The present invention relates to 3,4-substituted piperidinyl based renin inhibitor compounds bearing at 4-position isoquimolone and having the Formula (I): The invention further relates to pharmaceutical compositions containing said compounds, as well as their use in treating cardiovascular events and renal insufficiency.
Declarations under Rule 4.17:
— as to applicant’s entitlement to apply for and be granted a patent (Rule 4.17(H))
TITLE OF THE INVENTION

3, 4 - SUBSTITUTED PIPERIDINE DERIVATIVES AS RENIN INHIBITORS

JOINT RESEARCH AGREEMENT

The claimed invention was made as a result of activities undertaken within the scope of a joint research agreement between Merck & Co., Inc. and Actelion Pharmaceuticals Ltd. The agreement was executed on December 4, 2003. The field of the invention is described below.

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Nos, 61/128,520, filed May 22, 2008.

FIELD OF THE INVENTION

The invention relates to novel renin inhibitors of the general formula (I). The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I) and especially their use as renin inhibitors in cardiovascular events and renal insufficiency.

BACKGROUND OF THE INVENTION

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT1 and AT2. Whereas AT1 seems to transmit most of the known functions of Ang II, the role of AT2 is still unknown.

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., 
Cardiovasc. Drugs, 1995, 9, 645). The only substrate known for renin is angiotensinogen, which 
can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave 
bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., J. 
Hypertens., 1993, 11, 1155). In patients, inhibition of ACE thus leads to bradykinin 
accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-
0.2%) (Israili Z. H. et al., Annals of Internal Medicine, 1992, 117, 234). Chymase is not inhibited 
by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with 
ACE inhibitors. Blockade of the ATi receptor (e.g. by losartan) on the other hand overexposes 
other AT-receptor subtypes (e.g. AT2) to Ang II, whose concentration is significantly increased 
by the blockade of ATi receptors. In summary, renin inhibitors are expected to demonstrate a 
different pharmaceutical profile than ACE inhibitors and ATi blockers with regard to efficacy in 
blocking the RAS and in safety aspects.

The present invention relates to the identification of renin inhibitors of a non-
peptidic nature and of low molecular weight. Described are orally active renin inhibitors of long 
duration of action which are active in indications beyond blood pressure regulation where the 
tissular renin-chymase system may be activated leading to pathophysiological altered local 
functions such as renal, cardiac and vascular remodeling, atherosclerosis, and possibly restenosis. 
The compounds described in this invention represent a novel structural class of renin inhibitors.

SUMMARY OF THE INVENTION

The present invention is directed to certain compounds and their use in the 
inhibition of the renin enzyme, including treatment of conditions known to be associated with the 
renin system.

The invention in particular is directed to compounds of Formula I:
and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, meso-forms, salts, solvates, and morphological forms thereof, wherein constituent members are provided herein.
DETAILED DESCRIPTION OF THE DISCLOSURE

The present invention provides compounds having Formula I:

![Chemical Structure Image]

or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein:

- $R^1$ is selected from the group consisting of: C6-alkyl, C3-C6 cycloalkyl, C2-C6 alkenyl, C3-C6 cycloalkenyl and C2-C6 alkynyl, wherein each of the foregoing is optionally substituted with 1-3 halogens and/or C1-C5 alkoxy;

- $V$ is selected from the group consisting of: hydrogen, halogen, Q-C6 alkyl, C3-C6 cycloalkyl, C2-C6 alkenyl, C3-C6 cycloalkenyl, C2-C6 alkynyl, cyano and C1-C5 alkoxy, wherein said alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl and alkoxy are optionally substituted with 1-3 substituents, each of which is independently selected from the group consisting of: halogen, C1-C5 alkyl, C2-C5 alkenyl, cyano and C1-C5 alkoxy, wherein each of the foregoing alkyl, alkenyl and alkoxy substituents is optionally substituted with 1-3 halogens;

- $W$ is cyclopropyl, unsubstituted or mono-, di-, tri-, tetra- or penta-substituted with fluorine;

- $X$ is selected from the group consisting of: OR2, R2, -(C1-C5 alkylene)-(O)0-1aryl and -(C1-C5 alkylene)-(O)0-1heteroaryl,

wherein R2 is selected from the group consisting of: hydrogen, C1-C5 alkyl, C3-C6 alkyl, C2-C5 alkyl, C3-C8 cycloalkenyl, C2-C5 alkynyl, C1-C5-cyano, -(C1-C5 alkylene)-O-R3, -(C1-C5 alkylene)-N-(R3)=O-(C1-C5 alkyl), -(C1-C5 alkylene)-C(=O)-N-(C1-C5 alkyl), -(C1-C5 alkylene)-C(=O)-N-(C1-C5 alkyl), -(C1-C5 alkylene)-C(=O)-N-(C1-C5 alkyl), -(C1-C5 alkylene)-C(=O)-N-(C1-C5 alkyl) and -(C1-C5 alkylene)-S-(C1-C5 alkyl), -(C1-C5 alkylene)-S-(C1-C5 alkyl) and -(C1-C5 alkylene)-S-(C1-C5 alkyl) and -(C1-C5 alkylene)-S-(C1-C5 alkyl), wherein R2, except hydrogen, is optionally substituted with 1-3 substituents, independently selected from the group consisting of: halogen, C(=O)OH, C1-C5 alkyl, C2-C5...
alkenyl, and C1-C5 alkoxy, wherein each of the alkyl, alkenyl, and alkoxy substituents is optionally substituted with 1-3 halogens,

wherein the heteroaryl of the -(C1-C5 alkylene)-(0) θ-l-heteroaryl contains 1-3 heteroatoms, independently selected from the group consisting of: N, O and S, wherein each N is optionally in the form of an oxide and each S is optionally in the form of an oxide selected from the group consisting of: S(=O) and S(=O)2,

wherein the aryl and heteroaryl of -(C1-C5 alkylene)-(0) θ-l-aryl and -(C1-C5 alkylene)-(O)0- l-heteroaryl, respectively, are optionally substituted with 1-4 halogens, and

wherein R.3 is selected from the group consisting of: hydrogen, C1-C6 alkyl, C3-C6 cycloalkyl, C2-C6 alkenyl, C3-C6 cycloalkenyl, and C2-C6 alkynyl, wherein each of the foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynyl substituents is optionally substituted with 1-3 halogens;

Z is C1-C2 alkylene optionally substituted with 1-2 substituents, independently selected from the group consisting of: halogen, C1-C3 alkyl and C3 cycloalkyl, wherein the foregoing alkyl and cycloalkyl substituents are optionally substituted with 1-3 halogens;

n1 is 0 or 1;

Y is (i) a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic monocyclic ring ("monocyclic ring") or (ii) a fused ring system which is a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic ring which is fused to a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic ring ("fused ring"),

wherein the heterocyclic ring(s) of (i) or (ii) contain from 1-3 heteroatoms, independently selected from N, O and S, wherein each N is optionally in the form of an oxide and each S is optionally in the form of an oxide selected from the group consisting of: S(=O) and S(=O)2,

wherein the heterocyclic or carbocyclic ring(s) of (i) or (ii) is optionally mono-, di-, tri-, tetra-, penta- or hexa-substituted, each substituent of which is independently selected from the group consisting of:

(1) halogen,
(2) -OH,
(3) -NH(R4),
(4) oxo,
(5) -C(=O)-R4,
(6) -O-C(=O)-R4,
(7) C1-C5 alkyl optionally substituted with 1-3 halogens,
(8) C3-C8 cycloalkyl optionally substituted with 1-3 halogens,
(9) C2-C5 alkenyl optionally substituted with 1-3 halogens,
(10) C3-C8 cycloalkenyl optionally substituted with 1-3 halogens,
(11) C2-C5 alkynyl optionally substituted with 1-3 halogens,
(12) C1-C5 alkoxy optionally substituted with 1-3 halogens,
(13) cyano,
(14) C1-C5-cyano optionally substituted with 1-3 halogens,
(15) -OCF3,
(16) -C(R5)3,
(17) -(C1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(18) -N(R4)-(C1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(19) -O-(C1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(20) -S-(C1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(21) -S(O)-(C1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(22) -S(O)2-(C1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(23) -(C1-C5 alkylene)-N(R4)-(C1-C5 alkylene)-R6 optionally substituted with 1-3 halogens,
(24) -(C1-C5 alkylene)-N(R4)-C(O)-(C1-C5 alkylene)-0R6 optionally substituted with 1-3 halogens,
(25) -(C1-C5 alkylene)-N(R4)(R6) optionally substituted with 1-3 halogens,
(26) -CKC1-C5 alkylene)-C(R4)2-C(O)0R6 optionally substituted with 1-3 halogens,
(27) -(C1-C5 alkylene)-C(R4)2-C(O)-C1-C5 alkylene)-R6 optionally substituted with 1-3 halogens,
(28) -CHC1-C5 alkylene)-mo\phi holine optionally substituted with 1-3 halogens,
(29) -OC(0)-morpholine,
(30) -SR6,
(31) -S(O)-R6,
(32) -S(O)2-R
(33) -N(R4)(R6),
(34) -(C1-C5 alkylene)-C(R4)2-(R6) optionally substituted with 1-3 halogens,
(35) -(R7)O_IR8,
(36) C2-C5 alkenyl-OR6 optionally substituted with 1-3 halogens,
(37) C2-C5 alkynyl-OR6 optionally substituted with 1-3 halogens,
(38) -(C1-C5 alkylene)-C(O)-(C1-C5 alkylene)-R6 optionally substituted with 1-3 halogens,
(39) -(C1-C5 alkylene)-0-C(O)-(C1-C5 alkylene)-R6 optionally substituted with 1-3 halogens,
(40) -(C1-C5 alkylene)-C(O)-N(R4)(R6) optionally substituted with 1-3 halogens,
(41) -(C1-C5 alkylene)-O-C(=O)-N(R4)(R6) optionally substituted with 1-3 halogens,
(42) -(C1-C5 alkylene)-SR6 optionally substituted with 1-3 halogens,
(43) -(C1-C5 alkylene)-S(=O)-R6 optionally substituted with 1-3 halogens, and
(44) -(C1-C5 alkylene)-S(=O)2-R6 optionally substituted with 1-3 halogens,
wherein R4 is selected from the group consisting of: hydrogen, C1-C6 alkyl, C3-C8 cycloalkyl, C2-C6 alkenyl, C3-C8 cycloalkenyl and C2-C6 alkynyl, wherein each of the foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynyl substituents is optionally substituted with 1-3 halogens,
wherein R5 is halogen,
wherein R6 is selected from the group consisting of: hydrogen, C1-C6 alkyl, C3-C8 cycloalkyl, C2-C6 alkenyl, C3-C8 cycloalkenyl and C2-C6 alkynyl, wherein each of the foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynyl substituents is optionally substituted with 1-3 halogens,
wherein R7 is selected from the group consisting of: -C(H)(OH)-, -C(=O)-, -OC(=O)-, -C(O)O-, -0-, -OC(O)O-, C1-C5 alkylene, C2-C5 alkylene, -N(R4)-, -S-, -S(O)-, -S(O)2-, -N(R4)-C(=O)-, -C(=O)-N(R4)-, -OC(=O)-N(R4)-, -N(R4)-C(0)O-, -N(R4)-S(=O)2-, and -S(O)2-N(R4)-, wherein each of the foregoing alkylene and alkynylene substituents is optionally substituted with 1-3 halogens, and wherein R4 is defined above, and
wherein R8 is a five- or six-membered saturated or unsaturated heterocyclic or carbocyclic ring which is optionally mono-, di-, tri-, tetra- or penta-substituted, wherein each substituent is independently selected from the group consisting of: halogen, -OH, -SR4, -N(R4)(R6), C1-C5 alkyl, C3-C8 cycloalkyl, C2-C5 alkenyl, C3-C6 cycloalkenyl, C2-C5 alkynyl, C1-C5 alkoxy, cyano and Ci-C5-cyano, wherein said heterocyclic ring contains from 1 to 3 heteroatoms, independently selected from N, O and S, wherein each N is optionally in the form of an oxide and each S is optionally in the form of an oxide selected from the group consisting of: S(=O) and S(=O)2, and wherein R4 and R6 are defined above.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein R1 is -CH3 or -CH2CH3.

In particular embodiments, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, wherein R1 is -CH3.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein V is hydrogen or halogen.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein V is H or Cl.
In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein W is cyclopropyl.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein X is H.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein \((Z)_n\) I is -CH2- or a bond.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein:

- \(R_1\) is C1-C2 alkyl optionally substituted with 1-3 halogens,
- V is hydrogen or halogen,
- W is cyclopropyl,
- X is hydrogen, and
- Z is -CH2-.

In another embodiment, the invention provides compounds of Formula I, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof, wherein Y is optionally mono-, di-, tri-, tetra- or penta-substituted as described in Formula I.

In another embodiment, the invention provides compounds of Formula II, or a pharmaceutically acceptable salt thereof, or an optical isomer thereof.

wherein:

- A is selected from the group consisting of:
  - (1) hydrogen,
  - (2) halogen,
(3) Ci-Cs alkyl,
(4) C1-C5 alkoxy, and
(5) \(-\text{S-(CH}_2\text{)}_0\text{-3-CH}_3\),

wherein (3) and (4) are optionally substituted with 1-3 halogens,

B is selected from the group consisting of:

(1) hydrogen,
(2) halogen,
(3) Ci-C_5 alkyl,
(4) C1-C5 alkoxy,
(5) \(-\text{OH}\),
(6) \(-\text{CF}_3\),
(7) \(-\text{CC=O)-(CH}_3\),
(8) \(-\text{O-(Cl-Cs alkylene)-O-cyclopropyl}\),
(9) \(-\text{O-(Cl-Cs alkylene)-O-(CH}_2\text{)}_0\text{-2-CH}_3\),
(10) \(-\text{(Ci-C5 alkylene)-O-(CH}_2\text{)}_0\text{-2-CH}_3\),
(11) \(-\text{OC(0) - morpholine}\),
(12) \(-\text{O-(Ci-C5 alkylene)-morpholine}\),
(13) \(-\text{O-(Ci-C5 alkylene)-C(CH}_3\text{)}_2\text{-C(=O)OH}\),
(14) \(-\text{CKC1-C5 alkylene)-C(CH}_3\text{)}_2\text{-C(=O)OCH}_3\),

\begin{center}
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(15)

and

(16)

wherein (3), (4), (8), (9), (10), (12), (13), (14), (15) and (16) are optionally substituted with 1-3 halogens,

C is selected from the group consisting of:

(1) hydrogen,
(2) C1-C5 alkyl optionally substituted with 1-3 halogens, and
(3) C1-C5 alkoxy optionally substituted with 1-3 halogens, and

D is selected from the group consisting of:

(1) hydrogen,
(2) halogen,
(3) Ci-C_5 alkyl,
(4) C1-C5 alkoxy,
(5) C1-C5-cyano,
(6) C2-C5 alkenylene-O-(CH2)0-2-CH3,
(7) -(Cl-C5 alkenylene)-N(H)-C(=O)-(CH2)0-2-CH3,
(8) -(Ci-C5 alkenylene)-N(H)-C(=O)-(CH2)0-2-CH3,
(9) -(C1-C5 alkenylene)-O-CHF2,
(10) -(C1-C5 alkenylene)-O-(CH2)0-2-CH3,
(11) -O-(Ci-C5 alkenylene)-O-(CH2)0-2-CH3,
(12) -(C1-C5 alkenylene)-OH,
(13) -S-(Ci-C5 alkenylene)-OH,
(14) -SCF3
(15) -N(H)-(C1-C5 alkenylene)-O-(CH2)0-2-CH3,

wherein F, G and H are independently selected from the group consisting of: hydrogen, halogen and C1-C3 alkyl optionally substituted with 1-3 halogens, and

wherein R9 is selected from the group consisting of: -CH2-, -C(H)(OH)- and _C(=O)-,

wherein (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13) and (15) are optionally substituted with 1-3 halogens, and

wherein R1, V, X and (Z)_n I are as described in Formula I.

The compounds of Formula I above, and pharmaceutically acceptable salts thereof, are renin inhibitors. The compounds are useful for inhibiting renin and treating conditions such as hypertension.

Any reference to a compound of formula (I) is to be understood as referring also to optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, meso-forms, as well as salts (especially pharmaceutically acceptable salts) and solvates (including hydrates) of such compounds, and morphological forms, as appropriate and expedient. The present invention encompasses all these forms. Mixtures are separated in a manner known per se, e.g. by column chromatography, thin layer chromatography (TLC), high performance liquid chromatography (HPLC), or crystallization. The compounds of the present invention may have chiral centers, e.g. one chiral center (providing for two stereoisomers, (R) and (S)), or two chiral centers (providing for up to four stereoisomers, (R,S,R), (S,S), (R,S) and (S,R)). This invention includes all of these optical isomers and mixtures thereof. Unless specifically mentioned otherwise, reference to one isomer applies to any of the possible isomers. Whenever the isomeric composition is
unspecified, e.g., when bonds to a chiral carbon are depicted as straight lines, it is understood that both (R) and (S) configurations of that chiral carbon and, hence, both enantiomers and mixtures thereof are represented.

In addition, compounds with carbon-carbon double bonds may occur in Z- and E- forms with all isomeric forms of the compounds being included in the present invention.

Compounds of the invention also include nitrosated compounds of formula (I) that have been nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulphydryl condensation) and/or nitrogen. The nitrosated compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For example, known methods for nitrosating compounds are described in U.S. Pat. Nos. 5,380,758, 5,703,073, 5,994,294, 6,242,432 and 6,218,417; WO 98/19672; and Oae et al., Org. Prep. Proc. Int., 15(3): 165-198 (1983).

Salts are preferably the pharmaceutically acceptable salts of the compounds of Formula (I). The expression "pharmaceutically acceptable salts" encompasses either salts with inorganic acids or organic acids like hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, phosphorous acid, nitrous acid, citric acid, formic acid, acetic acid, oxalic acid, maleic acid, lactic acid, tartaric acid, fumaric acid, benzoic acid, mandelic acid, cinnamic acid, palmoic acid, stearic acid, glutamic acid, aspartic acid, methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, p-toluenesulfonic acid, salicylic acid, succinic acid, trifluoroacetic acid, and the like that are non toxic to living organisms or, in case the compound of formula (I) is acidic in nature, with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like. For other examples of pharmaceutically acceptable salts, reference can be made notably to "Salt selection for basic drugs", Int. J. Pharm. (1986), 33, 201-217.

The invention also includes derivatives of the compound of Formula I, acting as prodrugs. These prodrugs, following administration to the patient, are converted in the body by normal metabolic processes to the compound of Formula 1. Such prodrugs include those that demonstrate enhanced bioavailability (see Table 4 below), tissue specificity, and/or cellular delivery, to improve drug absorption of the compound of Formula 1. The effect of such prodrugs may result from modification of physicochemical properties such as lipophilicity, molecular weight, charge, and other physicochemical properties that determine the permeation properties of the drug.

The general terms used hereinbefore in Formula I and hereinafter preferably have, within this disclosure, the following meanings, unless otherwise indicated. Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.
The term "alkyl", alone or in combination with other groups, unless indicated otherwise, means saturated, straight and branched chain groups with one to six carbon atoms (which may be represented by "C\_1-6 alkyl" or "C1-C6 alkyl"). When the intended meaning is other than this, for example, when the number of carbon atoms is in the range of one to four carbon atoms, this meaning is represented in like fashion as "C1.4 alkyl" or "C1-C4 alkyl". Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

Structural depictions of compounds may show a terminal methyl group as "-CH3", "CH3", "-Me", "Me" or "\(\text{CH}_3\)" (i.e., these have equivalent meanings). A terminal ethyl group may be depicted as "-CH2CH3", "CH2CH3", "-Et", "Et" or "\(\text{CH}_2\text{CH}_3\)" (i.e., these have equivalent meanings).

The term "alkylene" refers to any divalent linear or branched chain aliphatic hydrocarbon radical having a number of carbon atoms in the specified range. Thus, for example, "-C1-C6 alkylenes" refers to any of the C1 to C6 linear or branched alkenyls, and "-C1-C4 alkylenes" refers to any of the C1 to C4 linear or branched alkenyls. A class of alkenylenes of particular interest with respect to the invention is -(CH2)l-6-, and sub-classes of particular interest include -(CH2)l-4-, -(CH2)l-3-, -(CH2)l-2-, and -CH2-. Another sub-class of interest is an alkenylene selected from the group consisting of -CH2-, -CH(CH3)-, and -C(CH3)2-. Expressions such as "C1-C4 alkylen-phenyl" and "C1-C4 alkyl substituted with phenyl" have the same meaning and are used interchangeably.

The term "alkenyl", alone or in combination with other groups, unless indicated otherwise, means unsaturated (i.e., having at least one double bond) straight and branched chain groups with two to six carbon atoms (which may be represented by "C2-6 alkenyl" or "C2-C6 alkenyl"). When the intended meaning is other than this, for example, when the number of carbon atoms is in the range of two to four carbon atoms, this meaning is represented in like fashion as "C2-4 alkenyl" or "C2-C4 alkenyl".

The term "alkenylene" refers to any divalent linear or branched chain aliphatic mono-unsaturated hydrocarbon radical having a number of carbon atoms in the specified range. The term "alkynyl", alone or in combination with other groups, unless indicated otherwise, means unsaturated (i.e., having at least one triple bond) straight and branched chain groups with two to six carbon atoms (which may be represented by "C2-6 alkynyl" or "C2-C6 alkynyl"). When the intended meaning is other than this, for example, when the number of carbon atoms is in the range of two to four carbon atoms, this meaning is represented in like fashion as "C2-4 alkynyl" or "C2-C4 alkynyl".

The term "alkoxy", alone or in combination with other groups, refers to an R-O- group, wherein R is an alkyl group. Examples of alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.
The term "hydroxy-alkyl", alone or in combination with other groups, refers to an HO-R- group, wherein R is an alkyl group. Examples of hydroxy-alkyl groups are HO-CH₂-, HO-CH₂CH₂-, HO-CH₂CH₂CH₂- and CH₃CH(OH)-.

The term "halogen" means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, especially fluorine or chlorine.

The term "cycloalkyl", alone or in combination with other groups, unless indicated otherwise, means a saturated cyclic hydrocarbon ring system with 3 to 8 carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. This may be represented by "C₃-8 cycloalkyl" or "C₃-C₈ cycloalkyl"). When the intended meaning is other than this, for example, when the number of carbon atoms is in the range of three to six carbon atoms, this meaning is represented in like fashion as "C₃-6 cycloalkyl" or "C₃-C₆ cycloalkyl".

The term "carbocycle" (and variations thereof such as "carbocyclic" or "carbocyclyl") as used herein, unless otherwise indicated, refers to a C₃ to C₈ monocyclic saturated or unsaturated ring. The carbocycle may be attached to the rest of the molecule at any carbon atom which results in a stable compound. Saturated carbocyclic rings are also referred to as cycloalkyl rings, e.g., cyclopropyl, cyclobutyl, etc.

The term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") broadly refers to a stable 4- to 8-membered, saturated or unsaturated monocyclic ring which contains one or more heteroatoms (e.g., from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) selected from N, O and S and a balance of carbon atoms (typically at least one carbon atom); wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. Unless otherwise specified, the heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Unless otherwise specified, when the heterocyclic ring has substituents, it is understood that the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results.

The term "aryl", alone or in combination, relates to a phenyl, naphthyl or indanyl group, preferably a phenyl group. The abbreviation "Ph" represents phenyl.

The term "heteroaryl", alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzfused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzfused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing two heteroatoms independently selected from oxygen, nitrogen and sulfur and benzfused derivatives of such rings; five-membered aromatic rings containing three nitrogen atoms and benzfused derivatives thereof; a tetrazolyl ring; a thiazinyl ring; or coumarinyl. Examples of such ring systems are furanyl, thienyl,
pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, benzothienyl, quinazolyl and quinoxalyl.

Specific examples of compounds of formula I, and pharmaceutically acceptable salts thereof, include those listed below:

fr<my-N'-Cyclopropyl-4-(1'-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-N-(3-[(2-(methyloxy)ethyl]oxy]-5-[3-(methyloxy)propyl]phenyl)methyl)-3-piperidinecarboxamide (Ex. 1)

fr<ms-4-(7-Chloro-1'-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-N'-cyclopropyl-(3-[(2-(methyloxy)ethyl]oxy]-5-[3-(methyloxy)propyl]phenyl)methyl)-3-piperidinecarboxamide (Ex. 2)

The present invention also encompasses a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and the compound of Formula I or a pharmaceutically acceptable crystal form or hydrate thereof. A preferred embodiment is a pharmaceutical composition of the compound of Formula I, comprising, in addition, a second agent.

List of abbreviations:

BINAP 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BOC r-butyloxy carbonyl
BSA bovine serum albumin
COD 1,5-cyclooctadiene
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCM dichloromethane
DIBAL-H diisobutylaluminum hydride
DMAP 4-dimethylamino pyridine
DME 1,2-dimethoxyethane
DMF N,N-dimethylformamide
DMP Dess-Martin periodinane
DMSO dimethyl sulfoxide
DPPB 1,4-bis(diphenylphosphino)butane
DPPF 1,1'-bis(diphenylphosphino)ferrocene
EDTA ethylenediaminetetraacetic acid
EIA enzyme immunoassay
Et2O diethylether
EtOAc ethyl acetate
HATU O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
Hex hexanes
KHMDS potassium hexamethyldisilazide
wCPBA meta-chloroperbenzoic acid
MeOH methanol
NBS N-bromo succinimide
NMO N-methylmorpholine-N-oxide
«-PrOH iso-propanol
PBS phosphate-buffered saline
PG protecting group
PPh3 triphenylphosphate
RT room temperature
TBAF tetrabutylammonium fluoride
TFA trifluoroacetic acid
THF tetrahydrofuran
TMEDA N,N,N',N'-tetramethylethylenediamine
ToI toluene

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, an alkyl group described as C1 - C6 alkyl means the alkyl group can contain 1, 2, 3, 4, 5 or 6 carbon atoms.

When a given range includes 0 (e.g., (CH2)0-3), 0 implies a direct covalent bond.

When any variable occurs more than one time in any constituent or in any formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence.

Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

The term "substituted" (e.g., as in "aryl which is optionally substituted with one or more substituents ...") includes mono- and poly-substitution by a named substituent to the extent such single and multiple substitution (including multiple substitution at the same site) is chemically allowed and results in a stable compound.

A "stable" compound is a compound which can be prepared and isolated and whose structure and properties remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (e.g., therapeutic or prophylactic administration to a subject).

In compounds of the invention having pyridyl N-oxide moieties, the pyridyl-N-oxide portion is structurally depicted using conventional representations such as
which have equivalent meanings.

The invention relates to a method for the treatment and/or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, systolic hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system, which method comprises administrating a compound as defined above to a human being or animal.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases, which are associated with a dysregulation of the renin-angiotensin system as well as for the treatment of the above-mentioned diseases.

The invention also relates to the use of compounds of formula (I) for the preparation of a medicament for the treatment and/or prophylaxis of the above-mentioned diseases.

Compounds of formula (I) or the above-mentioned pharmaceutical compositions are also of use in combination with other pharmacologically active compounds comprising ACE-inhibitors, neutral endopeptidase inhibitors, angiotensin II receptor antagonists, endothelin receptors antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists or with other drugs beneficial for the prevention or the treatment of the above-mentioned diseases.

The term “administration” and variants thereof (e.g., “administering” a compound) in reference to a compound of Formula I mean providing the compound or a prodrug of the compound to the individual in need of treatment or prophylaxis. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (e.g., an agent such as anangiotensin II receptor antagonist, ACE inhibitor, or other active agent which is known to
reduce blood pressure), "administration" and its variants are each understood to include provision
of the compound or prodrug and other agents at the same time or at different times. When the
agents of a combination are administered at the same time, they can be administered together in a
single composition or they can be administered separately.

As used herein, the term "composition" is intended to encompass a product comprising the
specified ingredients in the specified amounts, as well as any product which results, directly or
indirectly, from combining the specified ingredients in the specified amounts.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical
composition must be compatible with each other and not deleterious to the recipient thereof.

The term "subject" as used herein refers to an animal, preferably a mammal, most preferably a
human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or
pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal
or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In
one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation
of the symptoms of the disease or condition being treated. In another embodiment, the effective
amount is a "prophylactically effective amount" for prophylaxis of the symptoms of the disease
or condition being prevented. The term also includes herein the amount of active compound
sufficient to inhibit renin and thereby elicit the response being sought (i.e., an "inhibition
effective amount"). When the active compound (i.e., active ingredient) is administered as the
salt, references to the amount of active ingredient are to the free form (i.e., the non-salt form) of
the compound.

In a preferred embodiment, this amount is comprised between 1 mg and 1000 mg
per day. In a particularly preferred embodiment, this amount is comprised between 1 mg and 500
mg per day. In a more particularly preferred embodiment, this amount is comprised between
1 mg and 200 mg per day.

In the method of the present invention (i.e., inhibiting renin), the compounds of Formula 1,
on optionally in the form of a salt, can be administered by any means that produces contact of the
active agent with the agent's site of action. They can be administered by any conventional means
available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or
in a combination of therapeutic agents. They can be administered alone, but typically are
administered with a pharmaceutical carrier selected on the basis of the chosen route of
administration and standard pharmaceutical practice. The compounds of the invention can, for
example, be administered orally, parenterally (including subcutaneous injections, intravenous,
intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in
the form of a unit dosage of a pharmaceutical composition containing an effective amount of the
compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and
vehicles. Liquid preparations suitable for oral administration (e.g., suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water, glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (e.g., powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as a solubility aid. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions for use in the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition, edited by A. R. Gennaro, Mack Publishing Co., 1990.

Methods of Synthesis

Compounds of the present invention can be made by a variety of methods depicted in the illustrative synthetic reaction schemes shown and described below. The starting materials and reagents used in preparing these compounds generally are either available from commercial suppliers, such as Aldrich Chemical Co., or are prepared by methods known to those skilled in the art following procedures set forth in references such as Fieser and Fieser's Reagents for Organic Synthesis; Wiley & Sons: New York, Volumes 1-21; R. C. LaRock, Comprehensive Organic Transformations, 2nd edition Wiley-VCH, New York 1999; Comprehensive Organic Synthesis, B. Trost and I. Fleming (Eds.) vol. 1-9 Pergamon, Oxford, 1991; Comprehensive Heterocyclic Chemistry, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1984, vol. 1-9; Comprehensive Heterocyclic Chemistry II, A. R. Katritzky and C. W. Rees (Eds) Pergamon, Oxford 1996, vol. 1-11; and Organic Reactions, Wiley & Sons: New York, 1991, Volumes 1-40. The following synthetic reaction schemes and examples are merely illustrative of some methods by which the compounds of the present invention can be synthesized, and various modifications to these synthetic reaction schemes can be made and will be suggested to one skilled in the art having referred to the disclosure contained in this application.

The starting materials and the intermediates of the synthetic reaction schemes can be isolated and purified if desired using conventional techniques, including but not limited to, filtration, distillation, crystallization, chromatography, and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

Unless specifically stated otherwise, the experimental procedures were performed under the following conditions. Evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 pascals: 4.5-30 mm Hg) with a bath temperature of up to 60°C. Reactions are typically run under nitrogen atmosphere at ambient temperature if not otherwise mentioned. Anhydrous solvent such as THF, DMF, Et₂O, DME and Toluene are commercial grade. Reagents are commercial
grade and were used without further purification. Flash chromatography is run on silica gel (230-400 mesh). The course of the reaction was followed by either thin layer chromatography (TLC) or nuclear magnetic resonance (NMR) spectrometry and reaction times given are for illustration only. The structure and purity of all final products were ascertained by TLC, mass spectrometry, \textsuperscript{1}H NMR and high-pressure liquid chromatography (HPLC). Chemical symbols have their usual meanings. The following abbreviations have also been used: v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (liter(s)), mL (milliliter(s)), g (gram(s)), mg (milligram(s)), mol (mole(s)), mmol (millimole(s)), eq. (equivalent(s)). Unless otherwise specified, all variables mentioned below have the meanings as provided above.

Generally, compounds of the present invention can be prepared via the coupling of an appropriately substituted isoquinolone I with an appropriately functionalized amine II, followed by the removal of the BOC-protecting group from amide III (Scheme 1).
Synthesis of the requisite isoquinolone I can, for example, be performed as exemplified in Scheme 2. Typically, metal-catalyzed Suzuki coupling of boronate VI, prepared from known triflate V (see Ujjarnwalla, Feroze et al., Bioorg. Med. Chem. Lett.; 15 (18), 2005, p. 4023-4028), with iodide VII, can provide α,β-unsaturated ester VIII. Reduction of the double bond, most conveniently accomplished using either magnesium or samarium iodide, and subsequent base-mediated equilibration, would then afford saturated ester IX as a single diastereomer. Its conversion to the corresponding isoquinolone X can be realized in two steps via the initial treatment of ester IX with wCPBA; or an equivalent oxidant, followed by the reaction of the resulting quinoline N-oxide with TFAA in triethylamine; or an equivalent rearrangement promoter. Isoquinolone XI can be readily accessed via N-alkylation of isoquinolone X with an appropriate reagent and for cases where V is a halogen such as chlorine or bromine, it can be further modified via, for example, typical metal-mediated couplings such as the Suzuki or Buchwald-Hartwig variants. Finally, saponification of isoquinolone XI would furnish isoquinolone I.
In most cases, approaches to the preparation of amine II used in Scheme 1 have already been disclosed in a published patent application WO 2007/009250 A1. Those not already known can be synthesized according to, for example, methods exemplified in Scheme 3. Where appropriate, aldehyde XII is first regioselectively brominated. The resulting bromide XIII is then subjected to the usual reductive amination conditions to afford amine XIV. If necessary, amine XV could subsequently be protected as its corresponding JV-BOC derivative XVI. Using typical metal-mediated couplings such as the Suzuki or Buchwald-Hartwig variants, the R chain in amine II can be appended onto either amine XIV or amine XV. Simple chemical modifications such as hydrogenation, Wittig olefination, reduction, acylation, ozonolysis, oxidation and others, where necessary, may be carried out to arrive at the desired R group in amine II. Finally, for amine XVI, a simple deprotection step is required.
Indole is another common scaffold seen in amine II. These amines can be prepared, for example, from alkylation of indole XVIII under typical reaction conditions. Again, simple chemical modifications such as hydrogenation, Wittig olefination, reduction, acylation, ozonolysis, oxidation and others, where necessary, may be carried out to arrive at the desired R group in amine II. Finally, reductive amination of XIX would furnish the desired amine II. Should indole XVIII not be commercially available, it can be accessed via, for example, a simple formylation of indole XVII, which is most conveniently accomplished with POCI₃ in DMF.

For compounds of the present invention bearing an alkoxy group at position 4 of the piperidine ring, they are most conveniently accessed via an initial amide formation between amine II and β-ketoester XX, followed by the addition of Gignard reagent synthesized from quinoline VII and an appropriate source of magnesium. Functionalization of the resulting alcohol XXII via, for example, alkylation with a suitable electrophile, if necessary, would precede the conversion of quinoline XXIII into the desired isoquinolone XXV using chemistries already described in Scheme II. Finally, BOC removal can be accomplished under typical conditions (Scheme 5).
Representative cyclopropylamine building blocks are shown in Table 1.

**Table 1**

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</table>
Amine 1

\(N\)-(2,3-Dichlorobenzyl)cyclopropanamine

Amine 1 was prepared according to the procedure described in WO 2007/009250 A1 patent.

Amine 2

\(N\)-[5-Chloro-2-(3-methoxypropyl)-4-pyridinyl]methyl)cyclopropanamine

Amine 2 was prepared according to the procedure described in WO 2007/009250 A1 patent.

Amine 3

\(N\)-[{2-Chloro-5-[3-(methyloxy)propyl]phenyl}methyl)cyclopropanamine

Amine 3 was prepared according to the procedure described in WO 2007/009250 A1 patent.

Amine 4

\(N\)-[{2-Chloro-5-[2-(methyloxy)ethyl]phenyl}methyl)cyclopropanamine

Amine 4 was prepared according to the procedure described in WO 2007/009250 A1 patent.

Amine 5

\(N\)-[{2,3-Dichloro-5-[3-(methoxypropyl)propyl]phenyl}methyl)cyclopropanamine

Step 1: 5-Bromo-2,3-dichlorobenzaldehyde

To a TFA solution (0.38 M) of 2,3-dichlorobenzaldehyde (1 eq.) was added sulfuric acid (5 eq.). Over a period of 3 h, ZV-bromosuccinimide (1.5 eq.) was added portionwise at RT to afford, in the end, a yellow-orange solution. After 72 h, the crude reaction mixture was diluted with 9:1 (v/v)
hexanes: ether and then washed sequentially with water, 1 N aq. NaOH, water and brine. The organic extract was dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the title compound as a white solid.

Step 2: N-[(5-Bromo-2,3-dichlorophenyl)methyl]cyclopropanamine

5-Bromo-2,3-dichlorobenzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH₂Cl₂ (0.1 M). To this was then added MgSO₄ (1 eq.) and the resulting suspension was stirred at RT for 18 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in a 2:1 (v/v) mixture of THF: MeOH (0.17 M). To this solution was added sodium borohydride (10 eq.) portionwise and the resulting mixture was stirred at RT for 48 h. The reaction was quenched with 1 N aq. HCl, neutralized with 1 N aq. NaOH and extracted with ether. The combined organic extracts were then washed with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo.

Purification of the crude product thus obtained by way of flash chromatography (SiO₂, Hex → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 3: N-[(2,3-Dichloro-5-[(1E)-3-(methyloxy)-1-propen-1-yl]phenyl)methyl]cyclopropanamine

N-[(5-Bromo-2,3-dichlorophenyl)methyl]cyclopropanamine (1 eq.) from the previous step and 4,4,5,5-tetramethyl-2-[(1E)-3-(methyloxy)-1-propen-1-yl]-1,3,2-dioxaborolane (1.5 eq.) were combined in a 5:1 (v/v) mixture of DMF: «-PrOH (0.17 M). To this solution was then added trans-bis(triphenylphosphine) palladium(II) bromide (0.05 eq.) and the vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 N aq. Na₂CO₃ (2 eq.) was added and the resulting biphasic suspension was heated at 90°C for 8 h. The now black suspension was cooled to RT, diluted with water and extracted with ether. The combined organic extracts were then washed further with 1 N aq. NaOH, water and brine. This was then dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford a viscous red oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, Hex → 3:7 (v/v) Hex : EtOAc) afforded the title compound as a yellow oil.

Step 4: Amine 5

N-[(2,3-Dichloro-5-[(1E)-3-(methyloxy)-1-propen-1-yl]phenyl)methyl]cyclopropanamine (1 eq.) from the previous step and 10% w/w palladium over charcoal (0.1 eq.) were suspended in EtOAc (0.03 M). The vessel was then evacuated and purged with H₂. Under a balloon-filled H₂ atmosphere, the reaction suspension was stirred at RT for 2 h. The reaction was then quenched with CH₂Cl₂, filtered through a bed of celite and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, Hex → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.
Amine 6

\[ N-\{(2,3-\text{Dichloro}-5-[2-(\text{methyloxy})\text{ethyl}]\text{phenyl})\text{methyl}\}\text{cyclopropanamine} \]

Step 1: 1,1-Dimethylethyl[(5-bromo-2,3-dichlorophenyl)methyl]cyclopropylcarbamate

\[ N-\text{KS-Bromo}^-\text{-dichlorophenyl}\text{Omethyl} \text{cyclopropanamine} \ (1 \text{ eq.}) \text{ from Step 2, Amine} \]

5 and \( d\text{-t} \text{er-t-bu} \text{tyl}^-\text{dicarbo} \text{nate} \ (1.1 \text{ eq.}) \) were combined in \( \text{CH}_2\text{Cl}_2 \) (0.17 M). To this solution was then added Hunig's base (1.2 eq.) and the resulting yellow solution was stirred at RT for 3 h. The reaction mixture was then diluted with ether and washed sequentially with water and brine. The organic layer was then dried over \( \text{Na}_2\text{SO}_4 \), filtered and the filtrate concentrated \textit{in vacuo} to afford a yellow oil.

Purification of the crude product thus obtained by way of flash chromatography (SiO\(_2\), Hex \( \rightarrow \) 3:7 \( v/v \)

Hex : EtOAc) afforded the title compound as a colorless oil.

Step 2: 1,1-Dimethylethyl cyclopropyl[[2,3-dichloro-5-ethenylphenyl]methyl]carbamate

1,1-Dimethylethyl[(5-bromo-2,3-dichlorophenyl)methyl]cyclopropylcarbamate (1 eq.) from the previous step and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 eq.) were combined in a 2:1 \( v/v \) mixture of DMF: n-PrOH (0.1 M). To this solution was then added palladium(II) acetate (0.05 eq.) and triphenylphosphine (0.15 eq.) before the vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 N aq. \( \text{Na}_2\text{C}^\theta_3 \) (2 eq.) was added and the resulting biphasic suspension was heated at 90\(^\circ\)C for 18 h. The now black suspension was cooled to RT, diluted with water and extracted with 1:1 \( v/v \) hexanes: ether. The combined organic extracts were then washed further with 1 N aq. NaOH, water and brine. This was then dried over \( \text{Na}_2\text{SO}_4 \), filtered and the filtrate concentrated \textit{in vacuo} to afford a pale yellow oil. Purification of the crude product thus obtained by way of flash chromatography (SiO\(_2\), Hex \( \rightarrow \) 9:1 \( v/v \) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 3: 1,1-Dimethylethyl cyclopropyl[[2,3-dichloro-5-(2-hydroxyethyl)phenyl]methyl]carbamate

1,1-Dimethylethyl cyclopropyl[[2,3-dichloro-5-ethenylphenyl]methyl]carbamate (1 eq.) from the previous step, [Ir(COD)Cl]\(_2\) (0.025 eq.) and DPPB (0.05 eq.) were combined in THF (0.11 M). To this solution was then added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.3 eq.) and the resulting red solution was stirred at RT for 12 h. Finally, sodium perborate (0.1 M aqueous solution, 1 eq.) was added and the now black biphasic solution was vigorously stirred at RT for another 12 h. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were then washed further with 1 N aq. NaOH, water and brine. This was then dried over \( \text{Na}_2\text{SO}_4 \), filtered and the filtrate concentrated \textit{in vacuo} to afford a pale yellow oil. Purification of the crude product thus obtained by way of flash chromatography (SiO\(_2\), 9:1 \( v/v \) Hex : EtOAc \( \rightarrow \) 3:7 \( v/v \) EtOAc : Hex) afforded the title compound as a colorless oil.

Step 4: 1,1-Dimethylethyl cyclopropyl[[2,3-dichloro-5-[2-(methyloxy)ethyl]phenyl]methyl]carbamate

1,1-Dimethylethyl cyclopropyl[[2,3-dichloro-5-[2-hydroxyethyl]phenyl]methyl]carbamate (1 eq.) was taken up in THF (0.3 M). To this solution was then added sodium hydride (60% w/w dispersion in oil, 1 eq.) and the resulting suspension was stirred at RT for 5 min. Finally, iodomethane (10 eq.) was added and the now pale yellow solution was stirred in
darkness at RT for another 10 h. The volatiles were then removed in vacuo and the resulting residue partitioned between ether and 1 N aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were then washed further with 1 N aq. NaOH, water and brine. This was then dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo to give the title compound (contaminated with oil) as a pale yellow oil.

Step 5: **Amine 6**

$\text{1,1-Dimethylethyl cyclopropyl(2,3-dichloro-5-[2-}$

(methylxylo)ethyl]phenyl)methyl)carbamate (1 eq.) from the previous step was taken up in CH$_2$Cl$_2$ (0.1 M). To this solution was then added HCl (4.0 M in dioxane, 30 eq.) and the resulting solution was stirred at RT for 2 h. The reaction was then quenched with 1 N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, 9:1 (v/v) Hex : EtOAc $\rightarrow$ EtOAc) afforded the title compound as a colorless oil.

**Amine 7**

$\text{iV-(2-Methyl-5-[3-(methylxylo)propylphenyl]methyl)cyclopropanamine}$

Step 1: 5-Chloro-$\eta$-cyclopropyl-2-methylbenzamide

To a toluene solution (1 M) of 5-chloro-2-methylbenzoic acid (1 eq.) and DMF (1.2 eq.) was added at 0 ºC oxalyl chloride (1.2 eq.) dropwise over 1 h. The resulting solution was stirred at 0 ºC for 2 h before the volatiles were removed in vacuo. The resulting residue was taken up in dichloromethane (1 M), cooled to 0 ºC and added sequentially cyclopropylamine (1.5 eq.) and Hunig's base (2 eq.) dropwise. The resulting suspension was stirred at RT for 18 h. The reaction was quenched with 1 N aq. HCl and extracted with dichloromethane. The combined organic extracts were dried over MgSO$_4$, filtered and the filtrate concentrated in vacuo $\rightarrow$ 1/3 in volume. The resulting white suspension was added an equivalent volume of hexanes and the title compound was isolated via vacuum filtration.

Step 2: $\text{N-[(5-Chloro-2-methylphenyl)methyl]cyclopropanamine}$

At 0 ºC, a suspension of 5-chloro-$\eta$-cyclopropyl-2-methylbenzamide (1 eq.) from the previous step in THF (0.4 M) was added borane (1.0 M in THF, 3 eq.). The resulting suspension was warmed to RT over 1 h and then heated at reflux for 1 h. The now pale yellow solution was re-cooled to 0 ºC and carefully quenched with 1 N aq. HCl. The resulting mixture was heated at reflux for 1 h to ensure complete breakdown of the amine-borane complex. Following careful neutralization with 1 N aq. NaOH, the aqueous layer was separated and back extracted with EtOAc. The combined organic extracts were washed with brine, dried over MgSO$_4$ and filtered. The filtrate was concentrated in vacuo and the crude product thus obtained was purified further by way of flash chromatography (SiO$_2$, Hex $\rightarrow$ 4:1 (v/v) Hex : Et$_2$O) to reveal the title compound as a colorless oil.

Step 3: 1,1-Dimethylethyl [(5-chloro-2-methylphenyl)methyl]cyclopropylcarbamate
A THF solution (0.3 M) of 7V-[5-chloro-2-methylphenyl]methyl]cyclopropanamine from the previous step (1 eq.) was added at -78 °C potassium hexamethyldisilazide (0.5 M in toluene, 1.2 eq.). After 1 h of stirring at -78 °C, di-fert-butyl dicarbonate (1.1 eq.) was added and the resulting mixture was slowly warmed to RT over 2 h. The reaction was quenched with sat. aq. NH₄Cl and then extracted with ether. The combined organic extracts were washed with brine, dried over MgSO₄, filtered and the filtrate concentrated in vacuo. Further purification by way of flash chromatography (SiO₂, Hex : EtOAc - EtOAc) afforded the title compound as a colorless oil.

Step 4: 1,1-Dimethylethyl cyclopropyl[2-methyl-5-[1,1'-3-(methyloxy)-1-propyl-1-y]phenyl]methyl]carbamate

1,1-Dimethylethyl [5-chloro-2-methylphenyl]methyl]cyclopropylcarbamate (1 eq.) from the previous step and 4,4,5,5-tetramethyl-2-[(1E)-3-(methyloxy)-1-propen-1-yl]-1,3,2-dioxaborolane (1 eq.) were combined in rc-ButOH (0.48 M). To this solution was then added tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (0.02 eq.), [2',6'-bis(methyloxy)-2-biphenyl][dicyclohexyl]phosphane (0.08 eq.) and powdered potassium phosphate (2 eq.). The vessel was repeatedly evacuated and back-filled with nitrogen before the resulting suspension was heated at 100°C for 16 h. The now black suspension was cooled to RT, diluted with EtOAc and filtered through a pad of SiO₂. The filtrate was then concentrated in vacuo and the crude product thus obtained was directly subjected to purification by way of flash chromatography (SiO₂, Hex : EtOAc) afforded the title compound as a pale yellow oil.


1,1-Dimethylethyl cyclopropyl[2-methyl-5-[1E]-3-(methyloxy)-1-propen-1-yl]phenyl]methyl]carbamate (1 eq.) from the previous step and 10% w/w palladium over charcoal (0.1 eq.) were suspended in EtOAc (0.08 M). The vessel was then evacuated and purged with H₂. Under a balloon-filled H₂ atmosphere, the reaction suspension was stirred at RT for 2 h. The reaction was then quenched with CH₂Cl₂, filtered through a bed of celite and the filtrate concentrated in vacuo.

Purification of the crude product thus obtained by way of flash chromatography (SiO₂, Hex : EtOAc) afforded the title compound as a colorless oil.

Step 6: Amine

1,1-Dimethylethyl cyclopropyl[2-methyl-5-[3-(methyloxy)propyl]phenyl]methyl]carbamate (1 eq.) from the previous step was taken up in CH₂Cl₂ (0.1 M). To this solution was then added HCl (4.0 M in dioxane, 30 eq.) and the resulting solution was stirred at RT for 2 h. The reaction was then quenched with 1N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.
Amine 8

$N'\{[2\text{-methyl-5-}[2\text{-methyloxy}ethyl]phenyl]methyl\}cyclopropanamine$

Amine 8 was prepared according to the procedure described in Amine 6 but using instead 1,1-dimethylethyl [(5-chloro-2-methylphenyl)methyl]cyclopropylcarbamate from Step 3, Amine 7 as the substrate, $«\text{BuOH}$ as the solvent, tris(dibenzylideneacetone)dipalladium(0) chloroform adduct as the palladium source, [2',6'-bis(methyloxy)-2-biphenyl]l(dicyclohexyl)phosphane as the ligand and powdered potassium phosphate as the base for the Suzuki coupling (step 2).

Amine 9

$N'\{[2,3\text{-difluoro-5-}[3\text{-methyloxy}propyl]phenyl]methyl\}cyclopropanamine$

Amine 9 was prepared according to the procedure described in Amine 5 but using instead 2,3-difluorobenzaldehyde as starting material.

Amine 10

$N'\{[3\text{-Methoxyloxy}-5-][3\text{-methyloxy}propyl]phenyl]methyl\}cyclopropanamine$

Step 1: 3-Bromo-5-hydroxybenzaldehyde

To a toluene solution (1.6 M) of n-butyl lithium (2.5 M in hexane, 2.1 eq.) was added at -10°C n-butyl magnesium chloride (2.0 M in THF, 0.6 eq.). The reaction mixture was stirred at -10°C for 30 min before a toluene solution (0.7 M) of 3,5-dibromophenol (1 eq.) was added dropwise at -10°C over a period of 35 min. After stirring at -10°C for a further 30 min, the reaction mixture was cooled to -40°C before DMF (20 eq.) was added dropwise over 20 min. The reaction mixture was then slowly warmed to RT and allowed to stir at RT for 1 h. The reaction was carefully quenched with 1 N aq. HCl and extracted with ether. The combined organic extracts were washed with water and brine, dried over MgSO₄ and filtered. Concentration of the filtrate in vacuo afforded a yellow solid. Recrystallization of the crude product thus obtained from ether - hexane afforded the title compound as a beige powder.

Step 2: 3-Hydroxy-5-[(I€)-3-(methyloxy)-1-propen-1-yl]benzaldehyde

3-Bromo-5-hydroxybenzaldehyde (1 eq.) from the previous step and 2-[(I€)-3-methoxyprop-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 eq.) were combined in DMF (0.05 M). To this solution was then added palladium acetate (0.1 eq.), triphenylphosphine (0.2 eq.) and 2 M aq. sodium carbonate (4 eq.). The resulting suspension was heated at 80°C for 16 h. The reaction mixture was quenched with 1 N aq. HCl and extracted with ether. The combined organic extracts were washed with water, sat. aq. NaHCO₃ and brine. Drying over MgSO₄, filtration and concentration of the filtrate in vacuo afforded the crude product as a brown tar. Further purification by way of flash chromatography (SiO₂, 4:1 (v/v) Hex : EtOAc $\rightarrow$ 2:1 (v/v) Hex : EtOAc) afforded the title compound as a yellow oil.
Step 3: 3-(Methyloxy)-5-[(1E)-3-(methyloxy)-l-prop-l-en-l-yl]benzaldehyde

3-Hydroxy-5-[(1E)-3-(methyloxy)-l-prop-l-en-l-yl]benzaldehyde (1 eq.) from the previous step and iodomethane (2.2 eq.) were combined in acetone (0.07 M). To this solution was then added potassium carbonate (2 eq.) and the reaction suspension was heated at reflux for 16 h. The resulting reaction mixture was concentrated in vacuo and the residue partitioned between water and ether. The aqueous wash was separated and back-extracted with ether. The combined organic extracts were washed further with brine, dried over MgSO₄, filtered and the filtrate concentrated in vacuo. Further purification of the crude product thus obtained by way of flash chromatography (SiO₂, 19:1 (v/v) Hex : EtOAc → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a yellow oil.

Step 4: N-([3-(Methyloxy)-5-[(1E)-3-(methyloxy)-l-prop-l-en-l-yl]phenyl]methyl)cyclopropanamine

To a solution of 3-(methyloxy)-5-[(1E)-3-(methyloxy)-l-prop-l-en-l-yl]benzaldehyde (1 eq.) from the previous step (1 eq.) in dichloromethane (0.5 M) was added cyclopropylamine (2 eq.) and magnesium sulfate (1.5 eq.). The resulting suspension was stirred at RT for 12 h. The insolubles were removed via filtration. Concentration of the filtrate in vacuo afforded the crude imine as a yellow oil. This was then taken up in methanol (0.3 M) and then added at 0 °C sodium borohydride (1.5 eq.) portionwise over 5 min. The reaction mixture was slowly warmed to RT over 1 h and then stirred at RT for 2 h. After carefully quenching with sat. aq. NaHCO₃, the resulting mixture was extracted with ether. The combined organic extracts were washed with water and brine, dried over MgSO₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a golden, yellow oil.

Step 5: Amine 10

To a solution of N-([3-(methyloxy)-5-[(1E)-3-(methyloxy)-l-prop-l-en-l-yl]phenyl]methyl)cyclopropanamine (1 eq.) from the previous step in EtOAc (0.04 M) was added palladium (10% w/w over activated carbon, 0.1 eq). The vessel was evacuated and back filled with hydrogen. The reaction suspension was then stirred under a balloon atmosphere of hydrogen for 1.5 h. The reaction was quenched with dichloromethane and filtered through a bed of celite. The insolubles were washed further with EtOAc and methanol. Concentration of the filtrate in vacuo afforded the title compound as a colorless oil.

Amine 11

Amine 11 was prepared according to the procedure described in Amine 10 but using instead 2-bromoethyl methyl ether as the alkylating reagent, cesium carbonate as the base and DMF as the solvent in step 3.
Amine 12

4-{3,4-Dichloro-5-[(cyclopropylamino)methyl]phenyl}butanenitrile

Step 1: 1,1-Dimethylethyl cyclopropyl[[2,3-dichloro-5-(2-oxoethyl)phenyl]methyl]carbamate

1,1-Dimethylethyl cyclopropyl [[2,3-dichloro-5-(2-hydroxyethyl)phenyl]methyl] carbamate (1 eq.) from Step 3, Amine 6 and sodium bicarbonate (1 eq.) were suspended in CH$_2$Cl$_2$ (0.1 M). At 0°C, DMP (1 eq.) was added and the resulting mixture was stirred at 0°C for 15 min and then at RT for 45 min. The reaction was quenched with 1 N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo to afford the title compound as an unstable, colorless oil.

Step 2: 1,1-Dimethylethyl cyclopropyl[[2,3-dichloro-5-[(2E)-3-cyano-2-propen-1-yl]phenyl]-methyl]carbamate

To a THF (0.1 M) suspension of anhydrous lithium chloride (1.2 eq.) was added sequentially diethyl (cyanomethyl)phosphonate (1.2 eq.) and DBU (1 eq.). The resulting suspension was stirred at RT for 15 min before 1,1-dimethylethyl cyclopropyl [[2,3-dichloro-5-(2-oxoethyl)phenyl]methyl] carbamate (1 eq.) from the previous step was added dropwise as a THF (0.1 M) solution. The resulting pink suspension was allowed to stir at RT for 12 h before it was carefully quenched with 1 N aq. HCl and then extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo.

Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, Hex → 3:7 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 3: 1,1-Dimethylethyl cyclopropyl[[2,3-dichloro-5-(3-cyanopropyl)phenyl]methyl]carbamate

To a solution of 1,1-dimethylethyl cyclopropyl[[2,3-dichloro-5-[(2E)-3-cyano-2-propen-1-yl]phenyl]methyl]carbamate (1 eq.) from the previous step in EtOAc (0.04 M) was added palladium (10% w/w over activated carbon, 0.1 eq). The vessel was evacuated and back filled with hydrogen. The reaction suspension was then stirred under a balloon atmosphere of hydrogen for 1.5 h. The reaction was quenched with dichloromethane and filtered through a bed of celite. The insolubles were washed further with EtOAc. Concentration of the filtrate in vacuo afforded the title compound as a colorless oil.

Step 4: Amine 12

To a solution of 1,1-dimethylethyl cyclopropyl[[2,3-dichloro-5-(3-cyanopropyl)phenyl]methyl] carbamate (1 eq.) from the previous step in CH$_2$Cl$_2$ (0.06 M) was added zinc(II) bromide (10 eq.). The resulting suspension was sonicated for 15 min and then allowed to stir at RT for 18 h. The reaction was quenched with 1 N aq. NaOH and then extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, 9:1 (v/v) Hex : EtOAc → 3:7 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.
Amine 13

4-{3-[(Cyclopropylamino)methyl]-4,5-difluorophenyl}butanenitrile

Amine 13 was synthesized according to the procedure described in Amine 12 but using instead 1,1-dimethylethyl cyclopropyl[{2,3-difluoro-5-(2-hydroxyethyl)phenyl}methyl]carbamate prepared analogously from 2,3-difluorobenzaldehyde.

Amine 14

Methyl 4-{3,4-dichloro-5-[(cyclopropylamino)methyl]phenyl}butanoate

Amine 14 was prepared according to the procedure described in Amine 12 but replacing anhydrous lithium chloride, diethyl (cyanomethyl)phosphonate and DBU with methyl (triphenyl-λ3-phosphanylidene)acetate in the Wittig-olefination step (step 2).

Amine 15

N-({3-[(Methyloxy)propyl]-1-naphthaleny1}methyl)cyclopropanamine

Step 1: Methyl 3-[(E)-3-(methyloxy)-1-propen-1-yl]-1-naphthalencarboxylate 

Methyl 3-bromo-1-naphthalencarboxylate (1 eq.) and 4,4,5,5-tetramethyl-2-[(E)-3-(methyloxy)-1-propen-1-yl]l,3,2-dioxaborolane (1.5 eq.) were combined in a 5:1 (v/v) mixture of DMF: H-PrOH (0.2 M). To this solution was then added Na₂C₃ (2 eq.) was added and the resulting biphasic suspension was heated at 90°C for 8 h. The now black suspension was cooled to RT, diluted with water and extracted with 1:1 (v/v) hexanes: ether. The combined organic extracts were then washed further with 1 N aq. NaOH, 1 N aq. HCl, water and brine. This was then dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the title compound as a red oil.

Step 2: Methyl 3-{3-(Methyloxy)propyl}-1-naphthalencarboxylate 

Methyl 3-[(E)-3-(methyloxy)-1-propen-1-yl]-1-naphthalencarboxylate (1 eq.) from the previous step and 10% w/w palladium over charcoal (0.1 eq.) were suspended in MeOH (0.08 M). The vessel was then evacuated and purged with H₂. Under a balloon-filled H₂ atmosphere, the reaction suspension was stirred at RT for 2 h. The reaction was then quenched with CH₂Cl₂, filtered through a bed of celite and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂; Hex → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 3: 3-{3-(Methyloxy)propyl}-1-naphthalencarboxylic acid 

Methyl 3-{3-(Methyloxy)propyl}-1-naphthalencarboxylate (1 eq.) from the previous step was taken up in a 2:1 (v/v) mixture of MeOH: THF (0.08 M). To this solution was then added LiOH (2.0 M aq. solution, 3 eq.) and the resulting cloudy solution was vigorously stirred at RT for 24 h. The
volatiles were then removed *in vacuo* and the pH of the residue was carefully adjusted to ~2 with 1 N aq. HCl before it was extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate *in vacuo* afforded the title compound as a white solid.

**Step 4: N-Cyclopropyl-3-[3-(methyloxy)propyl]-1-naphthalencarboxamide**

To a CH₂Cl₂ solution (0.1 M) of 3-[3-(methyloxy)propyl]-1-naphthalencarboxylic acid (1 eq.) from the previous step was added at 0 °C oxalyl chloride (1.2 eq.) followed by a few drops of DMF. The resulting solution was stirred at RT for 2 h before the volatiles were removed *in vacuo*. The resulting residue was taken up in dichloromethane (0.1 M), cooled to 0 °C and added sequentially Hunig’s base (1.2 eq.) and cyclopropylamine (1.1 eq.) dropwise. The resulting suspension was stirred at RT for 18 h. The reaction was quenched with 1 N aq. HCl and extracted with ether. The combined organic extracts were washed further with 1 N aq. NaOH, water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate *in vacuo* afforded the title compound as a white solid.

**Step 5: Amine 15**

To a THF solution (0.1 M) of N-cyclopropyl-3-[3-(methyloxy)propyl]-1-
naphthalencarboxamide (1 eq.) from the previous step was added, at reflux, borane-methyl sulfide complex (6.6 eq.). To the reaction vessel was the attached a short path distillation apparatus and most of the volatiles were slowly distilled off over a period of 1.5 h. The now yellow solution was re-cooled to 0 °C and carefully quenched with 1 N aq. HCl. The resulting mixture was heated at reflux for 1 h to ensure complete breakdown of the amine-borane complex. Following careful neutralization with 1 N aq. NaOH, the aqueous layer was separated and back extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated *in vacuo* and the crude product thus obtained was purified further by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc \( \rightarrow \) 3:7 (v/v) Hex : EtOAc) to reveal the title compound as a colorless oil.

**Amine 16**

Methyl (2-[3,4-Dichloro-5-[(cyclopropylamino)methyl]phenyl]ethyl)carbamate

**Step 1: 1,1-Dimethylethyl cyclopropyl[(2,3-dichloro-5-formylphenyl)methyl]carbamate**

To a dichloromethane (0.03 M) solution of 1,1-dimethylethyl cyclopropyl[(2,3-dichloro-5-ethenylphenyl)methyl]carbamate (1 eq.) from Step 2, Amine 6 was bubbled at -78 °C freshly generated ozone until a persistent blue color was obtained. To this was then added triphenylphosphine (1.2 eq.) in one rapid portion and the resulting mixture was slowly warmed to RT over 3 h. The volatiles were removed *in vacuo* and the remaining residue was triturated with 2:1 (v/v) Hex : Et₂O. The insolubles were removed via filtration and the filtrate was concentrated *in vacuo*. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, Hex \( \rightarrow \) 1:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.
Step 2: 1,1-Dimethylethyl cyclopropyl[(2,3-dichloro-5-(hydroxymethyl)phenyl)methyl]carbamate

To a methanol (0.16 M) solution of 1,1-dimethylethyl cyclopropyl[(2,3-dichloro-5-formyl)phenyl]methyl]carbamate from the previous step was added at 0°C sodium borohydride (1.3 eq.). The resulting solution was stirred at 0°C for 2 h before the volatiles were removed in vacuo. The resulting residue was then partitioned between ether and 1 N aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, Hex $\rightarrow$ 3:7 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 3: 3,4-Dichloro-5-[(cyclopropyl[(1,1-dimethylethyl)oxy]carbonyl]amino)methyl]phenyl)methyl methanesulfonate

To a solution of 1,1-dimethylethyl cyclopropyl[(2,3-dichloro-5-(hydroxymethyl)phenyl)methyl] carbamate (1 eq.) from the previous step in dichloromethane (0.1 M) was added sequentially at 0°C Hunig’s base (3 eq.) and methanesulfonyl chloride (1.1 eq.). The resulting solution was stirred at 0°C for 30 min and then at RT for 15 min. The reaction mixture was then diluted with ether and carefully quenched with 1 N aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo to afford the crude title compound as a colorless oil.

Step 4: 1,1-Dimethylethyl cyclopropyl[(2,3-dichloro-5-(cyanomethyl)phenyl)methyl]carbamate

To a solution of 3,4-dichloro-5-[(cyclopropyl[(1,1-dimethylethyl)oxy]carbonyl]amino)methyl]phenyl] methyl methanesulfonate (1 eq.) from the previous step in DMSO (0.48 M) was added potassium cyanide (1.3 eq.) and sodium iodide (0.1 eq.). The resulting solution was stirred at RT for 3 h before it was diluted with ether and quenched with 1 N aq. NaOH. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, 19:1 (v/v) Hex : EtOAc $\rightarrow$ 3:7 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 5: 1,1-Dimethylethyl [(5-(2-aminoethyl)-2,3-dichlorophenyl)methyl]cyclopropylcarbamate

To a solution of 1,1-dimethylethyl cyclopropyl[(2,3-dichloro-5-(cyanomethyl)phenyl)methyl] carbamate (1 eq.) from the previous step and cobalt(II) chloride hexahydrate (2 eq.) in methanol (0.07 M) was added sodium borohydride (10 eq.) portionwise at 0°C. The resulting mixture was stirred at 0°C for 10 min and then at RT for 2 h. The now brown suspension was quenched with 1 N aq. NaOH and then extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$ and filtered through a bed of celite. Concentration of the filtrate in vacuo afforded the crude title compound as a pale brown, amorphous solid.
Step 6: 1,1-Diaethylethyl cyclopropyl[2,3-dichloro-5-(2-[(methylxy)carbonyl]amino)ethyl]phenyl]methyl carbamate

To a solution of 1,1-dimethylethyl [(5-(2-aminoethyl)-2,3-
dichlorophenyl)methyl]cyclopropylcarbamate (1 eq.) from the previous step in dichloromethane (0.07 M) was added sequentially at 0°C Hunig’s base (1.2 eq.) and methyl chloroformate. The resulting solution was then allowed to warm slowly to RT over 3 h. The crude reaction mixture was subsequently diluted with ether and washed sequentially with 1 N aq. NaOH, 1 N aq. HCl, water and brine. The ether extract was then dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 19:1 (v/v) Hex : EtOAc -> EtOAc) afforded the title compound as a pale yellow oil.

Step 7: Amine 16

To a solution of 1,1-dimethylethyl cyclopropyl[2,3-dichloro-5-(2-[(methylxy)carbonyl]amino)ethyl]phenyl]methyl carbamate (1 eq.) from the previous step in CH₂Cl₂ (0.06 M) was added HCl (4.0 M in dioxane, 30 eq.). The resulting solution was stirred at RT for 3 h. The reaction was then quenched with 1 N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 24:1 (v/v) CH₂Cl₂ : MeOH) afforded the title compound as a colorless oil.

Amine 17

JV-(8-Quinolinylmethyl)cyclopropanamine

To a dichloromethane (0.13 M) solution of 8-quinolinecarbaldehyde (1 eq.) was added magnesium sulphate (1 eq.) and cyclopropyl amine (2 eq.). The resulting suspension was stirred at RT for 16 h. The insolubles were removed via filtration and rinsed with dichloromethane before the combined filtrate was concentrated in vacuo. The crude imine thus obtained was taken up in methanol (0.13 M) and then added sodium borohydride (1.5 eq.) portionwise. The reaction mixture was stirred at RT for 2 h before it was quenched with 1 N aq. HCl. The pH of the solution was then adjusted to ~ 10 with 1 N aq. NaOH before it was extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the crude title compound as a yellow oil.

Amine 18

JV-(8-Isoquinolinylmethyl)cyclopropan amine

Amine 18 was prepared according to the procedure described in Amine 17 but using instead 8-Isoquinolinecarbaldehyde as starting material.
Amine 19

\[ \text{N-}(5\text{-Isoquinoliny1methyl)cyclopropanamine} \]

\text{Amine 19} was prepared according to the procedure described in \text{Amine 17} but using instead 5-isoquinolinecarbaldehyde as starting material.

Amine 20

\[ \text{N-}(5\text{-Quinolmylmethyl)cyclopropanamine} \]

\text{Amine 20} was prepared according to the procedure described in \text{Amine 17} but using instead 5-quinolinecarbaldehyde as starting material.

Amine 21

\[ \text{N-}(1\text{-Isoquinolinolnymethyl)cyclopropanamine} \]

\text{Amine 21} was prepared according to the procedure described in \text{Amine 17} but using instead 1-isoquinolinecarbaldehyde as starting material.

Amine 22

\[ \text{N-}([2\text{-}[3\text{-Methyloxy}]\text{propyl}-4\text{-quinolinyl}]\text{methyl)cyclopropanamine} \]

\text{Amine 22} was prepared according to the procedure described in \text{WO 2007/09250 A1} patent.

Amine 23

\[ \text{N-}([6\text{-}[3\text{-Methyloxy}]\text{propyl}-8\text{-quinolinyl}]\text{methyl)cyclopropanamine} \]

Step 1: \[ 6\text{-}([\text{I,I-Dimethylethyl}]\text{dimethyl}silyl)xy1\text{methyl}-8\text{-quinolinecarbaldehyde} \]

To a THF (0.06 M) solution of 8-bromo-6-\([\text{I,I-Dimethylethyl}]\text{dimethyl}silyl)xy1\text{methyl}-8\text{-quinolinecarbaldehyde} methylquinolone (1 eq.) was added at -78°C. Butyl lithium (2.5 M in hexane, 2.1 eq.) was dropwise over a period of 10 min. The resulting yellow solution was stirred at -78°C for 15 min before DMF (2 eq.) was added dropwise over a period of 10 min. The now red solution was stirred at -78°C for another 2 h before the reaction mixture was quenched with the addition of sat. aq. \(\text{NH}_4\text{Cl}\). The aqueous layer was separated and back-extracted with ether. The combined organic extracts were then washed with brine, dried over \(\text{Na}_2\text{SO}_4\), filtered and the filtrate concentrated \textit{in vacuo}. Purification of the crude product thus obtained by way of flash chromatography (SiO\(_2\), Hex \(\rightarrow\) 3:7 (v/v) Hex : EtOAc) afforded the title compound as a yellow oil that solidified upon standing.

Step 2: \[ N\text{-}([6\text{-}([\text{I,I-Dimethylethyl}]\text{dimethyl}silyl)xy1\text{methyl}-8\text{-quinolinyl}]\text{methyl)cyclopropanamine} \]

To a dichloromethane (0.12 M) solution of 6-\([\text{I,I-Dimethylethyl}]\text{dimethyl}silyl)xy1\text{methyl}-8\text{-quinolinecarbaldehyde} (1 eq.) from the previous step was added magnesium sulphate (1 eq.) and cyclopropyl amine (2 eq.). The resulting suspension was stirred at RT for 16 h. The insolubles were
removed via filtration and rinsed with dichloromethane before the combined filtrate was concentrated in vacuo. The crude imine thus obtained was taken up in methanol (0.12 M) and then added sodium borohydride (1.5 eq.) portionwise. The reaction mixture was stirred at RT for 2 h. The volatiles were then removed in vacuo and the resulting residue was partitioned between ether and 1 N aq. NaOH. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo to afford the crude title compound as a yellow oil.

Step 3: 1,1-Dimethylethyl cyclopropyl [[6-((1,1-dimethylethyl)(dimethyl)silyl)oxy]methyl]-8-quinolinyl[methyl]carbamate

To a solution of $N^\prime$-[[6-((1,1-dimethylethyl)(dimethyl)silyl)oxy]methyl]-8-quinolinyl[methyl]cyclopropanamine (1 eq.) from the previous step in dichloromethane (0.12 M) was added sequentially Hünig's base (1.2 eq.) and bis(1,1-dimethylethyl)dicarbonate (1.1 eq.). The resulting solution was stirred at RT for 8 h. The volatiles were then removed in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, Hex : EtOAc) afforded the title compound as a colorless oil.

Step 4: 1,1-Dimethylethyl cyclopropyl[[6-(hydroxymethyl)-8-quinolinyl][methyl]carbamate

To a solution of 1,1-dimethylethyl cyclopropyl[[6- ((1,1-dimethylethyl)(dimethyl)silyl)oxy]methyl]-8-quinolinyl[methyl]carbamate (1 eq.) from the previous step in THF (0.12 M) was added TBAF (1.0 M in hexane, 1.6 eq.). The resulting solution was stirred at RT for 2 h before the volatiles were removed in vacuo. The resulting residue was partitioned between ether and water. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, 9:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 5: 1,1-Dimethylethyl cyclopropyl[[6-formyl-8-quinolinyl][methyl]carbamate

To a suspension of 1,1-dimethylethyl cyclopropyl[[6-(hydroxymethyl)-8-quinolinyl][methyl]carbamate (1 eq.) from the previous step and sodium bicarbonate (1.1 eq.) in dichloromethane (0.1 M) was added DMP (1.1 eq.) at 0°C. The resulting mixture was stirred at RT for 2 h before it was quenched with sat. aq. NaHSO$_3$ and then extracted with Et$_2$O. The combined organic extracts were washed further with 1 N aq. NaOH, water and brine, dried over Na$_2$SO$_4$, and filtered. Concentration of the filtrate in vacuo afforded the crude title compound as a white solid.

Step 6: Methyl 3-[(cyclopropyl [[(1,1-dimethylethyl)oxy]carbonyl] amino)methyl]-6-quinolinyl-2-propenoate

To a solution of 1,1-dimethylethyl cyclopropylK6-formyl-8-quinolinyl*methy*carbamate (1 eq.) from the previous step in dichloromethane (0.06 M) was added methyl (triphenylphosphoranylidene)acetate (1.1 eq.) at 0°C. The resulting solution was then allowed to warm slowly to RT over 4 h. The volatiles were then removed in vacuo. Purification of the crude product thus obtained by way of
flash chromatography (\( \text{SiO}_2 \), 9:1 (v/v) Hex : EtOAc -> 3:7 (v/v) Hex : EtOAc) afforded the title compound as a white solid.

Step 7: Methyl 3-\{8-[\{cyclopropyl\{\{1,1\text{-dimethylethyl}\}oxy\}carbonyl\}amino\}methyl\}-6-quinolinyl]-propanoate

To a solution of methyl 3-\{8-[\{cyclopropyl\{\{1,1\text{-dimethylethyl}\}oxy\}carbonyl\}amino\}methyl\]-6-quinolinyl]-2-propenoate (1 eq.) from the previous step in EtOAc (0.1 M) was added palladium (10% (w/w) over carbon, 0.1 eq.). The resulting suspension was evacuated and back-filled repeatedly with hydrogen. Finally, the reaction suspension was allowed to stir under a hydrogen-filled balloon atmosphere for 3 h. The reaction was quenched with the addition of dichloromethane and filtered through a bed of celite. The filtrate was then concentrated \textit{in vacuo}. Purification of the crude product thus obtained by way of flash chromatography (\( \text{SiO}_2 \), 9:1 (v/v) Hex : EtOAc -> EtOAc) afforded the title compound as a yellow oil.

Step 8: 1,1-Dimethylethyl cyclopropyl[6-(3-hydroxypropyl)-8-quinolinyl]methyl carbamate

To a solution of methyl 3-\{8-[\{cyclopropyl\{\{1,1\text{-dimethylethyl}\}oxy\}carbonyl\}amino\}methyl\]-6-quinolinyl]propanoate (1 eq.) from the previous step in THF (0.08 M) was added lithium borohydride (5 eq.). The resulting mixture was stirred at RT for 14 h before it was diluted with ether and quenched with 1 N aq. NaOH. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na\(_2\)SO\(_4\), and filtered. Concentration of the filtrate \textit{in vacuo} afforded the crude title compound as a colorless oil.

Step 9: 1,1-Dimethylethyl cyclopropyl[6-(3-methoxy[propyl]-8-quinolinyl]methyl] carbamate

To a solution of 1,1-dimethylethyl cyclopropyl[6-(3-hydroxypropyl)-8-quinolinyl]methyl] carbamate (1 eq.) from the previous step in THF (0.3 M) was added sodium hydride (60% (w/w) dispersion in paraffin oil, 1.2 eq.). The resulting suspension was stirred at RT for 15 min before iodomethane (1.4 eq.) was added. The now yellow solution was stirred at RT for 12 h before the reaction was quenched with the addition of 1 N aq. NaOH. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na\(_2\)SO\(_4\), filtered and the filtrate concentrated \textit{in vacuo}. Purification of the crude product thus obtained by way of flash chromatography (\( \text{SiO}_2 \), 9:1 (v/v) Hex : EtOAc -> EtOAc) afforded the title compound as a colorless oil.

Step 10: Amine 23

To a solution of 1,1-dimethylethyl cyclopropyl[6-(3-methoxy[propyl]-8-quinolinyl]methyl] carbamate (1 eq.) from the previous step in \( \text{CH}_2\text{Cl}_2 \) (0.06 M) was added HCl (4.0 M in dioxane, 30 eq.). The resulting solution was stirred at RT for 6 h. The reaction was then quenched with 1 N aq. NaOH and extracted with EtOAc. The combined organic extracts were then washed further with water and brine, dried over Na\(_2\)SO\(_4\) and filtered. Concentration of the filtrate \textit{in vacuo} afforded the title compound as a yellow oil.
Amine 24

\[ N^\prime-(3\text{-Chloro}-5-[3\text{-(methyloxy)}\text{propyl}]\text{phenyl})\text{methyl})\text{cyclopropanamine} \]

Step 1: \( N^\prime-(3\text{-Bromo}-5\text{-chlorophenyl})\text{methyl})\text{cyclopropanamine} \)

To a 4:1 (v/v) MeOH : THF solution (0.06 M) of 3-bromo-5-chlorobenzaldehyde (1 eq.) and cyclopropylamine (1.1 eq.) was added sodium cyanoborohydride (1.5 eq.) portionwise followed by neat acetic acid (3 eq.). The resulting mixture was stirred at RT for 20 h. The volatiles were then removed in vacuo. The resulting residue was taken up in ether and sat. aq. NH₄Cl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were then washed with brine, dried over MgSO₄ and filtered. Concentration of the filtrate in vacuo afforded the crude title compound as a yellow oil.

Step 2: \( N^\prime-(3\text{-Chloro}-5-[1\text{r}-3\text{(methyloxy)}\text{propen-1-yl}]\text{phenyl})\text{methyl})\text{cyclopropanamine} \)

To a 4:1 (v/v) DMF : propanol solution (0.15 M) of \( N^\prime-(3\text{-bromo}-5\text{-chlorophenyl})\text{methyl})\text{cyclopropanamine} \) (1 eq.) from the previous step and 4,4,5,5-tetramethyl-2-[((lR)-3-(methyloxy)-1-propen-1-yl]-l, 3,2-dioxaborolane (2 eq.) was added fr<m'y-dibromobis(triphenylphosphine) palladium(II) (0.05 eq.) followed by sodium carbonate (2 M aqueous solution, 3 eq.). The reaction vessel was evacuated and purged with nitrogen five times and then heated at 100°C for 2 h. The cooled reaction mixture was poured into aq. sat. NH₄Cl and then extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over MgSO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 3:7 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as an oil.

Step 3: Amine 24

To a solution of \( N^\prime-(3\text{-chloro}-5-[1\text{r}-3\text{(methyloxy)}\text{propen-1-yl}]\text{phenyl})\text{-methyl})\text{cyclopropanamine} \) (1 eq.) from the previous step in EtOAc (0.2 M) was added palladium (10% (w/w) on carbon, 0.4 eq.). The reaction vessel was evacuated and purged with hydrogen two times and then stirred at RT for 14 h. The reaction suspension was then filtered through a pad of silica gel and the insolubles rinsed with EtOAc. Concentration of the filtrate in vacuo afforded the title compound as a pale green oil.

Amine 25

\(^\wedge\text{1H-indol-5-yl)methyl)cyclopropanamine} \)

Step 1: 1-(3-Methoxypropyl)-1H-indole-3-carbaldehyde

To a DMF (0.1 M) solution of indole-3-carbaldehyde (1 eq.) was added sodium hydride (60% (w/w) dispersion in oil, 1.1 eq.) at 0⁰C followed by 1-bromo-3-methoxypropane (1.5 eq.). The reaction mixture was stirred at 50⁰C for 4 h. The mixture was then diluted with ether, washed with water and brine, dried over MgSO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 1:1 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as a colorless oil.
Step 2: Amine 25

To a 3:1 (v/v) CH₂Cl₂ : MeOH solution (0.1 M) of 1-(3-methoxypropyl)-4H-indole-3-carbaldehyde (1 eq) was added cyclopentyl amine (2 eq), acetic acid (2.5 eq) and then sodium triacetoxyborohydride (1.5 eq) at 0°C. The reaction was slowly warmed to RT and stirred at RT for 3h. The reaction was then quenched with saturated aq. NaHCO₃, extracted with dichloromethane, dried over MgSO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 96:4 (v/v) CH₂Cl₂ : 2.0 MNH₃ in MeOH) afforded the title compound as a black oil.

Amine 26

3-{3,4-Dichloro-5-[(cyclopropylamino)methyl]phenyl}propanenitrile

Step 1: (5-Bromo-2,3-dichlorophenyl)methanol

To a 5:1 (v/v) MeOH : THF solution (0.38 M) of 5-bromo-2,3-dichlorobenzaldehyde (1 eq.) from Step 1, Amine 5 was added at 0°C sodium borohydride (1.1 eq.) portionwise over 45 min. The reaction solution was stirred at 0°C for 2 h before the volatiles were removed in vacuo. The resulting residue was then partitioned between ether and 10% aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with 1 N aq. NaOH, water and brine, dried Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc → 3:7 (v/v) Hex : EtOAc) afforded the title compound as a white solid.

Step 2: [(5-Bromo-2,3-dichlorophenyl)methyl]oxy](1,1-dimethylethyl)dimethylsilane

To a DMF (0.34 M) solution of (5-bromo-2,3-dichlorophenyl)methanol (1 eq.) from the previous step was added chloro(1,1-dimethylethyl)dimethylsilane (1.1 eq.) and imidazole (1.5 eq.). The resulting yellow solution was stirred at RT for 16 h. The reaction mixture was then diluted with ether and washed sequentially with 10% aq. HCl, water and brine. The ether extract was dried Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the crude title compound as a colorless oil.

Step 3: [(2,3-Dichloro-5-ethenylphenyl)methyl]oxy](1,1-dimethylethyl)dimethylsilane

[(5-Bromo-2,3-dichlorophenyl)methyl]oxy](1,1-dimethylethyl)dimethylsilane (1 eq.) from the previous step and 2-ethenyl-4,5,5-tetramethyl-1,3,2-dioxaborolane (1 eq.) were combined in a 2:1 (v/v) mixture of DMF: «-PrOH (0.11 M). To this solution was then added palladium(II) acetate (0.05 eq.) and triphenylphosphine (0.15 eq.) before the vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 N aq. Na₂CO₃ (2 eq.) was added and the resulting biphasic suspension was heated at 90°C for 8 h. The now black suspension was cooled to RT, diluted with water and extracted with 1:1 (v/v) hexanes: ether. The combined organic extracts were then washed further with 1 N aq. NaOH, water and brine. This was then dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the crude title compound as a black oil.

\[
\text{[(2,3-Dichloro-5-ethenylphenyl)methyl]oxy} \text{]}\text{][l,l-dimethylethyl dimethylsilane} \quad (1 \text{ eq.})
\]

from the previous step, [Ir(COD)(Cl)]_2 (0.025 eq.) and DPPB (0.05 eq.) were combined in THF (0.1 M). To this solution was then added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.3 eq.) and the resulting red solution was stirred at RT for 16 h. Finally, sodium perborate (0.1 M aqueous solution, 1 eq.) was added and the now black biphasic solution was vigorously stirred at RT for another 8 h. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were then washed further with 1 N aq. NaOH, water and brine. This was then dried over Na_2SO_4, filtered and the filtrate concentrated in vacuo to afford a black oil. Purification of the crude product thus obtained by way of flash chromatography (SiO_2, 9:1 (v/v) Hex : EtOAc \rightarrow 1:1 (v/v) EtOAc : Hex) afforded the title compound as a pale yellow oil.


To a dichloromethane (0.1 M) solution of 2-[3,4-dichloro-5-[[[(l,l-
odimethylethyl)(dimethyl)silyl]oxy]methyl]phenyl]ethanol (1 eq.) from the previous step was added OC Hunig’s base (1.5 eq.) and methanesulfonyl chloride (1.1 eq.). The resulting suspension was stirred at O°C for 30 min and at RT for 15 min. The reaction was then diluted with ether and quenched with IN aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with 1 N aq. NaOH, water and brine, dried over Na_2SO_4, filtered and the filtrate concentrated in vacuo to give the title compound as a brown oil.


To a DMSO (0.4 M) solution of 2-[3,4-dichloro-5-[[[(l,l-
odimethylethyl)(dimethyl)silyl]oxy]methyl]phenyl]ethyl methanesulfonate (1 eq.) from the previous step was added potassium cyanide (1.3 eq.). The resulting solution was stirred at 90°C for 4 h. The reaction was then diluted with ether and quenched with water. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na_2SO_4, filtered and the filtrate concentrated in vacuo to give the title compound as a pink oil.

Step 7: 3-[3,4-Dichloro-5-[(hydroxymethyl)phenyl]propanenitrile

To a THF (0.1 M) solution of 3-[3,4-dichloro-5-[[[(l,l-
odimethylethyl)(dimethyl)silyl]oxy]methyl]phenyl]propanenitrile (1 eq.) from the previous step was added TBAF (1.0 M THF solution, 1.2 eq.). The resulting solution was stirred at RT for 3 h. The reaction was then diluted with ether and quenched with water. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na_2SO_4, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO_2, 9:1 (v/v) Hex : EtOAc \rightarrow 3:7 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.
Step 8: 3-(3,4-Dichloro-5-formylphenyl)propanenitrile

To a suspension of 3-[3,4-dichloro-5-(hydroxymethyl)phenyl]propanenitrile (1 eq.) from the previous step and sodium bicarbonate (1.1 eq.) in dichloromethane (0.1 M) was added DMP (1.1 eq.) at 0°C. The resulting mixture was stirred at RT for 2 h before it was quenched with sat. aq. NaHSO₃ and then extracted with Et₂O. The combined organic extracts were washed further with 1 N aq. NaOH, water and brine, dried over Na₂SO₄, and filtered. Concentration of the filtrate in vacuo afforded the crude title compound as a colorless oil.

Step 9: Amine 26

To a dichloromethane (0.11 M) solution of 3-(3,4-dichloro-5-formylphenyl)propanenitrile (1 eq.) from the previous step was added magnesium sulphate (1 eq.) and cyclopropylamine (1.2 eq.). The resulting suspension was stirred at RT for 16 h. The insolubles were removed via filtration and rinsed with dichloromethane before the combined filtrate was concentrated in vacuo. The crude imine thus obtained was taken up in methanol (0.11 M) and then added sodium borohydride (3 eq.) portionwise. The reaction mixture was stirred at RT for 16 h. The volatiles were then removed in vacuo and the resulting residue was partitioned between ether and 1 N aq. NaOH. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as a colorless oil.

Amine 27

N-[2-(3,4-Dichloro-5-[(cyclopropylamino)methyl]phenyl]ethyl]propanamide

Step 1: ([(5-(2-Azidoethyl)-2,3-dichlorophenyl)oxy][1,1-dimethylethyl]dimethylsilane

To a DMF (0.4 M) solution of 2-[3,4-dichloro-5-([(1,1-dimethylethyl)(dimethyl)silyl]oxy)methyl]phenyl]ethanamine methanesulfonate (1 eq.) from Step 5, Amine 26 was added at RT sodium azide (5 eq.). The resulting solution was stirred at RT for 12 h and then at 80°C for 3 h. The reaction mixture was then diluted with ether and washed with water. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the crude title compound as a pink oil.

Step 2: 2-[3,4-Dichloro-5-([(1,1-dimethylethyl) χ dimethyl)silyl]oxy)methyl]phenyl]ethanamine

To a THF (0.1 M) solution of ([(5-(2-azidoethyl)-2,3-dichlorophenyl)methyl]oxy)(1,1-dimethylethyl)dimethylsilane (1 eq.) from the previous step and triphenylphosphine (1.2 eq.) was added water (3 eq.). The resulting solution was stirred at 50°C for 18 h. The volatiles were then removed in vacuo and purification of the crude product thus obtained by way of flash chromatography (SiO₂, 96:4 (v/v) CH₂Cl₂ : 2.0 M NH₃ in MeOH) afforded the title compound as a colorless oil.
Step 3: N-[(2-[3,4-Dichloro-5-(([(1,1-dimethylethyl)(dimethyl)silyl]oxy)methyl)phenyl]ethyl)propanamide

To a DMF (0.2 M) solution of 2-[3,4-dichloro-5-(([(1,1-dimethylethyl)(dimethyl)silyl]oxy)methyl)phenyl]ethanamine (1 eq.) from the previous step, Hunig's base (3 eq.) and propionic acid (1.1 eq.) was added portionwise 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.2 eq.). The resulting reaction solution was stirred at RT for 48 h. The now reddish solution was diluted with ether and washed sequentially with 1N aq. NaOH, water and brine. The organic extract was then dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford a brown oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 7:3 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as a colorless oil.

Step 4: N-[(2-[3,4-Dichloro-5-(hydroxymethyl)phenyl]ethyl)propanamide

To a THF (0.12 M) solution of N-[(2-[3,4-dichloro-5-(([(1,1-dimethylethyl)(dimethyl)silyl]oxy)methyl)phenyl]ethyl)propanamide (1 eq.) from the previous step was added TBAF (1.0 M THF solution, 1.1 eq.). The resulting solution was stirred at RT for 2 h. The now orange solution was diluted with ether and quenched with 1N aq. NaOH. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the crude title compound as a pale yellow oil.

Step 5: IV-[2-(3,4-Dichloro-5-formylphenyl)ethyl]propanamide

To a suspension of N-[(2-[3,4-dichloro-5-(hydroxymethyl)phenyl]ethyl)propanamide (1 eq.) from the previous step and sodium bicarbonate (1.1 eq.) in dichloromethane (0.1 M) was added DMP (1.1 eq.) at 0°C. The resulting mixture was stirred at RT for 2 h before it was quenched with sat aq. NaHSO₃ and then extracted with Et₂O. The combined organic extracts were washed further with 1N aq. NaOH, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 19:1 (v/v) Hex : EtOAc → 3:7 (v/v) Hex : EtOAc) afforded the title compound as a white solid.

Step 6: Amine 27

To a dichloromethane (0.11 M) solution of N-[2-(3,4-dichloro-5-formylphenyl)ethyl]propanamide (1 eq.) from the previous step was added magnesium sulphate (1 eq.) and cyclopropylamine (1.2 eq.). The resulting suspension was stirred at RT for 16 h. The insolubles were removed via filtration and rinsed with dichloromethane before the combined filtrate was concentrated in vacuo. The crude imine thus obtained was taken up in methanol (0.11 M) and then added sodium borohydride (1.5 eq.) portionwise. The reaction mixture was stirred at RT for 8 h. The volatiles were then removed in vacuo and the resulting residue was partitioned between EtOAc and 1N aq. NaOH. The aqueous layer was separated and back-extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the
crude product thus obtained by way of flash chromatography (SiO$_2$, 95:5 CH$_2$Cl$_2$ : 2.0 M NH$_3$ in MeOH) afforded the title compound as a colorless oil.

**Amine 28**

*N-[3-Bromo-5-(3-methoxypropyl)benzyl] cyclopropanamine*

**Step 1**: 3-Bromo-5-(3-methoxypropyl)benzaldehyde

To a THF solution (0.3 M) of allyl methyl ether (3.1 eq.) at RT was added borane-methyl sulfide complex (1.0 eq.). The solution was stirred at RT for 30 min. To this solution was then added sequentially 3,5-dibromobenzaldehyde (1.0 eq.), Pd(dppe)Cl$_2$ (0.025 eq.) and solid sodium methoxide (1.5 eq.). The resulting mixture was heated to reflux for 15 h. The cooled reaction mixture was diluted with water and extracted with ether. The combined organic extracts were dried over MgSO$_4$, filtered and the filtrate concentrated *in vacuo*. Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$: 5:95 (v/v) EtOAc : Hex $\rightarrow$ 7:3 (v/v) EtOAc : Hex) afforded the title compound as a colorless oil.

**Step 2**: Amine 28

3-Bromo-5-(3-methoxypropyl)benzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH$_2$Cl$_2$ (0.19 M). To this was then added MgSO$_4$ (1 eq.) and the resulting suspension was stirred at RT for 23 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated *in vacuo*. The crude imine thus obtained was then re-taken up in MeOH (0.19 M). To this solution was added sodium borohydride (1.5 eq.) portionwise and the resulting mixture was stirred at 0°C for 30 min, then at RT for 16 h. The reaction was quenched by stirring with 2 N eq. HCl for 30 min. The resulting mixture was subsequently basified with 1 N eq. NaOH and the volatiles were removed *in vacuo*. The residue was extracted with Et$_2$O from water, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated *in vacuo* to afford the title compound as a colorless oil.

**Amine 29**

4-[(Cyclopropylamino)methyl]- 2-(methyloxy)ethyl]-2-naphthalenamine

**Step 1**: Methyl 3-[(2-(methyloxy)ethyl]amino]-1-naphthalencarboxylate

Freshly purified cesium carbonate (1.4 eq.), palladium(II) acetate (0.02 eq.) and rac-BINAP (0.03 eq.) were combined in anhydrous toluene (0.25 M). The vessel was repeatedly evacuated and back-filled with nitrogen. Finally, methyl 3-bromo-1-naphthalencarboxylate (1 eq.) and 2-methoxyethylamine (1.2 eq.) were added and the resulting mixture was heated at 100°C for 20 h. The now black suspension was cooled to RT, diluted with ether and filtered through a pad of celite. Concentration of the filtrate *in vacuo* afforded a brown oil that can be purified further by way of column chromatography (SiO$_2$, 19:1 (v/v) Hex : EtOAc $\rightarrow$ 1:1 (v/v) Hex : EtOAc) to afford the title compound as a yellow oil.
Step 2: 3-[[2-(Methyloxy)ethyl]amino]-1-naphthalenecarboxylic acid

Methyl 3-[[2-(methyloxy)ethyl]amino]-1-naphthalenecarboxylate (1 eq.) from the previous step was taken up in a 2:1 (v/v) mixture of MeOH: THF (0.08 M). To this solution was then added LiOH (1.0 M aq. solution, 3.4 eq.) and the resulting cloudy solution was vigorously stirred at RT for 16 h. The volatiles were then removed in vacuo and the pH of the residue was carefully adjusted to ~2 with 1 N aq. HCl before it was extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a yellow solid.

Step 3: N-Cyclopropyl-3-[[2-(methyloxy)ethyl]amino]-1-naphthalenecarboxamide

To a DMF (0.1 M) solution of 3-[[2-(methyloxy)ethyl]amino]-1-naphthalenecarboxylic acid (1 eq.) from the previous step, Hunig’s base (3 eq.) and cyclopropylamine (1.5 eq.) was added portionwise 0-(7-azabenotriazol-l-yl)-N,N,N’,N’-4etamethyluronium hexafluorophosphate (1.2 eq.). The resulting reaction solution was stirred at RT for 48 h. The now reddish solution was diluted with EtOAc and washed sequentially with 1 N aq. NaOH, water and brine. The organic extract was then dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford a brown oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 4:1 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as a white solid.

Step 4: Amine 29

To a THF solution (0.09 M) of iv-cyclopropyl-3-[[2-(methyloxy)ethyl]amino]-1-naphthalenecarboxamide (1 eq.) from the previous step was added, at reflux, borane-methyl sulfide complex (6.2 eq.). To the reaction vessel was then attached a short path distillation apparatus and most of the volatiles were slowly distilled off over a period of 1 h. The now brown solution was re-cooled to 0°C and carefully quenched with 1 N aq. HCl. The resulting mixture was heated at reflux for 1 h to ensure complete breakdown of the amine-borane complex. Following careful neutralization with 1 N aq. NaOH, the aqueous layer was separated and back extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo and the crude product thus obtained was purified further by way of flash chromatography (Siθ₂, 3:2 (v/v) Hex : EtOAc → EtOAc) to reveal the title compound as a yellow oil that rapidly darkened upon standing.

Amine 30

3-[[8-[(Cyclopropylamino)methyl]-6-quinolinyl]propanenitrile

Step 1: 1,1-Dimethylethyl {[6-(2-cyanoethyl)-8-quinolinyl]methyl}cyclopropylcarbamate

To a THF (0.13 M) suspension of freshly dried lithium chloride (1.2 eq.) and diethyl(cyanomethyl)phosphonate (1.2 eq.) was added DBU (1.2 eq.). The reaction suspension was stirred at RT for 30 min before 1,1-dimethylethyl cyclopropyl[6-formyl-8-quinolinyl]methyl]carbamate (1 eq., Amine 23, Step 5) was finally added. The resulting solution was then allowed to stir at RT for 16 h. The crude reaction mixture thus obtained was quenched with 10% aq. HCl and extracted with ether.
The combined organic extracts were washed further with 1 N aq. NaOH, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc -> 3:7 (v/v) Hex : EtOAc) afforded the title compound as a white solid.

Step 2: 1,1-Dimethyl ethyl [(6-(2-cyanoethyl)-8-quinolinylmethyl)cyclopropylcarbamate

To a solution of 1,1-dimethyl ethyl [(6-(2-cyanoethyl)-8-quinolinylmethyl)cyclopropylcarbamate (1 eq.) from the previous step in EtOAc (0.1 M) was added palladium (10% (w/w) over carbon, 0.2 eq.). The resulting suspension was evacuated and back-filled repeatedly with hydrogen. The reaction suspension was allowed to stir under a hydrogen-filled balloon atmosphere for 4 h. The reaction was quenched with the addition of dichloromethane and filtered through a bed of celite. The filtrate was then concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc -> 3:7 (v/v) Hex : EtOAc) afforded the title compound as a yellow oil.

Step 3: Amine 30

To a CH₂Cl₂ solution (0.05 M) of 1,1-dimethyl ethyl [(6-(2-cyanoethyl)-8-quinolinylmethyl)cyclopropylcarbamate (1 eq.) from the previous step was added zinc(II) bromide (10 eq.). The resulting suspension was sonicated for 15 min and stirred at RT for 13 h. The reaction was quenched with the addition of EtOAc and 1N aq. NaOH, and then sonicated for 15 min. The aqueous phase was separated and back-extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a yellow oil.

Amine 31

N-((3-[2-(Methoxy)ethyl]-1-naphthalenyl)methyl)cyclopropanamine

Step 1: Methyl 3-ethenyl-1-1-naphthalenecarboxy late

Methyl 3-bromo-1-naphthalenecarboxylate (1 eq.) and 2-ethenyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1 eq.) were combined in a 2:1 (v/v) mixture of DMF:rc-PrOH (0.1 M). To this solution was first added Pd(PPh₃)₄Br₂ (0.05 eq.) followed by 2 N aq. Na₂CO₃ (2 eq.). The biphasic suspension was evacuated and back-filled three times with nitrogen before it was heated at 90°C for 8 h. The now black suspension was cooled to RT, diluted with water and extracted with 1:1 (v/v) hexanes:ether. The combined organic extracts were then washed further with 1N aq. NaOH, 10% aq. HCl, water and brine. This was then dried over Na₂SO₄ and filtered through a pad of silica gel. Concentration of the filtrate in vacuo afforded the crude title compound as a golden yellow oil.

Step 2: Methyl 3-(2-hydroxyethyl)-1-1-naphthalenecarboxy late

Methyl 3-ethenyl-1-naphthalenecarboxylate (1 eq.) from the previous step, [Ir(COD)Cl]₂ (0.025 eq.) and DPPB (0.05 eq.) were combined in THF (0.12 M). To this solution was then added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.2 eq.) and the resulting red solution was stirred at RT for 16
h. Finally, sodium perborate (0.1 M aqueous solution, 2 eq.) was added and the now black biphasic solution was vigorously stirred at RT for another 12 h. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were then washed further with 1 N aq. NaOH, water and brine. This was then dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford a pale yellow oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc → 1:1 (v/v) EtOAc : Hex) afforded the title compound as a pale yellow oil.

Step 3: Methyl 3-[2-(methyloxy)ethyl]-1-naphthalencarboxylate

Methyl 3-(2-hydroxyethyl)-1-naphthalencarboxylate (1 eq.) from the previous step and iodomethane (19 eq.) were taken up in THF (0.3 M). To this solution was then added sodium hydride (60% w/w dispersion in oil, 1 eq.) and the resulting suspension was stirred at RT in darkness for 18 h. The volatiles were then removed in vacuo and the resulting residue partitioned between ether and 1 N aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were then washed further with 1 N aq. NaOH, water and brine. This was then dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford a yellow oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 19:1 (v/v) Hex : EtOAc → 1:1 (v/v) EtOAc : Hex) afforded the title compound as a pale yellow oil.

Step 4: [3-[2-(Methyloxy)ethyl]-1-naphthalenyl]methanol

Methyl 3-[2-(methyloxy)ethyl]-1-naphthalencarboxylate (1 eq.) from the previous step was taken up in toluene (0.1 M). To this solution was then added DIBAI-H (1.5 M toluene solution, 2.4 eq.) and the resulting solution was vigorously stirred at RT for 4 h. The reaction mixture thus obtained was quenched with 1 N aq. HCl and extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a colorless oil.

Step 5: 3-[2-(Methyloxy)ethyl]-1-naphthalencarbaldehyde

To a suspension of [3-[2-(methyloxy)ethyl]-1-naphthalenyl]methanol (1 eq.) from the previous step and sodium bicarbonate (1.1 eq.) in dichloromethane (0.1 M) was added DMP (1.1 eq.) at 0°C. The resulting mixture was stirred at RT for 2 h before it was quenched with sat. aq. NaHSO₃ and then extracted with Et₂O. The combined organic extracts were washed further with 1 N aq. NaOH, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 19:1 (v/v) Hex : EtOAc → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 6: **Amine 31**

To a dichloromethane (0.15 M) solution of 3-[2-(methyloxy)ethyl]-1-naphthalencarbaldehyde (1 eq.) from the previous step was added magnesium sulphate (1 eq.) and cyclopropyl amine (1.2 eq.). The resulting suspension was stirred at RT for 20 h. The insolubles were removed via filtration and rinsed with dichloromethane before the combined filtrate was concentrated in vacuo. The crude imine thus obtained was taken up in methanol (0.15 M) and then added sodium borohydride (1.5
eq.) portionwise. The reaction mixture was stirred at RT for 8 h. The volatiles were then removed in vacuo and the resulting residue was partitioned between EtOAc and 1 N eq. NaOH. The aqueous layer was separated and back-extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a colorless oil.

Amine 32

N-(2-[4-[(Cyclopropylamino)methyl]-2-naphthalenyl]ethyl)acetamide

Step 1: Methyl 3-[2-[(methylsulfonyl)oxy]ethyl]-1-naphthalenecarboxylate

To a dichloromethane (0.03 M) solution of methyl 3-(2-hydroxyethyl)-1-naphthalenecarboxylate (1 eq.) from Step 2, Amine 31 and Hunig’s base (1.5 eq.) was added at 0°C methanesulfonyl chloride (1.3 eq.). The resulting solution was stirred at 0°C for 30 min and then at RT for 15 min. The reaction mixture was subsequently quenched with 10% eq. HCl. The aqueous wash was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford a pale yellow oil. Concentration of the filtrate in vacuo afforded the crude title compound as a colorless oil.

Step 2: 3-(2-Azidoethyl)-1-naphthalenecarboxylate

To a DMF (0.25 M) solution of methyl 3-[2-[(methylsulfonyl)oxy]ethyl]-1-naphthalenecarboxylate (1 eq.) from the previous step was added sodium azide (5 eq.). The resulting solution was stirred at 55°C for 12 h and then at 80°C another 3 h. The reaction mixture was then diluted with ether and washed with water. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the crude title compound as a pink oil.

Step 3: Methyl 3-(2-aminoethyl)-1-naphthalenecarboxylate

To a THF (0.1 M) solution of 3-(2-azidoethyl)-1-naphthalenecarboxylate (1 eq.) from the previous step and triphenylphosphine (1.2 eq.) was added water (3 eq.). The resulting solution was stirred at 50°C for 5 h. The volatiles were then removed in vacuo and purification of the crude product thus obtained by way of flash chromatography (SiO₂, 96:4 (v/v) CH₂Cl₂ : 2.0 M NH₃ in MeOH) afforded the title compound as a colorless oil.

Step 4: Methyl 3-[2-(acetylamino)ethyl]-naphthalenecarboxylate

To a DMF (0.2 M) solution of methyl 3-(2-aminoethyl)-1-naphthalenecarboxylate (1 eq.) from the previous step, Hunig’s base (3 eq.) and acetic acid (1.1 eq.) was added portionwise O-[1-azabenzotriazol-1-yl]-N,N,N′,N′-tetramethyluronium hexafluorophosphate (1.1 eq.). The resulting reaction solution was stirred at RT for 48 h. The now reddish solution was diluted with ether and washed sequentially with 1 N eq. NaOH, water and brine. The organic extract was then dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford a pale yellow oil. Purification of the crude
product thus obtained by way of flash chromatography (SiO₂, 7:3 (v/v) Hex : EtOAc → EtOAc → 95:5 (v/v) CH₂Cl₂ : 2.0 M NH₃ in MeOH) afforded the title compound as a colorless oil.

Step 5: N-[2-[4-(Hydroxymethyl)-2-naphthalenyl]ethyl]acetamide

Methyl 3-[2-(acetylamino)ethyl]-naphthalenecarboxylate (1 eq.) from the previous step was taken up in THF (0.18 M). To this solution was then added lithium borohydride (12 eq.) and the resulting solution was vigorously stirred at 50°C for 5 h. The reaction mixture thus obtained was diluted further with ether and carefully quenched with 1 N aq. HCl. The aqueous layer was separated and back-extracted with EtOAc. The combined organic extracts were washed further with 1 N aq. NaOH, water and brine, dried over Na₂SΟ₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a white solid.

Step 6: N-[2-(4-Formyl-1-2-naphthalenyl)ethyl]acetamide

To a suspension of N-[2-(4-hydroxymethyl)-2-naphthalenyl]ethyl]acetamide (1 eq.) from the previous step and sodium bicarbonate (1.2 eq.) in dichloromethane (0.09 M) was added DMP (1.1 eq.) at 0°C. The resulting mixture was stirred at RT for 18 h before it was quenched with sat. aq. NaHSO₄ and then extracted with Et₂O. The combined organic extracts were washed further with 10% aq. HCl, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 19:1 (v/v) Hex : EtOAc → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 6: Amine 32

To a dichloromethane (0.12 M) solution of N-[2-(4-formyl-1-2-naphthalenyl]ethyl]acetamide (1 eq.) from the previous step was added magnesium sulphate (1 eq.) and cyclopropyl amine (2 eq.). The resulting suspension was stirred at RT for 48 h. The insolubles were removed via filtration and rinsed with dichloromethane before the combined filtrate was concentrated in vacuo. The crude imine thus obtained was taken up in methanol (0.12 M) and then added sodium borohydride (1.5 eq.) portionwise. The reaction mixture was stirred at RT for 3 h. The volatiles were then removed in vacuo and the resulting residue was partitioned between EtOAc and 1 N aq. NaOH. The aqueous layer was separated and back-extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na₂SΟ₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a colorless oil.

Amine 33

N-[2-(Bromophenyl)methyl]cyclopropanamine

To a THF solution (0.15 M) of 2-bromobenzyl alcohol (1 eq.) was added triethylamine (1.6 eq.). The reaction mixture was cooled to 0°C before methanesulfonyl chloride (1.3 eq.) was added dropwise. The resulting solution was then allowed to warm slowly to RT. After 1.5 h, cyclopropylamine (5 eq.) was added to the cloudy suspension. After another 18 h, the reaction mixture was diluted with ether and quenched with 1 N aq. NaOH. The organic extract was separated,
washed with brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 4:1 (v/v) Hex : EtOAc → 1:4 (v/v) Hex : EtOAc) afforded the title compound as a light yellow oil.

5 Amine 34

N-[[1-(2-Methoxyethyl)-1H-indol-3-yl]methyl]cyclopropanamine

Step 1: 1-(2-Methoxyethyl)-1H-indole-3-carbaldehyde

Indole-3-carbaldehyde (1 eq.) was dissolved in DMF (0.46 M). Sodium hydride was added (1.3 eq.) and the resulting solution was stirred at RT for 20 min. Potassium iodide (1 eq.) and 1-bromo-2-methoxyethane (2 eq.) were then added and the reaction solution was allowed to stir at RT for 48 h. The reaction mixture was subsequently quenched with brine and extracted with EtOAc. The combined organic extracts were dried over MgSO₄. Filtration and concentration of the filtrate in vacuo afforded a yellow oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as an orange oil.

Step 2: Amine 34

1-(2-Methoxyethyl)-1H-indole-3-carbaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were dissolved in CH₂Cl₂ (0.15 M). Magnesium sulfate (1 eq.) and formic acid (0.1 eq.) were then added and the resulting suspension was stirred at RT for 8 h. The insolubles were removed via filtration and the filtrate was concentrated in vacuo. The residue was then taken up in MeOH (0.15 M) and sodium borohydride (1.5 eq) was added portionwise. The resulting suspension was stirred at RT for 16 h. The volatiles were removed in vacuo. The resulting residue was then taken up in ether, quenched carefully with 1 N aq. HCl and then neutralized with 1 N aq. NaOH. The aqueous wash was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, EtOAc → 7:3 (v/v) EtOAc : MeOH) afforded the title compound as an orange oil.

Amine 35

N-[[1-(2,2,2-Trifluoroethyl)-1H-indol-3-yl]methyl]cyclopropanamine

Amine 35 was prepared according to the procedure described in Amine 34 but using instead 1-iodo-2,2,2-trifluoroethane as the alkylation reagent in step 1.

Amine 36

N-[[1-(4,4,4-Trifluorobutyl)-1H-indol-3-yl]methyl]cyclopropanamine

Amine 36 was prepared according to the procedure described in Amine 34 but using instead 1-iodo-4,4,4-trifluorobutane as the alkylation reagent in step 1.
Amine 37

\[ N-\{1-\text{Butyl-} 1/-\text{indol-3-yl}\text{methyl}\}\text{cyclopropanamine} \]

Amine 37 was prepared according to the procedure described in Amine 34 but using instead 1-iodobutane as the alkylation reagent in step 1.

Amine 38

\[ \text{N-}\{1-[3-(\text{Ethylloxy})\text{propyl]}1 \text{-} H-\text{indol-3-yl}\text{methyl}\}\text{cyclopropanamine} \]

Amine 38 was prepared according to the procedure described in Amine 34 but using instead 1-bromo-3-ethoxypropane as the alkylation reagent in step 1.

Amine 39

\[ \text{N-}\{1,1,1,3,3,3\text{-hexafluoro-2-(iodomethyl)propane}\}\text{cyclopropanamine} \]

Amine 39 was prepared according to the procedure described in Amine 34 but using instead 1,1,3,3,3-hexafluoro-2-(iodomethyl)propane as the alkylation reagent in step 1.

Amine 40

\[ \text{N-}\{3-[3-(\text{Cyclopropylamino})\text{methyl}]- 1H-\text{-indol-1-yl}\}\text{propyl}\}\text{acetamide} \]

Step 1: \( \text{tert-Butyl\{3-[3-\text{formyl-1}\text{-} H-\text{-indol-1-yl}\}\text{propyl}\}\text{carbamate} \)

Indole-3-carbaldehyde (1 eq.) was dissolved in DMF (0.15 M). Sodium hydride was added (1.3 eq.) and the resulting solution was stirred at RT for 20 min. Tetrabutylammonium iodide (1 eq.) and tert-butyl 3-bromopropyli carbamate (2 eq.) were then added and the reaction solution was allowed to stir at RT for 18 h. The reaction mixture was subsequently quenched with sat. aq. NaHCO₃ and extracted with EtOAc. The combined organic extracts were dried over MgSO₄. Filtration and concentration of the filtrate in vacuo afforded a yellow oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 7:3 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as a light pink solid.

Step 2: \( \text{N-[3-(3-Formyl-1/-indol-1-yl)propyl]}\text{acetamide} \)

To a stirred dichloromethane (0.09 M) solution of tert-butyl [3-(3-formyl-l/-7-indol-l-yl)propyl] carbamate from the previous step was added HCl (4 N solution in dioxane, 45 eq.). The resulting solution was stirred at RT for 1 h before the volatiles were removed in vacuo. Dichloromethane was then added to the red residue and the volatiles were again removed in vacuo to afford a red gum. To the crude amine thus obtained was then added dichloromethane (0.09 M) and triethylamine (2.2 eq.). When the reaction solution became homogeneous, acetyl chloride (1.05 eq.) was added and the resulting mixture was allowed to stir at RT for another 2 h. The reaction was finally quenched with 1 N aq. NaOH and extracted with dichloromethane. The combined organic extracts were dried over MgSO₄, filtered and concentration of the filtrate in vacuo afforded the crude title compound as a yellow solid.
Step 3: Amine 40

//-[3-(3-Formyl-l-indol-l-yl)propyl]acetamide (1 eq.) from the previous step and
cyclopropylamine (2 eq.) were dissolved in CH₂Cl₂ (0.1 M). Magnesium sulfate (2 eq.) and formic acid
(0.2 eq.) were then added and the resulting suspension was stirred at RT for 20 h. The insolubles were
removed via filtration and the filtrate was concentrated in vacuo. The residue was then taken up in
MeOH (0.1 M) and sodium borohydride (1 eq) was added portionwise. The resulting suspension was
stirred at RT for 16 h. The volatiles were removed in vacuo. The resulting residue was then taken up in
ether, quenched carefully with 1 N aq. HCl and then neutralized with 1 N aq. NaOH. The aqueous wash
was separated and back-extracted with ether. The combined organic extracts were washed further with
water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the
crude product thus obtained by way of flash chromatography (SiO₂, 1:9 (v/v) MeOH : EtOAc ➔ 1:1 (v/v)
EtOAc : MeOH) afforded the title compound as a white solid.

Amine 41

yV-(3-[3-[(Cyclopropylamino)methyl]-1H-indol-1-yl]propyl)propanamide

Amine 41 was prepared according to the procedure described in Amine 40 but using
instead propionyl chloride as the alkylation reagent in step 2.

Amine 42

N°-FS-KCyclopropylaminoethyO-l-1H-indol-1-yljethyOacetamide

Amine 42 was prepared according to the procedure described in Amine 40 but using
instead tert-buty 1 2-bromoethylcarbamate as the alkylation reagent in step 1.

Amine 43

N°-(2-[3-[(Cyclopropylamino)methyl]-1H-indol-1-yl]ethyl)propanamide

Amine 42 was prepared according to the procedure described in Amine 40 but using
instead tert-butyl 2-bromoethylcarbamate as the alkylation reagent in step 1 and propionyl chloride as the
alkylation reagent in step 2

Amine 44

N°-[1-(2-Propen-1-yl)-l-1H-indol-3-yl]methyl)cyclopropanamine

Step 1: 1-Allyl-l-/indole-3-carbaldehyde

Indole-3-carbaldehyde (1 eq.) was dissolved in DMF (0.46 M). Sodium hydride was
added (2.5 eq.) and the resulting solution was stirred at RT for 20 min. AUIY1 bromide (1 eq.) was then
added and the reaction solution was allowed to stir at RT for 20 h. The reaction mixture was
subsequently quenched with brine and extracted with EtOAc. The combined organic extracts were dried
over MgSO₄. Filtration and concentration of the filtrate in vacuo afforded a yellow oil. Purification of
the crude product thus obtained by way of flash chromatography (SiO$_2$, 4:1 (v/v) Hex : EtOAc $\rightarrow$ 3:7 (v/v) Hex : EtOAc) afforded the title compound as a light yellow oil.

Step 2: Amine 44

1-Allyl-1\textit{H}-indole-3-carbaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were dissolved in MeOH (0.05 M). Sodium cyanoborohydride (2 eq.) and acetic acid (4 eq.) were then added and the resulting suspension was stirred at RT for 18 h. The volatiles were subsequently removed \textit{in vacuo}. The resulting residue was then taken up in ether, quenched carefully with 1 N aq. NaOH. The aqueous wash was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated \textit{in vacuo}. Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, EtOAc $\rightarrow$ 4:1 (v/v) EtOAc : MeOH) afforded the title compound as a yellow oil.

Amine 45

\textit{N-}\{1-(Phenylmethyl)-1\textit{H}-indol-3-yl\}methyl\}cyclopropanamine

Amine 45 was prepared according to the procedure described in Amine 44 but using instead benzyl bromide as the alkylation reagent in step 1.

Amine 46

\textit{N-}\{1-(2-Pyridinylmethyl)-1\textit{H}-indol-3-yl\}methyl\}cyclopropanamine

Amine 46 was prepared according to the procedure described in Amine 44 but using instead tetrabutylammonium iodide (1 eq.) and 2-picolyI chloride hydrochloride (1.5 eq.) as the alkylation mixture in step 1.

Amine 47

\textit{N-}\{1-(3-Pyridinylmethyl)-1\textit{H}-indol-3-yl\}methyl\}cyclopropanamine

Amine 47 was prepared according to the procedure described in Amine 44 but using instead tetrabutylammonium iodide (1 eq.) and 3-picolyI chloride hydrochloride (1.5 eq.) as the alkylation mixture in step 1.

Amine 48

\textit{N-}\{1-(4-Pyridinylmethyl)-1\textit{H}-indol-3-yl\}methyl\}cyclopropanamine

Amine 48 was prepared according to the procedure described in Amine 44 but using instead 4-picolyI bromide hydrobromide (1 eq.) as the alkylation reagent in step 1.
Amine 49

\[ N\{(1\text{-}(4\text{-Fluorophenyl)methyl})\text{-}l\text{-}indol\text{-}3\text{-}yl}\text{-}methyl\}\text{-}cyclopropanamine \]

Amine 49 was prepared according to the procedure described in Amine 44 but using instead 1-(bromomethyl)-4-fluorobenzene (1.5 eq.) as the alkylation reagent in step 1.

Amine 50

\[ N\{(1\text{-}(4\text{-Chlorophenyl)methyl})\text{-}l\text{-}indol\text{-}3\text{-}yl}\text{-}methyl\}\text{-}cyclopropanamine \]

Amine 50 was prepared according to the procedure described in Amine 44 but using instead 1-(bromomethyl)-4-chlorobenzene (1.5 eq.) as the alkylation reagent in step 1.

Amine 51

\[ N\{(1\text{-}(3\text{-Fluorophenyl)methyl})\text{-}l\text{-}indol\text{-}3\text{-}yl}\text{-}methyl\}\text{-}cyclopropanamine \]

Amine 51 was prepared according to the procedure described in Amine 44 but using instead 1-(bromomethyl)-3-fluorobenzene (1.5 eq.) as the alkylation reagent in step 1.

Amine 52

\[ N\{(1\text{-}(3\text{-Chlorophenyl)methyl})\text{-}l\text{-}indol\text{-}3\text{-}yl}\text{-}methyl\}\text{-}cyclopropanamine \]

Amine 52 was prepared according to the procedure described in Amine 44 but using instead 1-(bromomethyl)-3-chlorobenzene (1.5 eq.) as the alkylation reagent in step 1.

Amine 53

\[ 3\text{-}(3\text{-}(\text{Cyclopropylamino)methyl})\text{-}l\text{-}indol\text{-}3\text{-}yl}\text{-}methyl\}\text{-}benzonitrile \]

Amine 53 was prepared according to the procedure described in Amine 44 but using instead 1-(bromomethyl)-3-cyanobenzene (1.5 eq.) as the alkylation reagent in step 1.

Amine 54

\[ N\{(1\text{-}(3\text{-Methylphenyl)methyl})\text{-}l\text{-}indol\text{-}3\text{-}yl}\text{-}methyl\}\text{-}cyclopropanamine \]

Amine 54 was prepared according to the procedure described in Amine 44 but using instead 1-(bromomethyl)-3-methylbenzene (1.5 eq.) as the alkylation reagent in step 1.

Amine 55

\[ y\text{V}\{(5\text{-Fluoro}-l\text{-}[3\text{-}(\text{methyloxy})\text{propyl}]\text{-}l\text{-}indol\text{-}3\text{-}yl}\text{-}methyl\}\text{-}cyclopropanamine \]

Amine 55 was prepared according to the procedure described in Amine 44 but using instead tetrabutylammonium iodide (1 eq.) and 1-bromo-3-methoxypropane (2.1 eq.) as the alkylation mixture and 5-fluoro-l/f-indole-3-carbaldehyde (1 eq.) as the starting indole in step 1.
Amine 56

N-[[6-Bromo-1-(phenylmethyl)-1//-indol-3-yl]methyl]cyclopropanamine

Step 1: 6-Bromo-1 H-indole-S-carbaldehyde

To a DMF (0.47 M) solution of 6-bromo-1 H-indole (1 eq.) was added at 0°C phosphorus oxychloride (1.2 eq.). The resulting solution was warmed to RT and stirred at RT for 16 h. The resulting solution was re-cooled to 0°C and then carefully added NaOH (2 M eq. solution, 2.8 eq.). After stirring at RT for another 2 h, the crude reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried over MgSCV. Filtration and concentration of the filtrate in vacuo afforded a yellow oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, Hex → EtOAc) afforded the title compound as a brown solid.

Step 2: 1-Benzyl-6-bromo-1//-indole-3-carbaldehyde

6-Bromo-1//-indole-3-carbaldehyde (1 eq.) from the previous step was dissolved in DMF (0.19 M). Sodium hydride was added (1.5 eq.) and the resulting solution was stirred at RT for 20 min. Benzyl bromide (1 eq.) was then added and the reaction solution was allowed to stir at RT for 24 h. The reaction mixture was subsequently quenched with water and extracted with EtOAc. The combined organic extracts were dried over MgSO₄. Filtration and concentration of the filtrate in vacuo afforded a yellow oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 4:1 (v/v) Hex : EtOAc → 3:7 (v/v) Hex : EtOAc) afforded the title compound as a yellow solid.

Step 3: Amine 56

1-Benzyl-6-bromo-1 H-indole-S-carbaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were dissolved in MeOH (0.05 M). Sodium cyanoborohydride (2 eq.) and acetic acid (4 eq.) were then added and the resulting suspension was stirred at RT for 16 h. The volatiles were subsequently removed in vacuo. The resulting residue was then taken up in ether, quenched carefully with 1 N eq. NaOH. The aqueous wash was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, EtOAc → 2:3 (v/v) EtOAc : MeOH) afforded the title compound as a yellow oil.

Amine 57

N-[[1-[3-Fluorophenyl)methyl]-6-(methyloxy)-1 H-indol-3-yl]methyl]cyclopropanamine

Amine 57 was prepared according to the procedure described in Amine 44 but using instead 1-(bromomethyl)-3-fluorobenzene (1.5 eq.) as the alkylation reagent in step 2 and 6-methoxy-1//-indole-3-carbaldehyde (1 eq.) as the starting indole in step 1.

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**Amine 58**

\[ \text{N-\{[4-Methyl-l-(phenylmethyl)-l-indol-3-yl]raethyl\}cyclopropanamine} \]

Amine 58 was prepared according to the procedure described in Amine 56 but using instead 4-methyl-l \( H \)-indole (1 eq.) as the starting indole in step 1 and benzyl bromide (1 eq.) as the alkylation reagent in step 2.

**Amine 59**

\[ 3-[(Cyclopropylamino)methyl]-l-(phenylmethyl)-l \( H \)-indole-4-carbonitrile \]

Amine 59 was prepared according to the procedure described in Amine 56 but using instead 1\( H \)-indole-4-carbonitrile (1 eq.) as the starting indole in step 1 and benzyl bromide (1 eq.) as the alkylation reagent in step 2.

**Amine 60**

\[ \text{N-\{[4-Fluoro-l-(phenylmethyl)-l-indol-3-yl]methyl\}cyclopropanamine} \]

Amine 60 was prepared according to the procedure described in Amine 56 but using instead 4-fluoro-1\( H \)-indole (1 eq.) as the starting indole in step 1 and benzyl bromide (1.5 eq.) as the alkylation reagent in step 2.

**Amine 61**

\[ \text{N-\{[4-Fluoro-l-\{3-fluorophenyl\}methyl]-l-indol-3-yl\}methyl\}cyclopropanamine} \]

Amine 61 was prepared according to the procedure described in Amine 56 but using instead 4-fluoro-1\( H \)-indole (1 eq.) as the starting indole in step 1 and 1-(bromomethyl)-3-fluorobenzene (1.5 eq.) as the alkylation reagent in step 2.

**Amine 62**

\[ \text{N-\{[4-Fluoro-l-\{3-(methyloxy)propyl\}l-indol-3-yl\}methyl\}cyclopropanamine} \]

Amine 62 was prepared according to the procedure described in Amine 56 but using instead 4-fluoro-1\( H \)-indole (1 eq.) as the starting indole in step 1. Furthermore, 1-bromo-3-methoxypropane (2 eq.) and tetrabutylammonium iodide (1 eq.) were used as the alkylation mixture in step 2.

**Amine 63**

\[ \text{N-\{[4-Chloro-l-\{3-(methyloxy)propyl\}l-indol-3-yl\}methyl\}cyclopropanamine} \]

Amine 63 was prepared according to the procedure described in Amine 56 but using instead 4-chloro-1\( H \)-indole (1 eq.) as the starting indole in step 1. Furthermore, 1-bromo-3-methoxypropane (2 eq.) and tetrabutylammonium iodide (1 eq.) were used as the alkylation mixture in step 2.
Amine 64
\[ ^{-\left[ ^{\text{Chloro}}\text{-phenylmethyO}\text{-} \text{H}-\text{indol}\text{-}S\text{-} \text{y} \text{llmethyllcyclopropanamine} \right]} \]

Amine 64 was prepared according to the procedure described in Amine 56 but using instead 4-chloro-\text{H}-indole (1 eq.) as the starting indole in step 1 and benzyl bromide (1.5 eq.) as the alkylation reagent in step 2.

Amine 65
\[ ^{\text{N}}\text{-}\left[ ^{\text{4-Bromo-1}}\text{-(phenylrnethyl)-} \text{H}-\text{indol-3-yl} \text{methyl} \right]\text{cyclopropanamine} \]

Amine 65 was prepared according to the procedure described in Amine 56 but using instead 4-bromo-\text{H}-indole (1 eq.) as the starting indole in step 1 and benzyl bromide (1.5 eq.) as the alkylation reagent in step 2.

Amine 66
\[ ^{\text{N}}\text{-}\left[ ^{\text{4-Bromo-1}}\text{-(3- fluorophenyl)methyl}\right]\text{-} \text{H}-\text{indol-3-yl} \text{methyl} \text{cyclopropanamine} \]

Amine 66 was prepared according to the procedure described in Amine 56 but using instead 4-bromo-\text{H}-indole (1 eq.) as the starting indole in step 1 and 1-(bromomethyl)-3-fluorobenzene (1.5 eq.) as the alkylation reagent in step 2.

Amine 67
\[ ^{\text{N}}\text{-}\left[ ^{\text{4-Bromo-1}}\text{-[3-(methyloxy)propyl]-} \text{H}-\text{indol-3-yl} \text{methyl} \right]\text{cyclopropanamine} \]

Amine 67 was prepared according to the procedure described in Amine 56 but using instead 4-bromo-\text{H}-indole (1 eq.) as the starting indole in step 1. Furthermore, 1-bromo-3-methoxypropane (2 eq.) and tetrabutylammonium iodide (1 eq.) were used as the alkylation mixture in step 2.

Amine 68
\[ ^{\text{N}}\text{-}\left[ ^{\text{4-Fluoro-1}}\text{-} \text{H}-\text{indol-3-yl} \text{methyl} \right]\text{cyclopropanamine} \]

Amine 68 was prepared according to the procedure described in Amine 56 but using instead 4-fluoro-\text{H}-indole (1 eq.) as the starting indole in step 1. Furthermore, step 2 was not necessary.

Amine 69
\[ ^{\text{1}}\text{-[3-[(Cyclopropylamino)methyl]-5- [3-(methyloxy)propyl]phenyl} \text{ethanone} \]

Amine 69 was prepared according to the procedure described in WO 2007/009250 Al patent.
Amine 70
5-[(Cyclopropylamino)methyl]-1,3-bis[3-(methyloxy)propyl]-2,4(1H,3H)-pyrimidinedione

Step 1: 1,3-Bis(3-methoxypropyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde

To a DMF (0.35 M) solution of 5-formyluracil (1 eq.) was added sequentially at O°C 1-bromo-3-methoxypropane (2.2 eq.) and DBU (2.2 eq.). The resulting solution was stirred at RT for 72 h. The volatiles were then removed in vacuo. The crude product mixture thus obtained was directly subjected to purification by way of column chromatography (SiO₂, EtOAc) to afford the title compound as a white solid.

Step 2: Amine 70

To a dichloromethane (0.1 M) solution of 1,3-bis(3-methoxypropyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde (1 eq.) from the previous step was added magnesium sulphate (1 eq.) and cyclopropyl amine (2 eq.). The resulting suspension was stirred at RT for 16 h. The insolubles were removed via filtration and rinsed with dichloromethane before the combined filtrate was concentrated in vacuo. The crude imine thus obtained was taken up in methanol (0.1 M) and then added sodium borohydride (1.5 eq.) portionwise. The reaction mixture was stirred at RT for 16 h before it was quenched with sat. aq. NaHCO₃ and then extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of column chromatography (SiO₂, CH₂Cl₂ → 85:15 (v/v) CH₂Cl₂ : 2 M NH₃ in MeOH) afforded the title compound as a white solid.

Amine 71
N-[5-(3-Methoxypropyl)-2,3-dimethylbenzy]cyclopropanamine

Step 1: 5-Bromo-2,3-dimethylbenzoic acid

To a stirred acetic acid solution (0.2 M) of 2,3-dimethylbenzoic acid (1 eq.) was added sequentially nitric acid (12 eq.), water (25 eq.) and bromine (1.1 eq.). Finally, silver nitrate (1 M aqueous solution, 1.3 eq.) was added dropwise over a period of 30 min. After another hour of stirring at RT, the crude reaction mixture was diluted with water and extracted with EtOAc. The combined organic extracts were then washed with brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Trituration of the crude product thus obtained in hexanes afforded the title compound as a yellow solid.

Step 2: 5-Bromo-N-cyclopropyl-2,3-dimethylbenzamide

To a stirred DMF (0.2 M) solution of 5-bromo-2,3-dimethylbenzoic acid (1 eq.) from the previous step was added HATU (1.3 eq.), cyclopropylamine (1.2 eq.) and Hunig’s base (3 eq.). The resulting reaction mixture was stirred at RT for 18 h. The reaction was then quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 7:3 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as a white solid.
Step 3: \(N\)-Cyclopropyl-5-[(L\text{-})-3-methoxy-1-propen-1-yl]-2,3-dimethylbenzamide

5-Bromo-\(N\)-cyclopropyl-2,3-dimethylbenzamide (1 eq.) from the previous step and 4,4,5,5-tetramethyl-2-[(L\text{-})-3-(methyloxy)-l-propen-1-yl]-1,3,2-dioxaborolane (1.5 eq.) were combined in a 5:1 (v/v) mixture of DMF: \(\alpha\)-PrOH (0.1 M). To this solution was then added \textit{trans-}

bis(triphenylphosphine) palladium(II) bromide (0.05 eq.) and the vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 M aq. \(\text{Na}_2\text{CO}_3\) (3 eq.) was added and the resulting biphasic suspension was heated at 100\(^\circ\text{C}\) for 18 h. The now black suspension was cooled to RT, diluted with water and extracted with ether. The combined organic extracts were then washed with water and brine, dried over \(\text{Na}_2\text{SO}_4\), filtered and the filtrate concentrated \textit{in vacuo}. Purification of the crude product by way of flash chromatography (\(\text{SiO}_2\), 9:1 (v/v) Hex: EtOAc \(\rightarrow\) EtOAc) afforded the title compound as a yellowish oil.

Step 4: \(N\)-Cyclopropyl-5-(3-methoxypropyl)-2,3-dimethylbenzamide

\(N\)-Cyclopropyl-5-[(L\text{-})-3-methoxy-1-propen-1-yl]-2,3-dimethylbenzamide (1 eq.) from the previous step and 10% w/w palladium over charcoal (0.05 eq.) were suspended in EtOAc (0.2 M). The vessel was then evacuated and purged with \(\text{H}_2\). Under a balloon-filled \(\text{H}_2\) atmosphere, the reaction suspension was stirred at RT for 6 h. The reaction suspension was then filtered through a bed of celite and the filtrate concentrated \textit{in vacuo} to afford the title compound as a white solid.

Step 5: Amine 71

To a refluxing solution of \(N\)-cyclopropyl-5-(3-methoxypropyl)-2,3-dimethylbenzamide (1 eq.) from the previous step in THF (0.1 M) equipped with a short-path distillation apparatus was added dropwise borane-dimethyl sulfide complex (6 eq.). The solution was concentrated to 0.3 M over 30 min and HCl (2 N aq. solution, 6.5 eq.) was added. The mixture was stirred at 80\(^\circ\text{C}\) for 1 h, cooled to RT, rendered basic with 2 N aq. \(\text{NaOH}\) and extracted with EtOAc. The combined organic extracts were then washed with brine, dried over \(\text{Na}_2\text{SO}_4\), filtered and the filtrate concentrated \textit{in vacuo}. Purification of the crude product by way of flash chromatography (\(\text{SiO}_2\), 9:1 (v/v) Hex: EtOAc \(\rightarrow\) EtOAc) afforded the title compound as a pale yellow oil.

Amine 72

iV-[2-Chloro-5-(2-methoxyethoxy)benzyl]cyclopropanamine

Step 1: 1-Chloro-4-(2-methoxyethoxy)-2-methylbenzene

To a stirred solution of 4-chloro-3-methylphenol (1 eq.) in DMF (0.7 M) was added \(\text{K}_2\text{CO}_3\) (1.2 eq.). The mixture was stirred at 50\(^\circ\text{C}\) for 5 min before 1-bromo-2-methoxyethane (1.5 eq.) was added. After 2 h at 70\(^\circ\text{C}\), the reaction mixture was cooled down to RT and then diluted with water and ether. The organic phase was separated and washed sequentially with 2 N aq. \(\text{NaOH}\), water and brine. The organic extract was dried over \(\text{Na}_2\text{SO}_4\), filtered and the filtrate concentrated \textit{in vacuo} to afford the title compound as a yellowish oil.
Step 2: 2-(Bromomethyl)-1-chloro-4-(2-methoxyethoxy)benzene

A mixture of 1-chloro-4-(2-methoxyethoxy)-2-methylbenzene (1 eq.) from the previous step, NBS (1.1 eq.) and benzoyl peroxide (0.05 eq.) in CCl₄ (0.2 M) was refluxed for 2 h. The volatiles were then removed in vacuo and the resulting residue was suspended in hexanes. The insolubles were removed via filtration and washed further with hexanes. The filtrate was concentrated in vacuo to afford the title compound as a colorless oil.

Step 3: 2-Chloro-5-(2-methoxyethoxy)benzaldehyde

2-(Bromomethyl)-1-chloro-4-(2-methoxyethoxy)benzene (1 eq.) from the previous step and NMO (3 eq.) were stirred in dioxane (0.3 M) at 90°C for 6 h. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate and extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc → EtOAc) afforded the title compound.

Step 4: Amine 72

2-Chloro-5-(2-methoxyethoxy)benzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH₂Cl₂ (0.2 M). To this was then added MgSO₄ (1.5 eq.) and the resulting suspension was stirred at RT for 18 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in a 2:1 (v/v) mixture of THF: MeOH (0.2 M). To this solution was added sodium borohydride (5 eq.) portionwise and the resulting mixture was stirred at RT for 18 h. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were then washed with brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, 9:1 (v/v) Hex: EtOAc → EtOAc) afforded the title compound as a yellowish oil.

Amine 73

N-(2-Naphthylmethyl)cyclopropanamine

Amine 73 was prepared according to the procedure described in Amine 17 but using instead 2-naphthaldehyde as the starting material.

Amine 74

N-[3-[(Trifluoromethyl)thio]phenyl]methyl)cyclopropanamine

Amine 74 was prepared according to the procedure described in Amine 17 but using instead 3-[(trifluoromethyl)thio]benzaldehyde as the starting material.
Amine 75

iV-{{5-[(3-(Methyloxy)propyl)-2-(methylthio)phenyl]methyl}cyclopropan amine

Step 1: Methyl 5-bromo-2-(methylthio)benzoate

To a DMF (0.2 M) suspension of cesium carbonate (3 eq.) and 5-bromo-2-mercaptobenzoic acid (1 eq.) was added iodomethane (5 eq.). The resulting suspension was then stirred at RT for 1 h. The volatiles were removed before EtOAc and sat. aq. NH₄Cl were added. The organic phase was separated, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to a pale yellow oil. This was taken up again in DMF (0.2 M) and added sequentially sodium hydride (3 eq.) and iodomethane (5 eq.). The reaction vessel was then sealed and heated to 70°C for 16 h. After cooling to RT, EtOAc and sat. aq. NH₄Cl were added to the crude reaction mixture. The organic phase was separated, dried over MgSO₄, filtered and the filtrate concentrated in vacuo to a brown oil. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, DMF : EtOAc → 7:3 (v/v) Hex : EtOAc) afforded the title compound as a light yellow solid.

Step 2: Methyl 5-[3-(methyloxy)propyl]-2-(methylthio)benzoate

To a THF (0.29 M) solution of 9-BBN (2 eq.) was added allyl methyl ether (2.1 eq.) dropwise and the resulting solution was stirred at RT until no more gaseous evolution was observed. The reaction mixture was then heated to 50°C for 1 h. To this solution was subsequently added a DMF (0.34 M) solution of methyl 5-bromo-2-(methylthio)benzoate (1 eq.) from the previous step, potassium phosphate (2.5 eq.) and [1r-bis(diphenylphosphino)ferrocene]dipalladium(II) dichloromethane complex (0.1 eq.). The resulting red suspension was heated at 80°C for 16 h. After cooling to RT, the reaction was diluted with ether and water. The organic layer was separated and washed further with water and brine, dried over MgSO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc → 7:3 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 3: 5-[3-(Methyloxy)propyl]-2-(methylthio)benzyl alcohol

Methyl 5-[3-(methyloxy)propyl]-2-(methylthio)benzoate (1 eq.) from the previous step was taken up in THF (0.1 M) and then added lithium aluminum hydride (1 eq.). The reaction mixture thus obtained was stirred at RT for 16 h. The reaction was then quenched with 1N aq. HCl and extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the crude title compound as a white solid.

Step 4: 5-[3-(Methyloxy)propyl]-2-(methylthio)benzaldehyde

To a dichloromethane solution of 5-[3-(methyloxy)propyl]-2-(methylthio)benzyl alcohol (1 eq.) from the previous step was added sodium bicarbonate (5 eq.) and DMP (1.1 eq.). The resulting reaction suspension was stirred for 1.5 h at RT. The reaction was quenched with sat. aq. NaHSO₃ and then extracted with dichloromethane. The combined organic extracts were washed further with 1N aq. NaOH, water and brine, dried over MgSO₄ and filtered. Concentration of the filtrate in vacuo afforded the crude title compound as a colorless oil.
Step 5: **Amine 75**

5-[(3-(Methyloxy)propyl)-2-(methylthio)benzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH$_2$Cl$_2$ (0.1 M). To this was then added MgSO$_4$ (2 eq.) and formic acid (0.1 eq.) before the resulting suspension was allowed to stir at RT for 20 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in MeOH (0.1 M). To this solution was added sodium borohydride (5 eq.) portionwise and the resulting mixture was stirred at RT for 16 h. The reaction was quenched with 1 N aq. HCl, neutralized with 1 N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over MgSO$_4$, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO$_2$, 3:2 (v/v) Hex: EtOAc → 1:4 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

**Amine 76**

yV-[3-Bromo-5-(3-methoxypropyl)-4-methylbenzyl]cyclopropanamine

Step 1: 3,5-Dibromo-N-cyclopropyl-4-methylbenzamide

To a stirred solution of 3,5-dibromo-4-methylbenzoic acid (1 eq.) in DMF (0.4 M) was added HATU (1.3 eq.), cyclopropylamine (1.1 eq.) and Hunig's base (3 eq.). The resulting yellow mixture was stirred at RT for 18 h. The reaction was then quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo. Trituration of the crude product thus obtained in a mixture of ether and hexanes afforded the title compound as an off-white solid.

Step 2: 3-Bromo-N-cyclopropyl-5-[(lil)-3-methoxyprop-1-en-1-yl]-4-methylbenzamide

To a solution of 3,5-dibromo-N-cyclopropyl-4-methylbenzamide (1 eq.) from the previous step and 4,4,5,5-tetramethyl-2-[(lil)-3-(methoxy)-1-propen-1-yl]-1,3,2-dioxaborolane (1.1 eq.) in DMF (0.1 M) was added 2,2′-bis(triphenylphosphine) palladium(II) bromide (0.05 eq.). The vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 M aq. Na$_2$CO$_3$ (3 eq.) was added and the resulting mixture was heated at 100°C for 1 h. The now black suspension was cooled to RT, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed further with water and ethyl acetate. The filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO$_2$, 9:1 (v/v) Hex: EtOAc → EtOAc) afforded the title compound as a yellow-orange oil.

Step 3: 3-Bromo-N-cyclopropyl-5-(3-methoxypropyl)-4-methylbenzamide

To a solution of 3-bromo-N-cyclopropyl-5-[(lil)-3-methoxyprop-1-en-1-yl]-4-methylbenzamide (1 eq.) from the previous step in refluxing toluene (0.1 M) was added portionwise benzenesulfonyl hydrazide (6 eq.) over 2 h. After heating at reflux for another hour, the now black reaction suspension was cooled to RT, quenched with saturated aqueous sodium bicarbonate and
extracted with ethyl acetate. The combined organic extracts were then washed with brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc -> EtOAc) afforded the title compound as a yellow oil.

**Step 4: Amine 76**

To a stirred solution of 3-bromo-N-cyclopropyl-5-(3-methoxypropyl)-4-methylbenzamide (1 eq.) from the previous step in THF (0.2 M) was added sequentially sodium borohydride (4 eq.) and BF₃·THF complex (4.5 eq.). The reaction solution thus obtained was heated at 40°C for 5 h, cooled to 0°C and then poured slowly into 6 N aq. HCl (4.5 eq.). The resulting mixture was re-heated at 50°C for 1 h, cooled to RT, basified with 10 N aq. NaOH and finally extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to give the title compound as a colorless oil.

**Amine 77**

*N-{[(3,5-Bis[3-(methoxy)propyl]phenyl)methyl]cyclopropanamine*

**Step 1: N-{[3,5-Dibromophenyl)methyl]cyclopropanamine**

3,5-Dibromobenzaldehyde (1 eq.), cyclopropylamine (2 eq.) and magnesium sulfate (1 eq.) were stirred in dichloromethane (0.1 M) for 20 h. The insolubles were then removed via filtration through a pad of celite and washed further with dichloromethane. The filtrate was concentrated in vacuo to afford the crude imine which was then immediately re-taken up in MeOH (0.1 M). To this solution was added sodium borohydride (5 eq.) portionwise and the resulting mixture was stirred at RT for 4 h. The reaction was quenched with 1 N aq. HCl, neutralized with 1 N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over MgSO₄, and filtered. Concentration of the filtrate in vacuo afforded the title compound as a pale yellow oil.

**Step 2: tert-Butyl cyclopropyl(3,4-dibromobenzyl)carbamate**

*N-{[3,5-Dibromophenyl]methyl}cyclopropanamine (1 eq.) from the previous step and di-tert-butyl dicarbonate (1 eq.) were taken up in dichloromethane (0.12 M). To this was then added Hunig’s base (1.3 eq.) and the resulting mixture was stirred at RT for 16 h. The volatiles were removed in vacuo and the resulting residue was taken up in a 1:1 (v/v) mixture of hexanes and ether. This suspension was subsequently washed with 10% aq. HCl, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of column chromatography (SiO₂, Hex → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a pale yellow oil.

**Step 3: tert-Butyl \(^{8}S\text{-bisKIZ}\)^{8}S-methoxy-1-propen-1-y\(^{8}benzyl\)jyclopropylcarbamate**

To a solution of tert-butyl cyclopropyl(3,4-dibromobenzyl)carbamate (1 eq.) from the previous step and 4,4,5,5-tetramethyl-2-[(1H)-3-(methoxy)-1-propen-1-yl]-1,3,2-dioxaborolane (2.2 eq.) in DMF (0.14 M) was added fr^\text{"ms-bis(triphenylphosphine) palladium(II)} bromide (0.1 eq.). The vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 M aq. Na₂CO₃ (6 eq.) was added and the resulting mixture was heated at 90°C for 6 h. The now black suspension was cooled to RT, diluted...
with water and extracted with ether. The combined organic extracts were washed further with 10% aq. HCl, 1 N aq. NaOH, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex → 1:1 (v/v) Hex: EtOAc) afforded the title compound as a pale yellow oil.

5 Step 4: tert-Butyl [3,5-bis(3-methoxypropyl)benzyl]cyclopropylcarbamate
tert-Butyl [3,5-bis(1E)-3-methoxy-1-propen-1-yl]benzyl]cyclopropylcarbamate (1 eq.) from the previous step and 10% w/w palladium over charcoal (0.1 eq.) were suspended in EtOAc (0.05 M). The vessel was then evacuated and purged with H₂. Under a balloon-filled H₂ atmosphere, the reaction suspension was stirred at RT for 3 h. The reaction suspension was then quenched with dichloromethane and filtered through a bed of celite. Concentration of the filtrate in vacuo to afford the title compound as a yellow oil.

10 Step 5: Amine 77

To a solution of tert-butyl [3,5-bis(3-methoxypropyl)benzyl]cyclopropylcarbamate (1 eq.) from the previous step in CH₂Cl₂ (0.1 M) was added HCl (4.0 M in dioxane, 30 eq.). The resulting solution was stirred at RT for 2 h. The reaction was then quenched with 1 N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂: 4:1 (v/v) Hex: EtOAc → EtOAc) afforded the title compound as a colorless oil.

20 Amine 78

N-[3-(3-Methoxypropyl)-5-methylbenzyl]cyclopropanamine

Step 1: tert-Buty 1st-bromo-S-formylbenzy)cyclopropylcarbamate

To a toluene (0.1 M) solution of n-butyl lithium (2.5 M in hexanes, 1.2 eq.) was added at -78°C w-butyl magnesium bromide (2.0 M in THF, 0.4 eq.). The resulting suspension was stirred at -10°C for 20 min before tert-butyl cyclopropyl(3,4-dibromobenzyl)carbamate (1 eq., Amine 77, Step 2) was added. The now yellow-red suspension was stirred at 0°C for 30 min before DMF (30 eq.) was added dropwise neat at -78°C. The reaction mixture was allowed to warm slowly to RT over 3 h. The now black suspension was quenched with 10% aq. HCl and then extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂: 1:1 (v/v) Hex: EtOAc) afforded the title compound as a golden yellow oil.

Step 2: tert-Butyl cyclopropyl[3-formyl-5-[(1E)-3-methoxy-1-propen-1-yl]benzyl]carbamate

To a solution of tert-butyl (S-bromo-S-formylbenzy)cyclopropylcarbamate (1 eq.) from the previous step and 4,4,5,5-tetramethyl-2-[(1E)-3-(methoxy)-1-propen-1-yl]-1,3,2-dioxaborolane (1 eq.) in DMF (0.2 M) was added tetra- bis(triphenylphosphine) palladium(II) bromide (0.05 eq.). The vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 M aq. Na₂CO₃ (3 eq.) was added and the resulting mixture was heated at 90°C for 6 h. The now black suspension was cooled to
RT, diluted with water and extracted with ether. The combined organic extracts were washed further with 10%aq. HCl, 1N aq. NaOH, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex → 3:7(v/v) Hex: EtOAc) afforded the title compound as a pale yellow oil.

**Step 3: tert-Butyl cyclopropyl[3-(3-methoxypropyl)-5-methylbenzyl]carbamate**

tert-Butyl cyclopropyl[3-formyl-5-[(l£)-3-methoxy-1-propen-1-yl]benzyl]carbamate (1 eq.) from the previous step and 10% w/w palladium over charcoal (0.1 eq.) were suspended in EtOAc (0.1 M). The vessel was then evacuated and purged with H₂. Under a balloon-filled H₂ atmosphere, the reaction suspension was stirred at RT for 3 h. The reaction suspension was then quenched with dichloromethane and filtered through a bed of celite. Concentration of the filtrate in vacuo to afford the title compound as a yellow oil.

**Step 5: Amine 78**

 ether-butyl cyclopropyl[3-(3-methoxypropyl)-5-methylbenzyl]carbamate (1 eq.) from the previous step in CH₂Cl₂ (0.1 M) was added HCl (4.0 M in dioxane, 30 eq.). The resulting solution was stirred at RT for 2 h. The reaction was then quenched with 1N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a colorless oil.

**Amine 79**

N-[2-Bromo-3,5-bis(3-methoxypropyl)benzyl]cyclopropanamine

**Step 1: 3,5-Dibromo-N-cyclopropylbenzamide**

To a stirred solution of 3,5-dibromobenzoic acid (1 eq.) in DMF (0.15 M) was added HATU (1.3 eq.), cyclopropylamine (1.1 eq.) and Hunig’s base (3 eq.). The resulting yellow mixture was stirred at RT for 18 h. The reaction was then quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄ and filtered and the filtrate concentrated in vacuo. Trituration of the crude product thus obtained in a mixture of ether and hexanes afforded the title compound as a white solid.

**Step 2: N-Cyclopropyl-3,5-bis[(l£)-3-methoxypropyl-1-en-1-yl]benzamide**

To a solution of 3,5-dibromo-N-cyclopropylbenzamide (1 eq.) from the previous step and 4,4,5,5-tetramethyl-2-[(l£)-3-(methyloxy)-1-propen-1-yl]-1,3,2-dioxaborolane (2.3 eq.) in DMF (0.13 M) was added /rørø-bis(triphenylphosphine) palladium(II) bromide (0.1 eq.). The vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 M aq. Na₂CO₃ (6 eq.) was added and the resulting mixture was heated at 90°C for 16 h. The now black suspension was cooled to RT, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed further with 1N aq. NaOH, 10%aq. HCl, water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the crude title compound as a black oil.
Step 3: N-Cyclopropyl-3,5-bis(3-methoxypropyl)benzamide

An EtOAc (0.15 M) solution of JV-cyclopropyl-3,5-bis[(lE)-3-methoxyprop-1-yl]benzamide (1 eq.) from the previous step was eluted through an H-Cube hydrogenation apparatus equipped with a 10% palladium over carbon cartridge at a rate of 1 mL/min with EtOAc as the eluent. The hydrogenation was carried out using full hydrogen setting at RT. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as a colorless oil.

Step 4: 2-Bromo-N-cyclopropyl-3,5-bis(3-methoxypropyl)benzamide

To a THF (0.1 M) solution of N-cyclopropyl-3,5-bis(3-methoxypropyl)benzamide (1 eq.) from the previous step and freshly distilled TMEDA (1 eq.) was added at -78°C /-butyl lithium (1.7 M in pentanes, 1 eq.) dropwise over 10 min. The resulting reaction mixture was then slowly warmed to 0°C over 1 h and stirred at 0°C for 1 h. With the now orange reaction solution re-cooled to -78°C, 1,2-dibromotetrafluoroethane was added neat, dropwise over 10 min. The cooling bath was removed and the reaction mixture was stirred at RT for 18 h. The reaction was then quenched with 1 N aq. NaOH and extracted with EtOAc. The combined organic extracts were washed further with 10% aq. HCl, water and brine, dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 9:1 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as a pale yellow oil.

Step 5: Amine 79

A stirred solution of 2-bromo-N-cyclopropyl-3,5-bis(3-methoxypropyl)benzamide (1 eq.) from the previous step in THF (0.16 M) was added sequentially sodium borohydride (4 eq.) and BF₃-THF complex (4.5 eq.). The reaction solution thus obtained was heated at 4°C for 5 h, cooled to 0°C and then poured slowly into 6 N aq. HCl (4.5 eq.). The resulting mixture was re-heated at 50°C for 1 h, cooled to RT, basified with 10 N aq. NaOH and finally extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO₂, 4:1 (v/v) Hex : EtOAc → EtOAc) afforded the title compound as a colorless oil.

Amine 80

N-[2-Chloro-3,5-bis(3-methoxypropyl)benzyl]cyclopropanamine

Step 1: 2-Chloro-NV-cyclopropyl-3,5-bis(3-methoxypropyl)benzamide

To a DMF (0.13 M) solution of 2-bromo-NV-cyclopropyl-3,5-bis(3-methoxypropyl)benzamide (1 eq., Amine 79, Step 4) was added copper(I) chloride (2 eq.). The suspension was sealed and heated in a microwave at 150°C for 10 min. The reaction was then quenched with 10% aq. HCl and extracted with EtOAc. The combined organic extracts were washed further with 1 N aq. NaOH, water and brine, dried over Na₂SO₄, filtered, and the filtrate concentrated in vacuo.
Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, 4:1 (v/v) Hex : EtOAc $\rightarrow$ EtOAc) afforded the title compound as a pale yellow oil.

Step 2: Amine 80

To a stirred solution of 2-chloro-$N$-cyclopropyl-3,5-bis(3-methoxypropyl)benzamide (1 eq.) from the previous step in THF (0.06 M) was added sequentially sodium borohydride (4.2 eq.) and BF$_3$-THF complex (4.5 eq.). The reaction solution thus obtained was heated at 40°C for 5 h, cooled to O°C and then poured slowly into 6 N aq. HCl (4.5 eq.). The resulting mixture was re-heated at 50°C for 1 h, cooled to RT, basified with 10 N aq. NaOH and finally extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of flash chromatography (SiO$_2$, 4:1 (v/v) Hex : EtOAc $\rightarrow$ EtOAc) afforded the title compound as a colorless oil.

Amine 81

i-$N$-[2-Methoxy-3,5-bis(3-methoxypropyl)benzyl]cyclopropanamine

Step 1: 2-Methoxy-3,5-bis[(1$E$)-3-methoxyprop-1-en-1-yl]benzaldehyde

To a solution of 3,5-dibromo-2-methoxybenzaldehyde (1 eq.) and 4,4,5,5-tetramethyl-2-[(1$E$)-3-(methyloxy)-1-propen-1-yl]-1,3,2-dioxaborolane (2.2 eq.) in DMF (0.1 M) was added trans-bis(triphenylphosphine) palladium(II) bromide (0.1 eq.). The vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 M aq. Na$_2$CO$_3$ (6.5 eq.) was added and the resulting mixture was heated at 90°C for 16 h. The now black suspension was cooled to RT, diluted with water and extracted with ether. The combined organic extracts were washed further with 1 N aq. NaOH, 10% aq. HCl, water and brine, dried over Na$_2$SO$_4$ and filtered. Concentration of the filtrate in vacuo afforded the crude title compound as a brown oil.

Step 2: 2-Methoxy-3,5-bis(3-methoxypropyl)benzaldehyde

2-Methoxy-3,5-bis[(1$E$)-3-methoxyprop-1-en-1-yl]benzaldehyde (1 eq.) from the previous step and 10% w/w palladium over charcoal (0.1 eq.) were suspended in EtOAc (0.1 M). The vessel was then evacuated and purged with H$_2$. Under a balloon-filled H$_2$ atmosphere, the reaction suspension was stirred at RT for 4 h. The reaction suspension was then quenched with dichloromethane and filtered through a bed of celite. Concentration of the filtrate in vacuo to afford the crude product as a yellow oil. Further purification by way of flash chromatography (SiO$_2$, Hex $\rightarrow$ EtOAc) afforded the title compound as a colorless oil.

Step 3: Amine 81

2-Methoxy-3,5-bis(3-methoxypropyl)benzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH$_2$Cl$_2$ (0.1 M). To this was then added MgSO$_4$ (1.2 eq.) and the resulting suspension was allowed to stir at RT for 20 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in MeOH (0.1 M). To this solution was added sodium borohydride (2 eq.)
portionwise and the resulting mixture was stirred at RT for 2.5 h. The reaction was quenched with 1 N aq. HCl, neutralized with 1 N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over MgSO\(_4\) and filtered. Concentration of the filtrate in vacuo afforded the title compound as a pale yellow oil.

5

**Amine 82**

\(\text{N-P-}^\text{A-Methoxypropyl-}^\text{S-trifluoromethylo-Benzylcyclopropanamine}\)

Step 1: 3-Bromo-5-(trifluoromethyl)benzaldehyde

To a stirred solution of \(\text{«-butyl lithium (2.5 M in hexanes, 0.8 eq.) in toluene (0.2 M) at -15^\circ\text{C}}\) was added dropwise \(\text{«-butyl magnesium chloride (2.0 M in THF, 0.4 eq.)}.\) After 20 min, a solution of 1,3-dibromo-5-(trifluoromethyl)benzene (1 eq.) in toluene was added over 10 min. The reaction mixture thus obtained was stirred at -15\(^\circ\text{C}\) for 2 h before DMF (3 eq.) was added. The reaction was allowed to warm to OC. After 45 min, saturated aqueous ammonium chloride was added. The reaction mixture was extracted with ethyl acetate. The combined organic extracts were then washed with brine, dried over Na\(_2\)SO\(_4\), filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO\(_2\), Hex -> 1:1 (v/v)) Hex: EtOAc afforded the title compound.

Step 2: 3-[[((\text{L})-3-Methoxypropyl-1-en-1-yl)-5-(trifluoromethyl)benzaldehyde

To a solution of 3-bromo-5-(trifluoromethyl)benzaldehyde (1 eq.) from the previous step and 4,4,5,5-tetramethyl-2-[[((\text{L})-3-(methyloxy)-1-propen-1-yl]-1,3,2-dioxaborolane (1.5 eq.) in DMF (0.2 M) was added \(\text{PdCl}_2\text{-bis(triphenylphosphine) palladium(II) bromide (0.05 eq.)}.\) The vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 M aq. Na\(_2\)CO\(_3\) (3 eq.) was added and the resulting mixture was stirred at 100\(^\circ\text{C}\) for 2 h. The now black suspension was cooled to RT, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over Na\(_2\)SO\(_4\), filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO\(_2\), 9:1 (v/v) Hex: EtOAc -> EtOAc) afforded the title compound as a yellow oil.

Step 3: \(\text{N-P-KI-Z^-S-Methoxypropyl-1-en-1-y^-S^-trifluoromethylo-Benzylcyclopropanamine}\)

3-[[((\text{L})-3-Methoxypropyl-1-en-1-yl)-5-(trifluoromethyl)benzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH\(_2\)Cl\(_2\) (0.2 M). To this was then added MgSO\(_4\) (1.5 eq.) and the resulting suspension was stirred at RT for 18 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in a 2:1 (v/v) mixture of THF: MeOH (0.2 M). To this solution was added sodium borohydride (5 eq.) portionwise and the resulting mixture was stirred at RT for 18 h. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were then washed with brine, dried over Na\(_2\)SO\(_4\), filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO\(_2\), 9:1 (v/v) Hex: EtOAc -> EtOAc) afforded the title compound.
Step 5: Amine 82

\[ \text{N-(fClTi-B-Methoxyprop-1-en-1-yl)-S-S-H} \ \pi \text{fluoromethyObenzylcyclopropanamine (1 eq.) from the previous step and 10\% w/w palladium over charcoal (0.1 eq.) were suspended in EtOAc (0.03 M). The vessel was then evacuated and purged with H}_2. \text{ Under a balloon-filled H}_2 \text{ atmosphere, the reaction suspension was stirred at RT overnight. The reaction was then filtered through a bed of celite and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO}_2, \text{Hex} \rightarrow 1:9 (v/v) \text{ Hex : EtOAc) afforded the title compound as a colorless oil.} \]

**Amine 83**

3-[(Cyclopropylamino)methyl]-5-(3-methoxypropyl)phenol

Amine 83 was prepared according to the procedure described in WO 2007/009250 A1 patent.

**Amine 84**

N-(3-Bromo-5-iodobenzyl)cyclopropanamine

Step 1: (3-Bromo-5-iodophenyl)methanol

To a solution of 3-bromo-5-iodobenzoic acid (1.0 eq.) in THF (0.2 M) at RT was added borane-methyl sulfide complex (1.5 eq.). After 3 days of stirring at RT, the reaction mixture was quenched cautiously with 2 N aq. HCl and extracted with ether. The combined organic extracts were washed with 1 N aq. NaOH, water and brine, dried over MgSO\(_4\) and filtered. Concentration of the filtrate in vacuo afforded the title compound as a colorless oil.

Step 2: 3-Bromo-5-iodobenzaldehyde

A mixture of (3-bromo-5-iodophenyl)methanol from the previous step (1.0 eq.) and Dess-Martin periodinane (1.18 eq.) was stirred at RT in dichloromethane (0.1 M) for 45 min. The reaction mixture was diluted with ether, filtered through a plug OfSiO\(_2\), and the silica washed with a 3:1 (v/v) mixture of hexanes : EtOAc. The filtrate was concentrated in vacuo and passed again through a plug OfSiO\(_2\), eluting with a 3:1 (v/v) mixture of hexanes : EtOAc to afford the title compound as a light yellow solid.

Step 3: Amine 84

3-Bromo-5-iodobenzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH\(_2\)Cl\(_2\) (0.1 M). To this was then added MgSO\(_4\) (1 eq.) and the resulting suspension was stirred at RT for 20 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in MeOH (0.5 M). To this solution was added sodium borohydride (1.5 eq.) portionwise and the resulting mixture was stirred at OC for 30 min, then at RT for 2 h. The reaction was quenched by stirring with 2 N aq. HCl for 25 min, basified with 1 N aq. NaOH and concentrated in vacuo. The residue was
extracted with ether from water, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the title compound as a light yellow oil.

**Amine 85**

5 N-Cyclopropyl-6-(3-methoxypropyl)inden-1-amine

Step 1: 6-[[(E)-3-Methoxyprop-1-en-1-yl]inden-1-one

To a solution of 6-bromoinidan-1-one (1 eq.) and 4,4,5,5-tetramethyl-2-[[(E)\>3-(methyloxy)-1-propen-1-yl]-1,3,2-dioxaborolane (1.3 eq.) in DMF (0.1 M) was added trans-bis(triphenylphosphine) palladium(II) bromide (0.05 eq.). The vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 M aq. Na₂CO₃ (3 eq.) was added and the resulting mixture was stirred at 100°C for 1 h. The now black suspension was cooled to RT, diluted with water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex → 1:1 (v/v) Hex: EtOAc) afforded the title compound as a beige solid.

Step 2: N-cyclopropyl-6-[[(E)-3-methoxyprop-1-en-1-yl]inden-1-amine

To a solution of 6-[[(E)-3-methoxyprop-1-en-1-yl]inden-1-one (1 eq.) from the previous step in MeOH (2 M) was added cyclopropylamine (2 eq.) and titanium(IV) isopropoxide (1.3 eq.). The solution was stirred at RT for 1 h before sodium borohydride (1 eq.) was added at 0°C. After 30 min, water was added and the mixture was extracted with ethyl acetate. The combined organic extracts were then washed with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo.

Purification of the crude product by way of flash chromatography (SiO₂, Hex → 1:9 (v/v) Hex : EtOAc) afforded the title compound.

Step 3: Amine 85

5 N-Cyclopropyl-6-[[E]-3-methoxyprop-1-en-1-yl]inden-1-amine

(1 eq.) from the previous step and 10% w/w palladium over charcoal (0.1 eq.) were suspended in EtOAc (0.2 M). The vessel was then evacuated and purged with H₂. Under a balloon-filled H₂ atmosphere, the reaction suspension was stirred at RT for 3 h. The reaction was then filtered through a bed of celite and the filtrate concentrated in vacuo to afford the title compound.

**Amine 86**

N-Cyclopropyl-7-(3-methoxypropyl)-1,2,3,4-tetrahydronaphthalen-1-amine

**Amine 86** was prepared according to the procedure described in **Amine 85** but using instead 7-bromo-3,4-dihydropnaphthalen-1(2H)-one as the starting material.
Amine 87

3-{3-Bromo-5-[(cyclopropylamino)methyl]-2-methylphenyl}-1-propanol

To a chloroform (0.1 M) solution of Amine 76 (1 eq.) was added iodontrimethylsilane (6 eq.). The resulting red solution was stirred at RT in darkness for 18 h. The reaction was quenched with methanol before the volatiles were removed in vacuo. The resulting residue was then partitioned between ether and 10% aq. HCl. The aqueous layer was separated, carefully brought to a pH of ~8 with 1 N aq. NaOH and extracted with EtOAc. The combined EtOAc extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, 97:3 (v/v) CH₂Cl₂ : 2.0 M NH₃ in MeOH) afforded the title compound as a colorless oil.

Amine 88

N-[3-Bromo-5-(3-ethoxypropyl)-4-methylbenzyl]cyclopropanamine

Step 1: Methyl 3-bromo-5-[(1E)-3-methoxy-1-propen-1-yl]-4-methylbenzoate

To a solution of methyl 3,5-dibromo-4-methylbenzoate (1 eq.) and 4,4,5,5-tetramethyl-2-[1(1E)-3-(methoxy)-1-propen-1-yl]-1,3,2-dioxaborolane (1.1 eq.) in DMF (0.1 M) was added trans-bis(triphenylphosphine) palladium(II) bromide (0.02 eq.). The vessel was repeatedly evacuated and back-filled with nitrogen. Finally, 2 M aq. Na₂CO₃ (3 eq.) was added and the resulting mixture was heated at 100°C for 2 h. The now black suspension was cooled to RT, diluted with water and extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, 9:1 (v/v) Hex: EtOAc) afforded the title compound as a colorless oil.

Step 2: Methyl 3-bromo-5-(3-methoxypropyl)-4-methylbenzoate

To a dichloromethane (0.2 M) solution of methyl 3-bromo-5-[(1E)-3-methoxy-1-propen-1-yl]-4-methylbenzoate (1 eq.) from the previous step was added Crabtree’s catalyst (0.01 eq.). The resulting orange red solution was bubbled with hydrogen for 10 min to activate the catalyst and then stirred at RT under a static balloon atmosphere of hydrogen for 3 h. Finally, removal of the volatiles in vacuo afforded the crude title compound as a yellow oil.

Step 3: Methyl 3-bromo-5-(3-iodopropyl)-4-methylbenzoate

To a chloroform (0.1 M) solution of methyl 3-bromo-5-(3-methoxypropyl)-4-methylbenzoate (1 eq.) from the previous step was added iodontrimethylsilane (10 eq.). The resulting red solution was stirred at RT in darkness for 18 h. The reaction was quenched with methanol before the volatiles were removed in vacuo. The resulting residue was then taken up in ether, washed sequentially with 10% aq. HCl, 1 N aq. NaOH, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex : EtOAc) afforded the title compound as an orange oil.
Step 4: Ethyl 3-bromo-5-(3-ethoxypropyl)-4-methylbenzoate

To an ethanol (0.1 M) solution of methyl 3-bromo-5-(3-iodopropyl)-4-methylbenzoate (1 eq.) from the previous step was added freshly prepared sodium ethoxide (3 eq.). The resulting solution was heated at reflux for 18 h. After cooling to RT, the volatiles were removed in vacuo. The resulting residue was then taken up in ether and washed further with 10% aq. HCl, 1 N aq. NaOH, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex -> 1:1 (v/v) Hex: EtOAc) afforded the title compound as a yellow oil.

Step 5: 3-Bromo-5-(3-ethoxypropyl)-4-methylbenzaldehyde

To a dichloromethane (0.07 M) solution of ethyl 3-bromo-5-(3-ethoxypropyl)-4-methylbenzoate (1 eq.) from the previous step was added DIBAL-H (1.5 M solution in toluene, 2.2 eq.). The resulting solution was stirred at RT for 1.5 h and then carefully quenched with 10% aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. The crude alcohol thus obtained was taken up again in dichloromethane (0.07 M) and then added Dess-Martin periodinane (1.0 eq.) and sodium bicarbonate (1.2 eq.). After stirring at RT for 40 min, the reaction mixture was diluted with ether and washed sequentially with sat. aq. NaHSO₃, 1 N aq. NaOH, water and brine. The organic extract was dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex -> 1:1 (v/v) Hex: EtOAc) afforded the title compound as a colorless oil.

Step 6: Amine 88

3-Bromo-5-(3-ethoxypropyl)-4-methylbenzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH₂Cl₂ (0.1 M). To this was then added MgSO₄ (1 eq.) and the resulting suspension was stirred at RT for 20 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in MeOH (0.5 M). To this solution was added sodium borohydride (1.5 eq.) portionwise and the resulting mixture was stirred at 0°C for 30 min, then at RT for 2 h. The reaction was quenched by stirring with 2 N aq. HCl for 25 min, basified with 1 N aq. NaOH and concentrated in vacuo. The residue was extracted with ether from water, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the title compound as a colorless oil.

Amine 89

*N-{3-Bromo-5-[3-(difluoromethoxy)propyl]-4-methylbenzyl}cyclopropanamine

Step 1: Methyl 3-bromo-5-(3-hydroxypropyl)-4-methylbenzoate

To a chloroform (0.1 M) solution of methyl 3-bromo-5-(3-methoxypropyl)-4-methylbenzoate (1 eq., Amine 88, Step 2) was added iodostrimethylsilane (3 eq.). The resulting red solution was stirred at RT in darkness for 18 h. The reaction was quenched with methanol before the
volatiles were removed in vacuo. The resulting residue was then taken up in ether, washed sequentially with 10% aq. HCl, 1 N aq. NaOH, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex → 3:7 (v/v) Hex: EtOAc) afforded the title compound as a pale yellow oil.

Step 2: Methyl 3-bromo-5-[3-(difluoromethoxy)propyl]-4-methylbenzoate

To an acetonitrile (0.6 M) suspension of methyl 3-bromo-5-(3-hydroxypropyl)-4-methylbenzoate (1 eq.) from the previous step and sodium sulfate (0.2 eq.) was added dropwise at 50°C difluoro(methylsulfonyl)acetic acid (1 eq.) over a period of 10 min. After the completion of addition, the reaction suspension was heated at 50°C for another 16 h. The reaction mixture was then cooled to RT, poured into water and extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex → 1:1 (v/v) Hex: EtOAc) afforded the title compound as a colorless oil.

Step 3: 3-Bromo-5-[3-(difluoromethoxy)propyl]-4-methylbenzaldehyde

To a dichloromethane (0.07 M) solution of methyl 3-bromo-5-[3-(difluoromethoxy)propyl]-4-methylbenzoate (1 eq.) from the previous step was added DIBAL-H (1.5 M solution in toluene, 2.2 eq.). The resulting solution was stirred at RT for 1.5 h and then carefully quenched with 10% aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with brine, dried OVCrNa₂SO₄, filtered and the filtrate concentrated in vacuo. The crude alcohol thus obtained was taken up again in dichloromethane (0.07 M) and then added Dess-Martin periodinane (1.0 eq.) and sodium bicarbonate (1.2 eq.). After stirring at RT for 40 min, the reaction mixture was diluted with ether and washed sequentially with sat. aq. NaHSO₃, 1 N aq. NaOH, water and brine. The organic extract was dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex → 1:1 (v/v) Hex: EtOAc) afforded the title compound as a colorless oil.

Step 6: Amine 89

3-Bromo-5-[3-(difluoromethoxy) propyl]-4-methylbenzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH₂Cl₂ (0.1 M). To this was then added MgSO₄ (1 eq.) and the resulting suspension was stirred at RT for 20 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in MeOH (0.5 M). To this solution was added sodium borohydride (1.5 eq.) portionwise and the resulting mixture was stirred at 0°C for 30 min, then at RT for 2 h. The reaction was quenched by stirring with with 2 N aq. HCl for 25 min, basified with 1 N aq. NaOH and concentrated in vacuo. The residue was extracted with ether from water, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the title compound as a colorless oil.
Amine 90

\( \Lambda^2\)-(3-Benzyl-5-methylbenzyl)cyclopropanamine

Step 1: 3-Benzyl-5-methylbenzaldehyde

To a DME solution (0.1 M) of (3-formyl-5-methylphenyl)boronic acid (1 eq.) was added cesium fluoride (3 eq.), tetrakis(triphenylphosphine)palladium (0.1 eq.) and benzyl bromide (1.2 eq.). The mixture was refluxed for 3 h, cooled down to RT and quenched with saturated aqueous sodium bicarbonate. The mixture was extracted with ethyl acetate. The combined organic extracts were then washed with brine, dried over \( \text{Na}_2\text{SO}_4 \), filtered and the filtrate concentrated \textit{in vacuo}. Purification of the crude product by way of flash chromatography (SiO\textsubscript{2}, Hex \( \rightarrow \) 7:3 (v/v) Hex: EtOAc) afforded the title compound.

Step 2: Amine 90

3-Benzyl-5-methylbenzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in \( \text{CH}_2\text{Cl}_2 \) (0.2 M). To this was then added \( \text{MgSO}_4 \) (1.5 eq.) and the resulting suspension was stirred at RT for 18 h. The insolubles were then removed \textit{via} filtration through a pad of celite and the filtrate was concentrated \textit{in vacuo}. The crude imine thus obtained was then re-taken up in a 2:1 (v/v) mixture of THF: MeOH (0.2 M). To this solution was added sodium borohydride (10 eq.) portionwise and the resulting mixture was stirred at RT for 18 h. The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The combined organic extracts were then washed with brine, dried over \( \text{Na}_2\text{SO}_4 \), filtered and the filtrate concentrated \textit{in vacuo}.

Purification of the crude product by way of flash chromatography (SiO\textsubscript{2}, CH\textsubscript{2}Cl\textsubscript{2} \( \rightarrow \) 9:1 (v/v) CH\textsubscript{2}Cl\textsubscript{2}: EtOH) afforded the title compound.

Amine 91

\( N\)-[3-Bromo-5-(3-fluorobenzyl)-4-methylbenzyl]cyclopropanamine

Step 1: Methyl 3-bromo-5-formyl-4-methylbenzoate

To a dichloromethane (0.16 M) solution of methyl 3-bromo-5-[(1\( \text{E} \)-3-methoxy-1-propenyl)-yl]-4-methylbenzoate (1 eq., \textbf{Amine 88, Step 1}) was bubbled at -78\(^\circ\)C with freshly generated ozone until a persistent blue color was observed. The reaction vessel was then thoroughly purged with nitrogen before triphenylphosphine (1.1 eq.) was added. The resulting mixture was slowly warmed to RT over 6 h. The volatiles were then removed \textit{in vacuo} and the resulting residue was suspended in a 1:1 (v/v) mixture of hexanes and ether. The insolubles were removed \textit{via} filtration through a pad of silica gel. Concentration of the filtrate thus obtained \textit{in vacuo} afforded a white solid. Further purification of the crude product by way of flash chromatography (SiO\textsubscript{2}, Hex \( \rightarrow \) 1:1 (v/v) Hex : EtOAc) afforded the title compound as a white solid.

Step 2: Methyl 3-bromo-5-(hydroxymethyl)-4-methylbenzoate

To a methanol (0.1 M) solution of methyl 3-bromo-5-formyl-4-methylbenzoate (1 eq.) from the previous step was added sodium borohydride (4 eq.) portionwise. The resulting mixture was
stirred at RT for 3 h. The reaction was subsequently quenched with cold 10% aq. HCl and extracted with ether. The combined organic extracts were then washed with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a white solid.

Step 3: Methyl 3-bromo-5-(iodomethyl)-4-methylbenzoate

To a dichloromethane (0.05 M) solution of triphenylphosphine (1.1 eq) was added iodine (1.1 eq.). The resulting orange-yellow suspension was stirred at RT for 30 min before imidazole (1.2 eq.) and finally methyl 3-bromo-5-(hydroxymethyl)-4-methylbenzoate (1 eq.) from the previous step were added. The now pale yellow solution was stirred at RT for another 30 min. The volatiles were removed in vacuo and the residue was triturated with a 1:1 (v/v) mixture of hexanes and ether. The insolubles were then removed via filtration through a pad of silica gel. Concentration of the filtrate in vacuo afforded the title compound as a white solid.

Step 4: Methyl 3-bromo-5-(3-fluorobenzyl)-4-methylbenzoate

To a THF (0.1 M) suspension of CuCN (2 eq.) was added at -78°C 3-fluorophenyl magnesium bromide (0.5 M solution in THF, 4 eq.) over a period of 5 min. The resulting mixture was stirred at -78°C for 20 min and then at O°C for another 20 min. The now yellow suspension was recooled to -78°C before methyl 3-bromo-5-(iodomethyl)-4-methylbenzoate (1 eq.) from the previous step was added. The resulting mixture was stirred at -78°C for 20 min, O°C for another 20 min and finally at RT for 16 h. The crude reaction mixture was quenched with a 3:1 (v/v) mixture of sat. aq. NH₄Cl: cone. NH₄OH and then extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Further purification of the crude product by way of flash chromatography (SiO₂: Hex → 1:1 (v/v) Hex: EtOAc) afforded the title compound as a colorless oil.

Step 5: 3-Bromo-5-(3-fluorobenzyl)-4-methylbenzaldehyde

To a dichloromethane (0.1 M) solution of methyl 3-bromo-5-(3-fluorobenzyl)-4-methylbenzoate (1 eq.) from the previous step was added DIBAL-H (1.5 M solution in toluene, 2.2 eq.). The resulting solution was stirred at RT for 1.5 h and then carefully quenched with 10% aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. The crude alcohol thus obtained was taken up again in dichloromethane (0.1 M) and then added Dess-Martin periodinane (1.0 eq.) and sodium bicarbonate (1.2 eq.). After stirring at RT for 40 min, the reaction mixture was diluted with ether and washed sequentially with sat. aq. NaHSO₃, 1 N aq. NaOH, water and brine. The organic extract was dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂: Hex → 1:1 (v/v) Hex: EtOAc) afforded the title compound as a colorless oil.
Step 6: Amine 91

3-Bromo-5-(3-fluorobenzyl)-4-methylbenzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH₂Cl₂ (0.1 M). To this was then added MgSO₄ (1 eq.) and the resulting suspension was stirred at RT for 20 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in MeOH (0.1 M). To this solution was added sodium borohydride (1.5 eq.) portionwise and the resulting mixture was stirred at O°C for 30 min, then at RT for 2 h. The reaction was quenched by stirring with with 2 N aq. HCl for 25 min, basified with 1 N aq. NaOH and concentrated in vacuo. The residue was extracted with ether from water, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the title compound as a colorless oil.

Amine 92

{3-Bromo-5-[(cyclopropylamino)methyl]-2-methylphenyl}(3-fluorobenzyl)methane

Step 1: 3-Bromo-5-[(1E)-3-methoxy-1-propen-1-yl]-4-methylbenzaldehyde

To a dichromethane (0.1 M) solution of methyl 3-bromo-5-[(1E)-3-methoxy-1-propen-1-yl]-4-methylbenzoate (1 eq., Amine 88, Step 1) was added DIBAL-H (1.5 M solution in toluene, 2.2 eq.). The resulting solution was stirred at RT for 1.5 h and then carefully quenched with 10% aq. HCl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. The crude alcohol thus obtained was taken up again in dichloromethane (0.1M) and then added Dess-Martin periodinane (1.0 eq.) and sodium bicarbonate (1.2 eq.). After stirring at RT for 40 min, the reaction mixture was diluted with ether and washed sequentially with sat. aq. NaHSO₃, 1N aq. NaOH, water and brine. The organic extract was dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product by way of flash chromatography (SiO₂, Hex → 1:1 (v/v) Hex: EtOAc) afforded the title compound as a colorless oil that solidified upon standing.

Step 2: N-3-Bromo-5-[(1E)-3-methoxy-1-propen-1-yl]-4-methylbenzyl)cyclopropylamine

3-Bromo-5-[(1E)-3-methoxy-1-propen-1-yl]-4-methylbenzaldehyde (1 eq.) from the previous step and cyclopropylamine (2 eq.) were combined in CH₂Cl₂ (0.1 M). To this was then added MgSO₄ (1 eq.) and the resulting suspension was stirred at RT for 20 h. The insolubles were then removed via filtration through a pad of celite and the filtrate was concentrated in vacuo. The crude imine thus obtained was then re-taken up in MeOH (0.1 M). To this solution was added sodium borohydride (1.5 eq.) portionwise and the resulting mixture was stirred at O°C for 30 min, then at RT for 2 h. The reaction was quenched by stirring with with 2 N aq. HCl for 25 min, basified with 1 N aq. NaOH and concentrated in vacuo. The residue was extracted with ether from water, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo to afford the title compound as a colorless oil.
Step 3: **tert-Butyl** (3-bromo-5-formyl-4-methylbenzyl)cyclopropylcarbamate

\[ \text{N-(3-Bromo-5-[(3-fluorophenyl)(hydroxyl)methyl]-4-methylbenzyl)cyclopropylamine} \] (1 eq.) from the previous step and di-**tert-butyl** dicarbonate (1.1 eq.) were taken up in dichloromethane (0.1 M). To this was then added Hunig's base (1.2 eq.) and the resulting mixture was stirred at RT for 3 h. The volatiles were removed *in vacuo* and the resulting residue was taken up in a 1:1 (v/v) mixture of hexanes and ether. This suspension was subsequently washed with 10% aq. HCl, water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated *in vacuo*. Purification of the crude product thus obtained by way of column chromatography (SiO$_2$, Hex → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 4: **tert-Butyl** (3-bromo-5-formyl-4-methylbenzyl)cyclopropylcarbamate

To a dichloromethane (0.08 M) solution of **tert-butyl** (3-bromo-5-[(3-fluorophenyl)(hydroxyl)methyl]-4-methylbenzyl)cyclopropylcarbamate (1 eq.) from the previous step was bubbled at -78°C with freshly generated ozone until a persistent blue color was observed. The reaction vessel was then thoroughly purged with nitrogen before triphenylphosphine (1 eq.) was added. The resulting mixture was slowly warmed to RT over 16 h. The volatiles were then removed *in vacuo* and the resulting residue was suspended in a 1:1 (v/v) mixture of hexanes and ether. The insolubles were removed via filtration through a pad of silica gel. Concentration of the filtrate thus obtained *in vacuo* afforded a colorless oil. Further purification of the crude product by way of flash chromatography (SiO$_2$, Hex → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 5: **tert-Butyl** (3-bromo-5-[(3-fluorophenyl)(hydroxyl)methyl]-4-methylbenzyl)cyclopropylcarbamate

To a THF (0.13 M) solution of **tert-butyl** (3-bromo-5-formyl-4-methylbenzyl)-cyclopropylcarbamate (1 eq.) from the previous step was added at 0°C 3-fluorophenyl magnesium bromide (0.5 M in THF, 1.1 eq.). The resulting solution was warmed slowly to RT over 2 h before it was quenched with sat. aq. NH$_4$Cl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated *in vacuo*. Further purification of the crude product by way of flash chromatography (SiO$_2$, Hex → 1:1 (v/v) Hex : EtOAc) afforded the title compound as a colorless oil.

Step 6: **tert-Butyl** P-bromo-S^-fluorobenzoylO^-methylbenzylcyclopropylcarbamate

To a dichloromethane (0.1 M) solution of **tert-butyl** (3-bromo-5-[(3-fluorophenyl)(hydroxyl)methyl]-4-methylbenzyl)cyclopropylcarbamate (1 eq.) from the previous step was added Dess-Martin periodinane (1.0 eq.) and sodium bicarbonate (1.2 eq.). After stirring at RT for 1 h, the reaction mixture was diluted with ether and washed sequentially with sat. aq. NaHSOs, 1 N aq. NaOH, water and brine. The organic extract was dried over Na$_2$SO$_4$, filtered and the filtrate concentrated *in vacuo* to afford the title compound as a colorless oil.
Step 7: **Amine 92**

**tert-Buty**l P-bromo-S^-fluorobenzoyl^-methylbenzy^cyclopropylcarbamate (1 eq.)

from the previous step in CH₂Cl₂ (0.1 M) was added HCl (4.0 M in dioxane, 20 eq.). The resulting solution was stirred at RT for 2 h. The reaction was then quenched with 1 N aq. NaOH and extracted with ether. The combined organic extracts were then washed further with water and brine, dried over Na₂SO₄ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a colorless oil.

**Example 1**

fra=5-N-Cyclopropyl-4-(1-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-N-[3-[[2-(methyl-oxy)ethyl]oxy]-5-
[3-(methyl-oxo)propyl phenyl]methyl]-3-piperidinecarboxam ide

![Chemical Structure](image)

**Step 1:** 1-(U-Dimethylethyl) 3-ethyl 4-[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-
1,3(2//-)pyridinedicarboxylate

To a dioxane solution (0.17 M) of 1-(U-dimethylethyl) 3-ethyl 4-
[(trifluoromethyl)sulfonyl]oxy]-5,6-dihydro-1,3(2//-)pyridinedicarboxylate (1 eq.) and 4,4,4',4',5,5,5',5'-
octamethyl-2,2'-bi-l,3,2-dioxaborolane (1.1 eq.) was added potassium acetate (3 eq.). The suspension was evacuated and back-filled with N₂. Finally, [1r-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.03 eq.) was added in one rapid portion and the reaction suspension was heated at 80°C for 14 h. The reaction was then quenched with the addition of diethyl ether and sat. aq. NH₄Cl. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of column chromatography (SiO₂, 95:5 → 80:20 (v/v) toluene : EtOAc) afforded the title compound as a golden yellow oil.

**Step 2:** 1-(1,1-Dimethylethyl) 3-ethyl 4-(7-chloro-4-quinolinyl)-5,6-dihydro-1,3(2//-)
pyridinedicarboxylate

To a 3:1 (v/v) toluene : ethanol solution (0.072 M) of 1-(1,1-dimethylethyl) 3-ethyl 4-
[(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydro-1,3(2//-)pyridinedicarboxylate (1 eq.) from the previous step and 7-chloro-4-iodoquinoline (1 eq.) was added sodium carbonate (2 M aq. solution, 3 eq.). The suspension was evacuated and back-filled with N₂. Finally, [1r'-bis(diphenylphosphino)ferrocene]-
dichloropalladium(II) (0.06 eq.) was added in one rapid portion and the reaction suspension was heated at 80°C for 20 h. The reaction was then quenched with the addition of EtOAc and water. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with 1N aq. NaOH, water and brine, dried over Na₂SO₄, filtered and the filtrate concentrated in vacuo.

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Purification of the crude product thus obtained by way of column chromatography (SiO$_2$, 90:10 (v/v) Hex
EtOAc $\rightarrow$ EtOAc) afforded the title compound as a pale, yellow oil.

Step 3: m-1-(1,1-Dimethylethyl) 3-ethyl 4-(7-chloro-4-quinolinyl)-1,3-piperidinedicarboxylate

To a deoxygenated 1.1 (v/v) MeOH : THF solution (0.1 M) of m-1-(1,1-dimethylethyl) 3-ethyl 4-(7-chloro-4-quinolinyl)-1,3-piperidinedicarboxylate (1 eq.) from the previous step was added, at -78 $^\circ$C, samarium iodide (0.5 M THF solution, 10 eq.). The resulting purple solution was stirred at -78 $^\circ$C for 1.5 h. The reaction was then quenched with the addition of glacial acetic acid before sat.
aq.
NaHCO$_3$ was added. The aqueous layer was separated and back-extracted with ether. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo. Purification of the crude product thus obtained by way of column chromatography (SiO$_2$, 95:5 (v/v)Hex : EtOAc $\rightarrow$ 3:7 (v/v)Hex : EtOAc) afforded the title compound as a colorless oil.

Step 4: trans-1-(1,1-Dimethylethyl) 3-ethyl 4-(7-chloro-4-quinolinyl)-1,3-piperidinedicarboxylate

To an ethanol solution (0.12 M) of trans-1-(1,1-dimethylethyl) 3-ethyl 4-(7-chloro-4-quinolinyl)-1,3-piperidinedicarboxylate (1 eq.) from the previous step was added freshly prepared sodium ethoxide (1.2 eq.). The resulting yellow-orange solution was heated at 55 $^\circ$C for 12 h. The volatiles were then removed in vacuo and the residue was partitioned between EtOAc and sat.
aq.
NH$_4$Cl. The aqueous layer was separated and back-extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$, filtered and the filtrate concentrated in vacuo.

Purification of the crude product thus obtained by way of column chromatography (SiO$_2$, 90:10 (v/v) Hex
EtOAc $\rightarrow$ EtOAc) afforded the title compound as a colorless oil.

Step 5: trans-1-(1,1-Dimethylethyl) 3-ethyl 4-(4-quinolinyl)-1,3-piperidinedicarboxylate

To a DMF solution (0.1 M) of trans-1-(1,1-dimethylethyl) 3-ethyl 4-(4-quinolinyl)-1,3-piperidinedicarboxylate (1 eq.) from the previous step and ammonium formate (7 eq.) was added [1,1$^\text{B}$bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.1 eq.). The resulting suspension heated at 80 $^\circ$C for 12 h. The now black suspension was cooled to RT, diluted with ether and washed sequentially with water, 1 N aq.
NaOH, water and brine. The organic extract was dried over Na$_2$SO$_4$, treated with charcoal and filtered through a bed of celite. Concentration of the filtrate in vacuo afforded the title compound as a colorless oil.

Step 6: trans-1-(1,1-Dimethylethyl) 3-ethyl 4-(l-oxido-4-quinolinyl)-1,3-piperidinedicarboxylate

To a dichloromethane solution (0.06 M) of trans-1-(1,1-dimethylethyl) 3-ethyl 4-(4-quinolinyl)-1,3-piperidinedicarboxylate (1 eq.) from the previous step was added 3-chloroperoxybenzoic acid (1 eq.). The resulting colorless solution was stirred at RT for 12 h. The reaction was then quenched with sat.
aq.
NaHSO$_3$ and 1 N aq.
NaOH. The aqueous layer was separated and back-extracted with
EtOAc. The combined organic extracts were washed further with water and brine, dried over Na$_2$SO$_4$ and filtered. Concentration of the filtrate in vacuo afforded the title compound as a pale yellow oil.
Step 7: \text{nms-1-[(l,l-Dimethylethyl)oxy]carbonyl]-4-(1-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-l,3-piperidinedicarboxylate}

To a toluene solution (0.06 M) of \text{\pi\alpha\omega-1-[(l,l-dimethylethyl)oxy]carbonyl]-3-ethyl 4-[(1-oxido-2,3-dihydro-4-quinolinyl)-l,3-piperidinedicarboxylate} (1 eq.) from the previous step was added triethylamine (3 eq.).

With the reaction vessel immersed in an ice-water bath, trifluoroacetic anhydride (3 eq.) was added dropwise neat over a period of 2 min. The resulting yellow solution was warmed slowly to RT and then allowed to stir at RT for 18 h. The reaction was quenched with the addition of EtOAc and sat. aq. \text{NH}_4\text{Cl}. The aqueous layer was separated and back-extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and the filtrate concentrated \textit{in vacuo}. The gummy, yellow oil thus obtained was immediately taken up in methanol (0.06 M). To this was then added sodium hydroxide (2 M aq. solution, 3 eq.) and dimethyl sulfate (4 eq.) at 0\textdegree C. The resulting yellow solution was warmed slowly to RT and then allowed to stir at RT for 12 h. The volatiles were removed \textit{in vacuo} and the residue was partitioned between EtOAc and sat. aq. \text{NH}_4\text{Cl}. The aqueous layer was separated and back-extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and the filtrate concentrated \textit{in vacuo}.

Purification of the crude product thus obtained by way of column chromatography (SiO\textsubscript{2} 95:5 (v/v) \text{CH}_2\text{Cl}_2 : 2.0 M \text{NH}_3 in MeOH) afforded the title compound as a white solid.

Step 8: \text{\pi\alpha\alpha\alpha-1-[(l,l-Dimethylethyl)oxy]carbonyl]-4-(1-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-3-piperidinedicarboxylic acid}

To a 2:1 (v/v) THF\textsubscript{MeOH} solution (0.04 M) of \text{\pi\alpha\omega\omega-1-(U-dimethylethyl)oxy]carbonyl]-3-ethyl 4-[(1-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-l,3-piperidinedicarboxylate} (1 eq.) from the previous step was added lithium hydroxide (1 M aq. solution, 3.1 eq.). The resulting cloudy solution was stirred vigorously at RT for 18 h. The volatiles were then removed \textit{in vacuo} and the residue was partitioned between EtOAc and 10% aq. HCl. The aqueous layer was separated and back-extracted with EtOAc. The combined organic extracts were washed further with water and brine, dried over Na\textsubscript{2}SO\textsubscript{4} and filtered. Concentration of the filtrate \textit{in vacuo} afforded the title compound as a white solid.

Step 9: \text{fr-\text{nms-1-Dimethylethyl 3-[(cyclopropyl][3-[(2-methyloxy)ethyl]oxy]-5-3-(methyloxy)propyl][phenyl]methyl]amino]carbonyl]-4-(1-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-1-piperidinedicarboxylate}

To a DMF (0.1 M) solution of \text{\pi\omega\omega-1-[(l,l-dimethylethyl)oxy]carbonyl]-4-(1-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-3-piperidinedicarboxylic acid} (1 eq.) from the previous step, Hunig’s base (3 eq.) and \text{Amine 11} (1 eq.) was added portionwise <9-(7-azabenzo[1,2-b:4,3-b]diazepin-1-yl)-N,N,N'-tetramethyluronium hexafluorophosphate (1.2 eq.). The resulting reaction solution was stirred at RT for 48 h. The yellow solution was diluted with Et\textsubscript{2}O and washed sequentially with 10% aq. HCl, 1 N aq. NaOH and brine. The organic extract was then dried over Na\textsubscript{2}SO\textsubscript{4} and filtered and the filtrate concentrated \textit{in vacuo} to afford a colorless oil. Purification of the crude product thus obtained by way of
flash chromatography (SiO$_2$, 7:3 (v/v) Hex : EtOAc $\rightarrow$ EtOAc) afforded the title compound as a colorless oil.

Step 10: *trans*-N-Cyclopropyl-4-(1-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-N-[[3-[[2-(methylxy)ethyl]oxy]-5-[[3-(methylxy)propyl]phenyl]methyl]-3-piperidinocarboxamide

To a CH$_2$Cl$_2$ solution (0.05 M) of fr<ms-l,l-dimethylethyl 3-[[cyclopropyl[[3-[[2-(methylxy)ethyl]oxy]-5-[[3-(methylxy)propyl]phenyl]methyl]amino]carbonyl]-4-(1-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-l-piperidinocarboxylate (1 eq.) from the previous step was added HCl (4.0 M dioxane solution, 30 eq.). The resulting solution was stirred at RT for 4 h. Following the removal of the volatiles in vacuo, the resulting residue was directly loaded onto a SiO$_2$ column packed with 94:6 (v/v)

CH$_2$Cl$_2$: 2.0 M NH$_3$ in MeOH. Elution with the same solvent system furnished the title compound as a white froth. MS (ESI+, M+H): 562. $^1$H NMR (CDCl$_3$): $\delta$ (ppm) 0.85 (brs, 2H), 0.93-1.03 (br m, 2H), 1.55-1.63 (m, IH), 1.79 (brs, IH), 1.72-1.81 (m, 2H), 1.96-2.00 (br m, IH), 2.42-2.52 (m, 2H), 2.65-2.73 (br m, IH), 2.90-2.99 (m, 2H), 3.23-3.40 (m, 7H), 3.43 (s, 3H), 3.63-3.78 (m, 7H), 3.84-3.91 (m, IH), 3.93-3.98 (m, IH), 4.18 (d, $J$ = 14 Hz, IH), 4.48 (d, $J$ = 14 Hz, IH), 6.37 (s, 1H), 6.42 (s, IH), 6.56 (s, IH), 6.61 (s, IH), 7.28 (d, $J$ = 7 Hz, IH), 7.37 (d, $J$ = 7 Hz, IH), 7.59 (t, $J$ = 7 Hz, IH), 8.08 (d, $J$ = 7 Hz, IH). Human Renin IC$_{50}$ (buffer): 13 nM. Human Renin IC$_{50}$ (plasma): 39 nM.

**Example 2**

*trans*-4-(7-Chloro-1-methyl-2-oxo-1,2-dihydro-4-quinolinyl)-IV-cyclopropyl-IV-((3-[[2-(methylxy)ethyl]oxy]-5-[[3-(methylxy)propyl]phenyl]methyl)-3-piperidinocarboxamide

Prepared according to the procedure described in **Example 2** except the hydrogenation step (step 5) is omitted. The title compound was obtained as a white froth. MS (ESI+, M+H): 596. $^1$H NMR (CDCl$_3$): $\delta$ (ppm) 0.82-0.89 (brt, 2H), 0.93-1.00 (br m, 2H), 1.55-1.63 (m, IH), 1.79 (brs, IH), 1.72-1.80 (m, 2H), 1.90-1.94 (brm, IH), 2.42-2.52 (m, 2H), 2.62-2.68 (brm, IH), 2.86-2.95 (m, 2H), 3.23-3.25 (m, IH), 3.32-3.38 (m, 6H), 3.42 (s, 3H), 3.62-3.78 (m, 7H), 3.82-3.86 (m, IH), 3.92-3.96 (m, IH), 4.23 (d, $J$ = 14 Hz, IH), 4.38 (d, $J$ = 14 Hz, IH), 6.33 (s, IH), 6.41 (s, IH), 6.58 (s, IH), 6.59 (s, IH), 7.21 (d, $J$ = 7 Hz, IH), 7.36 (s, IH), 8.01 (d, $J$ = 1 Viz, IH). Human Renin IC$_{50}$ (buffer): 2.2 nM. Human Renin IC$_{50}$ (plasma): 7.6 nM.
Assays Demonstrating Biological Activity

Inhibition of human recombinant renin

Human recombinant renin (Proteos) in 50 mM MOPS pH 7.4, 100 mM NaCl, 0.002% Tween 20 at a final concentration of 100 pM is incubated with inhibitors from a 50 fold concentrated DMSO solution and 6 µM of an internally-quench fluorescent peptide: DNP-Lys-His-Pro-Phe-His-Leu-Val-Ile-His-D,L-Amp (SEQ ID NO: 1); Paschalidou K. et al, Biochem J., 2004, 382, 1031). The reactions take place in a Costar 384 well black plate (#3573) at 37°C for 3 hours. Fluorescence is measured at times 0 and 3 hours with a SpectraMax Gemini EM reader set at an excitation wavelength of 328 nm and at an emission wavelength of 388 nm. Background fluorescence at t=0 is subtracted from the measurement at t=3 hours. Inhibitory activity of the compounds is expressed as IC 50.

Inhibition of renin in human plasma

Human EDTA-collected plasma is rapidly thawed in warm water and centrifuged at 2900 g for 15 minutes at 4°C. The supernatant is collected and recombinant renin (Proteos) is added at a final concentration of 1 nM. The plasma is transferred to a Costar black 384 well plate (#3573). Renin inhibitors are added from a 17.5 fold concentrated DMSO solution and pre-incubated at 37°C for 10 minutes. The internally-quench fluorescent peptide QXL520™-Lys-His-Pro-Phe-His-Leu-Val-Ile-His-Lys (5-FAM) (Anaspec), SEQ ID NO: 2, is diluted in 3M Tris pH 7.2, 200 mM EDTA and added to the plasma. The final concentrations are: 6 µM substrate, 342 mM Tris, 23 mM EDTA. The plate is incubated at 37°C for 1 hour. The plate is read in a SpectraMax Gemini EM reader set at an excitation wavelength of 490 nm and an emission wavelength of 520 nM at times 0 and 1 hour. Background fluorescence at t=0 is subtracted from the measurement at t=1 hour. Inhibitory activity of the compounds is expressed as IC50.

In vivo animal model

Female double transgenic rats were purchased from RCC Ltd, Füllingsdorf, Switzerland. All animals were maintained under identical conditions and had free access to normal pelleted rat chow and water. Rats were initially treated with enalapril (1 mg/kg/day) during 2 months. After approximately two weeks following cessation of enalapril treatment the double transgenic rats become hypertensive and reach mean arterial blood pressures in the range of 160-170 mmHg.

Transmitter implantation - The rats were anaesthetised with a mixture of 90 mg/kg Ketamin-HCl (Ketavet, Parke-Davis, Berlin FRG) and 10 mg/kg xylazin (Rompun, Bayer, Leverkusen, FRG) i.p. The pressure transmitter was implanted under aseptic conditions into the peritoneal cavity with the sensing catheter placed in the descending aorta below the renal arteries.
pointing upstream. The transmitter was sutured to the abdominal musculature and the skin closed.

*Telemetry-System* - Telemetry units were obtained from Data Sciences (St. Paul, MN). The implanted sensor consisted of a fluid-filled catheter (0.7 mm diameter, 8 cm long; model TA1 1PA-C40) connected to a highly stable low-conductance strain-gauge pressure transducer, which measured the absolute arterial pressure relative to a vacuum, and a radio-frequency transmitter. The tip of the catheter was filled with a viscous gel that prevents blood reflux and was coated with an antithrombogenic film to inhibit thrombus formation. The implants (length = 2.5 cm, diameter = 1.2 cm) weighted 9 g and have a typical battery life of 6 months. A receiver platform (RPC-I, Data Sciences) connected the radio signal to digitized input that was sent to a dedicated personal computer (Compaq, deskpro). Arterial pressures were calibrated by using an input from an ambient-pressure reference (APR-I, Data Sciences). Systolic, mean and diastolic blood pressure was expressed in millimeter of mercury (mmHg).

*Hemodynamic measurements* - Double transgenic rats with implanted pressure transmitters were dosed by oral gavage with vehicle or 10 mg/kg of the test substance (n=6 per group) and the mean arterial blood pressure was continuously monitored. The effect of the test substance is expressed as maximal decrease of mean arterial pressure (MAP) in the treated group versus the control group.

**Results**

Compounds in accordance herewith were active, exhibiting an IC50 < 1 µM in both renin buffer and plasma assays.
WHAT IS CLAIMED IS:

1. A compound of formula I, or a pharmaceutically acceptable salt thereof having formula (I)

\[
\begin{align*}
&\text{wherein:} \\
&R_1 \text{ is selected from the group consisting of: } \text{C}_1-\text{C}_6-\text{alkyl}, \text{C}_3-\text{C}_6 \text{ cycloalkyl, C}_2-\text{C}_6 \text{ alkenyl, C}_3-\text{C}_6 \text{ cycloalkenyl and C}_2-\text{C}_6 \text{ alkynyl, wherein each of the foregoing is optionally} \\
&\text{substituted with } 1-3 \text{ halogens and/or C}_1-\text{C}_5 \text{ alkoxy;} \\
&V \text{ is selected from the group consisting of: hydrogen, halogen, C}_1-\text{C}_6 \text{ alkyl, C}_3-\text{C}_6 \text{ cycloalkyl, C}_2-\text{C}_6 \text{ alkenyl, C}_3-\text{C}_6 \text{ cycloalkenyl, C}_2-\text{C}_6 \text{ alkynyl, cyano and C}_1-\text{C}_5 \text{ alkoxy,} \\
&\text{wherein said alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl and alkoxy are} \\
&\text{optionally substituted with } 1-3 \text{ substituents, each of which is independently selected from the} \\
&\text{group consisting of: halogen, C}_1-\text{C}_5 \text{ alkyl, C}_2-\text{C}_5 \text{ alkenyl, cyano and C}_1-\text{C}_5 \text{ alkoxy, wherein} \\
&\text{each of the foregoing alkyl, alkenyl and alkoxy substituents is optionally substituted with } 1-3 \text{ halogens;} \\
&W \text{ is cyclopropyl, unsubstituted or mono-, di-, tri-, tetra- or penta-substituted with} \\
&\text{fluorine;} \\
&X \text{ is selected from the group consisting of: OR.2, R.2, -(C}_1-\text{C}_5 \text{ alkylen})-(O)0-1\text{-aryl and} \\
&-(C}_1-\text{C}_5 \text{ alkylen})-(O)0-1\text{-heteroaryl,} \\
&\text{wherein R.2 is selected from the group consisting of: hydrogen, C}_1-\text{C}_5 \text{ alkyl, C}_3-\text{C}_8 \text{ cycloalkyl, C}_2-\text{C}_5 \text{ alkenyl, C}_3-\text{C}_8 \text{ cycloalkenyl, C}_2-\text{C}_5 \text{ alkynyl, C}_1-\text{C}_5 \text{cyano, -(C}_1-\text{C}_5 \text{ alkylen})-O-R3, -(C}_1-\text{C}_5 \text{ alkylen})-N(-R3)-C(=O)-(C}_1-\text{C}_5 \text{ alkyl), -(C}_1-\text{C}_5 \text{ alkylen})-C(=O)-N(-R3)-(C}_1-\text{C}_5 \text{ alkyl), -(C}_1-\text{C}_5 \text{ alkylen})-O-C(=O)-N(-R3)-(C}_1-\text{C}_5 \text{ alkyl), -(C}_1-\text{C}_5 \text{ alkylen})-S-(C}_1-\text{C}_5 \text{ alkyl), -(C}_1-\text{C}_5 \text{ alkylen})-S(=O)-(C}_1-\text{C}_5 \text{ alkyl) and -(C}_1-\text{C}_5 \text{ alkylen})-S(=O)2-(C}_1-\text{C}_5 \text{ alkyl),}
\end{align*}
\]
wherein R2, except hydrogen, is optionally substituted with 1-3 substituents, independently selected from the group consisting of: di-, tri-, tetra- or hexa-substituted each substituent of which is independently selected from: C1-C5 alkyl optionally substituted with 1-3 halogens.

(8) C1-C8 cycloalkyl optionally substituted with 1-3 halogens.

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(9) C2-C5 alkenyl optionally substituted with 1-3 halogens,
(10) C3-C8 cycloalkenyl optionally substituted with 1-3 halogens,
(11) C2-C5 alkylnyl optionally substituted with 1-3 halogens,
(12) C1-C5 alkoxy optionally substituted with 1-3 halogens,
(13) cyano,
(14) Ci-C5-cyano optionally substituted with 1-3 halogens,
(15) -OCF3,
(16) -C(R5)3,
(17) -(C1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(18) -N(R4)-(C 1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(19) -Q-(C 1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(20) -S-(C1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(21) -S(=O)-(C1-Cs alkylene)-OR6 optionally substituted with 1-3 halogens,
(22) -S(=O)2-(C1-C5 alkylene)-OR6 optionally substituted with 1-3 halogens,
(23) -(C1-C5 alkylene)-N(R4)-(C1-C5 alkylene)-R6 optionally substituted with 1-3 halogens,
(24) -(C1-C5 alkylene)-N(R4)-(C1-C5 alkylene)-R6 optionally substituted with 1-3 halogens,
(25) -(C1-C5 alkylene)-N(R4)(R6) optionally substituted with 1-3 halogens,
(26) -O-(C1-C5 alkylene)-C(R4)2-C(=O)OR6 optionally substituted with 1-3 halogens,
(27) -(C1-C5 alkylene)-C(R4)2-C(=O)OR6 optionally substituted with 1-3 halogens,
(28) -O-(C1-C5 alkylene)-morpholine optionally substituted with 1-3 halogens,
(29) -OC(=O)-morpholine,
(30) -SR6,
(31) -S(=O)-R6,
(32) -S(=O)2-R6
(33) -N(R4)(R6),
(34) -(C1-C5 alkylene)-C(R4)2-(R6) optionally substituted with 1-3 halogens,
(35) -(R7)0-1R8,
(36) C2-C5 alkenyl-OR6 optionally substituted with 1-3 halogens,
(37) C2-C5 alkylnyl-OR6 optionally substituted with 1-3 halogens,
(38) -(Ci-Cs alkylene)-C(=O)-(Ci-C5 alkylene)-R6 optionally substituted with 1-3 halogens,
(40) -(C1-C5 alkylene)-C(=O)-N(R4)(R6) optionally substituted with 1-3 halogens,
(41) -(C1-C5 alkylene)-O-C(=O)-N(R4)(R6) optionally substituted with 1-3 halogens,
(42) -(C1-C5 alkylene)-SR6 optionally substituted with 1-3 halogens,
(43) -(C1-C5 alkylene)-S(=O)-R6 optionally substituted with 1-3 halogens, and
(44) -(C1-C5 alkylene)-S(=O)2-R6 optionally substituted with 1-3 halogens,
wherein R4 is selected from the group consisting of: hydrogen, C1-C6 alkyl, C3-
C8 cycloalkyl, C2-C6 alkenyl, C3-C8 cycloalkenyl and C2-C6 alkynyl, wherein each of the
foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynyl substituents is optionally
substituted with 1-3 halogens,
wherein R5 is halogen,
wherein R6 is selected from the group consisting of: hydrogen, C1-C6 alkyl, C3-
C8 cycloalkyl, C2-C6 alkenyl, C3-C8 cycloalkenyl and C2-C6 alkynyl, wherein each of the
foregoing alkyl, cycloalkyl, alkenyl, cycloalkenyl and alkynyl substituents is optionally substituted
with 1-3 halogens,
wherein R7 is selected from the group consisting of: -C(H)(OH)-, -CC(=O)-,
-OC(=O)-, -C(=O)O-, -O-, -OC(=O)O-, C1-C5 alkylene, C2-C5 alkenylene, -N(R4)-, -S-,
-S(=O)-, -S(=O)2-, -N(R4)-C(=O)-, -C(=O)-N(R4)-, -OC(=O)-N(R4)-, -N(R4)-C(=O)O-,
-N(R4)-S(=O)2- and -S(=O)2-N(R4)-, wherein each of the foregoing alkylene and alkynylene
substituents is optionally substituted with 1-3 halogens, and wherein R4 is defined above, and
wherein R8 is a five- or six-membered saturated or unsaturated heterocyclic or
carbocyclic ring which is optionally mono-, di-, tri-, tetra- or penta-substituted, wherein each
substituent is independently selected from the group consisting of: halogen, -OH, -SR4,
-N(R4)(R6), C1-C5 alkyl, C3-C8 cycloalkyl, C2-C5 alkenyl, C3-C6 cycloalkenyl, C2-C5
alkynyl, C1-C5 alkoxy, cyano and C1-C5-cyano, wherein said heterocyclic ring contains from 1
to 3 heteroatoms, independently selected from N, O and S, wherein each N is optionally in the
form of an oxide and each S is optionally is in the form of an oxide selected from the group
consisting of: S(=O) and S(=O)2, and wherein R4 and R6 are defined above.

2. The compound of Claim 1 wherein R1 is -CH3.
3. The compound of Claim 1 wherein V is hydrogen or halogen.
4. The compound of Claim 1 wherein V is hydrogen or chlorine.
5. The compound of Claim 1 wherein W is cyclopropyl.
6. The compound of Claim 1 wherein X is H.

7. The compound of Claim 1 wherein (Z)ₙ is -CH₂- or a bond.

8. The compound of Claim 1 wherein (Z)ₙ is -CH₂-.

9. The compound of Claim 1 wherein:
   R₁ is C₁-C₂ alkyl optionally substituted with 1-3 halogens,
   V is hydrogen or chlorine,
   W is cyclopropyl,
   X is hydrogen, and
   Z is -CH₂-.

10. The compound of Claim 1 wherein Y is

    optionally mono-, di-, tri-, tetra-, or penta-substituted as described in Claim 1.

11. The compound of Claim 10 having formula (II)

    wherein:

    A is selected from the group consisting of:
    (1) hydrogen,
    (2) halogen,
    (3) C₁-C₅ alkyl,
    (4) C₁-C₅ alkoxy, and
    (5) -S-(CH₂)₀-3-CH₃,

    wherein (3) and (4) are optionally substituted with 1-3 halogens,
B is selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- (3) C1-C5 alkyl,
- (4) C1-C5 alkoxy,
- (5) -OH,
- (6) -CF3,
- (7) -C(=O)-CH3,
- (8) -O-(C1-C5 alkylene)-O-cyclopropyl,
- (9) -CKC1-C5 alkylene)-O-(CH2)0-2-CH3,
- (10) -(C1-C5 alkylene)-O-(CH2)0-2-CH3,
- (11) -OC(=O)-morpholine,
- (12) -CKC1-C5 alkylene)-N(H)-C(=O)-O-(CH2)0-2-CH3,
- (13) -O-(C1-C5 alkylene)-C(CH3)2-C(=O)OH,
- (14) -O-(C1-C5 alkylene)-C(CH3)2-C(=O)OCH3,
- (15) 
  \[
  \begin{array}{c}
  \text{4} \\
  \text{1} \\
  \text{2} \\
  \text{3} \\
  \end{array}
  
  \begin{array}{c}
  \text{2} \\
  \text{1} \\
  \text{3} \\
  \text{4} \\
  \end{array}
  \]

and

- (16) 
  \[
  \begin{array}{c}
  \text{2} \\
  \text{1} \\
  \text{3} \\
  \text{4} \\
  \end{array}
  
  \begin{array}{c}
  \text{2} \\
  \text{1} \\
  \text{3} \\
  \text{4} \\
  \end{array}
  \]

wherein (3), (4), (8), (9), (10), (12), (13), (14), (15) and (16) are optionally substituted with 1-3 halogens.

C is selected from the group consisting of:

- (1) hydrogen,
- (2) C1-C5 alkyl optionally substituted with 1-3 halogens, and
- (3) C1-C5 alkoxy optionally substituted with 1-3 halogens, and

D is selected from the group consisting of:

- (1) hydrogen,
- (2) halogen,
- (3) C1-C5 alkyl,
- (4) C1-C5 alkoxy,
- (5) C1-C5-cyano,
- (6) C2-C5 alkenylene-O-(CH2)0-2-CH3,
- (7) -(C1-C5 alkylene)-N(H)-C(=O)-O-(CH2)0-2-CH3,
- (8) -(C1-C5 alkylene)-N(H)-C(=O)-(CH2)0-2-CH3,
(9) -(C1-C5 alkylene)-O-CHF2,
(10) -(C1-C5 alkylene)-O-(CH2)0-2-CH3,
(11) -O-(C1-C5 alkylene)-O-(CH2)0-2-CH3,
(12) -(C1-C5 alkylene)-OH,
(13) -S-(C1-C5 alkylene)-OH,
(14) -SCF3
(15) -N(H)-(C1-C5 alkylene)-O-(CH2)0-2-CH3, and

\[
\begin{align*}
\text{wherein F, G and H are independently selected from the group consisting of:} \\
\text{hydrogen, halogen and C1-C3 alkyl optionally substituted with 1-3 halogens, and} \\
\text{wherein R.9 is selected from the group consisting of: -CH2-, -C(H)(OH)- and} \\
\text{-C(=O)-},
\end{align*}
\]

wherein (3), (4), (5), (6), (7), (8), (9), (10), (11), (12), (13) and (15) are optionally substituted with 1-3 halogens.

12. The compound of Claim 1 which is:

Ex. 2

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable salt of the stereoisomer thereof.

13. The compound of Claim 1 which is:

Ex. 3
or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable salt of the stereoisomer thereof.

14. The following compound:

Ex. 2

or a pharmaceutically acceptable salt thereof.

15. The following compound:

Ex. 3

or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising an effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

17. Use of a compound according to Claim 1 for the manufacture of a medicament for the treatment or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system.
18. A method for the treatment or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intraocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system, comprising the administration to a patient of a pharmaceutically active amount of a compound according to Claim 1.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC: C07D 401/04 (2006.01), A61K 31/4709 (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC: C07D 401/04, A61K 31/4709

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN (chemical structure search), Delphion and Canadian Patent Database with keywords: piperidin* and renin

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>CA 2608685 (Ehara et al.) 30 November 2006 (30-1 1-2006) entire document</td>
<td>1-18</td>
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</table>

[X ] Further documents are listed in the continuation of Box C. [X ] 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
'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
'O' document referring to an oral disclosure, use, exhibition or other means
'P' document published prior to the international filing date but later than the priority date claimed
'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
'X' document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
'Y' document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
'&' document member of the same patent family

Date of the actual completion of the international search
13 July 2009 (13-07-2009)

Date of mailing of the international search report
12 August 2009 (12-08-2009)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C1 14 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001-819-953-2476

Authorized officer
Irena Wisniewska 819- 953-8589

Form PCT/ISA/210 (second sheet ) (July 2008) Page 4 of 5
**INTERNATIONAL SEARCH REPORT**

**Box No. II**  
**Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim Nos 18  
   because they relate to subject matter not required to be searched by this Authority, namely

   Claim 18 is directed to a method for treatment of the human or animal body which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effect or purpose/use of the product defined in claim 18.

2. [X] Claim Nos 1-11 and 16-18 (in part)  
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically

   The claims relate to an extremely large number of possible compounds. Therefore, the search has been carried out for compounds of formula I representing a generalization of examples given in the description.

3. [ ] Claim Nos  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 64(a).

**Box No. III**  
**Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claim Nos.

**Remark on Protest**  
[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.
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