i>J</i> = 8.46 Hz, 1H), 8.25 – 8.19 (m, 1H), 8.11 (s, 1H), 8.03 (d, <i>J</i> = 1.70 Hz, 1H), 7.75 – 7.61 (m, 3H), 3.79 (ddt, <i>J</i> = 3.44, 7.18, 10.76 Hz, 1H), 3.08–3.05 (m, 1H), 2.95–2.92 (m, 1H), 2.61 – 2.53 (m, 1H), 2.11 (t, <i>J</i> = 10.82 Hz, 1H), 2.00 – 1.85 (m, 2H), 1.75 – 1.68 (m, 4H), 1.62 – 1.26 (m, 7H)	351

47	3-(1-cyclobutylpiperidine-3-carbonyl)naphthalene-1-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.80 – 8.75 (m, 1H), 8.36 – 8.29 (m, 1H), 8.25 – 8.19 (m, 1H), 8.11 (s, 1H), 8.03 (d, <i>J</i> = 1.75 Hz, 1H), 7.76 – 7.61 (m, 3H), 3.77 (tt, <i>J</i> = 3.47, 10.69 Hz, 1H), 2.93 – 2.89 (m, 1H), 2.80 – 2.76 (m, 1H), 2.76 – 2.69 (m, 1H), 2.02 – 1.85 (m, 4H), 1.82 – 1.52 (m, 7H), 1.45 – 1.31 (m, 1H)	337
48	3-[1-(cyclopropylmethyl)piperidine-3-carbonyl]naphthalene-1-carboxamide	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.78 (d, <i>J</i> = 1.68 Hz, 1H), 8.33 (d, <i>J</i> = 8.43 Hz, 1H), 8.21 (dd, <i>J</i> = 1.32, 8.18 Hz, 1H), 8.11 (s, 1H), 8.04 (d, <i>J</i> = 1.70 Hz, 1H), 7.72 (ddd, <i>J</i> = 1.49, 6.87, 8.38 Hz, 1H), 7.69 – 7.60 (m, 2H), 3.82 (tt, <i>J</i> = 3.53, 10.88 Hz, 1H), 3.14 – 3.05 (m, 1H), 3.01 – 2.97 (m, 1H), 2.30 – 2.10 (m, 3H), 2.02 – 1.87 (m, 2H), 1.77 – 1.69 (m, 2H), 1.44 – 1.34 (m, 1H), 0.86–0.78 (m, 1H), 0.47–0.37 (m, 2H), 0.11 – 0.01 (m, 2H)	337
49	[1-(cyclopropylmethyl)-3-piperidyl]-(6-methoxy-5-methyl-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.63 (d, <i>J</i> = 1.81 Hz, 1H), 8.07 (d, <i>J</i> = 9.09 Hz, 1H), 8.02 (d, <i>J</i> = 8.99 Hz, 1H), 7.94 (dd, <i>J</i> = 1.88, 9.01 Hz, 1H), 7.52 (d, <i>J</i> = 9.07 Hz, 1H), 3.96 (s, 3H), 3.81 – 3.70 (m, 1H), 3.12 – 3.04 (m, 1H), 3.01 – 2.97 (m, 1H), 2.48 (s, 3H), 2.21 (qd, <i>J</i> = 6.60, 12.69 Hz, 2H), 2.12 (t, <i>J</i> = 10.85 Hz, 1H), 2.00 – 1.84 (m, 2H), 1.74 – 1.68 (m, 2H), 1.43 – 1.33 (m, 1H), 0.87 – 0.75 (m, 1H), 0.46 – 0.37 (m, 2H), 0.10 – 0.01 (m, 2H)	338

50	(6-methoxy-5-methyl-2-naphthyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (d, <i>J</i> = 1.78 Hz, 1H), 8.06 (d, <i>J</i> = 9.05 Hz, 1H), 8.03 (s, 1H), 7.93 (dd, <i>J</i> = 1.82, 9.02 Hz, 1H), 7.52 (d, <i>J</i> = 9.05 Hz, 1H), 3.96 (s, 3H), 3.73 (tt, <i>J</i> = 3.54, 10.60 Hz, 1H), 2.99 – 2.90 (m, 1H), 2.86-2.83 (m, 1H), 2.48 (s, 3H), 2.25 (t, <i>J</i> = 7.39 Hz, 2H), 2.07 (t, <i>J</i> = 10.77 Hz, 1H), 1.92 - 1.86 (m, 2H), 1.73 - 1.64 (m, 2H), 1.48 – 1.31 (m, 3H), 0.83 (t, <i>J</i> = 7.33 Hz, 3H)	326
51	(1-cyclopentyl-3-piperidyl)-(6-methoxy-5-methyl-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (d, <i>J</i> = 1.78 Hz, 1H), 8.06 (d, <i>J</i> = 9.05 Hz, 1H), 8.03 (s, 1H), 7.93 (dd, <i>J</i> = 1.82, 9.02 Hz, 1H), 7.52 (d, <i>J</i> = 9.05 Hz, 1H), 3.96 (s, 3H), 3.73 (tt, <i>J</i> = 3.54, 10.60 Hz, 1H), 2.99 – 2.90 (m, 1H), 2.86 - 2.83 (m, 1H), 2.48 (s, 3H), 2.25 (t, <i>J</i> = 7.39 Hz, 2H), 2.07 (t, <i>J</i> = 10.77 Hz, 1H), 1.92 - 1.86 (m, 2H), 1.73 - 1.64 (m, 2H), 1.48 – 1.31 (m, 3H), 0.83 (t, <i>J</i> = 7.33 Hz, 3H)	352
52	(1-cyclobutyl-3-piperidyl)-(6-methoxy-5-methyl-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (d, <i>J</i> = 1.78 Hz, 1H), 8.06 (d, <i>J</i> = 9.05 Hz, 1H), 8.03 (s, 1H), 7.93 (dd, <i>J</i> = 1.82, 9.02 Hz, 1H), 7.52 (d, <i>J</i> = 9.05 Hz, 1H), 3.96 (s, 3H), 3.73 (tt, <i>J</i> = 3.54, 10.60 Hz, 1H), 2.99 – 2.90 (m, 1H), 2.86 - 2.83 (m, 1H), 2.48 (s, 3H), 2.25 (t, <i>J</i> = 7.39 Hz, 2H), 2.07 (t, <i>J</i> = 10.77 Hz, 1H), 1.92 - 1.86 (m, 2H), 1.73-1.64 (m, 2H), 1.48 – 1.31 (m, 3H), 0.83 (t, <i>J</i> = 7.33 Hz, 3H)	338

53	2-[6-[1-(cyclopropylmethyl)piperidine-3-carbonyl]-2-methoxy-1-naphthyl]acetonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.71 (d, <i>J</i> = 1.67 Hz, 1H), 8.27 (d, <i>J</i> = 9.15 Hz, 1H), 8.12 (d, <i>J</i> = 8.97 Hz, 1H), 8.03 (dd, <i>J</i> = 1.78, 8.96 Hz, 1H), 7.63 (d, <i>J</i> = 9.13 Hz, 1H), 4.29 (s, 2H), 4.04 (s, 3H), 3.78 (tt, <i>J</i> = 3.48, 10.84 Hz, 1H), 3.10 - 3.07 (m, 1H), 3.00 - 2.97 (m, 1H), 2.29 - 2.08 (m, 3H), 2.02 - 1.84 (m, 2H), 1.75-1.69 (m, 2H), 1.43 - 1.33 (m, 1H), 0.89 - 0.75 (m, 1H), 0.46 - 0.37 (m, 2H), 0.11 - 0.00 (m, 2H)	363
54	2-[6-(1-cyclopentylpiperidine-3-carbonyl)-2-methoxy-1-naphthyl]acetonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.70 (d, <i>J</i> = 1.75 Hz, 1H), 8.26 (d, <i>J</i> = 9.08 Hz, 1H), 8.12 (d, <i>J</i> = 8.99 Hz, 1H), 8.03 (dd, <i>J</i> = 1.79, 8.93 Hz, 1H), 7.63 (d, <i>J</i> = 9.16 Hz, 1H), 4.29 (s, 2H), 4.04 (s, 3H), 3.75 (tt, <i>J</i> = 3.43, 10.57 Hz, 1H), 3.09 - 3.01 (m, 1H), 2.94 - 2.91 (m, 1H), 2.58 - 2.54 (m, 1H), 2.10 (t, <i>J</i> = 10.79 Hz, 1H), 1.99 - 1.86 (m, 2H), 1.81 - 1.65 (m, 4H), 1.60 - 1.27 (m, 7H)	377
55	2-[6-(1-cyclobutylpiperidine-3-carbonyl)-2-methoxy-1-naphthyl]acetonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.70 (d, <i>J</i> = 1.77 Hz, 1H), 8.27 (d, <i>J</i> = 9.10 Hz, 1H), 8.12 (d, <i>J</i> = 8.99 Hz, 1H), 8.03 (dd, <i>J</i> = 1.80, 8.94 Hz, 1H), 7.63 (d, <i>J</i> = 9.13 Hz, 1H), 4.29 (s, 2H), 4.04 (s, 3H), 3.72 (tt, <i>J</i> = 3.57, 10.76 Hz, 1H), 2.91 - 2.88 (m, 1H), 2.79 - 2.76 (m, 1H), 2.74 - 2.65 (m, 1H), 2.02 - 1.84 (m, 4H), 1.81 - 1.52 (m, 7H), 1.43 - 1.34 (m, 1H)	363

56	2-[2-methoxy-6-(1-propylpiperidine-3-carbonyl)-1-naphthyl]acetonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.70 (d, <i>J</i> = 1.78 Hz, 1H), 8.26 (d, <i>J</i> = 9.10 Hz, 1H), 8.12 (d, <i>J</i> = 8.99 Hz, 1H), 8.03 (dd, <i>J</i> = 1.80, 9.01 Hz, 1H), 7.63 (d, <i>J</i> = 9.17 Hz, 1H), 4.29 (s, 2H), 4.04 (s, 3H), 3.75 (tt, <i>J</i> = 3.47, 10.57 Hz, 1H), 2.99 – 2.91 (m, 1H), 2.86 – 2.83 (m, 1H), 2.25 (t, <i>J</i> = 7.39 Hz, 2H), 2.09 (t, <i>J</i> = 10.75 Hz, 1H), 1.90 (td, <i>J</i> = 4.26, 10.77 Hz, 2H), 1.74 – 1.67 (m, 2H), 1.48 – 1.30 (m, 3H), 0.83 (t, <i>J</i> = 7.37 Hz, 3H)	351
57	(1-cyclopentyl-3-piperidyl)-[4-(hydroxymethyl)-2-naphthyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.61 (d, <i>J</i> = 1.95 Hz, 1H), 8.21 – 8.15 (m, 1H), 8.12 – 8.07 (m, 1H), 8.01 (d, <i>J</i> = 1.74 Hz, 1H), 7.69 (ddd, <i>J</i> = 1.48, 6.86, 8.45 Hz, 1H), 7.63 (ddd, <i>J</i> = 1.27, 6.83, 8.04 Hz, 1H), 5.43 (t, <i>J</i> = 5.19 Hz, 1H), 5.00 (d, <i>J</i> = 4.50 Hz, 2H), 3.77 (tt, <i>J</i> = 3.60, 11.01 Hz, 1H), 3.10 – 3.02 (m, 1H), 2.96 – 2.92 (m, 1H), 2.59 – 2.52 (m, 1H), 2.09 (t, <i>J</i> = 10.77 Hz, 1H), 1.98 – 1.83 (m, 2H), 1.81 – 1.64 (m, 4H), 1.61 – 1.26 (m, 7H)	338
58	(1-cyclobutyl-3-piperidyl)-[4-(hydroxymethyl)-2-naphthyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.66 – 8.58 (m, 1H), 8.24 – 8.14 (m, 1H), 8.10 (d, <i>J</i> = 8.49 Hz, 1H), 8.04 – 7.97 (m, 1H), 7.69 (ddd, <i>J</i> = 1.66, 6.72, 8.41 Hz, 1H), 7.66 – 7.58 (m, 1H), 5.43 (s, 1H), 5.00 (d, <i>J</i> = 3.36 Hz, 2H), 3.74 (tt, <i>J</i> = 4.95, 10.40 Hz, 1H), 2.96 – 2.86 (m, 1H), 2.83 – 2.75 (m, 1H), 2.70 (p, <i>J</i> = 7.77 Hz, 1H), 2.03 – 1.83 (m, 4H), 1.81 – 1.54 (m, 7H), 1.45 – 1.30 (m, 1H)	324

59	[1-(cyclopropylmethyl)-3-piperidyl]-(8-methyl-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.65 – 8.60 (m, 1H), 8.06 – 7.96 (m, 2H), 7.85 (d, <i>J</i> = 8.06 Hz, 1H), 7.55 (dd, <i>J</i> = 6.98, 8.15 Hz, 1H), 7.47 (dt, <i>J</i> = 1.15, 6.96 Hz, 1H), 3.81 (tt, <i>J</i> = 3.50, 10.33 Hz, 1H), 3.17 – 3.08 (m, 1H), 2.99-2.94 (m, 1H), 2.75 (s, 3H), 2.27 – 2.16 (m, 2H), 2.16 – 2.09 (m, 1H), 1.97 - 1.89 (m, 2H), 1.75 - 1.69 (m, 2H), 1.46 – 1.32 (m, 1H), 0.86 - 0.76 (m, 1H), 0.48 – 0.34 (m, 2H), 0.10 – 0.00 (m, 2H)	308
60	(8-methyl-2-naphthyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.64 – 8.59 (m, 1H), 8.03 (d, <i>J</i> = 8.50 Hz, 1H), 7.98 (dd, <i>J</i> = 1.63, 8.57 Hz, 1H), 7.85 (d, <i>J</i> = 8.22 Hz, 1H), 7.55 (dd, <i>J</i> = 6.98, 8.15 Hz, 1H), 7.49 – 7.43 (m, 1H), 3.78 (tt, <i>J</i> = 3.48, 10.64 Hz, 1H), 3.01 - 2.98 (m, 1H), 2.87 – 2.80 (m, 1H), 2.75 (s, 3H), 2.28 – 2.22 (m, 2H), 2.07 (t, <i>J</i> = 10.75 Hz, 1H), 1.95 - 1.88 (m, 2H), 1.77 – 1.64 (m, 2H), 1.48 – 1.32 (m, 3H), 0.83 (t, <i>J</i> = 7.35 Hz, 3H)	296
61	(1-cyclopentyl-3-piperidyl)-(8-methyl-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 8.65 – 8.59 (m, 1H), 8.03 (d, <i>J</i> = 8.50 Hz, 1H), 8.00 (s, 1H), 7.85 (d, <i>J</i> = 8.10 Hz, 1H), 7.56 (dd, <i>J</i> = 6.98, 8.15 Hz, 1H), 7.47 (dt, <i>J</i> = 1.19, 7.03 Hz, 1H), 3.78 (tt, <i>J</i> = 3.49, 10.54 Hz, 1H), 3.14 – 3.05 (m, 1H), 2.94 - 2.91 (m, 1H), 2.75 (s, 3H), 2.57 – 2.51 (m, 1H), 2.09 (t, <i>J</i> = 10.77 Hz, 1H), 1.99 – 1.84 (m, 2H), 1.82 – 1.64 (m, 4H), 1.62 – 1.23 (m, 7H)	322

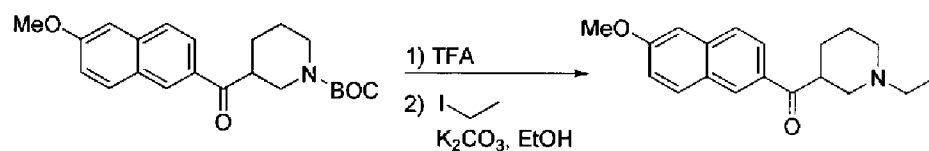
62	(1-cyclobutyl-3-piperidyl)-(8-methyl-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.63 – 8.59 (m, 1H), 8.03 (d, <i>J</i> = 8.56 Hz, 1H), 7.98 (dd, <i>J</i> = 1.63, 8.58 Hz, 1H), 7.85 (d, <i>J</i> = 8.13 Hz, 1H), 7.56 (dd, <i>J</i> = 6.99, 8.17 Hz, 1H), 7.47 (dt, <i>J</i> = 1.16, 6.91 Hz, 1H), 3.76 (tt, <i>J</i> = 3.47, 10.59 Hz, 1H), 2.97 – 2.89 (m, 1H), 2.79 – 2.77 (m, 1H), 2.76 (s, 3H), 2.72 – 2.65 (m, 1H), 2.01 – 1.83 (m, 4H), 1.80 – 1.53 (m, 7H), 1.46 – 1.33 (m, 1H)	308
63	(1-cyclopentyl-3-piperidyl)-[4-(1-hydroxyethyl)-2-naphthyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (t, <i>J</i> = 2.24 Hz, 1H), 8.21 – 8.15 (m, 2H), 8.12 (d, <i>J</i> = 1.68 Hz, 1H), 7.68 (ddd, <i>J</i> = 1.42, 6.83, 8.38 Hz, 1H), 7.61 (ddd, <i>J</i> = 1.10, 6.80, 8.08 Hz, 1H), 5.54 – 5.46 (m, 1H), 5.44 (d, <i>J</i> = 3.94 Hz, 1H), 3.76 (tt, <i>J</i> = 3.08, 9.98 Hz, 1H), 3.08 – 3.05 (m, 1H), 2.95 – 2.92 (m, 1H), 2.55 – 2.52 (m, 1H), 2.12 – 2.04 (m, 1H), 1.99 – 1.82 (m, 2H), 1.82 – 1.49 (m, 7H), 1.47 (d, <i>J</i> = 6.33 Hz, 2H), 1.45 – 1.26 (m, 4H)	352
64	(1-cyclobutyl-3-piperidyl)-[4-(1-hydroxyethyl)-2-naphthyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 – 8.56 (m, 1H), 8.22 – 8.16 (m, 2H), 8.12 (d, <i>J</i> = 1.73 Hz, 1H), 7.68 (ddd, <i>J</i> = 1.43, 6.87, 8.42 Hz, 1H), 7.61 (ddd, <i>J</i> = 1.11, 6.84, 8.12 Hz, 1H), 5.50 (t, <i>J</i> = 5.42 Hz, 1H), 5.44 (d, <i>J</i> = 4.10 Hz, 1H), 3.74 (tt, <i>J</i> = 3.41, 10.90 Hz, 1H), 2.92 – 2.90 (m, 1H), 2.80 – 2.77 (m, 1H), 2.75 – 2.65 (m, 1H), 2.01 – 1.80 (m, 4H), 1.80 – 1.53 (m, 7H), 1.47 (d, <i>J</i> = 6.36 Hz, 3H), 1.44 – 1.33 (m, 1H)	338

65	3-[3-(6-methoxynaphthalene-2-carbonyl)-1-piperidyl]cyclobutanecarbonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.63 (d, <i>J</i> = 1.50 Hz, 1H), 8.08 (d, <i>J</i> = 9.03 Hz, 1H), 7.97 – 7.86 (m, 2H), 7.41 (d, <i>J</i> = 2.56 Hz, 1H), 7.26 (dd, <i>J</i> = 2.55, 8.94 Hz, 1H), 3.92 (s, 3H), 3.71 (tt, <i>J</i> = 3.54, 10.69 Hz, 1H), 3.05–2.97 (m, 1H), 2.92 – 2.83 (m, 1H), 2.81 – 2.68 (m, 2H), 2.48–2.41 (m, 2H), 2.12 – 1.98 (m, 2H), 1.96 – 1.84 (m, 2H), 1.79 – 1.60 (m, 3H), 1.35 (qd, <i>J</i> = 4.70, 11.77 Hz, 1H)	349
66	[1-(3,3-difluorocyclobutyl)-3-piperidyl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.67 – 8.61 (m, 1H), 8.08 (d, <i>J</i> = 8.99 Hz, 1H), 7.97 – 7.87 (m, 2H), 7.41 (d, <i>J</i> = 2.58 Hz, 1H), 7.26 (dd, <i>J</i> = 2.53, 8.99 Hz, 1H), 3.92 (s, 3H), 3.73 (tt, <i>J</i> = 3.49, 10.95 Hz, 1H), 2.4 – 2.913 (m, 1H), 2.84 – 2.81 (m, 1H), 2.71 – 2.64 (m, 3H), 2.46 – 2.27 (m, 2H), 2.00 (t, <i>J</i> = 10.78 Hz, 1H), 1.92 – 1.89 (m, 1H), 1.82 (td, <i>J</i> = 3.28, 11.01 Hz, 1H), 1.78 – 1.63 (m, 2H), 1.45 – 1.29 (m, 1H)	360
67	[1-(cyclopropylmethyl)-3-piperidyl]-[4-(1-hydroxyethyl)-2-naphthyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (d, <i>J</i> = 1.91 Hz, 1H), 8.22 – 8.16 (m, 2H), 8.12 (d, <i>J</i> = 1.69 Hz, 1H), 7.68 (ddd, <i>J</i> = 1.45, 6.82, 8.38 Hz, 1H), 7.61 (ddd, <i>J</i> = 1.05, 6.75, 7.90 Hz, 1H), 5.55 – 5.46 (m, 1H), 5.44 (dd, <i>J</i> = 1.09, 4.33 Hz, 1H), 3.80 (t, <i>J</i> = 11.22 Hz, 1H), 3.11–3.08 (m, 1H), 3.01–2.98 (m, 1H), 2.29 – 2.08 (m, 3H), 1.98–1.83 (m, 2H), 1.4 – 1.723 (m, 2H), 1.47 (d, <i>J</i> = 6.30 Hz, 3H), 1.44 – 1.31 (m, 1H), 0.84 – 0.80 (m, 1H), 0.48 – 0.34 (m, 2H), 0.10 – 0.01 (m, 2H)	338

68	[4-(1-hydroxyethyl)-2-naphthyl]-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.59 (d, <i>J</i> = 1.60 Hz, 1H), 8.22 – 8.14 (m, 2H), 8.12 (d, <i>J</i> = 1.69 Hz, 1H), 7.68 (ddd, <i>J</i> = 1.43, 6.83, 8.35 Hz, 1H), 7.61 (ddd, <i>J</i> = 1.11, 6.88, 8.01 Hz, 1H), 5.55 – 5.46 (m, 1H), 5.44 (d, <i>J</i> = 4.26 Hz, 1H), 3.77 (td, <i>J</i> = 2.70, 10.80 Hz, 1H), 3.02 – 2.91 (m, 1H), 2.89 - 2.84 (m, 1H), 2.25 (t, <i>J</i> = 7.45 Hz, 2H), 2.13 – 2.01 (m, 1H), 1.91 - 1.87 (m, 2H), 1.74 -1.70 (m, 2H), 1.47 (dd, <i>J</i> = 1.21, 6.33 Hz, 3H), 1.46 - 1.40 (m, 3H), 0.83 (td, <i>J</i> = 2.36, 7.36 Hz, 3H)	326
69	[1-(cyclobutylmethyl)-3-piperidyl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.61 (d, <i>J</i> = 1.43 Hz, 1H), 8.06 (d, <i>J</i> = 8.99 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.41 (d, <i>J</i> = 2.57 Hz, 1H), 7.26 (dd, <i>J</i> = 2.53, 8.99 Hz, 1H), 3.92 (s, 3H), 3.70 (tt, <i>J</i> = 3.48, 10.90 Hz, 1H), 2.95 – 2.85 (m, 1H), 2.81 - 2.77f (m, 1H), 2.48 - 2.44 (m, 1H), 2.37 – 2.30 (m, 2H), 2.13 – 2.03 (m, 1H), 2.02 – 1.52 (m, 10H), 1.40 - 1.29 (m, 1H)	338
70	1-methyl-6-(1-propylpiperidine-3-carbonyl)-2-naphthonitrile	¹ H NMR (DMSO- <i>d</i> ₆) δ: 8.75 (d, <i>J</i> = 1.8 Hz, 1H), 8.31 (d, <i>J</i> = 8.9 Hz, 1H), 8.18 (d, <i>J</i> = 8.5 Hz, 1H), 8.10 (dd, <i>J</i> = 8.9, 1.8 Hz, 1H), 7.82 (d, <i>J</i> = 8.6 Hz, 1H), 3.77 (tt, <i>J</i> = 10.6, 3.6 Hz, 1H), 3.00 – 2.92 (m, 1H), 2.91 (s, 3H), 2.87 – 2.77 (m, 1H), 2.24 (t, <i>J</i> = 7.3 Hz, 2H), 2.11 (t, <i>J</i> = 10.7 Hz, 1H), 1.98 – 1.84 (m, 2H), 1.78 – 1.61 (m, 2H), 1.47 – 1.31 (m, 3H), 0.82 (t, <i>J</i> = 7.3 Hz, 3H)	321

71	6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-1-methyl-2-naphthonitrile	¹ H NMR (DMSO- <i>d</i> ₆) δ: 8.77 (d, <i>J</i> = 1.8 Hz, 1H), 8.31 (d, <i>J</i> = 8.9 Hz, 1H), 8.18 (d, <i>J</i> = 8.6 Hz, 1H), 8.11 (dd, <i>J</i> = 8.9, 1.8 Hz, 1H), 7.82 (d, <i>J</i> = 8.5 Hz, 1H), 3.80 (tt, <i>J</i> = 10.7, 3.6 Hz, 1H), 3.12 – 3.03 (m, 1H), 2.99 – 2.92 (m, 1H), 2.91 (s, 3H), 2.29 – 2.11 (m, 3H), 2.03 – 1.84 (m, 2H), 1.72 (td, <i>J</i> = 10.7, 10.0, 5.4 Hz, 2H), 1.46 – 1.31 (m, 1H), 0.86 – 0.72 (m, 1H), 0.47 – 0.33 (m, 2H), 0.10 – 0.01 (m, 2H)	333
72	6-(1-cyclobutylpiperidine-3-carbonyl)-1-methyl-2-naphthonitrile	¹ H NMR (DMSO- <i>d</i> ₆) δ: 8.76 (d, <i>J</i> = 1.8 Hz, 1H), 8.31 (d, <i>J</i> = 8.9 Hz, 1H), 8.19 (d, <i>J</i> = 8.6 Hz, 1H), 8.10 (dd, <i>J</i> = 9.0, 1.8 Hz, 1H), 7.82 (d, <i>J</i> = 8.6 Hz, 1H), 3.75 (tt, <i>J</i> = 10.5, 3.5 Hz, 1H), 2.91 (s, 3H), 2.90 – 2.83 (m, 1H), 2.79 – 2.66 (m, 2H), 2.00 – 1.84 (m, 4H), 1.82 – 1.52 (m, 7H), 1.38 (qd, <i>J</i> = 11.5, 4.4 Hz, 1H)	333
73	6-(1-cyclopentylpiperidine-3-carbonyl)-1-methyl-2-naphthonitrile	¹ H NMR (DMSO- <i>d</i> ₆) δ: 8.76 (d, <i>J</i> = 1.7 Hz, 1H), 8.31 (d, <i>J</i> = 8.9 Hz, 1H), 8.18 (d, <i>J</i> = 8.6 Hz, 1H), 8.10 (dd, <i>J</i> = 8.9, 1.8 Hz, 1H), 7.82 (d, <i>J</i> = 8.5 Hz, 1H), 3.77 (tt, <i>J</i> = 10.7, 3.6 Hz, 1H), 3.08 – 2.99 (m, 1H), 2.94 – 2.85 (m, 4H), 2.59 – 2.51 (m, 1H), 2.13 (t, <i>J</i> = 10.7 Hz, 1H), 2.02 – 1.82 (m, 2H), 1.79 – 1.21 (m, 12H)	347

Example 74: (1-ethyl-3-piperidyl)-(6-methoxy-2-naphthyl)methanone



5

To a solution of *tert*-butyl 3-(6-methoxynaphthalene-2-carbonyl)piperidine-1-carboxylate (1.666 g, 4.51 mmol) in DCM (5 mL) was added TFA (5.142 g, 45.1 mmol). The mixture was stirred at

room temperature for 1 h. The mixture was concentrated to give (6-methoxynaphthalen-2-yl)(piperidin-3-yl)methanone as a colorless oil and used directly without purification.

A mixture of (6-methoxy-2-naphthyl)-(3-piperidyl)methanone (67.3 mg, 0.25 mmol), iodoethane (46.8 mg, 0.300 mmol) and K₂CO₃ (41.5 mg, 0.3 mmol,) in EtOH (1 mL) was heated at 85 °C for 1 h. The mixture was cooled to room temperature, filtered, washed with EtOAc, and concentrated. The crude product was purified by preparative reverse phase HPLC to give the title compound (52.4 mg, 70.5% yield) as a light yellow oil. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.60 (d, *J* = 1.58 Hz, 1H), 8.06 (d, *J* = 9.02 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.40 (d, *J* = 2.62 Hz, 1H), 7.26 (dd, *J* = 2.56, 8.99 Hz, 1H), 3.92 (s, 3H), 3.72 (tt, *J* = 3.53, 10.88 Hz, 1H), 3.02 – 2.92 (m, 1H), 2.87 (d, *J* = 11.01 Hz, 1H), 2.35 (qd, *J* = 2.99, 7.15 Hz, 2H), 2.05 (t, *J* = 10.76 Hz, 1H), 1.87 (td, *J* = 3.87, 10.67 Hz, 2H), 1.76 – 1.63 (m, 2H), 1.45 – 1.30 (m, 1H), 0.98 (t, *J* = 7.14 Hz, 3H). LCMS (ESI) *m/z* 298 [M+H⁺].

The following compounds were prepared in a manner similar to example 74.

Example	Compound Name	¹ H NMR	<i>m/z</i> (M+H)
76	(1-cyclobutyl-3-piperidyl)-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 – 8.59 (m, 1H), 8.06 (d, <i>J</i> = 9.03 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.40 (d, <i>J</i> = 2.55 Hz, 1H), 7.26 (dd, <i>J</i> = 2.55, 8.97 Hz, 1H), 3.92 (s, 3H), 3.75 (m, 1H), 3.11 – 3.04 (m, 1H), 3.03 – 2.94 (m, 1H), 2.29 – 2.06 (m, 3H), 2.00 – 1.84 (m, 2H), 1.71 (m, 2H), 1.44 – 1.31 (m, 1H), 0.81 (m, 1H), 0.41 (m, 2H), 0.10 – 0.01 (m, 2H)	324

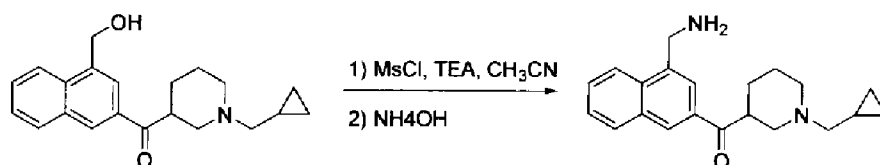
77	[1-(cyclopropylmethyl)-3-piperidyl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.64 – 8.59 (m, 1H), 8.06 (d, <i>J</i> = 8.99 Hz, 1H), 7.96 – 7.87 (m, 2H), 7.40 (d, <i>J</i> = 2.52 Hz, 1H), 7.26 (dd, <i>J</i> = 2.55, 8.98 Hz, 1H), 3.92 (s, 3H), 3.74 (ddt, <i>J</i> = 3.50, 7.01, 11.34 Hz, 1H), 3.12 – 3.04 (m, 1H), 2.98 (d, <i>J</i> = 11.13 Hz, 1H), 2.28 – 2.08 (m, 3H), 1.99 – 1.84 (m, 2H), 1.71 (ddt, <i>J</i> = 3.67, 7.64, 10.80 Hz, 2H), 1.44 – 1.31 (m, 1H), 0.86 – 0.77 (m, 1H), 0.41 (dtd, <i>J</i> = 3.38, 5.13, 8.19 Hz, 2H), 0.08 – 0.02 (m, 2H)	324
78	[1-(2-methoxyethyl)-3-piperidyl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.60 (d, <i>J</i> = 1.51 Hz, 1H), 8.06 (d, <i>J</i> = 8.97 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.40 (d, <i>J</i> = 2.53 Hz, 1H), 7.26 (dd, <i>J</i> = 2.55, 8.97 Hz, 1H), 3.92 (s, 3H), 3.72 (tt, <i>J</i> = 3.49, 10.89 Hz, 1H), 3.41 (t, <i>J</i> = 5.80 Hz, 2H), 3.19 (s, 3H), 3.04 – 2.96 (m, 1H), 2.89 – 2.86 (m, 1H), 2.16 (t, <i>J</i> = 10.84 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.88 – 1.85 (m, 1H), 1.67 – 1.67 (m, 2H), 1.43 – 1.29 (m, 1H)	328

79	[1-(2-fluoroethyl)-3-piperidyl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.64 – 8.58 (m, 1H), 8.06 (d, <i>J</i> = 8.99 Hz, 1H), 7.95 – 7.86 (m, 2H), 7.40 (d, <i>J</i> = 2.64 Hz, 1H), 7.26 (dd, <i>J</i> = 2.55, 8.95 Hz, 1H), 4.58 (t, <i>J</i> = 4.97 Hz, 1H), 4.46 (t, <i>J</i> = 4.94 Hz, 1H), 3.92 (s, 3H), 3.79 – 3.68 (m, 1H), 3.06 – 2.98 (m, 1H), 2.91 (d, <i>J</i> = 11.19 Hz, 1H), 2.69 (td, <i>J</i> = 1.12, 4.70 Hz, 1H), 2.62 (td, <i>J</i> = 1.14, 4.71 Hz, 1H), 2.21 (t, <i>J</i> = 10.87 Hz, 1H), 2.09 – 1.98 (m, 1H), 1.89 (dd, <i>J</i> = 3.73, 12.68 Hz, 1H), 1.73 – 1.69 (m, 2H), 1.42 – 1.31 (m, 1H)	316
81	(1-isopropyl-3-piperidyl)-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.62 – 8.56 (m, 1H), 8.06 (d, <i>J</i> = 8.95 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.40 (d, <i>J</i> = 2.52 Hz, 1H), 7.26 (dd, <i>J</i> = 2.57, 8.94 Hz, 1H), 3.92 (s, 3H), 3.68 (tt, <i>J</i> = 3.48, 10.72 Hz, 1H), 2.94 – 2.86 (m, 1H), 2.82 – 2.64 (m, 2H), 2.29 (t, <i>J</i> = 10.65 Hz, 1H), 2.12 (td, <i>J</i> = 3.07, 11.19 Hz, 1H), 1.88 – 1.85 (m, 1H), 1.77 – 1.57 (m, 2H), 1.38 (qd, <i>J</i> = 4.34, 12.11 Hz, 1H), 0.94 (dd, <i>J</i> = 0.67, 6.58 Hz, 6H)	312

84	3-[3-(6-methoxynaphthalene-2-carbonyl)-1-piperidyl]propanenitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.66 – 8.59 (m, 1H), 8.07 (d, <i>J</i> = 9.03 Hz, 1H), 7.97 – 7.85 (m, 2H), 7.41 (d, <i>J</i> = 2.55 Hz, 1H), 7.26 (dd, <i>J</i> = 2.55, 8.98 Hz, 1H), 3.92 (s, 3H), 3.75 - 3.69 (m, 1H), 3.07 – 2.98 (m, 1H), 2.91 (d, <i>J</i> = 11.20 Hz, 1H), 2.70 – 2.57 (m, 4H), 2.19 (t, <i>J</i> = 10.87 Hz, 1H), 2.05 – 1.96 (m, 1H), 1.91 (d, <i>J</i> = 12.64 Hz, 1H), 1.75 - 1.71 (m, 2H), 1.42 – 1.28 (m, 1H)	323
85	2-[3-(6-methoxynaphthalene-2-carbonyl)-1-piperidyl]acetonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.70 – 8.57 (m, 1H), 8.06 (d, <i>J</i> = 8.98 Hz, 1H), 7.96 – 7.82 (m, 2H), 7.41 (d, <i>J</i> = 2.54 Hz, 1H), 7.26 (dd, <i>J</i> = 2.53, 8.99 Hz, 1H), 3.92 (s, 3H), 3.81-3.75 (m, 1H), 3.75 (s, 2H), 3.00 – 2.92 (m, 1H), 2.86 – 2.78 (m, 1H), 2.35 (t, <i>J</i> = 10.74 Hz, 1H), 2.17 (td, <i>J</i> = 3.99, 10.87 Hz, 1H), 1.96 – 1.86 (m, 1H), 1.80 - 1.71 (m, 2H), 1.42 – 1.27 (m, 1H)	309

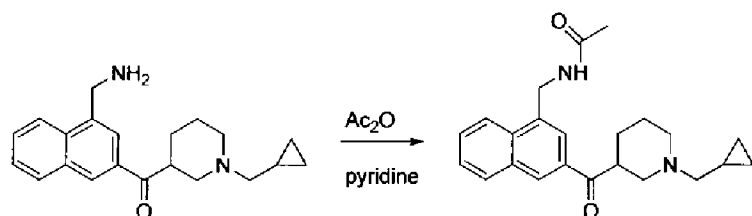
87	(1-ethyl-3-piperidyl)-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.60 (d, <i>J</i> = 1.58 Hz, 1H), 8.06 (d, <i>J</i> = 9.02 Hz, 1H), 7.96 – 7.86 (m, 2H), 7.40 (d, <i>J</i> = 2.62 Hz, 1H), 7.26 (dd, <i>J</i> = 2.56, 8.99 Hz, 1H), 3.92 (s, 3H), 3.72 (tt, <i>J</i> = 3.53, 10.88 Hz, 1H), 3.02 – 2.92 (m, 1H), 2.87 (d, <i>J</i> = 11.01 Hz, 1H), 2.35 (qd, <i>J</i> = 2.99, 7.15 Hz, 2H), 2.05 (t, <i>J</i> = 10.76 Hz, 1H), 1.87 (td, <i>J</i> = 3.87, 10.67 Hz, 2H), 1.76 – 1.63 (m, 2H), 1.45 – 1.30 (m, 1H), 0.98 (t, <i>J</i> = 7.14 Hz, 3H)	298
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Example 88: [4-(aminomethyl)-2-naphthyl]-[1-(cyclopropylmethyl)-3-piperidyl]methanone



To a solution of [1-(cyclopropylmethyl)-3-piperidyl]-[4-(hydroxymethyl)-2-naphthyl]methanone (263 mg, 0.813 mmol) and TEA (123 mg, 1.22 mmol) in acetonitrile (10 mL) at 0 °C was added methanesulfonyl chloride (1.057 mmol, 121 mg, 1.06 mmol) dropwise. The mixture was then stirred at room temperature for 2 h. This mixture was added to a solution of NH₄OH (28 mass% in water, 20 mL) and acetonitrile (40 mL) at 0 °C. The mixture was then warmed to room temperature and stirred for 18 h. The mixture was concentrated and purified by preparative reverse phase HPLC (Phenomenex Gemini-NX, 5-85% ACN in 0.1% Formic Acid (aq)) to give the title compound as a yellow solid. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.57 (d, *J* = 1.80 Hz, 1H), 8.17 – 8.14 (m, 1H), 7.97 – 7.92 (m, 1H), 7.71 – 7.65 (m, 1H), 7.63 – 7.56 (m, 2H), 4.86 (s, 2H), 4.22 (d, *J* = 2.32 Hz, 2H), 3.85 – 3.71 (m, 1H), 3.09 (d, *J* = 9.18 Hz, 2H), 2.99 (d, *J* = 10.88 Hz, 2H), 2.28 – 2.12 (m, 5H), 1.72 (td, *J* = 4.94, 8.99, 10.27 Hz, 4H), 0.88 – 0.72 (m, 2H), 0.45 – 0.38 (m, 2H), 0.10 – 0.01 (m, 2H). LCMS (ESI) *m/z* 323 [M+H⁺].

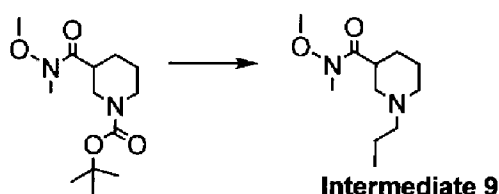
Example 89: *N*-[[3-[1-(cyclopropylmethyl)piperidine-3-carbonyl]-1-naphthyl]methyl]acetamide



To a solution of [4-(aminomethyl)-2-naphthyl]-[1-(cyclopropylmethyl)-3-piperidyl]methanone (32 mg, 0.1 mmol) in pyridine (0.5 mL) was added acetic anhydride (100 mg, 1.0 mmol). The mixture was stirred at room temperature for 4 h. The mixture was concentrated and purified by preparative reverse phase HPLC (Phenomenex Gemini-NX, 5-85% ACN in 0.1% Formic Acid (aq)) to give the title compound (14.7 mg, 39.7% yield) as a yellow solid. ¹H NMR (400 MHz, DMSO- *d*₆) δ 8.67 – 8.62 (m, 1H), 8.42 (t, *J* = 5.87 Hz, 1H), 8.20 (dd, *J* = 1.39, 8.08 Hz, 1H), 8.16 – 8.09 (m, 1H), 7.88 (d, *J* = 1.71 Hz, 1H), 7.71 (ddd, *J* = 1.44, 6.81, 8.39 Hz, 1H), 7.65 (ddd, *J* = 1.18, 6.88, 8.01 Hz, 1H), 4.75 (d, *J* = 5.80 Hz, 2H), 3.79 (ddt, *J* = 3.56, 7.12, 10.86 Hz, 1H), 3.11-3.08 (m, 1H), 3.02-2.99 (m, 2H), 2.30 – 2.18 (m, 2H), 2.15 (t, *J* = 9.47 Hz, 1H), 2.02 – 1.90 (m, 2H), 1.89 (s, 3H), 1.76-1.70 (m, 2H), 1.45 – 1.31 (m, 1H), 0.89 – 0.75 (m, 1H), 0.47-0.38 (m, 2H), 0.11 – 0.01 (m, 2H). LCMS (ESI) *m/z* 365 [M+H⁺].

Synthesis of Intermediates:

Intermediate 9: *N*-methoxy-*N*-methyl-1-propylpiperidine-3-carboxamide

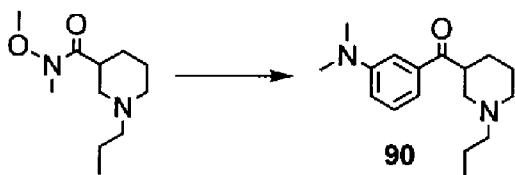


A solution of *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (1.0 g, 3.7 mmol) in 5 ml of DCM was charged with 5 ml of TFA and stirred at room temperature for one hour. The mixture was then concentrated in vacuo and azeotroped twice with toluene. The residue was then diluted with 5 ml of THF and 5 ml of methanol and charged with propionaldehyde (450 mg, 7.7 mmol) and Sodium Triacetoxyborohydride (1.6 g, 7.7 mmol). The mixture was then stirred at room temperature for one hour and concentrated in vacuo. The mixture was then diluted with ethyl acetate and water. The aqueous was discarded and the organic layer was washed once with water, dried over Na₂SO₄, filtered, and concentrated in

vacuo. The residue was then purified by silica-gel chromatography (1 -10% MeOH in DCM) to afford the the title compound (600 mg, 73% yield).

Synthesis of Final Compounds:

5 Example 90: [3-(dimethylamino)phenyl]-(1-propyl-3-piperidyl)methanone



A solution of 3-bromo-*N,N*-dimethylaniline (140 mg, 0.7 mmol) in 1.2 ml of THF was cooled to -78° C and charged with 2.5 M *n*-butyl lithium (0.28 ml, 0.7 mmol). After stirring at -78°C for 5 minutes, *N*-methoxy-*N*-methyl-1-propylpiperidine-3-carboxamide (75 mg, 0.35 mmol) dissolved in 250 ul of THF was added dropwise. The mixture was then allowed to warm to room temperature and stirred at room temperature for 30 minutes. The mixture was diluted with ethyl acetate and saturated NaHCO₃. The aqueous was discarded and the organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was then purified by preparatory HPLC (Phenomenex Gemini-NX, 20-60% ACN in NH₄OH (aq)) to afford the title compound (31mg, 31% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.32 (t, *J* = 7.9 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.14 (t, *J* = 2.2 Hz, 1H), 6.98 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.51 (tt, *J* = 10.6, 3.6 Hz, 1H), 3.29 (s, 4H), 2.94 (s, 5H), 2.94 – 2.85 (m, 1H), 2.80 (dt, *J* = 11.4, 3.7 Hz, 1H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.99 (t, *J* = 10.7 Hz, 1H), 1.92 – 1.76 (m, 2H), 1.72 – 1.57 (m, 2H), 1.47 – 1.36 (m, 2H), 1.39 – 1.24 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). LCMS *m/z*: 275 (M+H).

20 The following compounds were prepared in a manner similar to example 90.

Example	Compound Name	¹ H NMR	<i>m/z</i> (M+H)
91	(4-chlorophenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.99 – 7.91 (m, 2H), 7.63 – 7.55 (m, 2H), 3.54 (tt, <i>J</i> = 10.4, 3.7 Hz, 1H), 2.91 – 2.83 (m, 1H), 2.78 (d, <i>J</i> = 11.1 Hz, 1H), 2.22 (t, <i>J</i> = 7.4 Hz, 2H), 2.03 (t, <i>J</i> = 10.7 Hz, 1H), 1.94 – 1.76 (m, 2H), 1.74 – 1.57 (m, 2H), 1.46 – 1.24 (m, 3H), 0.82 (t, <i>J</i> = 7.4 Hz, 3H).	261

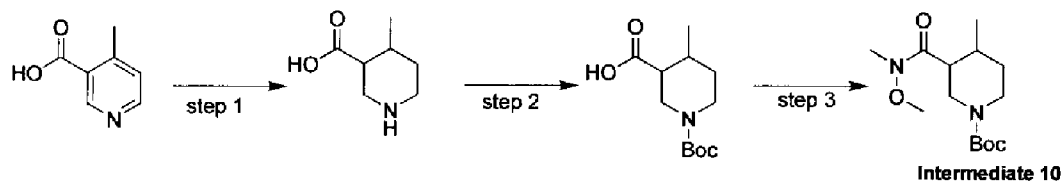
92	(3-chlorophenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.90 (dp, <i>J</i> = 3.2, 1.5 Hz, 2H), 7.70 (ddd, <i>J</i> = 8.0, 2.2, 1.1 Hz, 1H), 7.56 (t, <i>J</i> = 8.1 Hz, 1H), 3.56 (tt, <i>J</i> = 10.2, 3.6 Hz, 1H), 2.91 – 2.82 (m, 1H), 2.82 – 2.73 (m, 1H), 2.28 – 2.17 (m, 2H), 2.05 (dd, <i>J</i> = 11.4, 9.8 Hz, 1H), 1.90 (td, <i>J</i> = 11.0, 3.4 Hz, 1H), 1.80 (dd, <i>J</i> = 12.8, 3.9 Hz, 1H), 1.74 – 1.54 (m, 2H), 1.39 (dtd, <i>J</i> = 14.8, 7.4, 1.7 Hz, 2H), 1.37 – 1.25 (m, 1H), 0.82 (t, <i>J</i> = 7.4 Hz, 3H).	261
93	(1-propyl-3-piperidyl)-(6-quinolyl)methanone		266
94	(1-methylindazol-5-yl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.52 (d, <i>J</i> = 1.3 Hz, 1H), 8.24 (s, 1H), 7.94 (dd, <i>J</i> = 8.9, 1.5 Hz, 1H), 7.80 – 7.68 (m, 1H), 4.08 (s, 2H), 3.66 (tt, <i>J</i> = 10.8, 3.6 Hz, 1H), 2.97 – 2.88 (m, 1H), 2.84 (d, <i>J</i> = 11.0 Hz, 1H), 2.24 (t, <i>J</i> = 7.4 Hz, 2H), 2.05 (t, <i>J</i> = 10.8 Hz, 1H), 1.88 (td, <i>J</i> = 11.1, 4.1 Hz, 2H), 1.75 – 1.59 (m, 2H), 1.39 (tq, <i>J</i> = 11.4, 6.2, 5.0 Hz, 3H), 0.83 (t, <i>J</i> = 7.3 Hz, 3H).	266
95	(3-benzyloxyphenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.56 – 7.24 (m, 10H), 5.19 (s, 2H), 3.53 (tt, <i>J</i> = 10.5, 3.5 Hz, 1H), 2.91 – 2.74 (m, 2H), 2.22 (t, <i>J</i> = 7.4 Hz, 2H), 1.92 – 1.73 (m, 2H), 1.72 – 1.57 (m, 2H), 1.46 – 1.22 (m, 3H), 0.82 (t, <i>J</i> = 7.3 Hz, 3H).	282
96	(2-chlorophenyl)-(1-propyl-3-piperidyl)methanone		285

97	(4-methoxyphenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 7.93 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.9 Hz, 2H), 3.84 (s, 3H), 3.50 (tt, J = 10.7, 3.5 Hz, 1H), 2.92 – 2.78 (m, 2H), 2.23 (t, J = 7.4 Hz, 2H), 1.99 (t, J = 10.8 Hz, 1H), 1.91 – 1.76 (m, 2H), 1.72 – 1.58 (m, 2H), 1.48 – 1.23 (m, 3H), 0.83 (t, J = 7.4 Hz, 3H).	337
98	(3-methoxyphenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 7.53 (d, J = 7.6 Hz, 1H), 7.49 – 7.35 (m, 2H), 7.20 (dd, J = 8.1, 2.6 Hz, 1H), 3.81 (s, 3H), 3.54 (tt, J = 10.5, 3.6 Hz, 1H), 3.29 (s, 9H), 2.89 (dd, J = 11.6, 3.1 Hz, 1H), 2.79 (d, J = 11.3 Hz, 1H), 2.23 (t, J = 7.4 Hz, 2H), 2.02 (t, J = 10.7 Hz, 1H), 1.93 – 1.77 (m, 2H), 1.67 (s, 1H), 1.73 – 1.58 (m, 1H), 1.46 – 1.24 (m, 3H), 0.82 (t, J = 7.4 Hz, 3H).	266
99	(2-methoxyphenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> 6) δ 7.50 (td, J = 8.0, 7.5, 1.8 Hz, 1H), 7.37 (dd, J = 7.7, 1.8 Hz, 1H), 7.14 (d, J = 8.3 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 3.86 (s, 2H), 3.29 (s, 10H), 2.86 – 2.78 (m, 1H), 2.69 – 2.61 (m, 1H), 2.18 (t, J = 7.3 Hz, 2H), 1.97 (dt, J = 29.3, 10.4 Hz, 2H), 1.78 – 1.69 (m, 1H), 1.64 (dq, J = 12.6, 4.0 Hz, 1H), 1.55 – 1.40 (m, 1H), 1.41 – 1.27 (m, 3H), 0.79 (t, J = 7.4 Hz, 3H).	261

100	(1-propyl-3-piperidyl)-[4-(trifluoromethyl)phenyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.12 (d, <i>J</i> = 8.2 Hz, 2H), 7.89 (d, <i>J</i> = 8.2 Hz, 2H), 3.60 (tt, <i>J</i> = 10.5, 3.6 Hz, 1H), 2.93 – 2.85 (m, 1H), 2.77 (d, <i>J</i> = 11.0 Hz, 1H), 2.23 (s, 1H), 2.23 (dd, <i>J</i> = 14.7, 1.8 Hz, 1H), 2.07 (dd, <i>J</i> = 11.3, 10.0 Hz, 1H), 1.91 (td, <i>J</i> = 11.0, 3.2 Hz, 1H), 1.87 – 1.78 (m, 1H), 1.75 – 1.54 (m, 2H), 1.45 – 1.27 (m, 3H), 0.81 (t, <i>J</i> = 7.4 Hz, 3H).	261
101	(3,4-dichlorophenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.10 (d, <i>J</i> = 2.0 Hz, 1H), 7.90 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 7.80 (d, <i>J</i> = 8.4 Hz, 1H), 3.63 – 3.51 (m, 1H), 2.91 – 2.82 (m, 1H), 2.77 (d, <i>J</i> = 11.3 Hz, 1H), 2.28 – 2.17 (m, 2H), 2.05 (dd, <i>J</i> = 11.3, 10.0 Hz, 1H), 1.90 (td, <i>J</i> = 10.9, 3.4 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.73 – 1.54 (m, 1H), 1.46 – 1.24 (m, 3H), 0.82 (t, <i>J</i> = 7.4 Hz, 3H).	261
102	(2-phenylphenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.58 (td, <i>J</i> = 7.4, 1.7 Hz, 1H), 7.52 – 7.35 (m, 6H), 7.35 – 7.28 (m, 2H), 2.50 – 2.35 (m, 2H), 2.10 – 2.01 (m, 2H), 1.94 – 1.78 (m, 2H), 1.54 – 1.37 (m, 2H), 1.22 (h, <i>J</i> = 7.3 Hz, 3H), 1.18 – 1.09 (m, 1H), 0.72 (t, <i>J</i> = 7.4 Hz, 3H).	299

103	(1-propyl-3-piperidyl)-[4-(trifluoromethoxy)phenyl]methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.11 – 8.03 (m, 2H), 7.53 – 7.37 (m, 2H), 3.56 (tt, <i>J</i> = 10.5, 3.6 Hz, 1H), 2.93 – 2.84 (m, 1H), 2.78 (dd, <i>J</i> = 11.0, 4.1 Hz, 1H), 2.29 – 2.15 (m, 2H), 2.05 (t, <i>J</i> = 10.7 Hz, 1H), 1.86 (dtd, <i>J</i> = 24.2, 13.0, 12.0, 3.6 Hz, 2H), 1.65 (dddd, <i>J</i> = 24.4, 13.1, 9.7, 6.1 Hz, 2H), 1.46 – 1.17 (m, 3H), 0.82 (t, <i>J</i> = 7.4 Hz, 3H).	300
104	(3,4-dimethoxyphenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.64 (dd, <i>J</i> = 8.4, 2.0 Hz, 1H), 7.41 (d, <i>J</i> = 1.9 Hz, 1H), 7.03 (dd, <i>J</i> = 27.5, 8.3 Hz, 1H), 3.87 – 3.74 (m, 7H), 3.54 (tt, <i>J</i> = 10.7, 3.5 Hz, 1H), 3.29 (s, 5H), 2.93 – 2.78 (m, 2H), 2.23 (t, <i>J</i> = 7.4 Hz, 2H), 1.99 (t, <i>J</i> = 10.8 Hz, 1H), 1.91 – 1.75 (m, 2H), 1.72 – 1.59 (m, 2H), 1.37 (ddt, <i>J</i> = 33.1, 11.9, 6.2 Hz, 3H), 0.83 (t, <i>J</i> = 7.3 Hz, 3H).	307
105	(3,5-dimethoxyphenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.02 (d, <i>J</i> = 2.2 Hz, 2H), 3.80 (s, 5H), 3.52 (tt, <i>J</i> = 10.7, 3.6 Hz, 1H), 3.29 (s, 3H), 2.92 – 2.84 (m, 1H), 2.78 (dt, <i>J</i> = 11.7, 3.7 Hz, 1H), 2.23 (t, <i>J</i> = 7.4 Hz, 2H), 2.01 (t, <i>J</i> = 10.7 Hz, 1H), 1.84 (ddt, <i>J</i> = 25.3, 12.9, 6.0 Hz, 2H), 1.65 (dddd, <i>J</i> = 13.1, 9.3, 6.9, 3.1 Hz, 2H), 1.46 – 1.23 (m, 3H), 0.82 (t, <i>J</i> = 7.3 Hz, 3H).	315

106	(3,4-dimethylphenyl)-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.73 – 7.63 (m, 2H), 7.28 (d, <i>J</i> = 7.8 Hz, 1H), 3.52 (tt, <i>J</i> = 10.8, 3.6 Hz, 1H), 2.92 – 2.81 (m, 1H), 2.81 (d, <i>J</i> = 11.0 Hz, 1H), 2.29 (s, 5H), 2.23 (t, <i>J</i> = 7.4 Hz, 2H), 1.99 (t, <i>J</i> = 10.8 Hz, 1H), 1.91 – 1.75 (m, 2H), 1.65 (dtd, <i>J</i> = 15.7, 11.7, 10.2, 4.2 Hz, 2H), 1.47 – 1.21 (m, 3H), 0.83 (t, <i>J</i> = 7.4 Hz, 3H).	291
107	(1-propyl-3-piperidyl)-tetralin-6-yl-methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.63 (s, 1H), 7.19 (d, <i>J</i> = 8.1 Hz, 1H), 3.51 (tt, <i>J</i> = 10.7, 3.5 Hz, 1H), 2.92 – 2.78 (m, 1H), 2.78 (t, <i>J</i> = 5.5 Hz, 5H), 2.27 – 2.18 (m, 2H), 1.97 (t, <i>J</i> = 10.8 Hz, 1H), 1.90 – 1.65 (m, 6H), 1.69 – 1.57 (m, 2H), 1.47 – 1.37 (m, 2H), 1.40 – 1.21 (m, 2H), 0.83 (t, <i>J</i> = 7.4 Hz, 3H).	291
108	2,3-dihydro-1,4-benzodioxin-6-yl-(1-propyl-3-piperidyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 7.47 (dd, <i>J</i> = 8.5, 2.2 Hz, 1H), 7.40 (d, <i>J</i> = 2.2 Hz, 1H), 6.97 (d, <i>J</i> = 8.5 Hz, 1H), 4.36 – 4.24 (m, 4H), 3.52 – 3.32 (m, 1H), 2.91 – 2.76 (m, 2H), 2.23 (t, <i>J</i> = 7.4 Hz, 2H), 1.98 (t, <i>J</i> = 10.8 Hz, 1H), 1.90 – 1.74 (m, 2H), 1.64 (pt, <i>J</i> = 12.8, 6.4 Hz, 2H), 1.40 (q, <i>J</i> = 7.4 Hz, 2H), 1.38 – 1.19 (m, 2H), 0.83 (t, <i>J</i> = 7.4 Hz, 3H).	259

Synthesis of Intermediates**Intermediate 10: *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-methylpiperidine-1-carboxylate**

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Step 1:**4-methylpiperidine-3-carboxylic acid**

To a solution of 4-methylnicotinic acid (10.0 g, 73.0 mmol) in AcOH (200 mL) was added PtO₂ (1.0 g). The mixture was stirred at 25 °C under H₂ atmosphere (50 psi) for 72 h and filtered through a short pad of Celite. The filtrate was concentrated to give the crude 4-methylpiperidine-3-carboxylic acid (10.0 g, 96% yield) as a colorless oil. This crude was used directly without further purification.

Step 2:**1-(*tert*-butoxycarbonyl)-4-methylpiperidine-3-carboxylic acid**

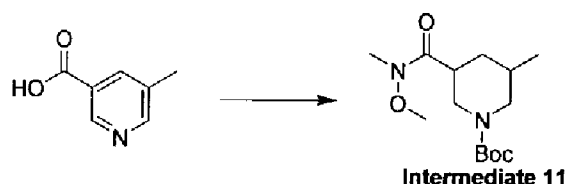
To a stirred and cooled (0 °C) solution of 4-methylpiperidine-3-carboxylic acid (10.0 g, 70 mmol) in THF (200 mL) and water (200 mL) was added Na₂CO₃ (22.2 g, 210 mmol) and (Boc)₂O (15.1 g, 70 mmol). After addition, the mixture was allowed to warm to 25 °C, and stirred for 2 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (petroleum ether: ethyl acetate = 2: 1) to afford the title compound (10.0 g, 58.8 % yield) as a colorless oil.

Step 3:***tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-methylpiperidine-1-carboxylate**

To a stirred and cooled (0 °C) solution of 1-(*tert*-butoxycarbonyl)-4-methylpiperidine-3-carboxylic acid (10.0 g, 41.3 mmol) in THF (300 mL) was added CDI (8.0 g, 49.6 mmol). After addition, stirring was continued for 1 h, then *N,O*-dimethylhydroxylamine hydrochloride (4.8 g, 49.6 mmol) and Et₃N (7.7 g, 49.6 mmol) was added. The resulting mixture was stirred at 25 °C for 17 h, at which time TLC showed the completion of the reaction. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (200 mL) and washed

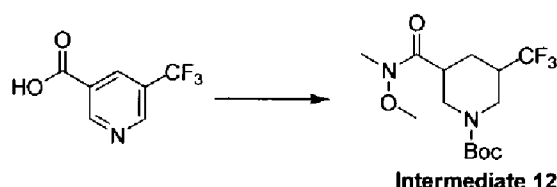
successively with 0.5 N aq. HCl (50 mL), sat aq. Na₂CO₃ (50 mL) and brine (50 mL). The organic layer was dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 5: 1) to give *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-methylpiperidine-1-carboxylate (8.5 g, 72.0 % yield) as a pale yellow solid.

Intermediate 11: *tert*-butyl 3-(methoxy(methyl)carbamoyl)-5-methylpiperidine-1-carboxylate



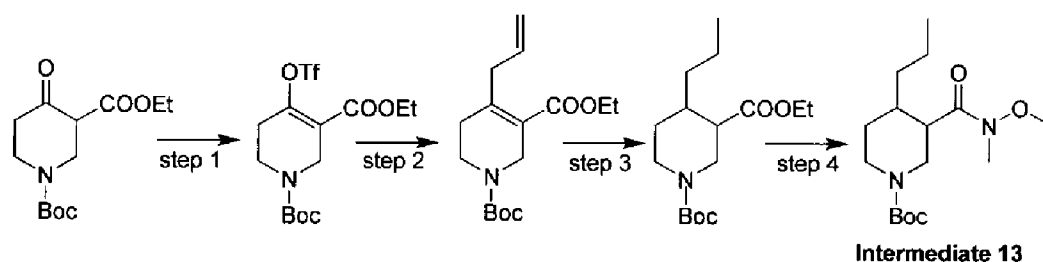
- 10 Prepared in an analogous manner to *tert*-butyl 3-(methoxy(methyl)carbamoyl)- 4-methylpiperidine-1-carboxylate (Intermediate 10), replacing 4-methylnicotinic acid with 5-methylnicotinic acid.

Intermediate 12: *tert*-butyl 3-(methoxy(methyl)carbamoyl)-5-(trifluoromethyl) piperidine-1-carboxylate



Prepared in an analogous manner to *tert*-butyl 3-(methoxy(methyl)carbamoyl)- 4-methylpiperidine-1-carboxylate (Intermediate 10), replacing 4-methylnicotinic acid with 5-(trifluoromethyl)nicotinic acid.

Intermediate 13: *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-propylpiperidine-1-carboxylate



5 Step 1:

1-*tert*-butyl 3-ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1,3(2H)-dicarboxylate

To a stirred and cooled solution (-78°C) of 1-*tert*-butyl 3-ethyl-4-oxopiperidine-1,3-dicarboxylate (11.7 g, 43.2 mmol) in dichloromethane (300 mL) was added diisopropyl ethyl amine (16.7 g, 129.6 mmol), followed by trifluoromethanesulfonic anhydride (14.6 g, 51.8 mmol). After addition, the resulting mixture was stirred at -78°C for 2 h and then concentrated under reduced pressure. The crude material was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 20:1) to give the title compound (8.5 g, 49% yield).

15 Step 2:

1-*tert*-butyl 3-ethyl 4-allyl-5,6-dihydropyridine -1,3-dicarboxylate

To a solution of 1-*tert*-butyl 3-ethyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1,3-dicarboxylate (8.0 g, 19.8 mmol) in THF (300 mL) was added LiCl (2.5 g, 59.6 mmol), allyltributylstannane (7.2 g, 21.8 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (1.15 g, 1.0 mmol). The resulting mixture was flushed with nitrogen and heated at 55°C for 4 h. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate (3×100 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and evaporated. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10:1) to give the title compound (5.0 g, 85.6 % yield) as an oil.

25

Step 3:

1-*tert*-butyl 3-ethyl 4-propylpiperidine-1,3-dicarboxylate

To a solution of 1-*tert*-butyl 3-ethyl 4-allyl-5,6-dihydropyridine-1,3-dicarboxylate (5.0 g, 17.0 mmol) in AcOH (100 mL) was added PtO_2 (0.5 g). The mixture was stirred at 50°C under H_2 atmosphere (50 psi) for 24 h and then filtered through a short pad of Celite. The filtrate was

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concentrated under reduced pressure to give the title compound (3.5 g, 69.1% yield) as a yellow oil.

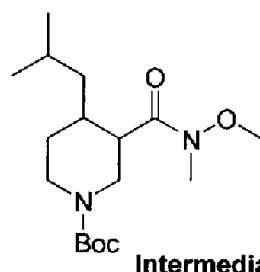
Step 4:

5 *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-propylpiperidine-1-carboxylate

To a stirred and cooled (-20 °C) solution of 1-*tert*-butyl 3-ethyl 4-propylpiperidine -1,3-dicarboxylate (3.5 g, 11.7 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.7 g, 17.5 mmol) in THF (50 mL) was added isopropylmagnesium chloride (2 N, 17.5 mL, 35.0 mmol) dropwise. After addition, the reaction mixture was warmed to room temperature and stirred at
 10 25 °C for 0.5 h. The mixture was quenched by addition of saturated aqueous NH₄Cl (20 mL), and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue and purified by silica gel silica-gel chromatography (petroleum ether: ethyl acetate = 5:1) to give the title compound (2.2 g, 61.0 % yield) as a yellow oil.

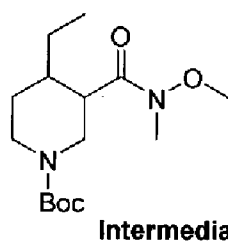
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Intermediate 14: *tert*-butyl 4-isobutyl-3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate



Prepared in an analogous manner to *tert*-butyl 3-(methoxy(methyl)carbamoyl)- 4-propylpiperidine-1-carboxylate (Intermediate 13), replacing allyltributylstannane with
 20 tributyl(2-methylallyl)stannane.

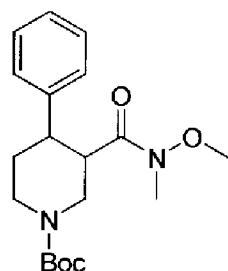
Intermediate 15: *tert*-butyl 4-ethyl-3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate



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Prepared in an analogous manner to *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-propylpiperidine-1-carboxylate (Intermediate 13), replacing allyltributylstannane with potassium trifluoro(vinyl)borate.

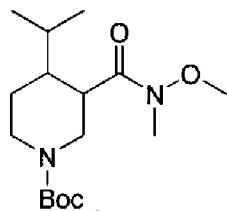
5 **Intermediate 16: *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-phenylpiperidine-1-carboxylate**



Intermediate 16

Prepared in an analogous manner to *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-propylpiperidine-1-carboxylate (Intermediate 13), replacing allyltributylstannane with
10 phenylboronic acid.

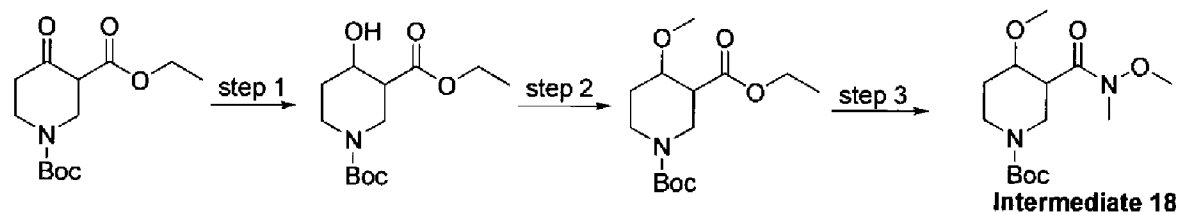
Intermediate 17: *tert*-butyl 4-isopropyl-3-(methoxy(methyl)carbamoyl)piperidine -1-carboxylate



Intermediate 17

15 Prepared in an analogous manner to *tert*-butyl-3-(methoxy(methyl)carbamoyl)-4-propylpiperidine-1-carboxylate (Intermediate 13), replacing allyltributylstannane with potassium isopropenyltrifluoroborate.

Intermediate 18: *tert*-butyl 4-methoxy-3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate



Step 1:

5 1-*tert*-butyl 3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate

To a stirred and cooled (0 °C) solution of 1-*tert*-butyl 3-ethyl-4-oxopiperidine-1,3-dicarboxylate (3.0 g, 11.1 mmol) in EtOH (60 mL) was added NaBH₄ (253 mg, 6.66 mmol). After addition, the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated. The crude was diluted with ethyl acetate (100 mL), washed with NaOH (aq. 1 N, 30 mL), dried (Na₂SO₄) and concentrated. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10:1) to give the title compound (2.8 g, 92.7% yield) as a colorless oil.

Step 2:

1-*tert*-butyl 3-ethyl 4-methoxypiperidine-1,3-dicarboxylate

15 To a solution of 1-*tert*-butyl 3-ethyl 4-hydroxypiperidine-1,3-dicarboxylate (1.0 g, 3.66 mmol) in iodomethane (20 mL) was added CaSO₄ (7.2 g, 53.0 mmol) and silver oxide (8.5 g, 36.6 mmol) at room temperature. The reaction mixture was stirred at room temperature for 24 h. Iodomethane was removed under reduced pressure. The residue was diluted with ethyl acetate (100 mL) and filtered. The filtrate was dried (Na₂SO₄) and concentrated. The crude was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10:1) to give the title compound (500 mg, 47.6% yield) as a yellow oil.

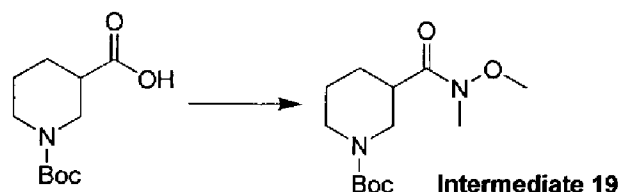
Step 3:

***tert*-butyl 4-methoxy-3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate**

25 To a stirred and cooled (-20 °C) solution of 1-*tert*-butyl 3-ethyl 4-methoxypiperidine-1,3-dicarboxylate (400 mg, 1.39 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (204 mg, 2.09 mmol) in THF (10 mL) was added isopropylmagnesium chloride (2 N, 2.1 mL, 4.20 mmol) dropwise. After addition, the reaction mixture was warmed to room temperature and stirred at 25 °C for 0.5 h. The mixture was quenched by addition of saturated aqueous NH₄Cl (15 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried (Na₂SO₄)

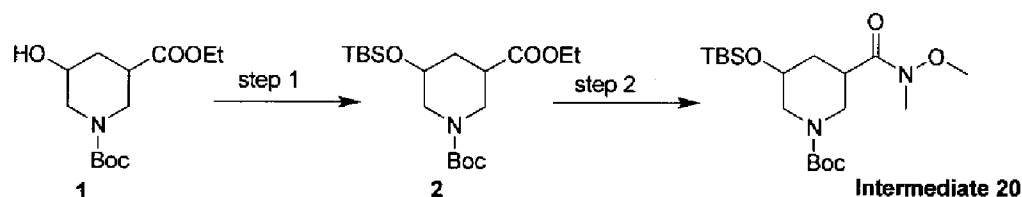
and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 5:1) to give the title compound (250 mg, 59.2% yield) as a yellow oil.

5 Intermediate 19: *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate



To a stirred and cooled (0°C) solution of 1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid (5.4 g, 23 mmol) in THF (120 mL) was added CDI (4.5 g, 28 mmol). After addition, stirring was continued for 1 h, then *N,O*-dimethylhydroxylamine hydrochloride (2.7 g, 28 mmol) and Et₃N (2.8 g, 28 mmol) were added. The resulting mixture was stirred at 25 °C for 12 h, at which time TLC showed the completion of the reaction. The solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (200 mL) and washed successively with 0.5 N aq. HCl (30 mL), sat aq. Na₂CO₃ (30 mL) and brine (30 mL). The organic layer was dried over Na₂SO₄ and evaporated under reduced pressure. The crude product was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 2:1) to give the title compound (4.0 g, 58 % yield).

20 Intermediate 20: *tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-5-(methoxy(methyl)carbamoyl)piperidine-1-dicarboxylate



Step 1:

25 1-*tert*-butyl 3-ethyl 5-((*tert*-butyldimethylsilyl)oxy)piperidine-1,3- dicarboxylate

To a stirred and cooled (0 °C) solution of 1-*tert*-butyl 3-ethyl 5-hydroxypiperidine-(1,3)-dicarboxylate (1.0 g, 3.7 mmol) in DMF (10 mL) was added TBSCl (0.67 g, 4.4 mmol) and imidazole (0.3 g, 4.4 mmol). After addition, the mixture was stirred at room temperature for 12

h and then diluted with ethyl acetate (50 mL). The resulting solution was washed with brine (3 × 30 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10:1) to give the title compound (888 mg, 52% yield) as a colorless oil.

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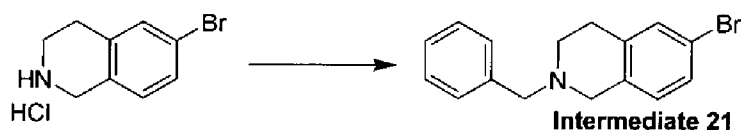
Step 2:***tert*-butyl 3-((*tert*-butyldimethylsilyl)oxy)-5-(methoxy(methyl)carbamoyl) piperidine-1-carboxylate**

To a stirred and cooled (-20 °C) solution of 1-*tert*-butyl 3-ethyl 5-((*tert*-butyldimethylsilyl)oxy)piperidine-1,3-dicarboxylate (800 mg, 2.1 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (312 mg, 3.2 mmol) in THF (15 mL) was added isopropylmagnesium chloride (2 N, 3.2 mL, 6.4 mmol) dropwise. After addition, the reaction mixture was warmed to room temperature and stirred at 25 °C for 0.5 h. The mixture was quenched by addition of saturated aqueous NH₄Cl (15 mL), and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 5: 1) to give the title compound (620 mg, 75% yield) as a white solid.

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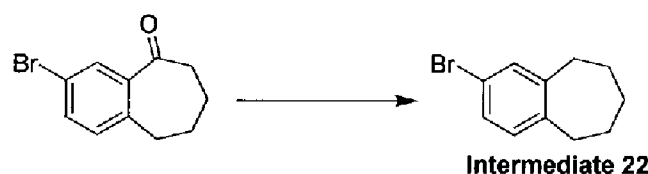
Intermediate 21: 2-benzyl-6-bromo-1,2,3,4-tetrahydroisoquinoline

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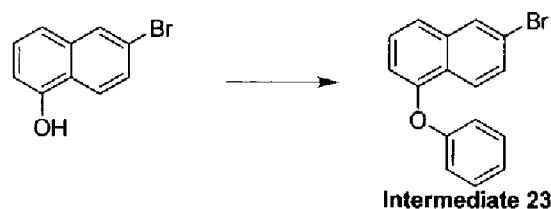


To a solution of 6-bromo-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.8 g, 11.3 mmol) in MeCN (50 mL) was added benzyl bromide (2.1 g, 12.4 mmol) and Cs₂CO₃ (11.1 g, 33.9 mmol). After addition, the resulting mixture was heated at reflux for 1 h. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (100 mL). The solution was then washed with brine (100 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10:1) to give the title compound (2.7 g, 79% yield) as a colourless oil.

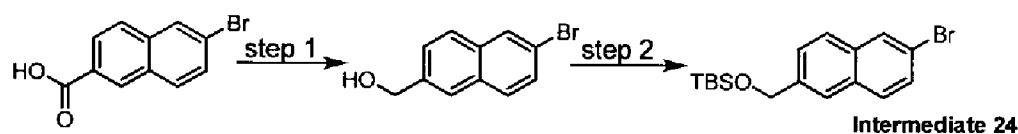
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Intermediate 22: 2-bromo-6,7,8,9-tetrahydro-5-benzo[7]annulene

To a solution of 3-bromo-6,7,8,9-tetrahydro-5-benzo[7]annulen-5-one (0.30 g, 1.2 mmol) in trifluoroacetic acid (4 mL) was added Et₃SiH (2 mL). The resulting mixture was stirred at 25 °C for 12 h. The solvent was evaporated under reduced pressure, and the residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 20:1) to give the title compound (0.15 g, 53.3 % yield).

Intermediate 23: 6-bromo-1-phenoxy-naphthalene

To a solution of 6-bromonaphthalen-1-ol (2.0 g, 9.0 mmol) in DCM (60 mL) was added phenylboronic acid (2.2 g, 18.0 mmol), Cu(OAc)₂ (3.3 g, 18.0 mmol), molecular sieves (1.5 g) and pyridine (5 mL). The resulting mixture was stirred at 25 °C for 18 h. The mixture was filtered through a short pad of Celite. The filtrate was washed successively with HCl (aq., 0.5 N, 20 mL), saturated aqueous Na₂CO₃ (20 mL), brine (20 mL), dried (Na₂SO₄), and evaporated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10:1) to give the title compound (0.4 g, 15 % yield).

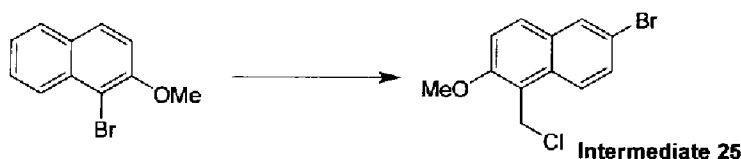
Intermediate 24: ((6-bromonaphthalen-2-yl)methoxy)(*tert*-butyl)dimethylsilane

Step 1:**(6-bromonaphthalen-2-yl)methanol**

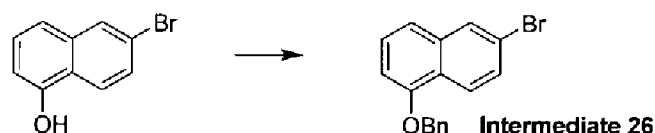
To a solution of 6-bromo-2-naphthoic acid (1.0 g, 4.0 mmol) in THF (20 mL) at 0 °C was added DIBAL-H (8.0 mL, 8.0 mmol). After addition, the reaction mixture was stirred at 25 °C for 16 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl (20 mL) and then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by chromatography (petroleum ether: ethyl acetate = 2:1) to give the title compound (0.7 g, 74 % yield) as a white solid.

Step 2:**((6-bromonaphthalen-2-yl)methoxy)(*tert*-butyl)dimethylsilane**

To a solution of (6-bromonaphthalen-2-yl)methanol (0.7 g, 2.97 mmol) in dichloromethane (20 mL) was added TBSCl (667 mg, 4.45 mmol) and imidazole (302 mg, 4.45 mmol). After the addition, the reaction mixture was stirred at 25 °C for 1 h. The reaction was then quenched by addition of saturated aqueous NH₄Cl (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 30: 1) to give the title compound (0.8 g, 77 % yield) as a colorless oil.

Intermediate 25: 6-bromo-1-(chloromethyl)-2-methoxynaphthalene

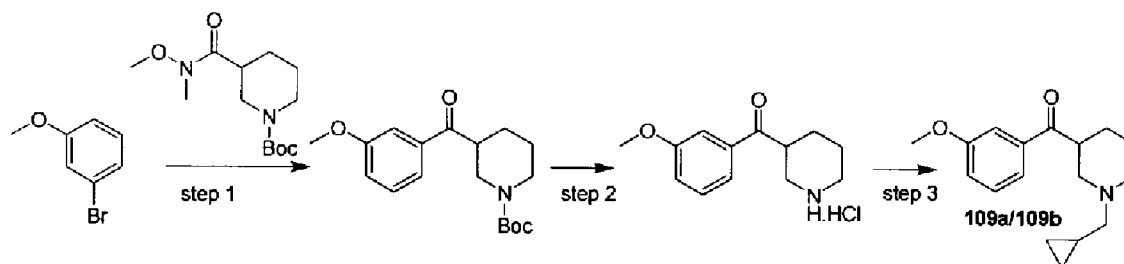
HCl (gas) was bubbled into a mixture of 1-bromo-2-methoxynaphthalene (20.0 g, 84 mmol), glacial acetic acid (60 ml), 37% aqueous formaldehyde (11.0 g, 134 mmol) and concentrated hydrochloride acid (42 mL) while at 60°C for 2 hours. After cooling to room temperature, the crude product was collected by filtration and then recrystallized in acetone to give the the title compound (13.0 g, 54% yield) as a purple solid.

Intermediate 26: 2-(benzyloxy)-6-bromonaphthalene

To a stirred and cooled (0 °C) solution of 6-bromo-2-naphthol (5.00 g, 22.4 mmol) in DMF (50 mL) was added sodium hydride (60%, 1.16 g, 29.1 mmol) in portions. After addition, stirring was continued for 15 min, and then benzyl bromide (3.5 g, 20.2 mmol) was added. The reaction mixture was stirred at room temperature for 18 h. The mixture was quenched by addition of saturated aqueous NH₄Cl (100 mL) and then extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed with water (3 x 100 mL), brine (100 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10: 1) to give the title compound (5.0 g, 71% yield) as a white solid.

Synthesis of final compounds

In many of the Examples below, enantiomers and diastereomers are exemplified by alphabetical designations following the numerical designation. For example, 1a and 1b designations would refer to the two enantiomers of example 1. In addition, 2a, 2b, 2c, and 2d designations would refer to the four diastereomers of example 2. Moreover, when enantiomers or diastereomers are designated, super-fluid chromatography (SFC) using the conditions described per example were used for purification. When racemic mixtures are exemplified, purification by methods other than SFC were used and enantiomers or diastereomers were not separated.

Examples 109a and 109b: (1-(cyclopropylmethyl)piperidin-3-yl)(3-methoxyphenyl)methanone

Step 1:***tert*-butyl 3-(3-methoxybenzoyl)piperidine-1-carboxylate**

To a stirred and cooled (-78 °C) solution of 1-bromo-3-methoxybenzene (187 mg, 1.0 mmol) in THF (10 mL) was added *n*-BuLi (2.5 M in hexane, 0.4 mL, 1.0 mmol). After addition, stirring at -78 °C was continued for 1 h, and then a solution of *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 10) (272 mg, 1.0 mmol) in THF (5 mL) was added dropwise. The resulting mixture was warmed up to room temperature and stirred for additional 2 h, at which time TLC indicated the reaction was completed. The mixture was quenched by addition of saturated aqueous NH₄Cl (10 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure, to give crude *tert*-butyl 3-(3-methoxybenzoyl)piperidine-1-carboxylate (160 mg, 50% yield). This crude was used directly without further purification.

Step 2:**(3-methoxyphenyl)(piperidin-3-yl)methanone hydrochloride**

To a solution of *tert*-butyl 3-(3-methoxybenzoyl)piperidine-1-carboxylate (160 mg, 0.5 mmol) in ethyl acetate (5 mL) was added HCl/ethyl acetate (2 M, 5 mL, 10 mmol). The mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure to give the crude (3-methoxyphenyl)(piperidin-3-yl) methanone hydrochloride (128 mg, 99% yield). This crude was used directly in next step without further purification.

Step 3:**(1-(cyclopropylmethyl)piperidin-3-yl)(3-methoxyphenyl)methanone**

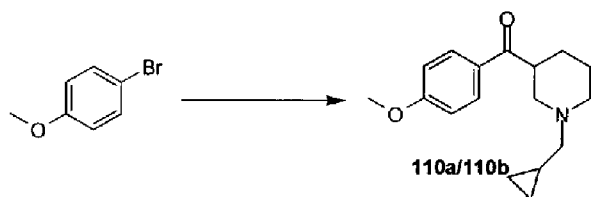
A solution of (3-methoxyphenyl)(piperidin-3-yl)methanone hydrochloride (128 mg, 0.5 mmol), cyclopropanecarbaldehyde (70 mg, 1.0 mmol) and triethyl amine (2 mL) in dichloromethane (10 mL) was stirred at room temperature for 1 h before NaBH(OAc)₃ (212 mg, 1.0 mmol) was added to the mixture. The mixture was stirred for another 1 h and then quenched by addition of saturated aqueous NH₄Cl (5 mL). The solution was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The crude was first purified by reverse phase HPLC, then the enantiomers were separated by supercritical fluid chromatography (SFC) to provide 26.7 mg of 109a and 46.3 mg of 109b.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μ m particle size) at 50% MeOH w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.

109a: ¹H NMR (400 MHz, CD₃OD) δ 7.57 (d, J = 7.6 Hz, 1 H), 7.47-7.41 (m, 2 H), 7.17 (dd, J = 8.4 Hz, 2.4 Hz, 1 H), 3.85 (s, 3 H), 3.65-3.62 (m, 1 H), 3.21-3.12 (m, 2 H), 2.32-2.31 (m, 2 H), 2.18-2.13 (m, 1 H), 2.04-1.90 (m, 2 H), 1.82-1.78 (m, 2 H), 1.45-1.42 (m, 1 H), 0.90-0.88 (m, 1 H), 0.56-0.52 (m, 2 H), 0.16-0.14 (m, 2 H); LCMS m/z 273.9 (M + H); SFC retention time: 4.15 min.

109b: ¹H NMR (400 MHz, CD₃OD) δ 7.57 (d, J = 7.6 Hz, 1 H), 7.48-7.41 (m, 2 H), 7.17 (dd, J = 8.4 Hz, 2.4 Hz, 1 H), 3.85 (s, 3 H), 3.65-3.62 (m, 1 H), 3.21-3.18 (m, 2 H), 2.32-2.31 (m, 2 H), 2.18-2.13 (m, 1 H), 2.03-1.90 (m, 2 H), 1.82-1.78 (m, 2 H), 1.45-1.42 (m, 1 H), 0.90-0.88 (m, 1 H), 0.56-0.52 (m, 2 H), 0.15-0.12 (m, 2 H); LCMS m/z 273.9 (M + H); SFC retention time: 4.75 min.

Examples 110a and 110b: (1-(cyclopropylmethyl)piperidin-3-yl)(4-methoxyphenyl)methanone

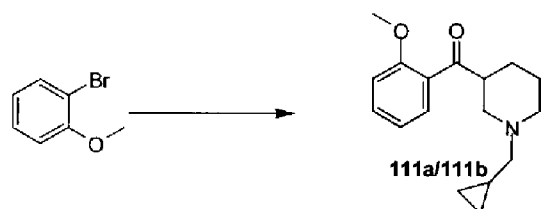


Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo- 3-methoxybenzene with 1-bromo-4-methoxybenzene.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μ m particle size) at 20% MeOH w/0.1%NH₄OH; 60 mL/min, 100 bars, 40 °C.

110a: ¹H NMR (400 MHz, CD₃OD) δ 7.98 (d, J = 8.8 Hz, 2 H), 7.03 (d, J = 9.2 Hz, 2 H), 3.88 (s, 3 H), 3.66-3.62 (m, 1 H), 3.20-3.12 (m, 2 H), 2.34-2.32 (m, 2 H), 2.17-2.16 (m, 1 H), 2.05-2.04 (m, 1 H), 1.96-1.92 (m, 1 H), 1.82-1.79 (m, 2 H), 1.46-1.45 (m, 1 H), 0.91-0.90 (m, 1 H), 0.57-0.52 (m, 2 H), 0.17-0.14 (m, 2 H); LCMS m/z 274.2 (M + H); SFC retention time: 6.87 min.

110b: ¹H NMR (400 MHz, CD₃OD) δ 7.99 (d, J = 8.8 Hz, 2 H), 7.04 (d, J = 8.8 Hz, 2 H), 3.89 (s, 3 H), 3.68-3.66 (m, 1 H), 3.25-3.10 (m, 2 H), 2.44-2.42 (m, 2 H), 2.30-2.29 (m, 1 H), 2.29-2.09 (m, 1 H), 1.94-1.92 (m, 1 H), 1.85-1.82 (m, 2 H), 1.56-1.47 (m, 1 H), 0.95-0.93 (m, 1 H), 0.60-0.56 (m, 2 H), 0.21-0.19 (m, 2 H); LCMS m/z 274.2 (M + H); SFC retention time: 6.19 min.

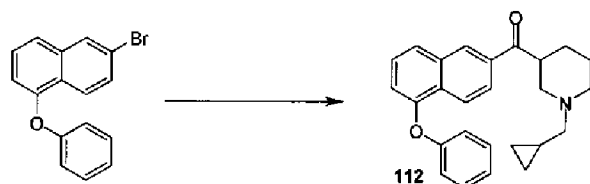
Example 111:**(1-(cyclopropylmethyl)piperidin-3-yl)(2-methoxyphenyl)methanone**

- 5 Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo- 3-methoxybenzene with 1-bromo-2-methoxybenzene.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μ m particle size) at 25% MeOH w/0.1%NH₄OH; 60 mL/min, 100 bars, 40 °C.

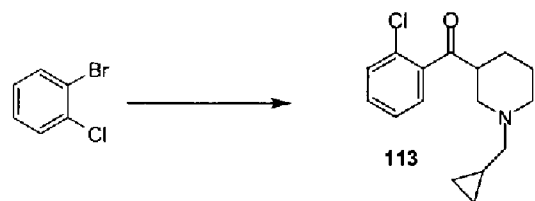
- 10 **111:** ¹H NMR (400 MHz, CD₃OD) δ 7.54-7.50 (m, 2 H), 7.13 (d, J = 8.8 Hz, 1 H), 7.02 (t, J = 7.4 Hz, 1 H), 3.94 (s, 3 H), 3.73-3.68 (m, 1 H), 3.15-3.11 (m, 1 H), 2.49-2.47 (m, 3 H), 2.35-2.33 (m, 1 H), 1.95-1.92 (m, 2 H), 1.80-1.74 (m, 2 H), 1.44-1.40 (m, 1 H), 0.97-0.93 (m, 1 H), 0.59-0.57 (m, 2 H), 0.22-0.20 (m, 2 H); LCMS m/z 273.9 (M + H); SFC retention time: 5.18 min.

15

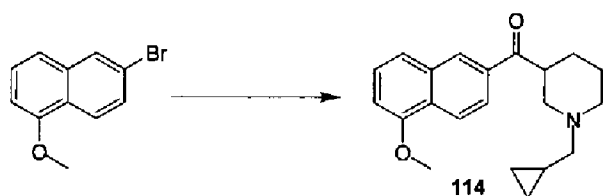
Example 112:**(1-(cyclopropylmethyl)piperidin-3-yl)(5-phenoxy-naphthalen-2-yl)methanone**

- 20 Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo- 3-methoxybenzene with 6-bromo-1-phenoxy-naphthalene (Intermediate 23).

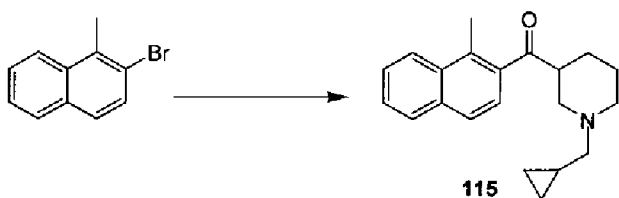
- ¹H NMR (400 MHz, CD₃OD) δ 8.56 (s, 1 H), 8.05 (d, J = 8.8 Hz, 1 H), 7.95 (d, J = 8.8 Hz, 1 H), 7.75 (d, J = 8.8 Hz, 1 H), 7.41(d, J = 8.8 Hz, 2 H), 7.31-7.25 (m, 1 H), 7.25-7.21 (m, 2 H), 7.11-7.09 (m, 2 H), 3.82-3.77 (m, 1 H), 3.31-3.16 (m, 2 H), 2.35-2.33 (m, 2 H), 2.24-2.23 (m, 1 H), 2.07-1.99 (m, 2 H), 1.85-1.80 (m, 2 H), 1.55-1.45 (m, 1 H), 0.91-0.89 (m, 1 H), 0.56-0.52 (m, 2 H), 0.19-0.14 (m, 2 H); LCMS m/z 386.2 (M + H).
- 25

Example 113:**(2-chlorophenyl)(1-(cyclopropylmethyl)piperidin-3-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo- 3-methoxybenzene with 1-bromo-2-chlorobenzene. ¹H NMR (400 MHz, CD₃OD) δ 7.50-7.40 (m, 4 H), 3.39-3.36 (m, 1 H), 3.22-3.19 (m, 1 H), 3.03-3.00 (m, 1 H), 2.30-2.29 (m, 2 H), 2.21-2.19 (m, 1 H), 2.07-2.06 (m, 1 H), 1.91-1.90 (m, 1 H), 1.78-1.77 (m, 1 H), 1.68-1.65 (m, 1 H), 1.47-1.43 (m, 1 H), 0.88-0.84 (m, 1 H), 0.54-0.49 (m, 2 H), 0.13-0.12 (m, 2 H); LCMS m/z 277.8 (M + H).

Example 114:**(1-(cyclopropylmethyl)piperidin-3-yl)(5-methoxynaphthalen-2-yl)methanone**

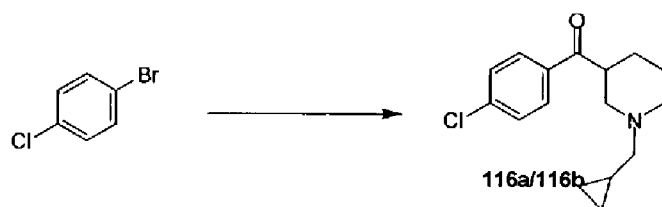
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo- 3-methoxybenzene with 6-bromo-1-methoxynaphthalene. ¹H NMR (400 MHz, CD₃OD) δ 8.44 (s, 1 H), 7.91-7.84 (m, 2 H), 7.75 (d, *J* = 8.8 Hz, 1 H), 7.20 (s, 1 H), 7.15 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 3.88 (s, 3 H), 3.74-3.71 (m, 1 H), 3.20-3.17 (m, 1 H), 3.13-3.10 (m, 1 H), 2.28-2.21 (m, 2 H), 2.18-2.15 (m, 1 H), 1.97-1.95 (m, 2 H), 1.77-1.76 (m, 2 H), 1.45-1.35 (m, 1 H), 0.51-0.48 (m, 2 H), 0.11-0.09 (m, 2 H); LCMS m/z 324.2 (M + H).

Example 115:**(1-(cyclopropylmethyl)piperidin-3-yl)(1-methylnaphthalen-2-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-1-methylnaphthalene. ¹H NMR (400 MHz, CD₃OD) δ 8.30-8.28 (m, 1 H), 8.03-8.01 (m, 1 H), 7.74 (d, *J* = 8.8 Hz, 1 H), 7.51-7.48 (m, 2 H), 7.33 (d, *J* = 8.8 Hz, 1 H), 3.53-3.52 (m, 1 H), 3.26-3.15 (m, 1 H), 3.01-2.96 (m, 1 H), 2.65 (s, 3 H), 2.20-2.13 (m, 3 H), 1.95-1.94 (m, 1 H), 1.86-1.85 (m, 1 H), 1.70-1.68 (m, 1 H), 1.42-1.41 (m, 1 H), 0.77-0.75 (m, 1 H), 0.43-0.40 (m, 2 H), 0.03-0.02 (m, 2 H); LCMS *m/z* 308.2 (M + H).

Examples 116a and 116b:

10 (4-chlorophenyl)(1-(cyclopropylmethyl)piperidin-3-yl)methanone

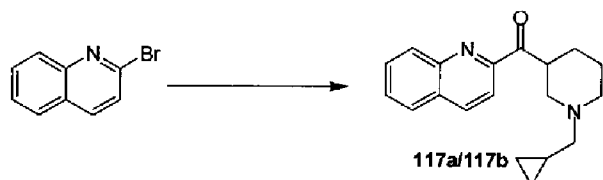


Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 1-bromo-4-chlorobenzene. SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μm particle size) at 25% EtOH w/0.1%NH₄OH; 60 mL/min, 100 bars, 40 °C. ¹H NMR (400 MHz, CD₃OD) δ 7.97 (dd, *J* = 6.8 Hz, 1.6 Hz, 2 H), 7.53 (dd, *J* = 6.8 Hz, 1.6 Hz, 2 H), 3.62-3.61 (m, 1 H), 3.20-3.13 (m, 2 H), 2.34-2.32 (m, 2 H), 2.21-2.20 (m, 1 H), 2.06-2.05 (m, 1 H), 1.90-1.83 (m, 1 H), 1.82-1.79 (m, 2 H), 1.45-1.41 (m, 1 H), 0.91-0.90 (m, 1 H), 0.56-0.53 (m, 2 H), 0.17-0.14 (m, 2 H); LCMS *m/z* 278.1 (M + H); SFC retention time: 5.66 min.

¹H NMR (400 MHz, CD₃OD) δ 7.99 (d, *J* = 8.8 Hz, 2 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 3.69-3.67 (m, 1 H), 3.32-3.19 (m, 2 H), 2.47-2.45 (m, 2 H), 2.23-2.22 (m, 1 H), 2.11-2.10 (m, 1 H), 2.05-1.92 (m, 1 H), 1.86-1.83 (m, 2 H), 1.51-1.49 (m, 1 H), 0.96-0.94 (m, 1 H), 0.61-0.57 (m, 2 H), 0.22-0.20 (m, 2 H); LCMS *m/z* 278.1 (M + H); SFC retention time: 6.51 min.

25 Examples 117a and 117b:

(1-(cyclopropylmethyl)piperidin-3-yl)(quinolin-2-yl)methanone

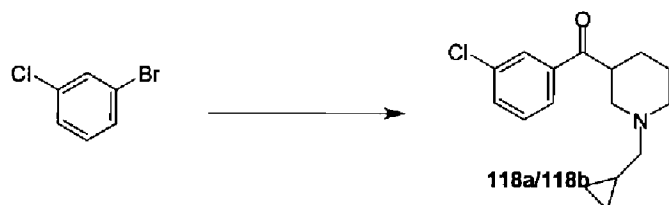


Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromoquinoline. SFC conditions: CHIRALPAK AD (250 x 30 mm, 20 μ m particle size) at 30% MeOH w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.

- 5 117a: ¹H NMR (400 MHz, CD₃OD) δ 8.44 (d, *J* = 8.8 Hz, 1 H), 8.17 (d, *J* = 8.4 Hz, 1 H), 8.08 (d, *J* = 8.8 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 7.84-7.83 (m, 1 H), 7.73-7.72 (m, 1 H), 4.50-4.45 (m, 1 H), 3.42-3.39 (m, 1 H), 3.18-3.15 (m, 1 H), 2.37-2.35 (m, 2 H), 2.26-2.25 (m, 1 H), 2.10-2.07 (m, 2 H), 1.87-1.84 (m, 2 H), 1.55-1.45 (m, 1 H), 0.93-0.92 (m, 1 H), 0.55-0.51 (m, 2 H), 0.18-0.13 (m, 2 H); LCMS *m/z* 295.2 (M + H); SFC retention time: 6.81 min.
- 10 117b: ¹H NMR (400 MHz, CD₃OD) δ 8.43 (d, *J* = 8.4 Hz, 1 H), 8.17 (d, *J* = 8.8 Hz, 1 H), 8.08 (d, *J* = 8.8 Hz, 1 H), 7.99 (d, *J* = 8.4 Hz, 1 H), 7.84-7.82 (m, 1 H), 7.73-7.71 (m, 1 H), 4.52-4.46 (m, 1 H), 3.45-3.42 (m, 1 H), 3.18-3.17 (m, 1 H), 2.43-2.41 (m, 2 H), 2.41-2.40 (m, 1 H), 2.25-2.23 (m, 1 H), 2.15-2.10 (m, 1 H), 1.89-1.84 (m, 2 H), 1.55-1.45 (m, 1 H), 0.97-0.95 (m, 1 H), 0.58-0.54 (m, 2 H), 0.20-0.17 (m, 2 H); LCMS *m/z* 295.2 (M + H); SFC retention time: 5.50
- 15 min.

Examples 118a and 118b:

(3-chlorophenyl)(1-(cyclopropylmethyl)piperidin-3-yl)methanone

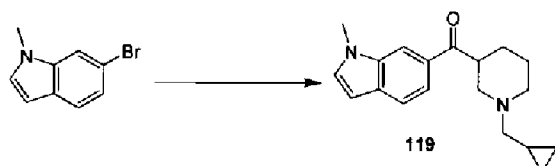


- 20 Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 1-bromo-3-chlorobenzene.
- SFC conditions: CHIRALPAK AD (250 x 30 mm, 20 μ m particle size) at 30% MeOH w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.
- 25 118a: ¹H NMR (400 MHz, CD₃OD) δ 7.95-7.91 (m, 2 H), 7.64-7.62 (m, 1 H), 7.54-7.50 (m, 1 H), 3.62-3.61 (m, 1 H), 3.21-3.13 (m, 2 H), 2.36-2.34 (m, 2 H), 2.18-2.13 (m, 1 H), 2.09-2.08 (m, 1 H), 1.98-1.95 (m, 1 H), 1.83-1.79 (m, 2 H), 1.45-1.44 (m, 1 H), 0.91-0.89 (m, 1 H), 0.57-0.54 (m, 2 H), 0.17-0.16 (m, 2 H); LCMS *m/z* 277.9 (M + H); SFC retention time: 3.97 min.
- 118b: ¹H NMR (400 MHz, CD₃OD) δ 7.95-7.91 (m, 2 H), 7.65-7.62 (m, 1 H), 7.55-7.51 (m, 1
- 30 H), 3.64-3.61 (m, 1 H), 3.21-3.14 (m, 2 H), 2.36-2.34 (m, 2 H), 2.18-2.13 (m, 1 H), 2.09-2.08

(m, 1 H), 1.98-1.95 (m, 1 H), 1.83-1.79 (m, 2 H), 1.45-1.42 (m, 1 H), 0.91-0.89 (m, 1 H), 0.57-0.53 (m, 2 H), 0.18-0.16 (m, 2 H); LCMS m/z 278.1 (M + H); SFC retention time: 4.26 min.

Example 119:

5 (1-(cyclopropylmethyl)piperidin-3-yl)(1-methyl-1H-indol-6-yl)methanone

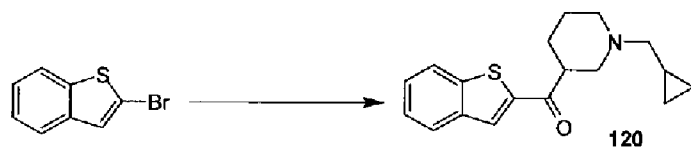


Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 6-bromo-1-methyl-1H-indole.

- 10 ^1H NMR (400 MHz, CD_3OD) δ 8.09 (s, 1 H), 7.69 (d, $J = 8.0$ Hz, 1 H), 7.61 (d, $J = 8.0$ Hz, 1 H), 7.40 (d, $J = 4.0$ Hz, 1 H), 6.50 (d, $J = 4.0$ Hz, 1 H), 3.89 (s, 3 H), 3.81-3.78 (m, 1 H), 3.24-3.15 (m, 2 H), 2.38-2.37 (m, 2 H), 2.01-1.98 (m, 1 H), 1.85-1.79 (m, 2 H), 1.27 (s, 1 H), 0.93-0.88 (m, 1 H), 0.58-0.52 (m, 2 H), 0.16-0.15 (m, 2 H); LCMS m/z 297.2 (M + H).

15 Example 120:

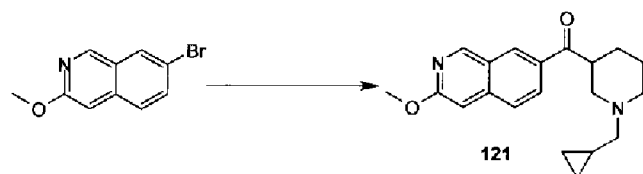
Benzo[*b*]thiophen-2-yl(1-(cyclopropylmethyl)piperidin-3-yl)methanone



Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromobenzo[*b*]thiophene.

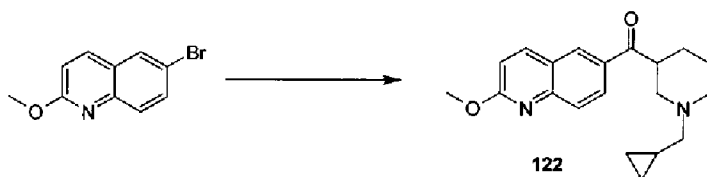
- 20 ^1H NMR (400 MHz, CD_3OD) δ 8.26 (s, 1 H), 8.01-7.99 (m, 1 H), 7.94-7.92 (m, 1 H), 7.52-7.48 (m, 1 H), 7.47-7.43 (m, 1 H), 3.70-3.67 (m, 1 H), 3.32-3.31 (m, 1 H), 3.31-3.25 (m, 1 H), 2.36-2.34 (m, 2 H), 2.25-2.24 (m, 1 H), 2.08-2.04 (m, 2 H), 1.85-1.84 (m, 2 H), 1.56-1.53 (m, 1 H), 0.93-0.92 (m, 1 H), 0.58-0.54 (m, 2 H), 0.17-0.16 (m, 2 H); LCMS m/z 299.8 (M + H).

25

Example 121:**(1-(cyclopropylmethyl)piperidin-3-yl)(3-methoxyisoquinolin-7-yl)methanone**

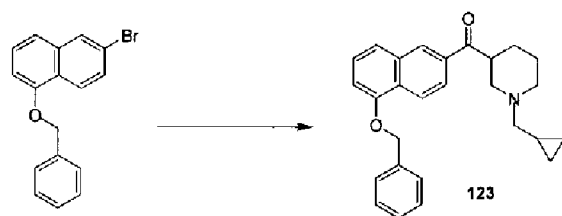
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 7-bromo-3-methoxyisoquinoline.

^1H NMR (400 MHz, CD_3OD) δ 9.13 (s, 1 H), 8.72 (s, 1 H), 8.11 (d, $J = 8.8$ Hz, 1 H), 7.83 (d, $J = 8.8$ Hz, 1 H), 7.16 (s, 1 H), 4.04 (s, 3 H), 3.82-3.79 (m, 1 H), 3.26-3.17 (m, 2 H), 2.37-2.27 (m, 2 H), 2.26-2.25 (m, 1 H), 2.08-2.01 (m, 2 H), 1.87-1.84 (m, 2 H), 1.55-1.45 (m, 1 H), 0.93-0.91 (m, 1 H), 0.57-0.52 (m, 2 H), 0.17-0.14 (m, 2 H); LCMS m/z 325.2 ($M + H$).

Example 122:**(1-(cyclopropylmethyl)piperidin-3-yl)(2-methoxyquinolin-6-yl)methanone**

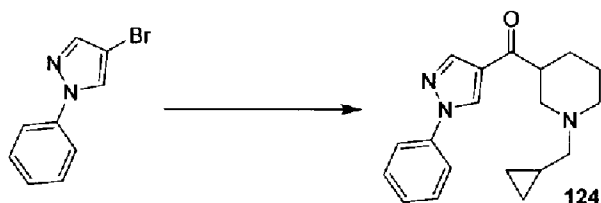
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 6-bromo-2-methoxyquinoline.

^1H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1 H), 8.25 (d, $J = 8.8$ Hz, 1 H), 8.16 (dd, $J = 8.8$ Hz, 2.0 Hz, 1 H), 7.86 (d, $J = 8.8$ Hz, 1 H), 7.02 (d, $J = 8.8$ Hz, 1 H), 4.07 (s, 3 H), 3.81-3.78 (m, 1 H), 3.32-3.31 (m, 1 H), 3.26-3.17 (m, 1 H), 2.36-2.35 (m, 2 H), 2.29-2.26 (m, 1 H), 2.08-2.05 (m, 2 H), 1.86-1.83 (m, 2 H), 1.51-1.48 (m, 1 H), 0.92-0.90 (m, 1 H), 0.57-0.52 (m, 2 H), 0.18-0.15 (m, 2 H); LCMS m/z 325.2 ($M+H$).

Example 123:**(5-(benzyloxy)naphthalen-2-yl)(1-(cyclopropylmethyl)piperidin-3-yl)methanone**

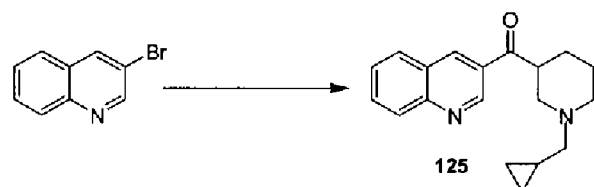
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 1-(benzyloxy)-6-bromonaphthalene (Intermediate 26)

^1H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1 H), 7.98-7.95 (m, 2 H), 7.85-7.84 (m, 1 H), 7.51-7.49 (m, 2 H), 7.40-7.34 (m, 3 H), 7.32-7.31 (m, 2 H), 5.24 (s, 2 H), 3.85-3.79 (m, 1 H), 3.31-3.28 (m, 1 H), 3.28-3.18 (m, 1 H), 2.39-2.34 (m, 2 H), 2.15-2.10 (m, 1 H), 2.04-2.01 (m, 1 H), 1.87-1.82 (m, 2 H), 1.53-1.48 (m, 2 H), 0.95-0.92 (m, 1 H), 0.57-0.49 (m, 2 H), 0.20-0.17 (m, 2 H); LCMS m/z 400.2 ($M + H$).

Example 124:**(1-(cyclopropylmethyl)piperidin-3-yl)(1-phenyl-1H-pyrazol-4-yl)methanone**

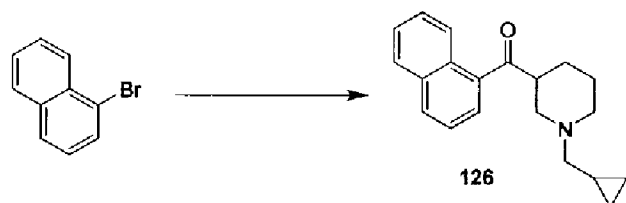
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 4-bromo-1-phenyl-1-pyrazole.

^1H NMR (400 MHz, CD_3OD) δ 8.95 (s, 1 H), 8.19 (s, 1 H), 7.86 (d, $J = 8.0$ Hz, 2 H), 7.55 (t, $J = 8.0$ Hz, 2 H), 7.42 (t, $J = 7.2$ Hz, 1 H), 3.40-3.33 (m, 1 H), 3.24-3.16 (m, 2 H), 2.37-2.35 (m, 2 H), 2.23-2.22 (m, 1 H), 2.07-2.01 (m, 2 H), 1.85-1.82 (m, 2 H), 1.52-1.48 (m, 1 H), 0.96-0.92 (m, 1 H), 0.58-0.56 (m, 2 H), 0.18-0.17 (m, 2 H); LCMS m/z 310.1 ($M + H$).

Example 125:**(1-(cyclopropylmethyl)piperidin-3-yl)(quinolin-3-yl)methanone**

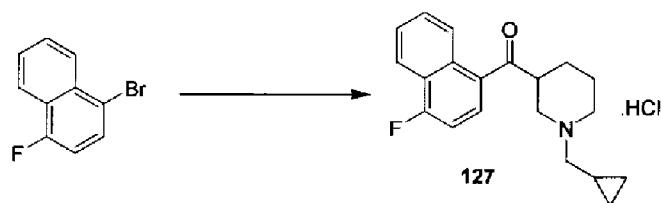
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 3-bromoquinoline.

^1H NMR (400 MHz, CD_3OD) δ 9.32 (s, 1 H), 9.04 (s, 1 H), 8.16 (d, $J = 8.4$ Hz, 1 H), 8.11 (d, $J = 8.4$ Hz, 1 H), 7.94 (t, $J = 7.2$ Hz, 1 H), 7.76 (t, $J = 7.2$ Hz, 1 H), 3.84-3.78 (m, 1 H), 3.32-3.30 (m, 1 H), 3.26-3.17 (m, 1 H), 2.39-2.34 (m, 2 H), 2.34-2.33 (m, 1 H), 2.20-2.10 (m, 2 H), 1.90-1.86 (m, 2 H), 1.58-1.45 (m, 1 H), 0.93-0.91 (m, 1 H), 0.57-0.53 (m, 2 H), 0.20-0.17 (m, 2 H); LCMS m/z 295.2 ($\text{M} + \text{H}$).

Example 126:**(1-(cyclopropylmethyl)piperidin-3-yl)(naphthalen-1-yl)methanone**

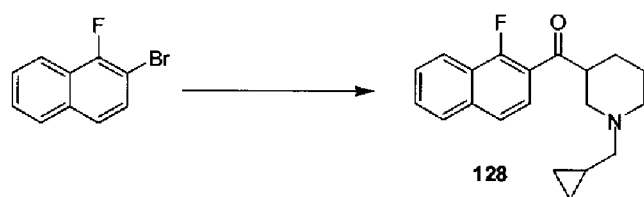
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 1-bromonaphthalene.

^1H NMR (400 MHz, CD_3OD) δ 8.27-8.25 (m, 1 H), 8.02 (d, $J = 8.4$ Hz, 1 H), 7.91-7.87 (m, 2 H), 7.55-7.51 (m, 3 H), 3.65-3.60 (m, 1 H), 3.28-3.23 (m, 1 H), 3.11-3.08 (m, 1 H), 2.41-2.36 (m, 3 H), 2.28-2.27 (m, 1 H), 1.93-1.89 (m, 1 H), 1.78-1.68 (m, 2 H), 1.51-1.48 (m, 1 H), 0.87-0.84 (m, 1 H), 0.51-0.47 (m, 2 H), 0.15-0.11 (m, 2 H); LCMS m/z 294.2 ($\text{M} + \text{H}$).

Example 127:**(1-(cyclopropylmethyl)piperidin-3-yl)(4-fluoronaphthalen-1-yl)methanone hydrochloride**

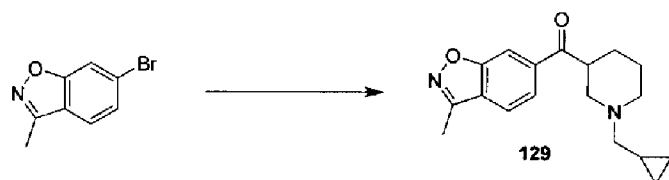
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 1-bromo-4-fluoronaphthalene.

¹H NMR (400 MHz, CD₃OD) δ 8.82-8.80 (m, 0.3 H), 8.61-8.59 (m, 0.6 H), 8.22-8.16 (m, 2 H), 7.73-7.69 (m, 2 H), 7.38-7.34 (m, 1 H), 4.30-3.75 (m, 3 H), 3.45-3.00 (m, 4 H), 2.13-1.63 (m, 4 H), 1.23-1.22 (m, 1 H), 0.87-0.80 (m, 2 H), 0.62-0.51 (m, 2 H); LCMS m/z 311.9 (M + H).

Example 128:**(1-(cyclopropylmethyl)piperidin-3-yl)(1-fluoronaphthalen-2-yl)methanone**

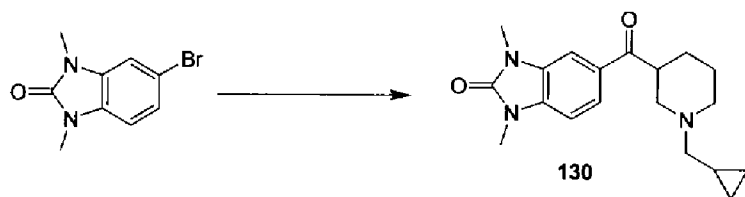
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-1-fluoronaphthalene.

¹H NMR (400 MHz, CD₃OD) δ 8.15-8.13 (m, 1 H), 7.88-7.87 (m, 1 H), 7.70-7.61 (m, 4 H), 3.60-3.55 (m, 1 H), 3.31-3.23 (m, 1 H), 3.04-3.01 (m, 1 H), 2.26-2.18 (m, 3 H), 2.02-1.98 (m, 2 H), 1.77-1.75 (m, 2 H), 1.39-1.38 (m, 1 H), 0.84-0.82 (m, 1 H), 0.48-0.46 (m, 2 H), 0.10-0.08 (m, 2 H); LCMS m/z 312.2 (M + H).

Example 129:**(1-(cyclopropylmethyl)piperidin-3-yl)(3-methylbenzo[d]isoxazol-6-yl)methanone**

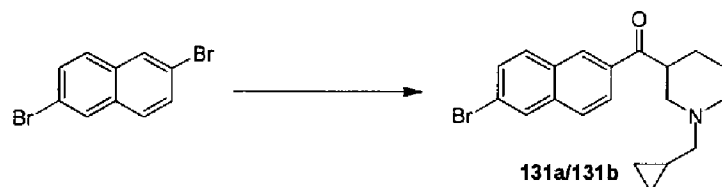
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 6-bromo-3-methylbenzo[d]isoxazole.

¹H NMR (400 MHz, CD₃OD) δ 8.18 (s, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.88 (d, *J* = 8.4 Hz, 1 H), 3.75-3.71 (m, 1 H), 3.24-3.22 (m, 1 H), 3.17-3.14 (m, 1 H), 2.59 (s, 3 H), 2.37-2.30 (m, 2 H), 2.28-2.26 (m, 1 H), 2.11-2.10 (m, 1 H), 2.02-2.01 (m, 1 H), 1.84-1.81 (m, 2 H), 1.47-1.44 (m, 1 H), 0.92-0.89 (m, 1 H), 0.56-0.51 (m, 2 H), 0.17-0.15 (m, 2 H); LCMS *m/z* 298.8 (*M* + *H*).

Example 130:**5-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-1,3-dimethyl-1H-benzo[d]imidazol-2-one**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 5-bromo-1,3-dimethyl-1*H*-benzo[d]imidazol-2(3*H*)-one.

¹H NMR (400 MHz, CD₃OD) δ 7.87 (d, *J* = 8.4 Hz, 1 H), 7.74 (s, 1 H), 7.23 (d, *J* = 8.4 Hz, 1 H), 3.73-3.63 (m, 1 H), 3.46 (s, 3 H), 3.45 (s, 3 H), 3.23-3.16 (m, 2 H), 2.36-2.35 (m, 2 H), 2.23-2.22 (m, 1 H), 2.09-2.07 (m, 1 H), 1.99-1.95 (m, 1 H), 1.83-1.78 (m, 2 H), 1.49-1.45 (m, 1 H), 0.93-0.90 (m, 1 H), 0.56-0.53 (m, 2 H), 0.18-0.15 (m, 2 H); LCMS *m/z* 328.2 (*M* + *H*).

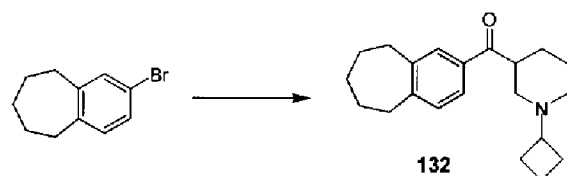
Examples 131a and 131b**(6-bromonaphthalen-2-yl)(1-(cyclopropylmethyl)piperidin-3-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2,6-dibromonaphthalene.

SFC conditions: CHIRALPAK OJ (250 x 30 mm, 5 μ m particle size) at 20% MeOH w/0.1%NH₄OH; 60 mL/min, 100 bars, 40 °C.

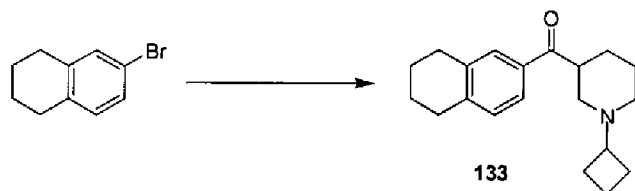
131a: ¹H NMR (400 MHz, CD₃OD) δ 8.60 (s, 1 H), 8.16 (s, 1 H), 8.05-7.98 (m, 2 H), 7.93 (d, J = 8.4 Hz, 1 H), 7.70 (d, J = 8.4 Hz, 1 H), 3.84-3.80 (m, 1 H), 3.26- 3.17 (m, 2 H), 2.37-2.35 (m, 3 H), 2.05-2.01 (m, 2 H), 1.87-1.83 (m, 2 H), 1.52-1.48 (m, 1 H), 1.20-1.16 (m, 1 H), 0.94-0.90 (m, 1 H), 0.57-0.52 (m, 2 H), 0.17-0.15 (m, 2 H); LCMS m/z 373.6 (M+H); SFC retention time: 3.38 min.

131b: ¹H NMR (400 MHz, CD₃OD) δ 8.60 (s, 1 H), 8.15 (s, 1 H), 8.05-7.99 (m, 2 H), 7.93 (d, J = 8.8 Hz, 1 H), 7.70 (d, J = 8.8 Hz, 1 H), 3.84-3.81 (m, 1 H), 3.27-3.17 (m, 2 H), 2.38-2.36 (m, 3 H), 2.05-2.01 (m, 2 H), 1.88-1.84 (m, 2 H), 1.52-1.48 (m, 1 H), 0.94-0.90 (m, 1 H), 0.56-0.53 (m, 2 H), 0.17-0.16 (m, 2 H); LCMS m/z 373.7 (M+H); SFC retention time: 3.99 min.

Example 132**(1-cyclobutylpiperidin-3-yl)(6,7,8,9-tetrahydro-5H-benzo[7]annulen-2-yl)methanone**

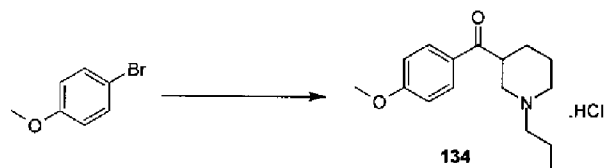
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-6,7,8,9-tetrahydro-5H-benzo[7]annulene (Intermediate 23), and cyclopropanecarbaldehyde with cyclobutanone.

¹H NMR (400 MHz, CD₃OD) δ 7.69-7.68 (m, 2 H), 7.23-7.21 (m, 1 H), 3.56-3.55 (m, 1 H), 2.95-2.86 (m, 7 H), 2.17-2.03 (m, 2 H), 1.90-1.86 (m, 6 H), 1.78-1.73 (m, 5 H), 1.65-1.55 (m, 4 H), 1.42-1.28 (m, 1 H); LCMS m/z 312.2 (M + H).

Example 133:**(1-cyclobutyl-3-piperidyl)-tetralin-6-yl-methanone**

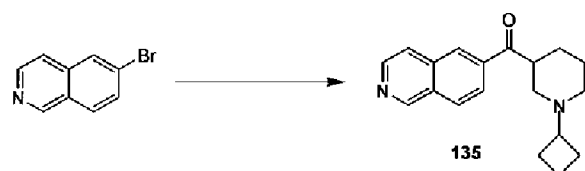
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 6-bromo-1,2,3,4-tetrahydronaphthalene, and cyclopropanecarbaldehyde with cyclobutanone. It should be noted that the halide- lithium exchange step should be controlled within 15 min.

^1H NMR (400 MHz, CD_3OD) δ 7.69-7.68 (m, 2 H), 7.20 (d, $J = 8.8$ Hz, 1 H), 3.87-3.82 (m, 1 H), 3.66-3.62 (m, 1 H), 3.40-3.32 (m, 1 H), 3.05-3.01 (m, 1 H), 2.82-2.75 (m, 5 H), 2.33-2.27 (m, 4 H), 2.19-2.14 (m, 1 H), 1.87-1.81 (m, 9 H), 1.62-1.58 (m, 1 H); LCMS m/z 297.9 ($M + H$).

Example 134:**(4-methoxyphenyl)(1-propylpiperidin-3-yl)methanone hydrochloride**

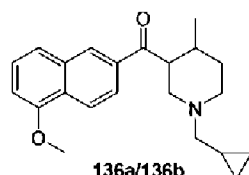
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 1-bromo-4-methoxybenzene, and cyclopropanecarbaldehyde with propionaldehyde.

^1H NMR (400 MHz, CD_3OD) δ 8.03-7.98 (m, 2 H), 7.05-7.03 (m, 2 H), 3.92-3.81 (m, 4 H), 3.63-3.60 (m, 1 H), 3.33-3.29 (m, 2 H), 3.17-3.10 (m, 4 H), 2.17-2.06 (m, 2 H), 1.88-1.81 (m, 3 H), 1.09-1.00 (m, 3 H); LCMS m/z 261.9 ($M + H$).

Example 135:**Cyclobutylpiperidin-3-yl)(isoquinolin-6-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl) methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 6-bromoisoquinoline, and cyclopropanecarbaldehyde with cyclobutanone.

¹H NMR (400 MHz, CD₃OD) δ 9.32 (s, 1 H), 8.60 (s, 1 H), 8.55 (d, *J* = 6.0 Hz, 1 H), 8.20-8.19 (m, 1 H), 8.16-8.15 (m, 1 H), 8.01 (d, *J* = 6.0 Hz, 1 H), 3.75-3.74 (m, 1 H), 3.06-3.02 (m, 1 H), 2.95-2.90 (m, 1 H), 2.85-2.83 (m, 1 H), 2.08-2.01 (m, 4 H), 1.91-1.75 (m, 5 H), 1.75-1.72 (m, 2 H), 1.47-1.43 (m, 1 H); LCMS *m/z* 295.1 (*M* + *H*).

Examples 136a and 136b:**(1-(cyclopropylmethyl)-4-methylpiperidin-3-yl)(5-methoxynaphthalen-2-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 6-bromo-1-methoxynaphthalene, and *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with *tert*-butyl 3-(methoxy(methyl) carbamoyl)-4-methylpiperidine-1-carboxylate (Intermediate 10). 129a and 129b correspond to the *cis*-enantiomers.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μm particle size) at 50% MeOH w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.

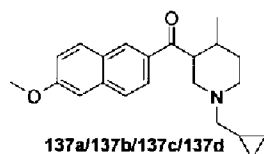
129a: ¹H NMR (400 MHz, CD₃OD) δ 8.50 (s, 1 H), 8.00-7.94 (m, 2 H), 7.87 (d, *J* = 8.8 Hz, 1 H), 7.32 (d, *J* = 2.0 Hz, 1 H), 7.24 (d, *J* = 8.8 Hz, 1 H), 4.00-3.94 (m, 4 H), 3.00-2.91 (m, 2 H), 2.75-2.61 (m, 1 H), 2.43-2.34 (m, 4 H), 2.20-2.17 (m, 1 H), 1.70-1.67 (m, 1 H), 0.97-0.92 (m, 1 H), 0.83-0.82 (m, 3 H), 0.60-0.58 (m, 2 H), 0.26-0.22 (m, 2 H); LCMS *m/z* 337.9 (*M* + *H*); SFC retention time: 6.35 min.

129b: ¹H NMR (400 MHz, CD₃OD) δ 8.50 (s, 1 H), 8.00 (d, *J* = 8.8 Hz, 2 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 7.36 (d, *J* = 2.0 Hz, 1 H), 7.28 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 4.29-4.28 (m, 1 H), 3.96 (s, 3 H), 3.58-3.50 (m, 2 H), 3.15-3.13 (m, 2 H), 2.63-2.40 (m, 1 H), 1.91-1.81 (m, 1 H), 1.39-

1.21 (m, 3 H), 0.92-0.90 (m, 4 H), 0.83-0.80 (m, 2 H), 0.55-0.45 (m, 2 H); LCMS m/z 337.9 (M+H); SFC retention time: 7.46 min.

Examples 137a, 137b, 137c, and 137d:

5 (1-(cyclopropylmethyl)-4-methylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone



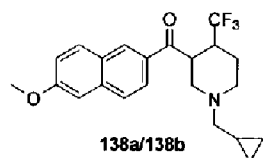
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-6-methoxynaphthalene, and *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-10 1-carboxylate with *tert*-butyl 3-(methoxy(methyl) carbamoyl)-4-methylpiperidine-1-carboxylate (Intermediate 10). SFC conditions: CHIRALPAK AD (250 x 30 mm, 10 μ m particle size) at 30% EtOH w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.

137a: ¹H NMR (400 MHz, CD₃OD) δ 8.46 (s, 1 H), 7.96-7.91 (m, 2 H), 7.84 (d, J = 8.8 Hz, 1 H), 7.29 (s, 1 H), 7.21 (d, J = 9.2 Hz, 1 H), 3.96 (s, 3 H), 2.96-2.94 (m, 2 H), 2.86-2.82 (m, 1 H), 15 2.42-2.37 (m, 4 H), 2.15-2.11 (m, 1 H), 1.68-1.64 (m, 1 H), 0.91-0.78 (m, 4 H), 0.56-0.51 (m, 2 H), 0.22-0.16 (m, 2 H); LCMS m/z 337.9 (M + H); SFC retention time: 3.21 min.

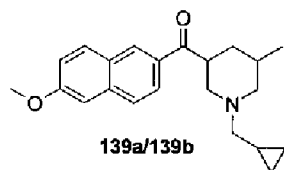
137b: ¹H NMR (400 MHz, CD₃OD) δ 8.53 (s, 1 H), 7.95-7.91 (m, 2 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.27 (d, J = 2.4 Hz, 1 H), 7.18 (d, J = 2.4 Hz, 1 H), 3.91 (s, 3 H), 3.59-3.57 (m, 1 H), 3.19-3.13 (m, 2 H), 2.30-2.28 (m, 2 H), 2.12-2.07 (m, 1 H), 1.97-1.94 (m, 1 H), 1.92-1.88 (m, 1 H), 20 1.53-1.49 (m, 1 H), 1.26-1.22 (m, 1 H), 0.85 (d, J = 6.4 Hz, 4 H), 0.51-0.46 (m, 2 H), 0.10-0.06 (m, 2 H); LCMS m/z 337.9 (M + H); SFC retention time: 2.77 min.

137c: ¹H NMR (400 MHz, CD₃OD) δ 8.44 (s, 1 H), 7.91-7.88 (m, 2 H), 7.81 (d, J = 8.8 Hz, 1 H), 7.27 (s, 1 H), 7.19 (d, J = 9.2 Hz, 1 H), 3.94-3.91 (m, 4 H), 2.93-2.91 (m, 2 H), 2.86-2.82 (m, 1 H), 2.39-2.34 (m, 4 H), 2.15-2.11 (m, 1 H), 1.66-1.62 (m, 1 H), 0.89-0.76 (m, 4 H), 0.54-25 0.52 (m, 2 H), 0.19-0.16 (m, 2 H); LCMS m/z 337.9 (M + H); SFC retention time: 3.63 min.

137d: ¹H NMR (400 MHz, CD₃OD) δ 8.53 (s, 1 H), 7.95-7.91 (m, 2 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.27 (d, J = 2.4 Hz, 1 H), 7.18 (d, J = 9.2 Hz, 1 H), 3.91 (s, 3 H), 3.59-3.57 (m, 1 H), 3.19-3.13 (m, 2 H), 2.30-2.28 (m, 2 H), 2.12-2.07 (m, 1 H), 1.97-1.94 (m, 1 H), 1.92-1.88 (m, 1 H), 1.53-1.49 (m, 1 H), 1.26-1.22 (m, 1 H), 0.88-0.82 (m, 4 H), 0.51-0.46 (m, 2 H), 0.11-0.10 (m, 2 30 H); LCMS m/z 337.9 (M + H); SFC retention time: 3.13 min.

Examples 138a and 138b:**(1-(cyclopropylmethyl)-4-(trifluoromethyl)piperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone**

- 5 Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-6-methoxynaphthalene, and *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with *tert*-butyl 3-(methoxy(methyl) carbamoyl)-5-(trifluoromethyl) piperidine-1-carboxylate (Intermediate 12). 138a and 138b correspond to the *cis*-enantiomers.
- 10 SFC conditions: CHIRALPAK AD (250 x 30 mm, 20 μ m particle size) at 30% MeOH w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.
- 138a: ¹H NMR (400 MHz, CD₃OD) δ 8.56 (s, 1 H), 7.99 (d, J = 9.2 Hz, 2 H), 7.90 (d, J = 9.2 Hz, 1 H), 7.35 (d, J = 2.0 Hz, 1 H), 7.28-7.26 (m, 1 H), 4.14-4.08 (m, 1 H), 3.98 (s, 3 H), 3.30-3.27 (m, 1 H), 2.97-2.93 (m, 1 H), 2.39-2.37 (m, 2 H), 2.24-2.11 (m, 3 H), 1.93-1.89 (m, 1 H),
- 15 1.33-1.29 (m, 1 H), 0.94-0.90 (m, 1 H), 0.57-0.53 (m, 2 H), 0.17-0.12 (m, 2 H); LCMS m/z 391.9 (M + H); SFC retention time: 3.74 min.
- 138b: ¹H NMR (400 MHz, CD₃OD) δ 8.56 (s, 1 H), 7.99 (d, J = 9.2 Hz, 2 H), 7.90 (d, J = 9.2 Hz, 1 H), 7.35 (d, J = 2.0 Hz, 1 H), 7.27 (dd, J = 9.2 Hz, 2.4 Hz, 1 H), 4.14-4.08 (m, 1 H), 3.98 (s, 3 H), 3.38-3.30 (m, 2 H), 2.97-2.93 (m, 1 H), 2.39-2.37 (m, 2 H), 2.24-2.11 (m, 3 H), 1.93-
- 20 1.89 (m, 1 H), 0.93-0.92 (m, 1 H), 0.62-0.51 (m, 2 H), 0.25-0.18 (m, 2 H); LCMS m/z 391.9 (M + H); SFC retention time: 4.27 min.

Example 139a and 139b**(1-(cyclopropylmethyl)-5-methylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone**

- 25 Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-6-methoxynaphthalene, and *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-

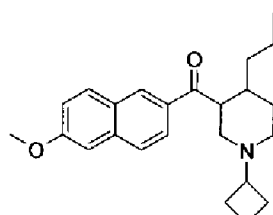
1-carboxylate with 3-(methoxy(methyl)carbamoyl)-5-methylpiperidine-1-carboxylate (Intermediate 11). 139a and 139b correspond to the *cis*-enantiomers.

139a: ^1H NMR (400 MHz, CD_3OD) δ 8.54 (s, 1 H), 7.99-7.95 (m, 2 H), 7.86 (d, $J = 8.4$ Hz, 1 H), 7.32 (s, 1 H), 7.23 (dd, $J = 8.4$ Hz, 2.0 Hz, 1 H), 3.96 (s, 3 H), 3.86-3.83 (m, 1 H), 3.29-3.27 (m, 1 H), 3.18-3.15 (m, 1 H), 2.42-2.37 (m, 2 H), 2.19-2.14 (m, 1 H), 2.03-2.00 (m, 2 H), 1.73-1.70 (m, 1 H), 1.16-1.13 (m, 1 H), 0.99-0.95 (m, 4 H), 0.59-0.56 (m, 2 H), 0.19-0.17 (m, 2 H); LCMS m/z 337.9 ($M + H$).

139b: ^1H NMR (400 MHz, CD_3OD) δ 8.46 (s, 1 H), 7.94 (d, $J = 8.8$ Hz, 2 H), 7.87 (d, $J = 9.2$ Hz, 1 H), 7.32 (s, 1 H), 7.22 (d, $J = 2.0$ Hz, 1 H), 3.97-3.92 (m, 4 H), 3.03-2.99 (m, 1 H), 2.79-2.77 (m, 1 H), 2.60-2.55 (m, 1 H), 2.36-2.31 (m, 2 H), 2.16-2.12 (m, 2 H), 2.03-2.00 (m, 1 H), 1.56-1.52 (m, 1 H), 1.13-1.10 (d, $J = 7.2$ Hz, 3 H), 0.96-0.94 (m, 1 H), 0.44-0.42 (m, 2 H), 0.12-0.09 (m, 2 H); LCMS m/z 337.9 ($M + H$).

Examples 140a, 140b, 140c, and 140d

(1-cyclobutyl-4-propylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone



140a/140b/140c/140d

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-6-methoxynaphthalene, *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate with 3-(methoxy(methyl)carbamoyl)-4-propylpiperidine-1-carboxylate (Intermediate 13), and cyclopropanecarbaldehyde with cyclobutanone.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μm particle size) at 15% MeOH w/0.1% NH_4OH ; 50 mL/min, 100 bars, 40 $^\circ\text{C}$.

140a: ^1H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1 H), 7.91 (dd, $J = 8.8$ Hz, 2.4 Hz, 2 H), 7.82 (d, $J = 8.8$ Hz, 1 H), 7.27 (d, $J = 2.4$ Hz, 1 H), 7.21-7.19 (m, 1 H), 3.93 (s, 3 H), 3.87-3.84 (m, 1 H), 2.84-2.83 (m, 1 H), 2.74-2.73 (m, 1 H), 2.65-2.55 (m, 1 H), 2.45-2.35 (m, 1 H), 2.20-2.06 (m, 4 H), 1.91-1.84 (m, 4 H), 1.73-1.71 (m, 2 H), 1.39-1.31 (m, 1 H), 1.25-1.15 (m, 1 H), 0.96-0.94 (m, 2 H), 0.65 (t, $J = 7.6$ Hz, 3 H); LCMS m/z 366.1 ($M + H$); SFC retention time: 5.08 min.

140b: ^1H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1 H), 8.01-7.95 (m, 2 H), 7.87 (d, $J = 8.8$ Hz, 1 H), 7.33 (s, 1 H), 7.27-7.24 (m, 1 H), 3.97 (s, 3 H), 3.70-3.64 (m, 1 H), 3.05-2.96 (m, 2 H), 2.84-

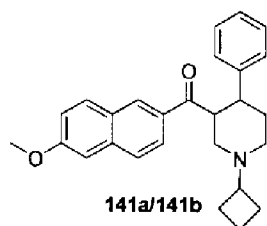
2.80 (m, 1 H), 2.13-2.09 (m, 1 H), 1.99-1.88 (m, 7 H), 1.74-1.72 (m, 2 H), 1.40-1.39 (m, 2 H), 1.30-1.20 (m, 4 H), 0.80 (t, $J = 7.2$ Hz, 3 H); LCMS m/z 366.1 ($M + H$); SFC retention time: 4.39 min.

140c: ^1H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1 H), 7.97-7.93 (m, 2 H), 7.87 (d, $J = 8.8$ Hz, 1 H), 7.32 (d, $J = 2.4$ Hz, 1 H), 7.24 (dd, $J = 8.8$ Hz, 2.4 Hz, 1 H), 4.03-4.01 (m, 1 H), 3.96 (s, 3 H), 3.29-3.20 (m, 1 H), 2.97-2.91 (m, 1 H), 2.89-2.83 (m, 1 H), 2.60-2.50 (m, 1 H), 2.22-2.19 (m, 3 H), 2.19-2.02 (m, 3 H), 1.95-1.85 (m, 1 H), 1.82-1.80 (m, 2 H), 1.48-1.29 (m, 3 H), 1.01-0.98 (m, 2 H), 0.67 (t, $J = 6.8$ Hz, 3 H); LCMS m/z 366.1 ($M + H$); SFC retention time: 5.84 min.

140d: ^1H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1 H), 8.01-7.95 (m, 2 H), 7.87 (d, $J = 8.8$ Hz, 1 H), 7.33 (s, 1 H), 7.24 (dd, $J = 9.2$ Hz, 2.4 Hz, 1 H), 3.97 (s, 3 H), 3.70-3.64 (m, 1 H), 3.05-2.96 (m, 2 H), 2.84-2.80 (m, 1 H), 2.13-2.09 (m, 1 H), 1.99-1.88 (m, 7 H), 1.74-1.72 (m, 2 H), 1.40-1.39 (m, 2 H), 1.30-1.20 (m, 4 H), 0.80 (t, $J = 7.2$ Hz, 3 H); LCMS m/z 366.0 ($M + H$); SFC retention time: 4.97 min.

Examples 141a and 141b:

(1-cyclobutyl-4-phenylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone



Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-6-methoxynaphthalene, *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with 3-(methoxy(methyl)carbamoyl)-4-phenylpiperidine-1-carboxylate (Intermediate 16), and cyclopropanecarbaldehyde with cyclobutanone. 141a and 141b correspond to the *cis*-enantiomers.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μm particle size) at 40% IPA w/0.1% NH_4OH ; 80 mL/min, 100 bars, 40 $^\circ\text{C}$.

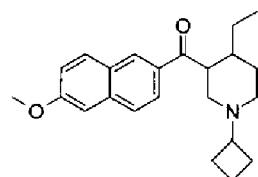
141a: ^1H NMR (400 MHz, CD_3OD) δ 8.29 (s, 1 H), 7.85 (d, $J = 8.8$ Hz, 1 H), 7.74 (s, 2 H), 7.29-7.23 (m, 3 H), 7.16-7.12 (m, 3 H), 7.02-6.95 (m, 1 H), 4.30 (t, $J = 4.4$ Hz, 1 H), 3.91 (s, 3 H), 3.20-3.17 (m, 1 H), 3.10-3.06 (m, 1 H), 2.91-2.82 (m, 1 H), 2.80-2.48 (m, 3 H), 2.19-2.09 (m,

1 H), 2.02-1.90 (m, 4 H), 1.64-1.60 (m, 3 H); LCMS m/z 400.0 (M + H); SFC retention time: 7.39 min.

141b: ¹H NMR (400 MHz, CD₃OD) δ 8.29 (s, 1 H), 7.85 (d, *J* = 9.2 Hz, 1 H), 7.74 (s, 2 H), 7.28-7.23 (m, 3 H), 7.17-7.12 (m, 3 H), 7.02-6.95 (m, 1 H), 4.29-4.28 (m, 1 H), 3.90 (s, 3 H), 3.19-3.12 (m, 1 H), 3.10-3.07 (m, 1H), 2.86-2.80 (m, 1 H), 2.76-2.51 (m, 3 H), 2.17-2.14 (m, 1 H), 2.00-1.90 (m, 4 H), 1.65-1.49 (m, 3 H); LCMS m/z 399.9 (M + H); SFC retention time: 9.22 min.

Examples 142a, 142b, 142c, and 142d

10 (1-cyclobutyl-4-ethylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone



Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-6-methoxynaphthalene, *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with 3-(methoxy(methyl)carbamoyl) -4-ethylpiperidine-1-carboxylate (Intermediate 15), and cyclopropanecarbaldehyde with cyclobutanone.

SFC conditions: CHIRALPAK OJ (250 x 30 mm, 5 μm particle size) at 20% IPA w/0.1%NH₄OH; 60 mL/min, 100 bars, 40 °C.

142a: ¹H NMR (400 MHz, CD₃OD) δ 8.54 (s, 1 H), 7.99-7.95 (m, 2 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.31 (d, *J* = 2.8 Hz, 1 H), 7.24 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 3.96 (s, 3 H), 3.65-3.62 (m, 1 H), 3.01-2.95 (m, 2 H), 2.81-2.79 (m, 1 H), 2.12-2.08 (m, 1 H), 1.98-1.70 (m, 9 H), 1.40-1.38 (m, 2 H), 1.17-1.13 (m, 1 H), 0.84 (t, *J* = 7.6 Hz, 3 H); LCMS m/z 351.9 (M + H); SFC retention time: 5.28 min.

142b: ¹H NMR (400 MHz, CD₃OD) δ 8.54 (s, 1 H), 7.99-7.95 (m, 2 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.31 (d, *J* = 2.8 Hz, 1 H), 7.23 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 3.96 (s, 3 H), 3.65-3.62 (m, 1 H), 3.01-2.95 (m, 2 H), 2.81-2.79 (m, 1 H), 2.12-2.08 (m, 1 H), 1.98-1.70 (m, 9 H), 1.40-1.38 (m, 2 H), 1.17-1.13 (m, 1 H), 0.84 (t, *J* = 7.6 Hz, 3 H); LCMS m/z 351.9 (M + H); SFC retention time: 5.93 min.

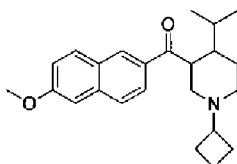
142c: ¹H NMR (400 MHz, CD₃OD) δ 8.50 (s, 1 H), 7.98-7.94 (m, 2 H), 7.87 (d, *J* = 8.8 Hz, 1 H), 7.33 (d, *J* = 2.0 Hz, 1 H), 7.26-7.23 (m, 1 H), 4.00-3.97 (m, 4 H), 3.08-3.01 (m, 1 H), 2.92-2.88 (m, 1 H), 2.75-2.65 (m, 2 H), 2.17-2.13 (m, 3 H), 2.03-1.96 (m, 4 H), 1.80-1.77 (m, 2 H),

1.42-1.38 (m, 1 H), 1.22-1.18 (m, 2 H), 0.73 (t, $J = 7.6$ Hz, 3 H); LCMS m/z 352.2 ($M + H$); SFC retention time: 7.65 min.

142d: ^1H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1 H), 7.98-7.95 (m, 2 H), 7.87 (d, $J = 9.2$ Hz, 1 H), 7.33 (d, $J = 2.8$ Hz, 1 H), 7.24 (dd, $J = 7.6$ Hz, 2.4 Hz, 1 H), 4.04-3.97 (m, 4 H), 3.14-3.12 (m, 1 H), 2.92-2.88 (m, 1 H), 2.75-2.65 (m, 2 H), 2.17-2.12 (m, 3 H), 2.02-1.96 (m, 4 H), 1.82-1.79 (m, 2 H), 1.42-1.38 (m, 1 H), 1.20-1.17 (m, 2 H), 0.73 (t, $J = 7.6$ Hz, 3 H); LCMS m/z 352.2 ($M + H$); SFC retention time: 8.25 min.

Examples 143a and 143 b

10 (1-cyclobutyl-4-isopropylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone

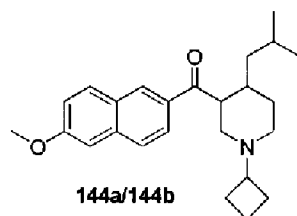


Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-6-methoxynaphthalene, *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with 3-(methoxy(methyl)carbamoyl)-4-isopropylpiperidine-1-carboxylate (Intermediate 17), and cyclopropanecarbaldehyde with cyclobutanone. 143a and 143b correspond to the *cis*-enantiomers.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 10 μm particle size) at 45% IPA w/0.1% NH_4OH ; 80 mL/min, 100 bars, 40 $^{\circ}C$.

143a: ^1H NMR (400 MHz, CD_3OD) δ 8.41 (s, 1 H), 7.93-7.89 (m, 2 H), 7.82 (d, $J = 8.8$ Hz, 1 H), 7.28 (d, $J = 2.4$ Hz, 1 H), 7.19 (dd, $J = 8.8$ Hz, 2.4 Hz, 1 H), 3.97-3.96 (m, 1 H), 3.92 (s, 3 H), 3.08-3.05 (m, 1 H), 2.85-2.82 (m, 1 H), 2.60-2.50 (m, 1 H), 2.19-2.16 (m, 2 H), 1.90-1.75 (m, 6 H), 1.59-1.45 (m, 2 H), 1.41-1.31 (m, 1 H), 1.29-1.19 (m, 1 H), 0.94 (d, $J = 6.8$ Hz, 3 H), 0.79 (d, $J = 6.8$ Hz, 3 H); LCMS m/z 366.2 ($M + H$); SFC retention time: 2.63 min.

143b: ^1H NMR (400 MHz, CD_3OD) δ 8.63 (s, 1 H), 8.02-7.96 (m, 2 H), 7.90 (d, $J = 8.4$ Hz, 1 H), 7.33 (d, $J = 5.6$ Hz, 1 H), 7.43 (dd, $J = 8.8$ Hz, 2.4 Hz, 1 H), 4.48-4.45 (m, 1 H), 3.95 (s, 3 H), 3.70-3.60 (m, 2 H), 3.19-3.16 (m, 1 H), 2.90-2.81 (m, 1 H), 2.50-2.27 (m, 4 H), 2.15-1.98 (m, 3 H), 1.89-1.79 (m, 3 H), 1.52-1.41 (m, 1 H), 1.29-1.19 (m, 1 H), 0.89 (d, $J = 6.4$ Hz, 3 H), 0.77 (d, $J = 6.4$ Hz, 3 H); LCMS m/z 365.9 ($M + H$); SFC retention time: 6.34 min.

Examples 144a and 144b**(1-(cyclobutyl-4-isobutylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-

- 5 methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 2-bromo-6-methoxynaphthalene, *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with 3-(methoxy(methyl)carbamoyl)-4-isobutylpiperidine-1-carboxylate (Intermediate 14), and cyclopropanecarbaldehyde with cyclobutanone.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 10 μ m particle size) at 30% EtOH

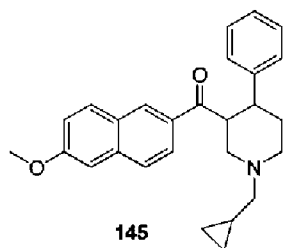
- 10 w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.

144a: ¹H NMR (400 MHz, CD₃OD) δ 8.36 (s, 1 H), 7.86-7.74 (m, 3 H), 7.21 (d, *J* = 2.4 Hz, 1H), 7.14-7.11 (m, 1 H), 3.85 (s, 3 H), 3.78-3.75 (m, 1 H), 2.81-2.72 (m, 1 H), 2.70-2.62 (m, 1 H), 2.59-2.50 (m, 1H), 2.35-2.22 (m, 1 H), 2.19-2.11 (m, 1 H), 2.05-1.92 (m, 3 H), 1.85-1.75 (m, 3 H), 1.68-1.64 (m, 3 H), 1.27-1.18 (m, 3 H), 0.64 (d, *J* = 6.4 Hz, 3 H), 0.32 (d, *J* = 6.4 Hz, 3 H);

15 LCMS *m/z* 380.0 (M + H); SFC retention time: 6.87 min.

144b: ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.50 (s, 1 H), 8.08 (d, *J* = 9.2 Hz, 1 H), 7.93-7.85 (m, 2H), 7.42 (d, *J* = 1.6 Hz, 1 H), 7.29 (dd, *J* = 8.4 Hz, 2.0 Hz, 1 H), 4.40-4.38 (m, 1 H), 3.95 (s, 3H), 3.26-3.21 (m, 2 H), 2.82-2.79 (m, 1 H), 2.42-2.32 (m, 5 H), 2.22-2.18 (m, 2 H), 1.83-1.71 (m, 3 H), 1.45-1.27 (m, 2 H), 0.78-0.72 (m, 4 H), 0.42 (d, *J* = 5.2 Hz, 3 H); LCMS *m/z* 380.0

20 (M + H); SFC retention time: 5.88 min.

Example 145:**(1-(cyclopropylmethyl)-4-phenylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone**

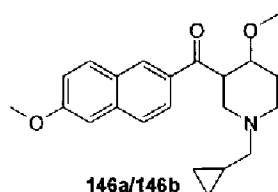
- 25 Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo- 3-methoxybenzene with 2-bromo-6-methoxynaphthalene, and *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-

1-carboxylate with 3-(methoxy(methyl)carbamoyl) -4-phenylpiperidine-1-carboxylate (Intermediate 16).

¹H NMR (400 MHz, CD₃OD) δ 7.81 (s, 1 H), 7.64-7.60 (m, 1 H), 7.59-7.56 (m, 2 H), 7.13-7.08 (m, 4 H), 6.96-6.94 (m, 2 H), 6.79-6.71 (m, 1 H), 4.57-4.51 (m, 1 H), 4.09-4.05 (m, 1 H), 3.88 (s, 3 H), 3.75-3.72 (m, 1 H), 3.59-3.55 (m, 1 H), 3.46-3.42 (m, 1 H), 3.13 (d, *J* = 7.6 Hz, 2 H), 2.68-2.61 (m, 1 H), 2.04-1.95 (m, 1 H), 1.27-1.10 (m, 2 H), 0.85-0.76 (m, 2 H), 0.56-0.50 (m, 2H); LCMS *m/z* 399.9 (M + H).

Examples 146a and 146b:

10 (1-(cyclopropylmethyl)-4-methoxypiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone

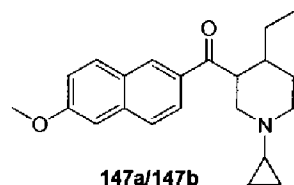


Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo- 3-methoxybenzene with 2-bromo-6-methoxynaphthalene, and *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with 3-(methoxy(methyl)carbamoyl) -4-methoxypiperidine-1-carboxylate (Intermediate 18). 146a and 146b correspond to the *cis*-enantiomers.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μm particle size) at 25% MeOH w/0.1%NH₄OH; 55 mL/min, 100 bars, 40 °C.

146a: ¹H NMR (400 MHz, CD₃OD) δ 8.42 (s, 1 H), 7.87-7.80 (m, 2 H), 7.71 (d, *J* = 8.8 Hz, 1 H), 7.17 (s, 1 H), 7.10-7.08 (m, 1 H), 3.82-3.79 (m, 4 H), 3.57-3.54 (m, 1 H), 3.18 (s, 3 H), 3.06-3.02 (m, 1 H), 2.21-2.07 (m, 5 H), 1.53-1.52 (m, 1 H), 1.15 (s, 1 H), 0.77-0.74 (m, 1 H), 0.42-0.37 (m, 2 H), 0.02-0.00 (m, 2 H); LCMS *m/z* 353.9 (M + H); SFC retention time: 3.60 min.

146b: ¹H NMR (400 MHz, CD₃OD) δ 8.42 (s, 1 H), 7.87-7.81 (m, 2 H), 7.72 (d, *J* = 8.8 Hz, 1 H), 7.18 (d, *J* = 2.4 Hz, 1 H), 7.09 (dd, *J* = 9.2 Hz, 2.0 Hz, 1 H), 3.82-3.80 (m, 4 H), 3.55-3.54 (m, 1 H), 3.18 (s, 3 H), 3.05-3.02 (m, 1 H), 2.21-2.07 (m, 5 H), 1.53-1.52 (m, 1 H), 1.15 (s, 1 H), 0.77-0.74 (m, 1 H), 0.41-0.37 (m, 2 H), 0.02-0.00 (m, 2 H); LCMS *m/z* 353.9 (M + H); SFC retention time: 4.18 min.

Examples 147a and 147b**(1-cyclopropyl-4-ethylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-

- 5 methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo- 3-methoxybenzene with 2-bromo-6-methoxynaphthalene, *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with 3-(methoxy(methyl)carbamoyl) -4-ethylpiperidine-1-carboxylate (Intermediate 15), and cyclopropanecarbaldehyde with (1-ethoxycyclopropoxy)trimethylsilane. 147a and 147b correspond to the *cis*-enantiomers.

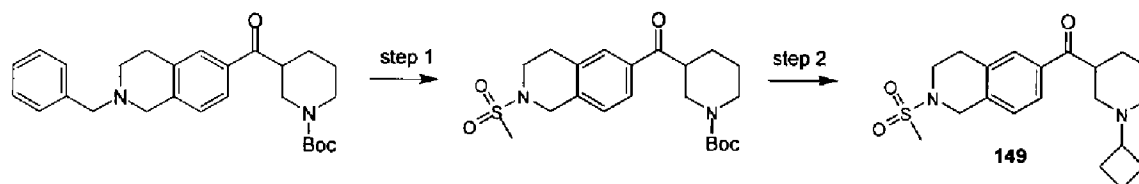
- 10 SFC conditions: CHIRALPAK AD (250 x 50 mm, 10 μ m particle size) at 25% IPA w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.

- 147a:** ¹H NMR (400 MHz, CD₃OD) δ 8.42 (s, 1 H), 7.92-7.88 (m, 2 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.28 (d, *J* = 2.4 Hz, 1 H), 7.20 (dd, *J* = 9.2 Hz, 2.8 Hz, 1 H), 3.93 (s, 3 H), 3.88-3.82 (m, 1 H), 2.87-2.85 (m, 2 H), 2.74-2.71 (m, 1 H), 2.53-2.48 (m, 1 H), 2.01-1.98 (m, 1 H), 1.88-1.84 (m, 2 H), 1.73-1.72 (m, 1 H), 1.52-1.43 (m, 1 H), 1.15-1.10 (m, 1 H), 0.70 (t, *J* = 7.6 Hz, 3 H), 0.49-0.40(m, 3 H), 0.29-0.23 (m, 1 H); LCMS *m/z* 337.9 (M + H); SFC retention time: 6.75 min.

- 147b:** ¹H NMR (400 MHz, CD₃OD) δ 8.42 (s, 1 H), 7.93-7.88 (m, 2 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.28 (d, *J* = 2.4 Hz, 1 H), 7.20 (dd, *J* = 9.2 Hz, 2.8 Hz, 1 H), 3.93 (s, 3 H), 3.88-3.83 (m, 1 H), 2.89-2.88 (m, 2 H), 2.76-2.73 (m, 1 H), 2.53-2.48 (m, 1 H), 2.03-2.00 (m, 1 H), 1.90-1.85 (m, 2 H), 1.78-1.75 (m, 1 H), 1.49-1.43 (m, 1 H), 1.18-1.14 (m, 1 H), 0.71 (t, *J* = 7.6 Hz, 3 H), 0.49-0.43 (m, 3 H), 0.31-0.28 (m, 1 H); LCMS *m/z* 337.9 (M + H); SFC retention time: 7.26 min.

Example 149:

- 25 **(1-cyclobutylpiperidin-3-yl)(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)methanone**



Step 1: *tert*-butyl 3-(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carbonyl)piperidine-1-carboxylate

To a stirred and cooled (0 °C) solution of *tert*-butyl 3-(2-benzyl-1,2,3,4-tetrahydro isoquinoline-6-carbonyl)piperidine-1-carboxylate (430 mg, 1.0 mmol) and Et₃N (1.5 mL) in dichloromethane (30 mL) was added 1-chloroethyl carbonochloridate (0.5 mL). The mixture was stirred at room temperature for 3 h and the solvent was evaporated. The residue was dissolved in MeOH (30 mL), stirred for another 16 h and then evaporated under reduced pressure to give crude *tert*-butyl 3-(2-(methyl sulfonyl)-1,2,3,4-tetrahydroisoquinoline-6-carbonyl)piperidine-1-carboxylate (200 mg, 58% yield).

To a solution of the above crude and Et₃N (1.5 mL) in dichloromethane (10 mL) was added MsCl (0.5mL). The mixture was stirred for 12 h and then evaporated under reduced pressure to give crude *tert*-butyl 3-(2-(methylsulfonyl)-1,2,3,4-tetrahydro isoquinoline-6-carbonyl)piperidine-1-carboxylate (240 mg, 99% yield).

Step 2:

(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)(piperidin-3-yl)methanone hydrochloride

To a solution of *tert*-butyl 3-(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinoline -6-carbonyl)piperidine-1-carboxylate (211 mg, 0.5 mmol) in ethyl acetate (5 mL) was added HCl (2 N in ethyl acetate, 5 mL). The mixture was stirred at room temperature for 1 h and then evaporated under reduced pressure to give the title compound (177 mg, 99% yield).

Step 3:

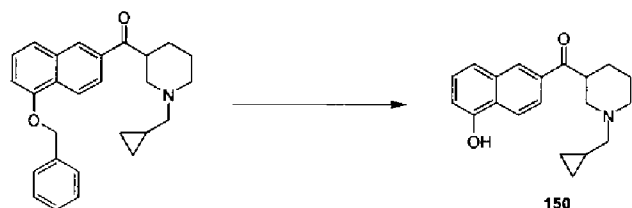
(1-cyclobutylpiperidin-3-yl)(2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)methanone

A solution of (2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)(piperidin-3-yl) methanone hydrochloride (177 mg, 0.5 mmol), cyclobutanone (70 mg, 1.0 mmol) and Et₃N (2 mL) in dichloromethane (10 mL) was stirred at room temperature for 1 h. Then NaBH(OAc)₃ (212 mg, 1.0 mmol) was added and stirring was continued for another 1 h. The reaction was quenched by addition of saturated aqueous NH₄Cl (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% NH₄OH (aq)) to provide 7.3 mg (11 % yield) of the title compound as a white solid.

^1H NMR (400 MHz, CD_3OD) δ 7.88-7.83 (m, 2 H), 7.36-7.34 (m, 1 H), 4.93-4.91 (m, 1 H), 4.52 (s, 2 H), 3.90-3.59 (m, 2 H), 3.57-3.56 (m, 3 H), 3.31-3.29 (m, 1 H), 3.08-3.04 (m, 3 H), 2.94 (s, 3 H), 2.80-2.75 (m, 1 H), 2.38-1.89 (m, 9 H); LCMS m/z 377.1 ($M + H$).

5 Example 150:

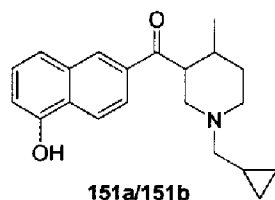
(1-(cyclopropylmethyl)piperidin-3-yl)(5-hydroxynaphthalen-2-yl)methanone



A mixture of (5-(benzyloxy)naphthalen-2-yl)(1-(cyclopropylmethyl)piperidin-3-yl) methanone (Example 15) (39 mg, 0.1 mmol) and Pd/C (50 mg) in methanol (20 mL) was stirred for 12 h under H_2 atmosphere (15 psi). The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% NH_4OH (aq)) to afford the title compound (22.2 mg, 71%) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1 H), 7.91 (d, $J = 8.8$ Hz, 2 H), 7.72 (d, $J = 8.8$ Hz, 1 H), 7.16 (d, $J = 8.0$ Hz, 2 H), 3.84-3.81 (m, 1 H), 3.31-3.19 (m, 2 H), 2.39-2.38 (m, 2 H), 2.32-2.29 (m, 1 H), 2.12-2.11 (m, 1 H), 2.04-2.01 (m, 1 H), 1.87-1.85 (m, 2 H), 1.53-1.50 (m, 1 H), 0.96-0.92 (m, 1 H), 0.57-0.55 (m, 2 H), 0.18-0.17 (m, 2 H); LCMS m/z 309.9 ($M + H$).

Examples 151a and 151b

(1-(cyclopropylmethyl)-4-methylpiperidin-3-yl)(5-hydroxynaphthalen-2-yl)methanone



Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (5-hydroxynaphthalen-2-yl)methanone (Example 150), replacing *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate with 3-(methoxy(methyl)carbamoyl)-4-methylpiperidine-1-carboxylate (Intermediate 10). 151a and 151b correspond to the *cis*-enantiomers.

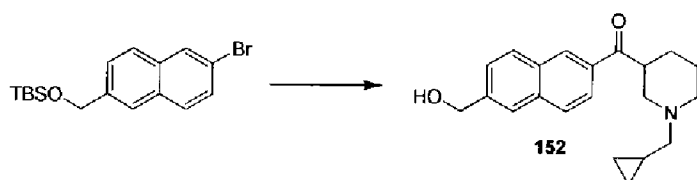
SFC conditions: CHIRALPAK AD (250 x 30 mm, 20 μm particle size) at 50% MeOH w/0.1% NH_4OH ; 80 mL/min, 100 bars, 40 $^\circ\text{C}$.

151a: ^1H NMR (400 MHz, CD_3OD) δ 8.30 (s, 1 H), 7.70 (t, $J = 8.0$ Hz, 2 H), 7.51 (d, $J = 8.4$ Hz, 1 H), 6.96 (d, $J = 8.0$ Hz, 2 H), 4.00-3.94 (m, 1 H), 3.11-3.01 (m, 2 H), 2.85-2.80 (m, 1 H), 2.69-2.67 (m, 2 H), 2.27-2.23 (m, 1 H), 1.95-1.90 (m, 1 H), 1.60-1.57 (m, 1 H), 1.05-0.90 (m, 2 H), 0.65-0.63 (m, 3 H), 0.51-0.49 (m, 2 H), 0.20-0.19 (m, 2 H); LCMS m/z 323.9 ($M + H$); SFC retention time: 1.93 min.

151b: ^1H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1 H), 7.84 (t, $J = 8.0$ Hz, 2 H), 7.64 (d, $J = 8.8$ Hz, 1 H), 7.08 (d, $J = 8.0$ Hz, 2 H), 4.15-4.11 (m, 1 H), 3.54-3.11 (m, 3 H), 2.94-2.92 (m, 2 H), 2.42-2.38 (m, 1 H), 2.05-2.02 (m, 1 H), 1.76-1.71 (m, 1 H), 1.19-1.15 (m, 1 H), 1.06-0.97 (m, 1 H), 0.78-0.73 (m, 3 H), 0.67-0.65 (m, 2 H), 0.38-0.35 (m, 2 H); LCMS m/z 323.9 ($M + H$); SFC retention time: 4.74 min

Example 152

(1-(cyclopropylmethyl)piperidin-3-yl)(6-(hydroxymethyl)naphthalen-2-yl)methanone

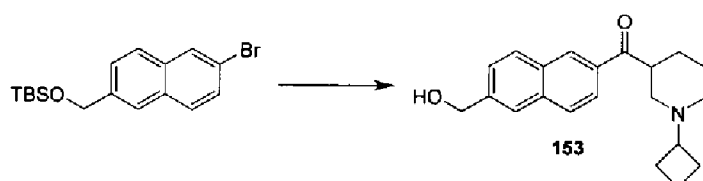


Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with ((6-bromonaphthalen-2-yl)methoxy)(*tert*-butyl)dimethyl silane (Intermediate 24).

^1H NMR (400 MHz, CD_3OD) δ 8.68 (d, $J = 7.6$ Hz, 1 H), 8.12-7.94 (m, 4 H), 7.64 (d, $J = 8.0$ Hz, 1 H), 4.84 (s, 2 H), 4.19-4.13 (m, 1 H), 3.86-3.82 (m, 1 H), 3.31-3.28 (m, 1 H), 3.17-3.04 (m, 3 H), 2.33-2.20 (m, 3 H), 1.90-1.62 (m, 2 H), 1.26-1.22 (m, 1 H), 0.86-0.80 (m, 2 H), 0.53-0.51 (m, 2 H); LCMS m/z 324 ($M + H$).

Example 153:

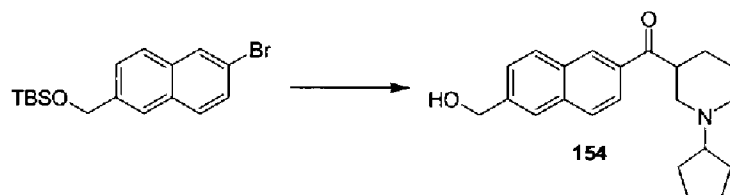
(1-cyclobutylpiperidin-3-yl)(6-(hydroxymethyl)naphthalen-2-yl)methanone



Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with ((6-bromonaphthalen-2-yl)methoxy)(*tert*-butyl)dimethyl silane (Intermediate 24), and cyclopropanecarbaldehyde with cyclobutanone.

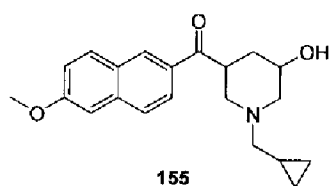
¹H NMR (400 MHz, CD₃OD) δ 8.66 (d, *J* = 5.6 Hz, 1 H), 8.13-7.94 (m, 4 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 4.84 (s, 2 H), 4.12-4.09 (m, 1 H), 3.80-3.78 (m, 1.5 H), 3.66-3.63 (m, 1.5 H), 3.12-3.10 (m, 1 H), 2.83-2.79 (m, 1 H), 2.42-2.34 (m, 5 H), 2.13-2.12 (m, 2 H), 1.93-1.91 (m, 2 H), 1.63-1.60 (m, 1 H); LCMS *m/z* 324 (M + H).

5

Example 154:**(1-(cyclopentylpiperidin-3-yl)(6-(hydroxymethyl)naphthalen-2-yl)methanone**

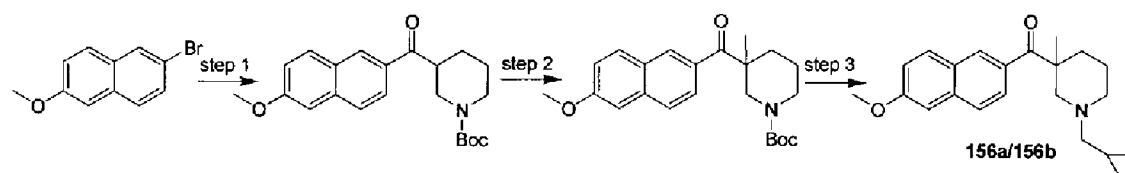
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with ((6-bromonaphthalen-2-yl)methoxy)(*tert*-butyl)dimethyl silane (Intermediate 24), and cyclopropanecarbaldehyde with cyclopentanone.

¹H NMR (400 MHz, CD₃OD) δ 8.64 (d, *J* = 4.0 Hz, 1 H), 8.07 (d, *J* = 8.4 Hz, 1 H), 8.04-7.96 (m, 2 H), 7.91 (s, 1 H), 7.61 (d, *J* = 8.8 Hz, 1 H), 4.81 (s, 2 H), 4.11-4.10 (m, 1 H), 3.78-3.62 (m, 3 H), 3.27-3.24 (m, 0.5 H), 3.03-2.97 (m, 1.5 H), 2.25-2.12 (m, 5 H), 1.88-1.61 (m, 7 H); LCMS *m/z* 338 (M + H).

Example 155**(1-(cyclopropylmethyl)-5-hydroxypiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate with *tert*-butyl 3-((*tert*-butyldimethyl silyl)oxy)-5-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 20).

¹H NMR (400 MHz, CD₃OD) δ 8.50 (s, 1 H), 7.95-7.91 (m, 2 H), 7.83 (d, *J* = 8.8 Hz, 1 H), 7.29 (d, *J* = 2.4 Hz, 1 H), 7.19 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 3.92 (s, 3 H), 3.90-3.80 (m, 2 H), 3.19-3.16 (m, 1 H), 2.38-2.33 (m, 2 H), 2.21-2.12 (m, 2 H), 1.86 (t, *J* = 10.4 Hz, 1 H), 1.44-1.26 (m, 2 H), 0.90-0.87 (m, 1 H), 0.54-0.50 (m, 2 H), 0.14-0.07 (m, 2 H); LCMS *m/z* 340.2 (M + H).

Examples 156a and 156b**(1-(cyclopropylmethyl)-3-methylpiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone****Step 1:*****tert*-butyl 3-(6-methoxy-2-naphthoyl)piperidine-1-carboxylate**

To a stirred and cooled (-78 °C) solution of 2-bromo-6-methoxynaphthalene (2.36 g, 10.0 mmol) in THF (30 mL) was added *n*-BuLi (2.5 M in hexane, 4.0 mL, 10.0 mmol). After addition, stirring at -78 °C was continued for 1 h, and then a solution of *tert*-butyl 3-

(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 10) (2.72 g, 10.0 mmol) in THF (10 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for an additional 2 h. The mixture was quenched by addition of saturated aqueous NH₄Cl (20 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure to give crude *tert*-butyl 3-(6-methoxy-2-naphthoyl)piperidine-1-carboxylate (1.9 g, 51% yield). This crude was used directly without further purification.

Step 2:***tert*-butyl 3-(6-methoxy-2-naphthoyl)-3-methylpiperidine-1-carboxylate**

To a stirred and cooled (-78 °C) solution of *tert*-butyl 3-(6-methoxy-2-naphthoyl) piperidine-1-carboxylate (369 mg, 1.0 mmol) in THF (10 mL) was added LiHMDS (1 N, 1.1 mL, 1.1 mmol). After addition, stirring was continued for 30 min and then MeI (282 mg, 2.0 mmol) was added. The mixture was warmed up to room temperature and stirred for another 2 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl (10 mL) and then extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 5:1) to give *tert*-butyl 3-(6-methoxy-2-naphthoyl)-3-methyl piperidine-1-carboxylate (200 mg, 52.2 % yield) as an oil.

Step 3:**(6-methoxynaphthalen-2-yl)(3-methylpiperidin-3-yl)methanone hydrochloride**

To a solution of *tert*-butyl 3-(6-methoxy-2-naphthoyl)-3-methylpiperidine-1-carboxylate (200 mg, 0.52 mmol) in ethyl acetate (10 mL) was added HCl (2 N in ethyl acetate, 10 mL, 20 mmol).

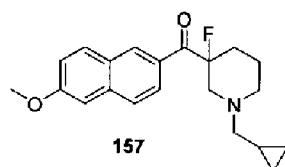
- 5 The reaction mixture was stirred at ambient temperature for 2 h and then concentrated under reduced pressure to give crude (6-methoxynaphthalen-2-yl)(3-methylpiperidin-3-yl) methanone hydrochloride (165 mg, 99.6% yield) as an oil.

- A solution of (6-methoxynaphthalen-2-yl)(3-methylpiperidin-3-yl)methanone hydrochloride (160 mg, 0.50 mmol), cyclopropanecarbaldehyde (42 mg, 0.60 mmol) and Et₃N (2 mL) in
 10 dichloroethane (10 mL) was stirred at room temperature for 1 h. Then NaBH(OAc)₃ (127 mg, 0.60 mmol) was added to the mixture. The mixture was stirred for another 1 h and then quenched by addition of saturated aqueous NH₄Cl (5 mL). The solution was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (base)
 15 then the enantiomers were separated by supercritical fluid chromatography (SFC) to provide 11.1 mg (7% yield) of 155a and 9.4 mg (6% yield) of 155b.

SFC conditions: CHIRALPAK IC (250 x 50 mm, 5 μm particle size) at 40% EtOH w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.

- 156a:** ¹H NMR (400 MHz, CD₃OD) δ 8.27 (s, 1 H), 7.87 (d, *J* = 9.2 Hz, 1 H), 7.82-7.77 (m, 2 H), 7.28 (d, *J* = 2.4 Hz, 1 H), 7.20 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 3.94 (s, 3 H), 3.64-3.60 (m, 1 H), 2.81-2.76 (m, 1 H), 2.42-2.04 (m, 4 H), 1.63-1.59 (m, 2 H), 1.47 (s, 3 H), 1.38-1.27 (m, 2 H), 0.59-0.55 (m, 1 H), 0.37-0.30 (m, 2 H), 0.10-0.03 (m, 2 H); LCMS *m/z* 338.2 (M + H); SFC retention time: 8.58 min.

- 156b:** ¹H NMR (400 MHz, CD₃OD) δ 8.23 (s, 1 H), 7.87 (d, *J* = 9.2 Hz, 1 H), 7.82-7.77 (m, 2 H), 7.26 (d, *J* = 2.4 Hz, 1 H), 7.18 (dd, *J* = 8.8 Hz, 2.4 Hz, 1 H), 3.94 (s, 3 H), 3.64-3.60 (m, 1 H), 2.81-2.76 (m, 1 H), 2.42-2.04 (m, 4 H), 1.63-1.59 (m, 2 H), 1.44 (s, 3 H), 1.38-1.27 (m, 2 H), 0.59-0.55 (m, 1 H), 0.37-0.30 (m, 2 H), 0.10-0.03 (m, 2 H); LCMS *m/z* 338.2 (M + H); SFC retention time: 6.93 min.

Example 157:**(1-(cyclopropylmethyl)-4-methoxypiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)-3-methylpiperidin-3-yl) (6-methoxynaphthalen-2-yl)methanone (Examples 156a and 156b), replacing iodomethane with N-Fluorodibenzenesulfonimide. Only one enantiomer was obtained due to stability issue.

SFC conditions: CHIRALPAK OJ (250 x 30 mm, 5 μ m particle size) at 25%

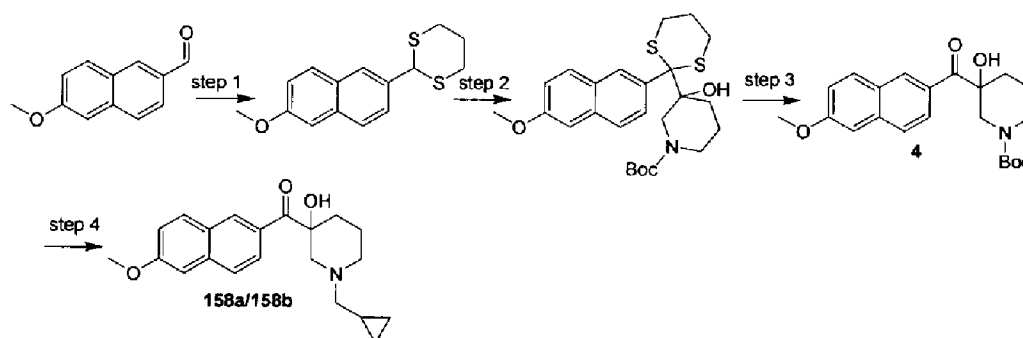
5 IPA w/0.1% NH₄OH; 60 mL/min, 100 bars, 40 °C.

¹H NMR (400 MHz, CDCl₃) δ 8.71 (s, 1 H), 8.08-8.05 (m, 1 H), 7.86 (d, *J* = 8.8 Hz, 1 H), 7.76 (d, *J* = 8.8 Hz, 1 H), 7.22-7.19 (m, 1 H), 7.19-7.15 (m, 1 H), 3.96 (s, 3 H), 3.44-3.41 (m, 1 H), 3.13-3.10 (m, 1 H), 2.73-2.65 (m, 1 H), 2.41-2.38 (m, 2 H), 2.22-2.10 (m, 2 H), 2.09-1.97 (m, 2 H), 1.79-1.78 (m, 1 H), 0.93-0.90 (m, 1 H), 0.52-0.50 (m, 2 H), 0.12-0.09 (m, 2 H); LCMS *m/z*

10 341.9 (M + H); SFC retention time: 6.20 min.

Examples 158a and 158b:

(1-(cyclopropylmethyl)-3-hydroxypiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone



15 Step 1:

2-(6-methoxynaphthalen-2-yl)-1,3-dithiane

A solution of 6-methoxy-2-naphthaldehyde (1.0 g, 5.4 mmol), propane-1,3-dithiol (618 mg, 6 mmol) and 4-methylbenzenesulfonic acid (172 mg, 1 mmol) in toluene (50 mL) was heated at 120°C for 16 h. The solvent was removed under reduced pressure, and the residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 5:1) to give 2-(6-methoxynaphthalen-2-yl)-1,3-dithiane (400 mg, 26.8 % yield) as an oil.

Step 2:

tert-butyl 3-hydroxy-3-(2-(6-methoxynaphthalen-2-yl)-1,3-dithian-2-yl)piperidine-1-carboxylate

To a stirred and cooled (0 °C) solution of 2-(6-methoxynaphthalen-2-yl)-1,3-dithiane (400 mg, 1.45 mmol) in THF (10 mL) was added LDA (2N, 0.8 mL, 1.6 mmol). After being stirred at -20 °C for 30 min, the mixture was cooled to -78 °C and a solution of *tert*-butyl 3-oxopiperidine-1-

carboxylate (289 mg, 1.45 mmol) in THF (5 mL) was added. The resulting mixture was stirred for another 2 h, and then quenched by the addition of saturated aqueous NH_4Cl (10 mL). The mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water (15 mL), brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 3:1) to give *tert*-butyl 3-hydroxy-3-(2-(6-methoxynaphthalen-2-yl)-1,3-dithian-2-yl)piperidine-1-carboxylate (200 mg, 29.0 % yield) as an oil.

Step 3:

***tert*-butyl 3-hydroxy-3-(6-methoxy-2-naphthoyl)piperidine-1-carboxylate**

A mixture of *tert*-butyl 3-hydroxy-3-(2-(6-methoxynaphthalen-2-yl)-1,3-dithian-2-yl)piperidine-1-carboxylate (180 mg, 0.38 mmol), pyridinium bromide perbromide (242 mg, 0.76 mmol) and Tetrabutylammonium bromide (15 mg) in dichloromethane (10 mL) and H_2O (3 mL) was stirred at room temperature for 8 h. The reaction mixture was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography (petroleum ether: ethyl acetate = 3: 1) to give *tert*-butyl 3-hydroxy-3-(6-methoxy-2-naphthoyl) piperidine-1-carboxylate (120 mg, 82.1 % yield) as a yellow oil.

Step 4:

(3-hydroxypiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone hydrochloride

To a solution of *tert*-butyl 3-hydroxy-3-(6-methoxy-2-naphthoyl)piperidine-1-carboxylate (100 mg, 0.26 mmol) in ethyl acetate (10 mL) was added HCl (2 N in ethyl acetate, 10 mL, 20 mmol). The reaction mixture was stirred at ambient temperature for 2 h and then concentrated under reduced pressure to give crude (3-hydroxypiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone hydrochloride (83 mg, 99.6% yield) as a yellow oil.

A solution of (3-hydroxypiperidin-3-yl)(6-methoxynaphthalen-2-yl)methanone hydrochloride (83 mg, 0.26 mmol), cyclopropanecarbaldehyde (28 mg, 0.40 mmol) and Et_3N (1 mL) in dichloroethane (10 mL) was stirred at room temperature for 1 h before $\text{NaBH}(\text{OAc})_3$ (84 mg, 0.40 mmol) was added to the mixture. The mixture was stirred for another 1 h and then quenched by addition of saturated aqueous NH_4Cl (5 mL). The solution was extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by reverse phase HPLC then the

enantiomers were separated by supercritical fluid chromatography (SFC) to provide 7.5 mg (11% yield) of 158a and 5.0 mg (9% yield) of 158b.

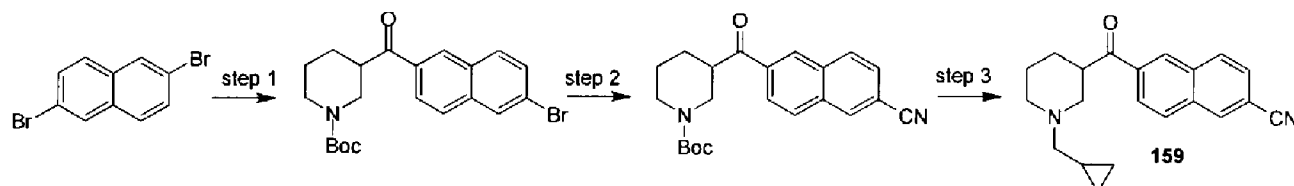
SFC conditions: CHIRALPAK AS (250 x 30 mm, 5 μ m particle size) at 30% MeOH w/0.1%NH₄OH; 60 mL/min, 100 bars, 40 °C.

- 5 **158a**: ¹H NMR (400 MHz, CD₃OD) δ 8.86 (s, 1 H), 8.13-8.10 (m, 1 H), 7.87 (d, J = 9.2 Hz, 1 H), 7.79 (d, J = 9.2 Hz, 1 H), 7.27 (d, J = 2.4 Hz, 1 H), 7.18 (dd, J = 9.2 Hz, 2.8 Hz, 1 H), 3.94 (s, 3 H), 3.00-2.98 (m, 1 H), 2.82-2.78 (m, 2 H), 2.37-2.27 (m, 3 H), 2.00-1.92 (m, 3 H), 1.76-1.71 (m, 1 H), 0.81-0.78 (m, 1 H), 0.46-0.42 (m, 2 H), 0.09-0.06 (m, 2 H); LCMS m/z 339.8 (M + H); SFC retention time: 7.10 min.
- 10 **158b**: ¹H NMR (400 MHz, CD₃OD) δ 8.70 (s, 1 H), 8.14-8.11 (m, 1 H), 7.88 (d, J = 9.2 Hz, 1 H), 7.80 (d, J = 9.2 Hz, 1 H), 7.28 (d, J = 2.4 Hz, 1 H), 7.19 (dd, J = 9.2 Hz, 2.8 Hz, 1 H), 3.94 (s, 3 H), 3.00-2.98 (m, 1 H), 2.82-2.78 (m, 2 H), 2.37-2.27 (m, 3 H), 2.00-1.92 (m, 3 H), 1.76-1.71 (m, 1 H), 0.81-0.78 (m, 1 H), 0.46-0.42 (m, 2 H), 0.09-0.06 (m, 2 H); LCMS m/z 340.2 (M + H); SFC retention time: 6.24 min.

15

Example 159:

6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-2-naphthonitrile



20 Step 1:

tert-butyl 3-(6-bromo-2-naphthoyl)piperidine-1-carboxylate

To a stirred and cooled (-78 °C) solution of 2,6-dibromonaphthalene (2.84 g, 10 mmol) in THF (30 mL) was added *n*-BuLi (2.5 M in hexane, 4.0 mL, 10.0 mmol). After the addition, stirring at -78 °C was continued for 1 h, and then a solution of *tert*-butyl 3-

- 25 (methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 10) (3.264 g, 12 mmol) in THF (20 mL) was added dropwise. The resulting mixture was warmed up to room temperature and stirred for additional 2 h. The mixture was quenched by addition of saturated aqueous NH₄Cl (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The
- 30 residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 5: 1) to give *tert*-butyl 3-(6-bromo-2-naphthoyl)piperidine-1-carboxylate (3.0 g, 71.9% yield) as a yellow oil.

Step 2:***tert*-butyl 3-(6-cyano-2-naphthoyl)piperidine-1-carboxylate**

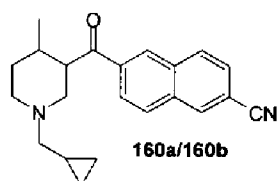
A mixture of *tert*-butyl 3-(6-bromo-2-naphthoyl)piperidine-1-carboxylate (209 mg, 0.5 mmol),
5 Zn(CN)₂ (116 mg, 1.0 mmol), Xant-phos (58 mg, 0.1 mmol), Pd₂(dba)₃ (46 mg, 0.05 mmol) and
Cs₂CO₃ (650 mg, 2.0 mmol) in dioxane (15.0 mL) was heated at 120 °C for 30 min under
microwave conditions. The solvent was evaporated under reduced pressure, and the residue was
purified by silica-gel chromatography (petroleum ether: ethyl acetate = 5: 1) to give *tert*-butyl 3-
(6-cyano-2-naphthoyl) piperidine-1-carboxylate (0.15 g, 82.4 % yield).

Step 3:**6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-2-naphthonitrile**

To a solution of *tert*-butyl 3-(6-cyano-2-naphthoyl)piperidine-1-carboxylate (0.15 g, 0.41 mmol)
in ethyl acetate (5.0 mL) was added HCl (2 N in ethyl acetate, 5.0 mL, 10 mmol). The reaction
15 mixture was stirred at 25 °C for 2 h and then concentrated under reduced pressure to give crude
6-(piperidine-3-carbonyl)-2-naphthonitrile hydrochloride (0.12 g, 97.1% yield).

A solution of 6-(piperidine-3-carbonyl)-2-naphthonitrile hydrochloride (0.12 g, 0.4 mmol),
cyclopropanecarbaldehyde (56 mg, 0.8 mmol) and Et₃N (1 mL) in dichloroethane (10 mL) was
stirred at room temperature for 1 h before NaBH(OAc)₃ (254 mg, 1.2 mmol) was added to the
20 mixture. The mixture was stirred for another 1 h and then quenched by the addition of saturated
aqueous NH₄Cl (5 mL). The solution was extracted with dichloromethane (2 x 20 mL). The
combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The
residue was purified by preparative HPLC HPLC (Phenomenx Gemini NX, 20-60% ACN in
0.1% NH₄OH (aq)) to give 20.6 mg (15% yield) of the title compound as a white solid.

25 ¹H NMR (400 MHz, CD₃OD) δ 8.76 (s, 1 H), 8.42 (d, *J*=9.6 Hz, 1 H), 8.26-8.08 (m, 3 H), 7.75
(d, *J*=7.2 Hz, 1 H), 4.26-4.23 (m, 1 H), 3.85-3.76 (m, 1 H), 3.24-3.20 (m, 2 H), 3.16-3.01 (m, 3
H), 2.28-2.11 (m, 3 H), 1.65-1.59 (m, 1 H), 1.24-1.22 (m, 1 H), 0.81-0.77 (m, 2 H), 0.52-0.46
(m, 2 H); LCMS: *m/z* 318.9 (M + H).

Examples 160a and 160b**6-(1-(cyclopropylmethyl)-4-methylpiperidine-3-carbonyl)-2-naphthonitrile**

Prepared in an analogous manner to 6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-2-naphthonitrile (Example 158), replacing *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with *tert*-butyl 3-(methoxy(methyl) carbamoyl)-4-methylpiperidine-1-carboxylate (Intermediate 10). 160a and 160b correspond to the *cis*-enantiomers.

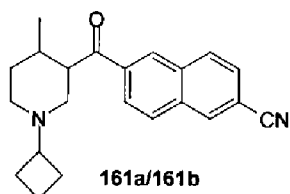
- 5 SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μ m particle size) at 25% EtOH w/0.1%NH₄OH; 60mL/min, 100 bars, 40 °C.

160a: ¹H NMR (400 MHz, CD₃OD) δ 8.74 (s, 1 H), 8.47 (s, 1 H), 8.27 (d, *J* = 8.4 Hz, 1 H), 8.18-8.12 (m, 2 H), 7.80 (d, *J* = 8.8 Hz, 1 H), 3.63-3.60 (m, 1 H), 3.31-3.21 (m, 2 H), 2.36 (d, *J* = 6.4 Hz, 1.5 H), 2.20-2.15 (m, 1.5 H), 1.96-1.92 (m, 1 H), 1.87-1.83 (m, 1 H), 1.57-1.54 (m, 1 H), 1.18 (t, *J* = 7.2 Hz, 2 H), 0.91 (d, *J* = 6.4 Hz, 4 H), 0.55-0.51 (m, 2 H), 0.16-0.12 (m, 2 H); LCMS *m/z* 333.0 (M + H); SFC retention time: 5.84 min.

- 160b:** ¹H NMR (400 MHz, CD₃OD) δ 8.74 (s, 1 H), 8.47 (s, 1 H), 8.27 (d, *J* = 8.8 Hz, 1 H), 8.18-8.12 (m, 2 H), 7.80 (d, *J* = 8.8 Hz, 1 H), 3.63-3.60 (m, 1 H), 3.31-3.21 (m, 2 H), 2.36 (d, *J* = 6.4 Hz, 1.5 H), 2.20-2.15 (m, 1.5 H), 1.96-1.92 (m, 1 H), 1.87-1.83 (m, 1 H), 1.57-1.54 (m, 1 H), 1.17 (t, *J* = 7.2 Hz, 2 H), 0.91 (d, *J* = 6.8 Hz, 4 H), 0.55-0.51 (m, 2 H), 0.16-0.12 (m, 2 H); LCMS *m/z* 333.2 (M + H); SFC retention time: 6.33 min.

Examples 161a and 161b:

6-(1-(cyclobutyl-4-methylpiperidine-3-carbonyl)-2-naphthonitrile



- 20 Prepared in an analogous manner to 6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-2-naphthonitrile (Example 158), replacing *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with *tert*-butyl 3-(methoxy(methyl) carbamoyl)-4-methylpiperidine-1-carboxylate (Intermediate 10), and cyclopropanecarbaldehyde with cyclobutanone. 161a and 161b correspond to the *cis*-enantiomers.

SFC conditions: CHIRALPAK OJ (200 x 30 mm, 5 μ m particle size) at 15%EtOH w/0.1%NH₄OH; 50 mL/min, 100 bars, 40 °C.

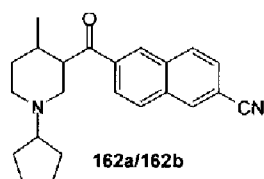
- 161a:** ¹H NMR (400 MHz, CD₃OD) δ 8.74 (s, 1 H), 8.48 (s, 1 H), 8.28 (d, *J* = 8.4 Hz, 1 H), 8.19-8.13 (m, 2 H), 7.81 (d, *J* = 8.4 Hz, 1 H), 3.62-3.58 (m, 1 H), 3.03-3.00 (m, 2 H), 2.85-2.80 (m, 1 H), 2.12-2.10 (m, 1 H), 1.97-1.91 (m, 7 H), 1.76-1.73 (m, 2 H), 1.54-1.50 (m, 1 H), 0.92 (d, *J* = 6.4 Hz, 3 H); LCMS *m/z* 332.9 (M + H); SFC retention time: 3.59 min.

161b: ^1H NMR (400 MHz, CD_3OD) δ 8.73 (s, 1 H), 8.48 (s, 1 H), 8.29 (d, $J = 8.4$ Hz, 1 H), 8.18-8.13 (m, 2 H), 7.81 (d, $J = 8.4$ Hz, 1 H), 3.62-3.58 (m, 1 H), 3.03-3.00 (m, 2 H), 2.85-2.80 (m, 1 H), 2.12-2.10 (m, 1 H), 1.97-1.91 (m, 7 H), 1.76-1.73 (m, 2 H), 1.54-1.50 (m, 1 H), 0.92 (d, $J = 6.4$ Hz, 3 H); LCMS m/z 332.9 ($M + H$); SFC retention time: 3.81 min.

5

Examples 162a and 162b

6-(1-cyclopentyl-4-methylpiperidine-3-carbonyl)-2-naphthonitrile



Prepared in an analogous manner to 6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-2-naphthonitrile (Example 158), replacing *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with *tert*-butyl 3-(methoxy(methyl) carbamoyl)-4-methylpiperidine-1-carboxylate (Intermediate 10), and cyclopropanecarbaldehyde with cyclopentanone. 162a and 162b correspond to the *cis*-enantiomers.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μm particle size) at 30% MeOH

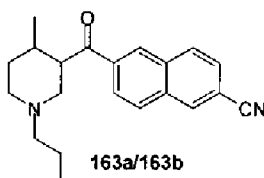
w/0.1% NH_4OH ; 60mL/min, 100 bars, 40 $^\circ\text{C}$.

162a: ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1 H), 8.45 (s, 1 H), 8.25 (d, $J = 8.4$ Hz, 1 H), 8.14-8.10 (m, 2 H), 7.78 (dd, $J = 1.6$ Hz, 8.4 Hz, 1 H), 3.60-3.58 (m, 1 H), 3.16-3.13 (m, 2 H), 2.64-2.60 (m, 1 H), 2.13-2.07 (m, 2 H), 1.94-1.92 (m, 2 H), 1.84-1.83 (m, 2 H), 1.76-1.74 (m, 2 H), 1.60-1.56 (m, 2 H), 1.50-1.40 (m, 2 H), 1.18-1.14 (m, 1 H), 0.87 (d, $J = 6.4$ Hz, 3 H); LCMS m/z 347.0 ($M+H$); SFC retention time: 6.15 min.

162b: ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1 H), 8.45 (s, 1 H), 8.25 (d, $J = 8.4$ Hz, 1 H), 8.14-8.10 (m, 2 H), 7.78 (dd, $J = 1.6$ Hz, 8.4 Hz, 1 H), 3.60-3.58 (m, 1 H), 3.16-3.13 (m, 2 H), 2.64-2.60 (m, 1 H), 2.13-2.07 (m, 2 H), 1.94-1.92 (m, 2 H), 1.84-1.83 (m, 2 H), 1.76-1.74v(m, 2 H), 1.60-1.56 (m, 2 H), 1.50-1.40 (m, 2 H), 1.18-1.14 (m, 1 H), 0.87 (d, $J = 6.4$ Hz, 3 H); LCMS m/z 347.0 ($M + H$); SFC retention time: 6.53 min.

Examples 163a and 163b:

6-(4-methyl-1-propylpiperidine-3-carbonyl)-2-naphthonitrile



Prepared in an analogous manner to 6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-2-naphthonitrile (Example 158), replacing *tert*-butyl 3-(methoxy (methyl)carbamoyl)piperidine-1-carboxylate with *tert*-butyl 3-(methoxy(methyl) carbamoyl)-4-methylpiperidine-1-carboxylate (Intermediate 10), and cyclopropanecarbaldehyde with propionaldehyde. 163a and 163b correspond to the *cis*-enantiomers.

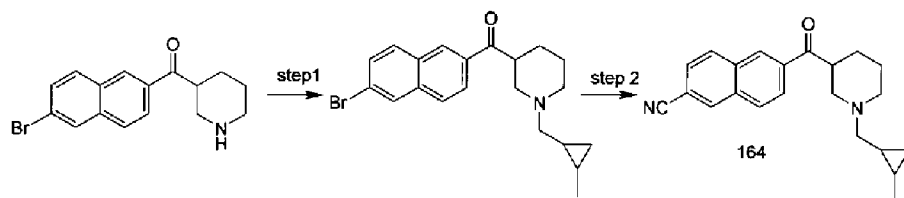
SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μ m particle size) at 20% IPA w/0.1%NH₄OH; 60mL/min, 100 bars, 40 °C.

163a: ¹H NMR (400 MHz, CD₃OD) δ 8.77 (s, 1 H), 8.48 (s, 1 H), 8.29 (d, *J* = 8.4 Hz, 1 H), 8.17-8.13 (m, 2 H), 7.81 (dd, *J* = 1.2 Hz, 8.8 Hz, 1 H), 3.72-3.68 (m, 1 H), 3.16-3.13 (m, 2 H), 2.49-2.45 (m, 2 H), 2.21-2.17 (m, 2 H), 1.98-1.96 (m, 1 H), 1.88-1.85 (m, 1 H), 1.62-1.56 (m, 3 H), 0.96-0.91 (m, 6 H); LCMS *m/z* 320.9 (M + H); SFC retention time: 5.05 min.

163b: ¹H NMR (400 MHz, CD₃OD) δ 8.76 (s, 1 H), 8.49 (s, 1 H), 8.28 (d, *J* = 8.4 Hz, 1 H), 8.19-8.13 (m, 2 H), 7.81 (dd, *J* = 1.6 Hz, 8.4 Hz, 1 H), 3.69-3.66 (m, 1 H), 3.14-3.11 (m, 2 H), 2.49-2.45 (m, 2 H), 2.21-2.17 (m, 2 H), 1.98-1.96 (m, 1 H), 1.88-1.84 (m, 1 H), 1.60-1.54 (m, 3 H), 0.96-0.91 (m, 6 H); LCMS *m/z* 320.9 (M + H); SFC retention time: 5.63 min.

Example 164:

6-(1-((2-methylcyclopropyl)methyl)piperidine-3-carbonyl)-2-naphthonitrile



Step 1:

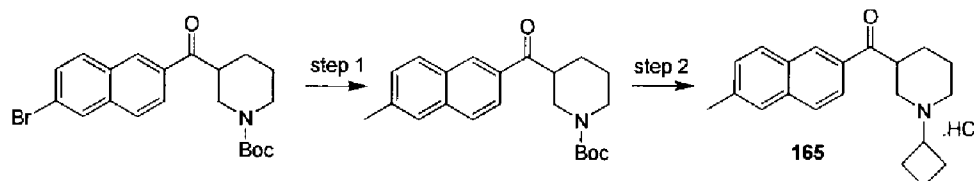
(6-bromonaphthalen-2-yl)(1-((2-methylcyclopropyl)methyl)piperidin-3-yl) methanone

A solution of (6-bromonaphthalen-2-yl)(piperidin-3-yl) methanone hydrochloride (Examples 23a and 23b) (129 mg, 0.43 mmol), 1-(bromomethyl)-2-methyl cyclopropane (126 mg, 0.85 mmol) and DIPEA (110 mg, 0.85 mmol) in dichloromethane (10 mL) was stirred at room temperature for 3 h. The solvent was evaporated under reduced pressure to give crude (6-bromonaphthalen-2-yl)(1-((2-methylcyclopropyl) methyl)piperidin-3-yl)methanone (100 mg, 61% yield).

Step 2:**6-(1-((2-methylcyclopropyl)methyl)piperidin-3-carbonyl)-2-naphthonitrile**

A mixture of (6-bromonaphthalen-2-yl)(1-((2-methylcyclopropyl)methyl)piperidin-3-yl)methanone (100 mg, 0.26 mmol), $\text{Zn}(\text{CN})_2$ (45 mg, 0.388 mmol), Xant-phos (30 mg, 0.052 mmol), $\text{Pd}_2(\text{dba})_3$ (24 mg, 0.026 mmol) and Cs_2CO_3 (169 mg, 0.52 mmol) in dioxane (5.0 mL) was heated at 120°C for 30 min under microwave conditions. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by reverse phase HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% Formic Acid (aq)) to give 20.2 mg (21.2% yield) of example 164.

^1H NMR (400 MHz, CD_3OD) δ 8.77 (s, 1 H), 8.45 (d, $J = 7.2$ Hz, 1 H), 8.26 (t, $J = 8.8$ Hz, 1 H), 8.18-8.13 (m, 2 H), 7.78 (d, $J = 7.6$ Hz, 1 H), 4.39-4.37 (m, 0.5 H), 4.21-4.17 (m, 0.5 H), 4.09-4.05 (m, 0.5 H), 3.83-3.76 (m, 1.5 H), 3.30-2.98 (m, 3 H), 2.29-2.12 (m, 3 H), 1.82-1.78 (m, 0.5 H), 1.65-1.59 (m, 1.5 H), 1.17-1.09 (m, 3 H), 0.90-0.88 (m, 2 H), 0.65-0.55 (m, 2 H); LCMS: m/z 333.0 (M + H).

Example 165:**(1-cyclobutylpiperidin-3-yl)(6-methylnaphthalen-2-yl)methanone hydrochloride****Step 1:*****tert*-butyl 3-(6-methyl-2-naphthoyl)piperidine-1-carboxylate**

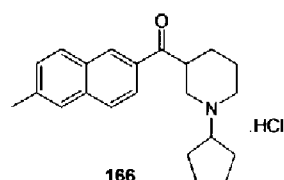
A mixture of *tert*-butyl 3-(6-bromo-2-naphthoyl)piperidine-1-carboxylate (Example 51) (450 mg, 1.10 mmol), $\text{Pd}(\text{PPh}_3)_4$ (112 mg, 0.11 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (411 mg, 3.24 mmol) and Cs_2CO_3 (708 mg, 2.20 mmol) in DMF (10 mL) was heated at 100 °C for 16 h, at which time TLC showed the completion of the reaction. After cooled, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10:1) to give *tert*-butyl 3-(6-methyl-2-naphthoyl)piperidine-1-carboxylate (300 mg, 77% yield).

Step 2:**(1-cyclobutylpiperidin-3-yl)(6-methylnaphthalen-2-yl)methanone hydrochloride**

To the solution of *tert*-butyl 3-(6-methyl-2-naphthoyl)piperidine-1-carboxylate (300 mg, 0.85 mmol) in ethyl acetate (20 mL) was added HCl (2 N in ethyl acetate, 15 mL, 30 mmol). The resulting mixture was stirred at ambient temperature for 1 h and then concentrated under reduced pressure to give crude (6-methylnaphthalen-2-yl) (piperidin-3-yl)methanone hydrochloride (244 mg, 99% yield).

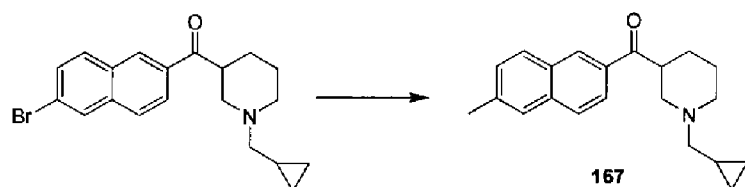
A mixture of (6-methylnaphthalen-2-yl)(piperidin-3-yl)methanone hydrochloride (100 mg, 0.35 mmol), cyclobutanone (50 mg, 0.70 mmol) and Et₃N (0.5 mL) in dichloromethane (10 mL) was stirred at room temperature for 1 h, then NaBH(OAc)₃ (171 mg, 1.04 mmol) was added. The mixture was stirred for another 1 h and then quenched by addition of saturated aqueous NH₄Cl (5 mL). The solution was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by preparative HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% Formic Acid (aq)) to give 28.0 mg (26.4% yield) of the title compound as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 12.54 (br. s, 1 H), 8.56 (s, 1 H), 7.97-7.94 (m, 2 H), 7.79 (d, *J* = 8.4 Hz, 1 H), 7.63 (s, 1 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 4.66-4.64 (m, 1 H), 3.60-3.57 (m, 2 H), 3.41-3.25 (m, 1 H), 2.84-2.79 (m, 3 H), 2.63-2.58 (m, 1 H), 2.53 (s, 3 H), 2.43-2.41 (m, 1 H), 2.29-2.26 (m, 3 H), 1.99-1.96 (m, 3 H), 1.79-1.77 (m, 1 H); LCMS *m/z* 307.8 (M + H).

Example 166:**(1-cyclopentylpiperidin-3-yl)(6-methylnaphthalen-2-yl)methanone**

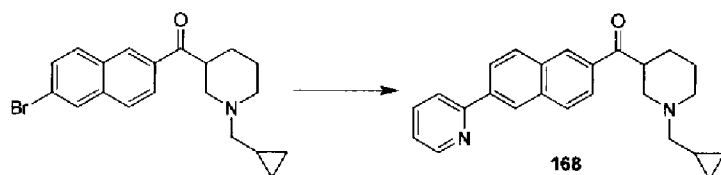
Prepared in an analogous manner to (1-cyclobutylpiperidin-3-yl)(6-methyl naphthalen-2-yl)methanone hydrochloride (example 164), replacing cyclobutanone with cyclopentanone.

¹H NMR (400 MHz, CDCl₃) δ 12.28 (br. s, 1 H), 8.59 (s, 1 H), 7.98-7.96 (m, 2 H), 7.80 (d, *J* = 8.4 Hz, 1 H), 7.63 (s, 1 H), 7.40 (d, *J* = 6.8 Hz, 1 H), 4.79-4.61 (m, 1 H), 3.81-3.65 (m, 2 H), 3.42-3.20 (m, 1 H), 3.05-2.91 (m, 1 H), 2.72-2.58 (m, 2 H), 2.53 (s, 3 H), 2.28-2.14 (m, 5 H), 2.03-1.87 (m, 5 H), 1.63-1.64 (m, 1 H); LCMS *m/z* 321.8 (M + H).

Example 167:**(1-(cyclopropylmethyl)piperidin-3-yl)(6-methylnaphthalen-2-yl)methanone**

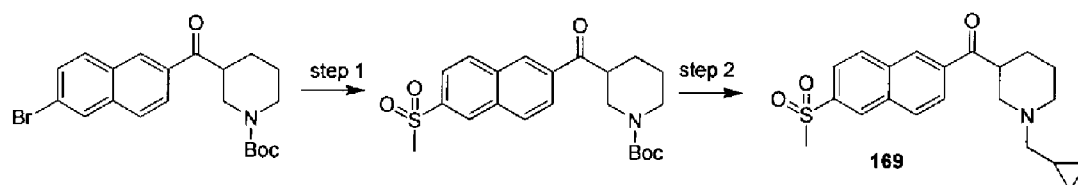
A mixture of (6-bromonaphthalen-2-yl)(1-(cyclopropylmethyl)piperidin-3-yl) methanone (100 mg, 0.27 mmol), Pd(PPh₃)₄ (28 mg, 0.03 mmol), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (108 mg, 0.81 mmol) and Cs₂CO₃ (176 mg, 0.54 mmol) in DMF (10 mL) was heated at 100 °C for 16 h, at which time TLC showed the completion of the reaction. After cooling to room temperature, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by preparative HPLC HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% NH₄OH (aq)) to afford the title compound (19.0 mg, 22.9% yield) as a white solid.

¹H NMR (400 MHz, CDCl₃) δ 8.47 (s, 1 H), 7.99 (dd, *J* = 8.4 Hz, 1.6 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 1 H), 7.80 (d, *J* = 8.4 Hz, 1 H), 7.64 (s, 1 H), 7.39 (d, *J* = 8.4 Hz, 1 H), 3.81-3.79 (m, 1 H), 3.28-3.25 (m, 1 H), 3.16-3.13 (m, 1 H), 2.54 (s, 3 H), 2.36-2.22 (m, 3 H), 2.02-1.95 (m, 2 H), 1.85-1.82 (m, 2 H), 1.56-1.45 (m, 1 H), 0.89-0.87 (m, 1 H), 0.52-0.48 (m, 2 H), 0.11-0.98 (m, 2 H); LCMS *m/z* 308 (M + H).

Example 168**(1-(cyclopropylmethyl)piperidin-3-yl)(6-(pyridin-2-yl)naphthalen-2-yl)methanone**

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl)(6-methyl naphthalen-2-yl)methanone (Example 167), replacing 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane with 2-pyridyl boronic acid.

¹H NMR (400 MHz, CD₃OD) δ 8.96 (d, *J* = 6.0 Hz, 1 H), 8.90-8.88 (m, 1 H), 8.79-8.77 (m, 1 H), 8.67-8.65 (m, 1 H), 8.62-8.60 (m, 1 H), 8.46-8.42 (m, 1 H), 8.24-8.13 (m, 4 H), 4.44-4.32 (m, 1 H), 3.88-3.79 (m, 2 H), 3.17-3.15 (m, 2 H), 3.04-3.00 (m, 1 H), 2.31-2.14 (m, 3 H), 1.80-1.60 (m, 2 H), 1.27-1.23 (m, 1 H), 0.82-0.78 (m, 2 H), 0.54-0.51 (m, 2 H); LCMS *m/z* 370.9 (M + H).

Example 169**(1-(cyclopropylmethyl)piperidin-3-yl)(6-(methylsulfonyl)naphthalen-2-yl)methanone****Step 1:*****tert*-butyl 3-(6-(methylsulfonyl)-2-naphthoyl)piperidine-1-carboxylate**

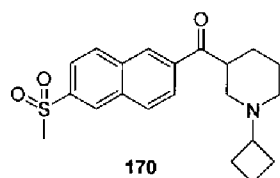
A mixture of *tert*-butyl 3-(6-bromo-2-naphthoyl)piperidine-1-carboxylate (Example 51) (800 mg, 1.92 mmol), NaSO₂Me (391 mg, 3.84 mmol), *S*-proline (350 mg, 1.92 mmol) and CuI (733 mg, 3.84 mmol) in DMSO (30 mL) was heated at 110 °C for 8 h. After cooling to room temperature, the reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10:1) to give *tert*-butyl 3-(6-(methylsulfonyl)-2-naphthoyl)piperidine-1-carboxylate (700 mg, 87.5% yield).

Step 2:**(1-(cyclopropylmethyl)piperidin-3-yl)(6-(methylsulfonyl)naphthalen-2-yl)methanone**

To a solution of *tert*-butyl 3-(6-(methylsulfonyl)-2-naphthoyl)piperidine-1-carboxylate (209 mg, 0.5 mmol) in ethyl acetate (5 mL) was added HCl (2 N in ethyl acetate, 5 mL, 10 mmol). The mixture was stirred at ambient temperature for 1 h and then evaporated under reduced pressure to give crude (6-(methylsulfonyl)naphthalene-2-yl)(piperidin-3-yl)methanone hydrochloride (177 mg, 99% yield).

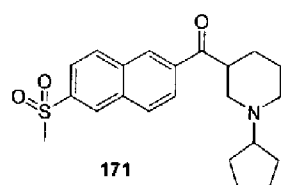
A solution of (6-(methylsulfonyl)naphthalen-2-yl)(piperidin-3-yl)methanone hydrochloride (177 mg, 0.5 mmol), cyclopropanecarbaldehyde (70 mg, 1.0 mmol) and Et₃N (2 mL) in dichloromethane (10 mL) was stirred at room temperature for 1 h before NaBH(OAc)₃ (212 mg, 1.0 mmol) was added. The mixture was stirred for another 1 h and then quenched by the addition of saturated aqueous NH₄Cl (5 mL). The solution was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% NH₄OH (aq)) to provide 39.8 mg (41 % yield) of the title compound.

¹H NMR (400 MHz, CD₃OD) δ 8.79 (s, 1 H), 8.60 (d, *J* = 4.8 Hz, 1 H), 8.32 (t, *J* = 9.2 Hz, 1 H), 8.22-8.16 (m, 2 H), 8.05-8.03 (m, 1 H), 4.38-4.32 (m, 0.5 H), 4.21-4.10 (m, 1 H), 3.86-3.75 (m, 1.5 H), 3.49-3.43 (m, 0.5 H), 3.25 (s, 3 H), 3.15-3.12 (m, 2 H), 3.01-2.96 (m, 1 H), 2.26-2.12 (m, 3 H), 1.86-1.81 (m, 0.5 H), 1.71-1.50 (m, 1 H), 1.23-1.21 (m, 1 H), 0.81-0.77 (m, 2 H), 0.51-0.48 (m, 2 H); LCMS *m/z* 371.8 (M + H).

Example 170:**(1-cyclobutylpiperidin-3-yl)(6-(methylsulfonyl)naphthalen-2-yl)methanone**

10 Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (6-(methylsulfonyl)naphthalen-2-yl)methanone (Example 169), replacing cyclopropanecarbaldehyde with cyclobutanone.

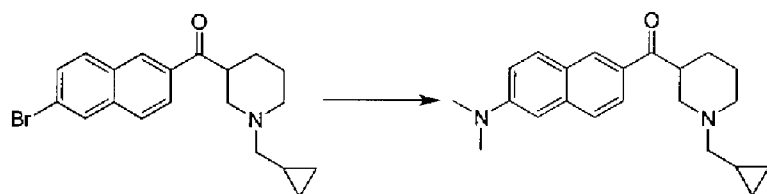
¹H NMR (400 MHz, CD₃OD) δ 8.77 (s, 1 H), 8.62 (d, *J* = 4.4 Hz, 1 H), 8.34 (d, *J* = 8.8 Hz, 1 H), 8.22-8.15 (m, 2 H), 8.06-8.05 (m, 1 H), 4.38-4.35 (m, 0.5 H), 4.14-4.08 (m, 1 H), 3.82-3.51 (m, 3 H), 3.38-3.35 (m, 0.5 H), 3.22 (s, 3 H), 3.14-3.06 (m, 1 H), 2.89-2.72 (m, 1 H), 2.37-2.25 (m, 5 H), 2.12-2.08 (m, 2 H), 1.94-1.87 (m, 2 H), 1.59-1.55 (m, 1 H); LCMS *m/z* 371.9 (M + H).

Example 171**(1-cyclopentylpiperidin-3-yl)(6-(methylsulfonyl)naphthalen-2-yl)methanone**

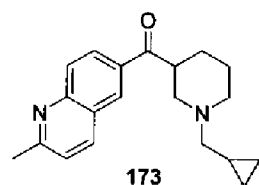
20

Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (6-(methylsulfonyl)naphthalen-2-yl)methanone (Example 169), replacing cyclopropanecarbaldehyde with cyclopentanone.

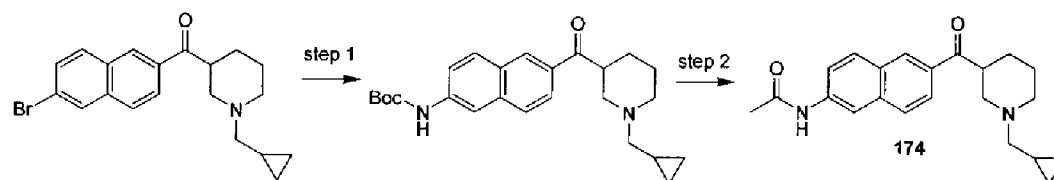
25 ¹H NMR (400 MHz, CD₃OD) δ 8.78 (s, 1 H), 8.61 (s, 1 H), 8.35-8.33 (m, 1 H), 8.23-8.17 (m, 2 H), 8.05 (d, *J* = 8.4 Hz, 1 H), 4.33-4.30 (m, 0.5 H), 4.17-4.11 (m, 1 H), 3.80-3.68 (m, 3 H), 3.64-3.62 (m, 0.5 H), 3.22 (s, 3 H), 2.99-2.95 (m, 1 H), 2.25-2.11 (m, 5 H), 1.85-1.79 (m, 4 H), 1.70-1.53 (m, 3 H); LCMS *m/z* 385.9 (M + H).

Example 172**(1-(cyclopropylmethyl)piperidin-3-yl)(6-(dimethylamino)naphthalen-2-yl)methanone hydrochloride**

- 5 A mixture of (6-bromonaphthalen-2-yl)(1-(cyclopropylmethyl)piperidin-3-yl) methanone (50 mg, 0.13 mmol), dimethylamine hydrochloride (32 mg, 0.39 mmol), Xant-phos (6 mg, 0.01 mmol), Pd₂(dba)₃ (18 mg, 0.02 mmol) and Cs₂CO₃ (127 mg, 0.39 mmol) in dioxane (5.0 mL) was heated at 120 °C for 30 min under microwave conditions. The solvent was evaporated under reduced pressure, and the residue was purified by preparative HPLC (Phenomenx Gemini
10 NX, 20-60% ACN in 0.1% Formic Acid (aq)) to give 2.4 mg (4.8% yield) of the title compound as a white solid.
- ¹H NMR (400 MHz, CD₃OD) δ 8.65 (d, *J* = 9.2 Hz, 1 H), 8.20-7.96 (m, 3 H), 7.64-7.57 (m, 2 H), 4.34-4.32 (m, 1 H), 4.13-4.09 (m, 1 H), 3.79-3.76 (m, 1 H), 3.31 (s, 6 H), 3.30-3.28 (m, 1 H), 3.14-3.01 (m, 3 H), 2.26-2.14 (m, 2 H), 1.97-1.95 (m, 1 H), 1.75-1.65 (m, 1 H), 1.29-1.21
15 (m, 1 H), 0.81-0.79 (m, 2 H), 0.60-0.49 (m, 2 H); LCMS *m/z* 336.9 (*M* + *H*).

Example 173**(1-(cyclopropylmethyl)piperidin-3-yl)(3-methylbenzo[d]isoxazol-6-yl)methanone**

- 20 Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl) (3-methoxyphenyl)methanone (Examples 109a and 109b), replacing 1-bromo-3-methoxybenzene with 6-bromo-2-methylquinoline.
- ¹H NMR (400 MHz, CD₃OD) δ 8.63 (s, 1 H), 8.43 (d, *J* = 8.8 Hz, 1 H), 8.25 (dd, *J* = 8.8 Hz, 1.6 Hz, 1 H), 8.03 (d, *J* = 8.8 Hz, 1 H), 7.54 (d, *J* = 8.8 Hz, 1 H), 3.85-3.82 (m, 1 H), 3.35-3.24 (m, 1
25 H), 3.20-3.17 (m, 1 H), 2.76 (s, 3 H), 2.37-2.36 (m, 2 H), 2.29-2.27 (m, 1 H), 2.06-2.03 (m, 2 H), 1.88-1.85 (m, 2 H), 1.50-1.49 (m, 1 H), 0.94-0.91 (m, 1 H), 0.56-0.53 (m, 2 H), 0.17-0.16 (m, 2 H); LCMS *m/z* 309.2 (*M* + *H*).

Example 174**(1-(cyclopropylmethyl)piperidin-3-yl)(6-(pyridin-2-yl)naphthalen-2-yl)methanone****Step 1:****5 tert-butyl (6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)naphthalen-2-yl) carbamate**

A mixture of (6-bromonaphthalen-2-yl)(1-(cyclopropylmethyl)piperidin-3-yl) methanone (200 mg, 0.54 mmol), *tert*-butyl carbamate (126 mg, 1.08 mmol), Xant-phos (69.5 mg, 0.12 mmol), Pd₂(dba)₃ (55 mg, 0.06 mmol) and Cs₂CO₃ (352 mg, 1.08 mmol) in dioxane (5.0 mL) was heated at 120 °C for 30 min under microwave conditions. The solvent was evaporated under reduced pressure, and the residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 2: 1) to give *tert*-butyl (6-(1-(cyclopropylmethyl) piperidine-3-

10 carbonyl)naphthalene-2-yl) carbamate (150 mg, 68.2% yield).

Step 2:**15 (6-aminonaphthalen-2-yl)(1-(cyclopropylmethyl)piperidin-3-yl)methanone hydrochloride**

To a solution of *tert*-butyl (6-(1-(cyclopropylmethyl)piperidine-3-carbonyl) naphthalen-2-yl)carbamate (150 mg, 0.37 mmol) in ethyl acetate (5 mL) was added HCl (2 N in ethyl acetate, 5.0 mL, 10.0 mmol). The resulting mixture was stirred at ambient temperature for 2 h. The solvent was evaporated under reduced pressure to give the crude (6-aminonaphthalen-2-yl)(1-

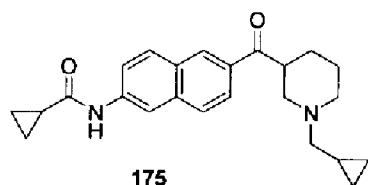
20 (cyclopropylmethyl)piperidin-3-yl) methanone hydrochloride (126 mg, 100% yield) as a white solid.

To a solution of (6-aminonaphthalen-2-yl)(1-(cyclopropylmethyl)piperidin-3-yl) methanone hydrochloride (60 mg, 0.17 mmol) and Et₃N (52 mg, 0.51 mmol) in THF (5 mL) was added acetic anhydride (35 mg, 0.34 mmol). After the addition, the reaction mixture was stirred at

25 ambient temperature for 3 h and then evaporated under reduced pressure. The residue was purified by preparative HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% Formic Acid (aq)) to give 4.9 mg (7.3% yield) of the title compound as a white solid.

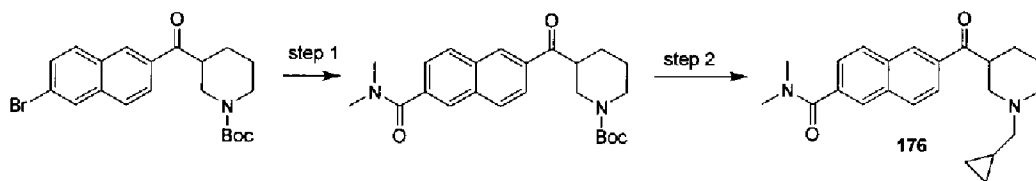
¹H NMR (400 MHz, CD₃OD) δ 8.60 (d, *J* = 11.6 Hz, 1 H), 8.35 (d, *J* = 11.2 Hz, 1 H), 8.05-8.02 (m, 2 H), 7.98-7.90 (m, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 4.13-4.10 (m, 1 H), 3.82-3.79 (m, 1 H), 3.14-3.06 (m, 3 H), 2.30-2.13 (m, 6 H), 1.90-1.60 (m, 2 H), 1.30-1.20 (m, 2 H), 0.82-0.78 (m, 2 H), 0.50-0.48 (m, 2 H); LCMS *m/z* 350.9 (M + H).

30

Example 175:**(1-(cyclopropylmethyl)piperidin-3-yl)(6-(pyridin-2-yl)naphthalen-2-yl)methanone**

Prepared in an analogous manner to *N*-(6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)naphthalen-2-yl)acetamide (Example 174), replacing acetic anhydride with cyclopropanecarbonyl chloride.

^1H NMR (400 MHz, CD_3OD) δ 8.57 (d, $J = 15.6$ Hz, 1 H), 8.31 (d, $J = 7.6$ Hz, 1 H), 8.03-7.96 (m, 2 H), 7.88 (d, $J = 5.2$ Hz, 1 H), 7.69 (d, $J = 8.8$ Hz, 1 H), 4.11-4.08 (m, 1 H), 3.77-3.74 (m, 1 H), 3.13-2.99 (m, 3 H), 2.17-2.10 (m, 3 H), 1.84-1.55 (m, 3 H), 1.28-1.16 (m, 2 H), 1.00-0.99 (m, 2 H), 0.92-0.90 (m, 2 H), 0.80-0.79 (m, 2 H), 0.47-0.46 (m, 2 H); LCMS m/z 377.0 ($M + \text{H}$).

Example 176:**6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-*N,N*-dimethyl-2-naphthamide****Step 1:*****tert*-butyl 3-(6-(dimethylcarbamoyl)-2-naphthoyl)piperidine-1-carboxylate**

A mixture of *tert*-butyl 3-(6-bromo-2-naphthoyl)piperidine-1-carboxylate (300 mg, 0.72 mmol), $\text{Pd}(\text{OAc})_2$ (73 mg, 0.07 mmol), dimethylamine hydrochloride (116.6 mg, 1.44 mmol), Na_2CO_3 (153 mg, 1.44 mmol) and Xantphos (70 mg, 0.14 mmol) in toluene (30 mL) was heated at 80 °C for 16 h under a CO atmosphere. After cooling to room temperature, the reaction mixture was diluted with water (30 mL) and extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 10:1) to give *tert*-butyl 3-(6-(dimethylcarbamoyl)-2-naphthoyl)piperidine-1-carboxylate (260 mg, 87.7% yield).

Step 2:**6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-*N,N*-dimethyl-2-naphthamide**

To a solution of *tert*-butyl 3-(6-(dimethylcarbamoyl)-2-naphthoyl)piperidine-1-carboxylate (205 mg, 0.5 mmol) in ethyl acetate (5 mL) was added HCl (2 N in ethyl acetate, 5 mL, 10 mmol).

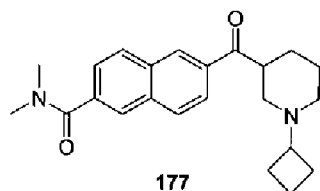
The resulting mixture was stirred at ambient temperature for 1 h and then concentrated under reduced pressure to give crude *N,N*-dimethyl-6-(piperidine-3-carbonyl)-2-naphthamide hydrochloride (173 mg, 99% yield).

A solution of *N,N*-dimethyl-6-(piperidine-3-carbonyl)-2-naphthamide hydrochloride (173 mg, 0.5 mmol), cyclopropanecarbaldehyde (70 mg, 1.0 mmol) and Et₃N (2 mL) in dichloromethane (10 mL) was stirred at room temperature for 1 h before NaBH(OAc)₃ (212 mg, 1.0 mmol) was added. The mixture was stirred for another 1 h and then quenched by the addition of saturated aqueous NH₄Cl (5 mL). The solution was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% NH₄OH (aq)) to give 9.8 mg (12% yield) of the title compound.

¹H NMR (400 MHz, CD₃OD) δ 8.72 (s, 1 H), 8.20 (d, *J* = 8.4 Hz, 1 H), 8.17-8.10 (m, 2 H), 8.03 (s, 1 H), 7.63 (d, *J* = 8.4 Hz, 1 H), 4.37-4.31 (m, 0.5 H), 4.17-4.09 (m, 1 H), 3.83-3.75 (m, 1 H), 3.48-3.39 (m, 0.5 H), 3.16 (s, 3 H), 3.13-3.07 (m, 2 H), 3.04 (s, 3 H), 2.26-2.12 (m, 3 H), 1.82-1.51 (m, 2 H), 1.23-1.18 (m, 1 H), 0.82-0.77 (m, 2 H), 0.51-0.47 (m, 2 H); LCMS *m/z* 364.9 (M + H).

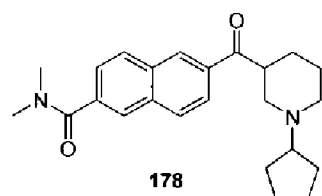
Example 177:

6-(1-cyclobutylpiperidine-3-carbonyl)-*N,N*-dimethyl-2-naphthamide



Prepared in an analogous manner to 6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-*N,N*-dimethyl-2-naphthamide (Example 176), replacing cyclopropanecarbaldehyde with cyclobutanone.

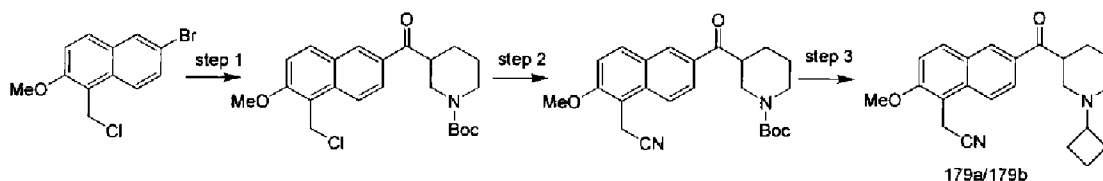
¹H NMR (400 MHz, CD₃OD) δ 8.70 (s, 1 H), 8.19 (d, *J* = 8.4 Hz, 1 H), 8.07-8.02 (m, 3 H), 7.62 (d, *J* = 8.4 Hz, 1 H), 4.12-4.06 (m, 1 H), 3.81-3.49 (m, 3 H), 3.40-3.37 (m, 1 H), 3.16 (s, 3 H), 3.04 (s, 3 H), 2.84-2.77 (m, 1 H), 2.37-2.27 (m, 5 H), 2.23-2.05 (m, 2 H), 1.92-1.87 (m, 2 H), 1.59-1.55 (m, 1 H); LCMS *m/z* 364.9 (M + H).

Example 178**6-(1-cyclobutylpiperidine-3-carbonyl)-*N,N*-dimethyl-2-naphthamide**

Prepared in an analogous manner to 6-(1-(cyclopropylmethyl)piperidine-3-carbonyl)-*N,N*-dimethyl-2-naphthamide (Example 176), replacing cyclopropanecarbaldehyde with cyclopentanone.

¹H NMR (400 MHz, CD₃OD) δ 8.71 (s, 1 H), 8.18 (t, *J* = 8.8 Hz, 1 H), 8.10-8.02 (m, 3 H), 7.62 (d, *J* = 8.4 Hz, 1 H), 4.32-4.16 (m, 1 H), 3.88-3.68 (m, 3 H), 3.63-3.60 (m, 0.5 H), 3.26 (s, 3 H), 3.04 (s, 3 H), 3.01-2.93 (m, 0.5 H), 2.28-2.15 (m, 5 H), 1.98-1.75 (m, 5 H), 1.69-1.50 (m, 3 H);

LCMS *m/z* 378.9 (*M* + *H*).

Examples 179a and 179b:**2-(6-(1-cyclobutylpiperidine-3-carbonyl)-2-methoxynaphthalen-1-yl)acetonitrile****Step 1:*****tert*-butyl 3-(5-(chloromethyl)-6-methoxy-2-naphthoyl) piperidine-1-carboxylate**

To a stirred and cooled (-78 °C) solution of 6-bromo-1-(chloromethyl)-2-methoxy naphthalene (1.5 g, 5.3 mmol) in tetrahydrofuran (50 mL) was added *n*-BuLi (2.5 M in hexane, 2.6 mL, 6.4 mmol). After the addition, stirring at -78 °C was continued for 1 h, and then a solution of *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 19) (1.4 g, 5.3 mmol) in THF (5 mL) was added dropwise. The resulting mixture was warmed to room temperature and stirred for additional 2 h. The mixture was quenched by the addition of saturated aqueous NH₄Cl (30 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 5: 1) to give *tert*-butyl 3-(5-(chloromethyl)-6-methoxy-2-naphthoyl)piperidine-1-carboxylate (1.0 g, 45%) as a yellow solid.

Step 2:***tert*-butyl 3-(5-(cyanomethyl)-6-methoxy-2-naphthoyl)piperidine-1-carboxylate**

To a solution of *tert*-butyl 3-(5-(chloromethyl)-6-methoxy-2-naphthoyl)piperidine-1-carboxylate (1.0 g, 2.4 mmol) in acetonitrile (20 mL) was added TMSCN (0.29 g, 2.9 mmol) and Me₄NF (0.27 g, 2.9 mmol). The reaction mixture was stirred at room temperature for 18 h. The reaction was diluted with water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na₂SO₄) and concentrated under reduced pressure. The crude was purified by silica-gel chromatography (petroleum ether: ethyl acetate = 2: 1) to give *tert*-butyl 3-(5-(cyanomethyl)-6-methoxy-2-naphthoyl)piperidine-1-carboxylate (0.5 g, 51%) as a yellow solid.

Step 3:**2-(2-methoxy-6-(piperidine-3-carbonyl)naphthalen-1-yl)acetonitrile 2,2,2-trifluoroacetate**

To a stirred and cooled (0 °C) solution of *tert*-butyl 3-(5-(cyanomethyl)-6-methoxy-2-naphthoyl)piperidine-1-carboxylate (500 mg, 1.2 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (2 mL). The resulting mixture was stirred at ambient temperature for 2 h and then evaporated under reduced pressure to give crude 2-(2-methoxy-6-(piperidine-3-carbonyl)naphthalen-1-yl)acetonitrile 2,2,2-trifluoroacetate (496 mg, 100%).

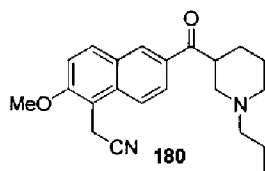
A solution of 2-(2-methoxy-6-(piperidine-3-carbonyl)naphthalen-1-yl)acetonitrile 2,2,2-trifluoroacetate (496 mg, 1.2 mmol), cyclobutanone (85 mg, 1.2 mmol) and Et₃N (2 mL) in dichloromethane (10 mL) was stirred at room temperature for 1 h before NaBH(OAc)₃ (254 mg, 1.2 mmol) was added. The mixture was stirred for another 1 h and then quenched by the addition of saturated aqueous NH₄Cl (10 mL). The solution was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by reverse phase HPLC (Phenomenx Gemini NX, 20-60% ACN in 0.1% NH₄OH (aq)) to afford a racemic mixture of 179a and 179b. The enantiomers were separated by supercritical fluid chromatography (SFC) to provide 88.3 mg of 179a (41% yield) and 64.6 mg (38% yield) of 179b.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 10 µm particle size) at 35% MeOH w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.

179a: ¹H NMR (400 MHz, CDCl₃) δ 8.43 (s, 1 H), 8.05 (d, *J* = 8.8 Hz, 1 H), 7.93 (d, *J* = 9.2 Hz, 1 H), 7.86 (d, *J* = 9.2 Hz, 1 H), 7.30 (d, *J* = 8.8 Hz, 1 H), 4.05 (s, 2 H), 3.98 (s, 3 H), 3.04-2.73 (m, 2 H), 1.99-1.36 (m, 14 H); LCMS *m/z* 363.1 (M + H); SFC retention time: 7.72 min.

179b: ^1H NMR (400 MHz, CDCl_3) δ 8.47 (s, 1 H), 8.09 (d, $J = 8.4$ Hz, 1 H), 7.98 (d, $J = 9.2$ Hz, 1 H), 7.91 (d, $J = 9.2$ Hz, 1 H), 7.35 (d, $J = 9.2$ Hz, 1 H), 4.10 (s, 2 H), 4.03 (s, 3 H), 3.71-3.68 (m, 1 H), 3.08-3.05 (m, 1 H), 2.96-2.94 (m, 1 H), 2.79-2.75 (m, 1 H), 2.01-1.49 (m, 12 H); LCMS m/z 363.1 ($M + H$); SFC retention time: 9.46 min.

5

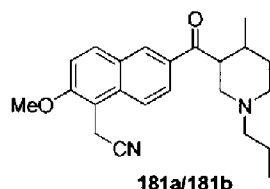
Example 180:**2-(2-methoxy-6-(1-propylpiperidine-3-carbonyl)naphthalen-1-yl)acetonitrile**

Prepared in an analogous manner to 2-(6-(1-cyclobutylpiperidine-3-carbonyl)-2-

10 methoxynaphthalen-1-yl)acetonitrile (Examples 179a and 179b), replacing cyclobutanone with propionaldehyde.

^1H NMR (400 MHz, CDCl_3) δ 8.48 (s, 1 H), 8.11 (d, $J = 8.8$ Hz, 1 H), 8.03-7.88 (m, 2 H), 7.35 (d, $J = 8.4$ Hz, 1 H), 4.11 (s, 2 H), 4.04 (s, 3 H), 3.73-3.71 (m, 1 H), 3.17-2.93 (m, 2 H), 2.36-2.34 (m, 2 H), 2.20-2.14 (m, 1 H), 2.02-2.98 (m, 2 H), 1.85-1.70 (m, 2 H), 1.65-1.45 (m, 3 H), 0.89 (s, 3 H); LCMS m/z 350.9 ($M + H$).

15

Examples 181a and 181b**2-(2-methoxy-6-(4-methyl-1-propylpiperidine-3-carbonyl)naphthalen-1-yl)acetonitrile**

20 Prepared in an analogous manner to 2-(6-(1-cyclobutylpiperidine-3-carbonyl)-2-methoxynaphthalen-1-yl)acetonitrile (Examples 180a and 180b), replacing *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 19) with *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-methylpiperidine-1-carboxylate (Intermediate 10), and cyclobutanone with propionaldehyde. 181a and 181b correspond to the *cis*-enantiomers.

25 SFC conditions: CHIRALPAK AD (250 X 30 mm, 20 μm particle size) at 40% MeOH w/0.1% NH_4OH ; 80 mL/min, 100 bars, 40 $^\circ\text{C}$.

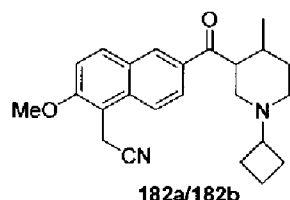
181a: ^1H NMR (400 MHz, CD_3OD) δ 8.71 (s, 1 H), 8.22 (d, $J = 9.2$ Hz, 1 H), 8.13-8.10 (m, 2 H), 7.62 (d, $J = 9.2$ Hz, 1 H), 4.61 (s, 1 H), 4.39-4.37 (m, 1 H), 4.28 (s, 2 H), 4.12 (s, 3 H), 3.51-3.35 (m, 2 H), 3.22-3.16 (m, 2 H), 2.61-2.48 (m, 1 H), 1.88-1.86 (m, 3 H), 1.55-1.31 (m, 2 H),

1.07 (t, $J = 7.6$ Hz, 3 H), 0.90 (d, $J = 6.8$ Hz, 3 H); LCMS m/z 365.2 (M + H); SFC retention time: 8.76 min.

181b: ^1H NMR (400 MHz, CD_3OD) δ 8.70 (s, 1 H), 8.22 (d, $J = 9.2$ Hz, 1 H), 8.13-8.11 (m, 2 H), 7.62 (d, $J = 9.2$ Hz, 1 H), 4.61 (s, 1 H), 4.28 (s, 2 H), 4.12 (s, 3 H), 4.08 (s, 1 H), 3.50-3.32 (m, 2 H), 3.24-3.15 (m, 2 H), 2.22-2.18 (m, 1 H), 1.88-1.86 (m, 3 H), 1.48-1.31 (m, 2 H), 1.05 (t, $J = 7.2$ Hz, 3 H), 0.90 (d, $J = 7.2$ Hz, 3 H); LCMS m/z 365.2 (M + H); SFC retention time: 7.29 min.

Examples 182a and 182b:

2-(6-(1-cyclobutyl-4-methylpiperidine-3-carbonyl)-2-methoxynaphthalen-1-yl)acetonitrile

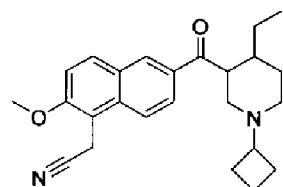


Prepared in an analogous manner to 2-(6-(1-cyclobutylpiperidine-3-carbonyl)-2-methoxynaphthalen-1-yl)acetonitrile (Examples 179a and 179b), replacing *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 19) with *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-methylpiperidine-1-carboxylate (Intermediate 10). 182a and 182b correspond to the *cis*-enantiomers.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μm particle size) at 50% MeOH w/0.1% NH_4OH ; 80 mL/min, 100 bars, 40 $^\circ\text{C}$.

182a: ^1H NMR (400 MHz, CDCl_3) δ 8.41 (s, 1 H), 8.07 (d, $J = 8.8$ Hz, 1 H), 7.99 (d, $J = 8.8$ Hz, 1 H), 7.93 (d, $J = 8.8$ Hz, 1 H), 7.36 (d, $J = 9.2$ Hz, 1 H), 4.12 (s, 2 H), 4.05 (s, 3 H), 3.88-3.85 (m, 1 H), 2.87-2.83 (m, 2 H), 2.78-2.75 (m, 1 H), 2.41-2.38 (m, 2 H), 2.12-2.08 (m, 4 H), 1.92-1.89 (m, 2 H), 1.73-1.70 (m, 3 H), 0.80 (d, $J = 3.2$ Hz, 3 H); LCMS m/z 376.9 (M + H); SFC retention time: 5.07 min.

182b: ^1H NMR (400 MHz, CDCl_3) δ 8.41 (s, 1 H), 8.07 (d, $J = 8.8$ Hz, 1 H), 7.99 (d, $J = 8.8$ Hz, 1 H), 7.93 (d, $J = 8.8$ Hz, 1 H), 7.36 (d, $J = 9.6$ Hz, 1 H), 4.12 (s, 2 H), 4.05 (s, 3 H), 3.88-3.85 (m, 1 H), 2.87-2.83 (m, 2 H), 2.78-2.75 (m, 1 H), 2.41-2.38 (m, 2 H), 2.12-2.08 (m, 4 H), 1.92-1.89 (m, 2 H), 1.73-1.70 (m, 3 H), 0.80 (d, $J = 2.8$ Hz, 3 H); LCMS m/z 376.9 (M + H); SFC retention time: 5.70 min.

Examples 183a, 183b, 183c, and 183d:**2-(6-(1-cyclobutyl-4-ethylpiperidine-3-carbonyl)-2-methoxynaphthalen-1-yl)acetonitrile****183a/183b/183c/183d**

Prepared in an analogous manner to 2-(6-(1-cyclobutylpiperidine-3-carbonyl)-2-

- 5 methoxynaphthalen-1-yl)acetonitrile (Examples 179a and 179b), replacing *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 19) with *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-ethylpiperidine-1-carboxylate (Intermediate 15).

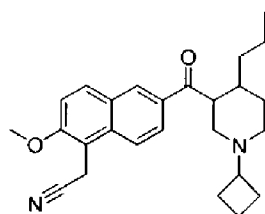
SFC conditions: CHIRALPAK AD (250 x 30 mm, 5 μ m particle size) at 20% MeOH

- 183a:** ^1H NMR (400 MHz, CD_3OD) δ 8.63 (s, 1 H), 8.18 (d, $J = 9.2$ Hz, 1 H), 8.13-8.06 (m, 2 H), 7.58 (d, $J = 9.2$ Hz, 1 H), 4.25 (s, 2 H), 4.09 (s, 3 H), 3.69-3.65 (m, 1 H), 3.06-2.97 (m, 2 H), 2.84-2.80 (m, 1 H), 2.13-2.10 (m, 1 H), 2.00-1.89 (m, 6 H), 1.73-1.71 (m, 3 H), 1.41-1.36 (m, 2 H), 1.38-1.35 (m, 1 H), 0.84 (t, $J = 7.2$ Hz, 3 H); LCMS m/z 391.0 ($M + H$); SFC retention time: 4.75 min.

- 183b:** ^1H NMR (400 MHz, CD_3OD) δ 8.66 (s, 1 H), 8.20 (d, $J = 9.6$ Hz, 1 H), 8.15-8.08 (m, 2 H), 7.60 (d, $J = 9.2$ Hz, 1 H), 4.27 (s, 2 H), 4.11 (s, 3 H), 3.72-3.68 (m, 1 H), 3.07-2.98 (m, 2 H), 2.84-2.82 (m, 1 H), 2.15-2.05 (m, 1 H), 2.01-1.87 (m, 6 H), 1.75-1.73 (m, 3 H), 1.40-1.37 (m, 2 H), 1.40-1.37 (m, 1 H), 0.86 (t, $J = 7.6$ Hz, 3 H); LCMS m/z 391.1 ($M + H$); SFC retention time: 5.10 min.

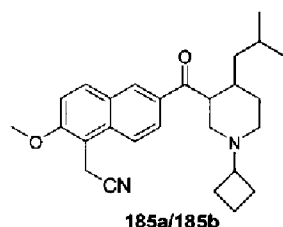
- 183c:** ^1H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1 H), 8.15 (d, $J = 9.2$ Hz, 1 H), 8.06 (s, 2 H), 7.56 (d, $J = 9.2$ Hz, 1 H), 4.24 (s, 2 H), 4.08 (s, 3 H), 3.91-3.89 (m, 1 H), 2.86-2.84 (m, 1 H), 2.80-2.76 (m, 1 H), 2.60-2.56 (m, 1 H), 2.52-2.46 (m, 1 H), 2.15-2.03 (m, 4 H), 1.95-1.86 (m, 4 H), 1.75-1.72 (m, 2 H), 1.47-1.43 (m, 1 H), 1.12-1.10 (m, 1 H), 0.69 (t, $J = 7.6$ Hz, 3 H); LCMS m/z 391.0 ($M + H$); SFC retention time: 5.68 min.

- 183d:** ^1H NMR (400 MHz, CD_3OD) δ 8.56 (s, 1 H), 8.15 (d, $J = 9.2$ Hz, 1 H), 8.06 (s, 2 H), 7.56 (d, $J = 9.2$ Hz, 1 H), 4.24 (s, 2 H), 4.08 (s, 3 H), 3.92-3.89 (m, 1 H), 2.86-2.84 (m, 1 H), 2.80-2.76 (m, 1 H), 2.60-2.56 (m, 1 H), 2.52-2.46 (m, 1 H), 2.15-2.03 (m, 4 H), 1.95-1.86 (m, 4 H), 1.75-1.72 (m, 2 H), 1.47-1.43 (m, 1 H), 1.12-1.10 (m, 1 H), 0.69 (t, $J = 7.6$ Hz, 3 H); LCMS m/z 391.2 ($M + H$); SFC retention time: 6.35 min.

Examples 184a, 184b, 184c, and 184d:**2-(6-(1-cyclobutyl-4-propylpiperidine-3-carbonyl)-2-methoxynaphthalen-1-yl)acetonitrile****184a/184b/184c/184d**

Prepared in an analogous manner to 2-(6-(1-cyclobutylpiperidine-3-carbonyl)-2-

- 5 methoxynaphthalen-1-yl)acetonitrile (Examples 179a and 179b), replacing *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 19) with *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-propylpiperidine-1-carboxylate (Intermediate 13).
- SFC conditions: CHIRALPAK AD (250 x 30 mm, 10 μ m particle size) at 35% MeOH w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.
- 10 **184a:** ¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1 H), 8.08 (d, J = 8.0 Hz, 1 H), 8.01 (d, J = 8.8 Hz, 1 H), 7.94 (d, J = 9.2 Hz, 1 H), 7.37 (d, J = 8.8 Hz, 1 H), 4.13 (s, 2 H), 4.06 (s, 3 H), 3.93-3.91 (m, 1 H), 2.88-2.81 (m, 2 H), 2.50-2.44 (m, 1 H), 2.18-1.95 (m, 9 H), 1.74-1.70 (m, 2 H), 0.98-0.85 (m, 4 H), 0.70 (t, J = 7.6 Hz, 3 H); LCMS m/z 405.0 (M + H); SFC retention time: 8.72 min.
- 15 **184b:** ¹H NMR (400 MHz, CDCl₃) δ 8.41 (s, 1 H), 8.07 (d, J = 9.2 Hz, 1 H), 8.00 (d, J = 9.2 Hz, 1 H), 7.93 (d, J = 8.8 Hz, 1 H), 7.36 (d, J = 9.2 Hz, 1 H), 4.12 (s, 2 H), 4.05 (s, 3 H), 3.90-3.88 (m, 1 H), 2.86-2.82 (m, 2 H), 2.50-2.44 (m, 1 H), 2.08-1.69 (m, 11 H), 1.73-1.69 (m, 1 H), 0.97-0.94 (m, 3 H), 0.69 (t, J = 7.2 Hz, 3 H); LCMS m/z 405.0 (M + H); SFC retention time: 9.46 min.
- 20 **184c:** ¹H NMR (400 MHz, CD₃OD) δ 8.66 (s, 1 H), 8.20 (d, J = 9.2 Hz, 1 H), 8.15-8.08 (m, 2 H), 7.60 (d, J = 9.2 Hz, 1 H), 4.27 (s, 2 H), 4.11 (s, 3 H), 3.68-3.66 (m, 1 H), 3.06-2.97 (m, 2 H), 2.82-2.80 (m, 1 H), 2.15-2.10 (m, 1 H), 2.00-1.88 (m, 7 H), 1.73-1.72 (m, 2 H), 1.41-1.25 (m, 5 H), 0.80 (t, J = 6.8 Hz, 3 H); LCMS m/z 405.0 (M + H); SFC retention time: 7.26 min.
- 25 **184d:** ¹H NMR (400 MHz, CD₃OD) δ 8.63 (s, 1 H), 8.18 (d, J = 9.2 Hz, 1 H), 8.13-8.06 (m, 2 H), 7.57 (d, J = 9.2 Hz, 1 H), 4.25 (s, 2 H), 4.09 (s, 3 H), 3.66-3.63 (m, 1 H), 3.04-2.96 (m, 2 H), 2.80-2.78 (m, 1 H), 2.12-2.08 (m, 1 H), 1.98-1.87 (m, 7 H), 1.70-1.70 (m, 2 H), 1.38-1.14 (m, 5 H), 0.78 (t, J = 7.2 Hz, 3 H); LCMS m/z 405.0 (M + H); SFC retention time: 8.34 min.

Examples 185a and 185b:**2-(6-(1-cyclobutyl-4-isobutylpiperidine-3-carbonyl)-2-methoxynaphthalen-1-yl)acetonitrile**

Prepared in an analogous manner to 2-(6-(1-cyclobutylpiperidine-3-carbonyl)-2-

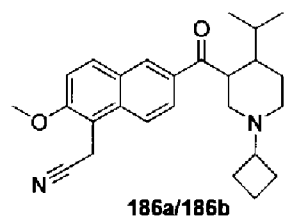
- 5 methoxynaphthalen-1-yl)acetonitrile (Examples 179a and 179b), replacing *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 19) with *tert*-butyl 3-(methoxy(methyl)carbamoyl)-4-isobutylpiperidine-1-carboxylate (Intermediate 14).

SFC conditions: CHIRALPAK OD (250 x 30 mm, 5 μ m particle size) at 30% MeOH

w/0.1%NH₄OH; 50 mL/min, 100 bars, 40 °C. 185a and 185b correspond to the *cis*-enantiomers.

- 10 **185a:** ¹H NMR (400 MHz, CD₃OD) δ 8.46 (s, 1 H), 8.09-8.05 (m, 1 H), 7.98 (d, *J* = 8.8 Hz, 2 H), 7.46 (d, *J* = 9.2 Hz, 1 H), 4.15 (s, 2 H), 3.98 (s, 3 H), 3.83-3.80 (m, 1 H), 2.86-2.80 (m, 1 H), 2.72-2.69 (m, 1 H), 2.52-2.61 (m, 1H), 2.41-2.25 (m, 1 H), 2.20-2.11 (m, 1 H), 2.09-1.91 (m, 3 H), 1.89-1.81 (m, 3 H), 1.67-1.65 (m, 3 H), 1.28-1.24 (m, 3 H), 0.82-0.63 (m, 3 H), 0.33 (d, *J* = 6.0 Hz, 3 H); LCMS *m/z* 419.0 (M + H); SFC retention time: 4.61 min.
- 15 **185b:** ¹H NMR (400 MHz, CD₃OD) δ 8.55 (s, 1 H), 8.15 (d, *J* = 9.2 Hz, 1 H), 8.06 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 9.2 Hz, 1 H), 4.24 (s, 2 H), 4.07 (s, 3 H), 3.91-3.87 (m, 1 H), 2.93-2.82 (m, 1 H), 2.80-2.75 (m, 1 H), 2.69-2.61 (m, 1H), 2.47-2.36 (m, 1 H), 2.31-2.21 (m, 1 H), 2.20-2.05 (m, 3 H), 1.97-1.89 (m, 3 H), 1.76-1.73 (m, 3 H), 1.37-1.33 (m, 3 H), 0.87-0.72 (m, 3 H), 0.41 (d, *J* = 6.4 Hz, 3 H); LCMS *m/z* 419.1 (M + H); SFC retention time: 5.26 min.

20

Examples 186a and 186b**2-(6-(1-cyclobutyl-4-isopropylpiperidine-3-carbonyl)-2-methoxynaphthalen-1-yl)acetonitrile**

- 25 Prepared in an analogous manner to 2-(6-(1-cyclobutylpiperidine-3-carbonyl)-2-methoxynaphthalen-1-yl)acetonitrile (Examples 179a and 179b), replacing *tert*-butyl 3-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (Intermediate 19) with *tert*-butyl 3-

(methoxy(methyl)carbamoyl)-4-isopropylpiperidine-1-carboxylate (Intermediate 17). 186a and 186b correspond to the *cis*-enantiomers.

SFC conditions: CHIRALPAK AD (250 x 30 mm, 10 μ m particle size) at 15% IPA

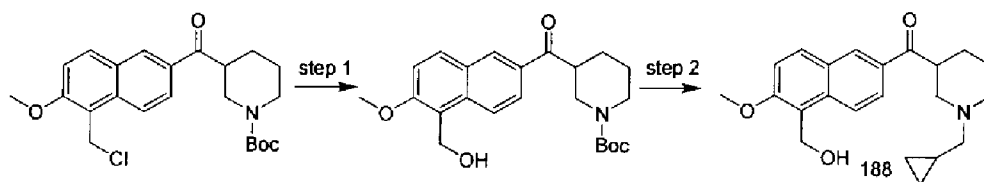
w/0.1%NH₄OH; 80 mL/min, 100 bars, 40 °C.

- 5 **186a**: ¹H NMR (400 MHz, CD₃OD) δ 8.52 (s, 1 H), 8.13-8.03 (m, 3 H), 7.58-7.45 (m, 1 H), 4.24 (s, 2 H), 4.07 (s, 3 H), 4.01-3.98 (m, 1 H), 3.11-3.08 (m, 1 H), 2.83-2.78 (m, 1 H), 2.63-2.51 (m, 1H), 2.21-2.12 (m, 2 H), 1.91-1.76 (m, 6 H), 1.54-1.52 (m, 2 H), 1.45-1.21 (m, 2 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 6.4 Hz, 3 H); LCMS *m/z* 404.9 (M + H); SFC retention time: 1.84 min.
- 10 **186b**: ¹H NMR (400 MHz, CD₃OD) δ 8.52 (s, 1 H), 8.13-8.03 (m, 3 H), 7.53 (d, *J* = 9.2 Hz, 1 H), 4.23 (s, 2 H), 4.06 (s, 3 H), 4.00-3.99 (m, 1 H), 3.10-3.07 (m, 1 H), 2.89-2.81 (m, 1 H), 2.61-2.56 (m, 1H), 2.20-2.16 (m, 2 H), 1.90-1.70 (m, 6 H), 1.62-1.45 (m, 2 H), 1.41-1.30 (m, 2 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 6.8 Hz, 3 H); LCMS *m/z* 405.0 (M + H); SFC retention time: 4.26 min.

15

Example 188

(1-(cyclopropylmethyl)piperidin-3-yl)(5-(hydroxymethyl)-6-methoxynaphthalen-2-yl)methanone hydrochloride



20 Step 1:

***tert*-butyl 3-(5-(hydroxymethyl)-6-methoxy-2-naphthoyl)piperidine-1-carboxylate**

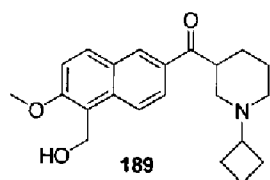
- To a solution of *tert*-butyl 3-(5-(chloromethyl)-6-methoxy-2-naphthoyl)piperidine-1-carboxylate (Examples 71a and 71b) (600 mg, 1.44 mmol) in dioxane (30 mL) and H₂O (30 mL) was added CaCO₃ (720 mg, 7.2 mmol). The reaction mixture was heated at 85 °C for 12 h. The mixture
- 25 was filtered while hot and the filtrate was concentrated under reduced pressure to give crude *tert*-butyl 3-(5-(hydroxymethyl)-6-methoxy-2-naphthoyl) piperidine-1-carboxylate (550 mg, 95.6% yield).

Step 2:**(1-(cyclopropylmethyl)piperidin-3-yl)(5-(hydroxymethyl)-6-methoxynaphthalen-2-yl)methanone hydrochloride**

To a solution of *tert*-butyl 3-(5-(hydroxymethyl)-6-methoxy-2-naphthoyl)piperidine-1-carboxylate (200 mg, 0.5 mmol) in ethyl acetate (5 mL) was added HCl (2 N in ethyl acetate, 5 mL, 10 mmol). The resulting mixture was stirred at ambient temperature for 1 h and then concentrated under reduced pressure to give crude (5-(hydroxymethyl)-6-methoxynaphthalen-2-yl)(piperidin-3-yl)methanone hydrochloride (168 mg, 99% yield).

A solution of (5-(hydroxymethyl)-6-methoxynaphthalen-2-yl)(piperidin-3-yl) methanone hydrochloride (168 mg, 0.5 mmol), cyclopropanecarbaldehyde (70 mg, 1.0 mmol) and Et₃N (2 mL) in dichloromethane (10 mL) was stirred at room temperature for 1 h before NaBH(OAc)₃ (212 mg, 1.0 mmol) was added. The mixture was stirred for another 1 h and then quenched by the addition of saturated aqueous NH₄Cl (10 mL). The solution was extracted with dichloromethane (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure. The residue was purified by reverse phase HPLC to provide 3.0 mg (2% yield) of the title compound.

¹H NMR (400 MHz, DMSO-*d*₆) δ 10.3 (br. s, 1 H), 8.39-8.30 (m, 1 H), 7.88-7.77 (m, 2 H), 7.67-7.65 (m, 1 H), 7.25-7.20 (m, 1 H), 4.84 (s, 2 H), 3.89-3.80 (m, 1 H), 3.64-3.57 (m, 3 H), 3.29-3.22 (m, 2 H), 2.75-2.52 (m, 4 H), 1.73-1.55 (m, 3 H), 1.12-1.01 (m, 1 H), 0.80-0.69 (m, 1 H), 0.24-0.23 (m, 2 H), 0.02-0.00 (m, 2 H); LCMS *m/z* 353.9 (M + H).

Example 189:**(1-cyclobutylpiperidin-3-yl)(5-(hydroxymethyl)-6-methoxynaphthalen-2-yl)methanone hydrochloride**

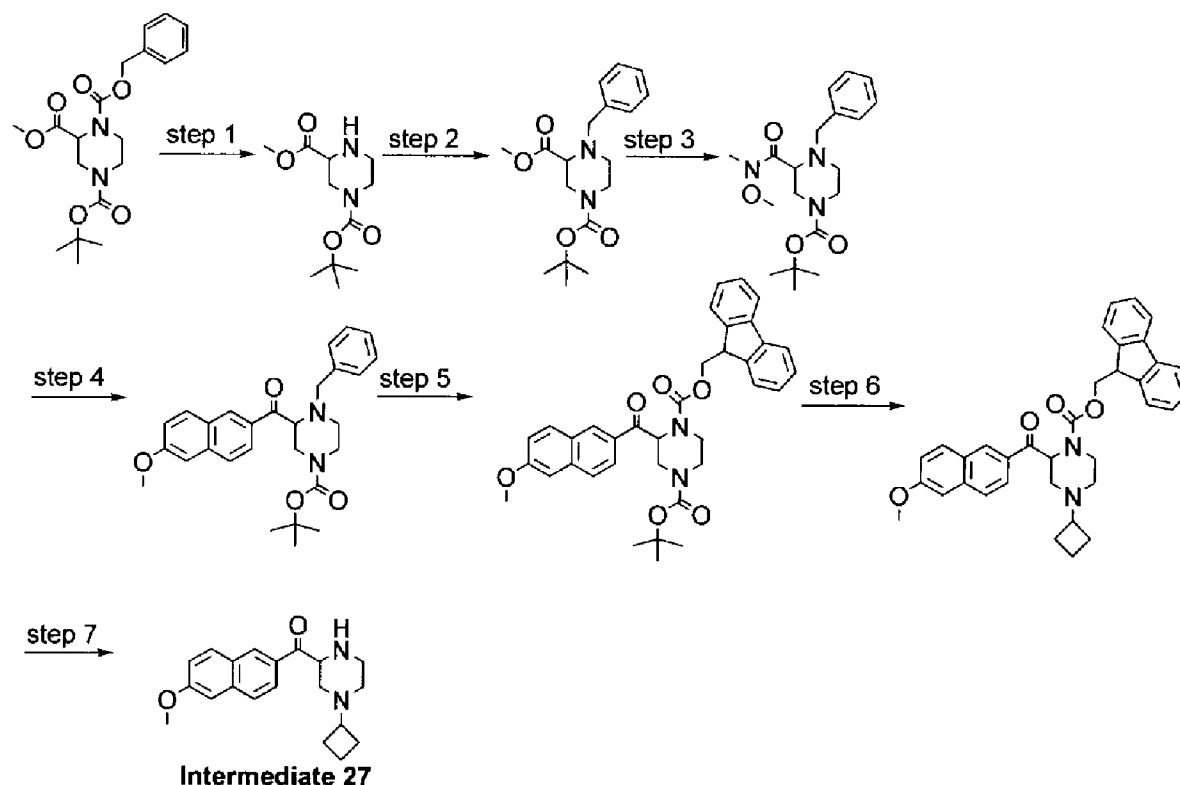
Prepared in an analogous manner to (1-(cyclopropylmethyl)piperidin-3-yl)(5-(hydroxymethyl)-6-methoxynaphthalen-2-yl)methanone hydrochloride (Example 184), replacing cyclopropanecarbaldehyde with cyclobutanone.

¹H NMR (400 MHz, DMSO-*d*₆) δ 11.1 (br. s, 1 H), 8.71 (s, 1 H), 8.26-8.23 (m, 1 H), 8.17-8.15 (m, 1 H), 8.04-8.02 (m, 1 H), 7.63-7.60 (m, 1 H), 5.22 (s, 2 H), 4.23-4.17 (m, 1 H), 4.02 (s, 3 H),

3.65-3.61 (m, 1 H), 2.92-2.89 (m, 2 H), 2.75-2.61 (m, 2 H), 2.44-2.37 (m, 2 H), 2.18-2.09 (m, 4 H), 1.93-1.89 (m, 1 H), 1.75-1.60 (m, 2 H), 1.55-1.45 (m, 1 H); LCMS m/z 353.9 (M + H).

Synthesis of Intermediates

5 Intermediate 27 : (4-cyclobutylpiperazin-2-yl)(6-methoxynaphthalen-2-yl)methanone



Step 1:

1-tert-butyl 3-methyl piperazine-1,3-dicarboxylate

- 10 1-benzyl 4-tert-butyl 2-methyl piperazine-1,2,4-tricarboxylate (10.0 g, 73.0 mmol) was dissolved in 150 ml of methanol and eluted over a cartridge of 10% Pd/C charged with H₂ at a pressure of 20 bar. The eluent was then concentrated in vacuo to afford the crude desired product.

15 Step 2:

1-tert-butyl 3-methyl 4-benzylpiperazine-1,3-dicarboxylate

- To a solution of 1-tert-butyl 3-methyl piperazine-1,3-dicarboxylate (10.0 g, 70 mmol) in THF (200 mL) was added triethyl amine and benzyl bromide. The mixture was then stirred at room temperature for 12 hours and concentrated in vacuo. The residue was then diluted with ethyl acetate and water. The aqueous layer was discarded and the organic layer was washed once with
- 20

water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was then purified by silica-gel chromatography (0 - 10 % MeOH in DCM) to afford the desired product.

Step 3:

5 1-*tert*-butyl 3-methyl 4-benzylpiperazine-1,3-dicarboxylate

To a mixture of *N,O*-Dimethylamine Hydrochloride (3.5g, 36 mmol) cooled to -78°C in THF (100 ml) was added a 2M isopropyl magnesium chloride in THF solution (36 ml, 72 mmol) dropwise. After addition, stirring was continued at -78°C for 5 minutes. The mixture was then warmed to 0°C and stirred at □°C for 5 minutes. The mixture was then re-cooled to -78°C and charged dropwise with a solution of 1-*tert*-butyl 3-methyl 4-benzylpiperazine-1,3-dicarboxylate (6.0 g, 18 mmol) in 20ml of THF. The mixture was then warmed to room temperature and stirred at room temperature for 30 minutes. The mixture was then diluted with ethyl acetate and water. The aqueous layer was discarded and the organic layer was washed once with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was then purified by silica-gel chromatography (1 -10% MeOH in DCM) to afford the title compound (6.5 g, 100% yield).

Step 4:

1-*tert*-butyl 4-benzyl-3-(6-methoxy-2-naphthoyl)piperazine-1-carboxylate

A solution of 2-bromo-6-methoxynaphthalene (3.9 g, 17 mmol) in THF was cooled to -78°C and charged with 2.5 M *n*-BuLi (7 ml, 17.5 mmol). The mixture was then stirred at -78°C for 5 minutes and then charged dropwise with a solution of 1-*tert*-butyl 3-methyl 4-benzylpiperazine-1,3-dicarboxylate (1.5g, 4.1 mmol) in 5ml of THF. The mixture was then warmed to room temperature and stirred at room temperature for 30 minutes. The mixture was then diluted with ethyl acetate and 1M NaHCO₃. The aqueous layer was discarded and the organic was washed once with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was then purified by silica-gel chromatography (1 -10% MeOH in DCM) to afford the title compound (1.52 g, 80 % yield).

Step 5:

30 1-(9H-fluoren-9-yl) methyl-4-*tert*-butyl-2-(6-methoxy-2-naphthoyl) piperazine-1,4-dicarboxylate

A solution of 1-*tert*-butyl-4-benzyl-3-(6-methoxy-2-naphthoyl)piperazine-1-carboxylate (640 mg, 1.4 mmol) in 5ml of DCM was charged with (9H-fluoren-9-yl)methyl chloroformate (1.4g, 5.6 mmol) and heated at 120°C for 3 hours. The mixture was then directly loaded onto silica

and purified by silica-gel chromatography (25 to 50% ethyl acetate in heptane) to afford the title compound (500 mg, 60% yield).

Step 6:

5 (9H-fluoren-9-yl)methyl-4-cyclobutyl-2-(6-methoxy-2-naphthoyl)piperazine-1-carboxylate

A solution of 1-(9H-fluoren-9-yl) methyl-4-*tert*-butyl-2-(6-methoxy-2-naphthoyl)piperazine-1,4-dicarboxylate (750 mg, 1.5 mmol) was dissolved in 5 ml of DCM and charged with 5 ml of TFA. The mixture was then stirred at room temperature for 1 hour, concentrated in vacuo, and azeotroped twice with methanol.

- 10 The crude residue was then diluted with 5 ml of DCM and charged with cyclobutanone (420 mg, 6.0 mmol) and sodium triacetoxyborohydride (1.3 g, 6.0 mmol). The mixture was then stirred at room temperature for one hour and concentrated in vacuo. The residue was then diluted with ethyl acetate and water. The aqueous was discarded and the organic was washed once with water, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was then purified by
15 silica-gel chromatography (1 -10% MeOH in DCM) to afford the title compound.

Step 7:

(4-cyclobutylpiperazin-2-yl)(6-methoxynaphthalen-2-yl)methanone

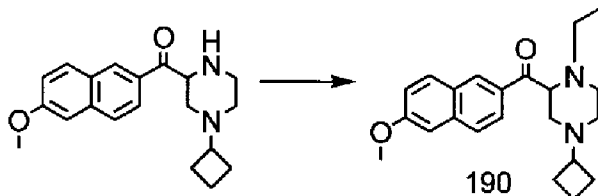
9H-fluoren-9-ylmethyl

- 20 To a solution of 4-cyclobutyl-2-(6-methoxynaphthalene-2-carbonyl)piperazine-1-carboxylate (150 mg, 0.27 mmol) in 500 ul of DCM was added 500 ul of Diethylamine. The mixture was stirred at room temperature for one hour and concentrated in vacuo to afford the title compound (100 mg, 100 % yield).

25 Synthesis of Final Compounds:

Example 190:

4-cyclobutyl-1-ethyl-piperazin-2-yl)-(6-methoxy-2-naphthyl)methanone



To a solution of (4-cyclobutylpiperazin-2-yl)-(6-methoxy-2-naphthyl)methanone (30 mg, 0.09 mmol) in 200 μ l of THF was added triethylamine (47 mg, 0.46 mmol) and iodoethane (72 mg, 0.46 mmol). The mixture was then stirred at room temperature for one hour. It was then diluted with ethyl acetate and saturated NaHCO_3 . The aqueous layer was discarded and the organic layer was dried over magnesium sulfate and concentrated in vacuo. The residue was then purified by silica-gel chromatography (0-10% MeOH in DCM) to afford the title compound (12 mg, 30% yield). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.80 (s, 1H), 8.04 (dd, $J = 9.0, 2.7$ Hz, 2H), 7.94 – 7.70 (m, 2H), 7.40 (d, $J = 2.6$ Hz, 1H), 7.26 (dd, $J = 8.9, 2.5$ Hz, 1H), 4.09 (s, 1H), 3.92 (s, 3H), 3.28 (s, 1H), 3.12 (d, $J = 11.0$ Hz, 1H), 2.68 (t, $J = 7.3$ Hz, 1H), 2.66 – 2.51 (m, 3H), 2.37 – 2.25 (m, 2H), 2.18 (dt, $J = 19.5, 10.0$ Hz, 2H), 2.05 – 1.94 (m, 1H), 1.79 – 1.51 (m, 3H), 0.96 (dt, $J = 21.1, 7.2$ Hz, 3H). $M+1$ (m/z) = 353.2.

The following compounds were prepared in a manner similar to Example 190.

Example	Compound Name	^1H NMR	m/z ($M+H$)
191	(1-benzyl-4-cyclobutyl-piperazin-2-yl)-(6-methoxy-2-naphthyl)methanone	^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ 8.79 (s, 1H), 8.10 – 8.00 (m, 1H), 7.91 (d, $J = 8.8$ Hz, 1H), 7.41 (d, $J = 2.5$ Hz, 1H), 7.37 – 7.17 (m, 1H), 5.75 (s, 1H), 4.24 (s, 1H), 3.92 (s, 3H), 3.78 (d, $J = 13.4$ Hz, 1H), 3.36 (d, $J = 13.4$ Hz, 1H), 3.28 (s, 0H), 2.93 (s, 1H), 2.73 – 2.65 (m, 2H), 2.51 (s, 2H), 2.32 (dt, $J = 21.1, 9.6$ Hz, 2H), 2.15 (t, $J = 9.7$ Hz, 1H), 1.76 – 1.67 (m, 1H), 1.57 (s, 3H).	415

192	[4-cyclobutyl-1-(cyclopropylmethyl)piperazin-2-yl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.78 (s, 1H), 8.08 – 7.95 (m, 2H), 7.95 – 7.66 (m, 2H), 7.43 – 7.15 (m, 1H), 5.75 (s, 1H), 4.17 (s, 1H), 3.90 (d, <i>J</i> = 8.3 Hz, 2H), 3.37 (q, <i>J</i> = 7.2 Hz, 2H), 3.27 (s, 2H), 3.21 (s, 1H), 3.01 (s, 1H), 2.73 – 2.54 (m, 3H), 2.49 – 2.39 (m, 2H), 2.14 (dd, <i>J</i> = 12.6, 7.2 Hz, 1H), 2.07 – 1.94 (m, 1H), 1.79 – 1.53 (m, 2H), 1.23 (t, <i>J</i> = 7.2 Hz, 3H), 1.04 – 0.94 (m, 1H), 0.45 – 0.29 (m, 1H), 0.38 (s, 1H), 0.06 (d, <i>J</i> = 5.4 Hz, 1H), -0.08 (d, <i>J</i> = 4.6 Hz, 2H).	440
193	3-[[4-cyclobutyl-2-(6-methoxynaphthalene-2-carbonyl)piperazin-1-yl]methyl]benzonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.74 (s, 1H), 8.07 (d, <i>J</i> = 9.1 Hz, 1H), 8.03 – 7.95 (m, 1H), 7.90 (d, <i>J</i> = 8.6 Hz, 1H), 7.74 – 7.61 (m, 4H), 7.51 (q, <i>J</i> = 8.1 Hz, 1H), 7.41 (d, <i>J</i> = 2.6 Hz, 1H), 7.27 (dd, <i>J</i> = 9.0, 2.5 Hz, 1H), 3.92 (s, 3H), 3.81 (d, <i>J</i> = 14.2 Hz, 1H), 3.48 (d, <i>J</i> = 14.1 Hz, 1H), 3.29 (d, <i>J</i> = 18.7 Hz, 4H), 2.69 (d, <i>J</i> = 10.5 Hz, 3H), 2.36 (s, 2H), 2.20 (d, <i>J</i> = 10.7 Hz, 1H), 1.72 (d, <i>J</i> = 10.0 Hz, 1H), 1.56 (s, 4H), 1.24 (s, 1H).	338

194	(4-cyclobutyl-1-methyl-piperazin-2-yl)-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.78 (s, 1H), 8.10 – 7.99 (m, 2H), 7.89 (d, <i>J</i> = 8.6 Hz, 1H), 7.40 (d, <i>J</i> = 2.5 Hz, 1H), 7.26 (dd, <i>J</i> = 8.9, 2.5 Hz, 1H), 3.92 (s, 3H), 2.95 (d, <i>J</i> = 11.2 Hz, 1H), 2.69 (dt, <i>J</i> = 21.4, 8.9 Hz, 3H), 2.32 (t, <i>J</i> = 10.8 Hz, 1H), 2.19 – 2.02 (m, 5H), 1.88 (s, 2H), 1.71 (td, <i>J</i> = 18.0, 17.2, 8.0 Hz, 2H), 1.62 – 1.52 (m, 2H), 1.28 – 1.15 (m, 1H).	440
195	2-[[4-cyclobutyl-2-(6-methoxynaphthalene-2-carbonyl)piperazin-1-yl]methyl]benzonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.65 (s, 1H), 8.05 (d, <i>J</i> = 9.0 Hz, 1H), 7.98 – 7.86 (m, 2H), 7.76 (t, <i>J</i> = 6.5 Hz, 1H), 7.67 (s, 1H), 7.75 – 7.56 (m, 2H), 1H, 4.66 (d, <i>J</i> = 5.5 Hz, 1H), 4.10 – 3.95 (m, 2H), 3.92 (s, 3H), 3.27 (s, 2H), 3.17 (d, <i>J</i> = 5.2 Hz, 2H), 2.65 (t, <i>J</i> = 7.5 Hz, 1H), 2.58 (s, 1H), 2.51 – 2.42 (m, 1H), 2.31 (s, 3H), 1.66 (q, <i>J</i> = 9.2 Hz, 1H), 1.51 (s, 1H), 1.52 – 1.39 (m, 1H), 1.23 (s, 1H), 0.98 (t, <i>J</i> = 7.1 Hz, 1H).	429
196	[4-cyclobutyl-1-(p-tolylmethyl)piperazin-2-yl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (s, 1H), 8.10 – 7.98 (m, 1H), 7.97 – 7.80 (m, 2H), 7.17 – 7.01 (m, 6H), 4.18 (d, <i>J</i> = 7.9 Hz, 1H), 3.92 (s, 3H), 3.96 – 3.82 (m, 1H), 3.17 (s, 2H), 2.96 – 2.87 (m, 1H), 2.76 – 2.60 (m, 3H), 2.37 – 2.24 (m, 1H), 2.25 (s, 1H), 1.88 (d, <i>J</i> = 15.9 Hz, 1H), 1.78 – 1.66 (m, 1H), 1.60 – 1.50 (m, 3H), 1.23 (s, 1H), 1.14 – 0.94 (m, 1H).	429

197	[4-cyclobutyl-1-(2-naphthylmethyl)piperazin-2-yl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.82 (s, 1H), 8.06 (t, <i>J</i> = 8.8 Hz, 2H), 7.99 – 7.66 (m, 4H), 7.59 – 7.34 (m, 5H), 7.27 (dd, <i>J</i> = 9.0, 2.6 Hz, 1H), 4.30 (s, 1H), 3.93 (d, <i>J</i> = 18.7 Hz, 1H), 3.92 (s, 3H), 3.29 – 3.14 (m, 4H), 2.98 (d, <i>J</i> = 12.2 Hz, 1H), 2.89 (s, 3H), 2.19 (d, <i>J</i> = 10.0 Hz, 1H), 1.86 (s, 3H), 1.57 (s, 4H), 1.24 (s, 2H).	465
198	[4-cyclobutyl-1-[[3-(trifluoromethyl)phenyl]methyl]piperazin-2-yl]-(6-methoxy-2-naphthyl)methanone	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.79 (s, 1H), 8.10 – 7.98 (m, 2H), 7.97 – 7.80 (m, 2H), 7.46 – 7.17 (m, 3H), 7.17 – 7.01 (m, 6H), 4.18 (d, <i>J</i> = 7.9 Hz, 1H), 3.92 (s, 3H), 3.96 – 3.82 (m, 1H), 3.78 – 3.68 (m, 1H), 3.17 (s, 2H), 2.96 – 2.87 (m, 1H), 2.76 – 2.60 (m, 3H), 2.37 – 2.24 (m, 1H), 2.25 (s, 3H), 2.13 (t, <i>J</i> = 10.3 Hz, 1H), 1.88 (d, <i>J</i> = 15.9 Hz, 3H), 1.78 – 1.66 (m, 1H), 1.60 – 1.50 (m, 3H), 1.23 (s, 1H), 1.14 – 0.94 (m, 1H).	483

199	4-[[4-cyclobutyl-2-(6-methoxynaphthalene-2-carbonyl)piperazin-1-yl]methyl]benzonitrile	¹ H NMR (400 MHz, DMSO- <i>d</i> ₆) δ 8.72 (s, 1H), 8.06 (d, <i>J</i> = 9.0 Hz, 1H), 8.02 – 7.95 (m, 1H), 7.90 (d, <i>J</i> = 8.7 Hz, 1H), 7.75 (dd, <i>J</i> = 8.0, 1.6 Hz, 2H), 7.56 – 7.49 (m, 2H), 7.40 (d, <i>J</i> = 2.5 Hz, 1H), 7.27 (dd, <i>J</i> = 8.9, 2.5 Hz, 1H), 4.05 (q, <i>J</i> = 5.3 Hz, 3H), 3.85 (d, <i>J</i> = 14.4 Hz, 1H), 3.52 (d, <i>J</i> = 14.5 Hz, 1H), 3.17 (dd, <i>J</i> = 5.3, 1.5 Hz, 3H), 2.94 (s, 1H), 2.68 (d, <i>J</i> = 10.3 Hz, 2H), 2.43 (s, 1H), 2.20 (d, <i>J</i> = 9.6 Hz, 1H), 1.84 (s, 2H), 1.71 (d, <i>J</i> = 10.2 Hz, 1H), 1.55 (s, 3H).	440
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EXAMPLE 200

5 *KDM2B TR-FRET Assay for determining inhibitor IC₅₀*

Full length KDM2B was cloned, expressed, and purified to homogeneity. Compound inhibition of KDM2B demethylase activity was assessed by monitoring the methylation status of a biotin-H3K36me₂ peptide substrate (H₂N-RKSAPATGGV(KMe₂)KPHRYRPGTV-NTPEGBiot; New England Peptide) in the presence of α -ketoglutarate (2-OG) and iron (Fe²⁺) using the TR-FRET assay technology (Cisbio). Specifically, in a 384 well ProxiPlate KDM2B (5 mM final), ascorbate (500 μ M final) and DTT (2 mM final) were combined with the biotin-H3K36me₂ peptide substrate (200 nM final), 2-OG (0.3 μ M or 6 μ M final; Sigma K2010) and Fe²⁺ (100 μ M final; Sigma F1543) in 50 mM HEPES (pH 6.5) and 0.01% Triton-X 100 either in the presence of DMSO (final 0.25% DMSO) or compound dilution series in DMSO and mixed.

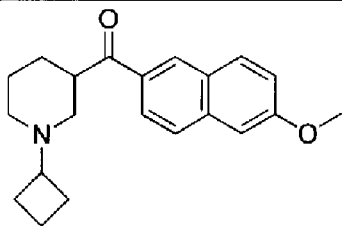
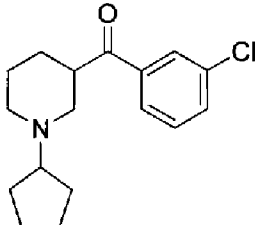
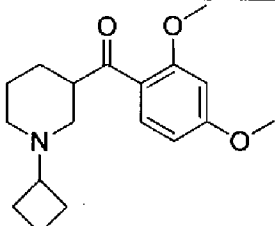
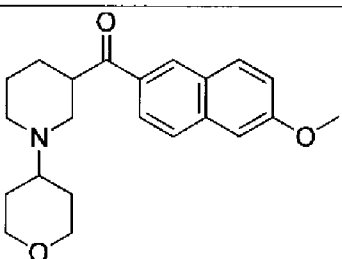
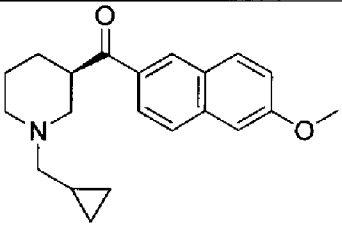
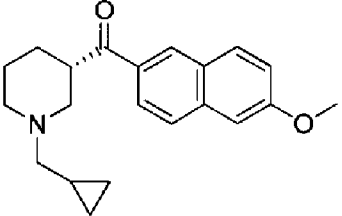
15 After a two hour incubation at room temperature, a mixture of EU-anti-H3K36me₁ antibody (2 nM final; Cisbio #64CUSKAZ), and Streptavidin-d₂ (50 nM final; Cisbio #64CUS000) in 200 mM KF, 200 mM EDTA, 0.1% BSA and 50 mM HEPES (pH 6.5) was added. After 1 hour incubation, the plates were read on an Envision instrument, the readouts were transformed into % inhibition, and IC₅₀ values were generated using a four parameter logistic model (XLFIT5).

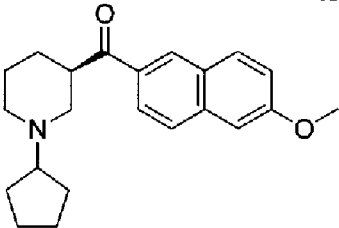
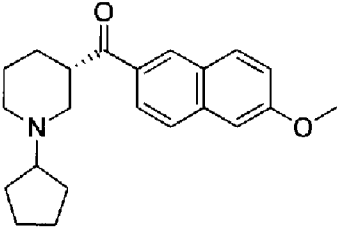
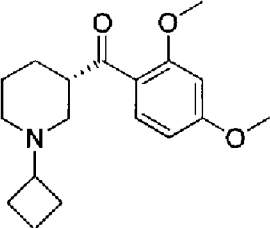
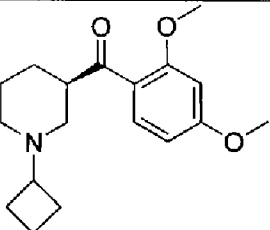
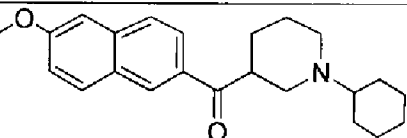
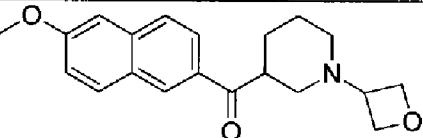
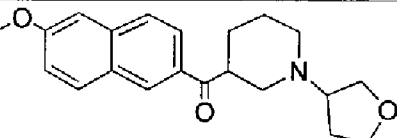
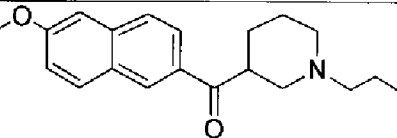
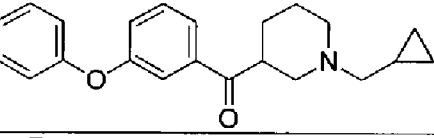
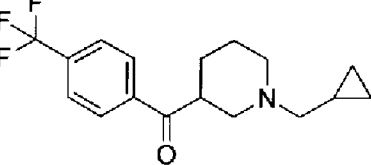
20 The KDM2B TR-FRET Assay described above represents an additional embodiment of the invention.

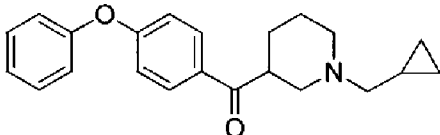
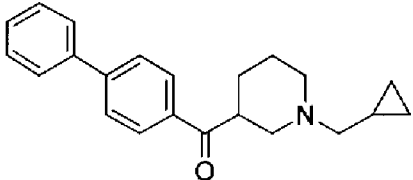
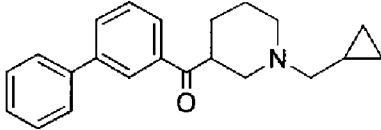
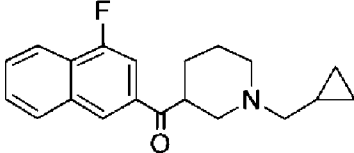
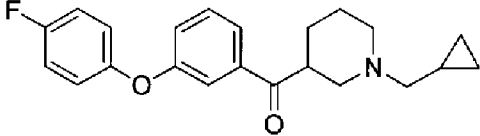
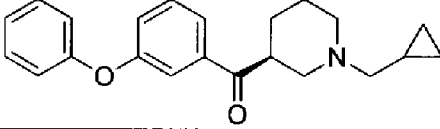
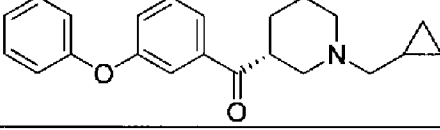
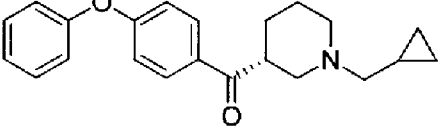
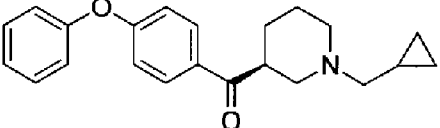
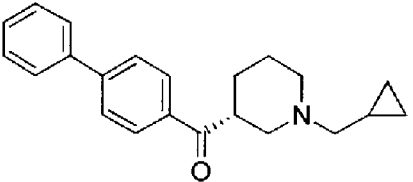
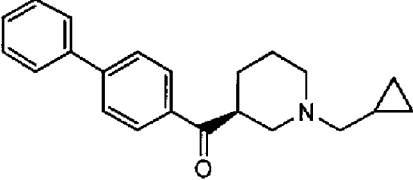
Data for representative compounds from the assay described in Example 200 is provided in the following Table.

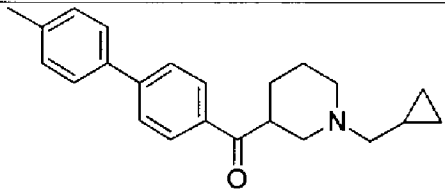
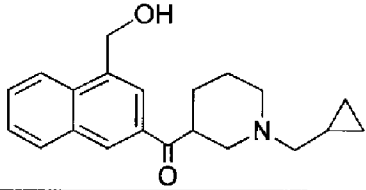
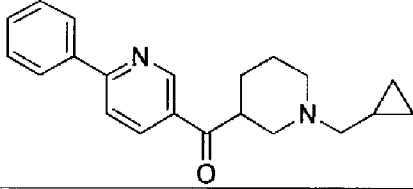
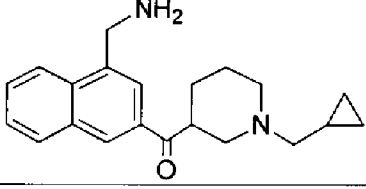
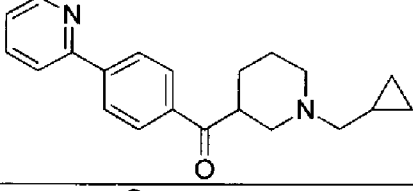
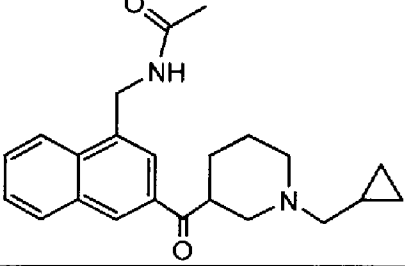
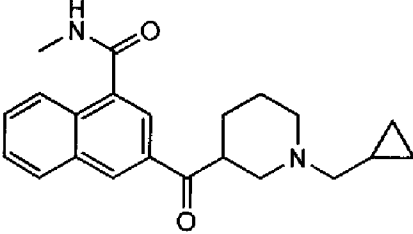
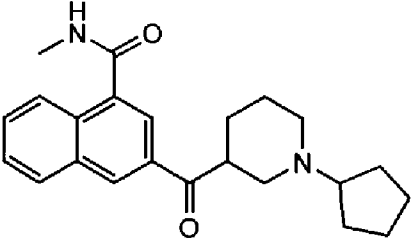
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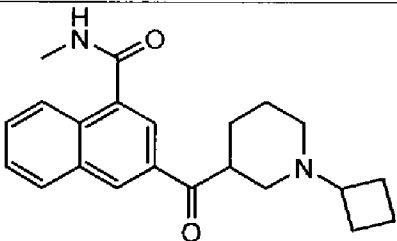
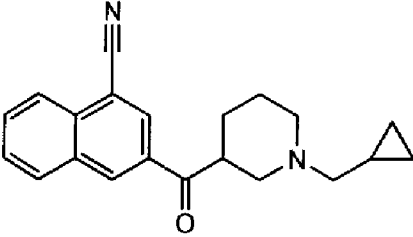
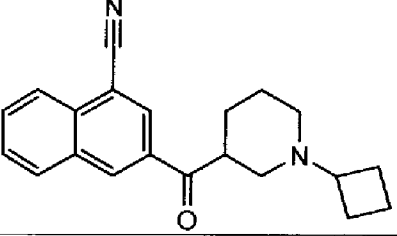
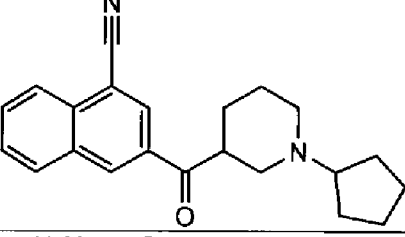
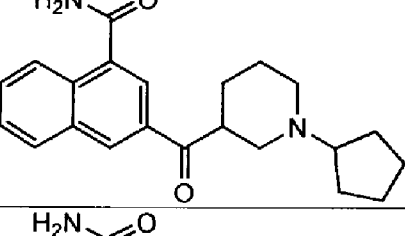
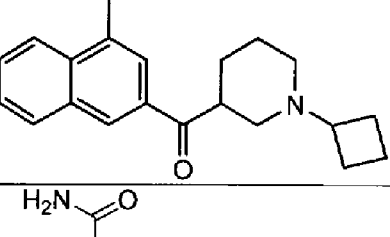
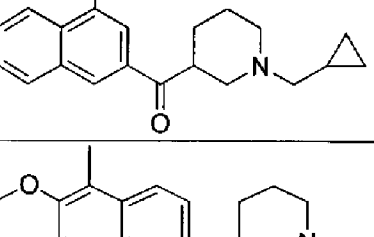
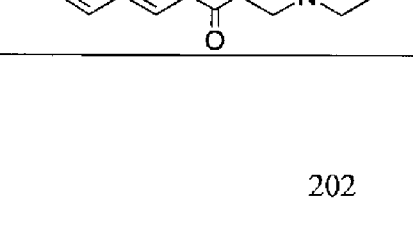
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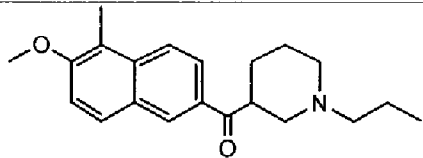
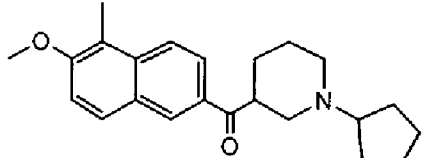
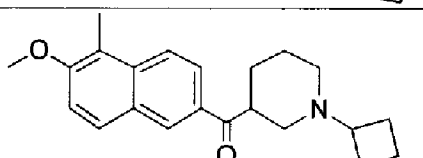
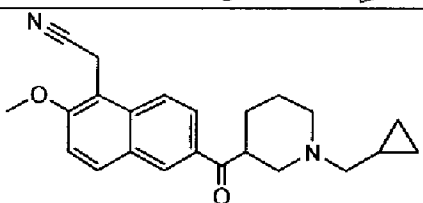
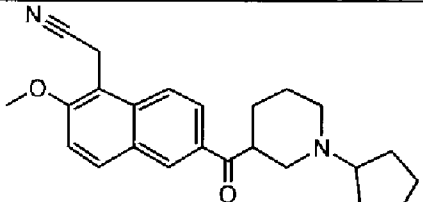
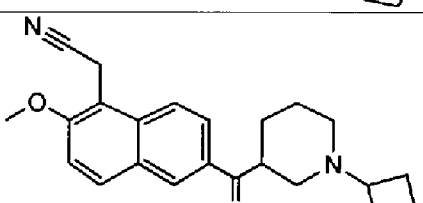
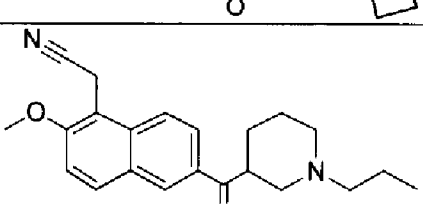
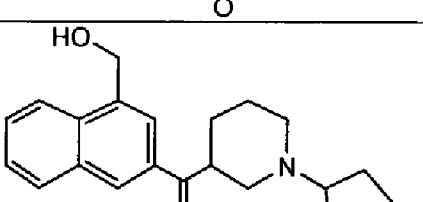
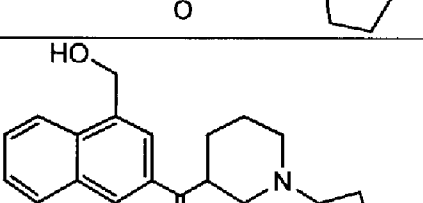
Example	Structure	KDM2B HTRF IC50 (uM)
1		0.25
3		23
5		2.5
6		2.6
7		0.123
8		2.7

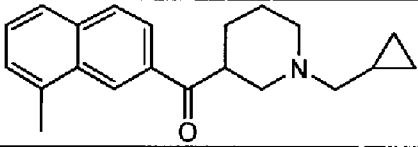
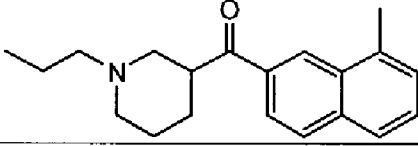
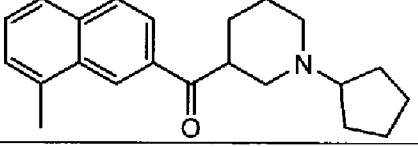
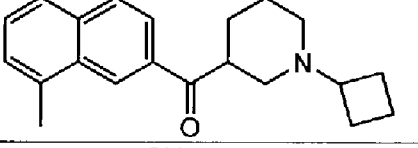
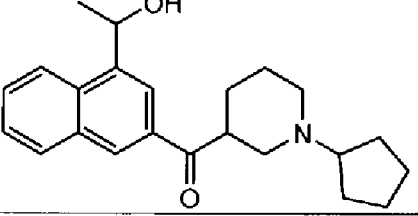
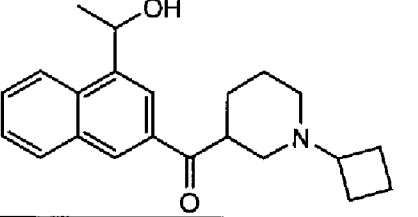
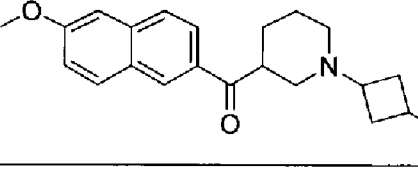
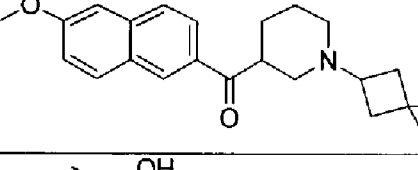
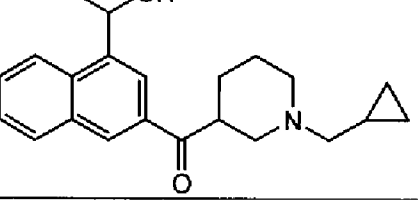
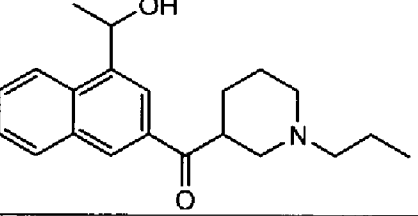
9		3
10		0.0566
11		0.153
12		9
13		0.713
14		1.2
15		0.43
18		0.161
21		0.461
22		1.4

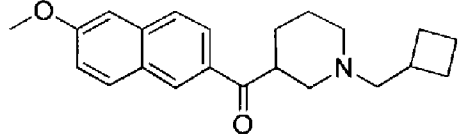
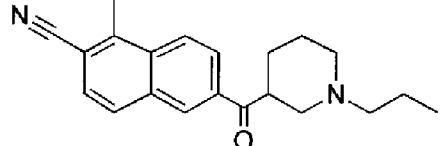
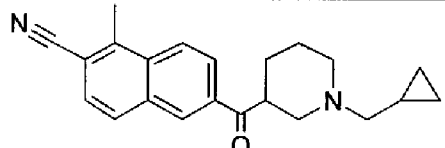
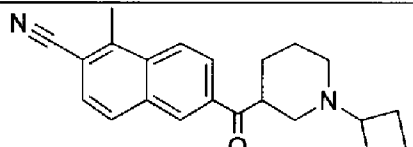
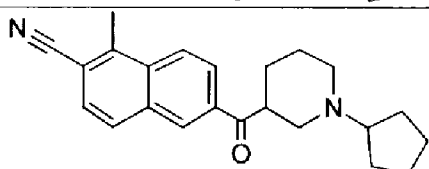
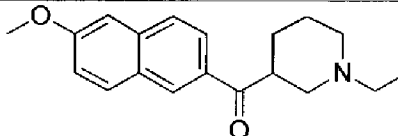
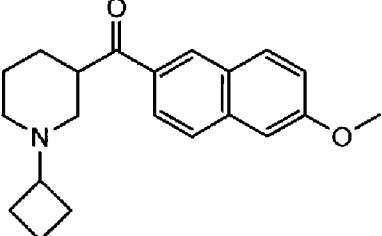
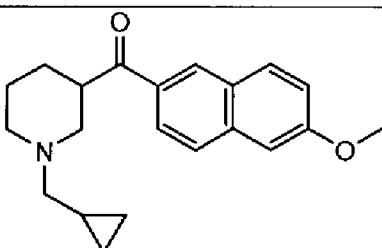
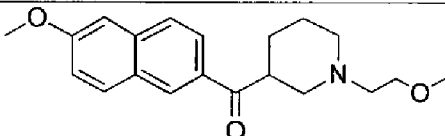
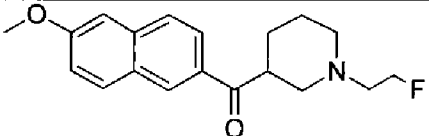
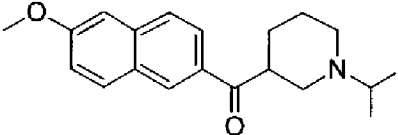
23		2.1
24		25++
25		1.4
26		0.551
27		0.221
28		1.7
29		0.148
30		5.9
31		0.136
32		4.1
33		0.0954

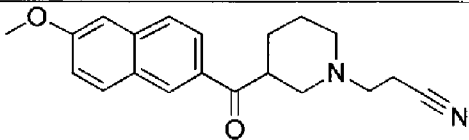
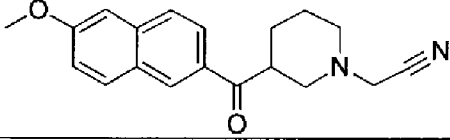
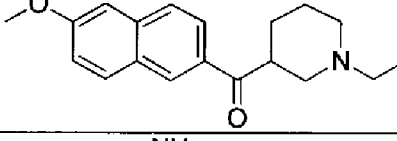
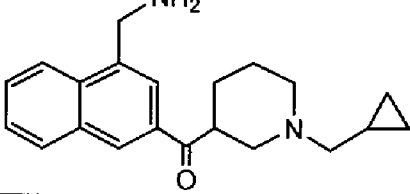
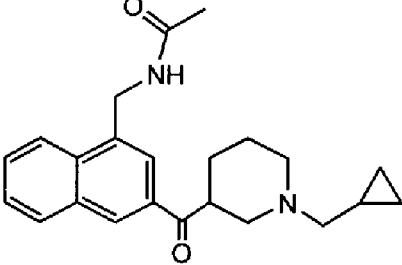
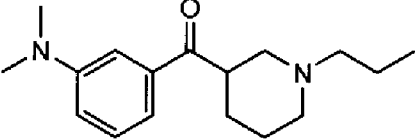
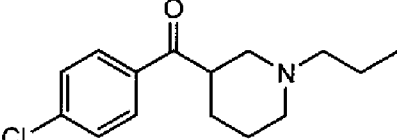
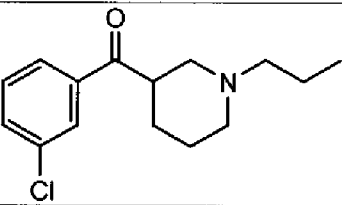
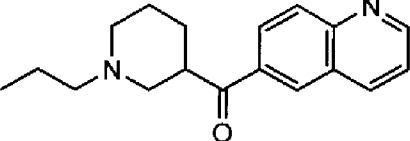
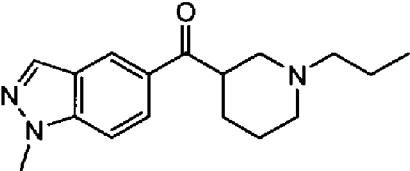
34		0.402
35		0.169
36		0.533
37		0.62
38		0.596
39		0.46
40		0.626
41		0.7

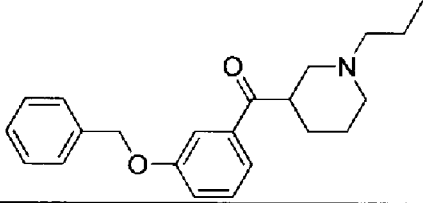
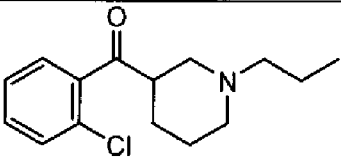
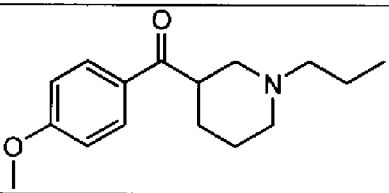
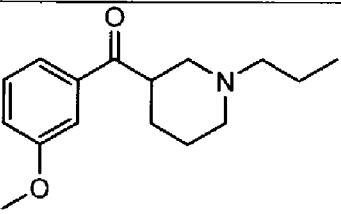
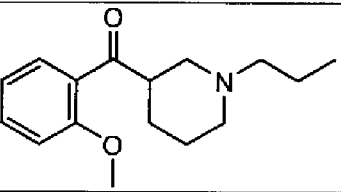
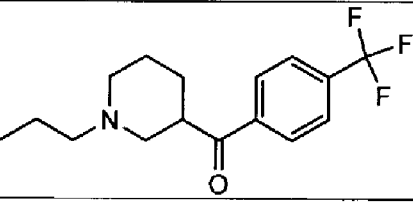
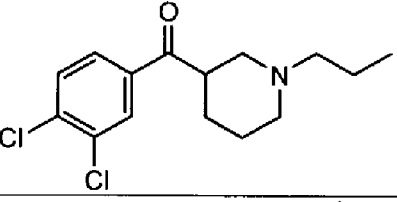
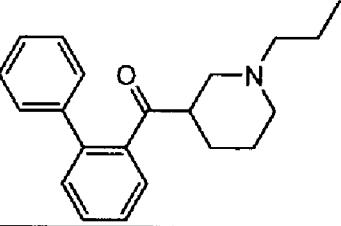
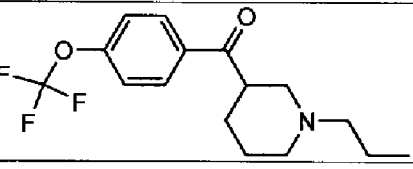
42		0.243
43		0.143
44		0.101
45		0.267
46		0.209
47		0.0997
48		0.18
49		0.163

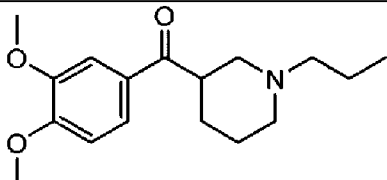
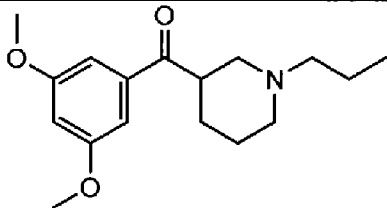
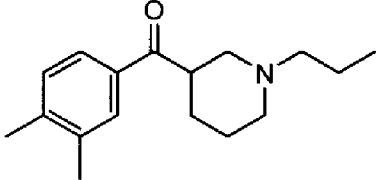
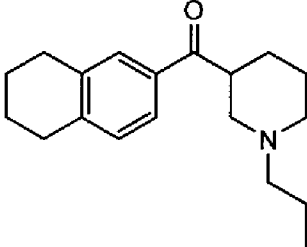
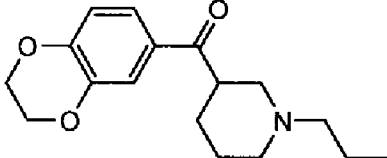
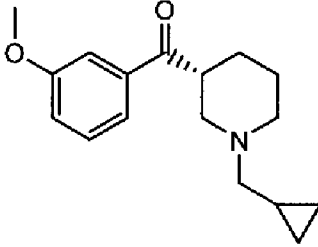
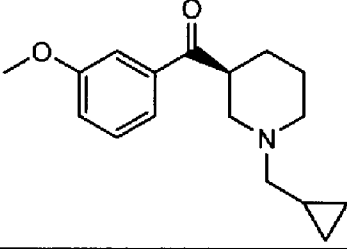
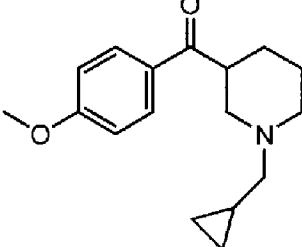
50		0.026
51		0.118
52		0.0394
53		0.0335
54		0.0395
55		0.0132
56		0.27
57		0.125
58		0.0476

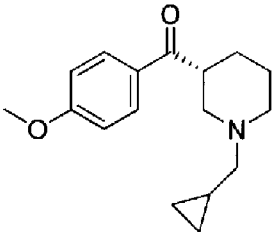
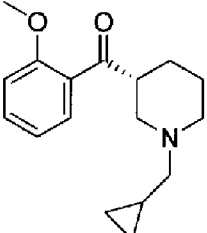
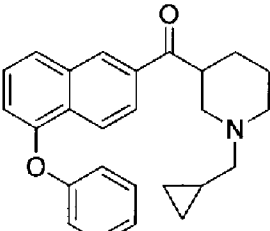
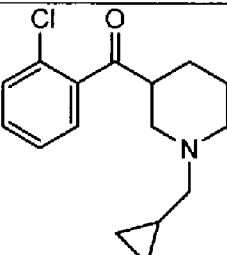
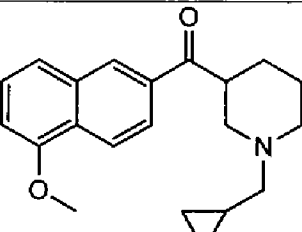
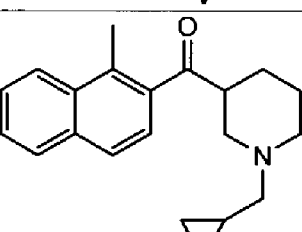
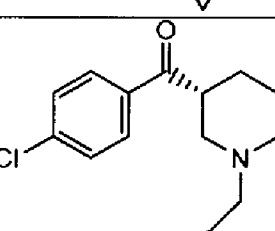
59		0.169
60		0.125
61		0.174
62		0.103
63		0.15
64		0.0438
65		0.309
66		0.0675
67		0.148
68		0.0762

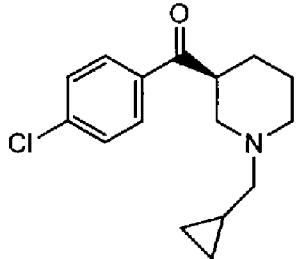
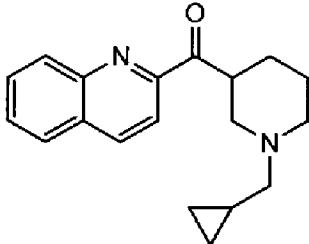
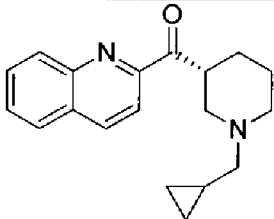
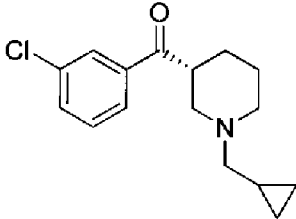
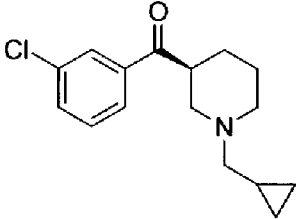
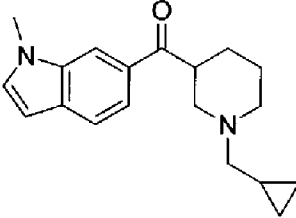
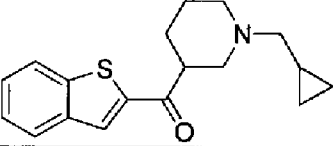
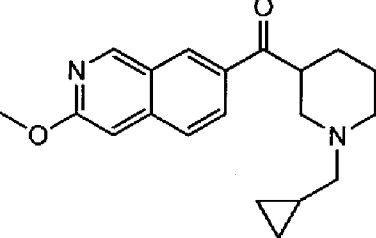
69		0.15
70		0.0918
71		0.132
72		0.0875
73		0.327
74		1.15
76		0.619
77		0.208
78		2.4
79		1.8
81		6.5

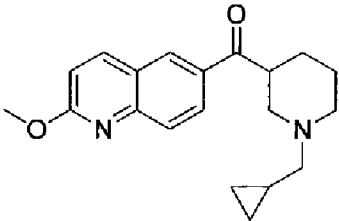
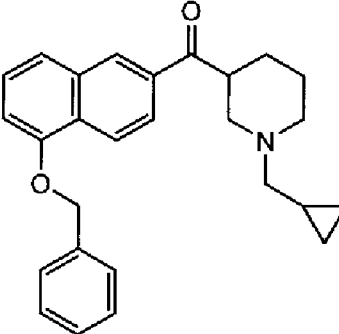
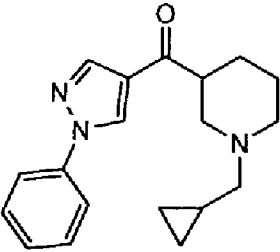
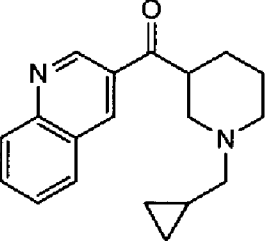
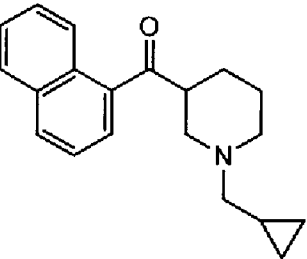
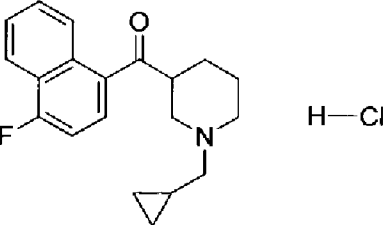
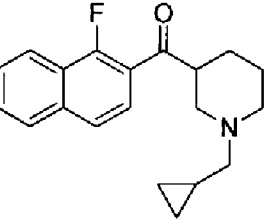
84		0.709
85		25++
87		
88		
89		
90		1.6
91		1.6
92		0.723
93		
94		0.122

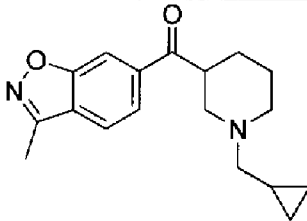
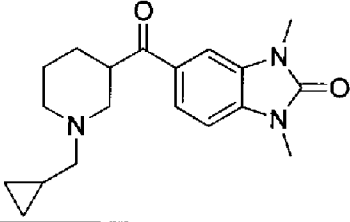
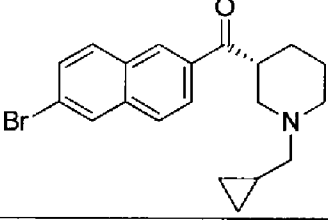
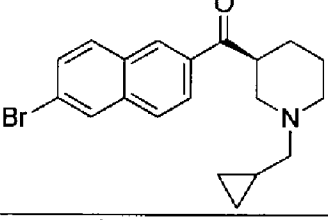
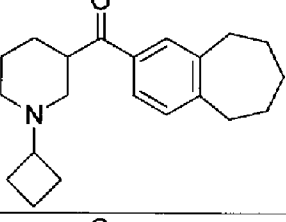
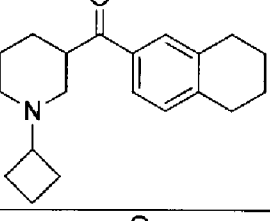
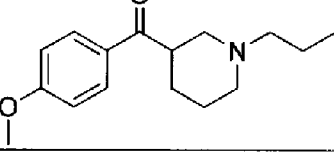
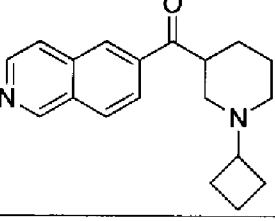
95		0.823
96		
97		0.93
98		1.6
99		5.5
100		1.2
101		0.279
102		5.8
103		2

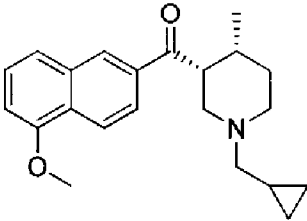
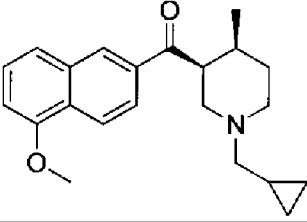
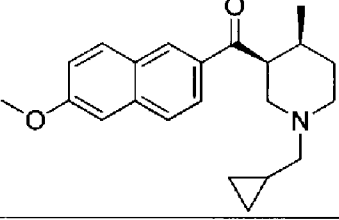
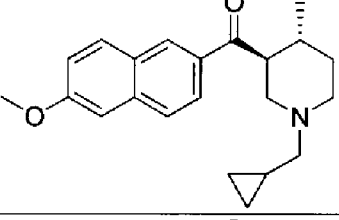
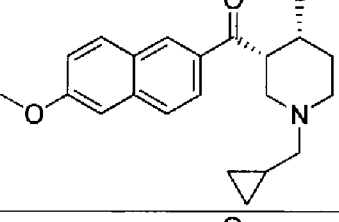
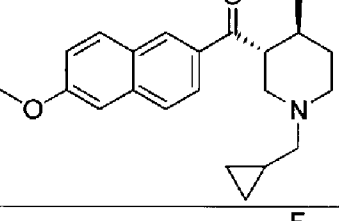
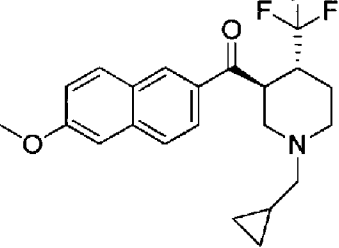
104		0.744
105		0.272
106		0.247
107		0.0998
108		0.297
109a		14.1
109b		1.3
110a		2

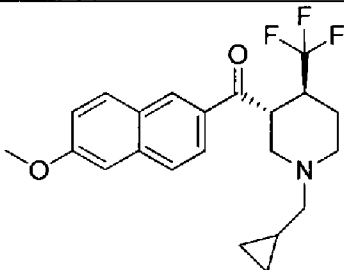
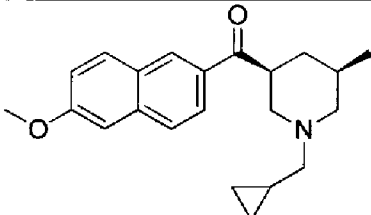
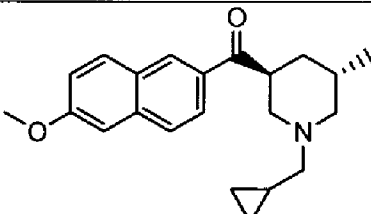
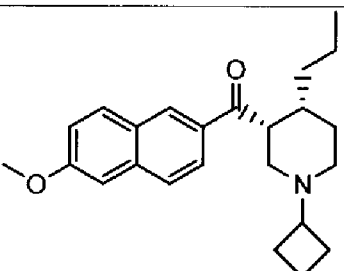
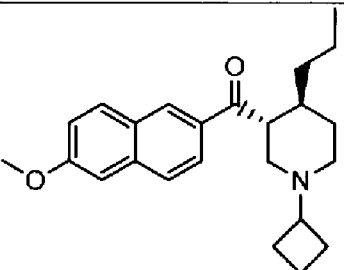
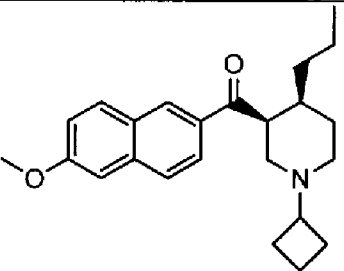
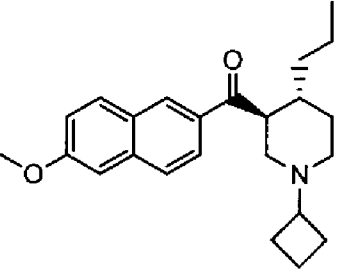
110b		5.3
111		3.1
112		0.175
113		5.4
114		0.22
115		0.439
116a		5.8

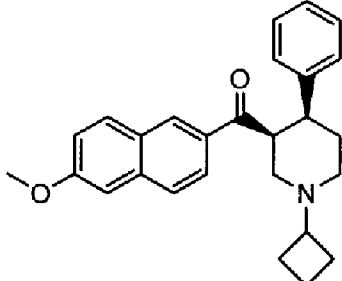
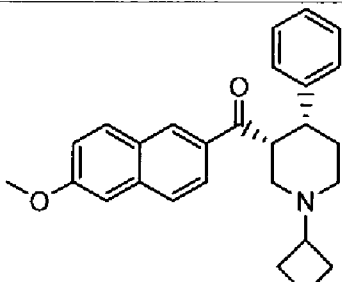
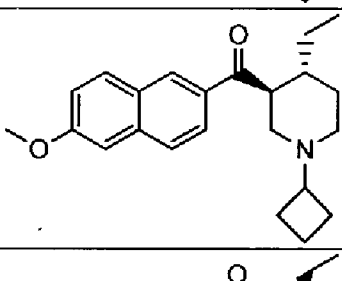
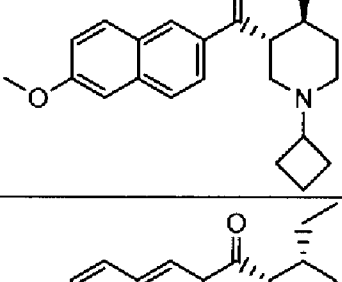
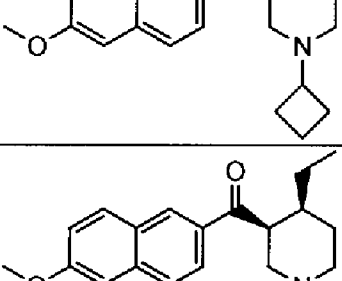
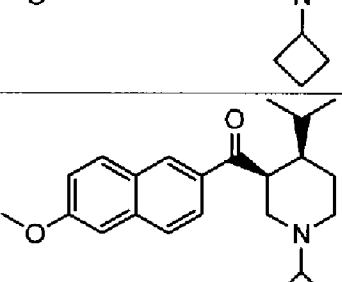
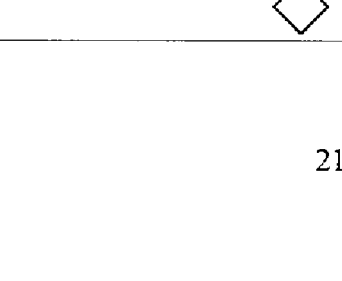
116b		1.4
117a		0.356
117b		0.75
118a		6.8
118b		0.661
119		2.3
120		0.389
121		0.38

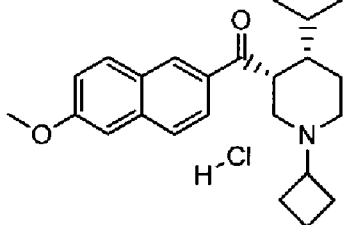
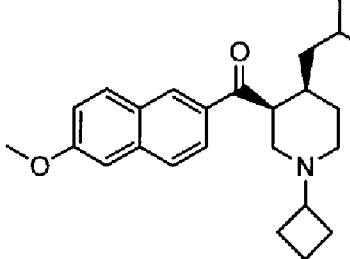
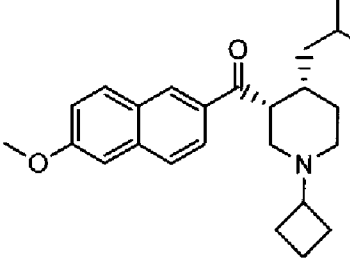
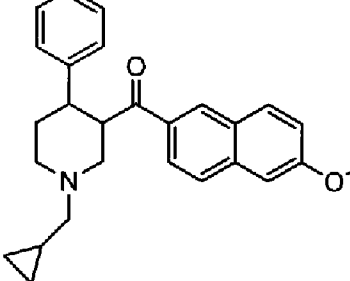
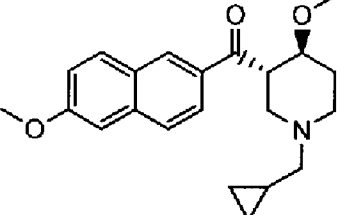
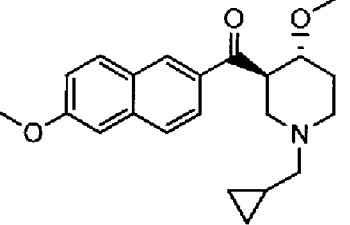
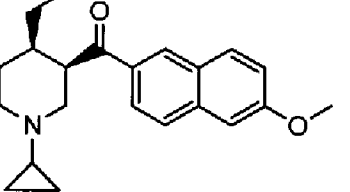
122		0.205
123		0.0909
124		0.656
125		0.489
126		3.8
127		1.9
128		0.133

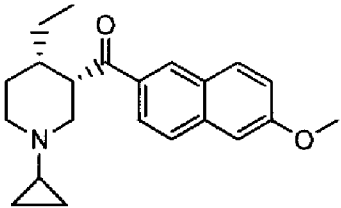
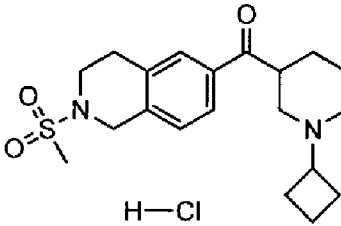
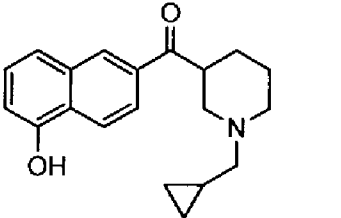
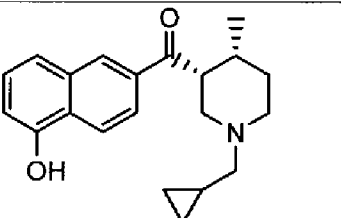
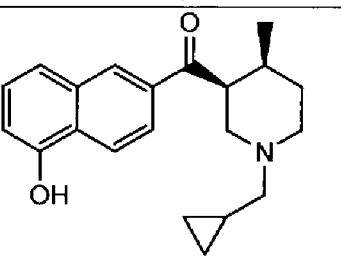
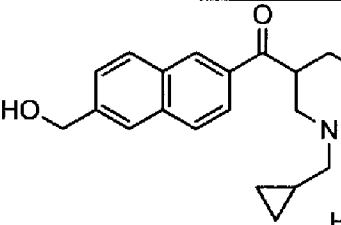
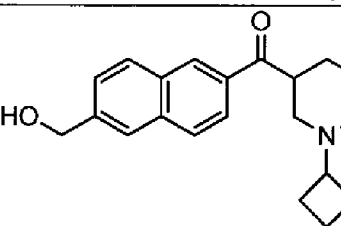
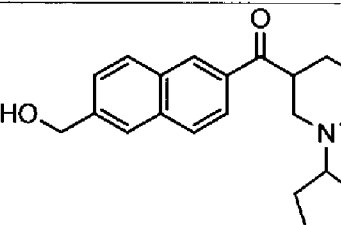
129		0.492
130		0.442
131a		0.226
131b		0.181
132		0.0553
133		0.103
134		
135		0.226

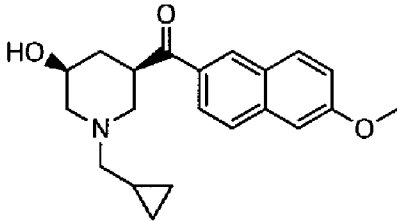
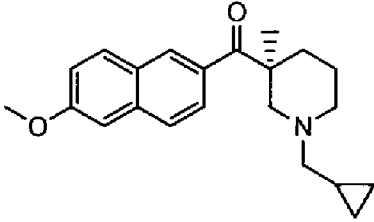
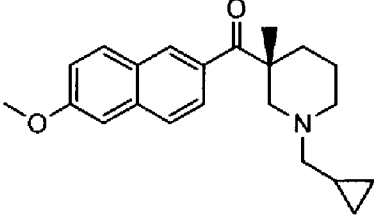
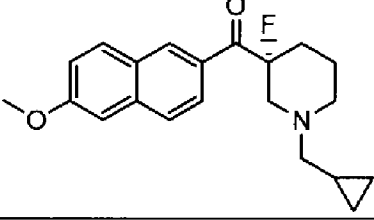
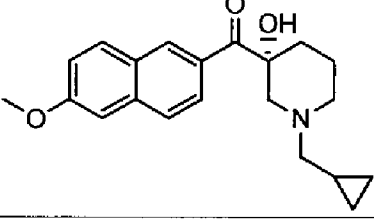
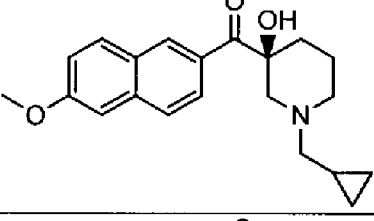
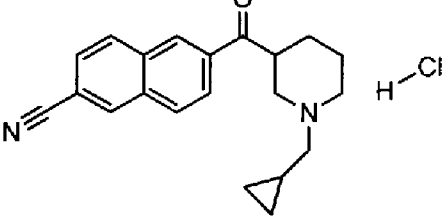
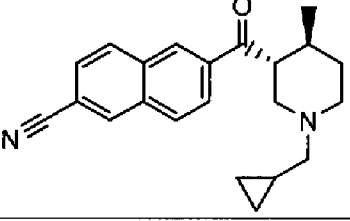
136a		0.0414
136b		1.2
137a		0.0706
137b		0.0928
137c		1.1
137d		3.3
138a		0.137

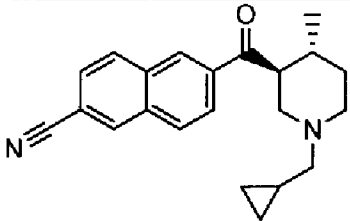
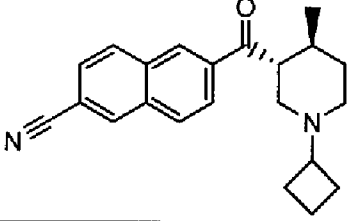
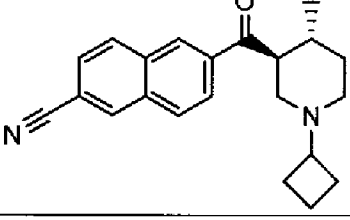
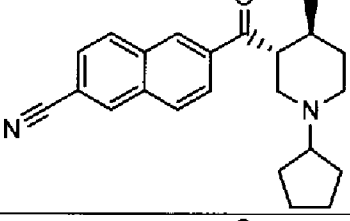
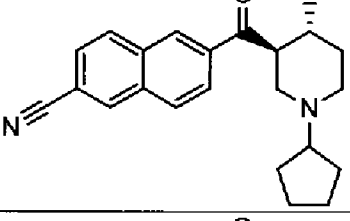
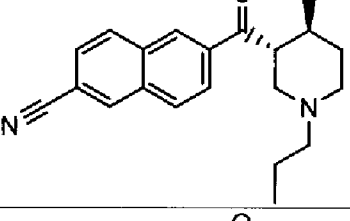
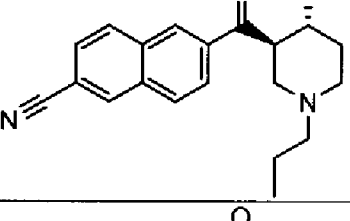
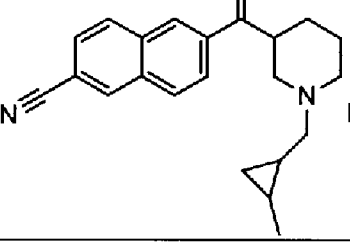
138b		4.8
139a		0.333
139b		9.7+
140a		0.31
140b		0.328
140c		0.00548
140d		0.00996

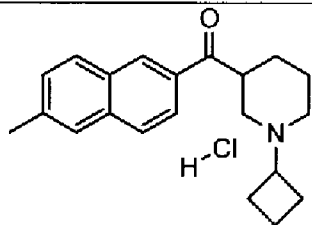
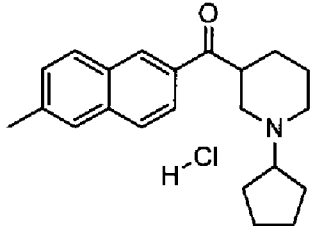
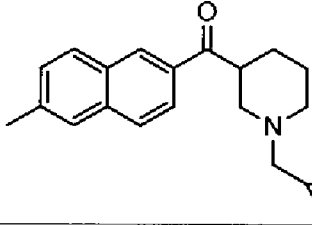
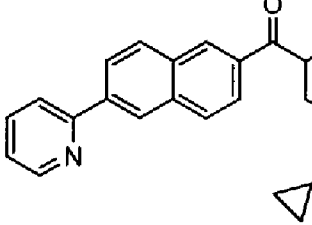
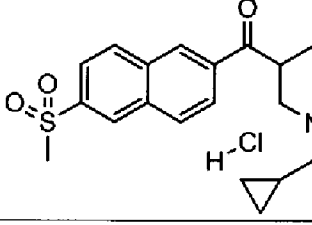
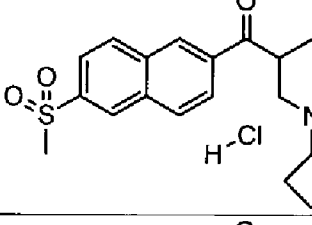
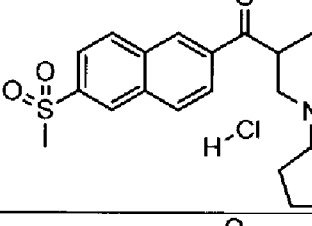
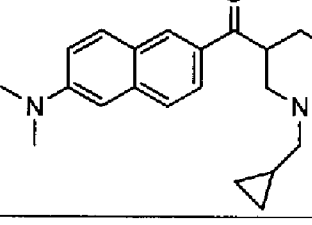
141a		1
141b		0.0987
142a		0.0114
142b		0.349
142c		0.207
142d		0.00656
143a		0.635

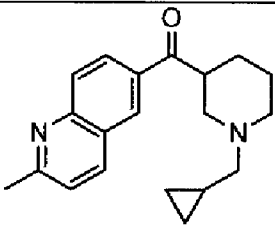
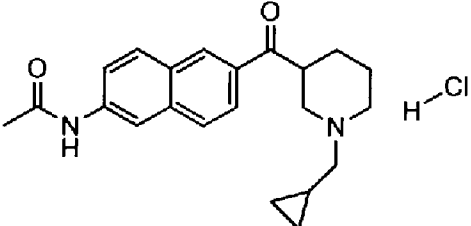
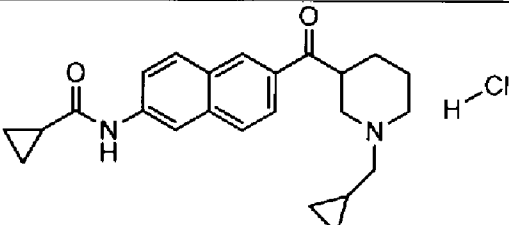
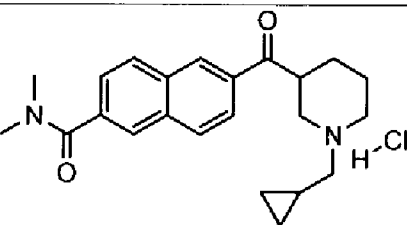
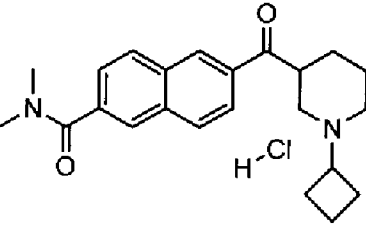
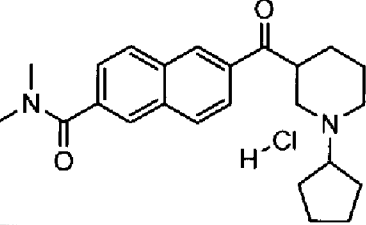
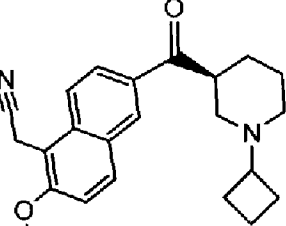
143b		0.0159
144a		0.0056
144b		0.269
145		0.312
146a		0.382
146b		0.129
147a		2

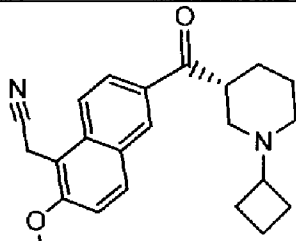
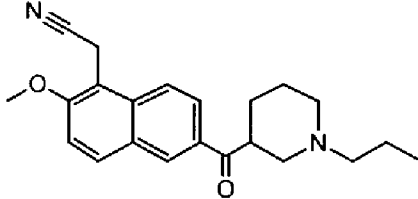
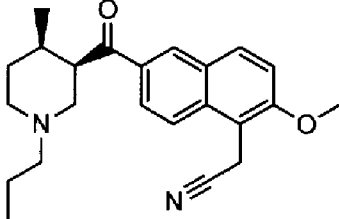
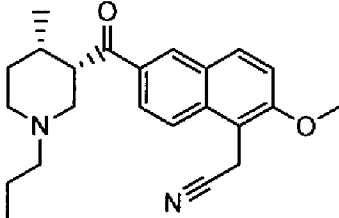
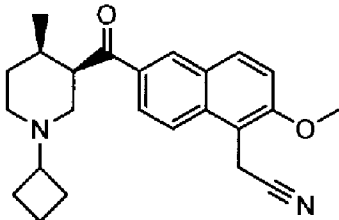
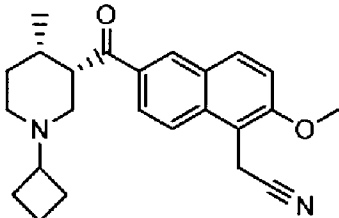
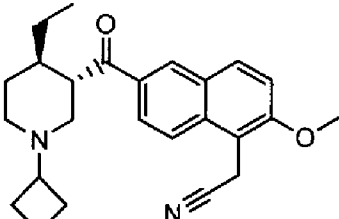
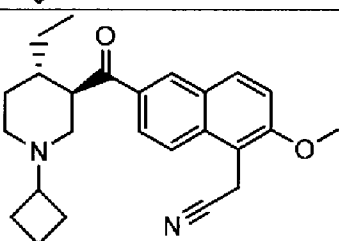
147b		0.0049
149		0.163
150		0.133
151a		0.315
151b		0.0395
152		0.234
153		0.409
154		0.183

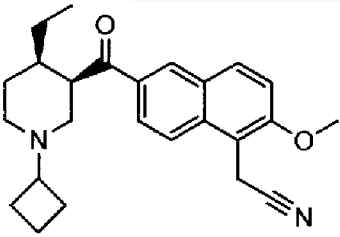
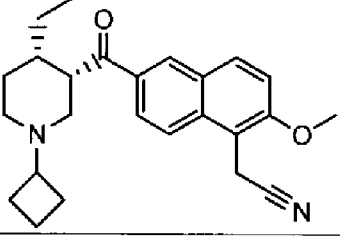
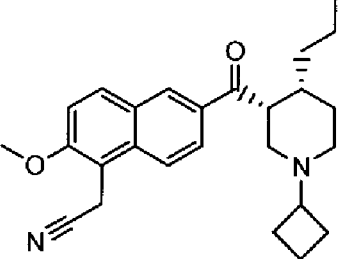
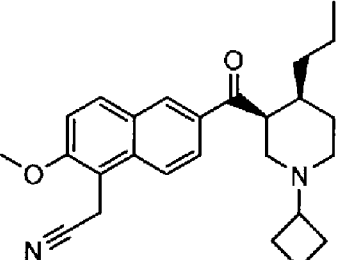
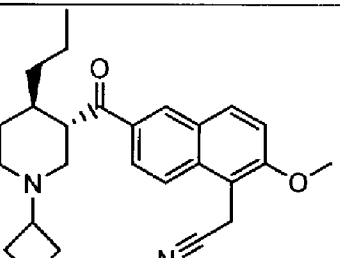
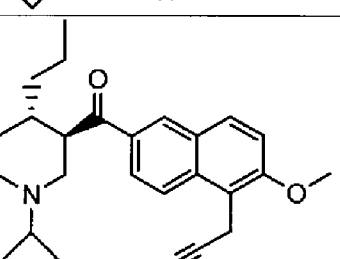
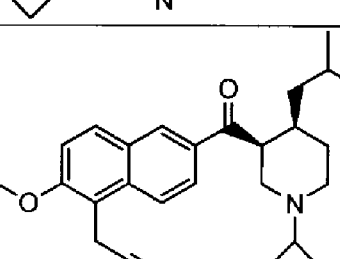
155		0.779
156a		25++
156b		25++
157		6.1
158a		1.9
158b		11.5
159		0.0688
160a		1.7

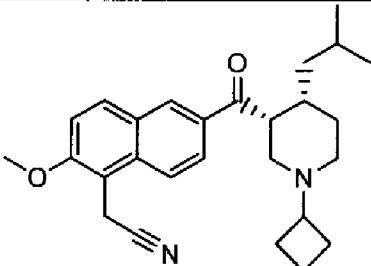
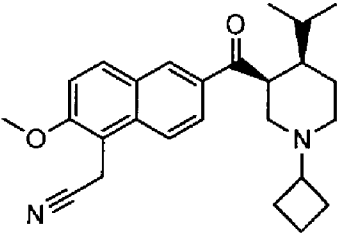
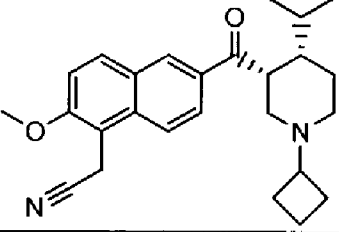
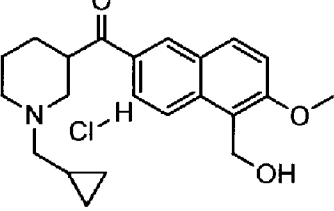
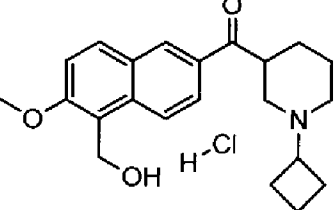
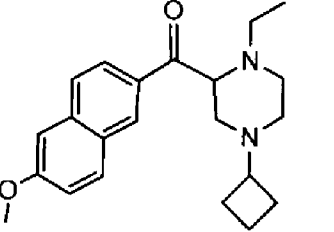
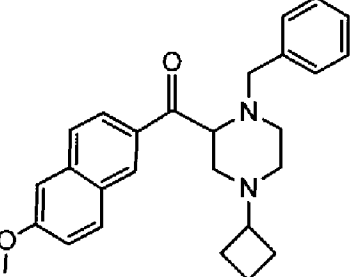
160b		0.113
161a		3
161b		0.0123
162a		0.814
162b		0.0857
163a		0.993
163b		0.0454
164		0.436

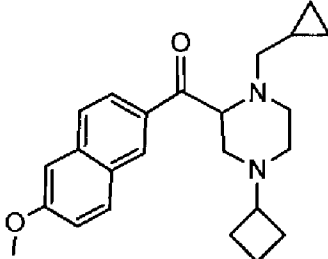
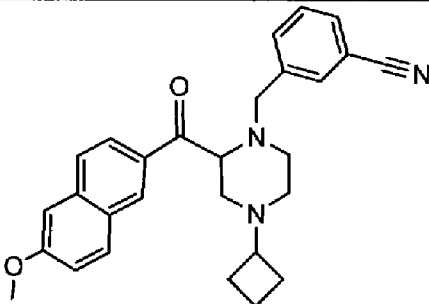
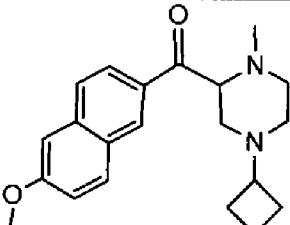
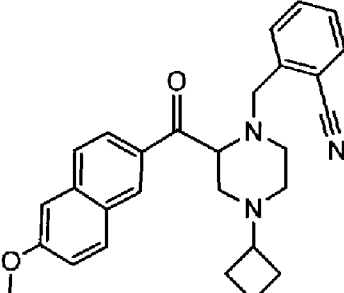
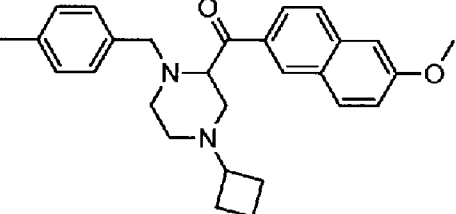
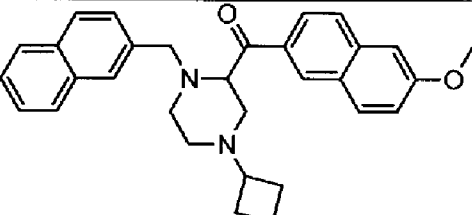
165		0.163
166		0.24
167		0.171
168		0.182
169		0.112
170		0.0426
171		0.102
172		0.316

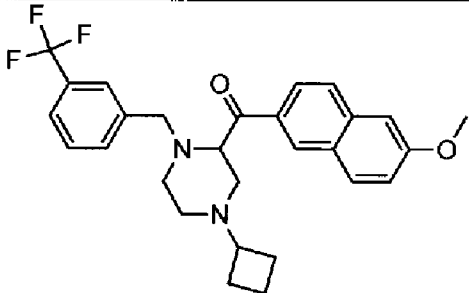
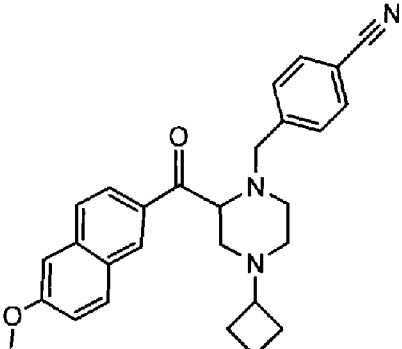
173		0.255
174		1.8
175		0.355
176		0.214
177		0.113
178		0.188
179a		0.00565

179b		0.361
180		
181a		1.3
181b		0.0123
182a		0.29
182b		0.00112
183a		0.0552
183b		0.00206

183c		0.078
183d		0.00153
184a		0.0774
184b		0.00141
184c		0.00313
184d		0.263
185a		0.0535

185b		0.002
186a		0.0701
186b		0.00212
188		0.133
189		0.0553
190		0.979
191		0.102

192		0.385
193		0.0223
194		1.7
195		0.176
196		0.138
197		0.165

198		0.302
199		0.0309

While a number of embodiments have been described, these examples may be altered to provide other embodiments that utilize the compounds and methods described herein.

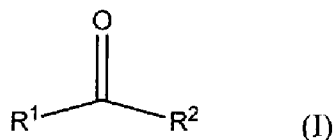
Therefore, the scope of this invention is to be defined by the appended claims rather than by the

5 specific embodiments that have been represented by way of example.

CLAIMS

We claim:

1. A compound of formula (I):



or a salt thereof, wherein:

R^1 is:

- a) a carbon-linked piperidine ring that is substituted on the piperidine ring nitrogen with a group R^x and that is optionally further substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, and $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo; or
- b) a carbon-linked piperazine ring that is substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, and $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$,

-C(O)-R^b, -C(O)-OR^b, -S(O)-R^b, -S(O)₂-R^b, -N(R^b)-C(O)-R^b, -N(R^b)-S(O)-R^b,
-N(R^b)-C(O)-N(R^b)₂, -N(R^b)-S(O)₂-R^b, and C₁₋₆alkyl that is optionally
substituted with one or more groups independently selected from halo;

each R^b is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, aryl, and C₂₋₆alkynyl, wherein each C₁₋₆alkyl, C₂₋₆alkenyl, aryl, and C₂₋₆alkynyl is
optionally substituted with one or more groups independently selected from the group consisting
of halo, -N(R^c)₂, -CN, -C(O)-N(R^c)₂, -S(O)-N(R^c)₂, -S(O)₂-N(R^c)₂, -O-R^c, -S-R^c, -O-C(O)-R^c,
-C(O)-R^c, -C(O)-OR^c, -S(O)-R^c, -S(O)₂-R^c, -N(R^c)-C(O)-R^c, -N(R^c)-S(O)-R^c, -N(R^c)-C(O)-
N(R^c)₂, and -N(R^c)-S(O)₂-R^c; or two R^b are taken together with the nitrogen to which they are
attached to form a pyrrolidino, piperidino, or piperazino ring;

each R^c is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl, wherein each C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl is optionally
substituted with one or more groups independently selected from the group consisting of oxo,
halo, amino, hydroxy, and C₁₋₆alkoxy; or two R^c are taken together with the nitrogen to which
they are attached to form a heterocyclyl that is optionally substituted with one or more groups
independently selected from the group consisting of oxo, halo and C₁₋₃alkyl that is optionally
substituted with one or more groups independently selected from the group consisting of oxo
and halo;

R^x is C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈carbocycle, oxetanyl, tetrahydrofuranyl, or
tetrahydropyranyl, wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈carbocycle is optionally
substituted with one or more groups independently selected from the group consisting of halo,
-CN, C₁₋₃alkoxy, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and C₃₋₈carbocycle that is
optionally substituted with one or more groups independently selected from the group consisting
of halo and C₁₋₃alkyl;

R² is a 5-10 membered heteroaryl or a 6-12 membered aryl, which 5-10 membered
heteroaryl, and 6-12 membered aryl is optionally substituted with one or more groups
independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl,
carbocycle, heterocycle, aryl, heteroaryl, halo, -NO₂, -N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂,
-S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-
R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, and -N(R^d)-S(O)₂-R^d; wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with
one or more groups independently selected from the group consisting of halo, -NO₂-N(R^d)₂, -CN,
-C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d,
-S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, -N(R^d)-S(O)₂-R^d, and

C₁₋₆alkyl that is optionally substituted with one or more groups independently selected from halo;

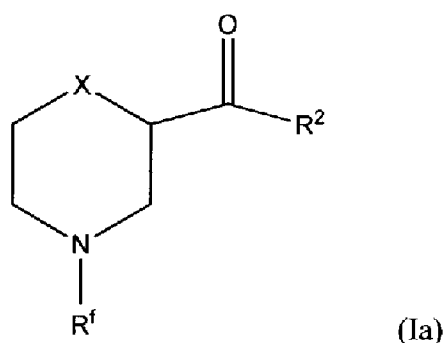
each R^d is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, aryl, and C₂₋₆alkynyl, wherein each C₁₋₆alkyl, C₂₋₆alkenyl, aryl, and C₂₋₆alkynyl is optionally substituted with one or more groups independently selected from the group consisting of halo, -N(R^e)₂, -CN, -C(O)-N(R^e)₂, -S(O)-N(R^e)₂, -S(O)₂-N(R^e)₂, -O-R^e, -S-R^e, -O-C(O)-R^e, -C(O)-R^e, -C(O)-OR^e, -S(O)-R^e, -S(O)₂-R^e, -N(R^e)-C(O)-R^e, -N(R^e)-S(O)-R^e, -N(R^e)-C(O)-N(R^e)₂, and -N(R^e)-S(O)₂-R^e; or two R^d are taken together with the nitrogen to which they are attached to form a pyrrolidino, piperidino, or piperazino ring; and

each R^e is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl, wherein each C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo, amino, hydroxy, and C₁₋₆alkoxy; or two R^e are taken together with the nitrogen to which they are attached to form a heterocyclyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo and C₁₋₃alkyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo and halo;

provided that when R² is 6-methoxy-2-naphthyl, then R¹ is not 1-(cyclopropylmethyl)piperidin-3-yl, 1-(cyclobutyl)piperidin-3-yl, 1-(cyclopentyl)piperidin-3-yl, or 1-(tetrahydropyranyl)piperidin-3-yl; and

provided that when R² is phenyl, naphthyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl, 2-methyl-6-quinolyl, 1,5-benzodioxepin-7-yl, benzo[b]thien-7-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 1H-1-(*tert*-butoxycarbonyl)-4-bromo-indol-2-yl, 1H-1-(*tert*-butoxycarbonyl)-4-cyano-indol-2-yl, 3,4-dihydroxyphenyl, 3-methoxy-4-hydroxyphenyl, 3,4-dimethoxyphenyl, 3-methoxycarbonyl-4-hydroxyphenyl, 4-hydroxyphenyl, or 2-hydroxyphenyl, then R¹ is not optionally substituted piperazine-2-yl.

2. The compound of claim 1 which is a compound of formula (Ia):



or a salt thereof, wherein:

5 X is CR^gR^h or NR^k ;

each R^f is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, and $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$;

10 wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$, and C_{1-6} alkyl that is optionally substituted with
15 one or more groups independently selected from halo;

each R^g is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, and $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$;

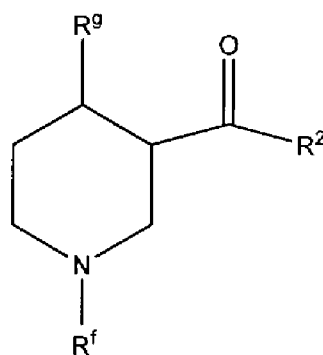
20 wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$, and C_{1-6} alkyl that is optionally substituted with
25 one or more groups independently selected from halo;

each R^h is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, and halo, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the

group consisting of halo, $-\text{NO}_2-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo; and

- 5 each R^k is independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-\text{NO}_2-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

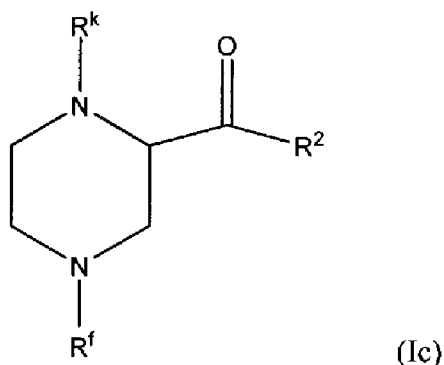
3. The compound of claim 1 which is a compound of formula (Ib):



(Ib)

or a salt thereof.

4. The compound of claim 1 which is a compound of formula (Ic):

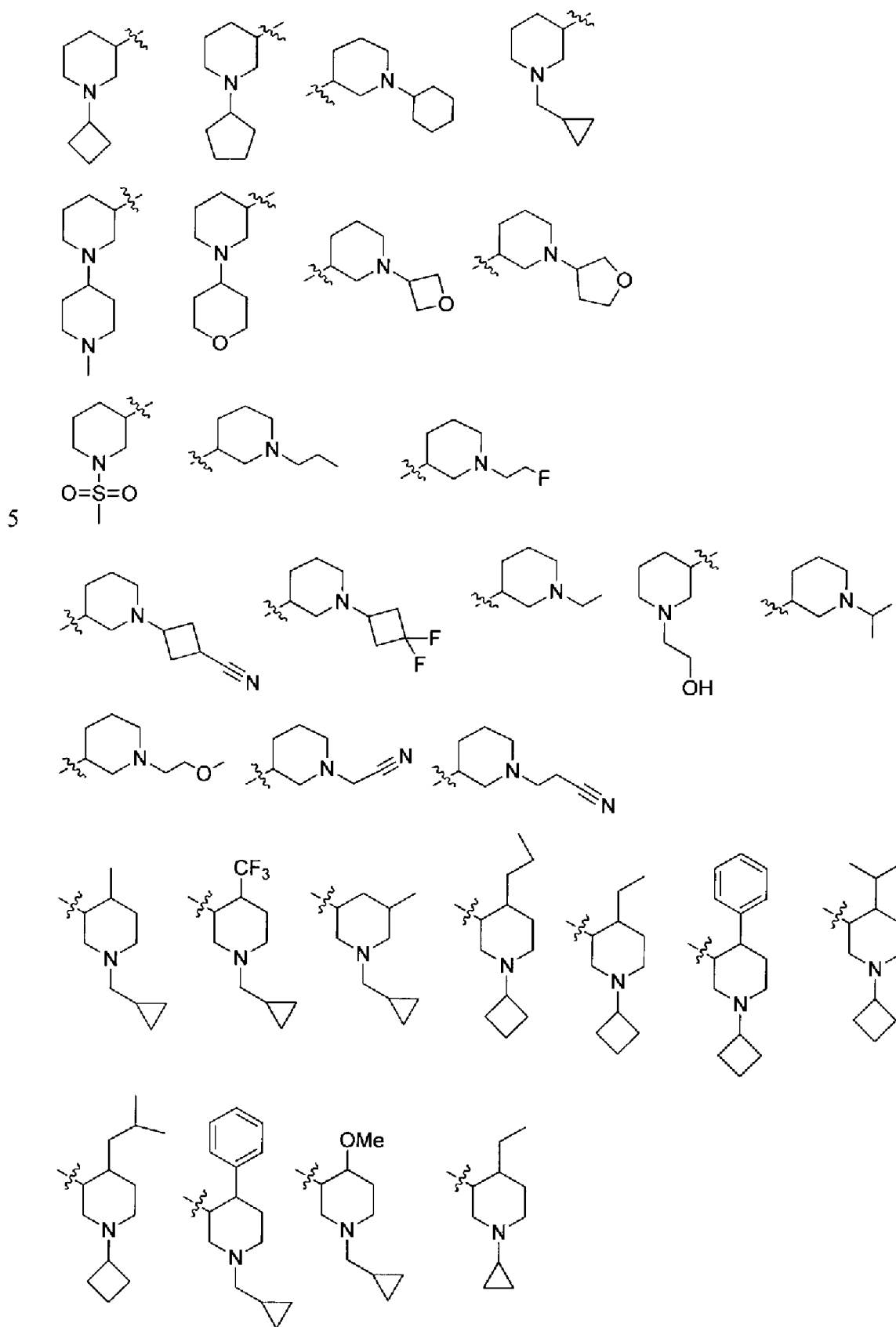


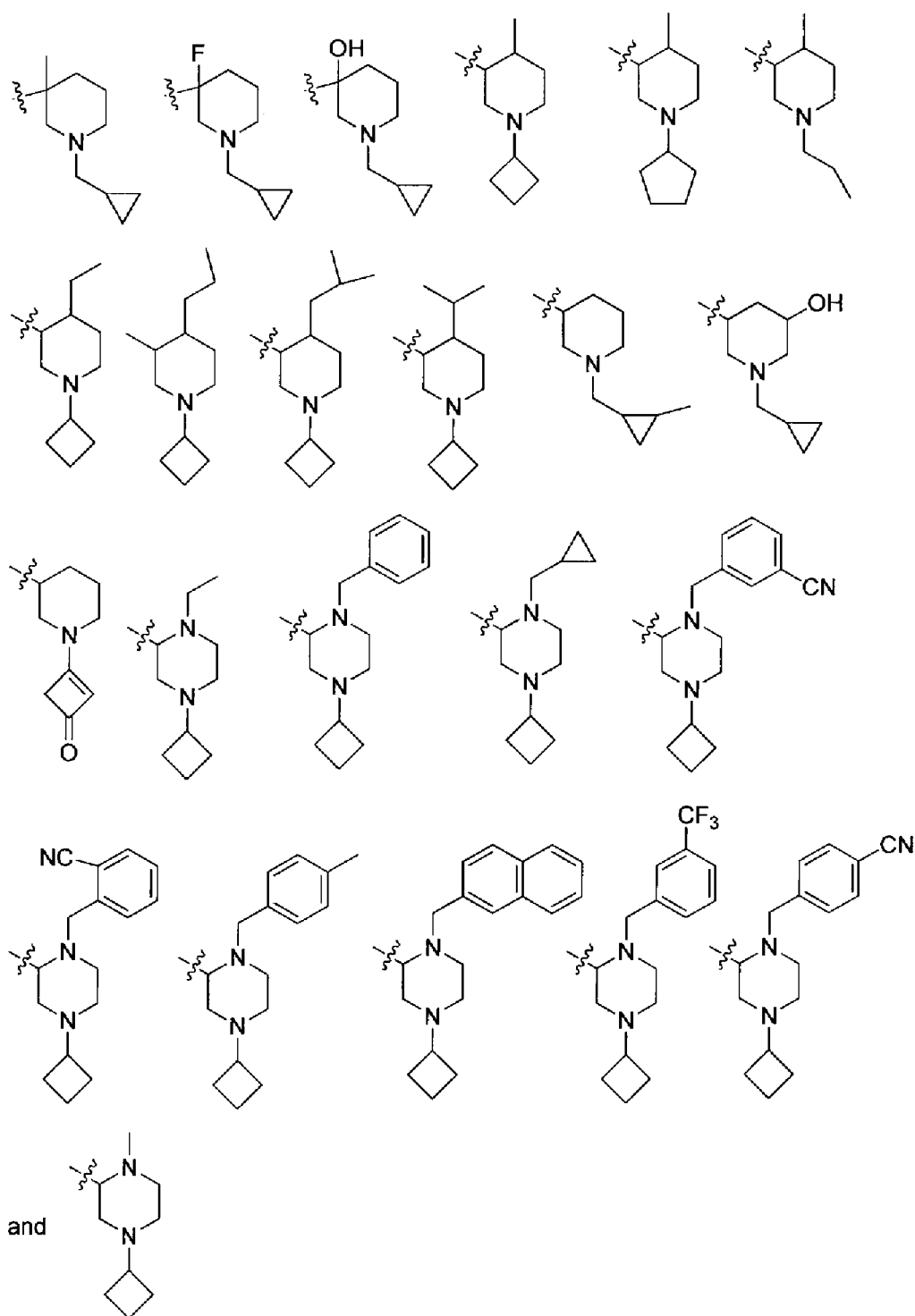
or a salt thereof.

5. The compound of claim 1 wherein R^1 is a carbon-linked piperidine ring that is substituted on the piperidine ring nitrogen with a group R^x and that is optionally further substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

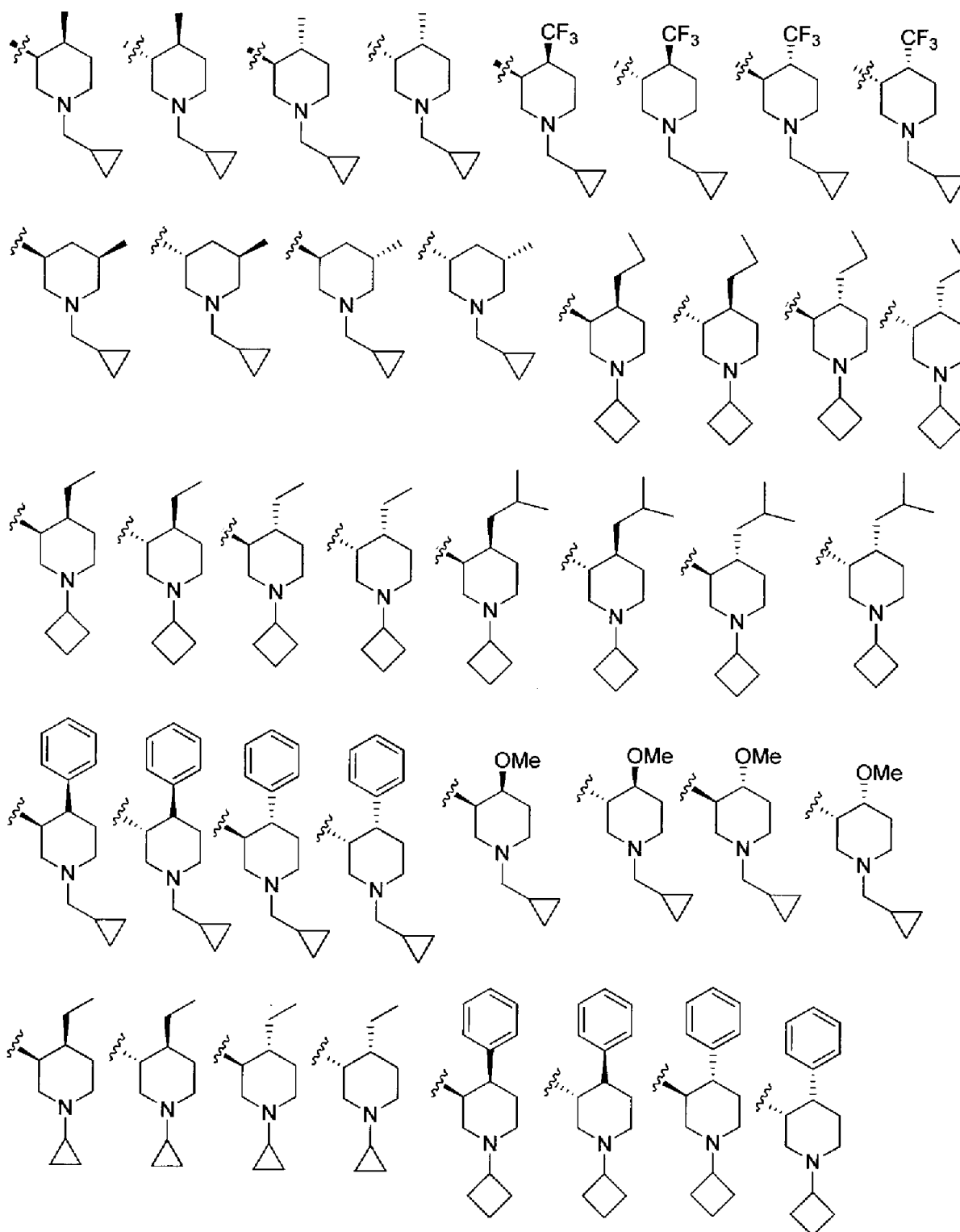
6. The compound of claim 1 wherein R^1 is a carbon-linked piperazine ring that is substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

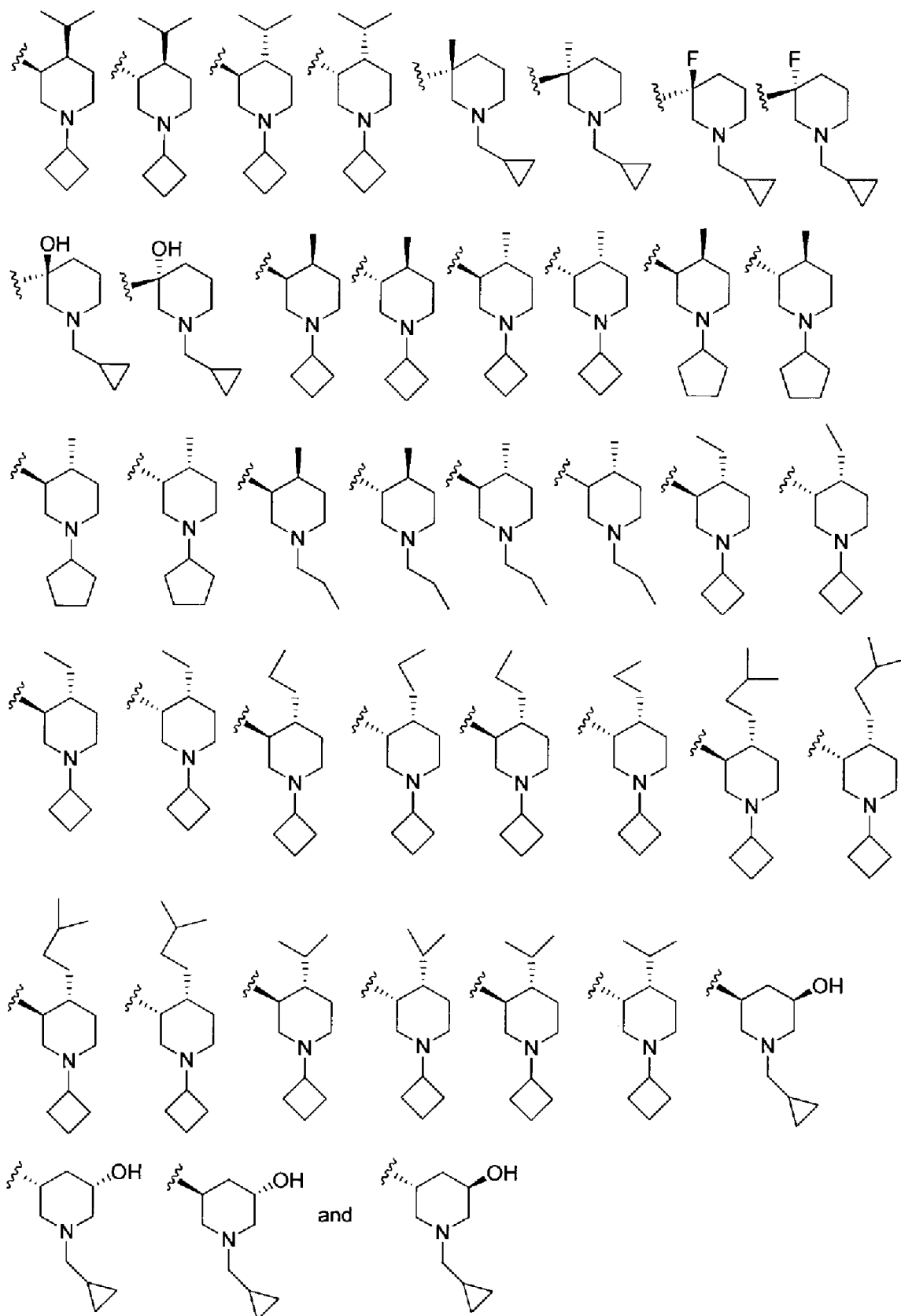
7. The compound of claim 1 wherein R¹ is selected from the group consisting of:





8. The compound of claim 1 wherein R¹ is selected from the group consisting of:

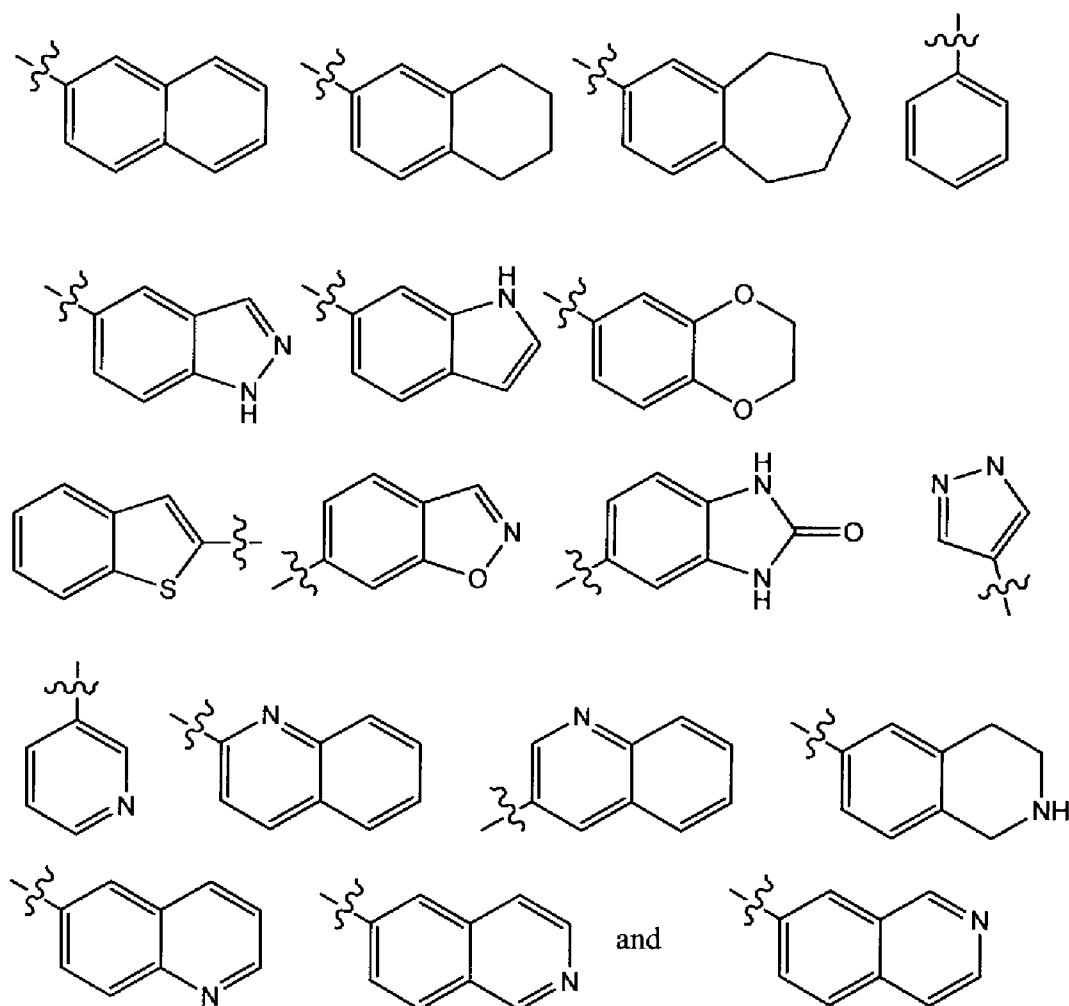




9. The compound of any one of claims 1-8 wherein R^2 is a ring selected from the group consisting of naphthyl, tetralinyl, phenyl, benzisoxazolyl, benzo[7]annulenyl, 1,4-benzodioxinyl,

benzimidazolyl-2-one, indolyl, indazolyl, thiophenyl, pyridyl, quinolyl, tetrahydroquinolyl, isoquinolyl, tetrahydroisoquinolyl, and pyrazolyl; which ring is optionally substituted with one or more groups independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, -NO₂, -N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, and -N(R^d)-S(O)₂-R^d; wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -NO₂, -N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, -N(R^d)-S(O)₂-R^d, and C₁₋₆alkyl that is optionally substituted with one or more groups independently selected from halo.

10. The compound of any one of claims 1-8 wherein R² is a ring selected from the group consisting of:



which ring is optionally substituted with one or more groups independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, -NO₂, -N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, and -N(R^d)-S(O)₂-R^d; wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -NO₂-N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, -N(R^d)-S(O)₂-R^d, and C₁₋₆alkyl that is optionally substituted with one or more groups independently selected from halo.

11. The compound of any one of claims 1-8 wherein R² is a naphthyl ring that is optionally substituted with one or more groups independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, -NO₂, -N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, and -N(R^d)-S(O)₂-R^d; wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -NO₂-N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, -N(R^d)-S(O)₂-R^d, and C₁₋₆alkyl that is optionally substituted with one or more groups independently selected from halo.

12. The compound of claim 11 wherein R² is a naphthyl ring that is optionally substituted with one or more groups independently selected from the group consisting of C₁₋₆alkyl, carbocycle, aryl, halo, -NO₂, -N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, and -N(R^d)-S(O)₂-R^d; wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -NO₂-N(R^d)₂, -CN, -C(O)-N(R^d)₂, -S(O)-N(R^d)₂, -S(O)₂-N(R^d)₂, -O-R^d, -S-R^d, -O-C(O)-R^d, -C(O)-R^d, -C(O)-OR^d, -S(O)-R^d, -S(O)₂-R^d, -N(R^d)-C(O)-R^d, -N(R^d)-S(O)-R^d, -N(R^d)-C(O)-N(R^d)₂, -N(R^d)-S(O)₂-R^d, and C₁₋₆alkyl that is optionally substituted with one or more groups independently selected from halo.

13. The compound of any one of claims 1-8 wherein R^2 is a phenyl ring that is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

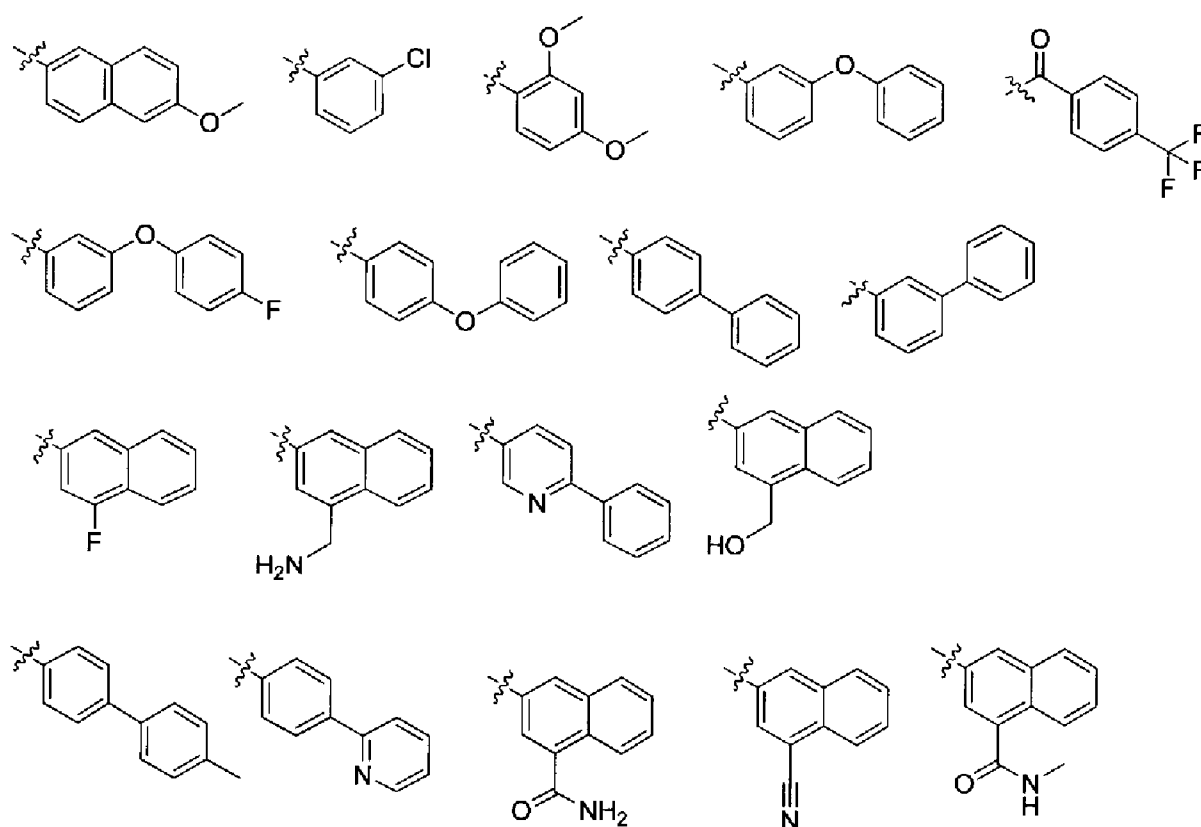
14. The compound of claim 13 wherein R^2 is a phenyl ring that is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, carbocycle, aryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

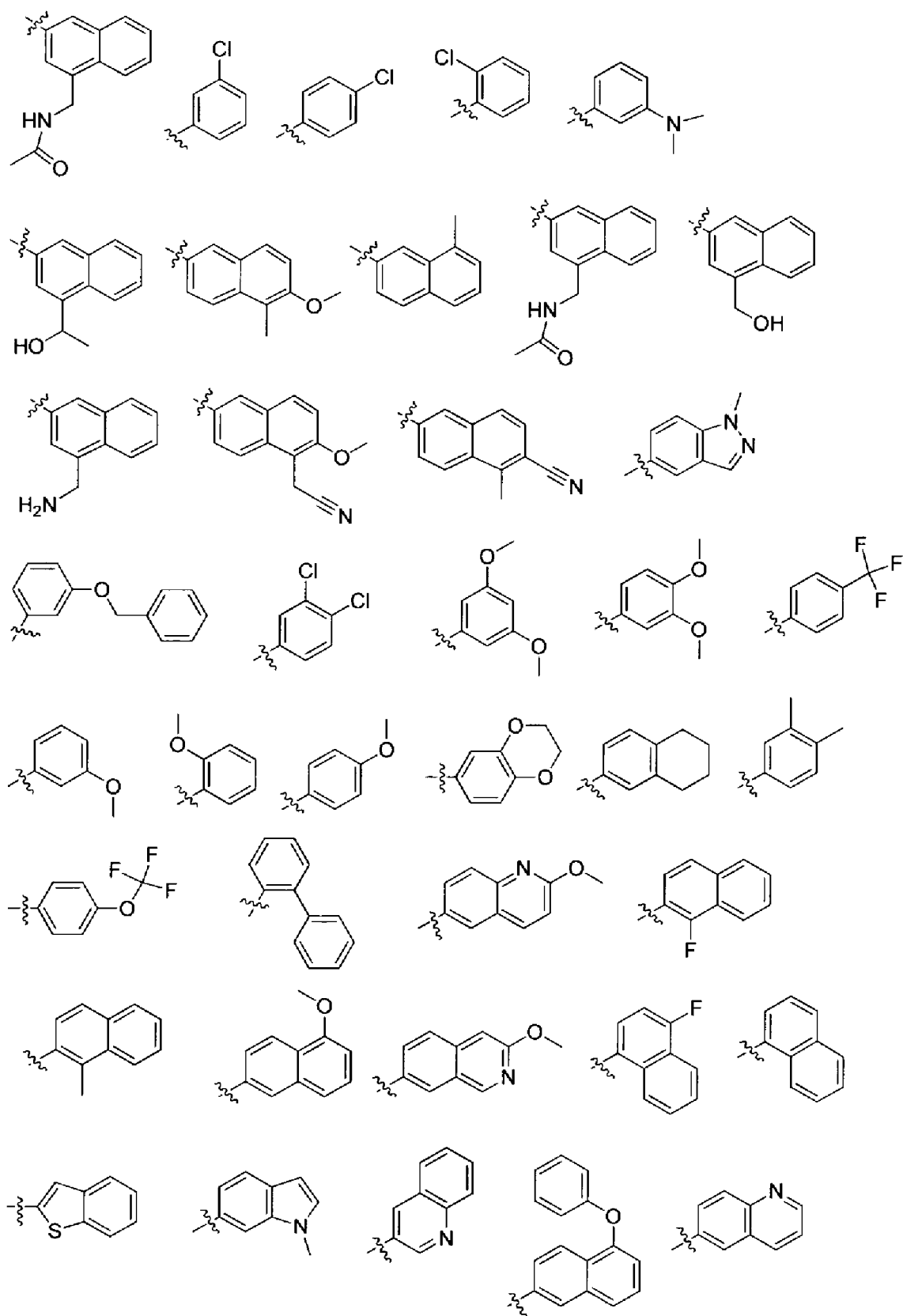
15. The compound of any one of claims 1-8 wherein R^2 is a quinolyl or isoquinolyl ring, which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

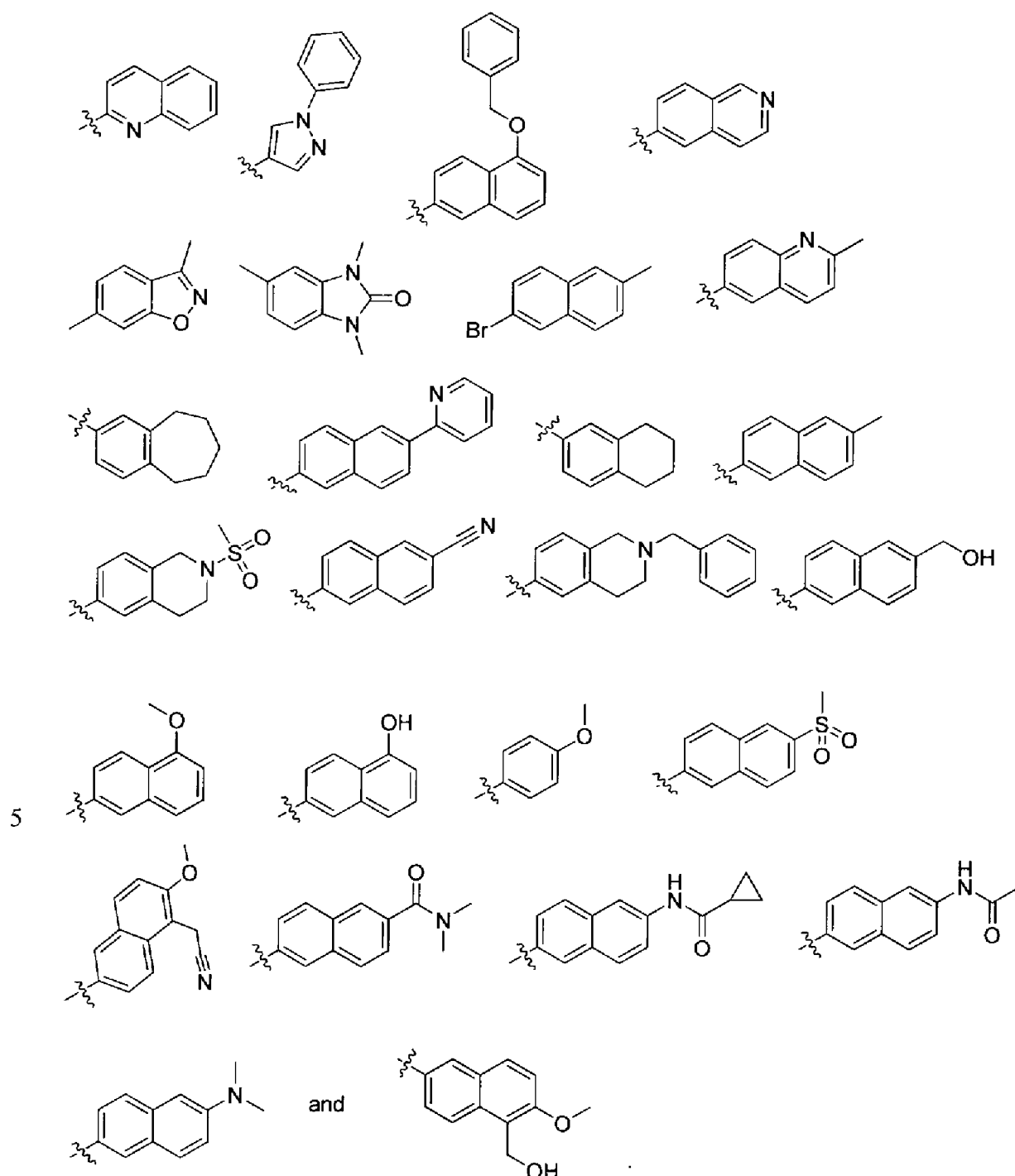
$C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

16. The compound of claim 15 wherein R^2 is a quinolyl or isoquinolyl ring, which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, carbocycle, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

17. The compound of any one of claims 1-8 wherein R^2 is selected from the group consisting of:





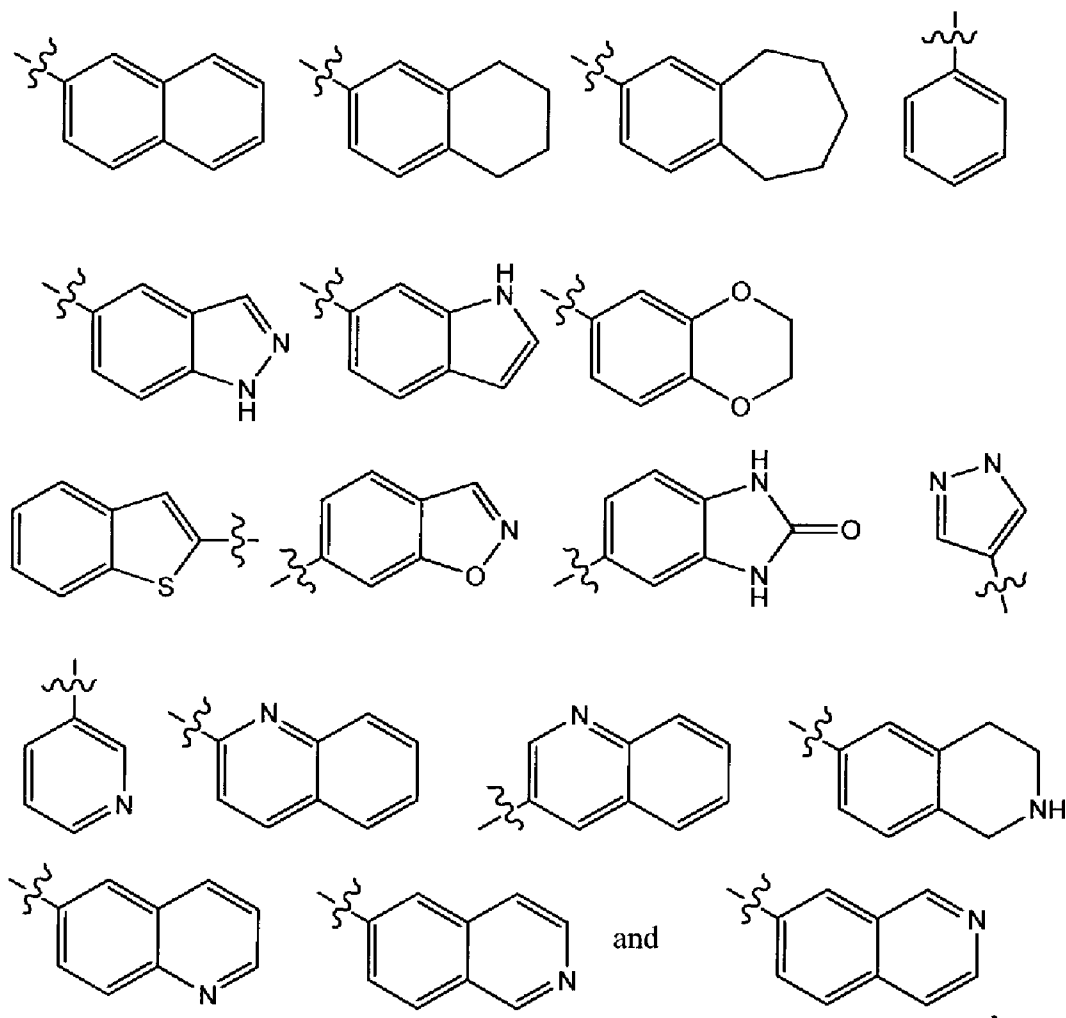


18. The compound of claim 1 wherein:

10 R^1 is a carbon-linked piperidine ring that is substituted on the piperidine ring nitrogen with a group R^x and that is optionally further substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-}

$_6$ alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo; and

R^2 is a ring selected from the group consisting of:



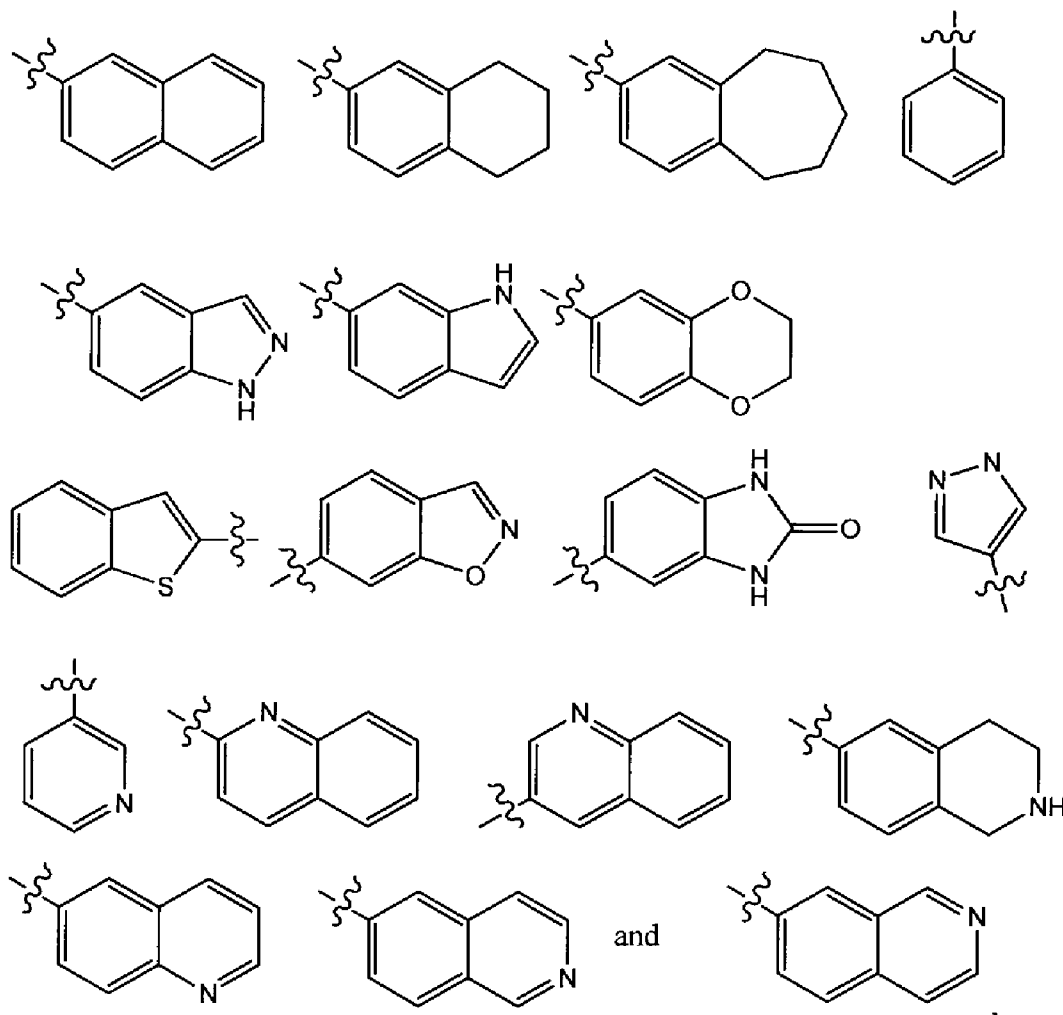
which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-$

$C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

19. The compound of claim 1 wherein:

- 5 R^1 is a carbon-linked piperazine ring that is substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein
- 10 each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or
- 15 more groups independently selected from halo; and

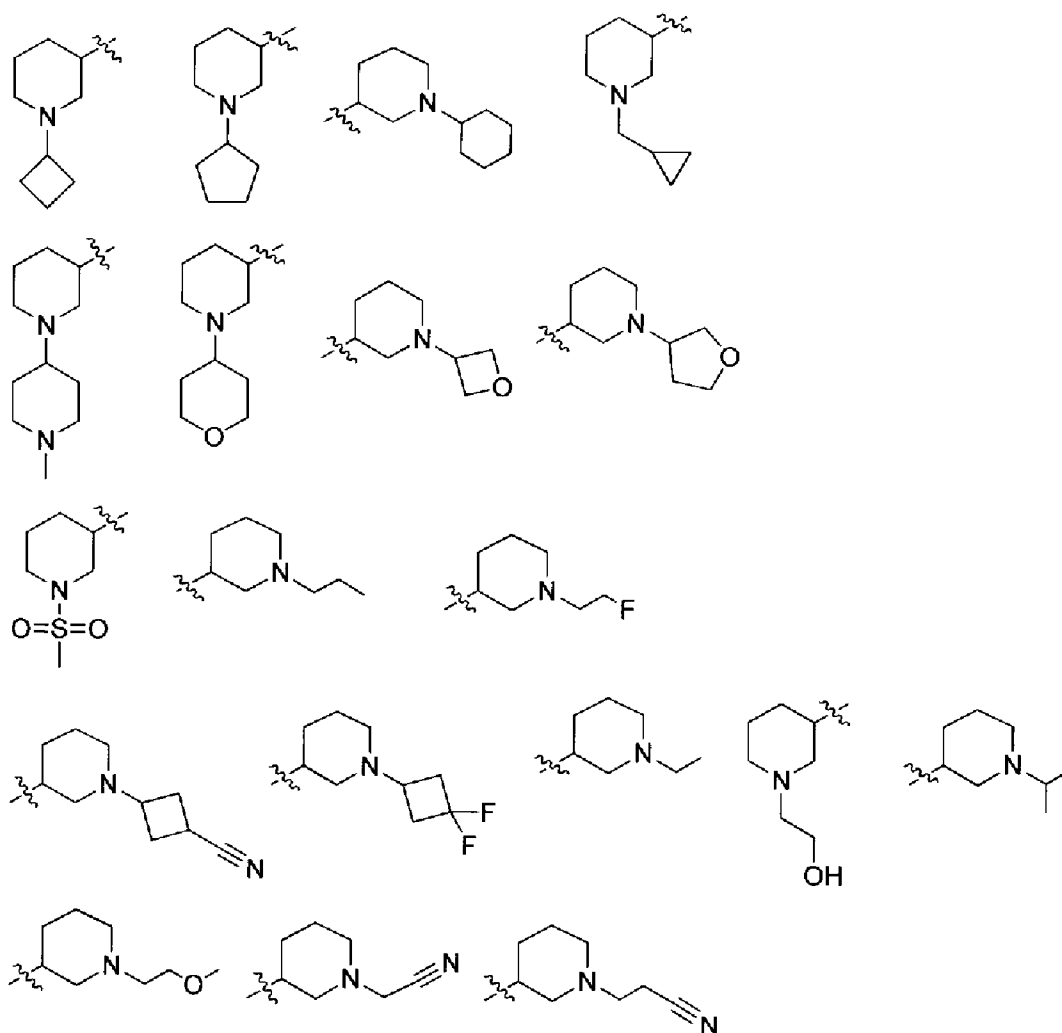
R^2 is a ring selected from the group consisting of:

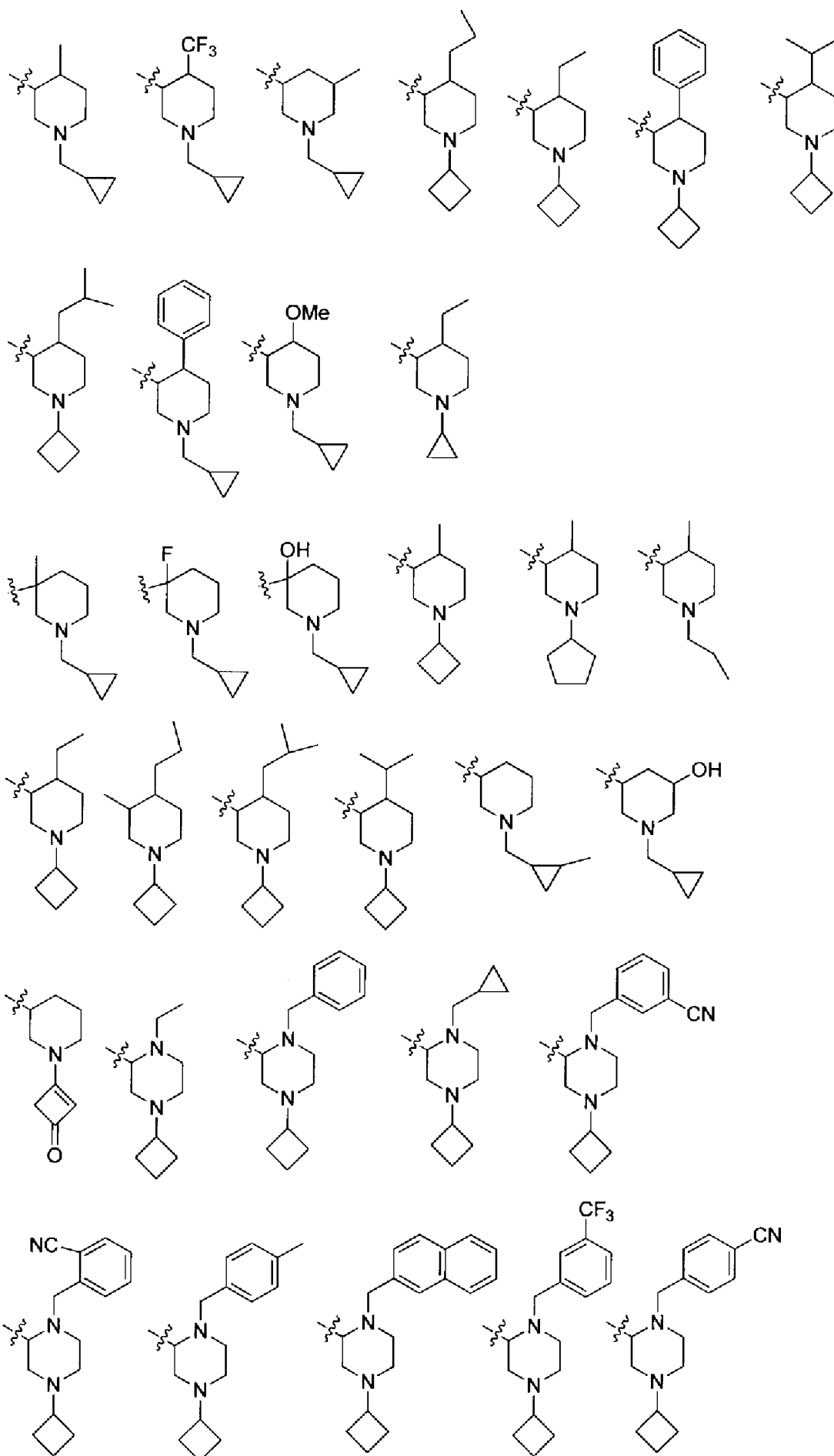


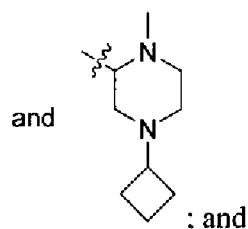
- which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

20. The compound of claim 1 wherein:

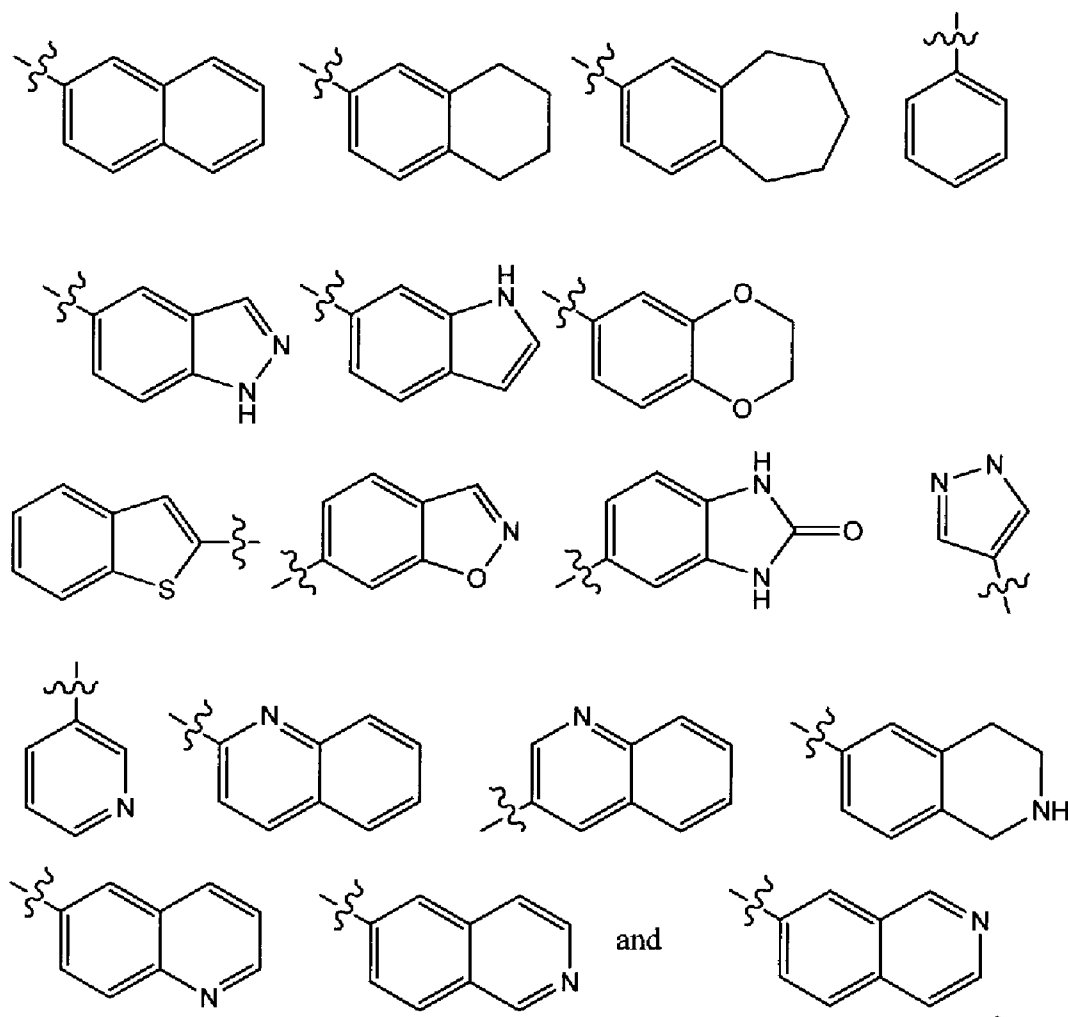
R^1 is selected from the group consisting of:







R^2 is a ring selected from the group consisting of:

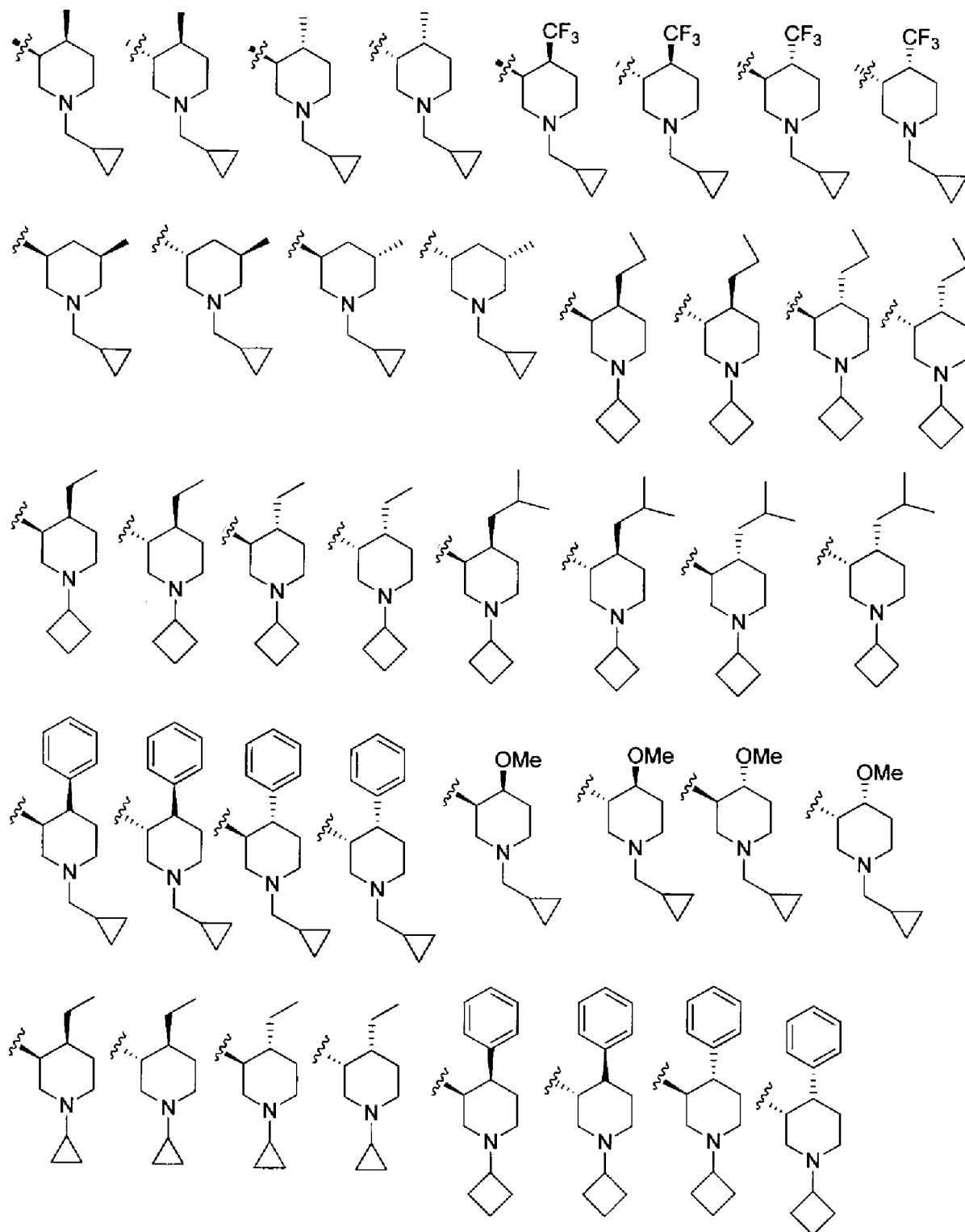


which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)$ -

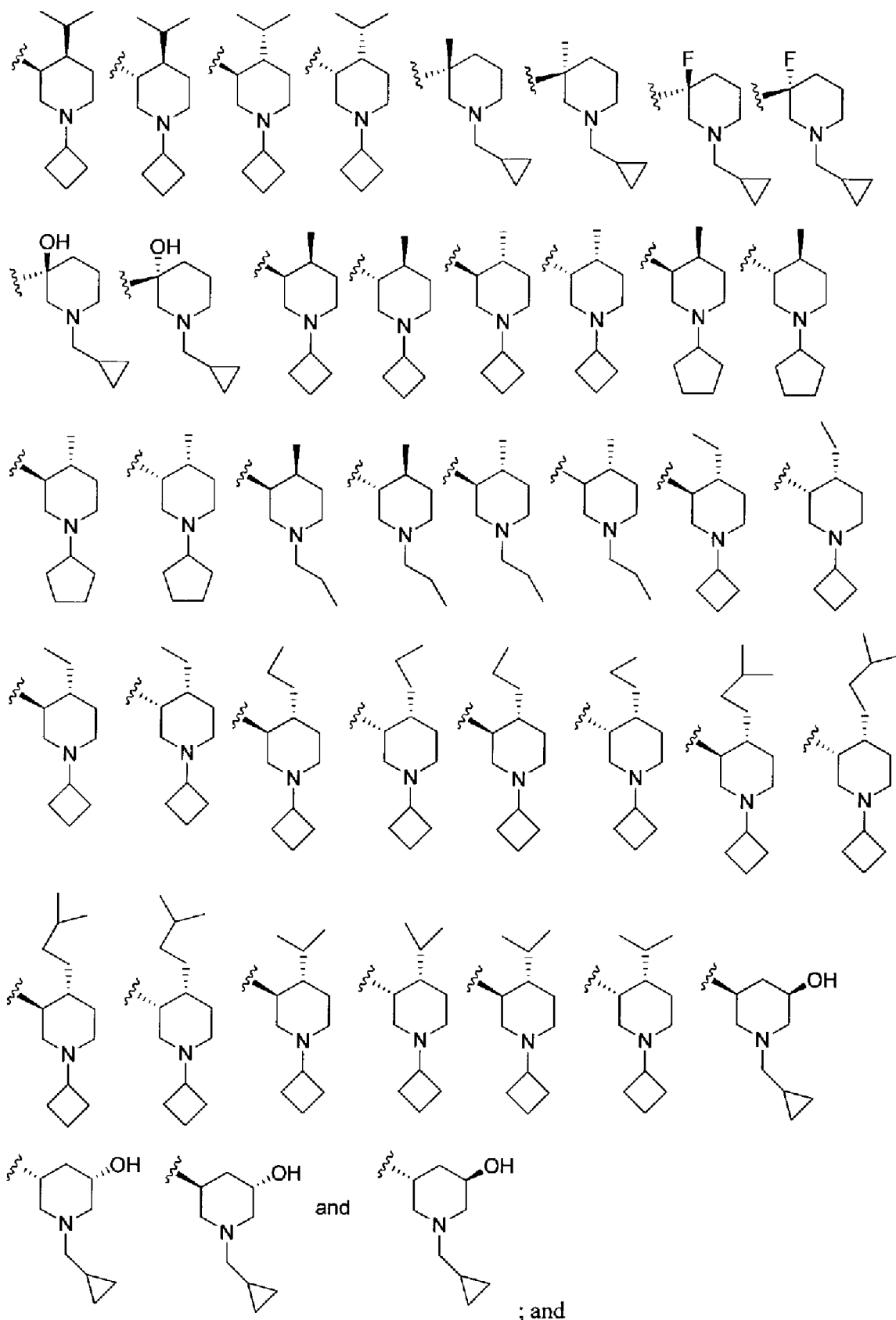
$C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

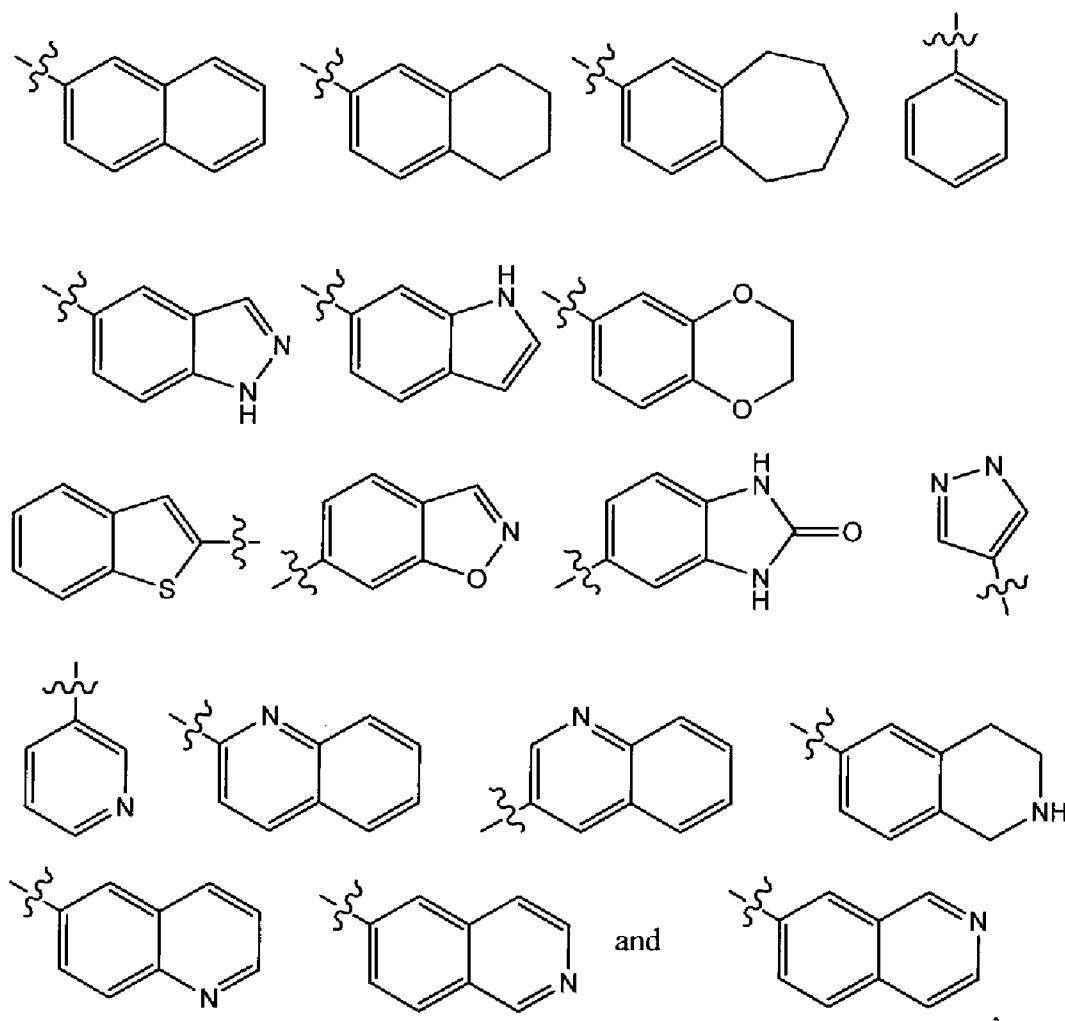
21. The compound of claim 1 wherein:

5 R^1 is selected from the group consisting of:



10



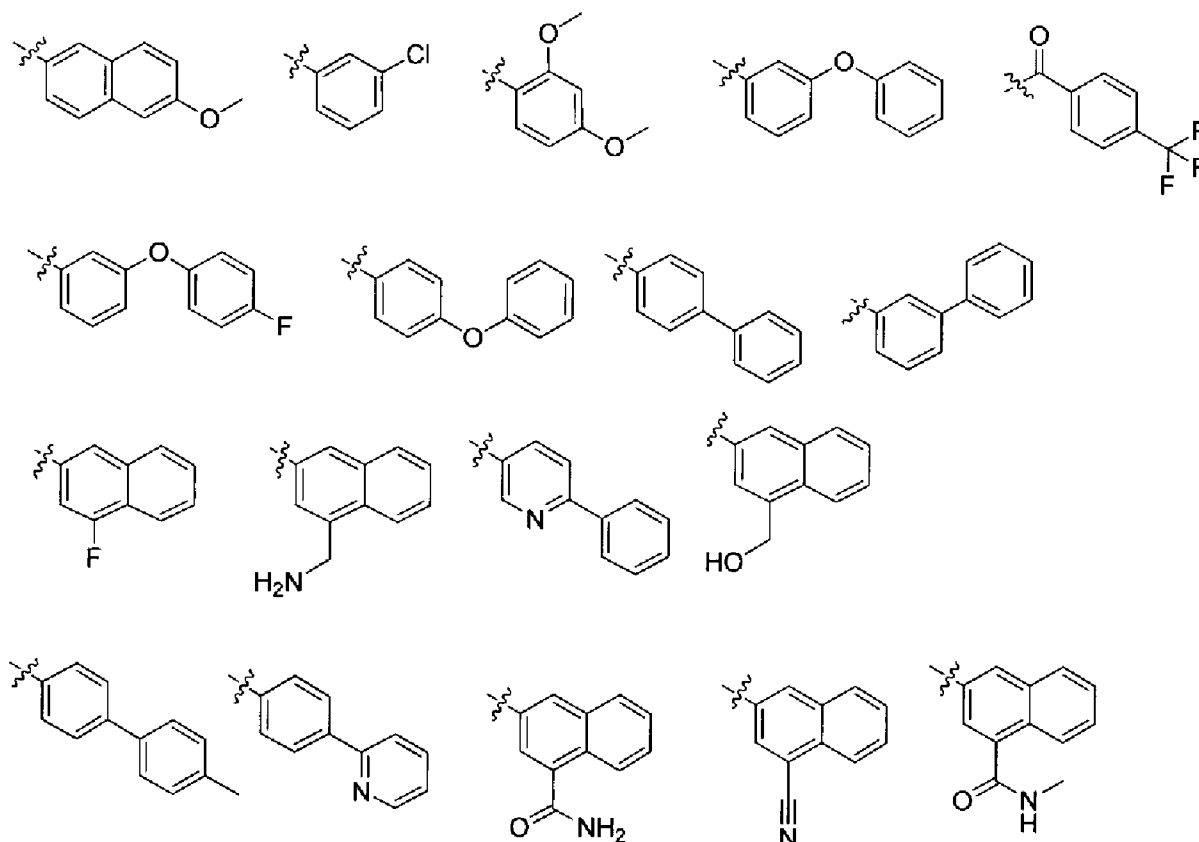


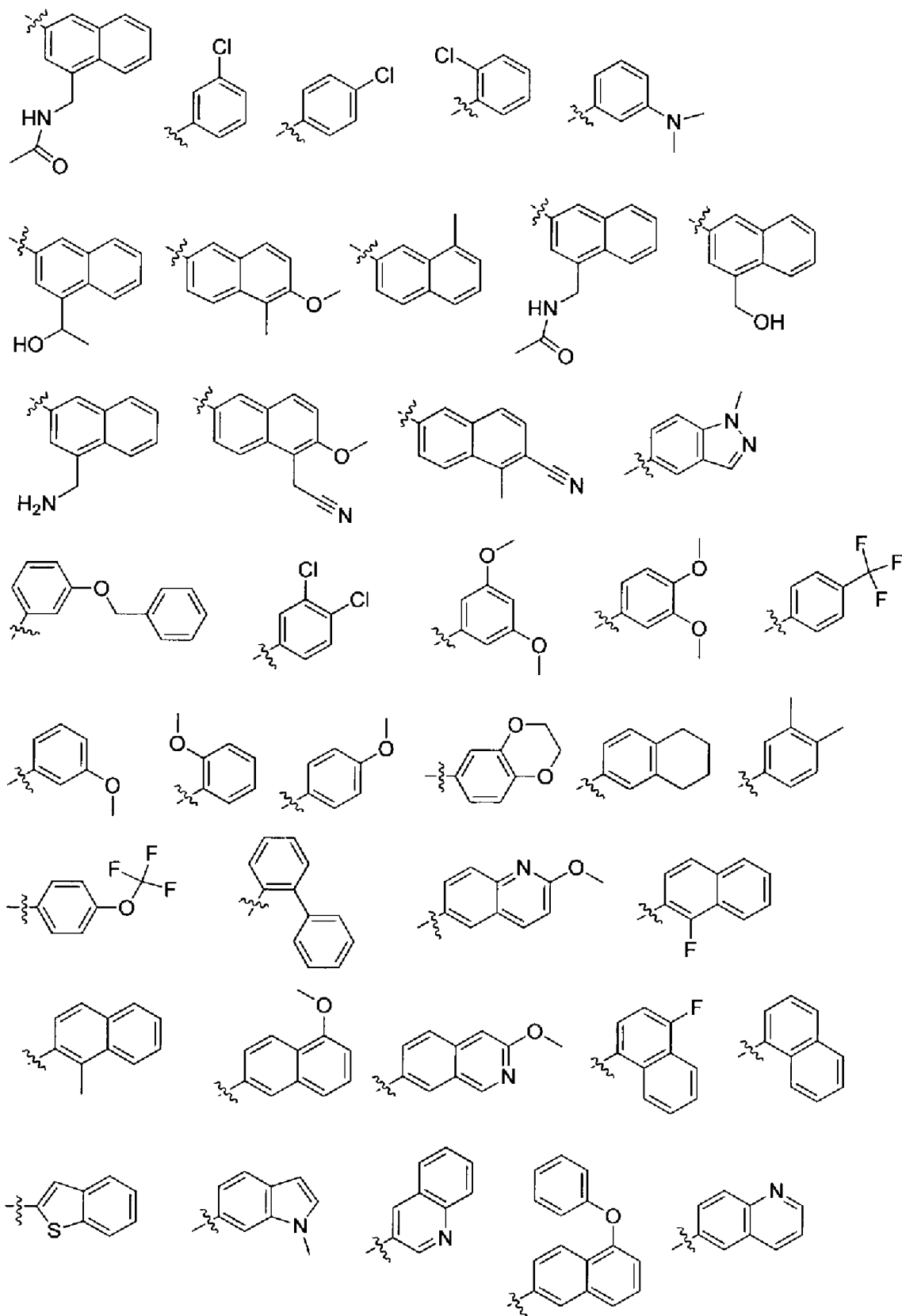
- 5 which ring is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle,
- 10 heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo.

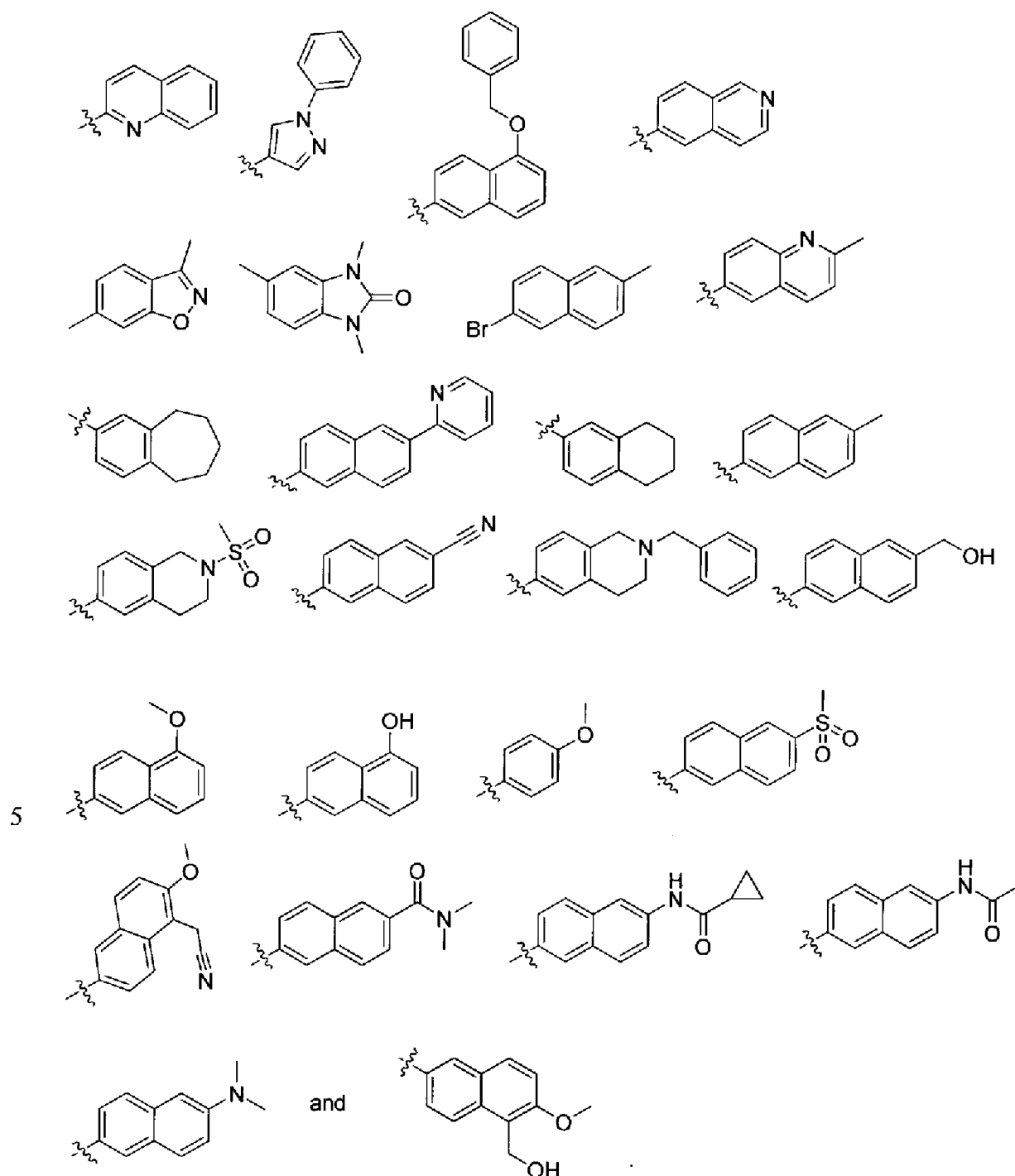
22. The compound of claim 1 wherein:

R^1 is a carbon-linked piperidine ring that is substituted on the piperidine ring nitrogen with a group R^x and that is optionally further substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8
 5 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is
 10 optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo; and

R^2 is selected from the group consisting of:







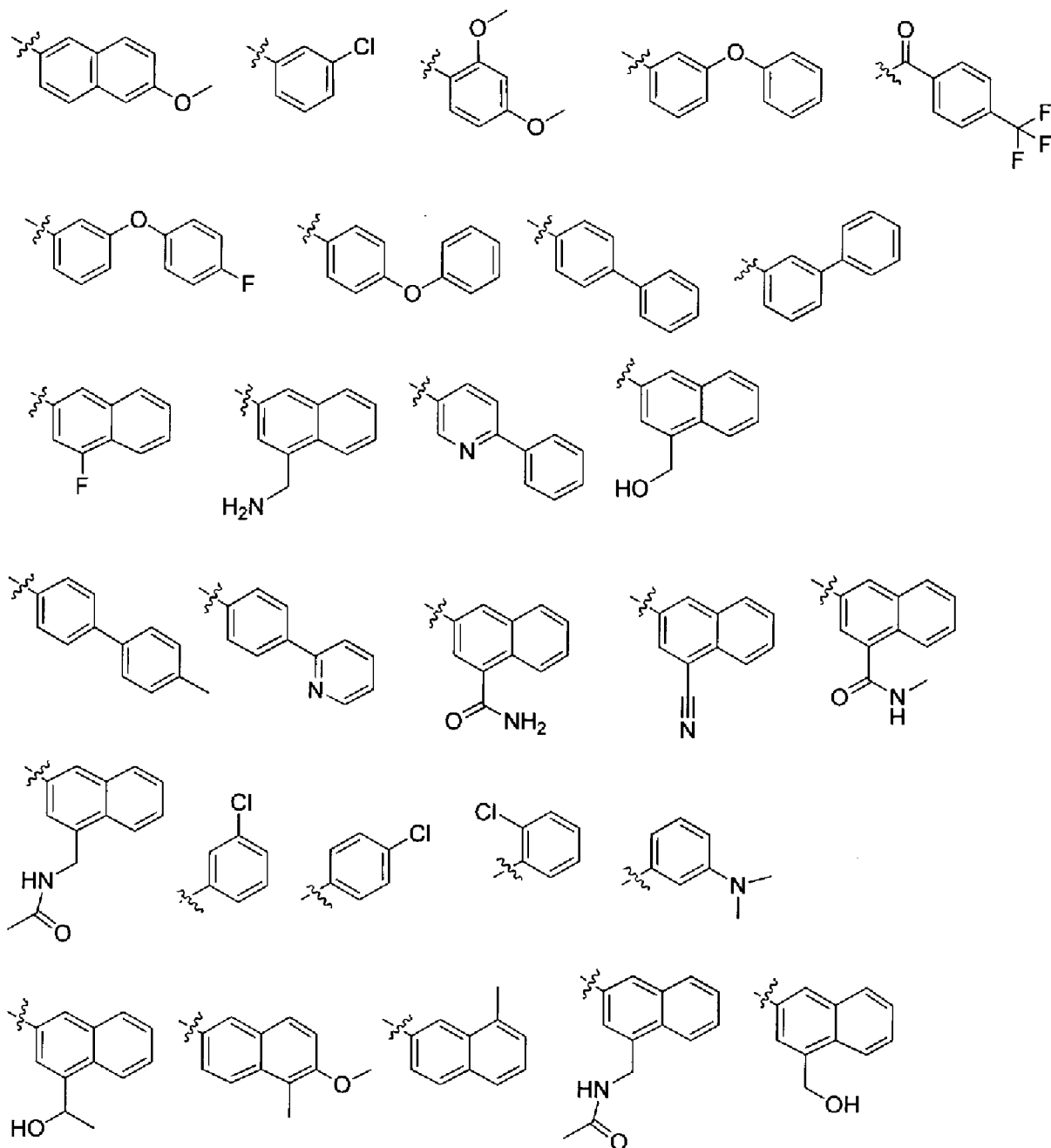
23. The compound of claim 1 wherein:

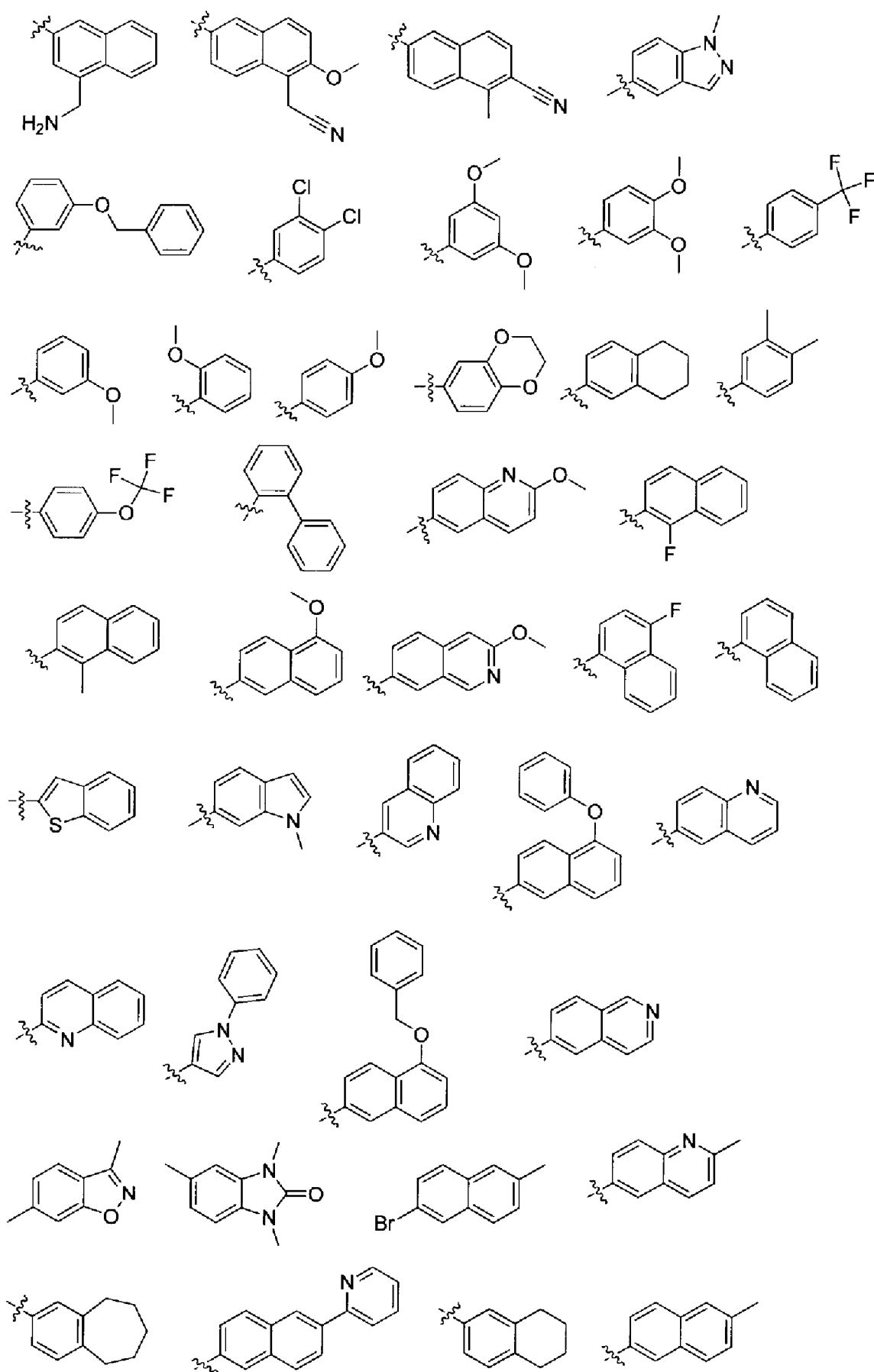
10 R^1 is a carbon-linked piperazine ring that is substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^b)_2$, $-CN$, $-C(O)-N(R^b)_2$, $-S(O)-N(R^b)_2$, $-S(O)_2-N(R^b)_2$, $-O-R^b$, $-S-R^b$, $-O-C(O)-R^b$, $-C(O)-R^b$, $-C(O)-OR^b$, $-S(O)-R^b$, $-S(O)_2-R^b$, $-N(R^b)-C(O)-R^b$, $-N(R^b)-S(O)-R^b$, $-N(R^b)-C(O)-N(R^b)_2$, and $-N(R^b)-S(O)_2-R^b$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, 3-8 membered heterocycle, aryl, and

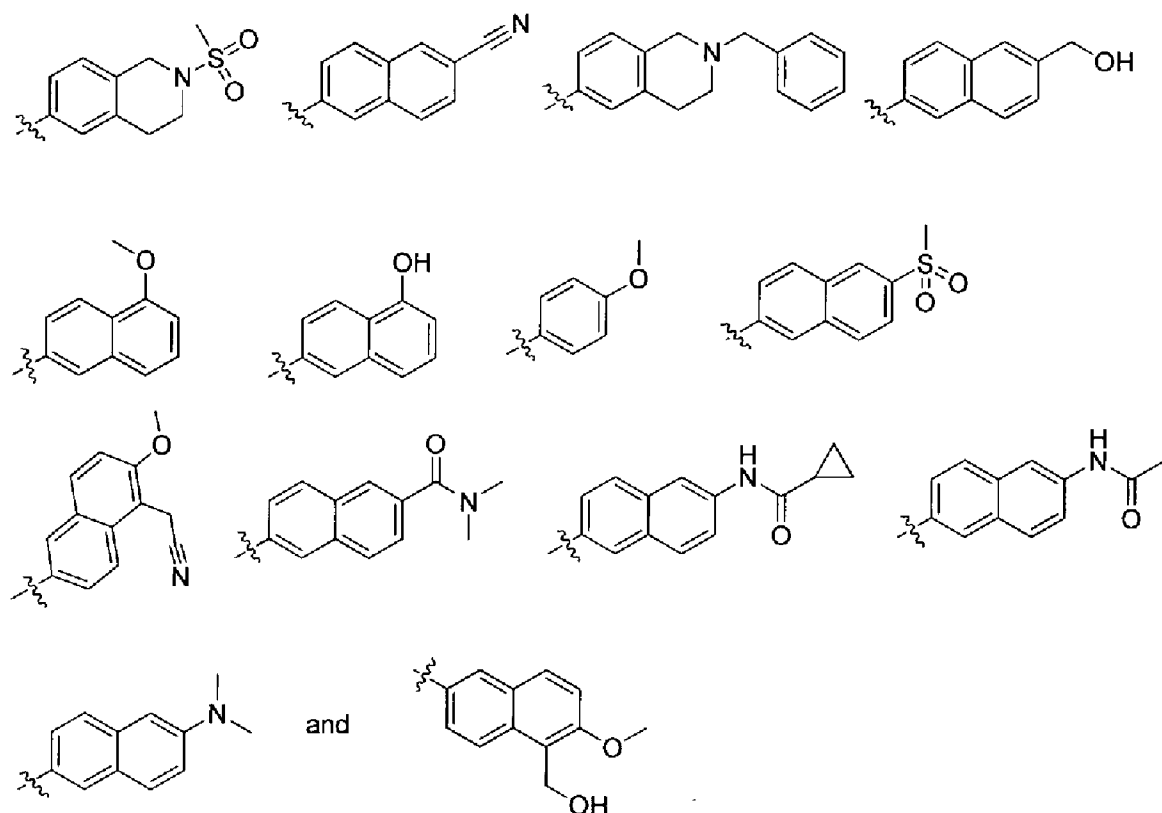
heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-\text{NO}_2$, $-\text{N}(\text{R}^b)_2$, $-\text{CN}$, $-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{S}(\text{O})_2-\text{N}(\text{R}^b)_2$, $-\text{O}-\text{R}^b$, $-\text{S}-\text{R}^b$, $-\text{O}-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{R}^b$, $-\text{C}(\text{O})-\text{OR}^b$, $-\text{S}(\text{O})-\text{R}^b$, $-\text{S}(\text{O})_2-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})-\text{R}^b$, $-\text{N}(\text{R}^b)-\text{C}(\text{O})-\text{N}(\text{R}^b)_2$, $-\text{N}(\text{R}^b)-\text{S}(\text{O})_2-\text{R}^b$, and C_{1-6} alkyl that is optionally substituted with one or

5 more groups independently selected from halo; and

R^2 is selected from the group consisting of:



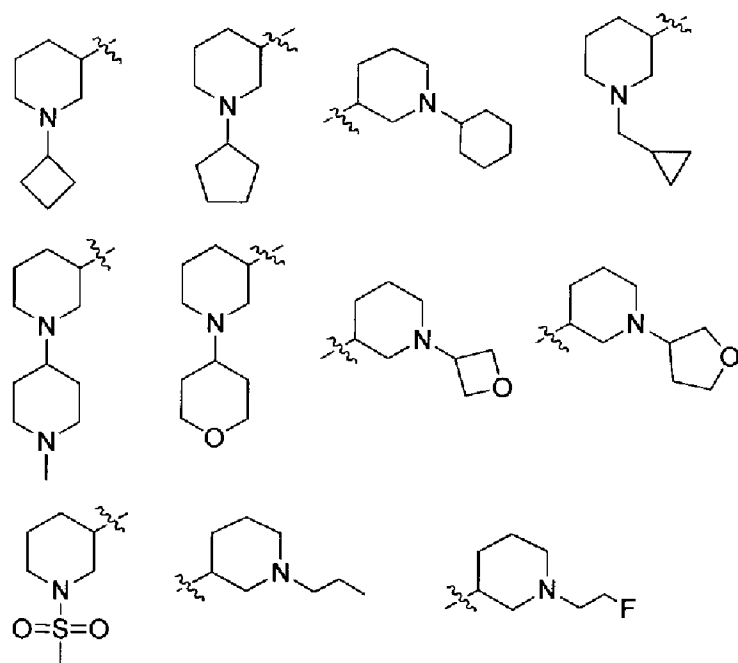


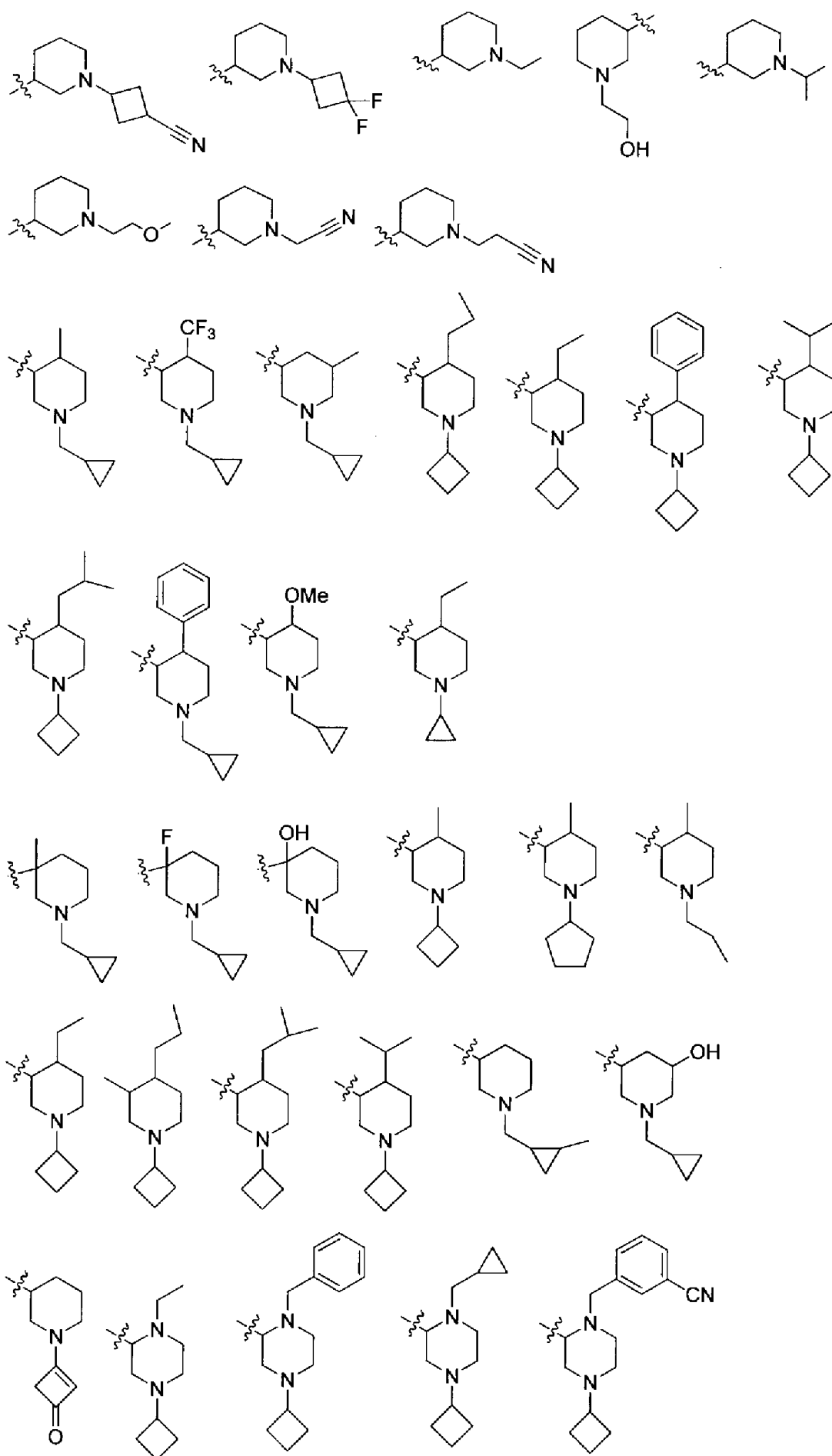


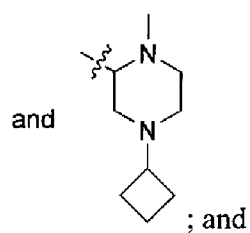
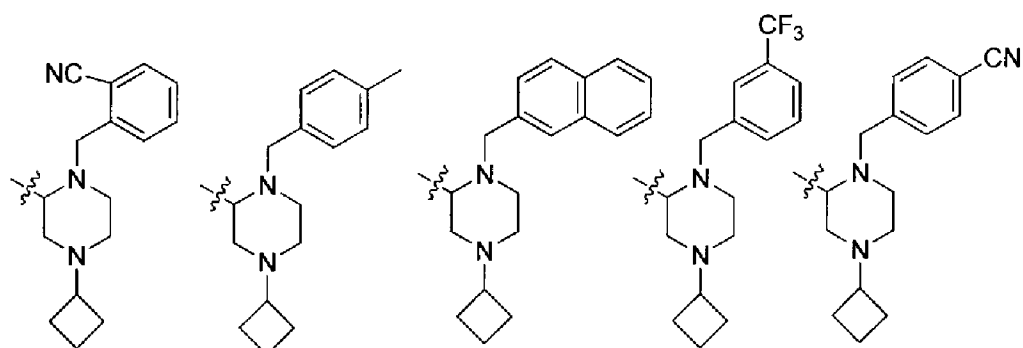
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24. The compound of claim 1 wherein:

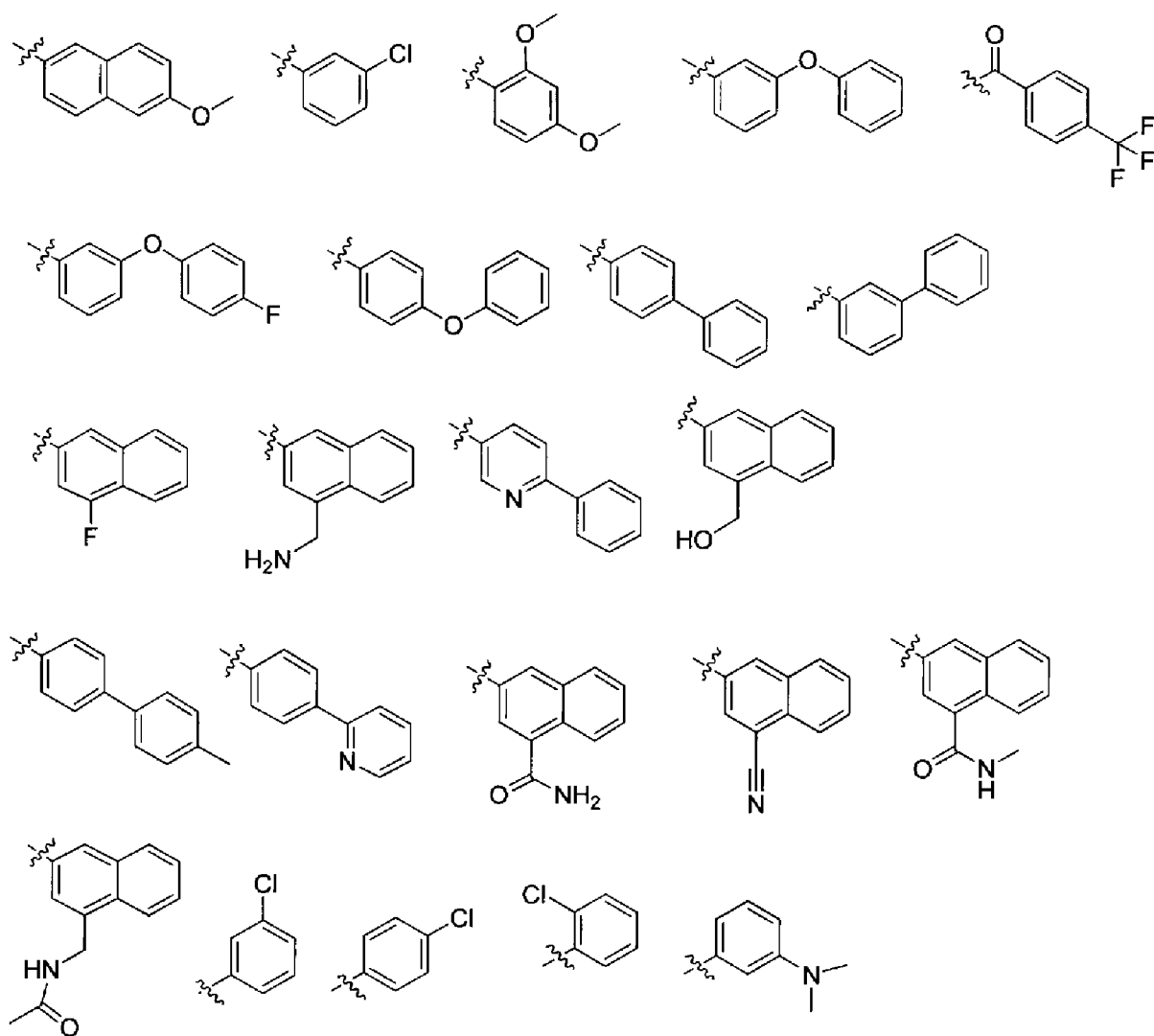
R^1 is selected from the group consisting of:

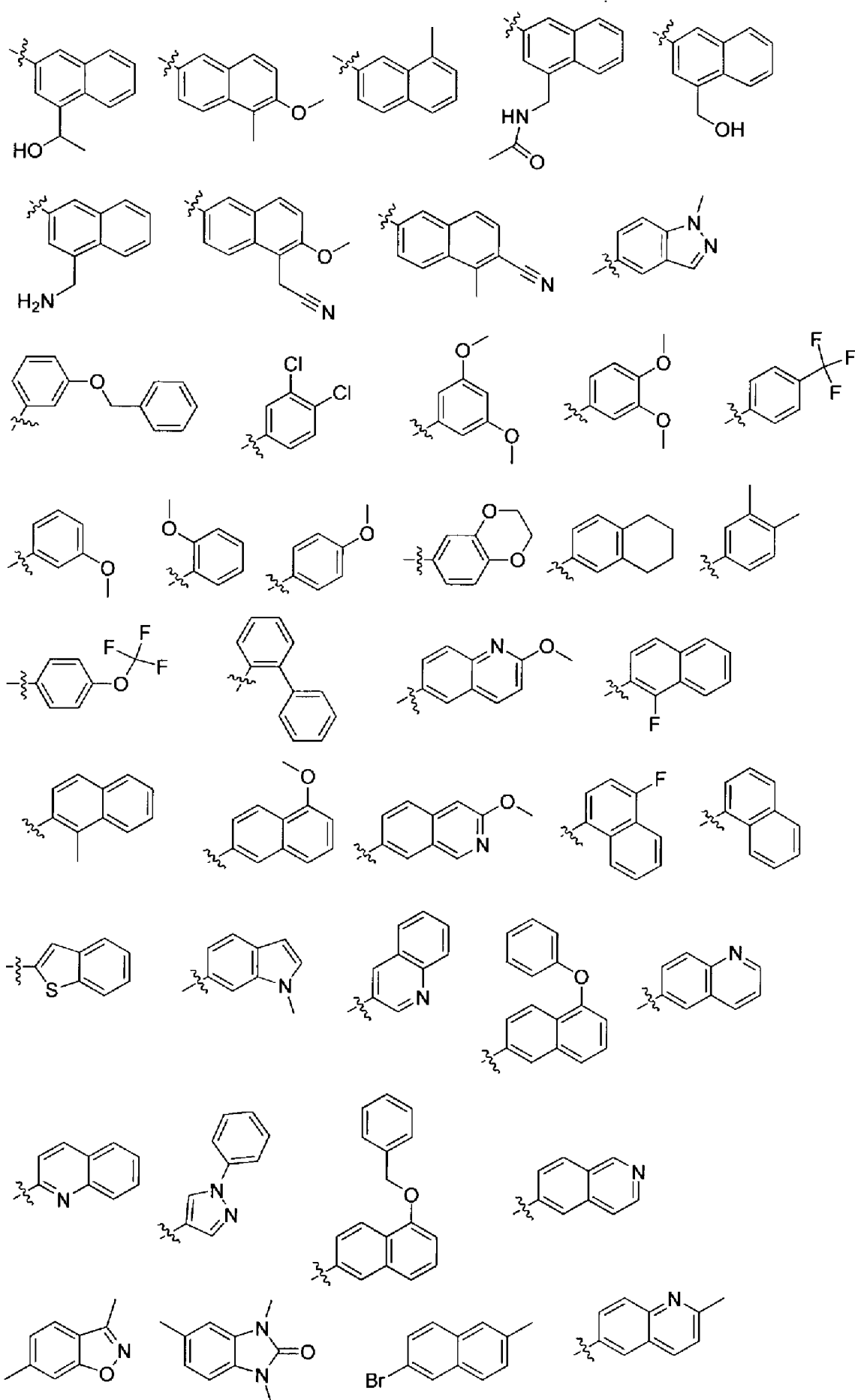


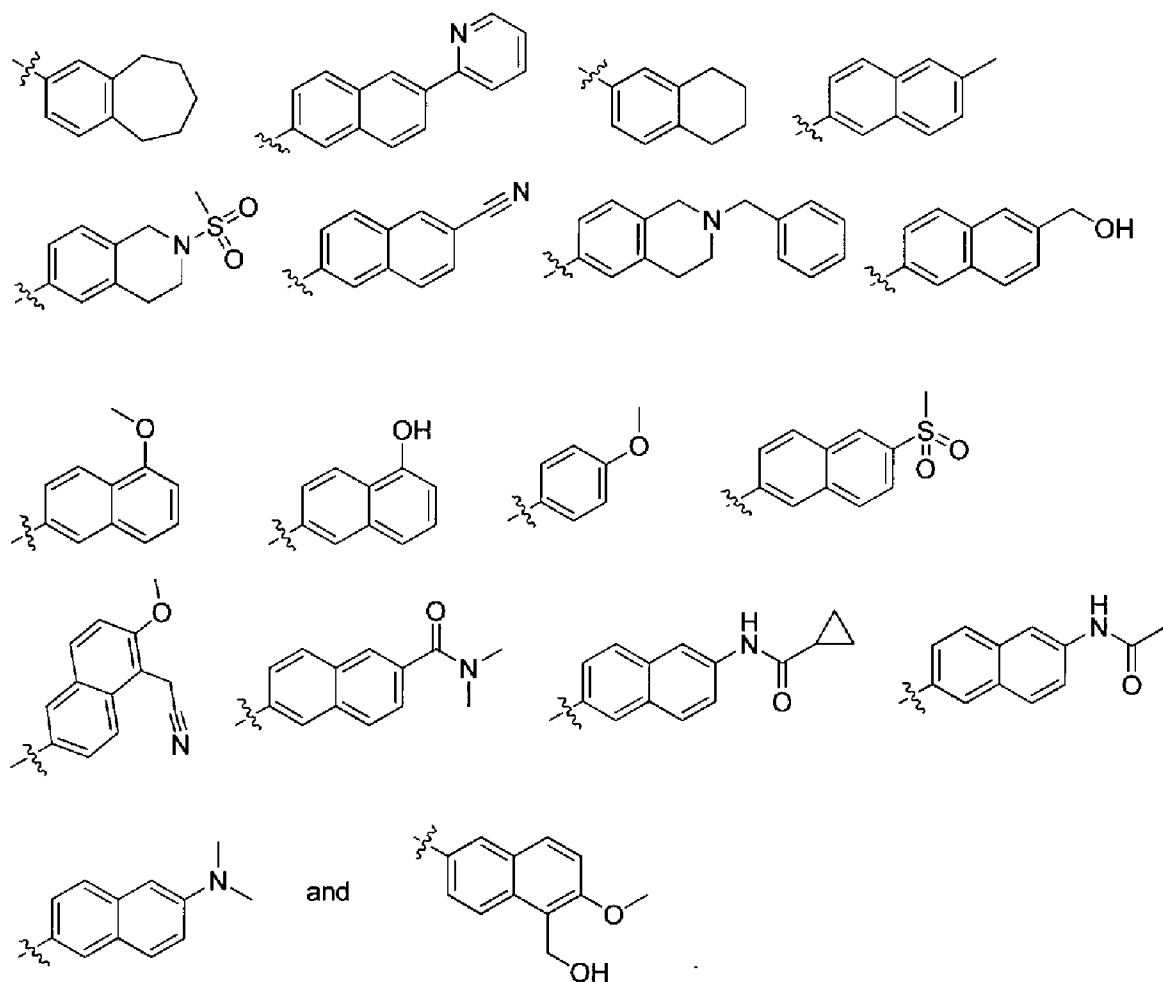




R^2 is selected from the group consisting of:

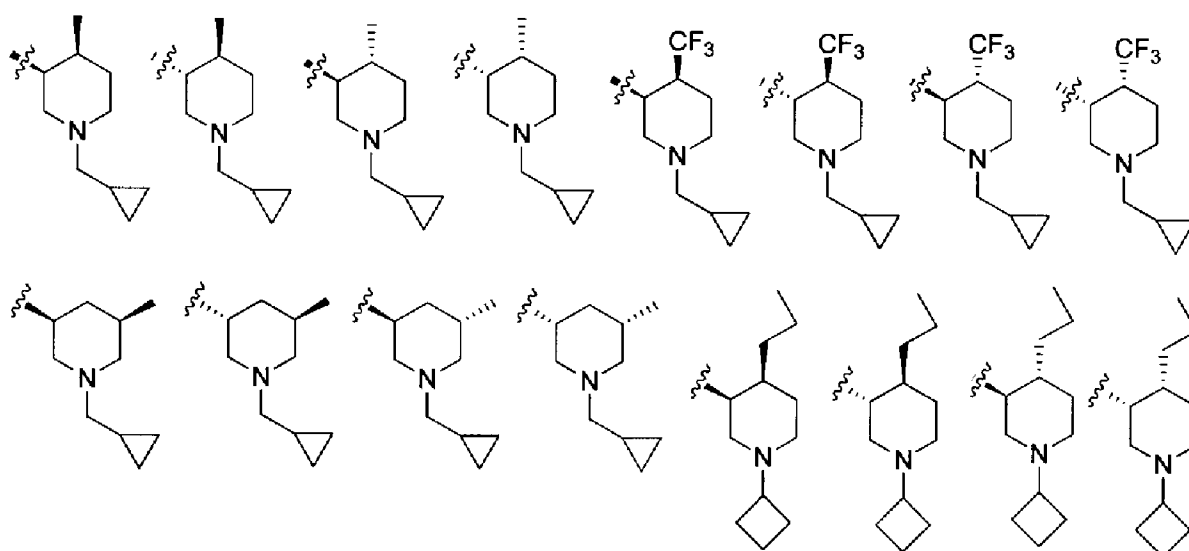


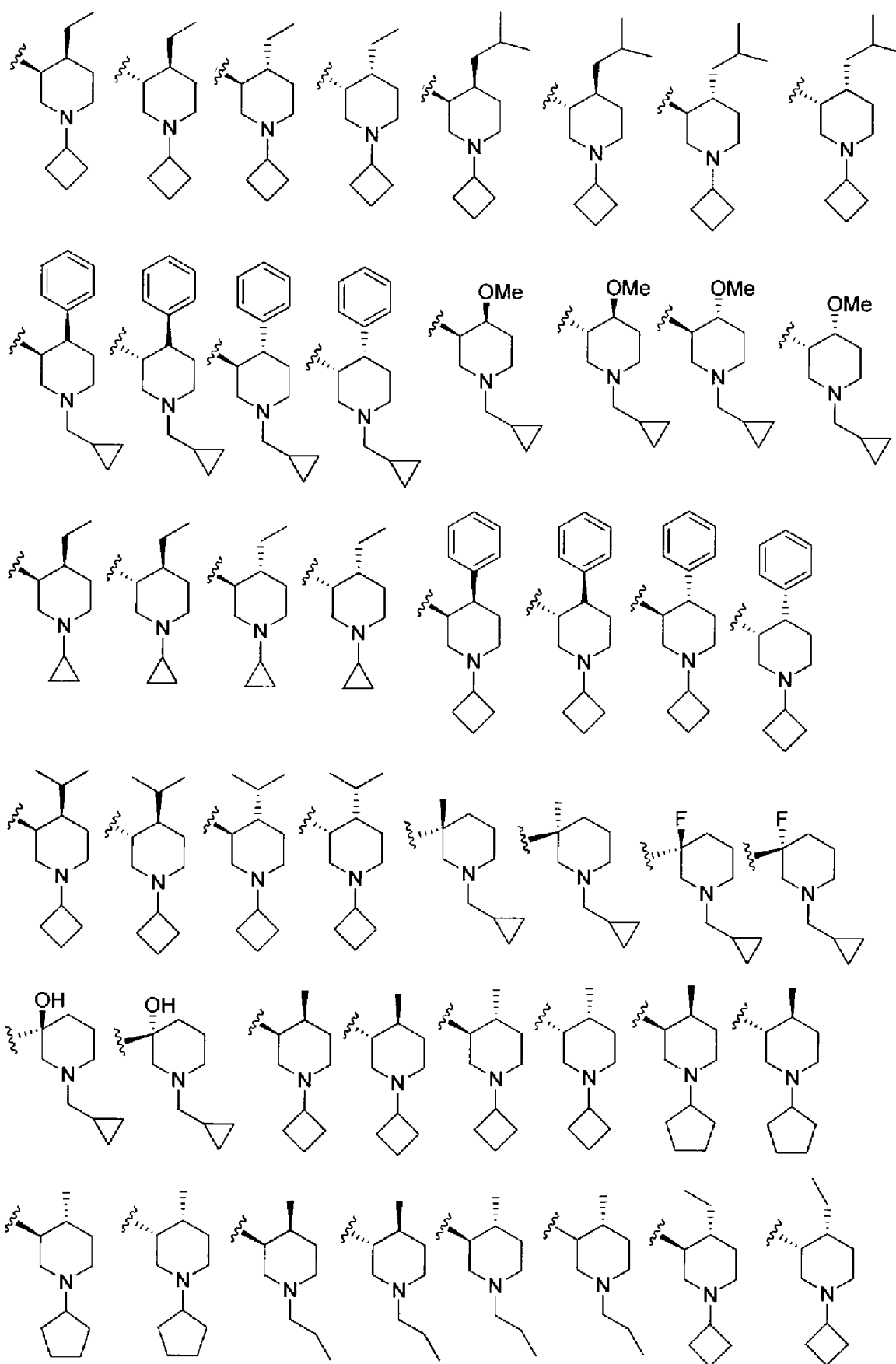


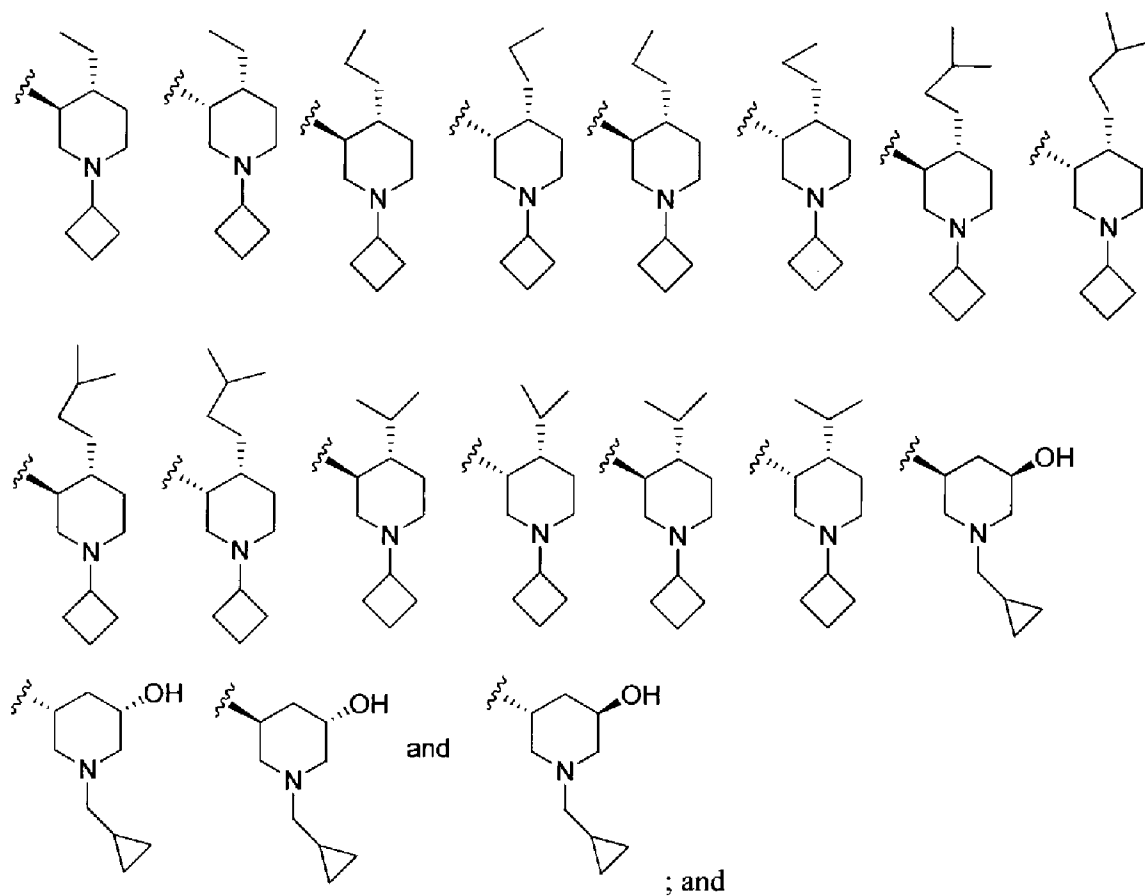


25. The compound of claim 1 wherein:

R^1 is selected from the group consisting of:

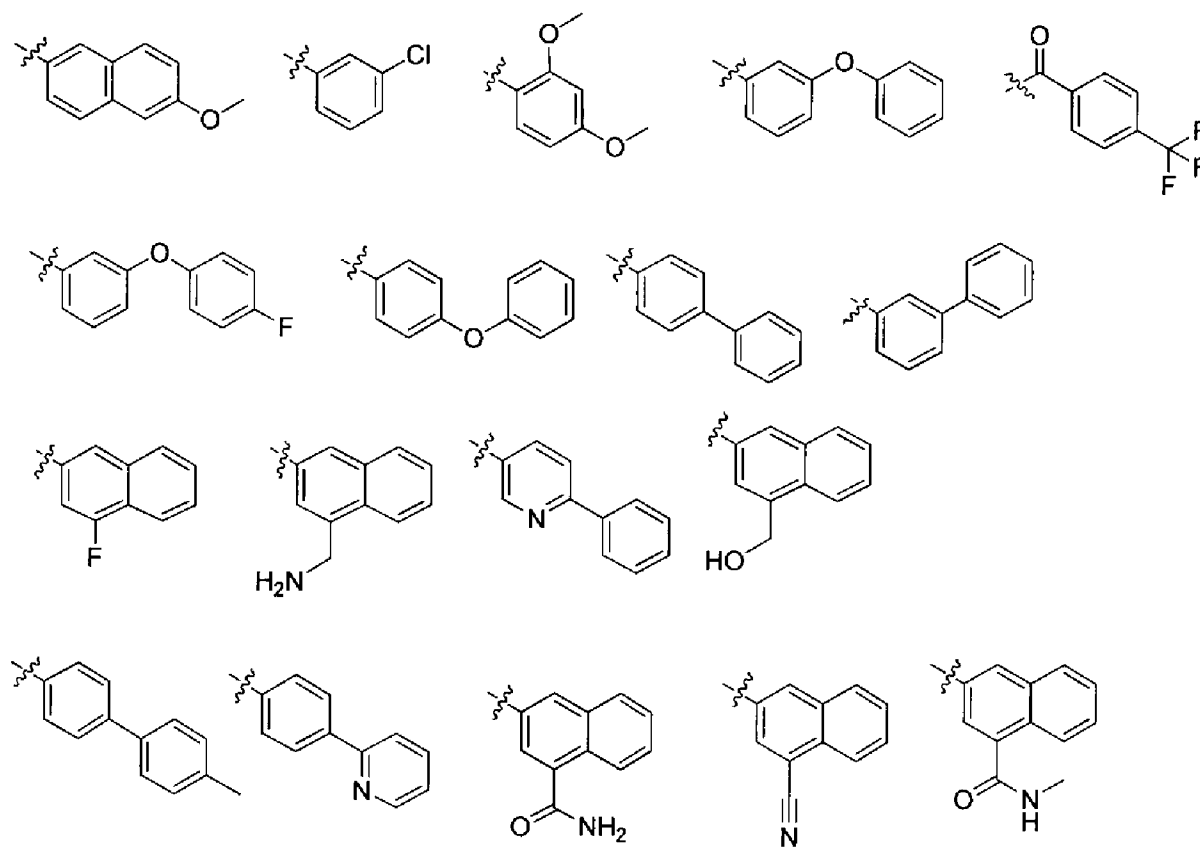


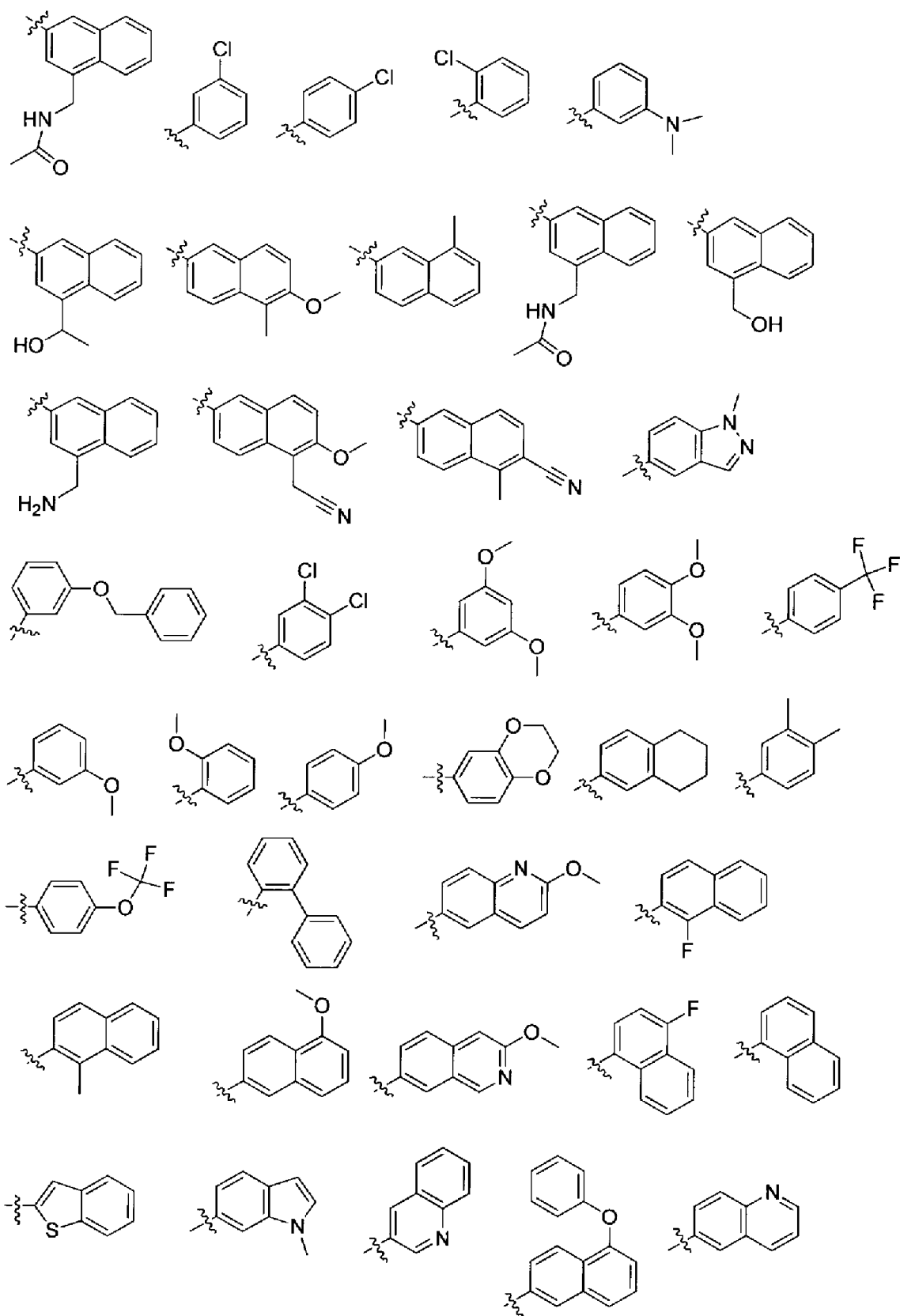




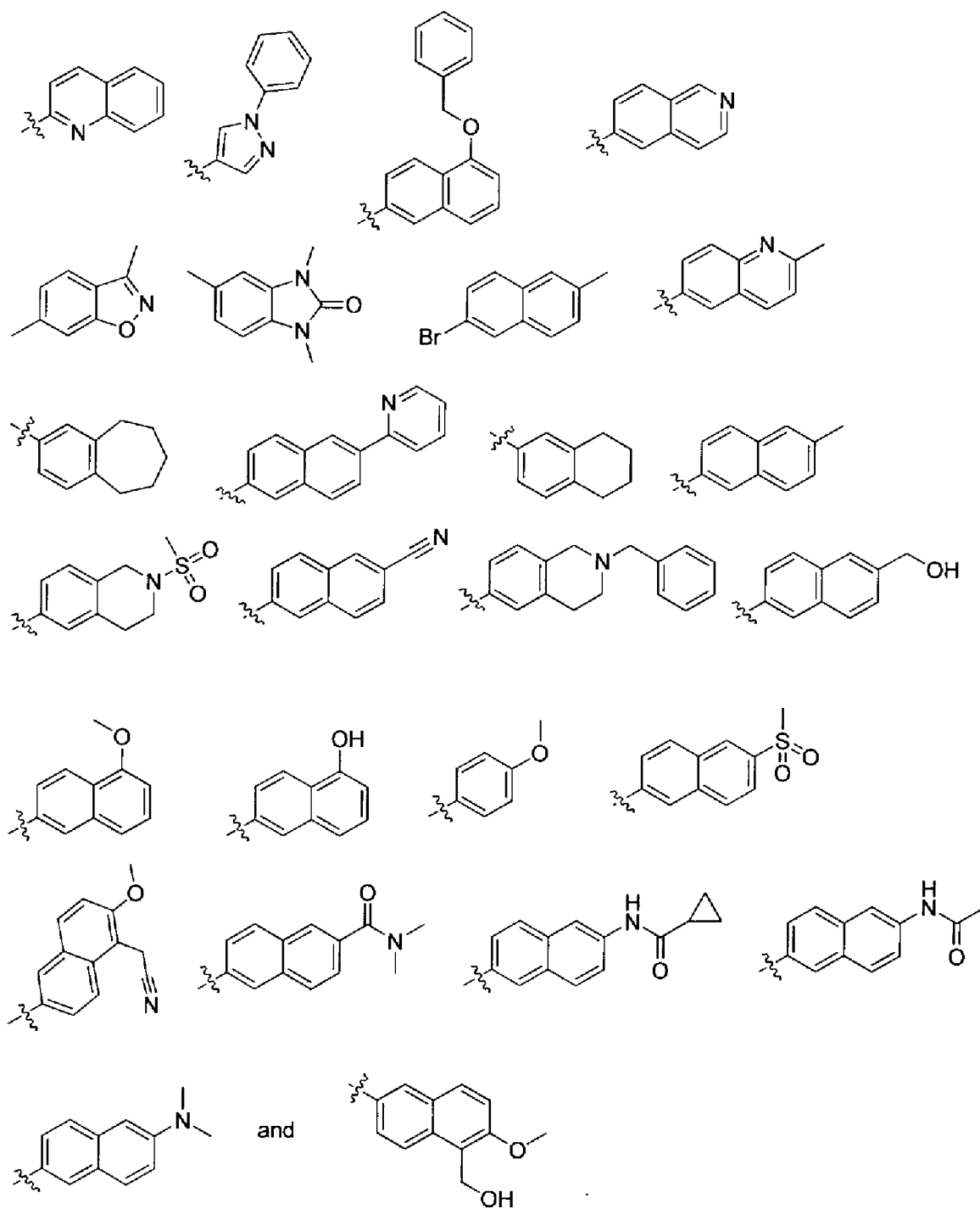
R^2 is selected from the group consisting of:

5

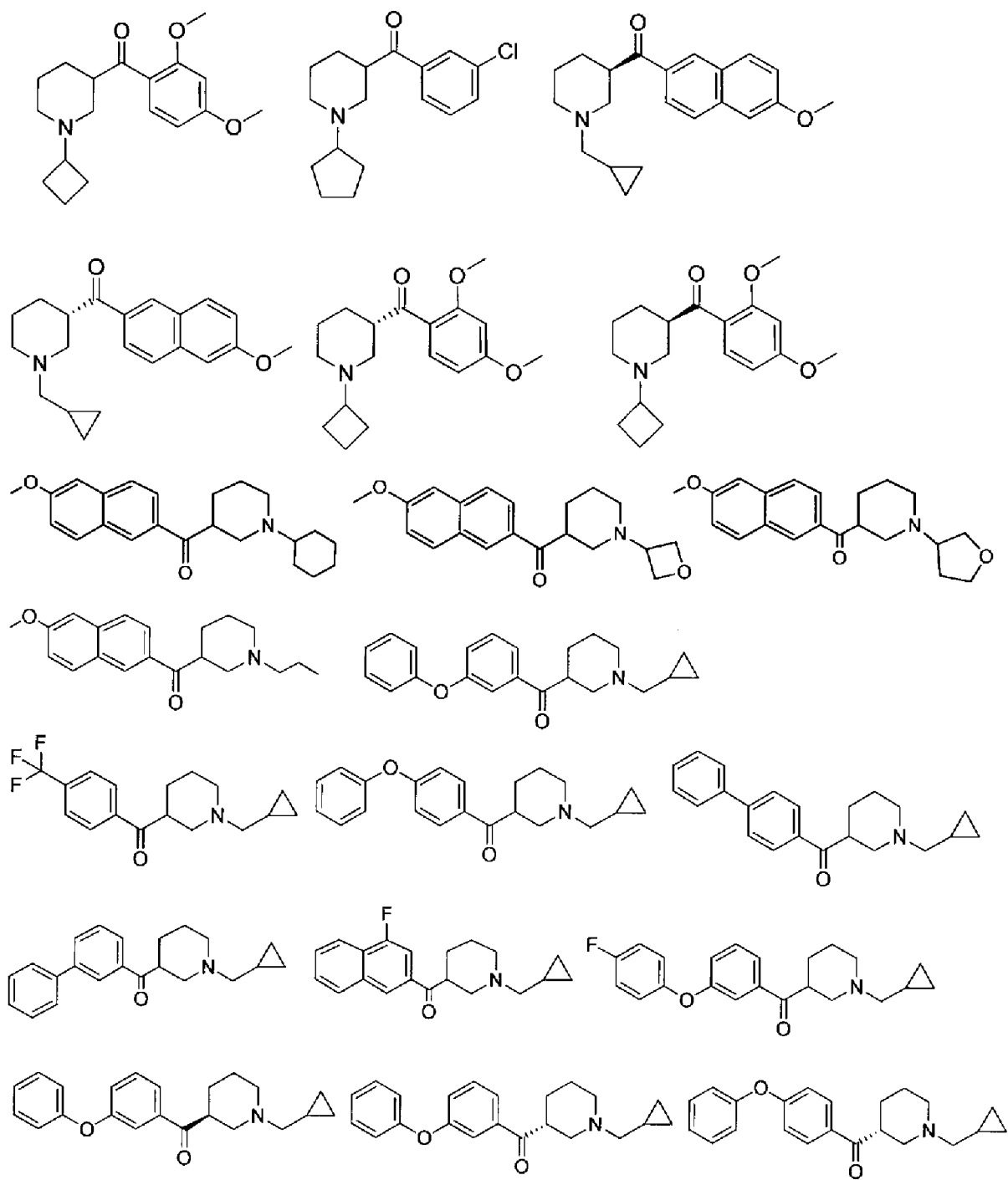


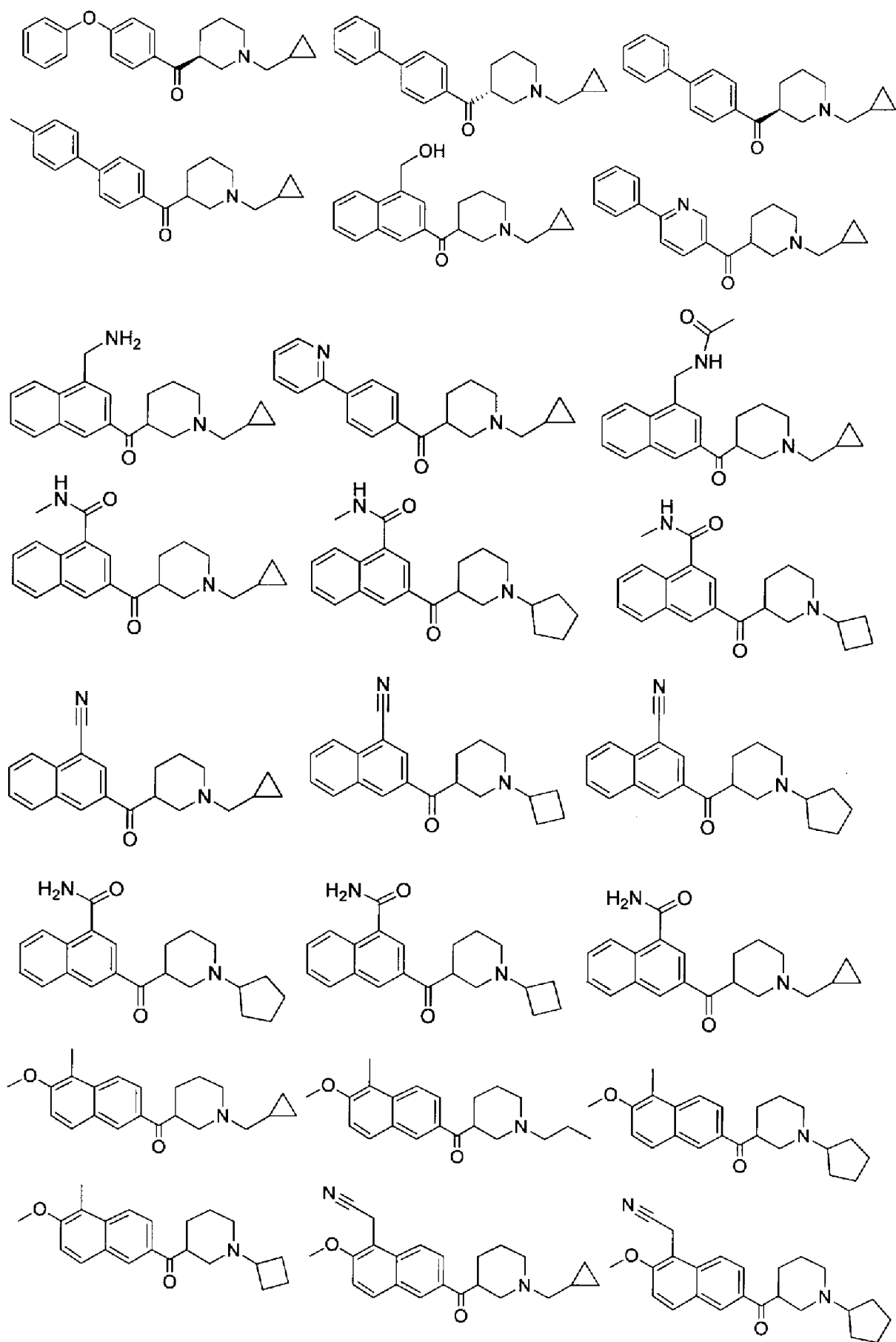


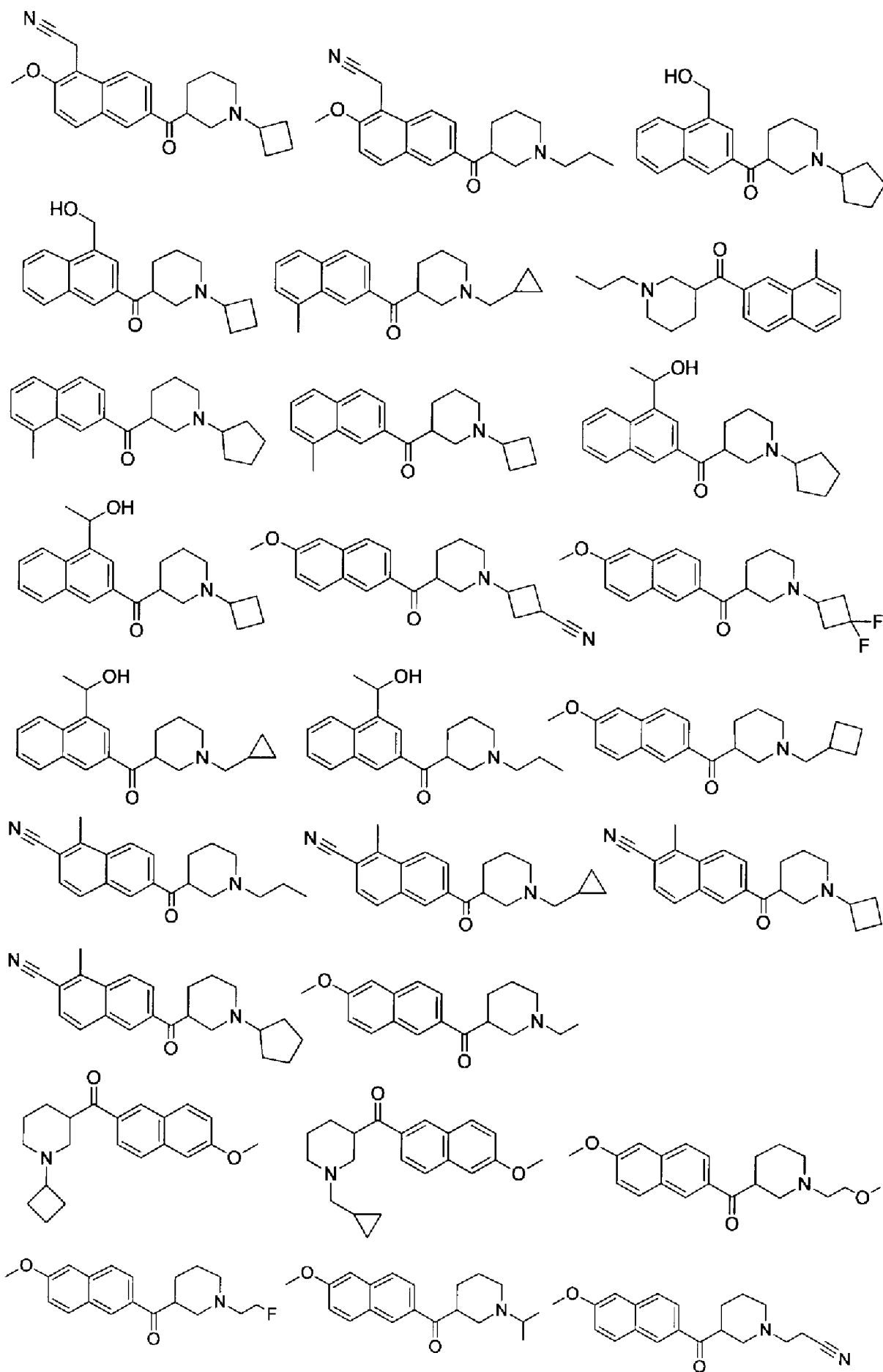
5

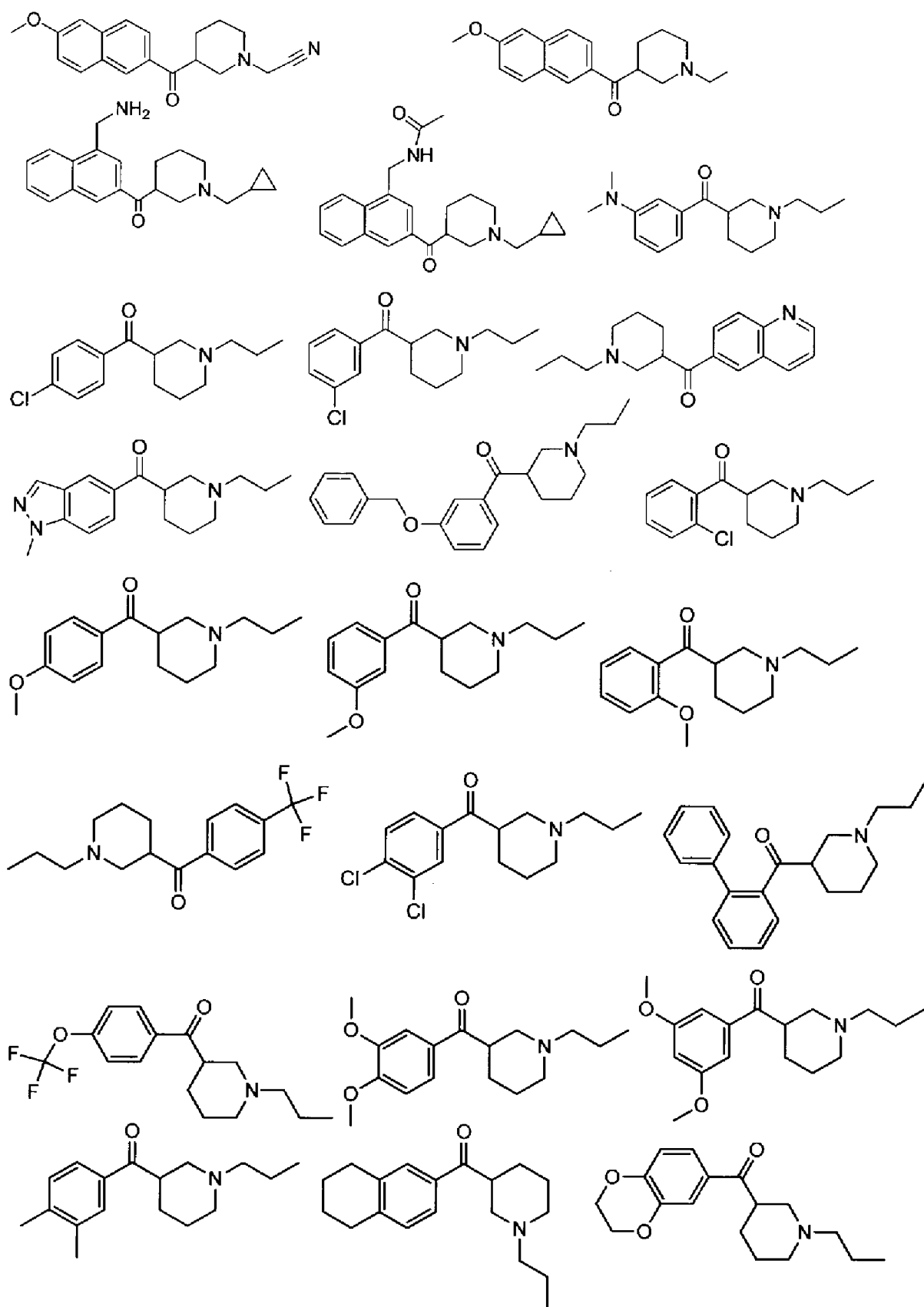


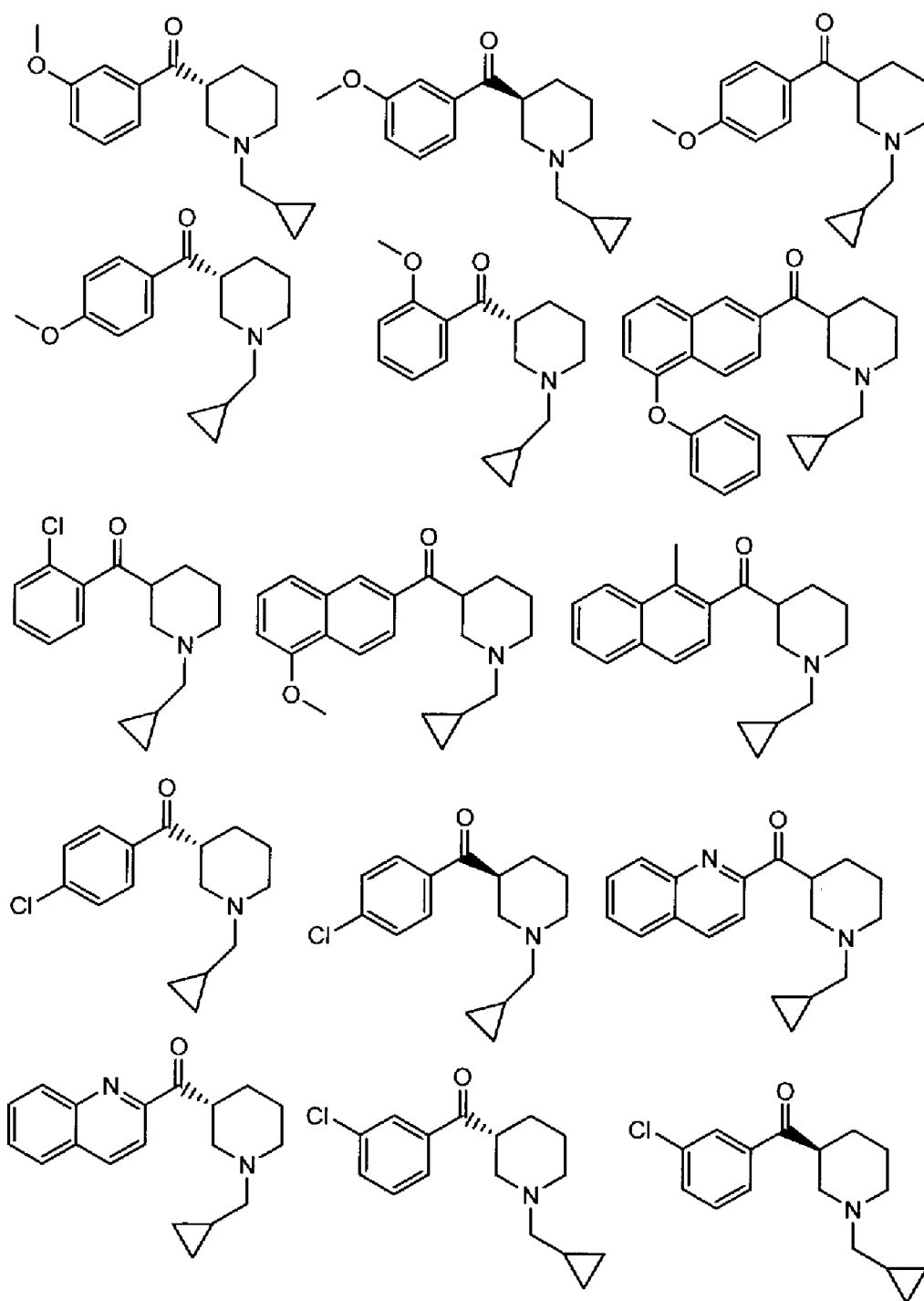
26. A compound selected from the group consisting of:

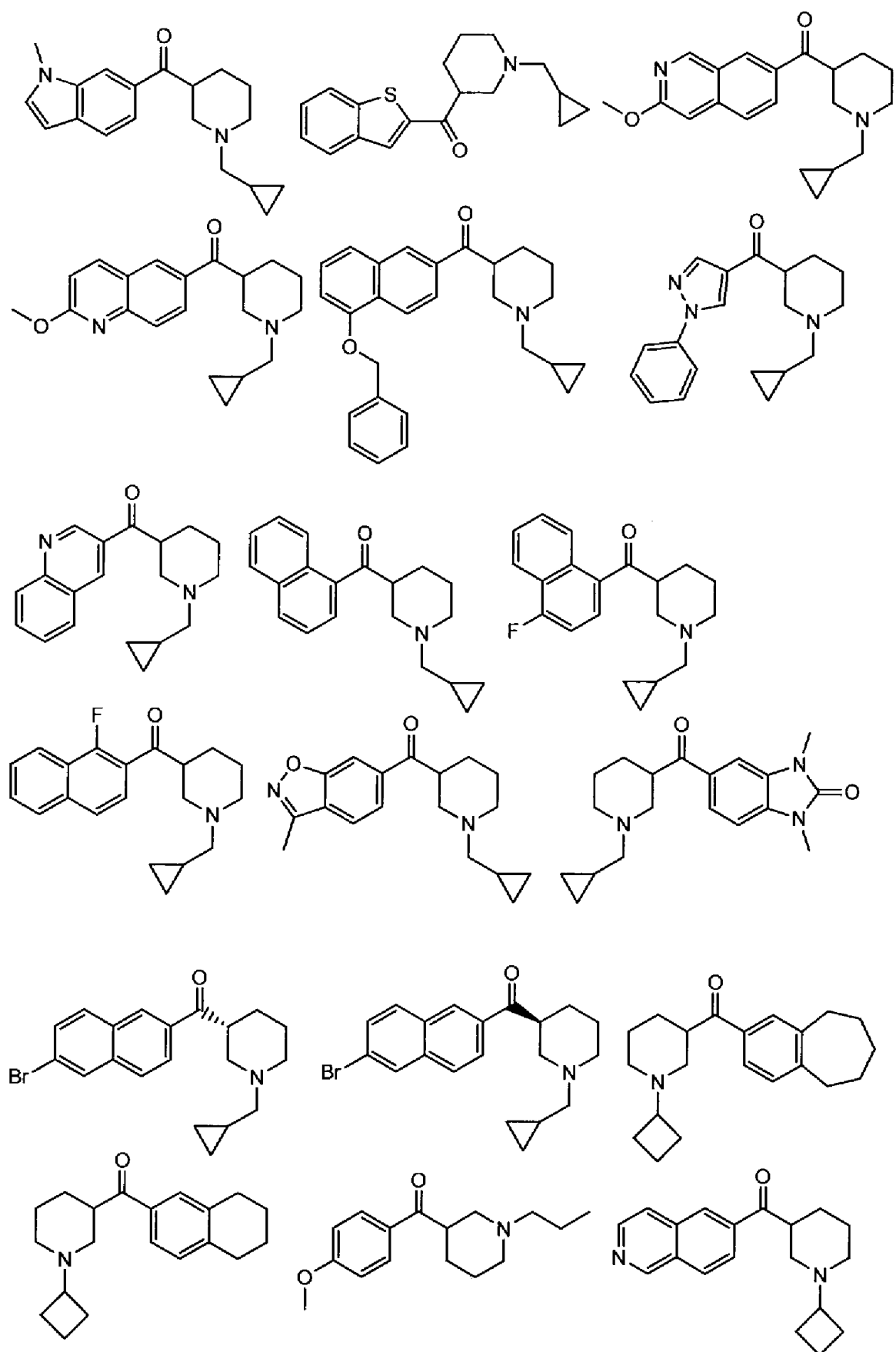


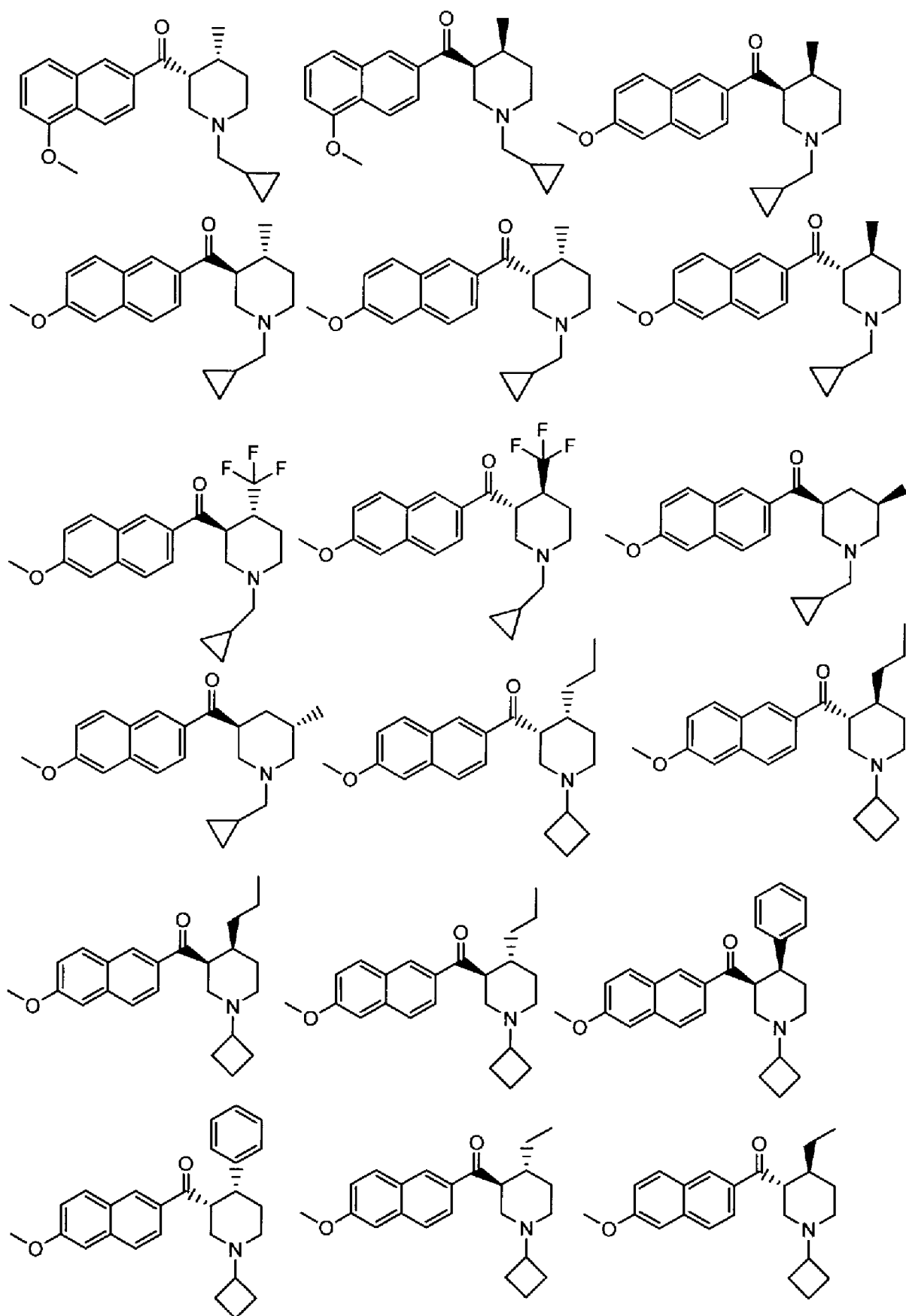


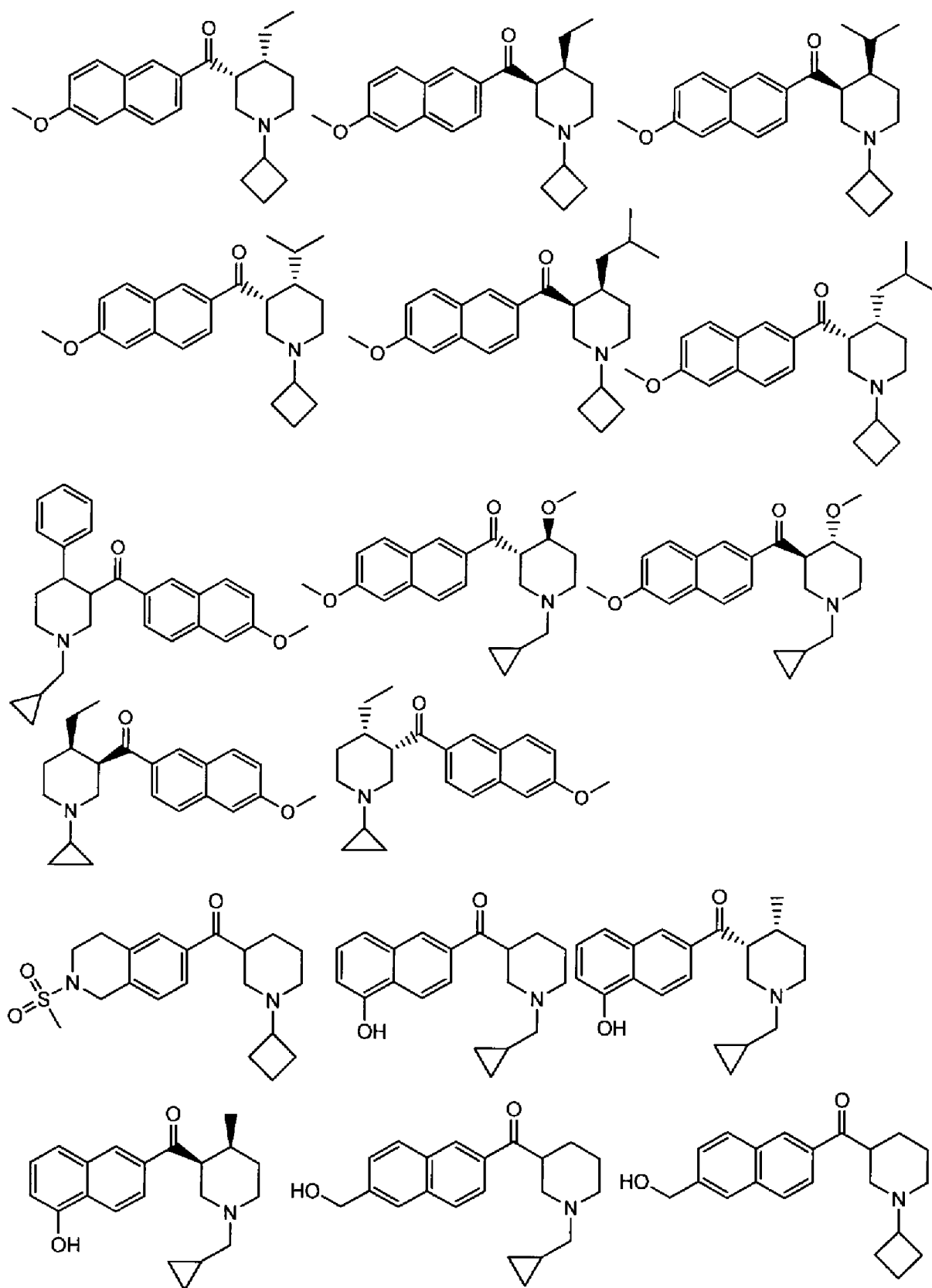


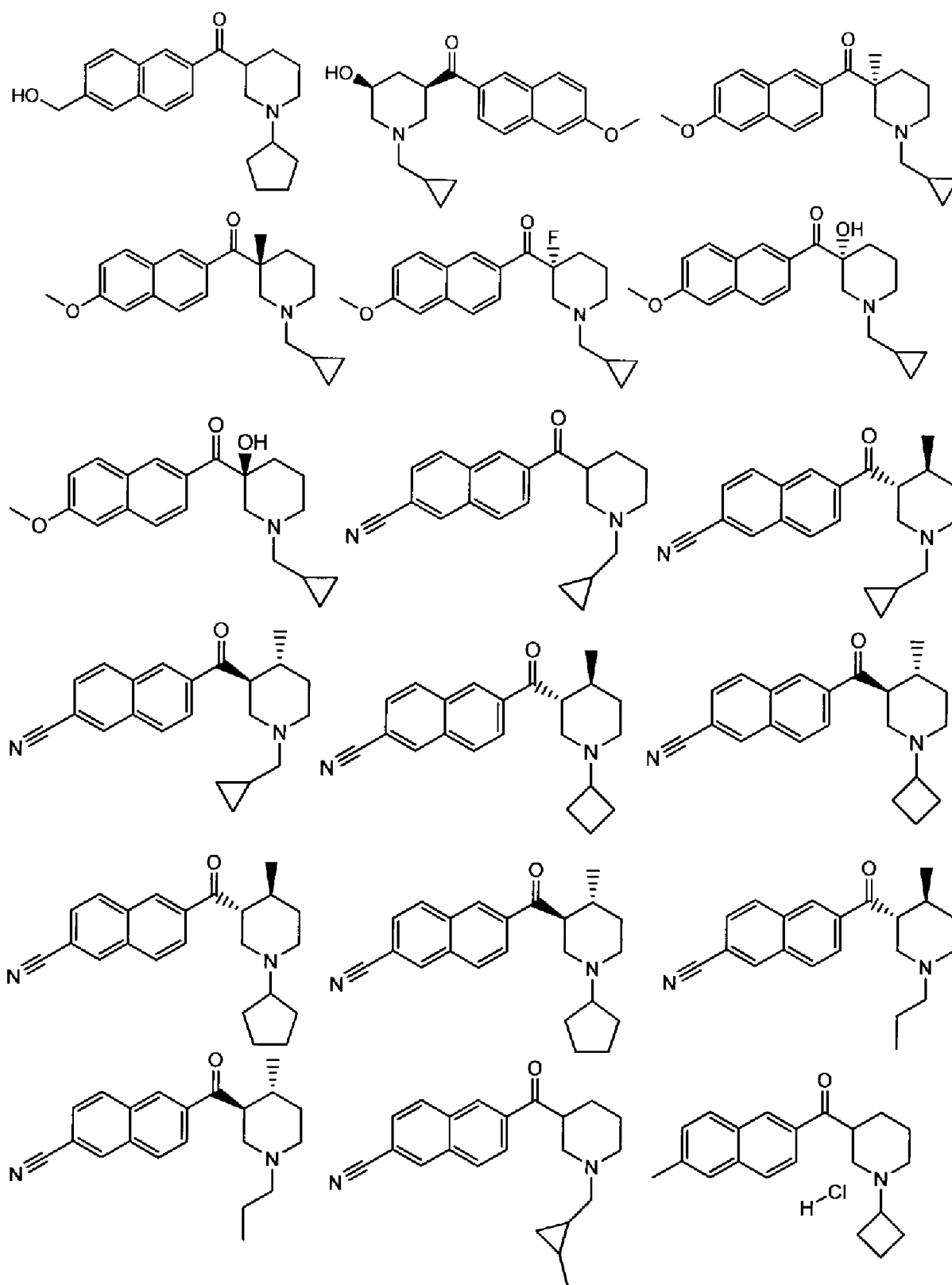


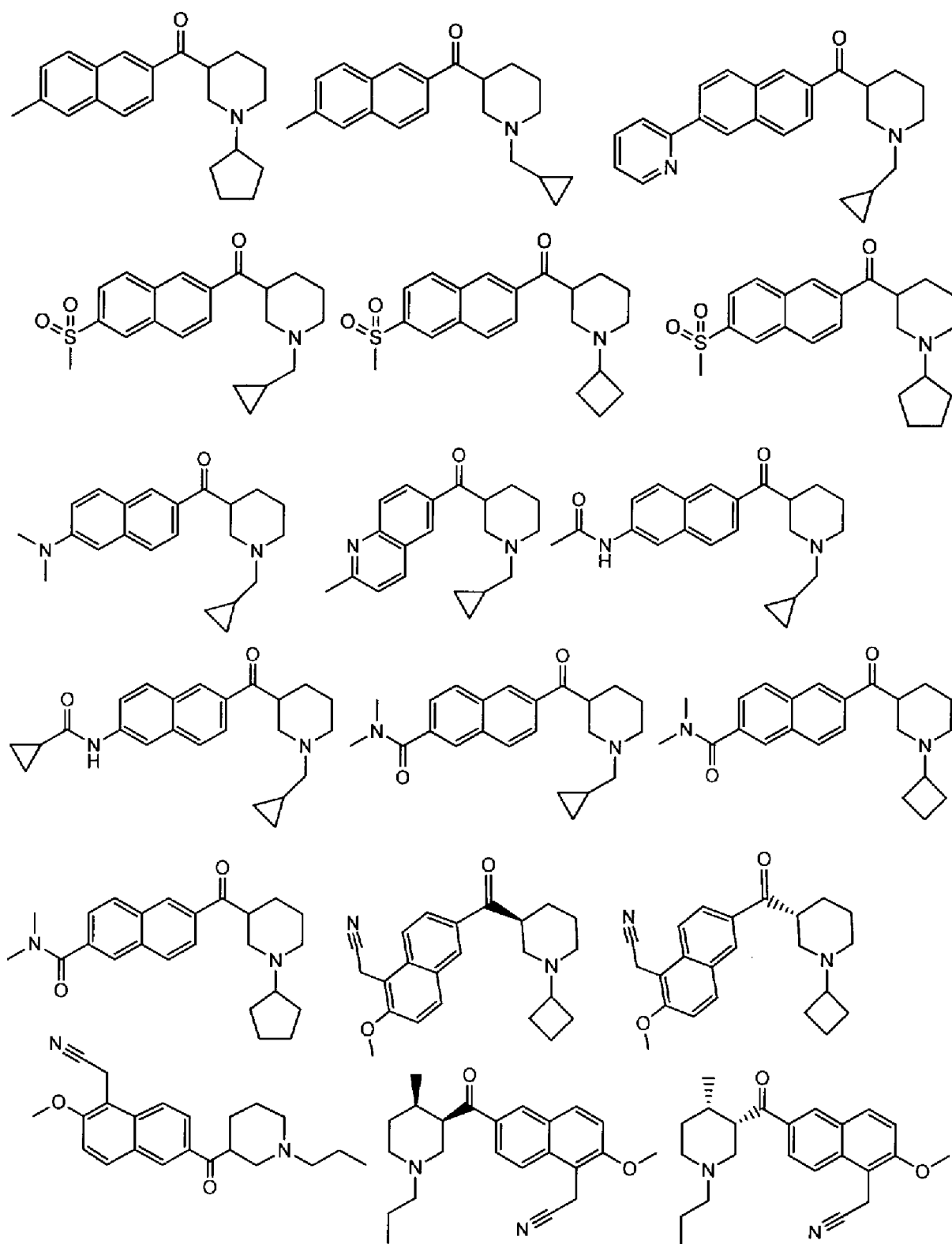


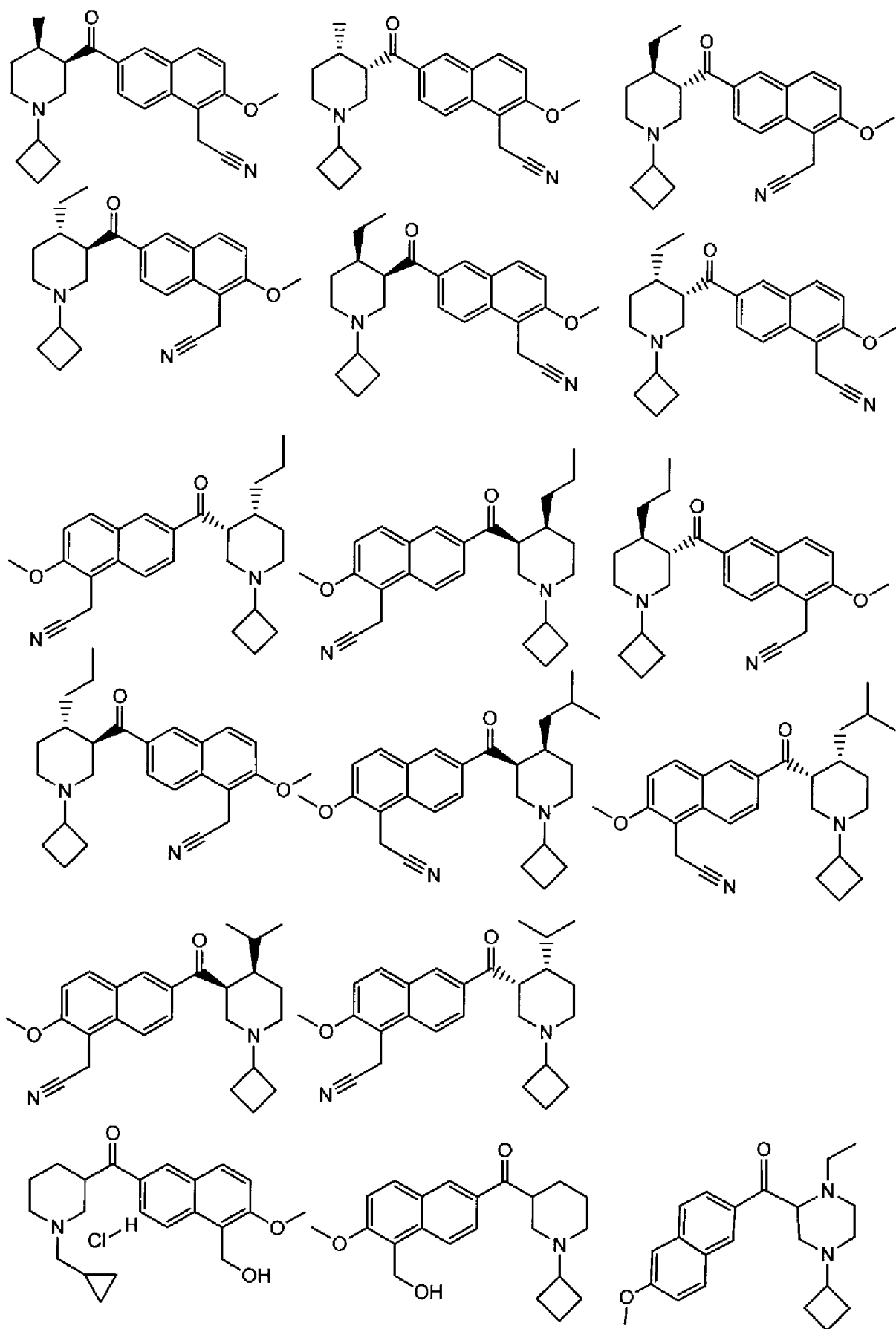


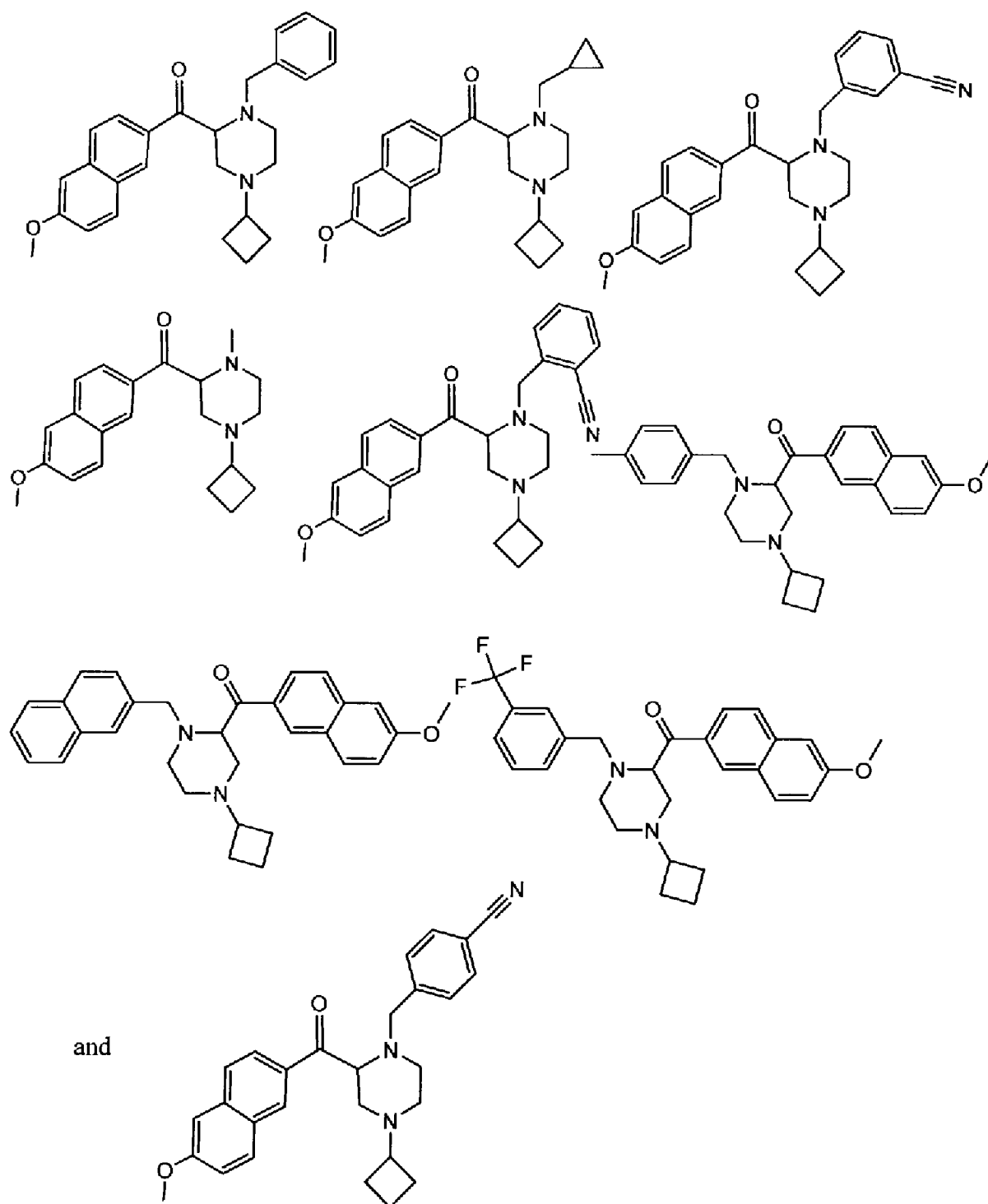








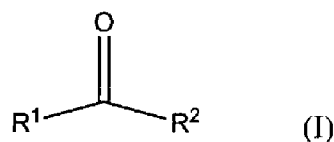




and salts thereof.

- 5 27. A composition comprising a compound as described in any one of claims 1-26, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

28. A method of treating cancer in a mammal in need thereof, comprising administering to the mammal, an effective amount of a compound as described in any one of claims 1-26, or a pharmaceutically acceptable salt thereof; or compound of formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

R¹ is:

c) a carbon-linked piperidine ring that is substituted on the piperidine ring nitrogen with a group R^x and that is optionally further substituted with one or more groups independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, -NO₂, -N(R^b)₂, -CN, -C(O)-N(R^b)₂, -S(O)-N(R^b)₂, -S(O)₂-N(R^b)₂, -O-R^b, -S-R^b, -O-C(O)-R^b, -C(O)-R^b, -C(O)-OR^b, -S(O)-R^b, -S(O)₂-R^b, -N(R^b)-C(O)-R^b, -N(R^b)-S(O)-R^b, -N(R^b)-C(O)-N(R^b)₂, and -N(R^b)-S(O)₂-R^b, wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -NO₂, -N(R^b)₂, -CN, -C(O)-N(R^b)₂, -S(O)-N(R^b)₂, -S(O)₂-N(R^b)₂, -O-R^b, -S-R^b, -O-C(O)-R^b, -C(O)-R^b, -C(O)-OR^b, -S(O)-R^b, -S(O)₂-R^b, -N(R^b)-C(O)-R^b, -N(R^b)-S(O)-R^b, -N(R^b)-C(O)-N(R^b)₂, -N(R^b)-S(O)₂-R^b, and C₁₋₆alkyl that is optionally substituted with one or more groups independently selected from halo; or

d) a carbon-linked piperazine ring that is substituted with one or more groups independently selected from the group consisting of C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈carbocycle, 3-8 membered heterocycle, aryl, heteroaryl, halo, -NO₂, -N(R^b)₂, -CN, -C(O)-N(R^b)₂, -S(O)-N(R^b)₂, -S(O)₂-N(R^b)₂, -O-R^b, -S-R^b, -O-C(O)-R^b, -C(O)-R^b, -C(O)-OR^b, -S(O)-R^b, -S(O)₂-R^b, -N(R^b)-C(O)-R^b, -N(R^b)-S(O)-R^b, -N(R^b)-C(O)-N(R^b)₂, and -N(R^b)-S(O)₂-R^b; wherein each C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈carbocycle, 3-8 membered heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, -NO₂, -N(R^b)₂, -CN, -C(O)-N(R^b)₂, -S(O)-N(R^b)₂, -S(O)₂-N(R^b)₂, -O-R^b, -S-R^b, -O-C(O)-R^b, -C(O)-R^b, -C(O)-OR^b, -S(O)-R^b, -S(O)₂-R^b, -N(R^b)-C(O)-R^b, -N(R^b)-S(O)-R^b, -N(R^b)-C(O)-N(R^b)₂, and -N(R^b)-S(O)₂-R^b.

$-N(R^b)-C(O)-N(R^b)_2$, $-N(R^b)-S(O)_2-R^b$, and C_{1-6} alkyl that is optionally substituted with one or more groups independently selected from halo;

each R^b is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, aryl, and C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, aryl, and C_{2-6} alkynyl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-N(R^c)_2$, $-CN$, $-C(O)-N(R^c)_2$, $-S(O)-N(R^c)_2$, $-S(O)_2-N(R^c)_2$, $-O-R^c$, $-S-R^c$, $-O-C(O)-R^c$, $-C(O)-R^c$, $-C(O)-OR^c$, $-S(O)-R^c$, $-S(O)_2-R^c$, $-N(R^c)-C(O)-R^c$, $-N(R^c)-S(O)-R^c$, $-N(R^c)-C(O)-N(R^c)_2$, and $-N(R^c)-S(O)_2-R^c$; or two R^b are taken together with the nitrogen to which they are attached to form a pyrrolidino, piperidino, or piperazino ring;

each R^c is independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo, amino, hydroxy, and C_{1-6} alkoxy; or two R^c are taken together with the nitrogen to which they are attached to form a heterocyclyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo and C_{1-3} alkyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo and halo;

R^x is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle, oxetanyl, tetrahydrofuranyl, or tetrahydropyranyl, wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} carbocycle is optionally substituted with one or more groups independently selected from the group consisting of halo, $-CN$, C_{1-3} alkoxy, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, and C_{3-8} carbocycle that is optionally substituted with one or more groups independently selected from the group consisting of halo and C_{1-3} alkyl;

R^2 is a 5-10 membered heteroaryl or a 6-12 membered aryl, which 5-10 membered heteroaryl, and 6-12 membered aryl is optionally substituted with one or more groups independently selected from the group consisting of C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, heteroaryl, halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, and $-N(R^d)-S(O)_2-R^d$; wherein each C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, carbocycle, heterocycle, aryl, and heteroaryl is optionally substituted with one or more groups independently selected from the group consisting of halo, $-NO_2$, $-N(R^d)_2$, $-CN$, $-C(O)-N(R^d)_2$, $-S(O)-N(R^d)_2$, $-S(O)_2-N(R^d)_2$, $-O-R^d$, $-S-R^d$, $-O-C(O)-R^d$, $-C(O)-R^d$, $-C(O)-OR^d$, $-S(O)-R^d$, $-S(O)_2-R^d$, $-N(R^d)-C(O)-R^d$, $-N(R^d)-S(O)-R^d$, $-N(R^d)-C(O)-N(R^d)_2$, $-N(R^d)-S(O)_2-R^d$, and

C₁₋₆alkyl that is optionally substituted with one or more groups independently selected from halo;

each R^d is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, aryl, and C₂₋₆alkynyl, wherein each C₁₋₆alkyl, C₂₋₆alkenyl, aryl, and C₂₋₆alkynyl is optionally substituted with one or more groups independently selected from the group consisting of halo, -N(R^e)₂, -CN, -C(O)-N(R^e)₂, -S(O)-N(R^e)₂, -S(O)₂-N(R^e)₂, -O-R^e, -S-R^e, -O-C(O)-R^e, -C(O)-R^e, -C(O)-OR^e, -S(O)-R^e, -S(O)₂-R^e, -N(R^e)-C(O)-R^e, -N(R^e)-S(O)-R^e, -N(R^e)-C(O)-N(R^e)₂, and -N(R^e)-S(O)₂-R^e; or two R^d are taken together with the nitrogen to which they are attached to form a pyrrolidino, piperidino, or piperazino ring; and

each R^e is independently selected from the group consisting of hydrogen, C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl, wherein each C₁₋₆alkyl, C₂₋₆alkenyl, and C₂₋₆alkynyl is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo, amino, hydroxy, and C₁₋₆alkoxy; or two R^e are taken together with the nitrogen to which they are attached to form a heterocyclyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo, halo and C₁₋₃alkyl that is optionally substituted with one or more groups independently selected from the group consisting of oxo and halo.

29. The method of claim 28, wherein the cancer comprises cancer stem/progenitor cells.

30. A method of inducing differentiation of a cancer stem/progenitor cell(s) in a mammal in need thereof, comprising administering to the mammal, an effective amount of a compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof.

31. A method of reducing activity of a cancer stem/progenitor cell(s) in a mammal in need thereof, comprising administering to the mammal, an effective amount of a compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof.

32. A method of depleting a cancer stem/progenitor cell in a mammal in need thereof, comprising administering to the mammal, an effective amount of a compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof.

33. A method of decreasing cancer initiation in a mammal in need thereof, comprising administering to the mammal, an effective amount of a compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof.

5 34. The method of any one of claims 28-33, wherein the cancer is lung cancer, a leukemia, or a lymphoma.

35. A compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof, for use in medical therapy.

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36. A compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof for the therapeutic or prophylactic treatment of cancer.

37. The compound of claim 36, wherein the cancer comprises cancer stem/progenitor cells.

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38. A compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof for inducing differentiation of a cancer stem/progenitor cell(s).

39. A compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof for reducing activity of a cancer stem/progenitor cell(s).

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40. A compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof for depleting a cancer stem/progenitor cell.

25 41. A compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof for decreasing cancer initiation.

42. The compound of any one of claims 36-41, wherein the cancer is lung cancer, a leukemia, or a lymphoma.

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43. The use of a compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof to prepare a medicament for treating cancer in a mammal.

44. The use of claim 43, wherein the cancer comprises cancer stem/progenitor cells.

45. The use of a compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof to prepare a medicament for inducing differentiation of a cancer stem/progenitor cell(s) in a mammal.

46. The use of a compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof to prepare a medicament for reducing activity of a cancer stem/progenitor cell(s) in a mammal.

47. The use of a compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof to prepare a medicament for depleting a cancer stem/progenitor cell in a mammal.

48. The use of a compound as described in any one of claims 1-26 and 28, or a pharmaceutically acceptable salt thereof to prepare a medicament for decreasing cancer initiation in a mammal.

49. The use of any one of claims 43-48 wherein the cancer is lung cancer, a leukemia, or a lymphoma.

50. A method of treating cancer in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

51. The method of claim 50, wherein the cancer comprises cancer stem/progenitor cells.

52. The method of claim 50 or 51, wherein the KDM2 inhibitor is effective to induce differentiation of a cancer stem/progenitor cell(s), reduce activity of a cancer stem/progenitor cell(s), and/or deplete a cancer stem/progenitor cell population in the individual.

53. The method of any one of claims 50-52, wherein the KDM2 inhibitor is effective to reduce Notch signaling in a cancer stem/progenitor cell(s) in the individual.

54. A method of inducing differentiation of a cancer stem/progenitor cell(s) in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

5 55. A method of reducing activity of a cancer stem/progenitor cell(s) in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

56. A method of depleting a cancer stem/progenitor cell population in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

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57. A method of decreasing cancer initiation in an individual in need thereof, comprising administering an effective amount of a KDM2 inhibitor to the individual.

58. The method of any one of claims 50-57, wherein the cancer is lung, leukemia (e.g.,
15 AML, ALL, MLL), or lymphoma.

59. The method of any one of claims 50-58, wherein the inhibitor is a KDM2B inhibitor.

60. The method of any one of claims 50-59, wherein the KDM2 inhibitor specifically binds
20 KDM2 and inhibits KDM2 demethylase activity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/012638

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/06 C07D405/06 C07D409/06 C07D413/06 C07D241/04
C07D211/30 A61K31/44 A61K31/444 A61K31/4439 A61K31/4433
A61K31/4436 A61K31/495 A61P35/00 A61P35/02 A61P31/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EP0-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	W0 2007/059323 A2 (CYTOKINETICS INC [US]) 24 May 2007 (2007-05-24) page 108; example 12; compound 2 page 109; example 12; compounds 1,3,4,16 page 110; example 12; compound 9 page 114; compounds 8, 13, 16, 21 page 115; compound 12 page 116 - page 142; example 12; compounds page 142 - page 145; examples 13,14 claims 1,76,78 ----- -/--	1-60

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/012638

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DIMMOCK J R ET AL: "4-(beta-Arylviny)-3-(beta-arylviny)keto) -1-ethyl-4-piperidinols ans Related Compounds: A Novel Class of Cytotoxic and Anticancer Agents", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 41, 1 January 1998 (1998-01-01), pages 4012-4020, XP002221590, ISSN: 0022-2623, DOI: 10.1021/JM9801455 abstract page 4013; compounds 11a-f, 12a-e page 4014; table 3; compounds 11a-f,12a-e page 4018, left-hand column, paragraph 3 - page 4019, left-hand column, paragraph 1 -----	1-60
X	AREEJ ABUHAMMAD ET AL: "Exploration of Piperidinols as Potential Antitubercular Agents", MOLECULES, vol. 19, no. 10, 10 October 2014 (2014-10-10), pages 16274-16290, XP002754932, DOI: 10.3390/molecules191016274 page 16278; table 1; compounds 1-7,9 -----	1-27,35
X	ANDREW R. GERMAIN ET AL: "Identification of small-molecule inhibitors of Trypanosoma cruzi replication", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 21, no. 23, 29 September 2011 (2011-09-29), - 1 December 2011 (2011-12-01), pages 7197-7200, XP028334866, ISSN: 0960-894X, DOI: 10.1016/J.BMCL.2011.09.057 [retrieved on 2011-09-29] page 7200; table 3; compound 13f -----	1-27,35
X	UPTON C ET AL: "Conformationally-restricted ligands for the histamine H1 receptor", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 10, no. 11, 1 June 2000 (2000-06-01), pages 1277-1279, XP004200574, ISSN: 0960-894X, DOI: 10.1016/S0960-894X(00)00199-2 page 1278; compounds 1,2,5-8 ----- -/--	1-27

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2016/012638

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G.V. PAVEL, ET AL: "Synthesis of hydrogenated heterocyclic compounds from alpha-methylidene-1, 5-diketones. 4. Hydropyridines based on the reaction of 1,3,5-triphenyl-2-aminomethyl-4-methylidene-1,5-pentadione with primary amines", CHEMISTRY OF HETEROCYCLIC COMPOUNDS, vol. 15, no. 10, 1 February 1979 (1979-02-01), pages 1107-1109, XP002754933, ISSN: 1573-8353, DOI: 10.1007/BF00471911 page 1107; compounds IVa, IVc, Vc -----	1-27
X	DE 28 22 360 A1 (BYK GULDEN LOMBERG CHEM FAB) 11 January 1979 (1979-01-11) example 1 -----	1-27
X	G.V. PAVEL ET AL: "Synthesis of substituted 3-benzoyl-1,2,3,4-tetrahydropyridines by the addition of primary amines to 1,3,5-triphenyl-2-methylidene-1,5-pentanedione", CHEMISTRY OF HETEROCYCLIC COMPOUNDS, vol. 15, no. 1, 1 January 1979 (1979-01-01), pages 85-86, XP002754934, ISSN: 1573-8353, DOI: 10.1007/BF00471206 page 85; compounds IVa, IVb -----	1-27
X,P	MUZALEVSKIY, VASILY M. ET AL: "Experimental and Theoretical Study of an Intramolecular CF ₃ -Group Shift in the Reactions of alpha-Bromoenones with 1,2-Diamines", CHEMISTRY - A EUROPEAN JOURNAL, vol. 21, no. 47, 2015, pages 16982-16989, XP002754935, ISSN: 1521-3765, DOI: 10.1002/chem.201502706 page 16985; table 1; compounds 4h, 4i -----	1-27
A	WO 2014/151106 A1 (QUANTICEL PHARMACEUTICALS INC [US]) 25 September 2014 (2014-09-25) page 1, paragraph [0003] examples 93,156,157,167 page 179, paragraph [00361] claims 1,55,56 -----	1-60
A	WO 2012/071469 A2 (NEVADA CANCER INST [US]) 31 May 2012 (2012-05-31) page 1, line 21 claims 1,5,6,8 figure 1D figures 2C,2D -----	1-60

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2016/012638

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