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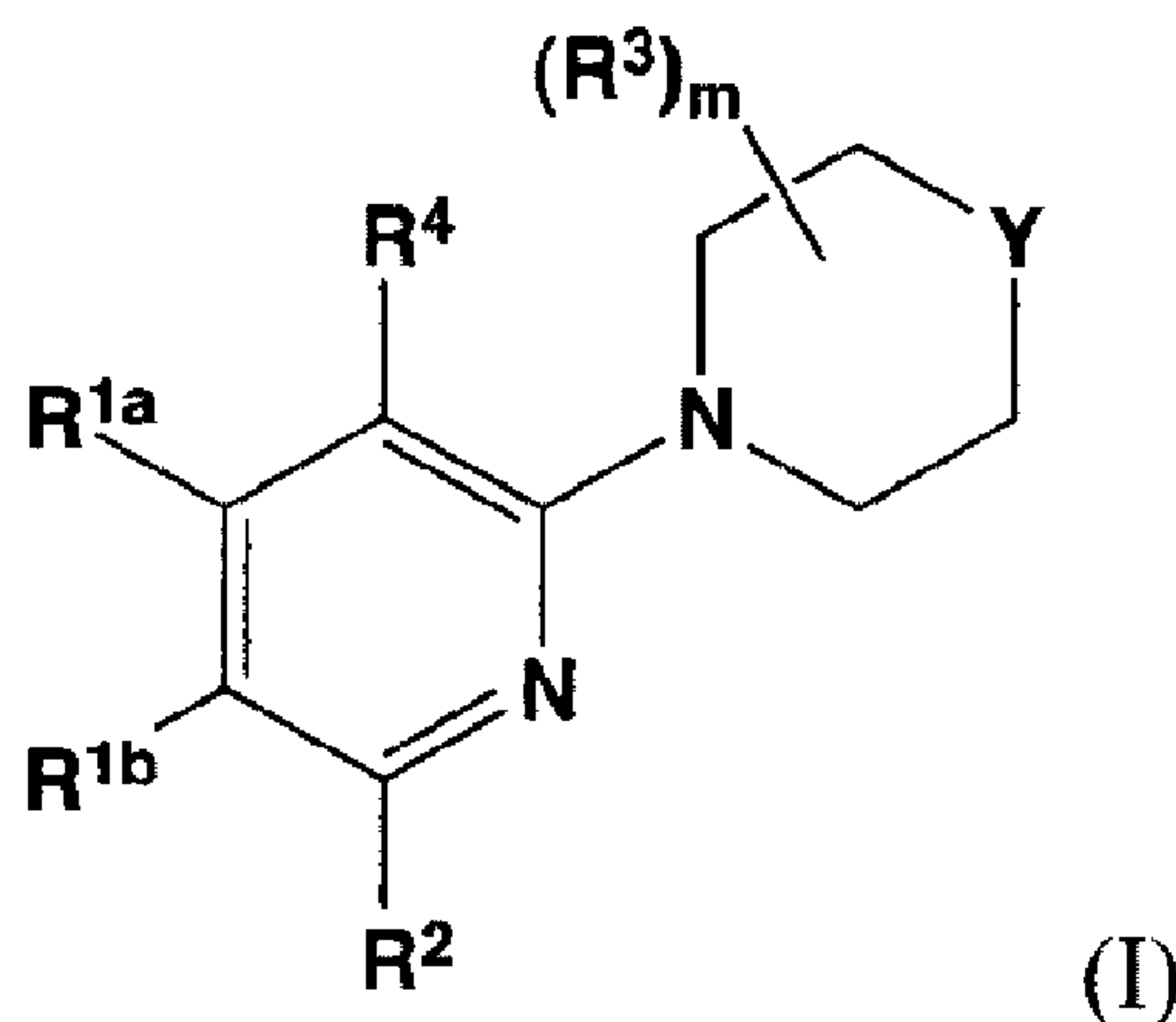
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(72) Inventeurs/Inventors:
CAO, SHELDON, US;
POPOVICI-MULLER, JANETA, US;
SALITURO, FRANCESCO G., US;
SAUNDERS, JEFFREY O., US;
TRAVINS, JEREMY, US;
...

(73) Propriétaire/Owner:
AGIOS PHARMACEUTICALS, INC., US

(74) Agent: GOWLING WLG (CANADA) LLP

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(54) Title: THERAPEUTICALLY ACTIVE COMPOSITIONS AND THEIR METHODS OF USE



(57) Abrégé/Abstract:

Provided are compounds with the following structure, formula (I) pharmaceutically acceptable salts thereof, use of those compounds for treating cancer and pharmaceutical compositions comprising those compounds.

(72) Inventeurs(suite)/Inventors(continued): TAN, XUEFEI, CN; YAN, SHUNQI, US; YE, ZHIXIONG, US

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(71) **Applicant** (*for all designated States except US*): **AGIOS PHARMACEUTICALS, INC.** [US/US]; 38 Sydney Street, Cambridge, MA 02139 (US).

(72) **Inventors; and**

(75) **Inventors/Applicants** (*for US only*): **CAO, Sheldon** [US/US]; 10521 Sand Crab Place, San Diego, CA 92130 (US). **POPOVICI-MULLER, Janeta** [US/US]; 5 Beaver Brook Road, Waltham, MA 02452 (US). **SALITURO, Francesco G.** [US/US]; 25 Baker Drive, Marlborough, MA 01752 (US). **SAUNDERS, Jeffrey** [US/US]; 117 Seymour Street, Concord, MA 01742 (US). **TAN, Xuefei** [US/CN]; Suite A1202, Zhubang 2000 Chier Business Center, No.100 Ba Li Zhuang Xi Li, Chaoyang District, Beijing 100025 (CN). **TRAVINS, Jeremy** [US/US]; 380
- Township Line Rd, Downingtown, PA 19335 (US). **YAN, Shunqi** [US/US]; 55 Stepping Stone, Irvine, CA 92603 (US). **YE, Zhixiong** [US/US]; 3 Banff St., West Windsor, NJ 08550 (US).

(74) **Agent:** **NTD PATENT AND TRADEMARK AGENCY LIMITED**; 10th Floor, Block A, Investment Plaza, 27 Jinrongdajie, Xicheng District, Beijing 100033 (CN).

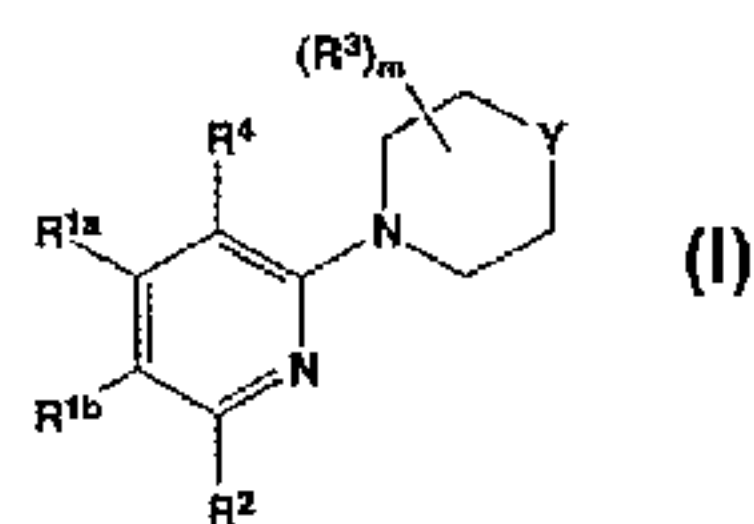
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(54) **Title:** THERAPEUTICALLY ACTIVE COMPOSITIONS AND THEIR METHODS OF USE



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DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

THERAPEUTICALLY ACTIVE COMPOSITIONS AND THEIR METHODS OF USE

CLAIM OF PRIORITY

This application claims priority from Chinese Patent Application No. CN 201110172169.1, filed June 17, 2011, U.S.S.N. 61/509,071, filed July 18, 2011 and U.S.S.N. 61/584,210, filed January 6, 2012.

BACKGROUND OF INVENTION

Isocitrate dehydrogenases (IDHs) catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate (*i.e.*, α -ketoglutarate). These enzymes belong to two distinct subclasses, one of which utilizes NAD(+) as the electron acceptor and the other NADP(+). Five isocitrate dehydrogenases have been reported: three NAD(+)-dependent isocitrate dehydrogenases, which localize to the mitochondrial matrix, and two NADP(+)-dependent isocitrate dehydrogenases, one of which is mitochondrial and the other predominantly cytosolic. Each NADP(+)-dependent isozyme is a homodimer.

IDH1 (isocitrate dehydrogenase 1 (NADP+), cytosolic) is also known as IDH; IDP; IDCD; IDPC or PICD. The protein encoded by this gene is the NADP(+)-dependent isocitrate dehydrogenase found in the cytoplasm and peroxisomes. It contains the PTS-1 peroxisomal targeting signal sequence. The presence of this enzyme in peroxisomes suggests roles in the regeneration of NADPH for intraperoxisomal reductions, such as the conversion of 2, 4-dienoyl-CoAs to 3-enoyl-CoAs, as well as in peroxisomal reactions that consume 2-oxoglutarate, namely the α -hydroxylation of phytanic acid. The cytoplasmic enzyme serves a significant role in cytoplasmic NADPH production.

The human IDH1 gene encodes a protein of 414 amino acids. The nucleotide and amino acid sequences for human IDH1 can be found as GenBank entries NM_005896.2 and NP_005887.2 respectively. The nucleotide and amino acid sequences for IDH1 are also described in, *e.g.*, Nekrutenko *et al.*, Mol. Biol. Evol. 15:1674-1684(1998); Geisbrecht *et al.*, J. Biol. Chem. 274:30527-30533(1999); Wiemann *et al.*, Genome Res. 11:422-435(2001); The MGC Project Team, Genome Res. 14:2121-2127(2004); Lubec *et al.*, Submitted (DEC-2008) to

UniProtKB; Kullmann *et al.*, Submitted (JUN-1996) to the EMBL/GenBank/DDBJ databases; and Sjoebloom *et al.*, Science 314:268-274(2006).

Non-mutant, *e.g.*, wild type, IDH1 catalyzes the oxidative decarboxylation of isocitrate to α -ketoglutarate thereby reducing NAD^+ (NADP^+) to NADP (NADPH), *e.g.*, in the forward reaction:

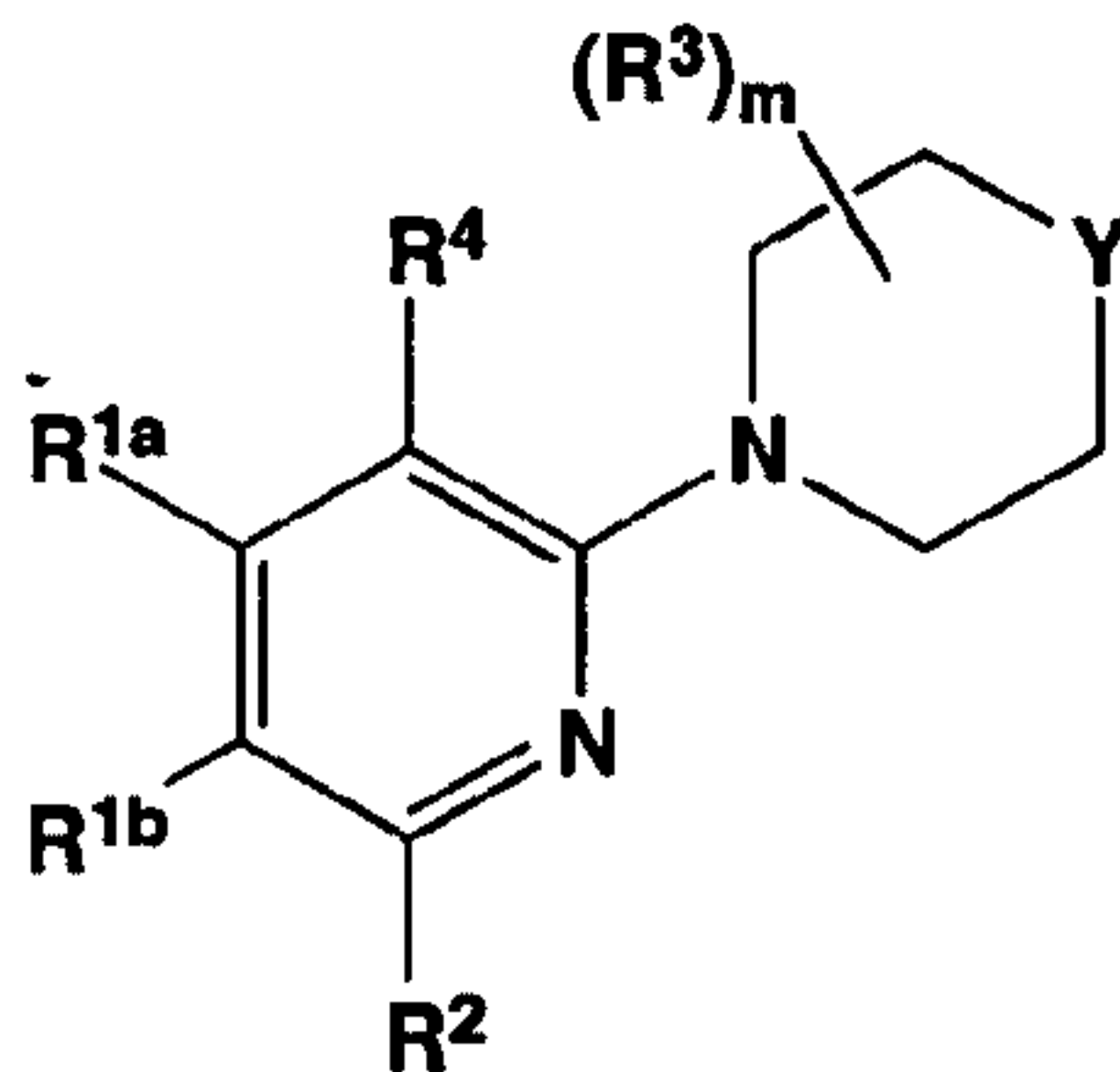


It has been discovered that mutations of IDH1 present in certain cancer cells result in a new ability of the enzyme to catalyze the NADPH-dependent reduction of α -ketoglutarate to *R*(-)-2-hydroxyglutarate (2HG). 2HG is not formed by wild-type IDH1. The production of 2HG is believed to contribute to the formation and progression of cancer (Dang, L et al, Nature 2009, 462:739-44).

The inhibition of mutant IDH1 and its neoactivity is therefore a potential therapeutic treatment for cancer. Accordingly, there is an ongoing need for inhibitors of IDH1 mutants having alpha hydroxyl neoactivity.

SUMMARY OF INVENTION

Described herein are compounds of Structural Formula I:



(I) or a pharmaceutically acceptable salt thereof, wherein:

Y is $-\text{N}(\text{R}^5)-$, $-\text{N}(\text{R}^5)-\text{CH}_2-$, $-\text{CH}_2-\text{N}(\text{R}^5)-$, or $-\text{CH}(\text{R}^5)-$;

each R^{1a} and R^{1b} is independently hydrogen, $-\text{C}_1-\text{C}_4$ alkyl, $-\text{N}(\text{R}^7)(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{N}(\text{R}^7)(\text{C}_1-\text{C}_4 \text{ alkyl})$, aryl, heteroaryl, heterocyclyl, $-\text{C}(\text{O})\text{N}(\text{R}^7)-\text{aryl}$, $-\text{N}(\text{R}^7)\text{C}(\text{O})-\text{aryl}$, $-(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{aryl}$, $-(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{heteroaryl}$, $-\text{O}-(\text{C}_0-\text{C}_4 \text{ alkylene})-\text{aryl}$, $-\text{O}-(\text{C}_0-\text{C}_4 \text{ alkylene})-\text{heteroaryl}$, $-\text{O}-(\text{C}_0-\text{C}_4 \text{ alkylene})-\text{heterocyclyl}$, $-\text{O}-(\text{C}_0-\text{C}_4 \text{ alkylene})-\text{carbocyclyl}$, $-\text{N}(\text{R}^7)-\text{aryl}$, $-\text{N}(\text{R}^7)-\text{heteroaryl}$, $-\text{N}(\text{R}^9)-\text{aryl}$, $-\text{N}(\text{R}^9)-\text{heteroaryl}$, $-\text{O}-(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{N}(\text{R}^7)\text{C}(\text{O})\text{O}-(\text{C}_1-\text{C}_4 \text{ alkylene})-\text{aryl}$, or $-\text{N}(\text{R}^9)-\text{C}(\text{O})-(\text{C}_2-\text{C}_4 \text{ alkenyl})$ wherein:

at least one of R^{1a} and R^{1b} is not hydrogen or methyl;
 any alkylene moiety present in R^{1a} or R^{1b} is optionally substituted with OH or F;
 each R^7 is independently selected from hydrogen and C_1 - C_4 alkyl; and
 any aryl, carbocyclyl, heteroaryl, or heterocyclyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from -G-L-M, halo, -NO₂, C_1 - C_6 alkyl, -C≡N, =O, -CF₃ and -OCF₃;

G is a bond or a bivalent C_1 - C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by -NR⁸-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO₂-, -C(=S)-, -C(=NR⁸)-, -N=N-, or -C(=N₂)-

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, -NR⁸-, -N(R⁸)C(O)-, -C(O)N(R⁸)-, -N(R⁸)SO₂-, SO₂N(R⁸)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO₂-, -C(=S)-, -C(=NR⁸)-, -N=N-, or -C(=N₂)-

M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -D-E, oxo, NO₂, halogen, CN, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl;

D is a covalent bond or a bivalent C_1 - C_6 saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of D are optionally and independently replaced by -NR⁸-, -S-, -O-, -C(O)-, -SO-, or -SO₂-;

E is hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, or C_2 - C_6 alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

each R⁸ is independently hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, -S(O)₂- C_2 - C_4 alkenyl, - C_1 - C_6 alkoxy, or an optionally substituted group selected from phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^2 is selected from phenyl, a 3-7 membered cycloalkyl, C_2 - C_4 alkyl, or CF_3 , wherein the phenyl or cycloalkyl is optionally substituted with a substituent selected from methyl or fluoro;

each R^3 is independently selected from halo, $-(C_1-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-C_1-C_4$ fluoroalkyl, $-C(O)-O-(C_1-C_4 \text{ alkyl})$, -phenyl, -heteroaryl, C_3 - C_7 cycloalkyl, $-CH_2-N(C_1-C_4 \text{ alkyl})_2$, $C(O)-N-(C_1-C_4 \text{ alkyl})_2$, $-C(O)-NH-(C_1-C_4 \text{ alkyl})$, $-C_1-C_4$ alkyl optionally substituted with one or more halo or $-OH$, or two R^3 's are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or fused phenyl is optionally substituted with 1 to 2 methyl;

R^4 is selected from hydrogen, $-CN$, halo, C_1-C_4 alkoxy, $-CH_2NH(C_1-C_4 \text{ alkyl})$, C_2-C_4 alkenyl, C_2-C_4 alkynyl, $-(C_1-C_4 \text{ alkyl})-O-(C_1-C_4 \text{ alkyl})$, C_1-C_4 fluoroalkyl, $C(O)-N-(C_1-C_4 \text{ alkyl})_2$, $-C(O)-NH-(C_1-C_4 \text{ alkyl})$, $-C(O)-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-OH$, $-S(O)_2-(C_1-C_4 \text{ alkyl})$, and a 5-membered heteroaryl;

R^5 is selected from: $-C(O)-(C_1-C_5 \text{ alkyl})$, $-C(O)-(C_2-C_6 \text{ alkenyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})-Q$, $-C(O)-(C_1-C_4 \text{ alkenylene})-Q$, $-C(O)-(C_0-C_2 \text{ alkylene})-N(R^6)-(C_0-C_2 \text{ alkylene})-Q$, $-C(O)-O-(C_0-C_2 \text{ alkylene})-Q$, $-C(O)-(C_1-C_2 \text{ alkylene})-O-(C_0-C_2 \text{ alkylene})-Q$, $-C(O)-C(O)-Q$, $-S(O)_2-Q$, $-C(O)-(C_1-C_4 \text{ alkylene})-O-C(O)-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_4 \text{ alkylene})-C(O)-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-N(R^6)-(C_1-C_4 \text{ alkylene})-O-C(O)-(C_1-C_4 \text{ alkyl})$, $-C(O)-N(R^6)-(C_1-C_4 \text{ alkylene})-C(O)-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})-N(R^6)-(C_1-C_6 \text{ alkyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})N(R^6)-(C_2-C_6 \text{ alkynyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})-N(R^6)-(C_2-C_6 \text{ alkenyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})-N(R^6)-(C_0-C_2 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_2 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_2 \text{ alkylene})-C(O)C(O)N(R^6)(C_1-C_4 \text{ alkyl})$, $-C(O)-O-(C_1-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-(C_0-C_4 \text{ alkylene})-O-C(O)-(C_1-C_4 \text{ alkyl})$, $-(C_0-C_4 \text{ alkylene})-C(O)-O-(C_1-C_4 \text{ alkyl})$, $-(C_0-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_2 \text{ alkylene})-S(O)_{0-2}-(C_1-C_4 \text{ alkyl})$, $-S(O)_2-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_4 \text{ alkylene})-C(O)C(O)N(R^6)(C_1-C_6 \text{ alkyl})$, $-C(O)-(C_1-C_4 \text{ alkylene})-N(R^6)S(O)_2-(C_1-C_6 \text{ alkyl})$, or $-C(O)-(C_1-C_4 \text{ alkylene})-N(R^6)S(O)_2Q$, wherein:

any alkylene moiety present in R^5 is optionally substituted with OCH_3 , OH or F ;

any terminal methyl moiety present in R^5 is optionally replaced with $-CH_2OH$, CF_3 , $-CH_2F$, $-CH_2Cl$, $C(O)CH_3$, $C(O)CF_3$, CN , $-OCH_3$, $-C(O)H$, $-OP(O)(OH)_2$, $-OP(O)(C_1-C_4 \text{ alkoxy})_2$ or CO_2H ;

each R^6 is independently selected from hydrogen and methyl;

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3 substituents independently selected from C₁-C₄ alkyl optionally substituted with -OH, C₁-C₄ alkoxy, -C(O)O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-(C₁-C₄ alkoxy), -CN, -OH, fluoro, chloro, and bromo;

R⁹ is selected from aryl and heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one or more substituents selected from -G-L-M, halo, C₁-C₆ alkyl, -C≡N, =O, -CF₃ and -OCF₃; and

m is 0, 1, 2 or 3.

The compound of formula I inhibits mutant IDH1, particularly mutant IDH1 having alpha hydroxyl neoactivity. Also described herein are pharmaceutical compositions comprising a compound of formula I or a salt thereof and methods of using such compositions to treat cancers characterized by the presence of a mutant IDH1.

DETAILED DESCRIPTION OF THE INVENTION

This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of “including,” “comprising,” or “having,” “containing”, “involving”, and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

Definitions:

The term “halo” or “halogen” refers to any radical of fluorine, chlorine, bromine or iodine.

The term “alkyl” refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms. For example, C₁-C₁₂ alkyl indicates that the group may have from 1 to 12 (inclusive) carbon atoms in it. The term “haloalkyl” refers to an alkyl in which one or more hydrogen atoms are replaced by halo, and includes alkyl moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkyl). The terms “arylalkyl” or “aralkyl” refer to an alkyl moiety in which an alkyl hydrogen atom is replaced by

an aryl group. Aralkyl includes groups in which more than one hydrogen atom has been replaced by an aryl group. Examples of “arylalkyl” or “aralkyl” include benzyl, 2-phenylethyl, 3-phenylpropyl, 9-fluorenyl, benzhydryl, and trityl groups.

The term “alkylene” refers to a divalent alkyl, e.g., $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{CH}_2\text{CH}_2-$ and $-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2-$.

The term “alkenyl” refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms and having one or more double bonds. Examples of alkenyl groups include, but are not limited to, allyl, propenyl, 2-butenyl, 3-hexenyl and 3-octenyl groups. One of the double bond carbons may optionally be the point of attachment of the alkenyl substituent.

The term “alkynyl” refers to a straight or branched hydrocarbon chain containing 2-12 carbon atoms and characterized in having one or more triple bonds. Examples of alkynyl groups include, but are not limited to, ethynyl, propargyl, and 3-hexynyl. One of the triple bond carbons may optionally be the point of attachment of the alkynyl substituent.

The term “alkoxy” refers to an $-\text{O}-\text{alkyl}$ radical. The term “haloalkoxy” refers to an alkoxy in which one or more hydrogen atoms are replaced by halo, and includes alkoxy moieties in which all hydrogens have been replaced by halo (e.g., perfluoroalkoxy).

The term “aryl” refers to a fully aromatic monocyclic, bicyclic, or tricyclic hydrocarbon ring system. Examples of aryl moieties are phenyl, naphthyl, and anthracenyl. Unless otherwise specified, any ring atom in an aryl can be substituted by one or more substituents.

The term “carbocyclyl” refers to a non-aromatic, monocyclic, bicyclic, or tricyclic hydrocarbon ring system. Carbocyclyl groups include fully saturated ring systems (e.g., cycloalkyls), and partially saturated ring systems.

The term “cycloalkyl” as employed herein includes saturated cyclic, bicyclic, tricyclic, or polycyclic hydrocarbon groups having 3 to 12 carbons. Any ring atom can be substituted (e.g., by one or more substituents). Examples of cycloalkyl moieties include, but are not limited to, cyclopropyl, cyclohexyl, methylcyclohexyl, adamantyl, and norbornyl.

The term “heteroaryl” refers to a fully aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (or the oxidized forms such as N^+-O^- , $\text{S}(\text{O})$ and $\text{S}(\text{O})_2$).

The term "heterocyclyl" refers to a nonaromatic, 3-10 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S (or the oxidized forms such as N^+-O^- , $S(O)$ and $S(O)_2$). The heteroatom may optionally be the point of attachment of the heterocyclyl substituent. Examples of heterocyclyl include, but are not limited to, tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino, pyrrolinyl, pyrimidinyl, and pyrrolidinyl. Heterocyclyl groups include fully saturated ring systems, and partially saturated ring systems.

Bicyclic and tricyclic ring systems containing one or more heteroatoms and both aromatic and non-aromatic rings where the point of attachment from the ring system to the rest of the molecule is through a non-aromatic ring are considered to be heterocyclyl groups. Bicyclic or tricyclic ring systems where an aryl or a heteroaryl is fused to a carbocyclyl or heterocyclyl and the point of attachment from the ring system to the rest of the molecule is through an aromatic ring are considered to be aryl or heteroaryl groups.

Aryl, heteroaryl, carbocyclyl (including cycloalkyl), and heterocyclyl groups, either alone or a part of a group (e.g., the aryl portion of an aralkyl group), are optionally substituted at one or more substitutable atoms with, unless specified otherwise, substituents independently selected from: halo, $-C\equiv N$, C_1 - C_4 alkyl, $=O$, $-OR^b$, $-OR^{b'}$, $-SR^b$, $-SR^{b'}$, $-(C_1-C_4 \text{ alkyl})-N(R^b)(R^b)$, $-(C_1-C_4 \text{ alkyl})-N(R^b)(R^{b'})$, $-N(R^b)(R^b)$, $-N(R^b)(R^{b'})$, $-O-(C_1-C_4 \text{ alkyl})-N(R^b)(R^b)$, $-O-(C_1-C_4 \text{ alkyl})-N(R^b)(R^{b'})$, $-(C_1-C_4 \text{ alkyl})-O-(C_1-C_4 \text{ alkyl})-N(R^b)(R^b)$, $-(C_1-C_4 \text{ alkyl})-O-(C_1-C_4 \text{ alkyl})-N(R^b)(R^{b'})$, $-C(O)-N(R^b)(R^b)$, $-(C_1-C_4 \text{ alkyl})-C(O)-N(R^b)(R^b)$, $-(C_1-C_4 \text{ alkyl})-C(O)-N(R^b)(R^{b'})$, $-OR^{b'}$, $R^{b'}$, $-C(O)(C_1-C_4 \text{ alkyl})$, $-C(O)R^{b'}$, $-C(O)N(R^{b'})(R^b)$, $-N(R^b)C(O)(R^b)$, $-N(R^b)C(O)(R^{b'})$, $-N(R^b)SO_2(R^b)$, $-SO_2N(R^b)(R^b)$, $-N(R^b)SO_2(R^{b'})$, and $-SO_2N(R^b)(R^{b'})$, wherein any alkyl substituent is optionally further substituted with one or more of $-OH$, $-O-(C_1-C_4 \text{ alkyl})$, halo, $-NH_2$, $-NH(C_1-C_4 \text{ alkyl})$, or $-N(C_1-C_4 \text{ alkyl})_2$;

each R^b is independently selected from hydrogen, and $-C_1-C_4$ alkyl; or

two R^b 's are taken together with the nitrogen atom to which they are bound to form a 4- to 8-membered heterocyclyl optionally comprising one additional heteroatom selected from N, S, and O; and

each R^b is independently selected from C₃-C₇ carbocyclyl, phenyl, heteroaryl, and heterocyclyl, wherein one or more substitutable positions on said phenyl, cycloalkyl, heteroaryl or heterocycle substituent is optionally further substituted with one or more of -(C₁-C₄ alkyl), -(C₁-C₄ fluoroalkyl), -OH, -O-(C₁-C₄ alkyl), -O-(C₁-C₄ fluoroalkyl), halo, -NH₂, -NH(C₁-C₄ alkyl), or -N(C₁-C₄ alkyl)₂.

Heterocyclyl groups, either alone or as part of a group, are optionally substituted on one or more any substitutable nitrogen atom with oxo, -C₁-C₄ alkyl, or fluoro-substituted C₁-C₄ alkyl.

The term “substituted” refers to the replacement of a hydrogen atom by another group.

As used herein, the term “elevated levels of 2HG” means 10%, 20% 30%, 50%, 75%, 100%, 200%, 500% or more 2HG then is present in a subject that does not carry a mutant IDH1 allele. The term “elevated levels of 2HG” may refer to the amount of 2HG within a cell, within a tumor, within an organ comprising a tumor, or within a bodily fluid.

The term “bodily fluid” includes one or more of amniotic fluid surrounding a fetus, aqueous humour, blood (*e.g.*, blood plasma), serum, Cerebrospinal fluid, cerumen, chyme, Cowper's fluid, female ejaculate, interstitial fluid, lymph, breast milk, mucus (*e.g.*, nasal drainage or phlegm), pleural fluid, pus, saliva, sebum, semen, serum, sweat, tears, urine, vaginal secretion, or vomit.

As used herein, the terms “inhibit” or “prevent” include both complete and partial inhibition and prevention. An inhibitor may completely or partially inhibit the intended target.

The term “treat” means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease/disorder (*e.g.*, a cancer), lessen the severity of the disease/disorder (*e.g.*, a cancer) or improve the symptoms associated with the disease/disorder (*e.g.*, a cancer).

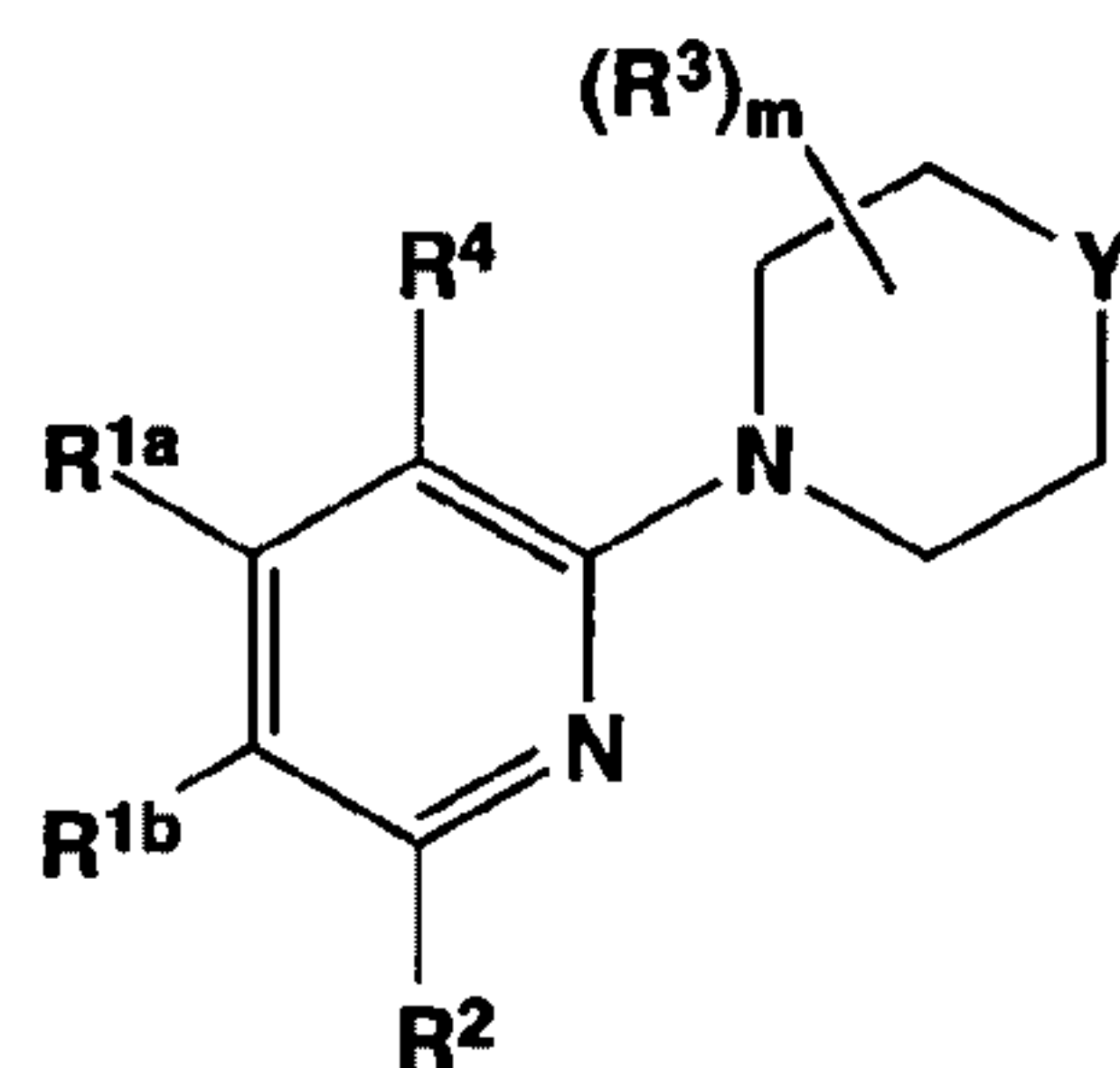
As used herein, an amount of a compound effective to treat a disorder, or a “therapeutically effective amount” refers to an amount of the compound which is effective, upon single or multiple dose administration to a subject, in treating a cell, or in curing, alleviating, relieving or improving a subject with a disorder beyond that expected in the absence of such treatment.

As used herein, the term “subject” is intended to include human and non-human animals. Exemplary human subjects include a human patient (referred to as a patient) having a disorder,

e.g., a disorder described herein or a normal subject. The term “non-human animals” of the invention includes all vertebrates, e.g., non-mammals (such as chickens, amphibians, reptiles) and mammals, such as non-human primates, domesticated and/or agriculturally useful animals, e.g., sheep, dog, cat, cow, pig, etc.

Compounds

Provided is a compound of Structural Formula I:



(I) or a pharmaceutically acceptable salt thereof, wherein:

Y is $-N(R^5)-$, $-N(R^5)-CH_2-$, $-CH_2-N(R^5)-$, or $-CH(R^5)-$;

each R^{1a} and R^{1b} is independently hydrogen, $-C_1-C_4$ alkyl, $-N(R^7)(C_1-C_4 \text{ alkylene})-$, $N(R^7)(C_1-C_4 \text{ alkyl})$, aryl, heteroaryl, heterocyclyl, $-C(O)N(R^7)-\text{aryl}$, $-N(R^7)C(O)-\text{aryl}$, $-(C_1-C_4 \text{ alkylene})-\text{aryl}$, $-(C_1-C_4 \text{ alkylene})-\text{heteroaryl}$, $-O-(C_0-C_4 \text{ alkylene})-\text{aryl}$, $-O-(C_0-C_4 \text{ alkylene})-\text{heteroaryl}$, $-O-(C_0-C_4 \text{ alkylene})-\text{heterocyclyl}$, $-O-(C_0-C_4 \text{ alkylene})-\text{carbocyclyl}$, $-N(R^7)-\text{aryl}$, $-N(R^7)-\text{heteroaryl}$, $-N(R^9)-\text{aryl}$, $-N(R^9)-\text{heteroaryl}$, $-O-(C_1-C_4 \text{ alkylene})-N(R^7)C(O)O-(C_1-C_4 \text{ alkylene})-\text{aryl}$, or $-N(R^9)-C(O)-(C_2-C_4 \text{ alkenyl})$ wherein:

at least one of R^{1a} and R^{1b} is not hydrogen or methyl;

any alkylene moiety present in R^{1a} or R^{1b} is optionally substituted with OH or F;

each R^7 is independently selected from hydrogen and C_1-C_4 alkyl; and

any aryl, carbocyclyl, heteroaryl, or heterocyclyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from $-G-L-M$, halo, $-NO_2$, C_1-C_6 alkyl, $-C\equiv N$, $=O$, $-CF_3$ and $-OCF_3$;

G is a bond or a bivalent C_1-C_6 saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by $-NR^8-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-SO-$, $-SO_2-$, $-C(=S)-$, $-C(=NR^8)-$, $-N=N-$, or $-C(=N_2)-$;

L is a covalent bond or a bivalent C₁₋₈ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, -NR⁸-, -N(R⁸)C(O)-, -C(O)N(R⁸)-, -N(R⁸)SO₂-, SO₂N(R⁸)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO₂-, -C(=S)-, -C(=NR⁸)-, -N=N-, or -C(=N₂)-

M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -D-E, oxo, NO₂, halogen, CN, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

D is a covalent bond or a bivalent C₁-C₆ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of D are optionally and independently replaced by -NR⁸-, -S-, -O-, -C(O)-, -SO-, or -SO₂-;

E is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

each R⁸ is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C₁-C₆ alkoxy, -S(O)₂-C₂-C₄ alkenyl, or an optionally substituted group selected from phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R² is selected from phenyl, a 3-7 membered cycloalkyl, C₂-C₄ alkyl, or CF₃, wherein the phenyl or cycloalkyl is optionally substituted with a substituent selected from methyl or fluoro;

each R³ is independently selected from halo, -(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl)-, C₁-C₄ fluoroalkyl, -C(O)-O-(C₁-C₄ alkyl), -phenyl, -heteroaryl, C₃-C₇ cycloalkyl, -CH₂-N(C₁-C₄ alkyl)₂, C(O)-N-(C₁-C₄ alkyl)₂, -C(O)-NH-(C₁-C₄ alkyl), -C₁-C₄ alkyl optionally substituted with one or more halo or -OH, or two R³s are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or fused phenyl is optionally substituted with 1 to 2 methyl;

R⁴ is selected from hydrogen, -CN, halo, C₁-C₄ alkoxy, -CH₂NH(C₁-C₄ alkyl), C₂-C₄ alkenyl, C₂-C₄ alkynyl, -(C₁-C₄ alkyl)-O-(C₁-C₄ alkyl), C₁-C₄ fluoroalkyl, C(O)-N-(C₁-C₄ alkyl)₂, -C(O)-NH-(C₁-C₄ alkyl), -C(O)-O-(C₁-C₄ alkyl), -C(O)-OH, -S(O)₂-(C₁-C₄ alkyl), and a 5-membered heteroaryl;

R^5 is selected from: $-C(O)-(C_1-C_5 \text{ alkyl})$, $-C(O)-(C_2-C_6 \text{ alkenyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})-Q$, $-C(O)-(C_1-C_4 \text{ alkenylene})-Q$, $-C(O)-(C_0-C_2 \text{ alkylene})-N(R^6)-(C_0-C_2 \text{ alkylene})-Q$, $-C(O)-O-(C_0-C_2 \text{ alkylene})-Q$, $-C(O)-(C_1-C_2 \text{ alkylene})-O-(C_0-C_2 \text{ alkylene})-Q$, $-C(O)-C(O)-Q$, $-S(O)_2-Q$, $-C(O)-(C_1-C_4 \text{ alkylene})-O-C(O)-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_4 \text{ alkylene})-C(O)-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-N(R^6)-(C_1-C_4 \text{ alkylene})-O-C(O)-(C_1-C_4 \text{ alkyl})$, $-C(O)-N(R^6)-(C_1-C_4 \text{ alkylene})-C(O)-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})-N(R^6)-(C_1-C_6 \text{ alkyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})N(R^6)-(C_2-C_6 \text{ alkynyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})-N(R^6)-(C_2-C_6 \text{ alkenyl})$, $-C(O)-(C_0-C_2 \text{ alkylene})-N(R^6)-(C_0-C_2 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_2 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_2 \text{ alkylene})-C(O)C(O)N(R^6)(C_1-C_4 \text{ alkyl})$, $-C(O)-O-(C_1-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-(C_0-C_4 \text{ alkylene})-O-C(O)-(C_1-C_4 \text{ alkyl})$, $-(C_0-C_4 \text{ alkylene})-C(O)-O-(C_1-C_4 \text{ alkyl})$, $-(C_0-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_2 \text{ alkylene})-S(O)_{0.2}-(C_1-C_4 \text{ alkyl})$, $-S(O)_2-(C_1-C_4 \text{ alkyl})$, $-C(O)-(C_1-C_4 \text{ alkylene})-C(O)C(O)N(R^6)(C_1-C_6 \text{ alkyl})$, $-C(O)-(C_1-C_4 \text{ alkylene})-N(R^6)S(O)_2-(C_1-C_6 \text{ alkyl})$, or $-C(O)-(C_1-C_4 \text{ alkylene})-N(R^6)S(O)_2Q$, wherein:

any alkylene moiety present in R^5 is optionally substituted with OCH_3 , OH or F ;
 any terminal methyl moiety present in R^5 is optionally replaced with $-CH_2OH$, CF_3 , $-CH_2F$, $-CH_2Cl$, $C(O)CH_3$, $C(O)CF_3$, CN , $-OCH_3$, $-C(O)H$, $-OP(O)(OH)_2$, $-OP(O)(C_1-C_4 \text{ alkoxy})_2$ or CO_2H ;

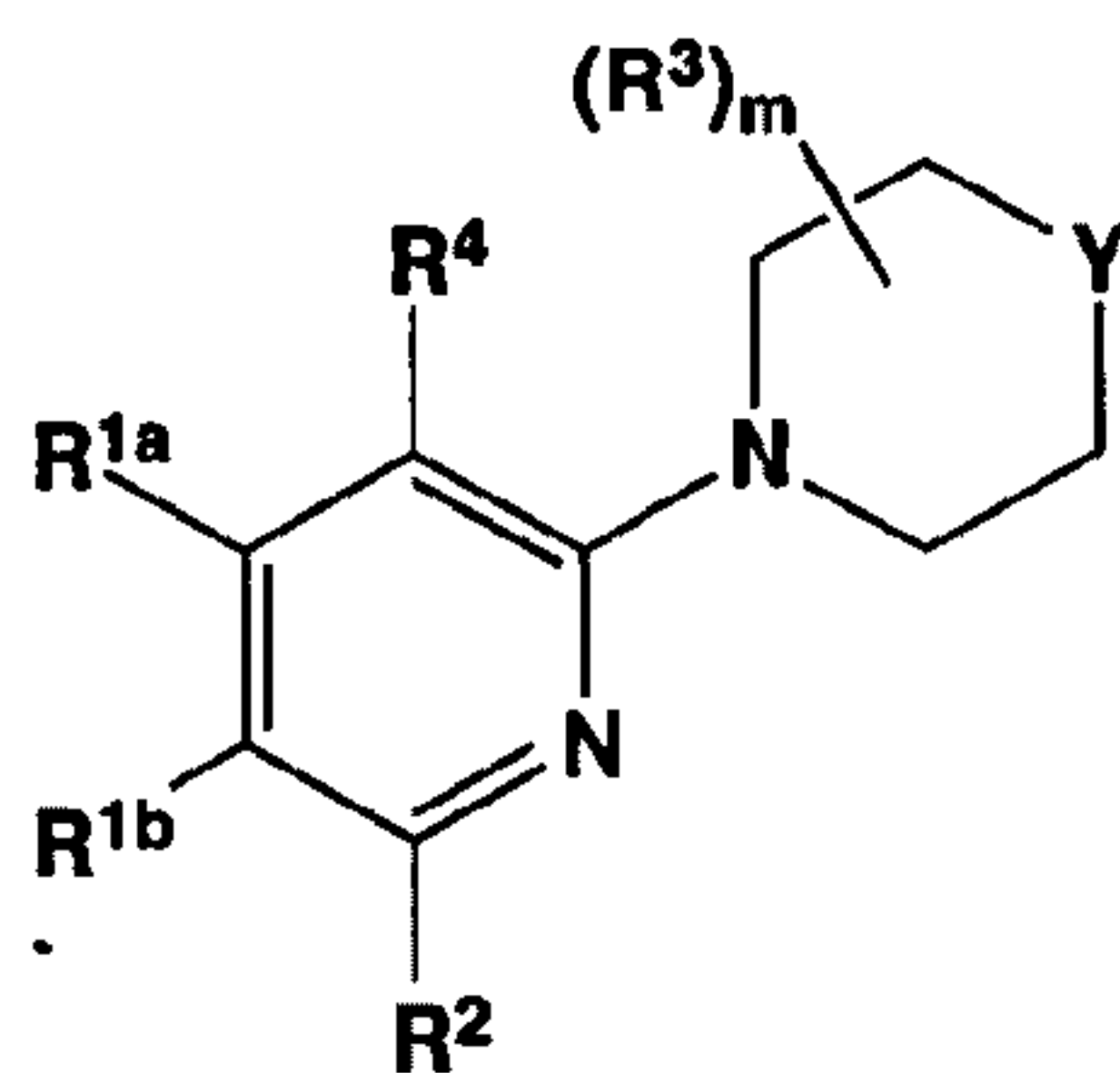
each R^6 is independently selected from hydrogen and methyl;

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3 substituents independently selected from C_1-C_4 alkyl optionally substituted with $-OH$, C_1-C_4 alkoxy, $-C(O)O-(C_1-C_4 \text{ alkyl})$, $-(C_1-C_4 \text{ alkylene})-(C_1-C_4 \text{ alkoxy})$, $-CN$, $-OH$, fluoro, chloro, and bromo;

R^9 is selected from aryl, and heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one or more substituents selected from $-G-L-M$, halo, C_1-C_6 alkyl, $-C\equiv N$, $=O$, $-CF_3$ and $-OCF_3$; and

m is 0, 1, 2 or 3.

In some embodiments, provided is a compound of Structural Formula I:



(I) or a pharmaceutically acceptable salt thereof, wherein:

Y is -N(R⁵)- or -CH(R⁵)-;

each R^{1a} and R^{1b} is independently hydrogen, -C₁-C₄ alkyl, -N(R⁷)(C₁-C₄ alkylene)-N(R⁷)(C₁-C₄ alkyl), aryl, heteroaryl, heterocyclyl, -C(O)N(R⁷)-aryl, -N(R⁷)C(O)-aryl, -(C₁-C₄ alkylene)-aryl, -(C₁-C₄ alkylene)-heteroaryl, -O-(C₁-C₄ alkylene)-aryl, -O-(C₁-C₄ alkylene)-heteroaryl, -O-(C₁-C₄ alkylene)-heterocyclyl, -N(R⁷)-aryl, or -N(R⁷)-heteroaryl, wherein:

at least one of R^{1a} and R^{1b} is not hydrogen or methyl;

any alkylene moiety present in R^{1a} or R^{1b} is optionally substituted with OH or F;

each R⁷ is independently selected from hydrogen and C₁-C₄ alkyl; and

any aryl, heteroaryl, or heterocyclyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from -G-L-M, halo, C₁-C₆ alkyl, -C≡N, =O, -CF₃ and -OCF₃;

G is a bond or a bivalent C₁-C₆ saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by -NR⁸-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO₂-, -C(=S)-, -C(=NR⁸)-, -N=N-, or -C(=N₂)-;

L is a covalent bond or a bivalent C₁₋₈ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, -NR⁸-, -N(R⁸)C(O)-, -C(O)N(R⁸)-, -N(R⁸)SO₂-, SO₂N(R⁸)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO₂-, -C(=S)-, -C(=NR⁸)-, -N=N-, or -C(=N₂)-; M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from -D-E, oxo, NO₂, halogen, CN, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

D is a covalent bond or a bivalent C₁-C₆ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of D are optionally and independently replaced by-NR⁸-, -S-, -O-, -C(O)-, -SO-, or-SO₂-;

E is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

each R⁸ is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or an optionally substituted group selected from phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R² is selected from phenyl, a 3-7 membered cycloalkyl, and C₂-C₄ alkyl, wherein the phenyl or cycloalkyl is optionally substituted with a substituent selected from methyl or fluoro;

each R³ is independently selected from -C₁-C₄ alkyl, -(C₁-C₄ alkyl)-O-(C₁-C₄ alkyl), -C₁-C₄ fluoroalkyl, -C(O)-O-(C₁-C₄ alkyl), -phenyl, -heteroaryl, C₃-C₇ cycloalkyl, -CH₂-N(C₁-C₄ alkyl)₂, C(O)-N-(C₁-C₄ alkyl)₂, and -C(O)-NH-(C₁-C₄ alkyl), or

or two R³s are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or fused phenyl is optionally substituted with 1 to 2 methyl groups;

R⁴ is selected from hydrogen, -CN, halo, C₁-C₄ alkoxy, -CH₂NH(C₁-C₄ alkyl), C₂-C₄ alkenyl, C₂-C₄ alkynyl, -(C₁-C₄ alkyl)-O-(C₁-C₄ alkyl), C₁-C₄ fluoroalkyl, C(O)-N-(C₁-C₄ alkyl)₂, -C(O)-NH-(C₁-C₄ alkyl), -C(O)-O-(C₁-C₄ alkyl), -C(O)-OH, -S(O)₂-(C₁-C₄ alkyl), and a 5-membered heteroaryl;

R⁵ is selected from: -C(O)-(C₁-C₄alkyl), -C(O)-(CH₂)₀₋₂-Q, -C(O)-(CH₂)₀₋₂-N(R⁶)-(CH₂)₀₋₂-Q, -C(O)-O-(CH₂)₁₋₂-Q, -C(O)-(CH₂)₁₋₂-O-(CH₂)₀₋₂-Q, -C(O)-C(O)-Q, -S(O)₂-Q, -C(O)-(C₁-C₄ alkylene)-O-C(O)-(C₁-C₄ alkyl), -C(O)-(C₁-C₄ alkylene)-C(O)-O-(C₁-C₄ alkyl), -C(O)-N(R⁶)-(C₁-C₄ alkylene)-O-C(O)-(C₁-C₄ alkyl), -C(O)-N(R⁶)-(C₁-C₄ alkylene)-C(O)-O-(C₁-C₄ alkyl), -C(O)-(CH₂)₀₋₂-N(R⁶)-(C₁-C₆ alkyl), -C(O)-(CH₂)₀₋₂-N(R⁶)-(C₂-C₆ alkynyl), -C(O)-(CH₂)₀₋₂-N(R⁶)-(C₂-C₆ alkenyl), -C(O)-(CH₂)₀₋₂-N(R⁶)-(CH₂)₀₋₂-O-(C₁-C₄ alkyl), -C(O)-(CH₂)₁₋₂-O-(C₁-C₄ alkyl), -C(O)-O-(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(CH₂)₀₋₄-O-C(O)-(C₁-C₄ alkyl), -(CH₂)₀₋₄-C(O)-O-(C₁-C₄ alkyl), -(CH₂)₀₋₄-O-(C₁-C₄ alkyl), -C(O)-(CH₂)₁₋₂-S-(C₁-C₄ alkyl), -S(O)₂-(C₁-

C₄ alkyl), -C(O)-(C₁-C₄ alkylene)-C(O)C(O)N(R⁶) (C₁-C₆ alkyl), -C(O)-(C₁-C₄ alkylene)-N(R⁶)S(O)₂-(C₁-C₆ alkyl), and -C(O)-(C₁-C₄ alkylene)-N(R⁶)S(O)₂Q, wherein:

any alkylene moiety present in R⁵ is optionally substituted with OH or F;

any terminal methyl moiety present in R⁵ is optionally replaced with -CH₂OH, CF₃, -CH₂F, -CH₂Cl, C(O)CH₃, or C(O)CF₃;

each R⁶ is independently selected from hydrogen and methyl;

Q is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3 substituents independently selected from C₁-C₄ alkyl, C₁-C₄ alkoxy, -CN, fluoro, chloro, and bromo; and

m is 0, 1, 2 or 3.

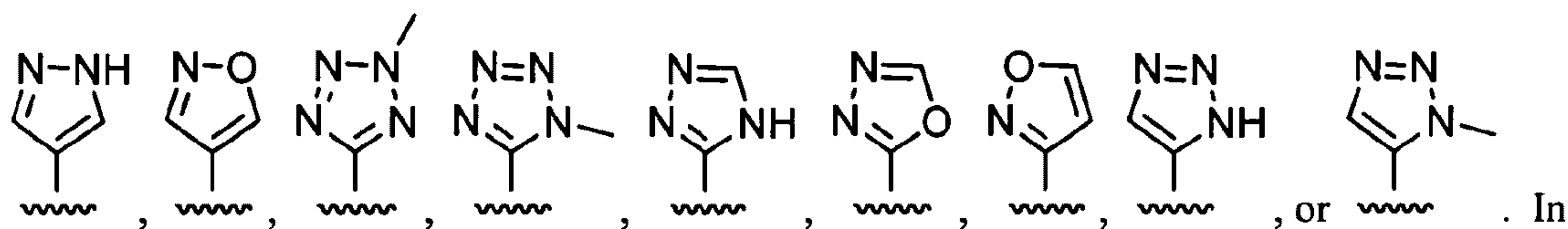
In some embodiments, m is 0, 1 or 2; and each R³, if present, is independently selected from methyl, ethyl, CF₃, isopropyl, cyclopropyl and phenyl. In some embodiments, R³ is methyl or cyclopropyl. In some embodiments, R³ is methyl. In some embodiments, R³ is cyclopropyl.

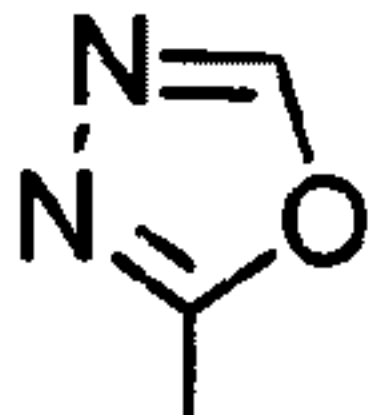
In some embodiments, m is 1. In some embodiments, m is 2.

In some embodiments, m is 1 and R³ is C₃₋₇ cycloalkyl (e.g., cyclopropyl). In some embodiments, m is 1 and R³ is C₁-C₄ (alkyl) (e.g., methyl or isopropyl). In some embodiments, m is 1 and R³ is haloalkyl (e.g., C₁-C₄ fluoroalkyl, e.g., CF₃). In some embodiments, m is 2, one R³ is C₁₋₄ alkyl (e.g., methyl) and the other R³ is halo (e.g., fluoro).

In some embodiments, R⁴ is -CN or -C(O)-O-(C₁-C₄ alkyl). In some embodiments, R⁴ is CN.

In some embodiments, R⁴ is:



some embodiments, R⁴ is .

In some embodiments, Y is -N(R₅)-CH₂- or -CH₂-N(R₅)-; R⁵ is -C(O)-Q and Q is cyclopropyl.

In some embodiments, Y is $-N(R^5)-$; R^5 is $-C(O)R^{10}$; and R^{10} is selected from heteroaryl, aryl, $-CH_2$ -aryl, $-CH_2$ -heteroaryl, and $-(CH_2)_2-O-CH_3$, wherein any aryl or heteroaryl portion of R^8 is optionally substituted with methyl.

In some embodiments, Y is $-N(R^5)-$; R^5 is selected from: $-C(O)-(C_1-C_5$ alkyl), $-C(O)-(C_2-C_6$ alkenyl), $-C(O)-(C_0-C_2$ alkylene)-Q, $-C(O)-(C_1-C_4$ alkenylene)-Q, $-C(O)-(C_0-C_2$ alkylene)- $N(R^6)-(C_0-C_2$ alkylene)-Q, $-C(O)-(C_1-C_2$ alkylene)-O-(C_0-C_2 alkylene)-Q, $-C(O)-(C_1-C_4$ alkylene)-O- $C(O)-(C_1-C_4$ alkyl), $-C(O)-(C_1-C_4$ alkylene)- $C(O)-O-(C_1-C_4$ alkyl), $-C(O)-(C_0-C_2$ alkylene)- $N(R^6)-(C_1-C_6$ alkyl), $-C(O)-(C_0-C_2$ alkylene)- $N(R^6)-(C_2-C_6$ alkynyl), $-C(O)-(C_0-C_2$ alkylene)- $N(R^6)-(C_2-C_6$ alkenyl), $-C(O)-(C_0-C_2$ alkylene)- $N(R^6)-(C_0-C_2$ alkylene)-O-(C_1-C_4 alkyl), $-(C_0$ alkylene)- $C(O)O-(C_1-C_4$ alkyl), $-C(O)-(C_1-C_2$ alkylene)-O-(C_1-C_4 alkyl), $-C(O)-(C_1-C_2$ alkylene)- $C(O)C(O)N(R)(C_1-C_4$ alkyl), or $-C(O)-(C_1-C_4$ alkylene)- $C(O)C(O)N(R^6)(C_1-C_6$ alkyl), wherein:

any alkylene moiety present in R^5 is optionally substituted with OCH_3 , OH or F;

any terminal methyl moiety present in R^5 is optionally replaced with $-CH_2OH$, CF_3 , $-CH_2F$, $-CH_2Cl$, $C(O)CH_3$, $C(O)CF_3$, CN, $-OCH_3$, $-C(O)H$, $-OP(O)(OH)_2$, $-OP(O)(C_1-C_4$ alkoxy) $_2$ or CO_2H ;

each R^6 is independently selected from hydrogen and methyl;

Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally substituted with up to 3 substituents independently selected from C_1-C_4 alkyl optionally substituted with OH, C_1-C_4 alkoxy, $-C(O)O-(C_1-C_4$ alkyl), $-(C_1-C_4$ alkylene)-(C_1-C_4 alkoxy), $-CN$, $-OH$, fluoro, chloro, and bromo.

In some embodiments, Y is $-N(R^5)-$; and R^5 is $-C(O)-(C_1-C_3$ alkyl)-O-(C_1-C_2 alkyl), $-C(O)-Q$, $-C(O)-(C_1-C_5$ alkyl), $-C(O)-(C_1-C_2$ alkylene)-Q, $-C(O)-(C_2-C_4$ alkenyl), $-C(O)O-(C_1-C_4$ alkyl), or $-C(O)-(C_1-C_4$ alkenylene)-Q; wherein: any alkylene moiety present in R^5 is optionally substituted with OH; any terminal methyl moiety present in R^5 is optionally replaced with $-OH$, CF_3 , OCH_3 , $-C(O)H$, $OP(O)(C_1-C_4$ alkoxy) $_2$, or $-OP(O)(OH)_2$ (or a salt thereof, such as a sodium salt); Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally

substituted with one substituent independently selected from C₁-C₄ alkyl optionally substituted with OH, C₁-C₄ alkoxy, -(C₁-C₄ alkylene)-(C₁-C₄ alkoxy), and -OH.

In some embodiments, Y is -N(R⁵)-; and R⁵ is -C(O)-(C₁-C₃ alkyl)-O-(C₁-C₂ alkyl). In some embodiments, Y is -N(R⁵)-; and R⁵ is -C(O)-(CH₂)₂-OCH₃. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-(C₁-C₃ alkyl)-CF₃. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-CH₂-CF₃. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-Q and Q is cyclopropyl, oxetanyl or furanyl. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-CH₂-CH₂OH. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-Q where Q is substituted with C₁₋₄ alkoxy. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-cyclopropyl substituted with C₁₋₄ alkoxy (e.g., ethoxy). In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-OCH₃. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-Q where Q is substituted with (C₁₋₄ alkylene)-OCH₃. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-cyclopropyl substituted with CH₂OCH₃. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-Q where Q is substituted with C₁₋₄ alkyl wherein alkyl is optionally substituted with -OH. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-cyclopropyl substituted with CH₂OH. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-Q where Q is substituted with OH. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-cyclopropyl substituted with OH. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-(C₁₋₄ alkyl)-OH. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-CH₂C(OH)(CH₃)₂. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-CH₂CH(OH)CH₃. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-CH₂CH₂CH₂OH. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-CH₂CH₂OH. In some embodiments, Y is -N(R⁵)-; and R⁵ is -C(O)-(C₁-C₄ alkyl). In some embodiments, Y is -N(R⁵)-; and R⁵ is -C(O)-CH₃. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-(C₁₋₄ alkyl)-(OCH₃)₂. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-CH₂CH₂C(H)(OCH₃)₂. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-(C₁₋₄ alkyl)-C(O)H. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-CH₂CH₂C(O)H. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-C(cyclopropyl)(OH). In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-(C₁₋₄ alkyl)-C(O)OCH₃. In some embodiments, Y is -N(R⁵)-; R⁵ is -C(O)-CH₂CH₂C(O)OCH₃. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-(C₀-C₂ alkylene)-Q. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-(C₀-C₂ alkylene)-Q, where Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl. In some embodiments, Y is -N(R⁵)- and R⁵

is -C(O)-CH₂-oxetanyl, -C(O)-CH₂-azetidinonyl, -C(O)-CH₂-pyrrolidinonyl, -C(O)-CH₂-cyclobutyl, -C(O)-CH₂-cyclopropyl, -C(O)-CH₂CH₂-cyclopropyl, -C(O)-CH₂-tetrahydrofuranyl, -C(O)-CH₂-dihydrofuranone, -C(O)-CH₂CH₂-oxetanyl, -C(O)-CH₂CH₂-furanyl, -C(O)-CH₂-tetrahydrofuranyl, -C(O)-CH₂CH₂-tetrahydrofuranyl or -C(O)-CH₂-cyclopentyl. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-(C₂-C₄ alkenyl)-OH. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-CH=CH-CH₂CH₂OH. In some embodiments, Y is -N(R⁵)- and R⁵ is -(C₀-C₄ alkylene)-C(O)-O-(C₁-C₄ alkyl). In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-O-(t-butyl). In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-(C₁-C₄ alkyl)-OP(O)(C₁-C₄ alkoxy)₂. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-CH₂CH₂CH₂-OP(O)(t-butoxy)₂. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-(C₁-C₄ alkyl)-OP(O)(OH)₂ or a salt thereof, such as a sodium salt. In some embodiments, Y is -N(R⁵)- and R⁵ is -C(O)-CH₂CH₂-OP(O)(t-butoxy)₂. In some embodiments, Y is -N(R⁵)-; and R⁵ is -C(O)-(C₁-C₅ alkyl). In some embodiments, Y is -N(R⁵)-; and R⁵ is -C(O)-pentyl. In some embodiments, Y is -N(R⁵)-; and R⁵ is -C(O)-(C₁-C₄ alkenylene)-Q. In some embodiments, Y is -N(R⁵)-; and R⁵ is -C(O)-CH=cyclobutyl.

In some embodiments, one of R^{1a} or R^{1b} is selected from hydrogen and methyl; and the other of R^{1a} or R^{1b} is selected from isopropyl, -N(CH₃)-(CH₂)₂-NH-CH₃, aryl, heteroaryl, -CH₂-aryl, -CH₂-heteroaryl, -O-CH₂-aryl, and -O-CH₂-heteroaryl; wherein any aryl or heteroaryl of R^{1a} or R^{1b} is optionally substituted with one or more substituents independently selected from alkoxy, OH, halo, C₁-C₆ alkyl, -CF₃, CN, -OC(O)CH₃, and -OCF₃.

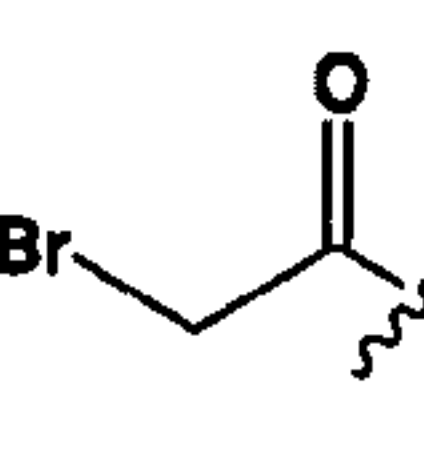
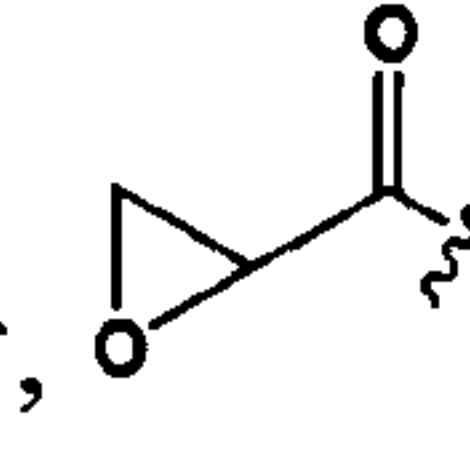
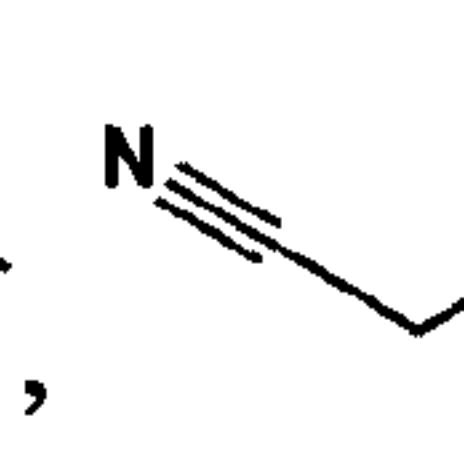
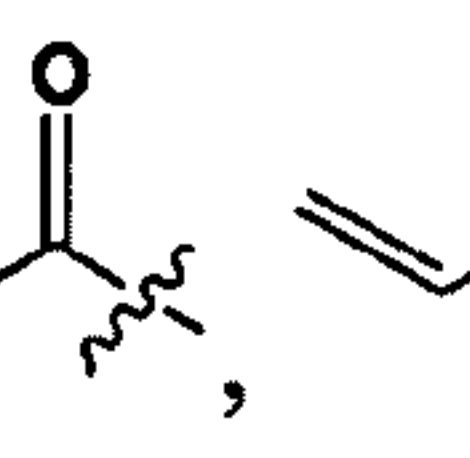
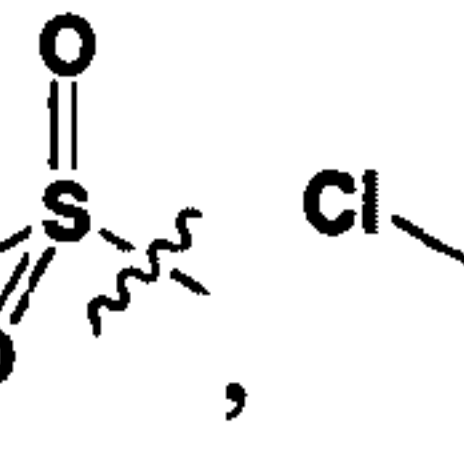
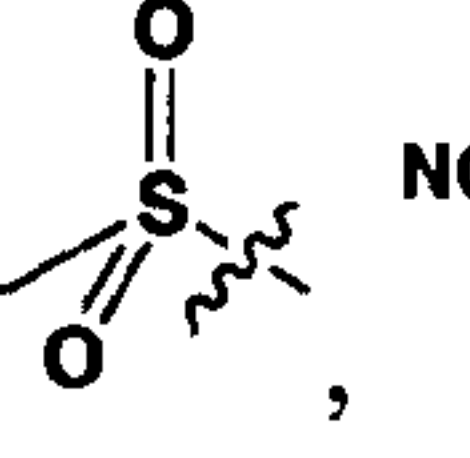
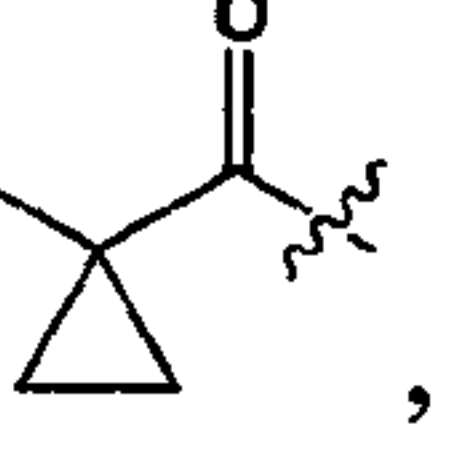
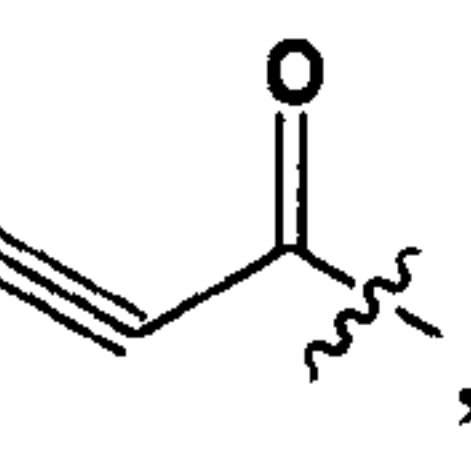
In some embodiments, one of R^{1a} or R^{1b} is selected from hydrogen and methyl; and the other of R^{1a} or R^{1b} is selected from aryl, heteroaryl, heterocyclyl, -(C₁-C₄ alkylene)-aryl, -(C₁-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-aryl, -O-(C₀-C₄ alkylene)-heteroaryl, -N(R⁷)-aryl, -N(R⁷)-heteroaryl, -N(R⁹)-aryl, or -N(R⁹)-heteroaryl, wherein said aryl, heterocyclyl, or heteroaryl is substituted with -G-L-M, CH₃, CN, alkoxy, OH, halo, C₁-C₆ alkyl, -CF₃, -OC(O)CH₃, or -OCF₃.

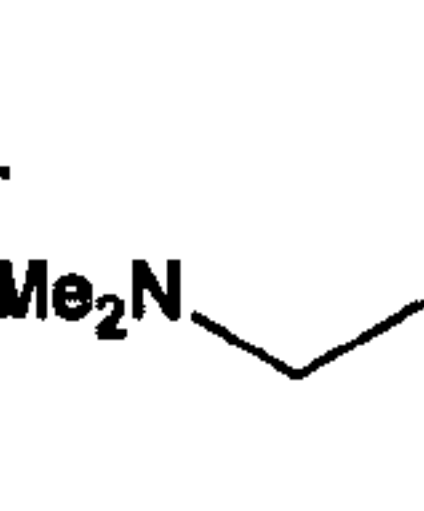
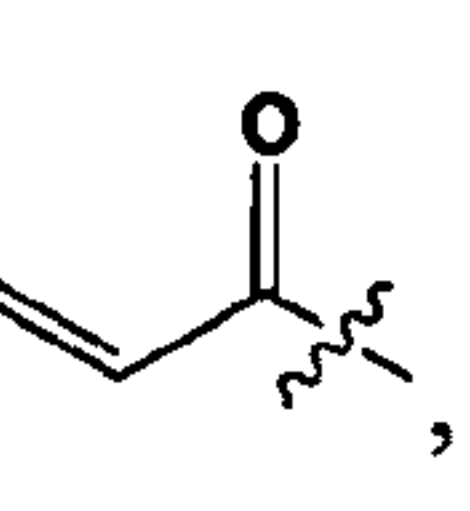
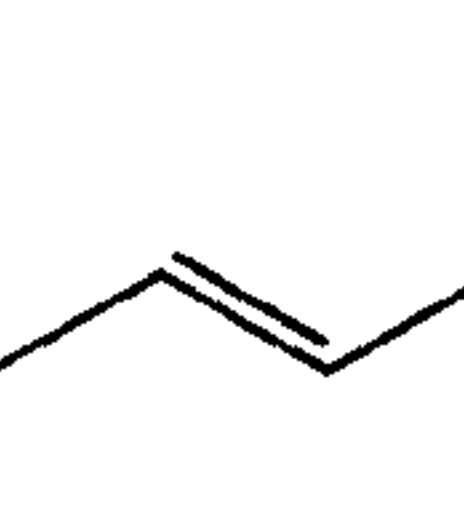
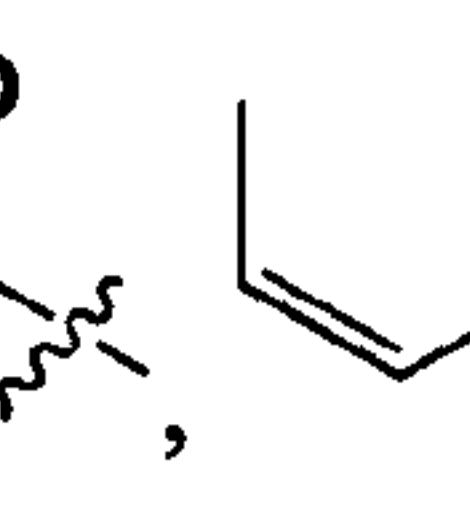
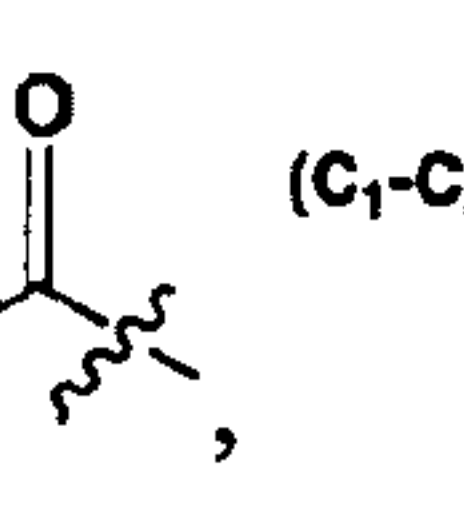
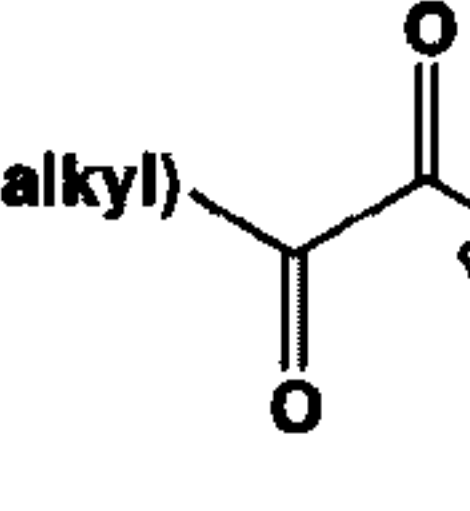
In some embodiments, one of R^{1a} or R^{1b} is selected from hydrogen and methyl; and the other of R^{1a} or R^{1b} is selected from aryl, heteroaryl, heterocyclyl, -(C₁-C₄ alkylene)-aryl, -(C₁-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-aryl, -O-(C₀-C₄ alkylene)-heteroaryl, -N(R⁷)-aryl, -

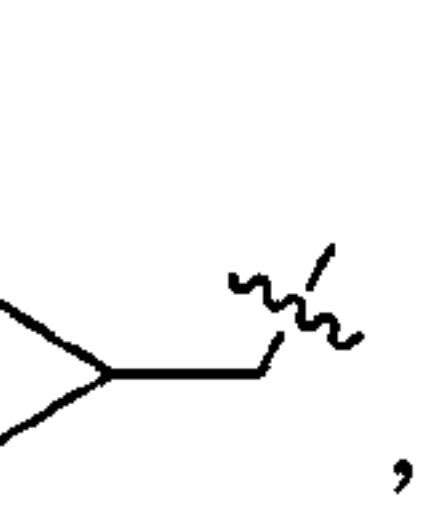
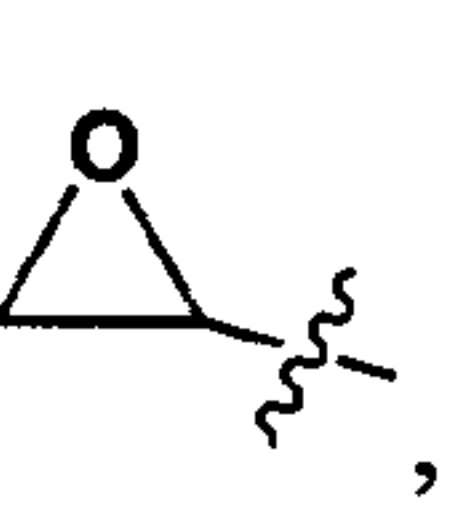
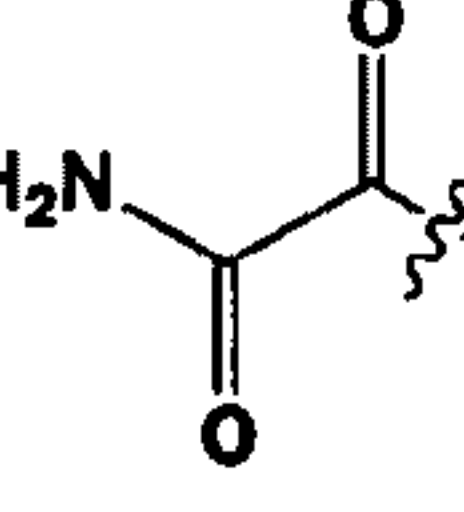
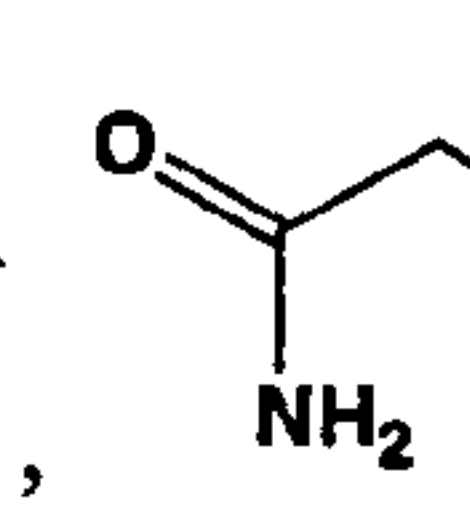
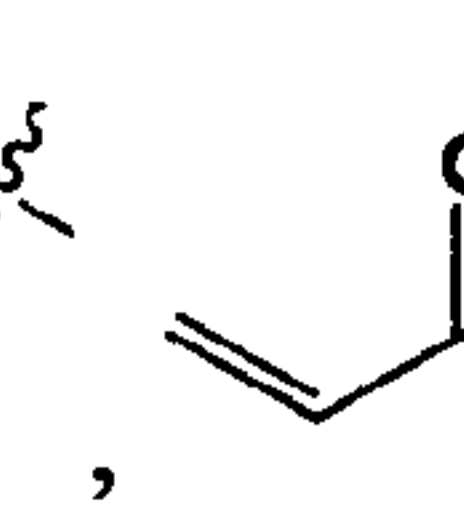
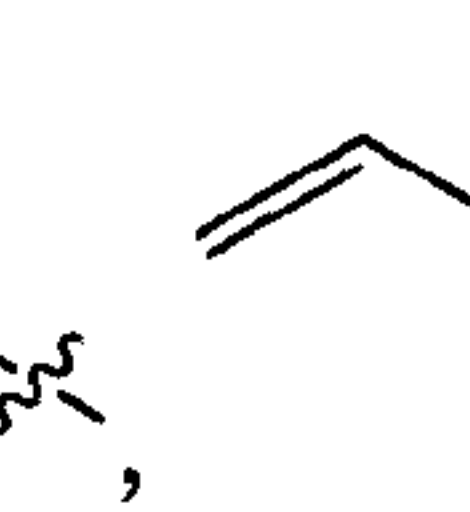
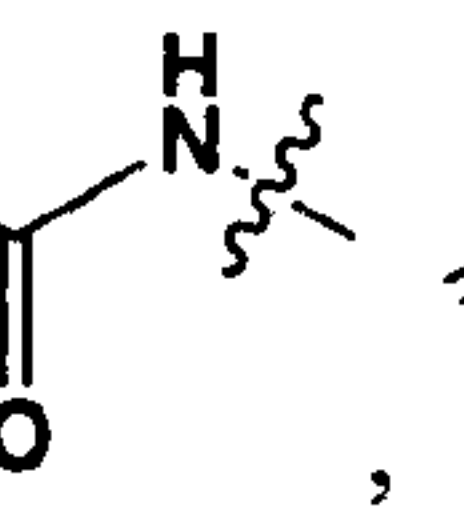
N(R⁷)heteroaryl, -N(R⁹)-aryl, or -N(R⁹)-heteroaryl, wherein said aryl or heteroaryl is substituted with -G-L-M, CH₃, or CN.

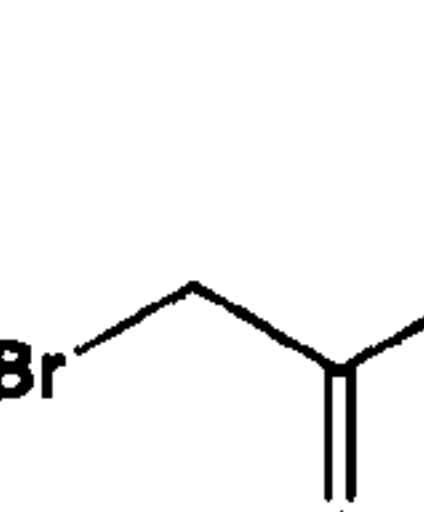
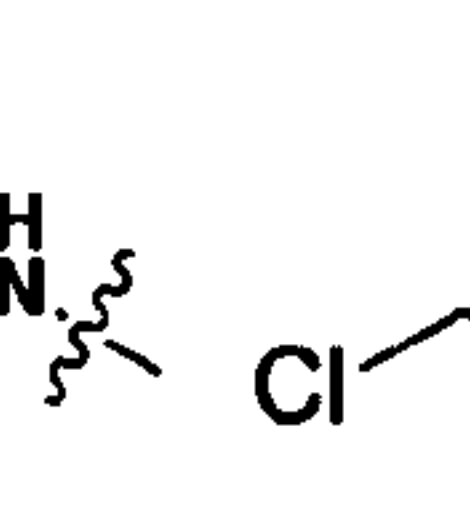
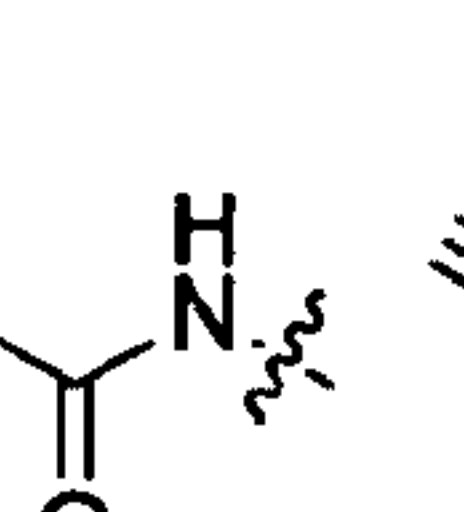
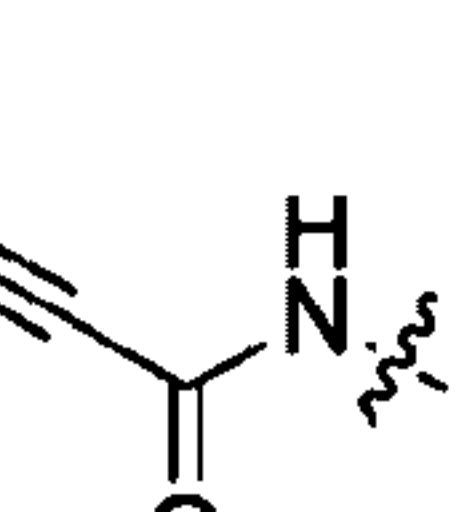
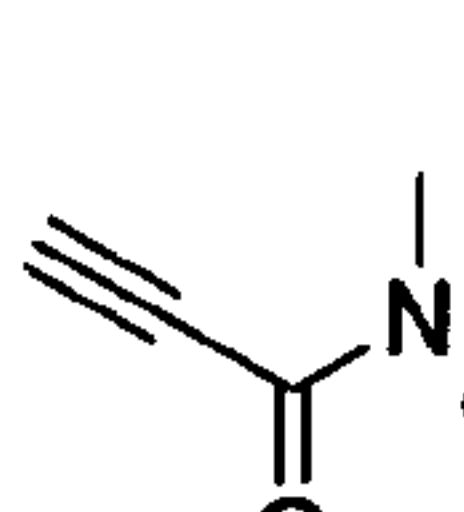
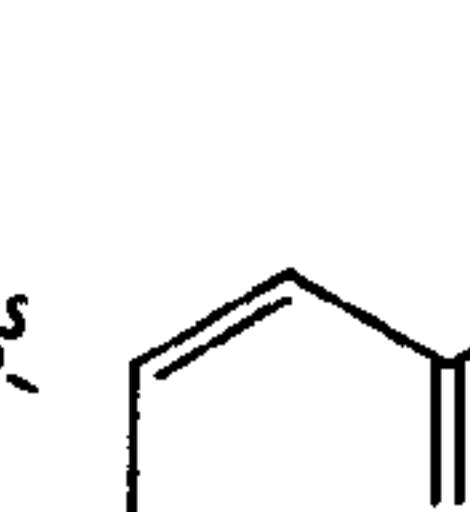
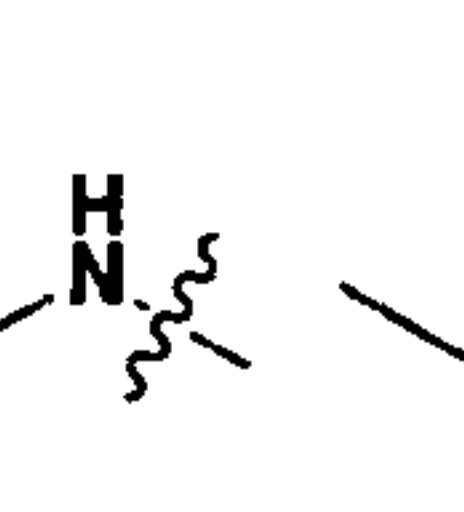
In some embodiments, R^{1a} is H and R^{1b} is aryl, heteroaryl, heterocyclyl, -(C₁-C₄ alkylene)-aryl, -(C₁-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-aryl, or -O-(C₀-C₄ alkylene)-heteroaryl, -N(R⁷)-aryl, -N(R⁷)heteroaryl, -N(R⁹)-aryl, -N(R⁹)-heteroaryl, wherein said aryl or heteroaryl is substituted with -G-L-M, CH₃, or CN. In some aspects of the preceding embodiments, R^{1a} is H and R^{1b} is aryl, heteroaryl, heterocyclyl, -CH₂-aryl, -CH₂-heteroaryl, -O-aryl, -O-heteroaryl, -O-(CH₂)-aryl, -O-CH(CH₃)-aryl, -O(CH)(C(CH₃)₂)-aryl, -O-CH(CH₂CH₃)-aryl, -NH-aryl, -NH-heteroaryl, -N(CH₃)-aryl, -N(CH₃)-heteroaryl, -N(aryl)-aryl, -N(heteroaryl)-heteroaryl, -O-(CH₂)-heteroaryl or -O-CH(CH₃)-heteroaryl, wherein aryl is phenyl, heteroaryl is pyridyl, pyrimidinyl, naphthyridinyl, quinolyl, isoquinolyl, isoxazolyl, benzoxazolyl, imidazopyrazinyl, benzothiazolyl, benzimidazolyl, pyrrollopyridinyl, pyrazolopyridinyl, indolyl, indazolyl, imidazopyridinyl, quinoxalinyl, quinazolinyl, pyridazinyl or pyrazolyl, and heterocyclyl is benzodioxole, pyridazinone, benzoxazolone, indolinone, N-methylindolinone, piperazinyl, N-methylisoquinolinone, tetrahydropyridinyl, dihydropyrrolyl and said phenyl, pyridyl, pyrimidinyl, naphthyridinyl, quinolyl, isoquinolyl, isoxazolyl, benzoxazolyl, imidazopyrazinyl, benzothiazolyl, benzimidazolyl, pyrrollopyridinyl, pyrazolopyridinyl, indolyl, indazolyl, imidazopyridinyl, quinoxalinyl, quinazolinyl, pyridazinyl, pyrazolyl, benzodioxole, pyridazinone, benzoxazolone, indolinone, N-methylindolinone, piperazinyl, N-methylisoquinolinone, tetrahydropyridinyl, or dihydropyrrolyl is substituted with -G-L-M, -CF₃, -OCF₃, halo (e.g., fluoro, chloro or bromo), CH₃, or CN.

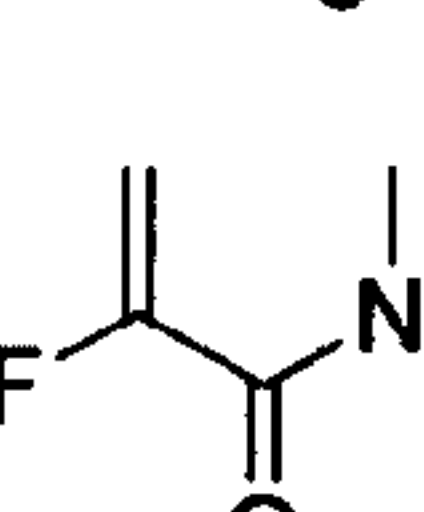
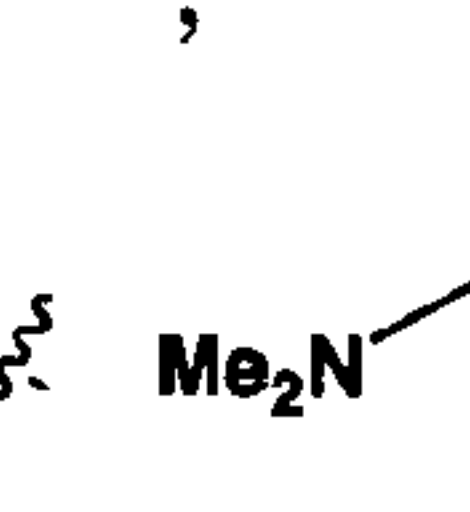
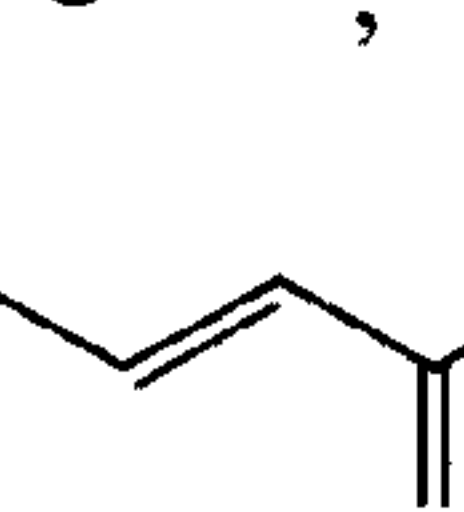
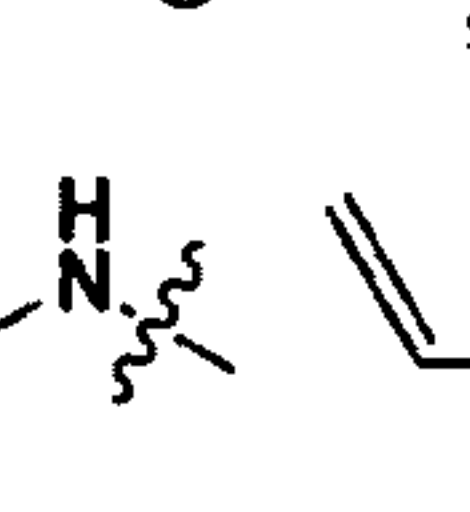
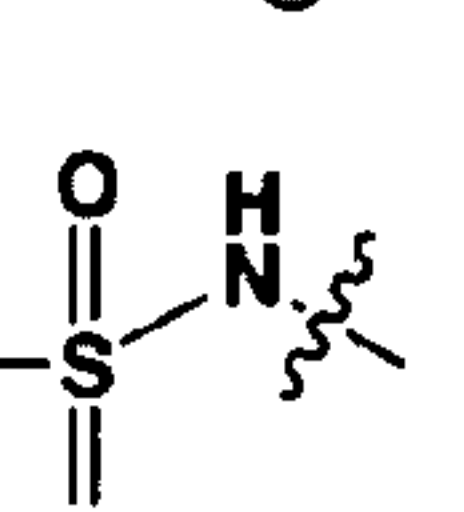
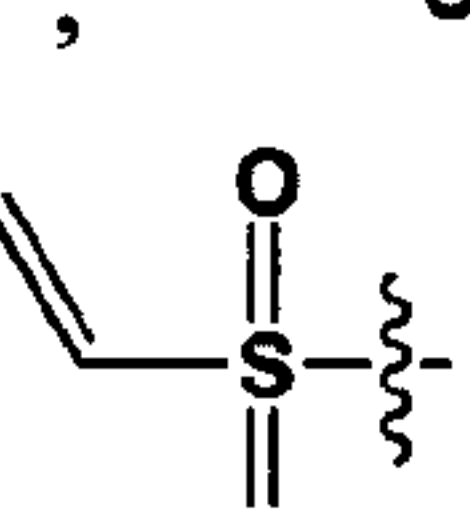
In some embodiments, R^{1a} is methyl and R^{1b} is aryl, heteroaryl, heterocyclyl, -O-(C₀-C₄ alkylene)-aryl, or -O-(C₀-C₄ alkylene)-heteroaryl, wherein said aryl or heteroaryl is substituted with -G-L-M, CH₃, or CN. In some aspects of the preceding embodiments, R^{1a} is methyl or H and R^{1b} is aryl, heteroaryl, heterocyclyl, -O-(CH₂)-aryl, -O-CH(CH₃)-aryl, -O-(CH₂)-heteroaryl or -O-CH(CH₃)-heteroaryl, wherein aryl is phenyl or naphthyl and heteroaryl is quinolinyl, pyrazolyl, isoquinolinyl, pyridyl, pyrimidinyl, indolyl, or pyrazolyl, and heterocyclyl is tetrahydropyridinyl and said phenyl, pyridyl, pyrimidinyl, indolyl, or pyrazolyl is substituted with -G-L-M, halo (e.g., chloro or fluoro), CH₃, or CN.

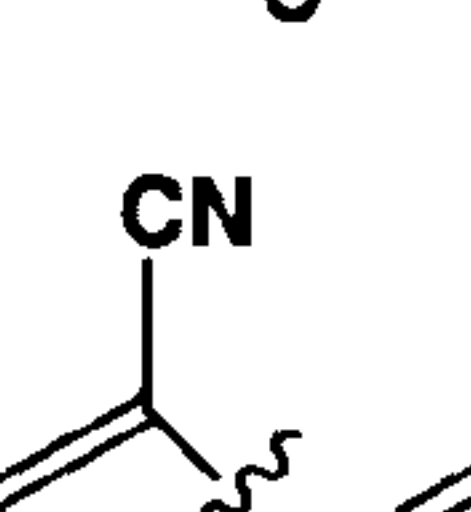









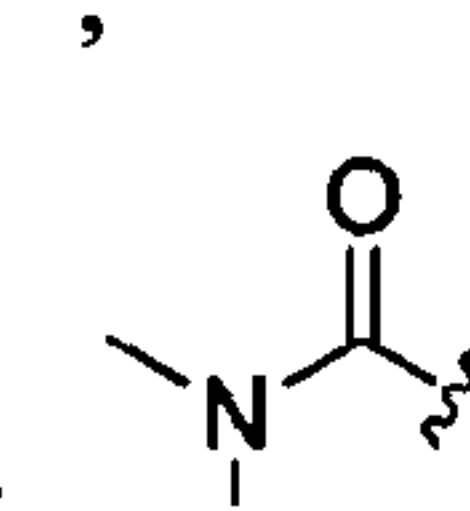
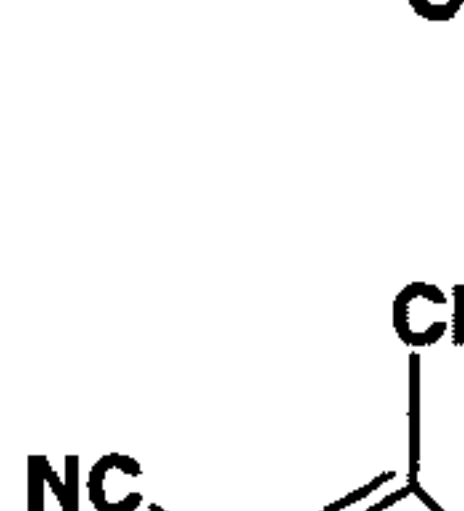
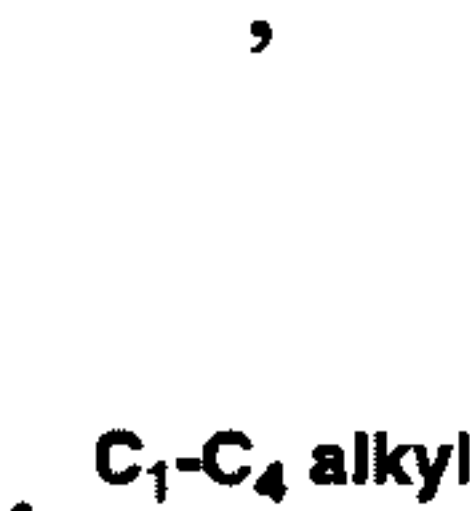
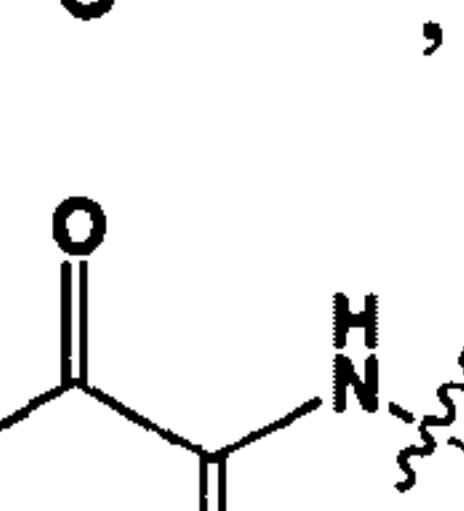







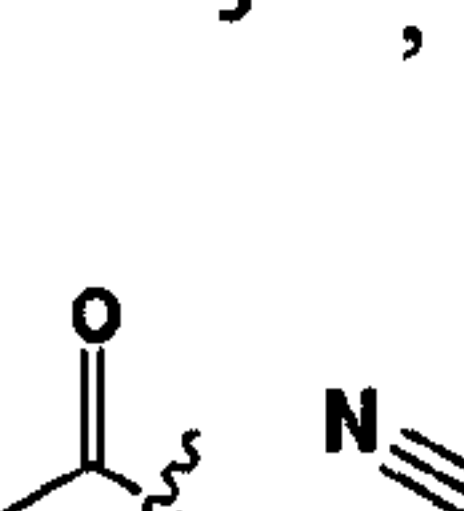
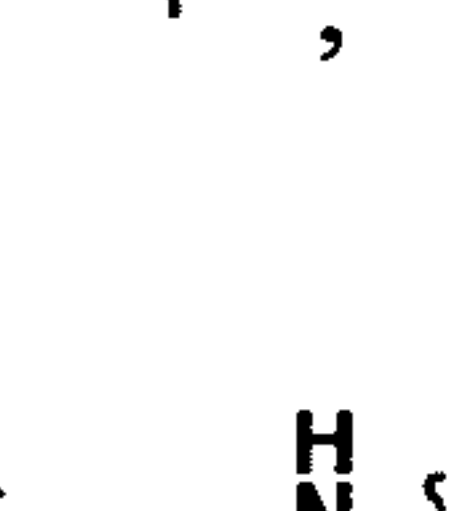








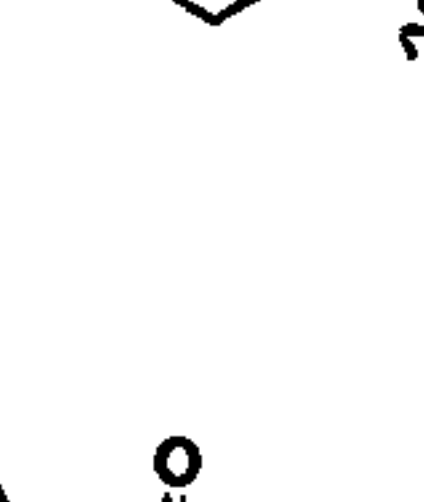
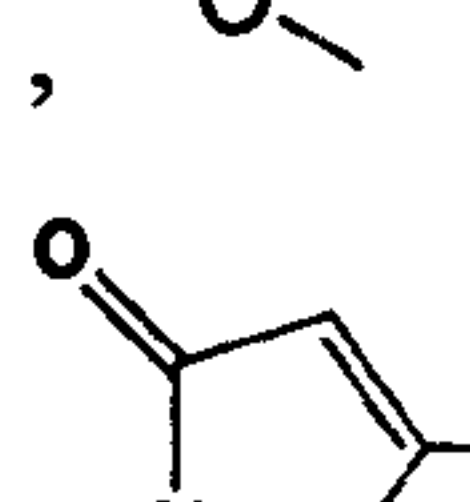
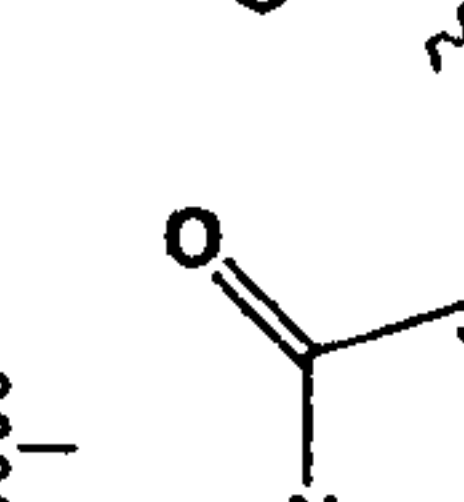
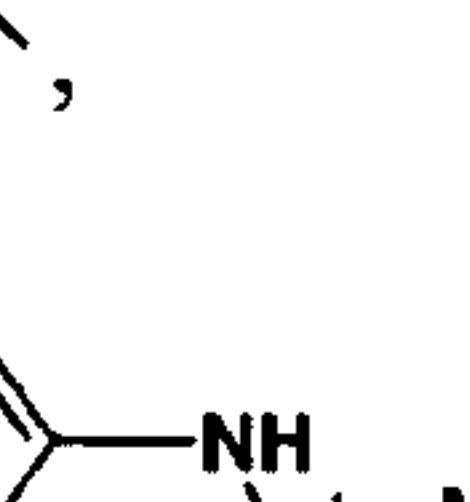
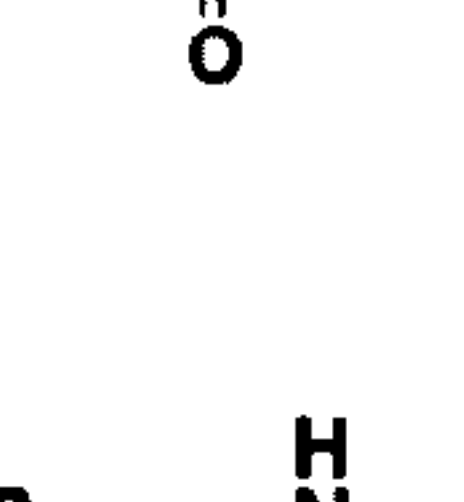
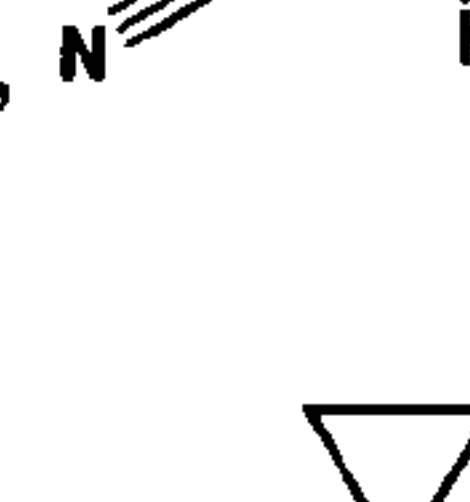
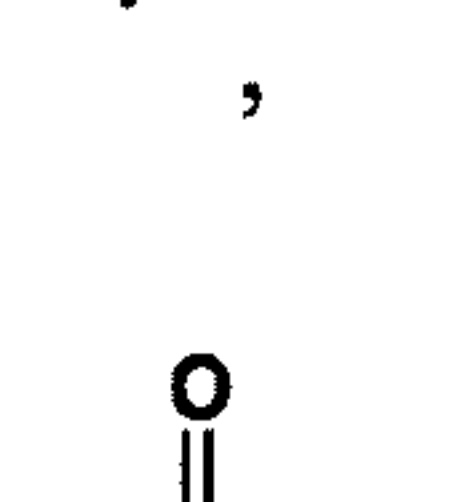








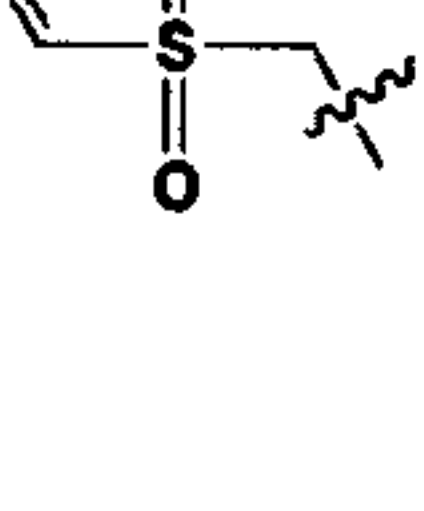
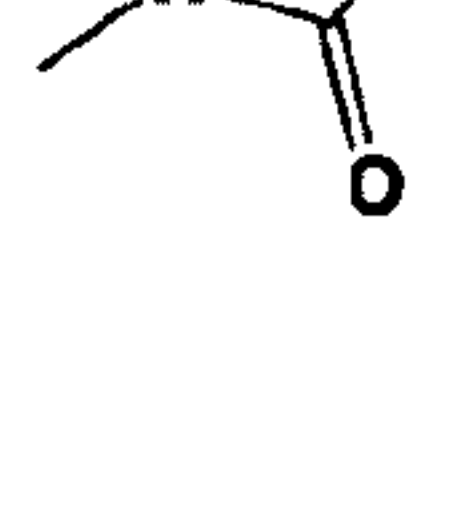







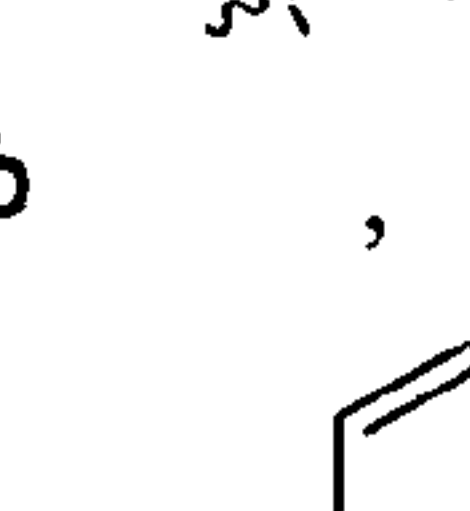
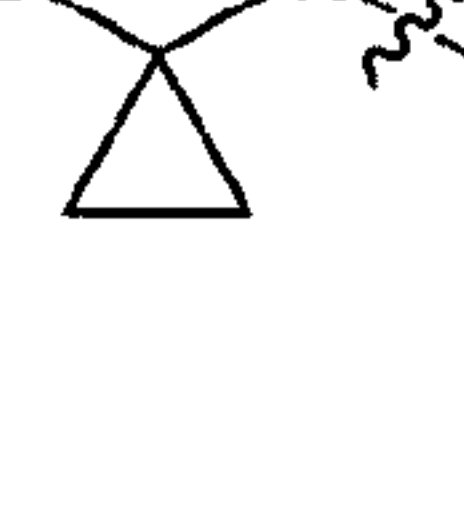
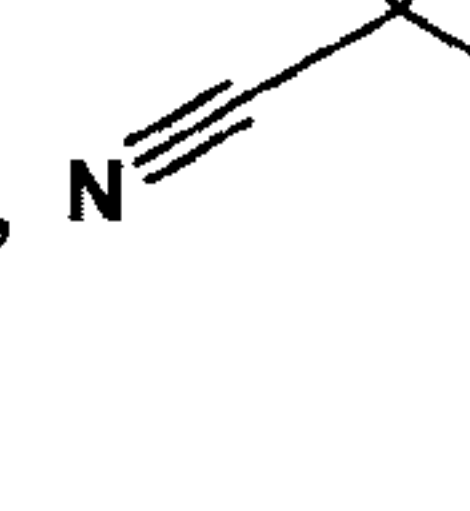
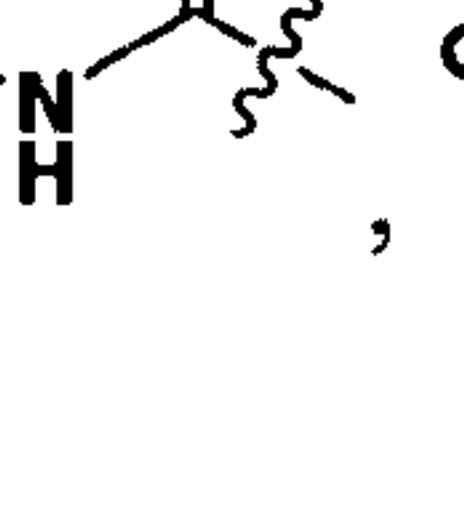


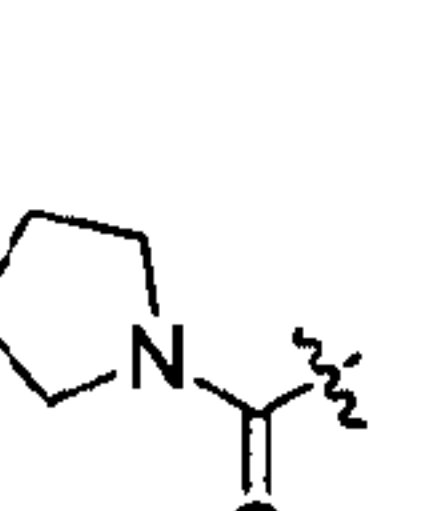
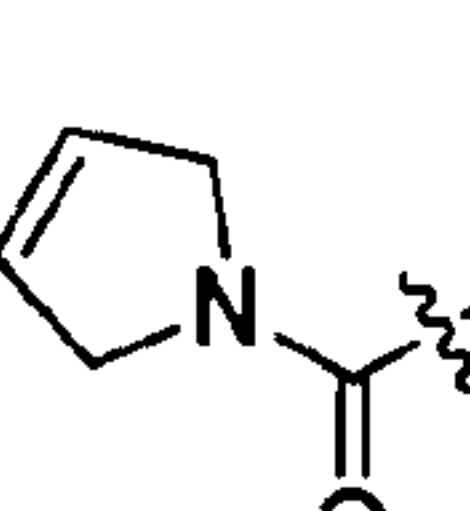
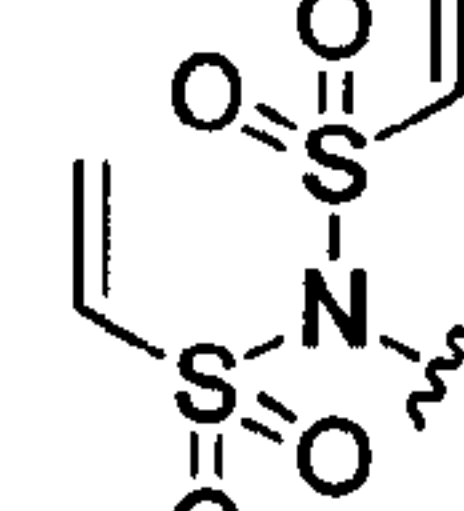
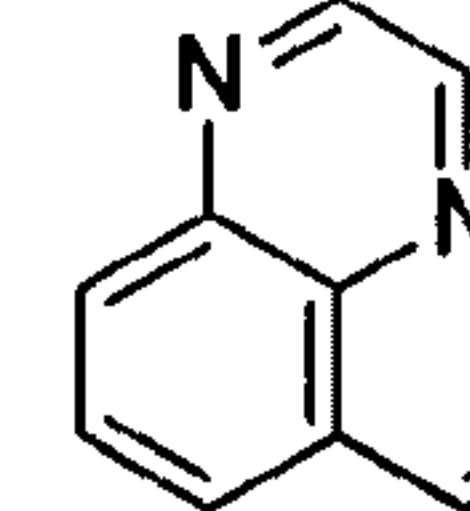
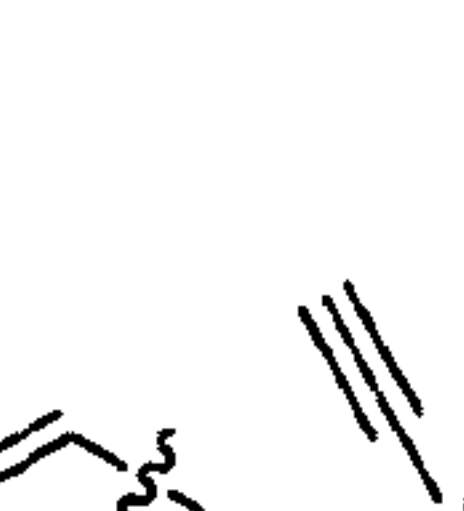










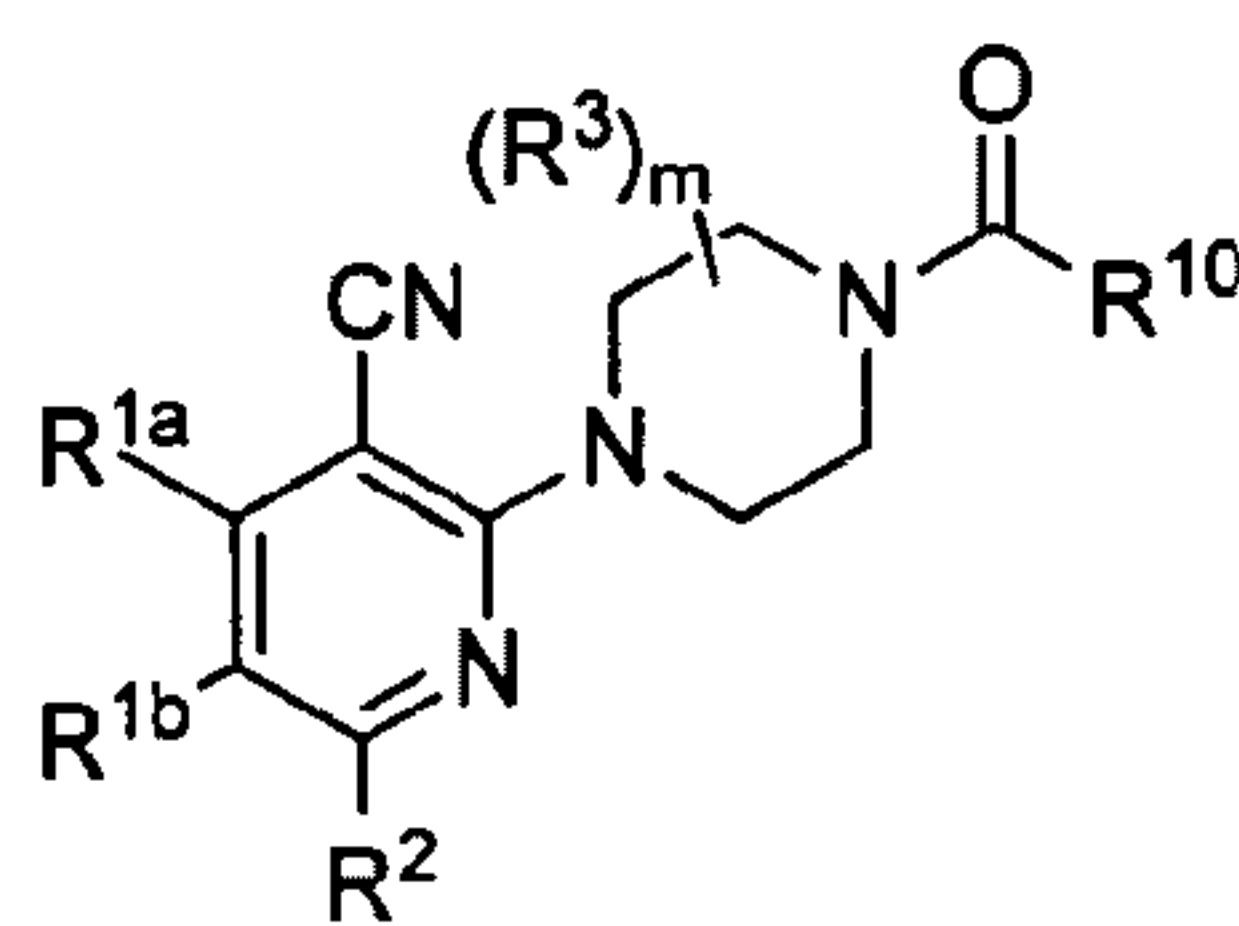



19

SO₂(CH₂)₁₋₄, -(CH₂)₁₋₄-NHSO₂Me, -NHSO₂(CH₂)₁₋₄, -O-SO₂CF₃, -SO₂NH-(C₁-C₄ alkyl), --SO₂NH-(C₂-C₄ alkenyl), SO₂-NH₂ or -NHSO₂Me.

In some embodiments, R² is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl. In some embodiments, R² is cyclopropyl. In some embodiments, R₂ is isopropyl.

In some embodiments, R⁴ is CN; Y is -N(R⁵)-; R⁵ is -C(O)R¹⁰; and the compound has Structural Formula II:



(II), or a pharmaceutically acceptable salt thereof, wherein:

one of R^{1a} or R^{1b} is selected from hydrogen and methyl;

the other of R^{1a} or R^{1b} is selected from aryl, heteroaryl, heterocyclyl, -(C₁-C₄ alkylene)-aryl, -(C₁-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-aryl, -O-(C₀-C₄ alkylene)-heteroaryl, -N(R⁷)-aryl, -N(R⁷)-heteroaryl, -N(R⁹)-aryl, or -N(R⁹)-heteroaryl, wherein said aryl, heterocyclyl, or heteroaryl is substituted with -G-L-M, CH₃, CN, alkoxy, OH, halo, C₁-C₆ alkyl, -CF₃, -OC(O)CH₃, or -OCF₃;

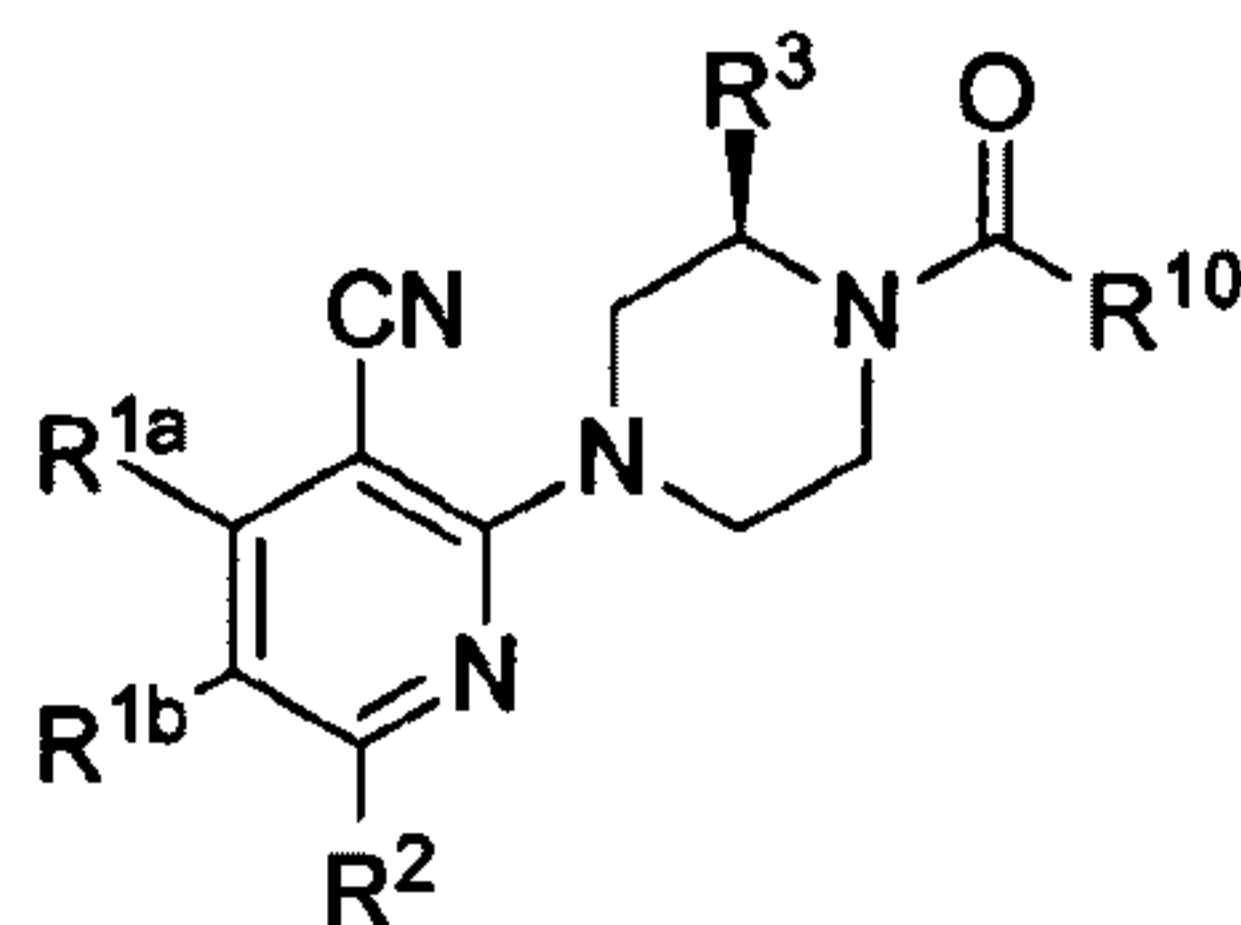
R² is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl;

each R³, if present, is selected from methyl, ethyl, isopropyl, CF₃, cyclopropyl and phenyl;

R¹⁰ is selected from -(C₁-C₃ alkyl)-O-(C₁-C₂ alkyl), Q, (C₁-C₅ alkyl), C₁-C₂ alkylene)-Q, (C₂-C₄ alkenyl), -O-(C₁-C₄ alkyl), or -(C₁-C₄ alkenylene)-Q; wherein: any alkylene moiety present in R¹⁰ is optionally substituted with OH; any terminal methyl moiety present in R¹⁰ is optionally replaced with -OH, CF₃, OCH₃, -C(O)H, -OP(O)(C₁-C₄ alkoxy)₂, or -OP(O)(OH)₂ (or a salt thereof, such as a sodium salt); Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally substituted with one substituent independently selected from C₁-C₄ alkyl optionally substituted with OH, C₁-C₄ alkoxy, -(C₁-C₄ alkylene)-(C₁-C₄ alkoxy), and -OH; and

m is 0, 1, or 2.

In certain embodiments, m is 1; and the compound has Structural Formula IIa:



, (IIa) or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} is hydrogen or methyl;

R^{1b} is selected from aryl, heteroaryl, heterocyclyl, $-(C_1-C_4 \text{ alkylene})\text{-aryl}$, $-(C_1-C_4 \text{ alkylene})\text{-heteroaryl}$, $-O-(C_0-C_4 \text{ alkylene})\text{-aryl}$, $-O-(C_0-C_4 \text{ alkylene})\text{-heteroaryl}$, $-N(R^7)\text{-aryl}$, $-N(R^7)\text{heteroaryl}$, $-N(R^9)\text{-aryl}$, or $-N(R^9)\text{-heteroaryl}$, wherein said aryl, heterocyclyl, or heteroaryl is substituted with $-G-L-M$, CH_3 , CN , alkoxy, OH , halo, C_1-C_6 alkyl, $-CF_3$, $-OC(O)CH_3$, or $-OCF_3$;

R^2 is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl;

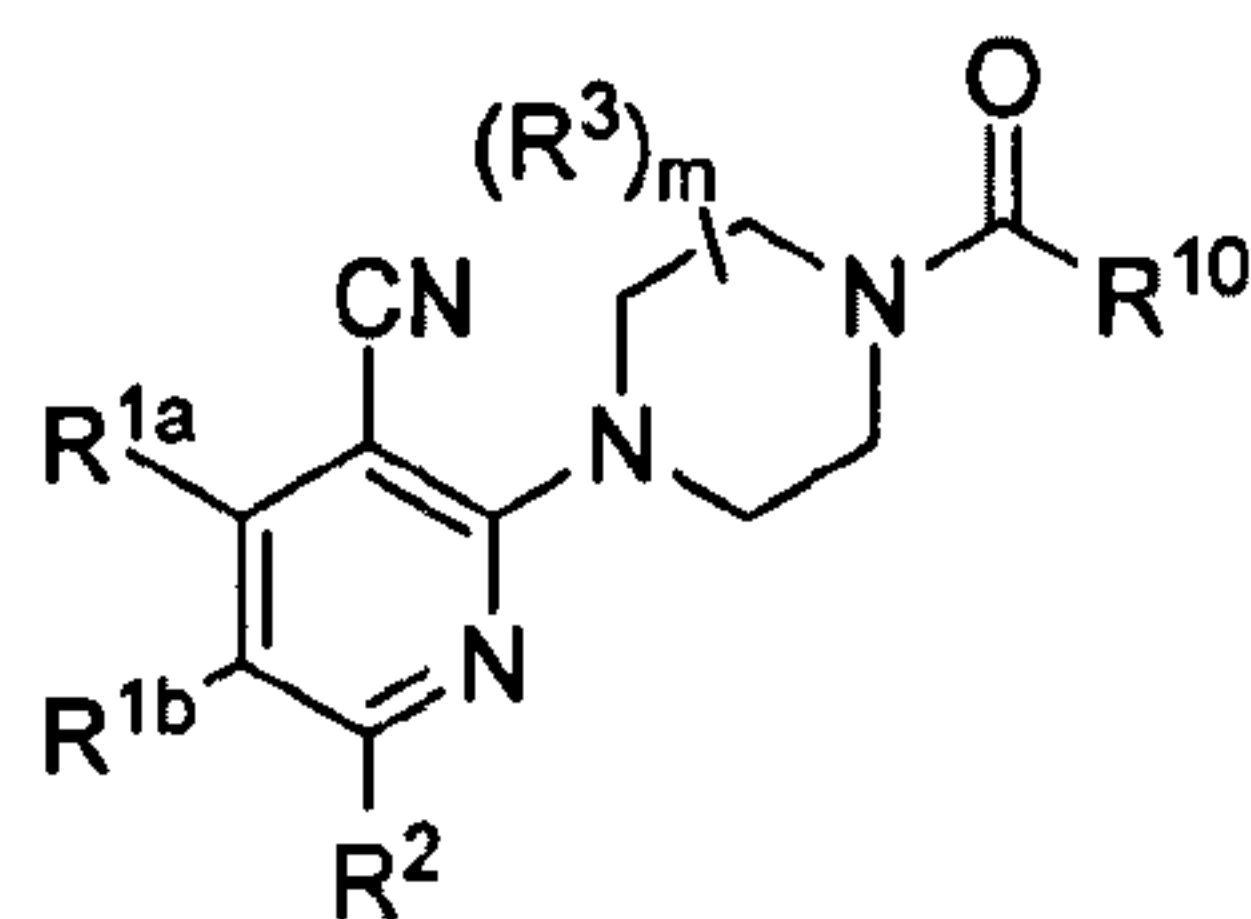
each R^3 , if present, is selected from methyl, isopropyl, and cyclopropyl;

R^{10} is selected from $-(C_1-C_3 \text{ alkyl})\text{-O}\text{-(}C_1\text{-}C_2 \text{ alkyl)}$, Q , $(C_1-C_5 \text{ alkyl})$, $C_1\text{-}C_2 \text{ alkylene}\text{-}Q$, $(C_2\text{-}C_4 \text{ alkenyl})$, $-O\text{-(}C_1\text{-}C_4 \text{ alkyl)}$, or $-(C_1\text{-}C_4 \text{ alkenylene})\text{-}Q$; wherein: any alkylene moiety present in R^{10} is optionally substituted with OH ; any terminal methyl moiety present in R^{10} is optionally replaced with $-OH$, CF_3 , OCH_3 , $-C(O)H$, $-OP(O)(C_1\text{-}C_4 \text{ alkoxy})_2$, or $-OP(O)(OH)_2$ (or a salt thereof, such as a sodium salt); Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally substituted with one substituent independently selected from $C_1\text{-}C_4$ alkyl optionally substituted with OH , $C_1\text{-}C_4$ alkoxy, $-(C_1\text{-}C_4 \text{ alkylene})\text{-(}C_1\text{-}C_4 \text{ alkoxy)}$, and $-OH$; and

m is 0, 1, or 2.

In some embodiments, R^4 is CN ; Y is $-N(R^5)\text{-}$; R^5 is $-C(O)R^{10}$; and the compound

has Structural Formula II:



(II), or a pharmaceutically acceptable salt thereof, wherein:

one of R^{1a} or R^{1b} is selected from hydrogen and methyl;

the other of R^{1a} or R^{1b} is selected from isopropyl, $-N(CH_3)-(CH_2)_2-NH-CH_3$, aryl, heteroaryl, $-CH_2$ -aryl, $-CH_2$ -heteroaryl, $-O-CH_2$ -aryl, and $-O-CH_2$ -heteroaryl; wherein any aryl or heteroaryl portion of R^{1a} or R^{1b} is optionally substituted with one or more substituents independently selected from alkoxy, hydroxy, halo, C_1 - C_6 alkyl, $-CF_3$, $-OC(O)CH_3$, and $-OCF_3$;

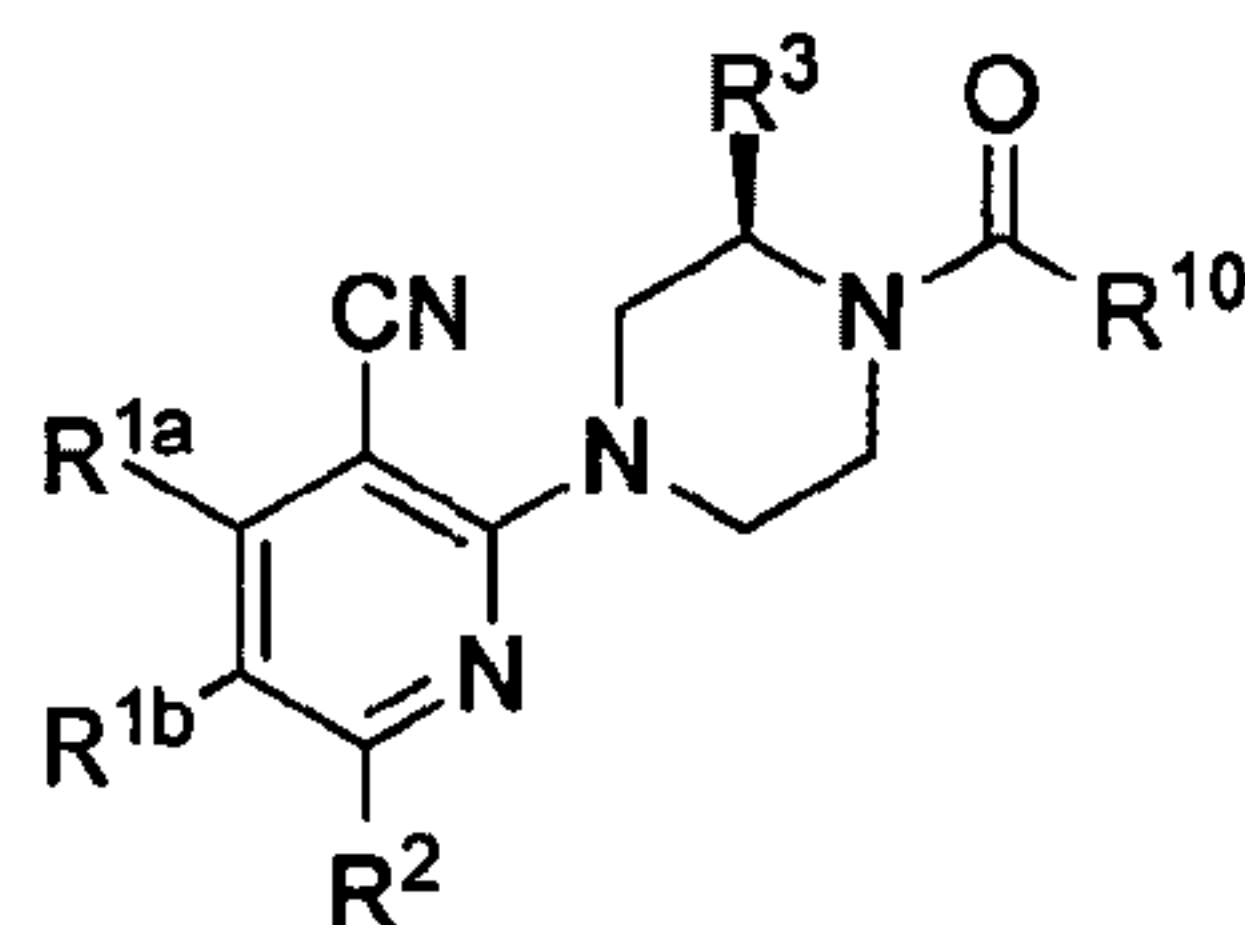
R^2 is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl;

each R^3 , if present, is selected from methyl, ethyl, isopropyl, cyclopropyl and phenyl;

R^{10} is selected from heteroaryl, aryl, $-CH_2$ -aryl, $-CH_2$ -heteroaryl, and $-(CH_2)_2-O-CH_3$, wherein any aryl or heteroaryl portion of R^{10} is optionally substituted with methyl; and

m is 0, 1, or 2.

In certain embodiments, m is 1; and the compound has Structural Formula IIa:



, (IIa) or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} is selected from hydrogen and methyl;

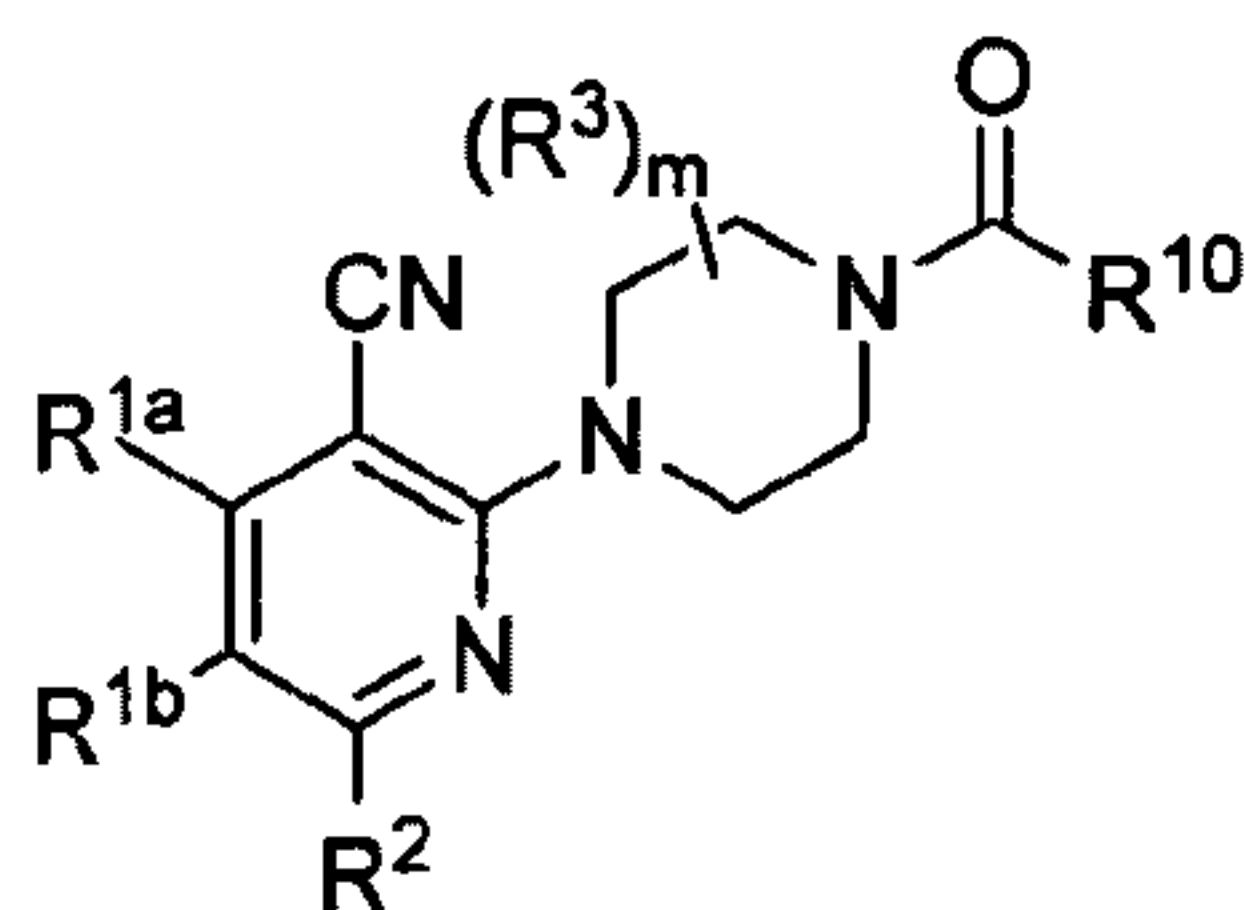
R^{1b} is selected from aryl, and heteroaryl; wherein the aryl or heteroaryl is optionally substituted with one or more substituents independently selected from methoxy, fluoro, chloro, methyl, $-CF_3$, $-OCF_3$;

R^2 is selected from isopropyl and cyclopropyl;

R^3 is selected from methyl, ethyl, isopropyl and cyclopropyl; and

R^{10} is selected from $-(CH_2)_2-O-CH_3$, furan-3-yl, 2-methylfuran-3-yl and thien-2-yl.

In some embodiments, R^4 is CN; Y is $-N(R^5)-$; R^5 is $-C(O)R^{10}$; and the compound has Structural Formula II:



(II), or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} is H;

R^{1b} is aryl, heteroaryl, $-O-(C_1-C_4 \text{ alkylene})\text{-aryl}$, or $-O-(C_1-C_4 \text{ alkylene})\text{-heteroaryl}$, wherein said aryl or heteroaryl is substituted with $-G-L-M$, CH_3 , or CN;

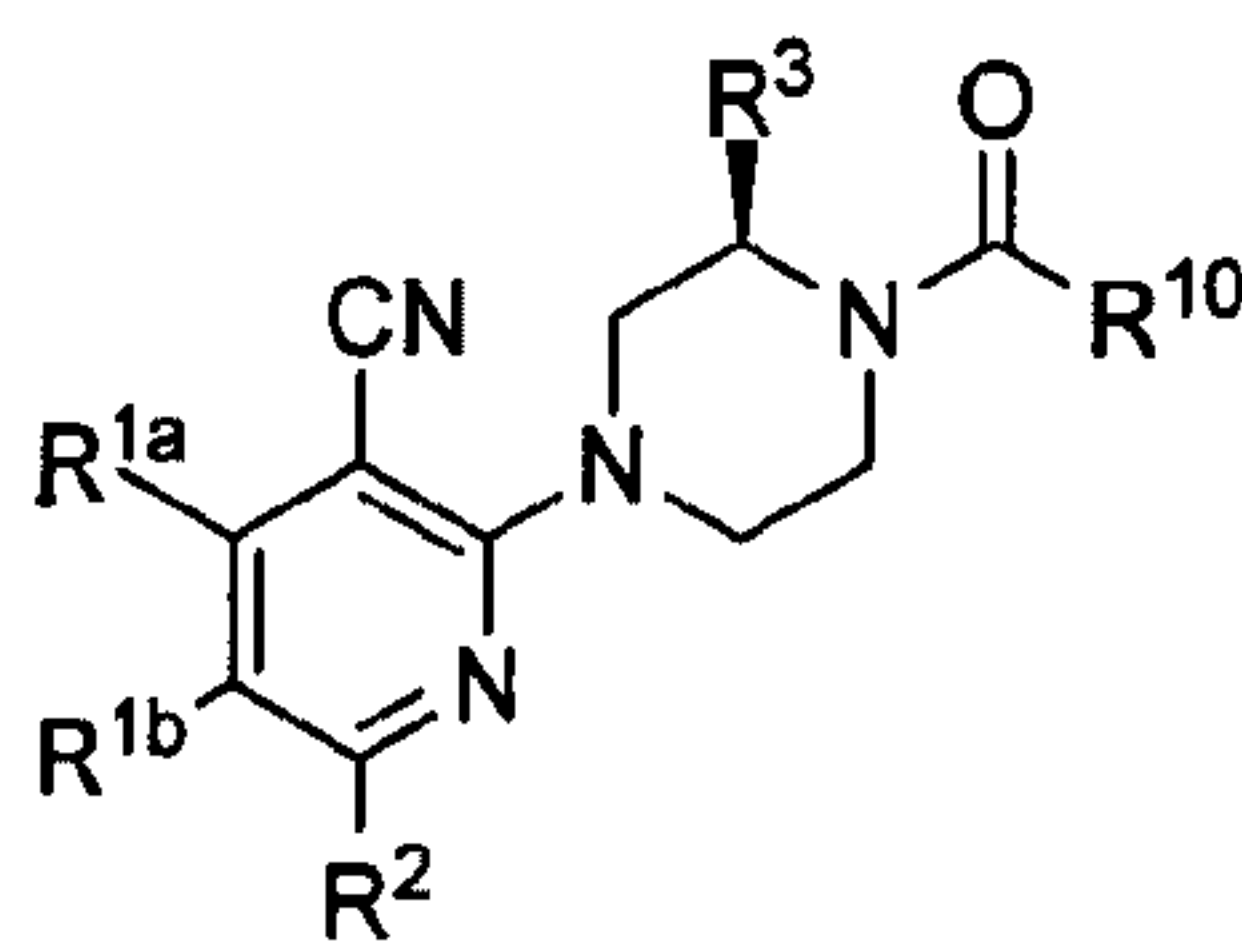
R^2 is selected from isopropyl, cyclopropyl, cyclohexyl, and phenyl;

each R^3 , if present, is selected from methyl, ethyl, isopropyl, cyclopropyl and phenyl;

R^{10} is selected from heteroaryl, aryl, $-CH_2\text{-aryl}$, $-CH_2\text{-heteroaryl}$, and $-(CH_2)_2\text{-O-CH}_3$, wherein any aryl or heteroaryl portion of R^{10} is optionally substituted with methyl; and

m is 0, 1, or 2.

In certain embodiments, m is 1; and the compound has Structural Formula IIa:



, (IIa) or a pharmaceutically acceptable salt thereof, wherein:

R^{1a} is H;

R^{1b} is aryl, heteroaryl, $-O-(CH_2)\text{-aryl}$, $-O-CH(CH_3)\text{-aryl}$, $-O-(CH_2)\text{-heteroaryl}$ or $-O-CH(CH_3)\text{-heteroaryl}$, wherein aryl is phenyl and heteroaryl is pyridyl, pyrimidinyl, indolyl, or pyrazolyl, and said phenyl, pyridyl, pyrimidinyl, indolyl or pyrazolyl is substituted with $-G-L-M$, CH_3 , or CN;

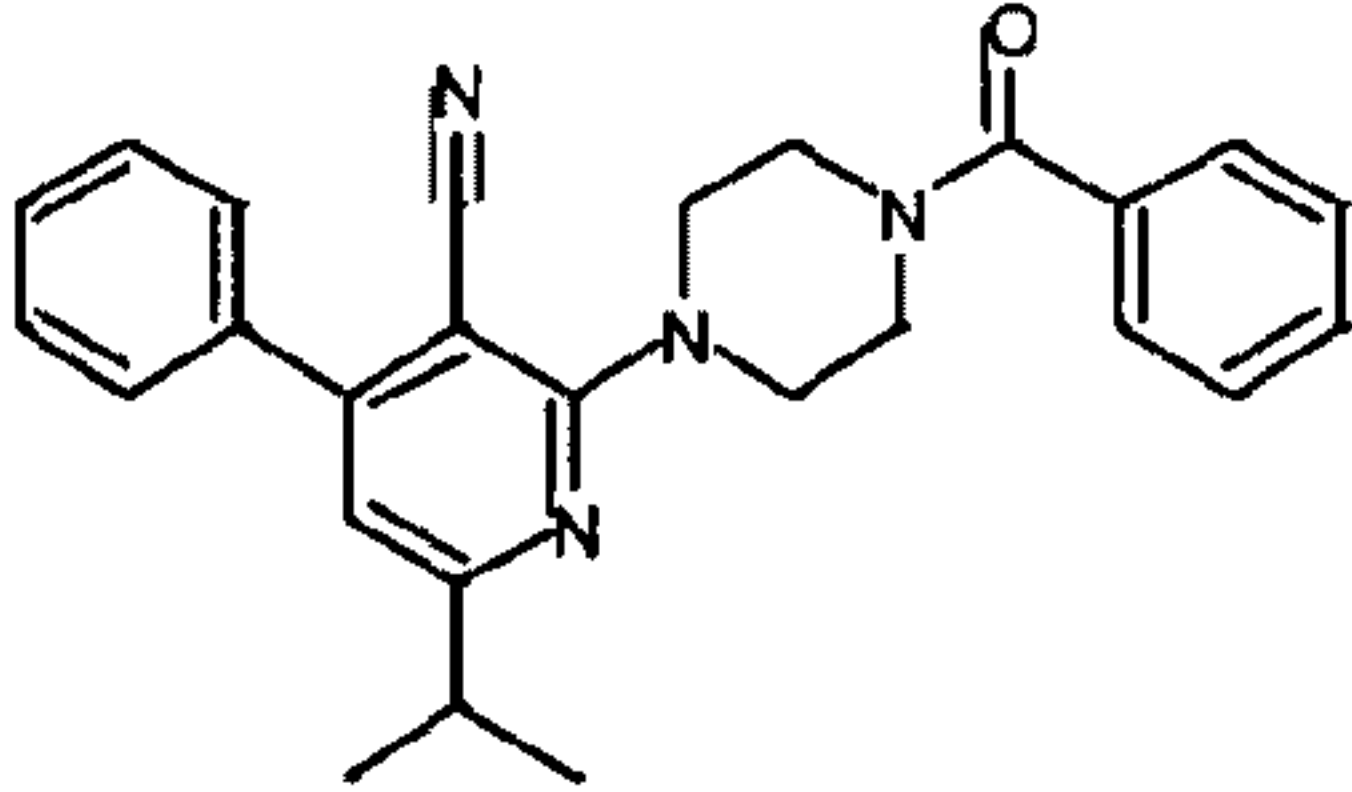
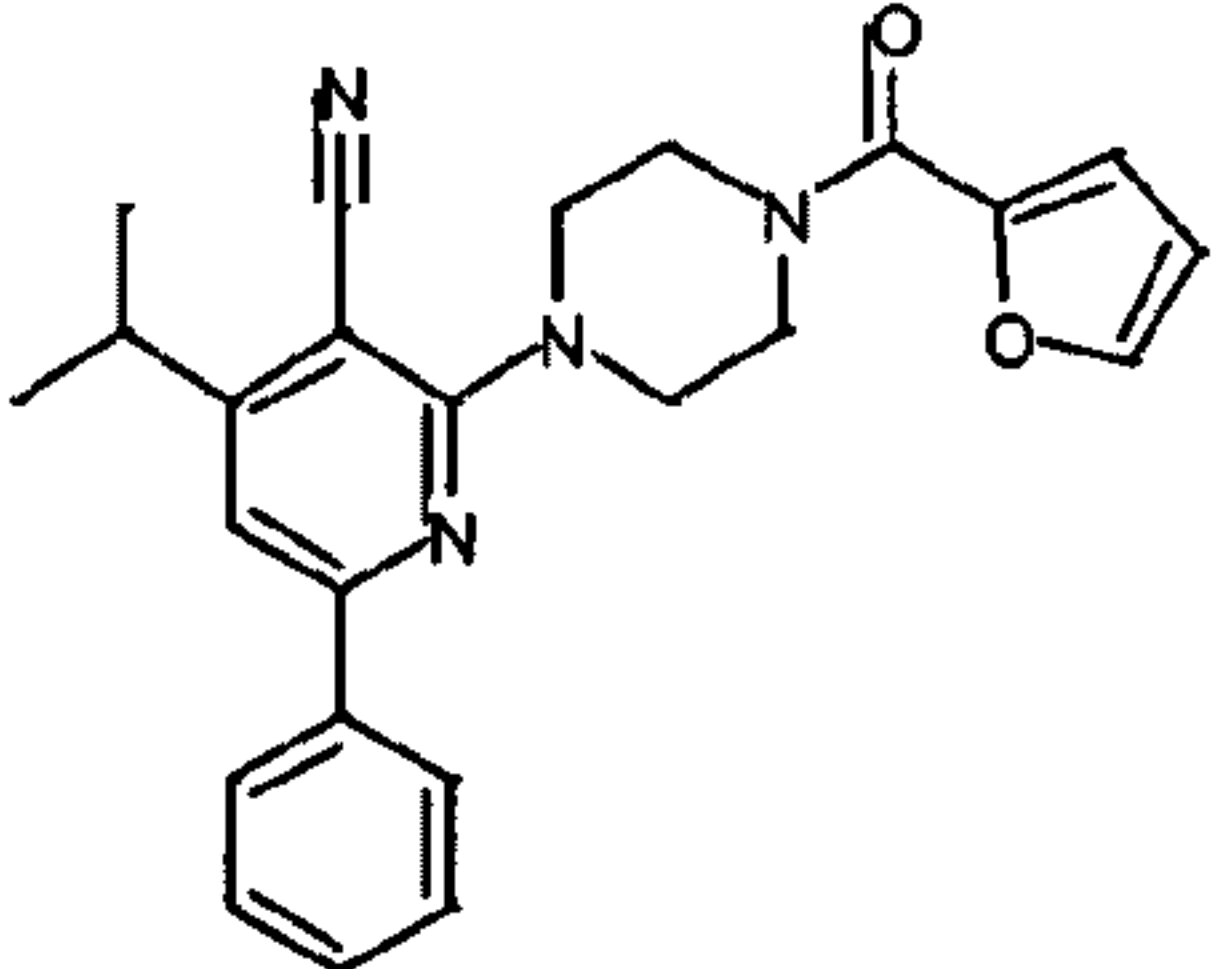
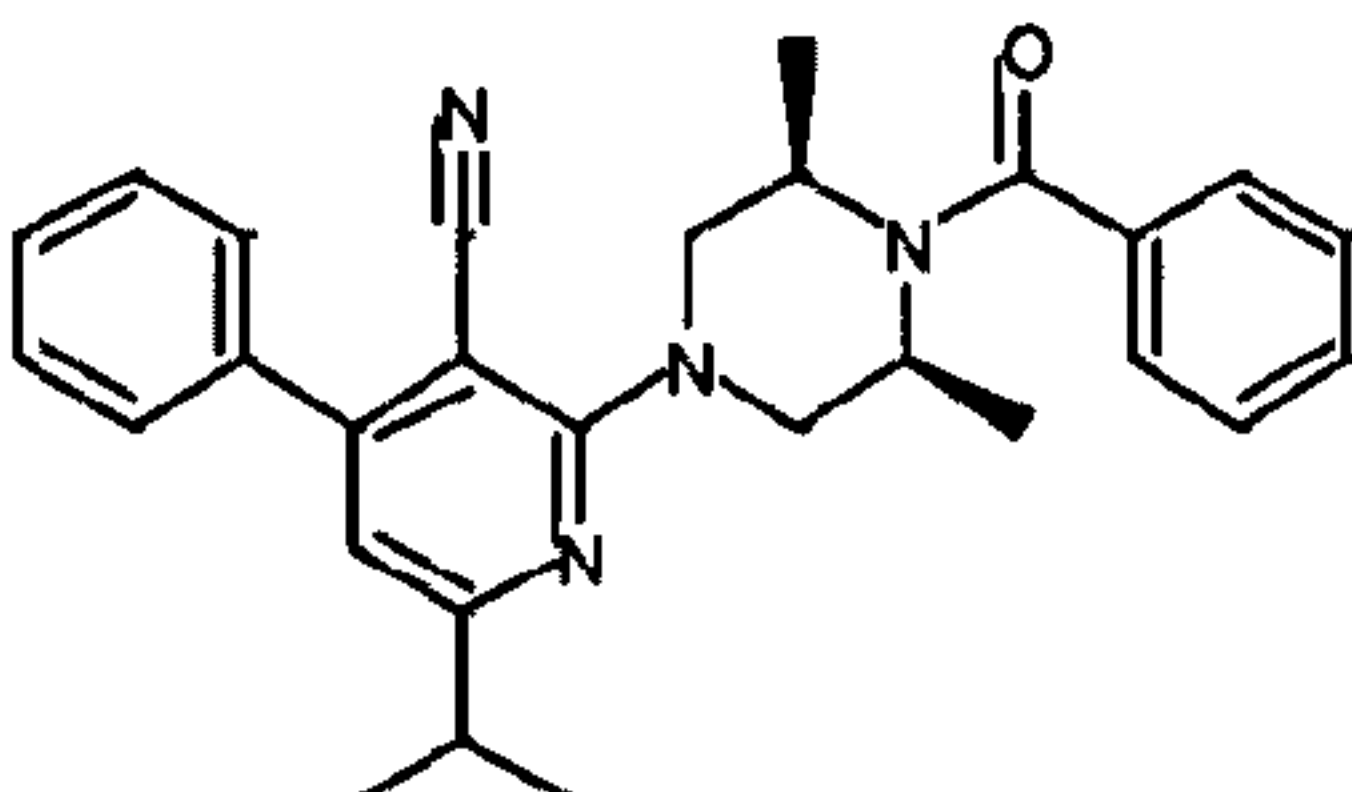
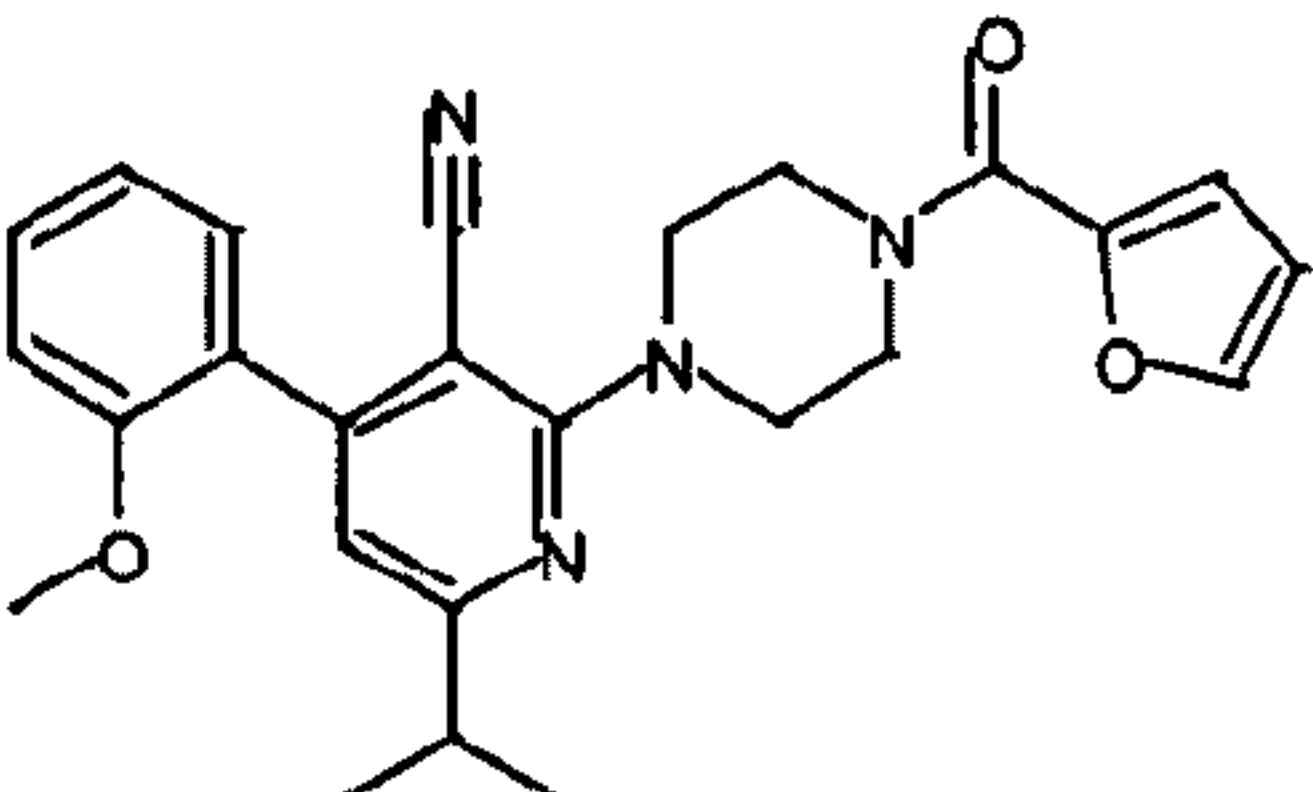
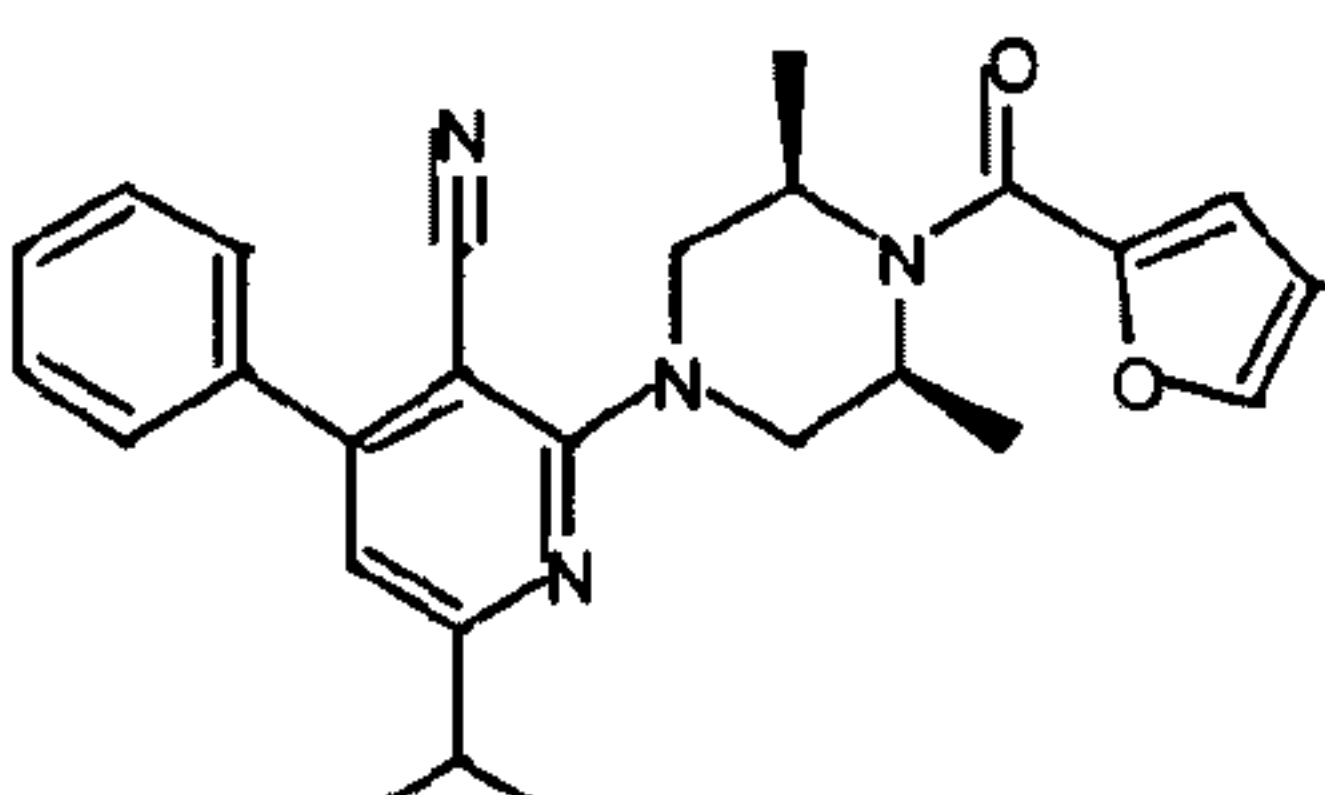
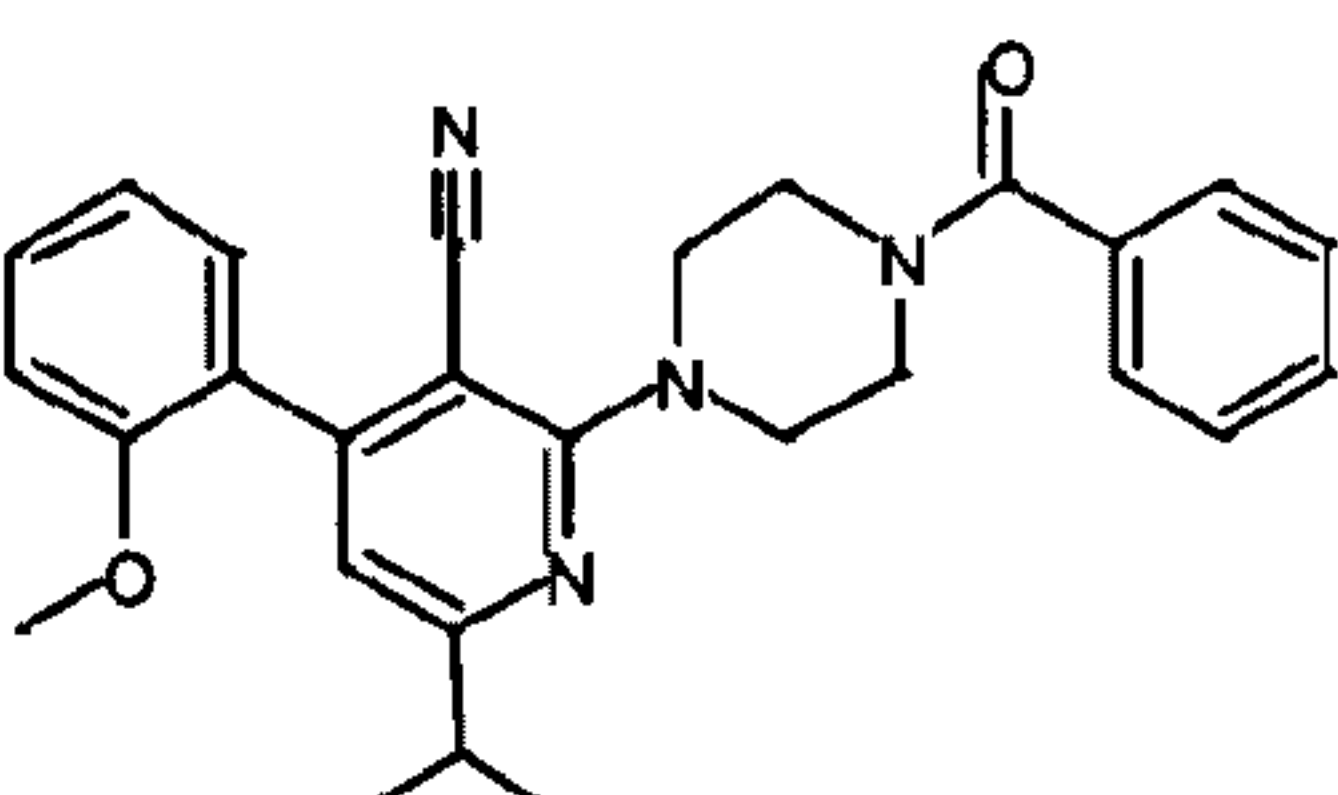
R^2 is selected from isopropyl and cyclopropyl;

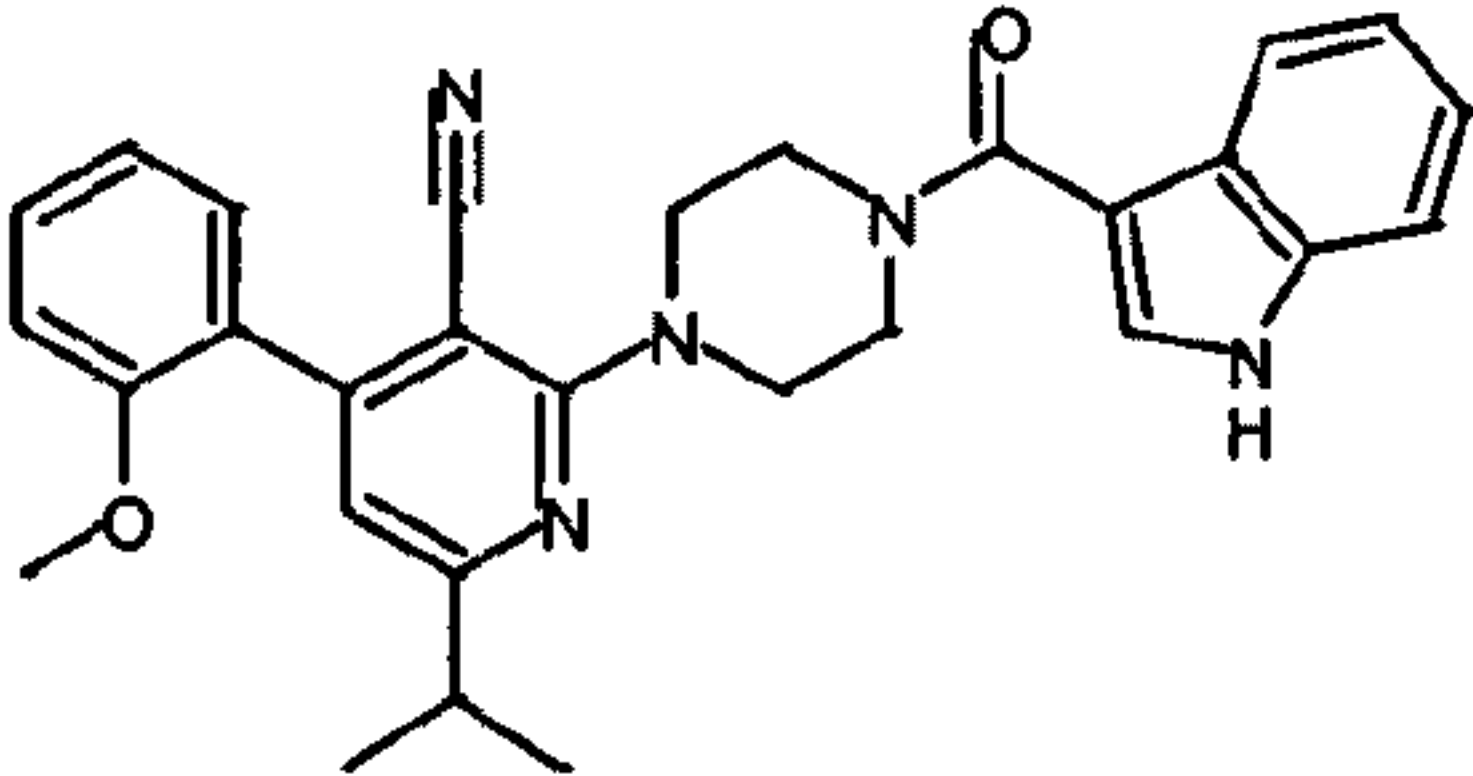
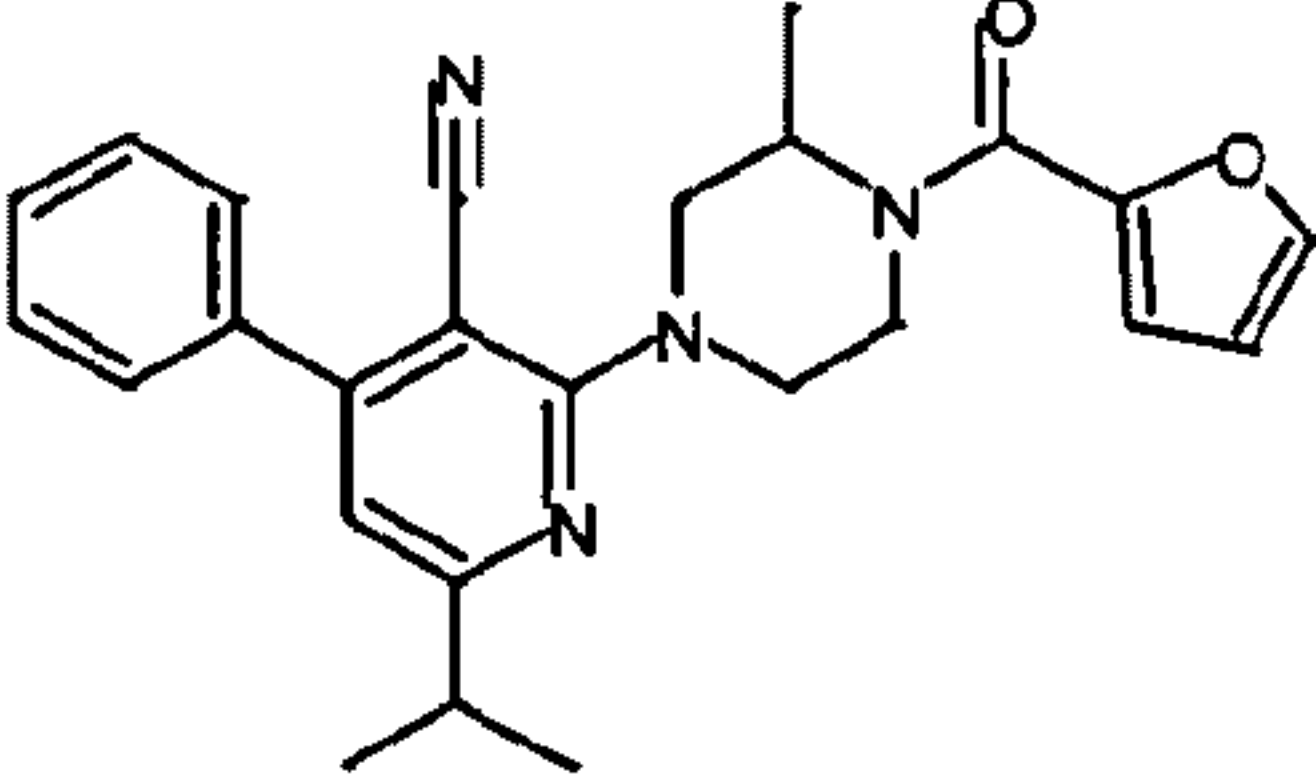
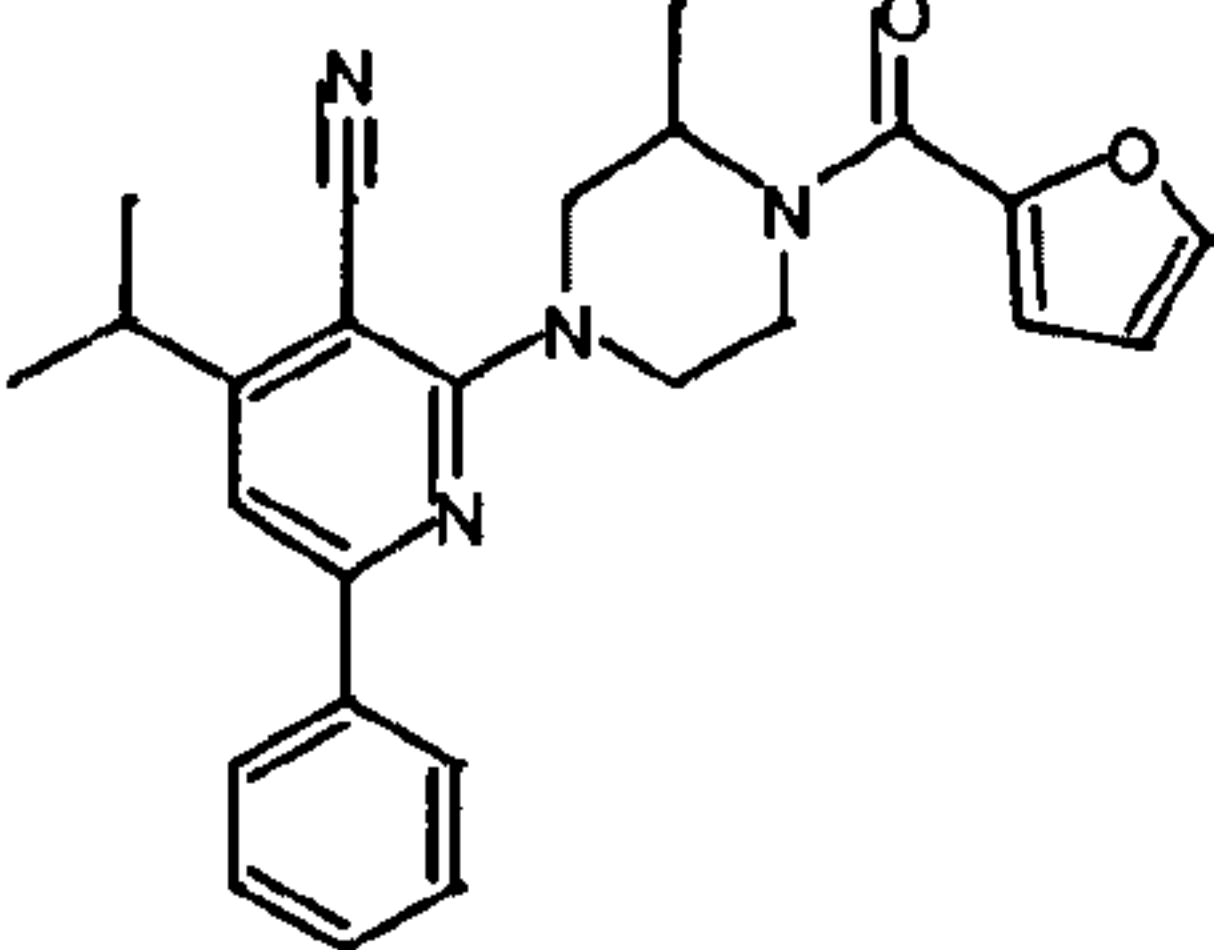
R^3 is selected from methyl, ethyl, isopropyl and cyclopropyl; and

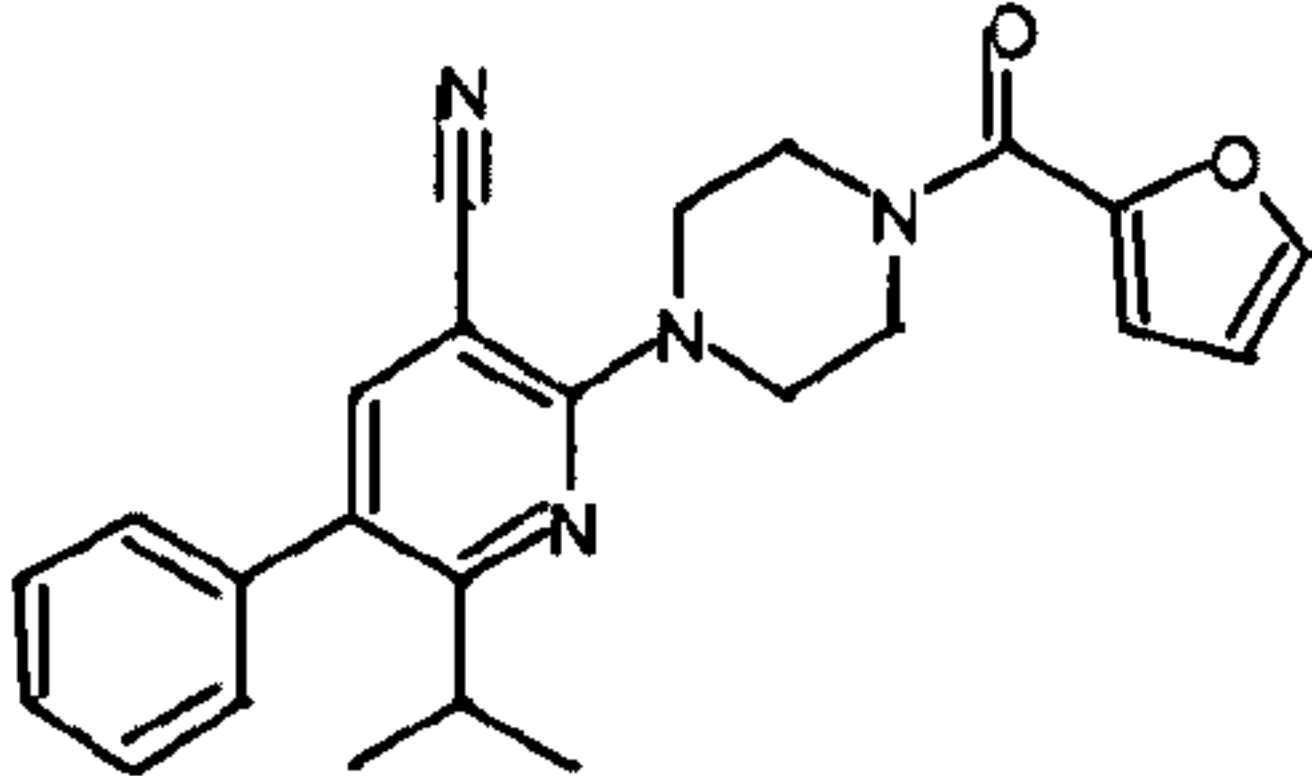
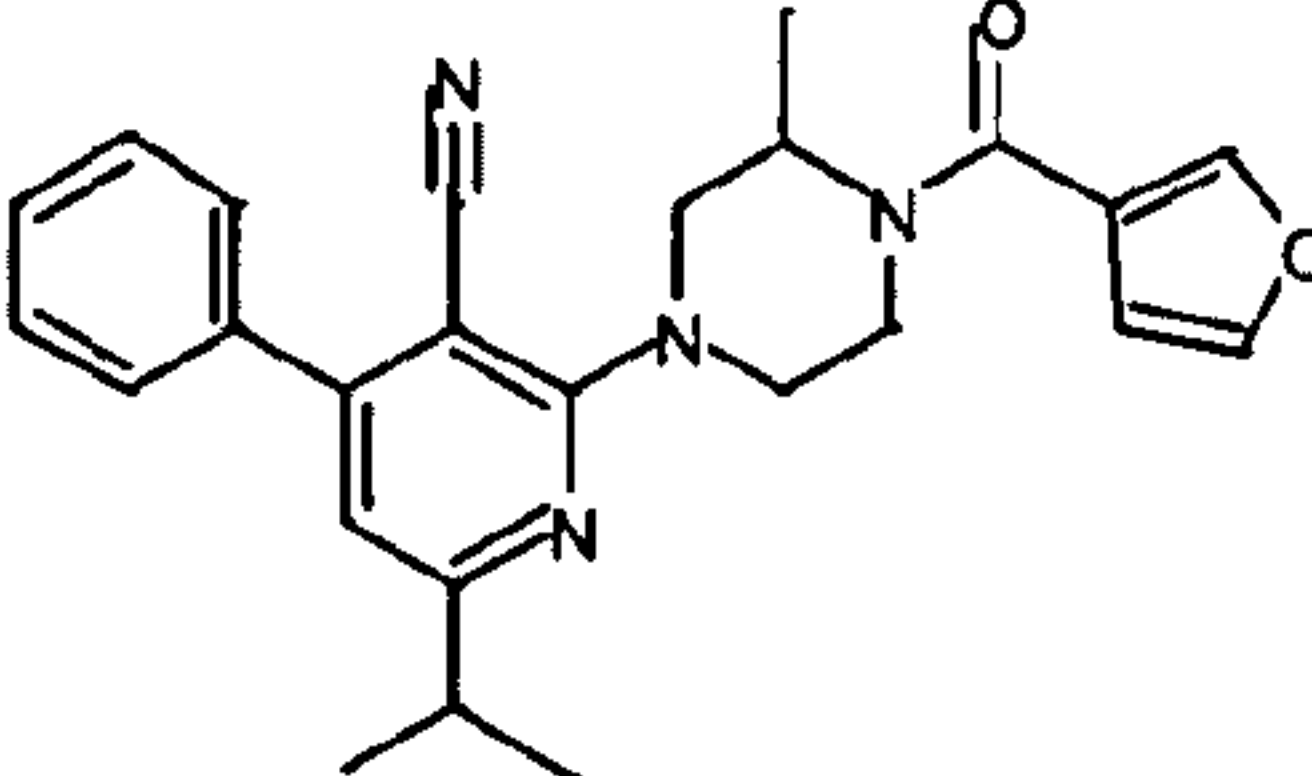
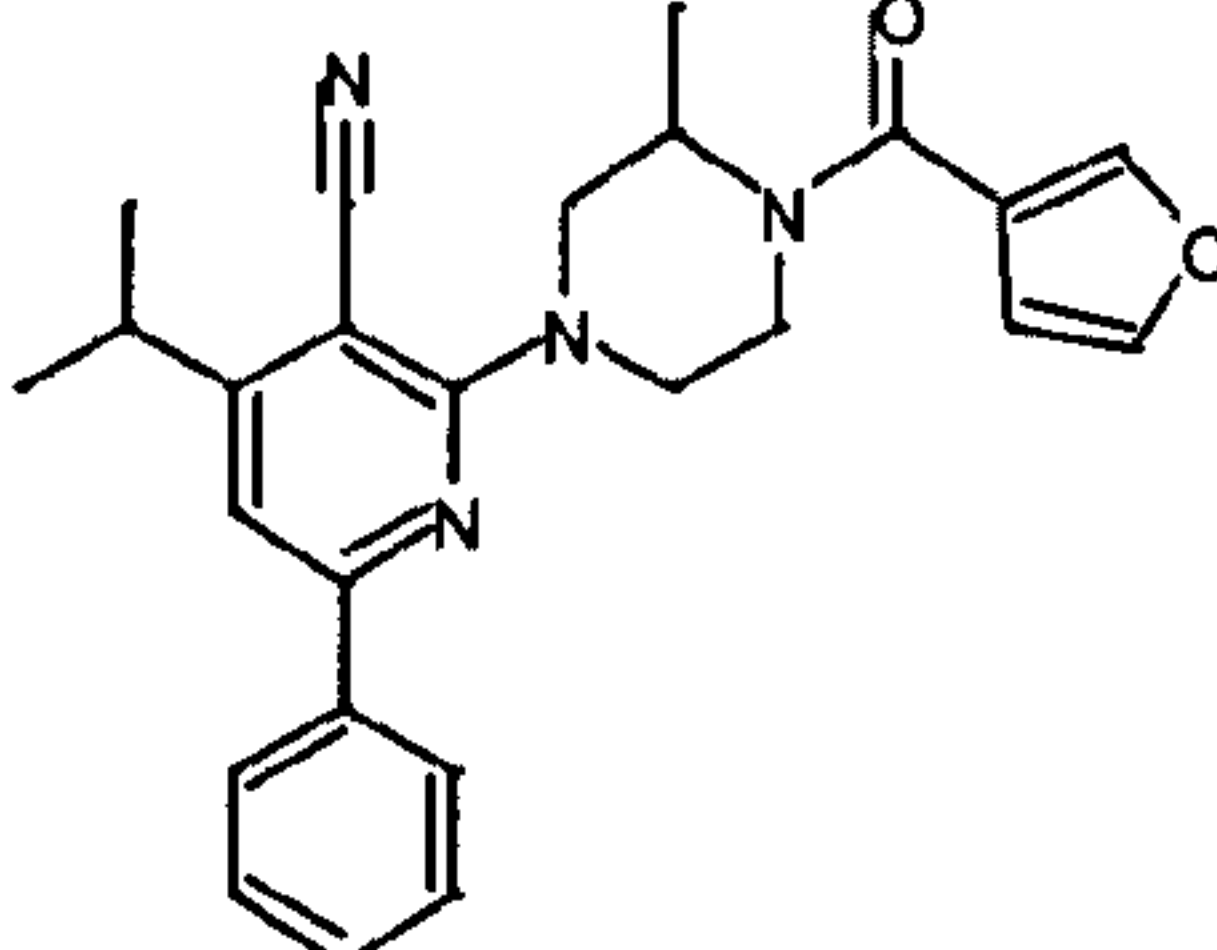
R^{10} is selected from $-(CH_2)_2\text{-O-CH}_3$, furan-3-yl, 2-methylfuran-3-yl and thien-2-yl.

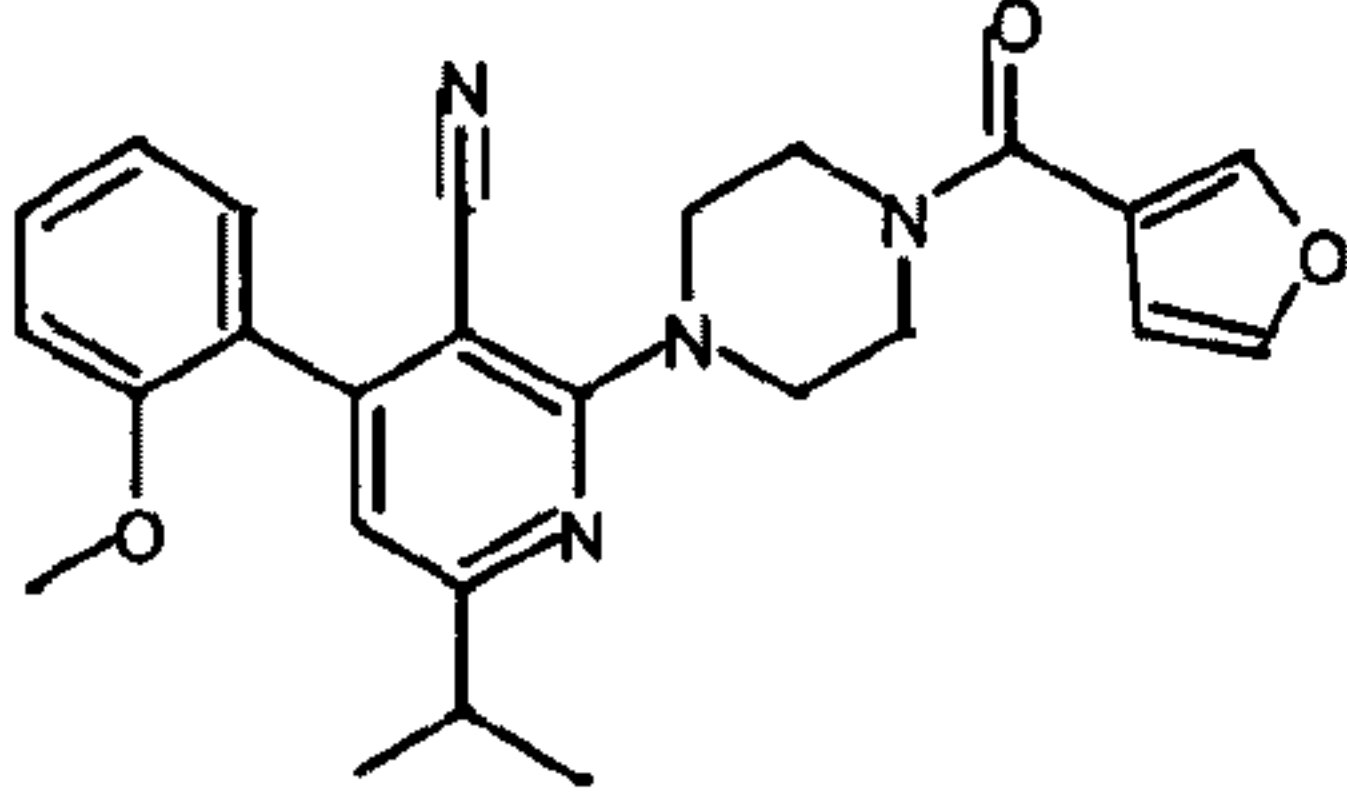
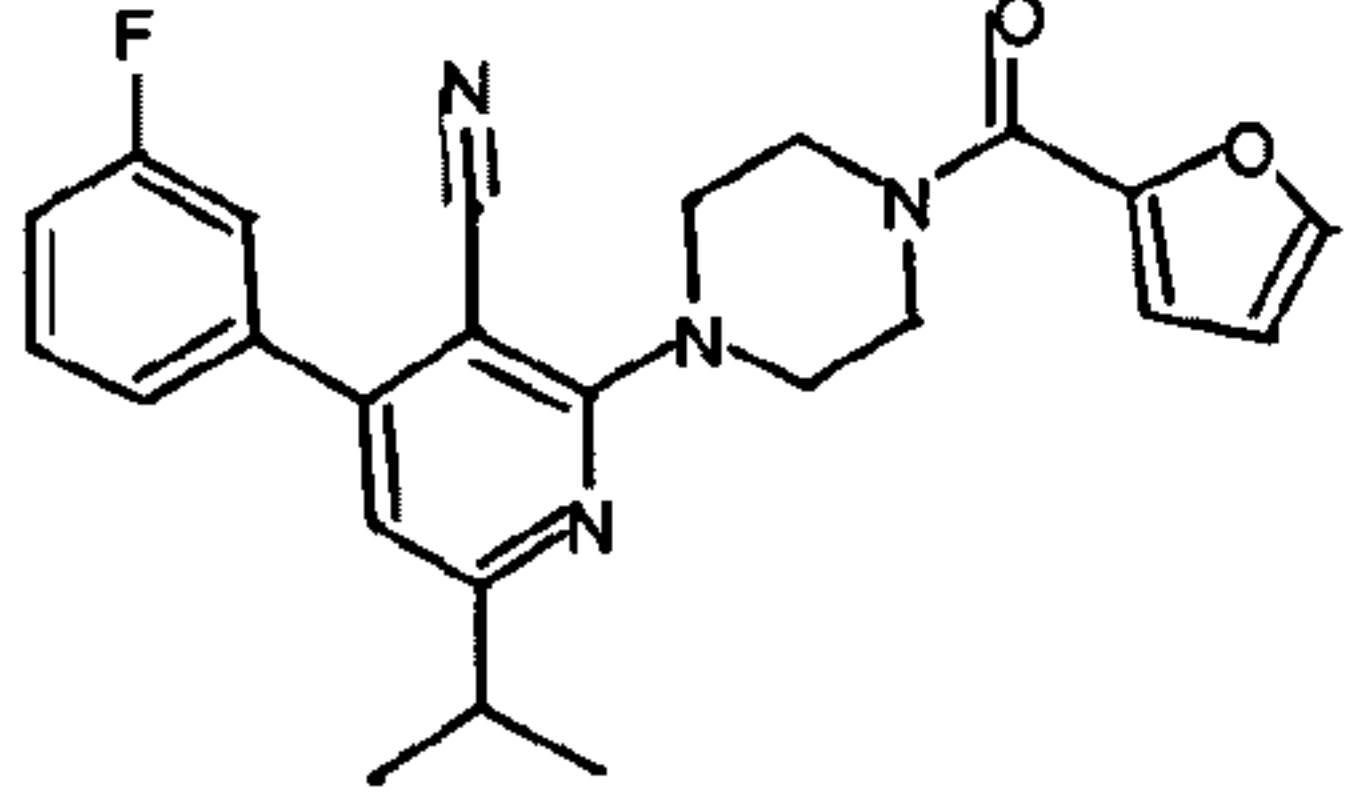
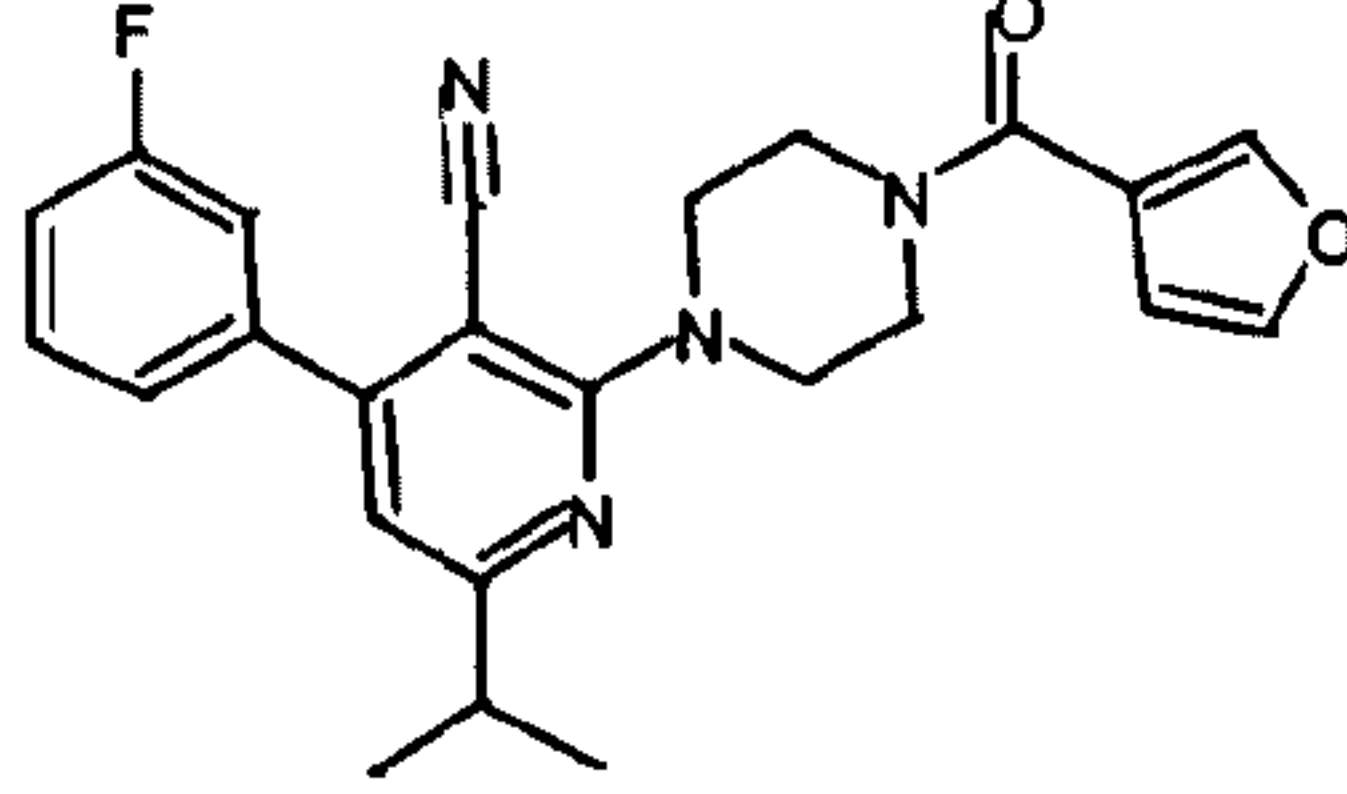
In another embodiment, the compound is selected from any one of the compounds set forth in Table 1, below.

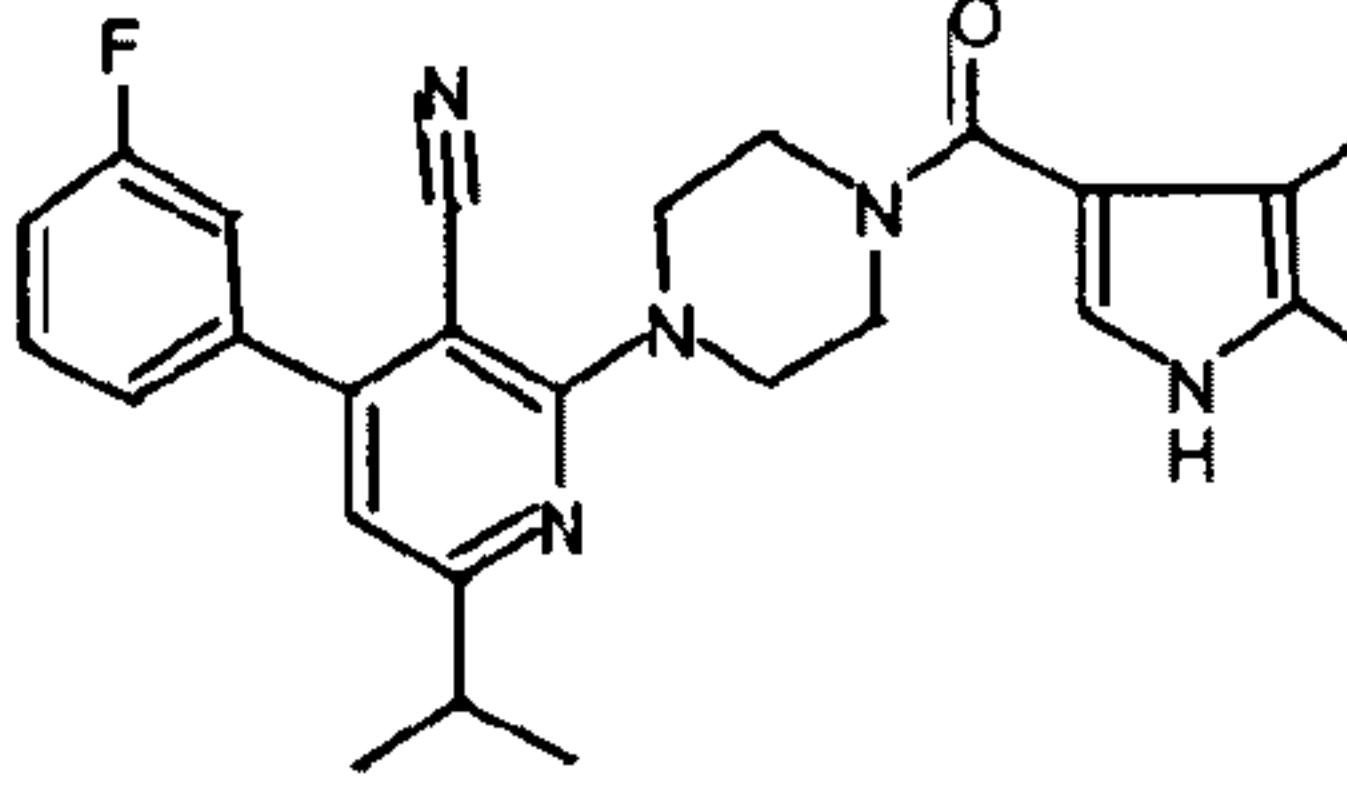
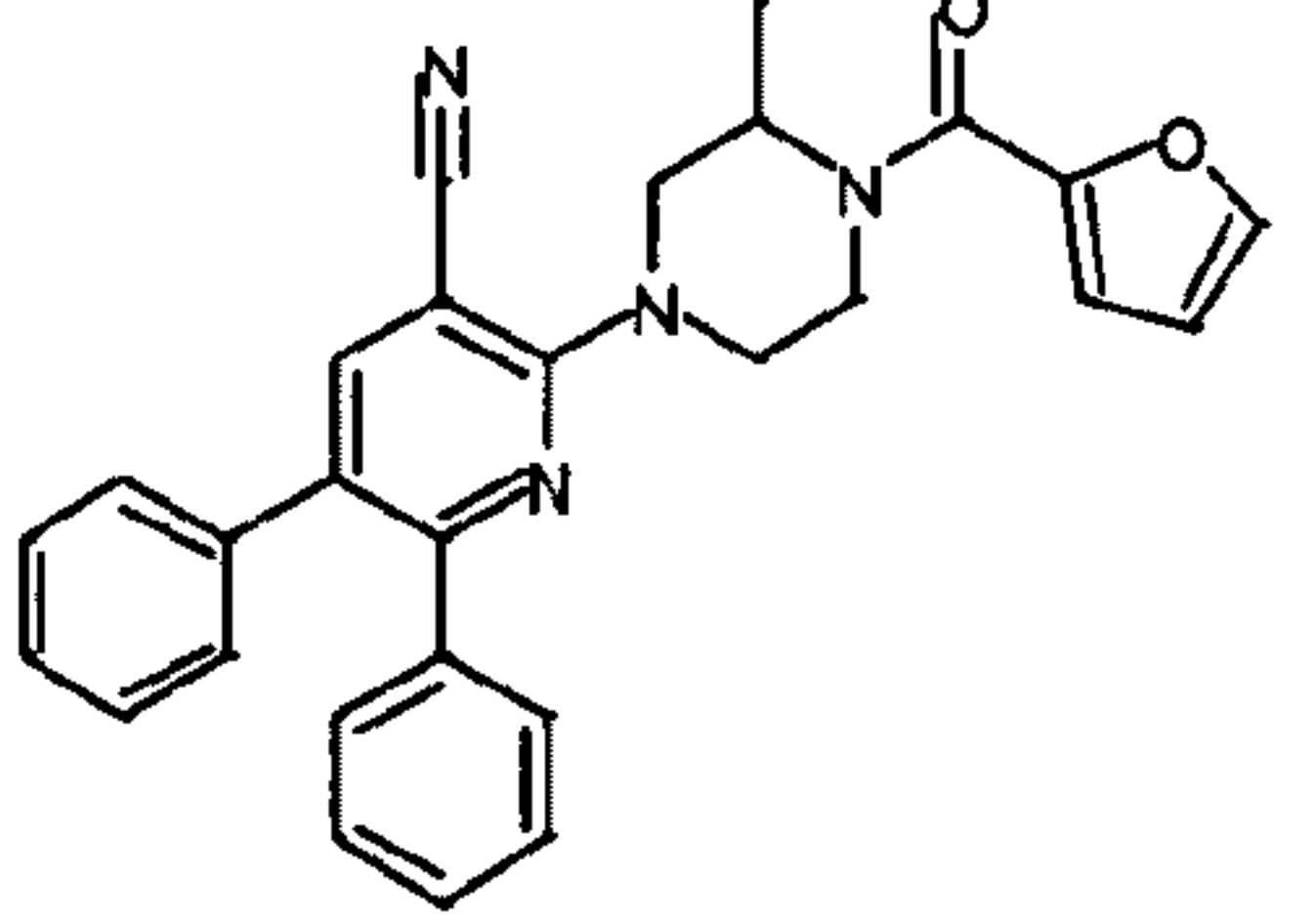
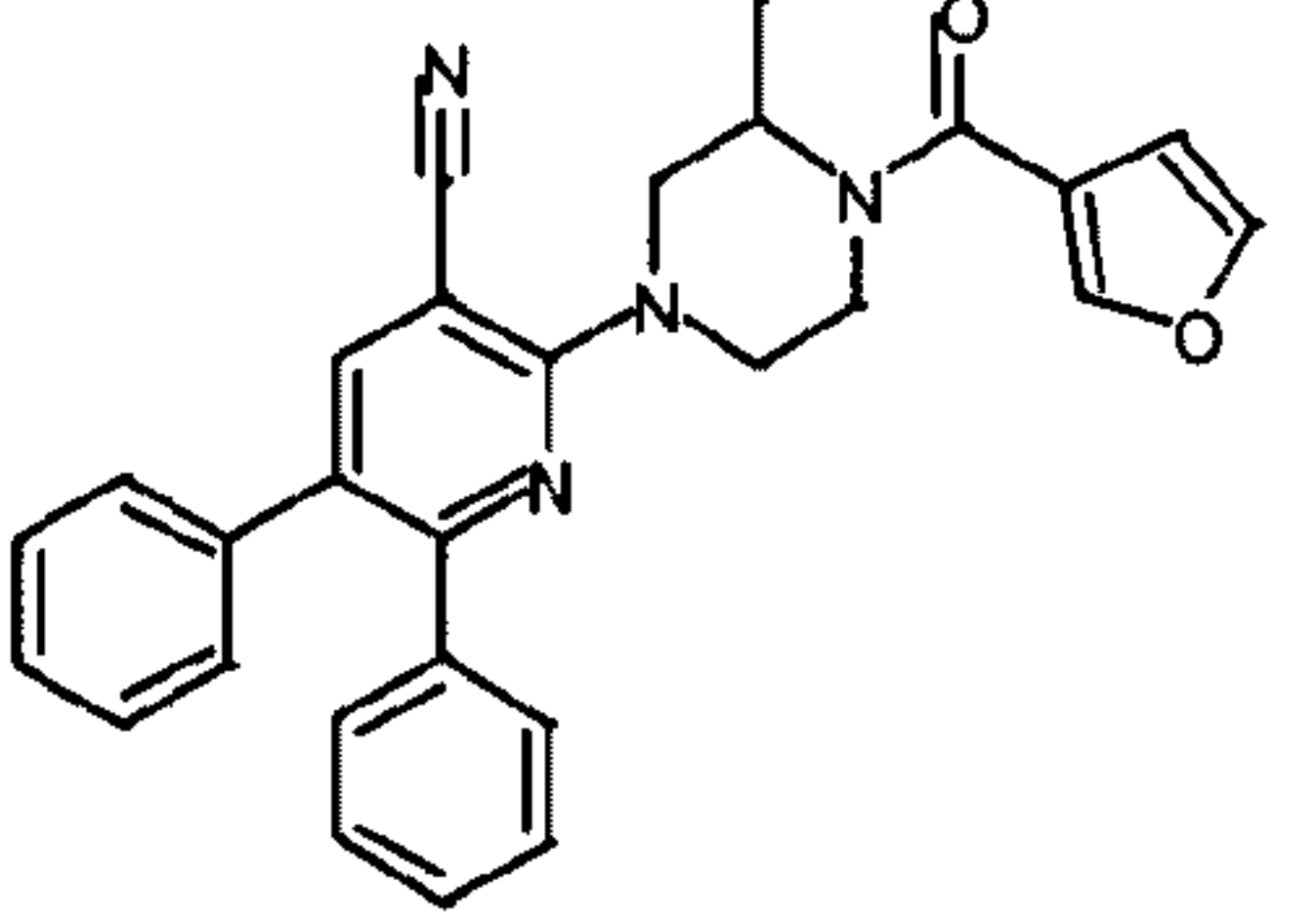
Table 1. Exemplary Compounds of Formula I.

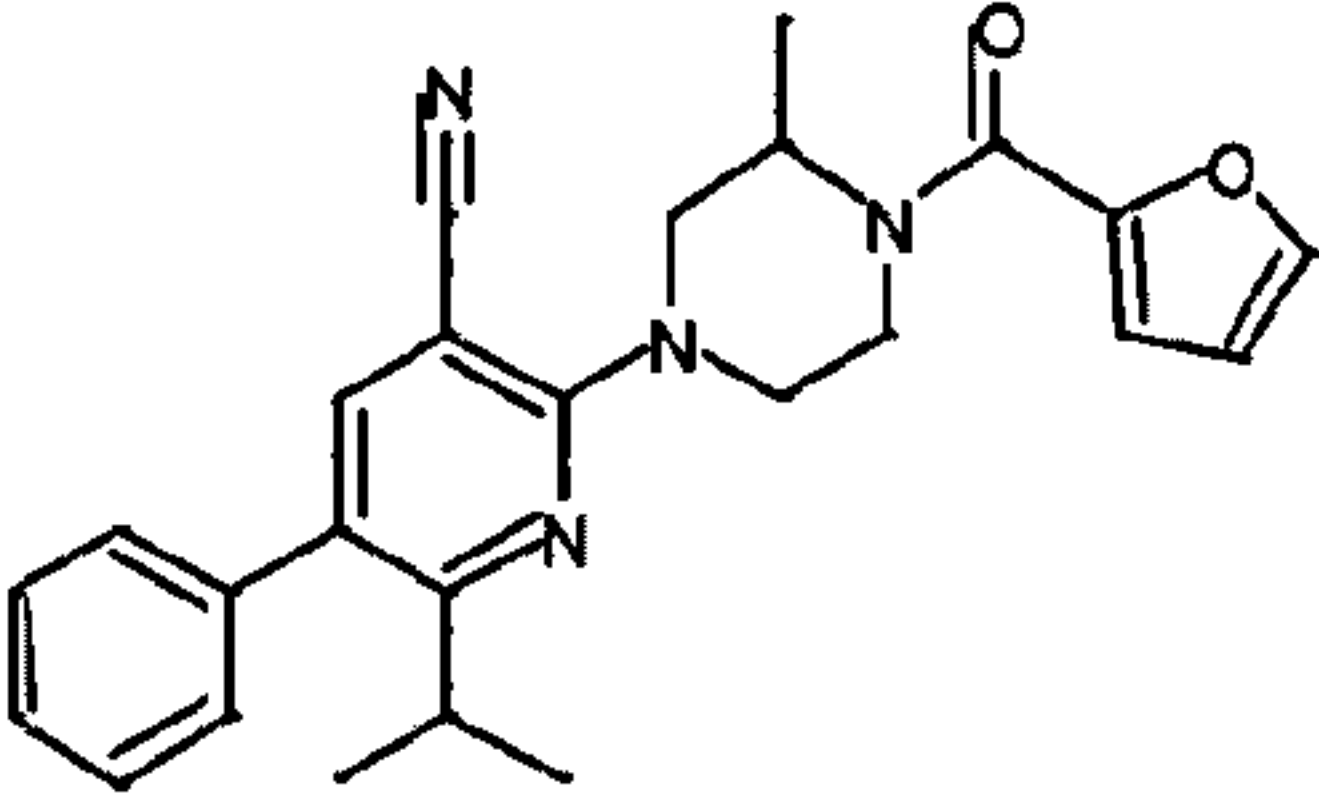
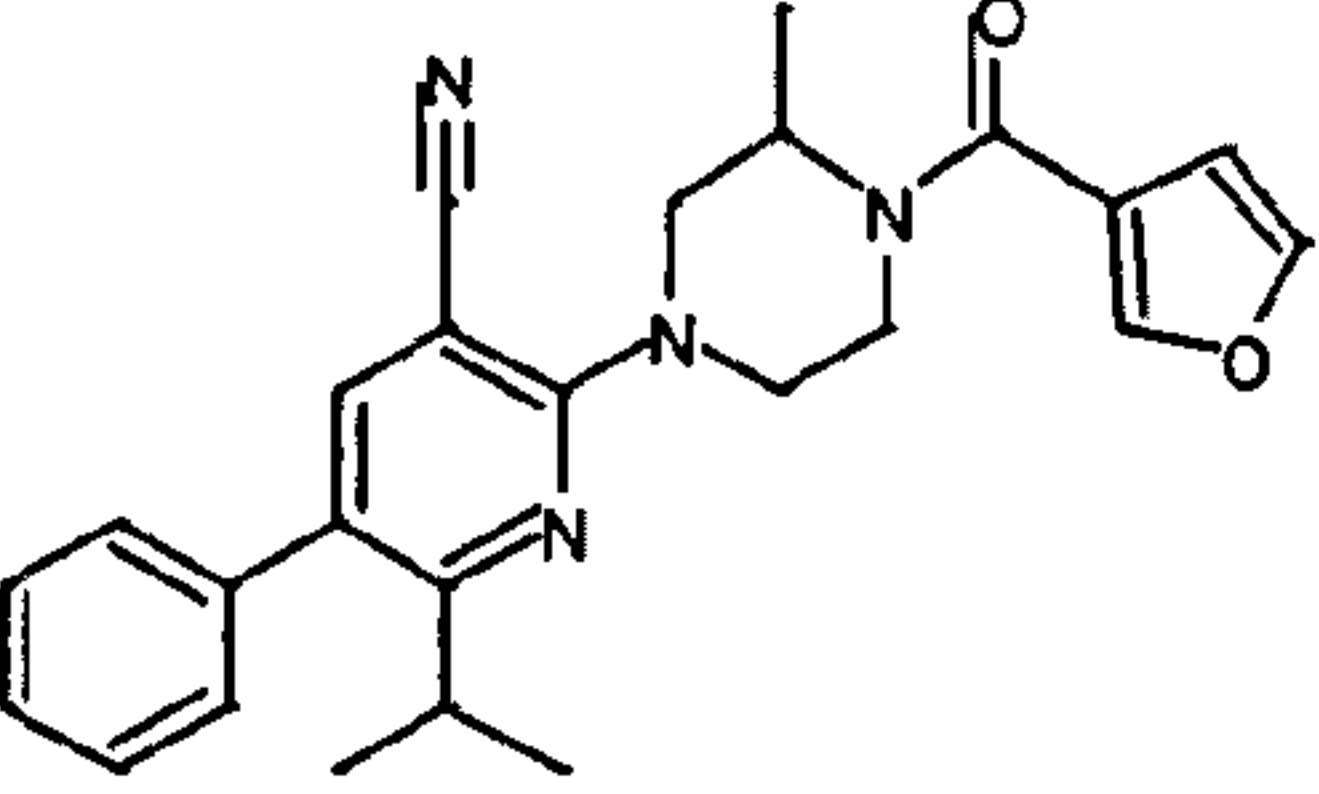
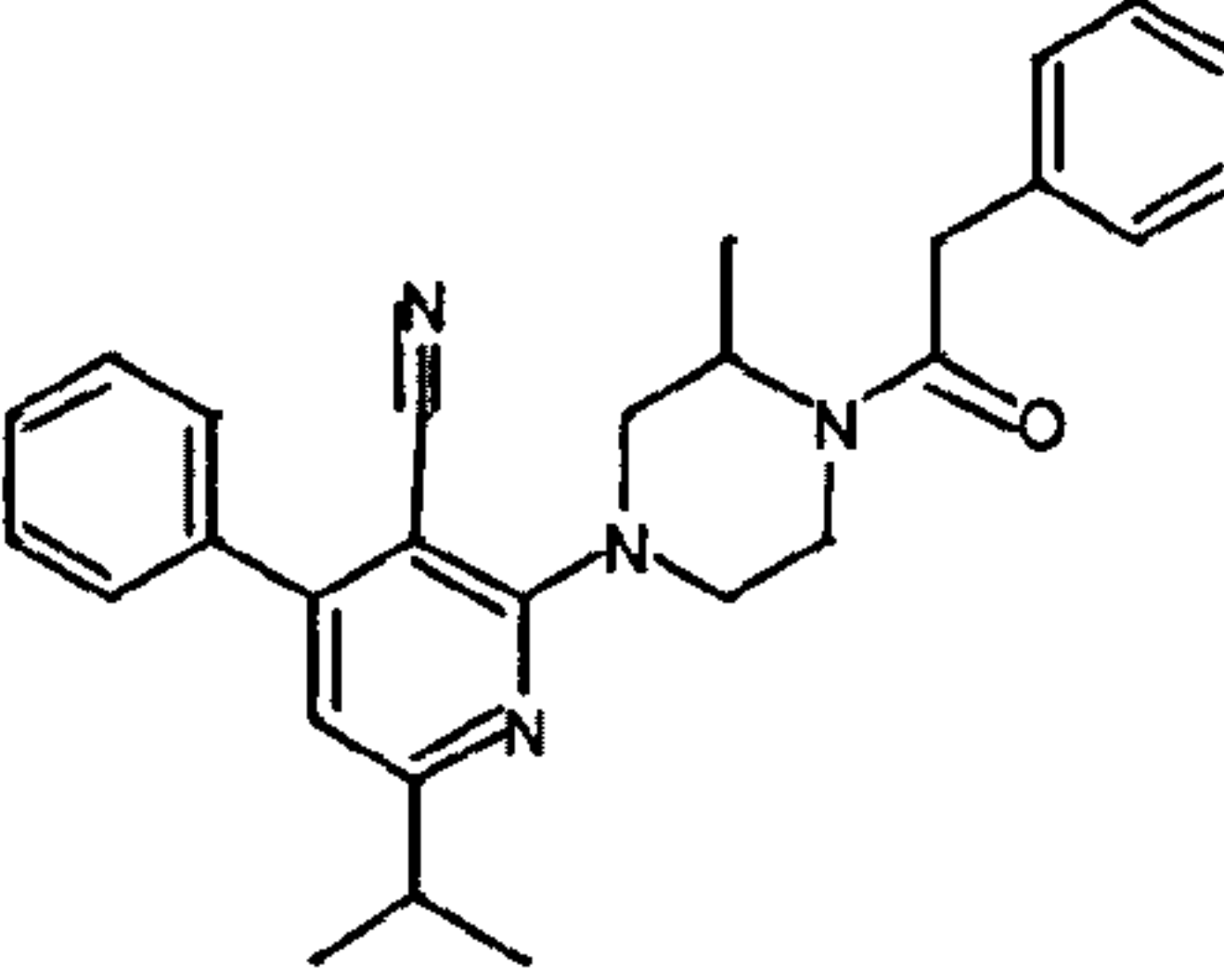
Cmpd No.	Structure	Cmpd No.	Structure
100		103	
101		104	
102		105	

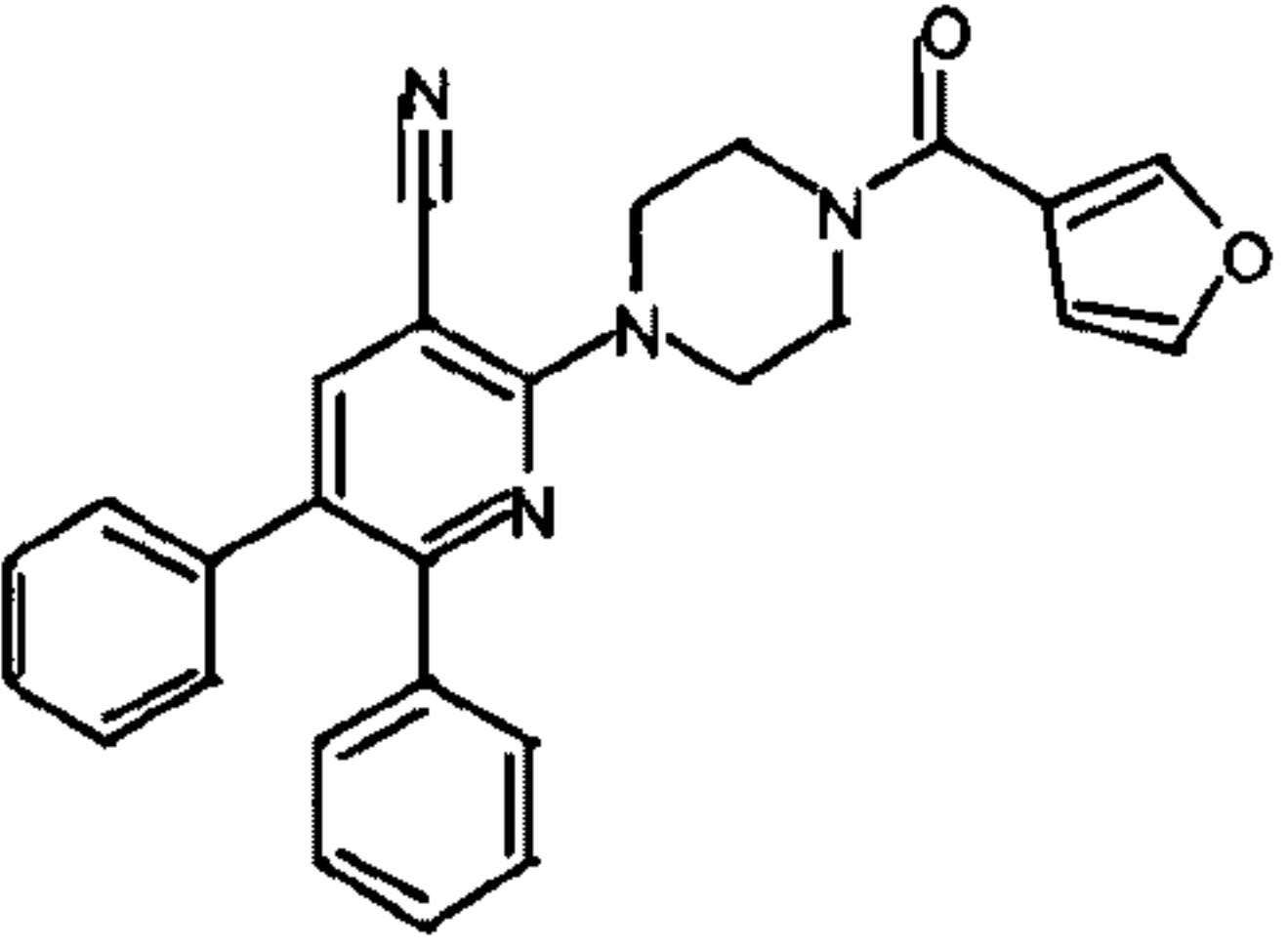
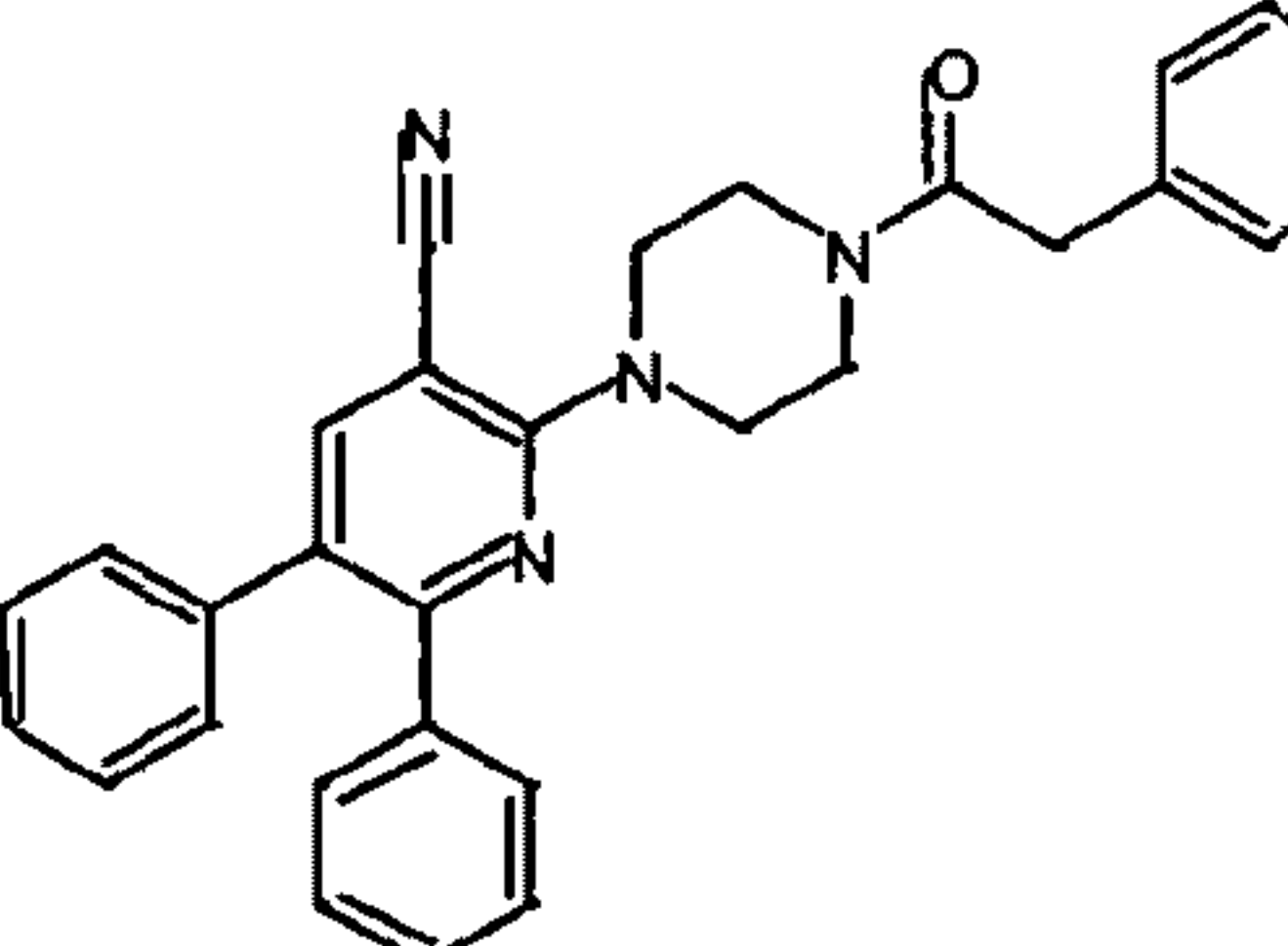
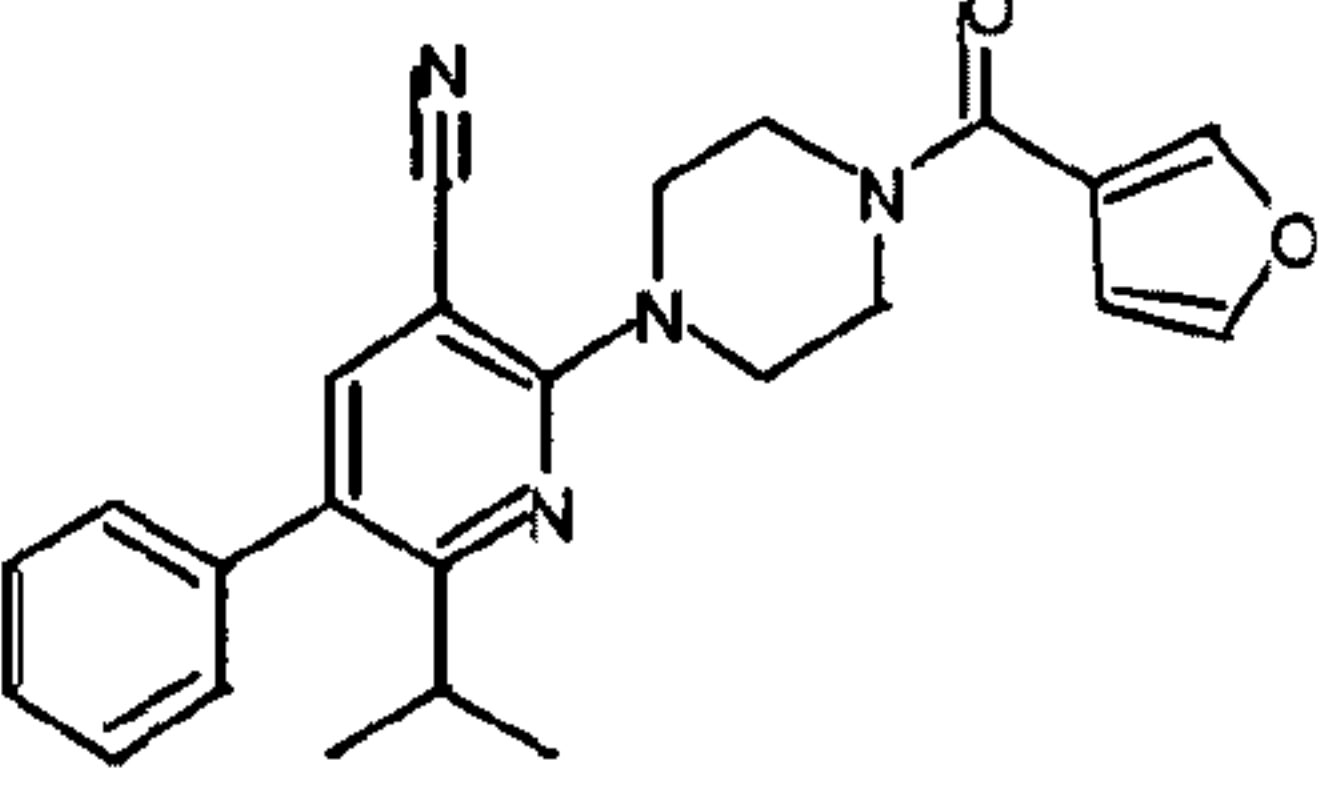
Cmpd No.	Structure
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107	
108	

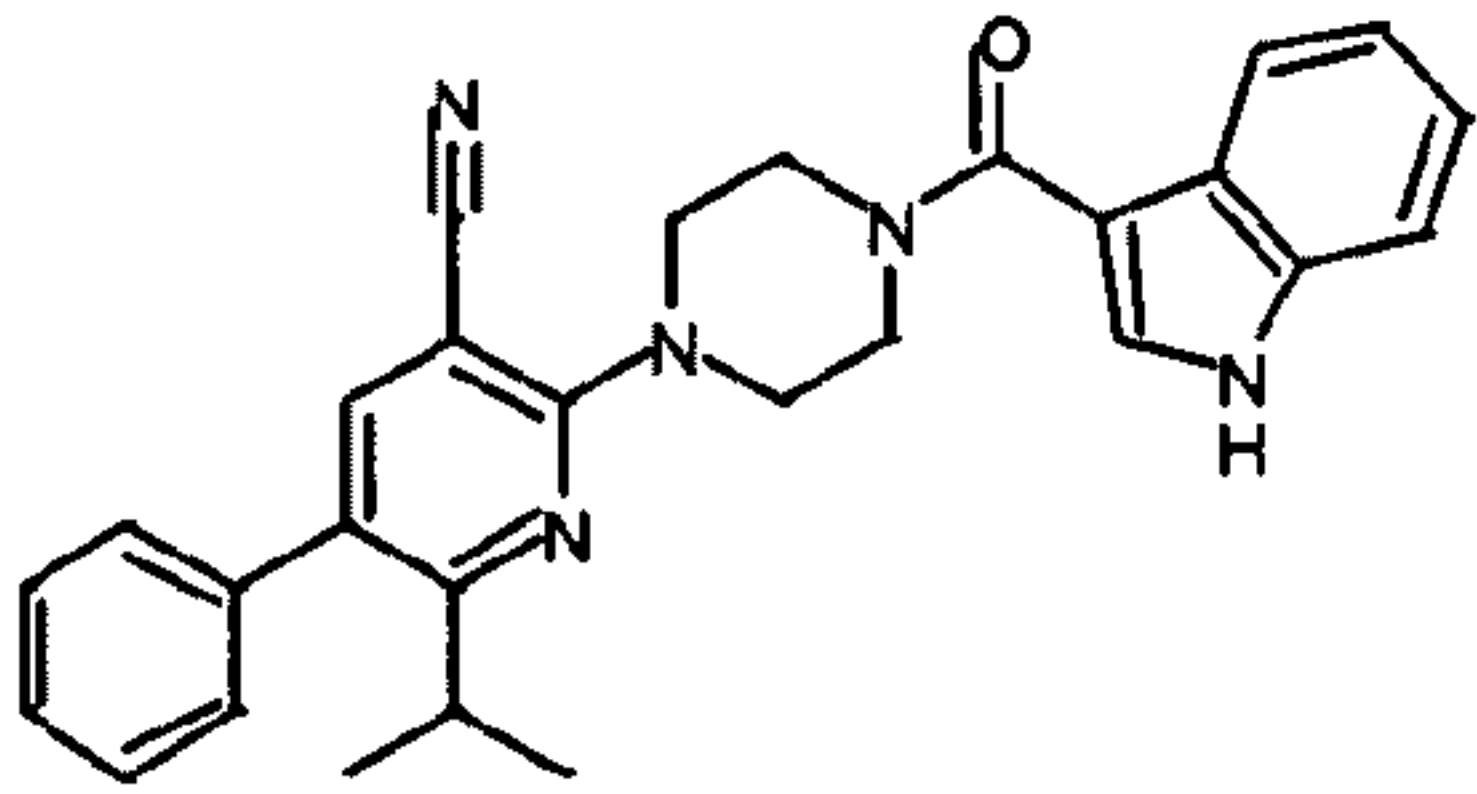
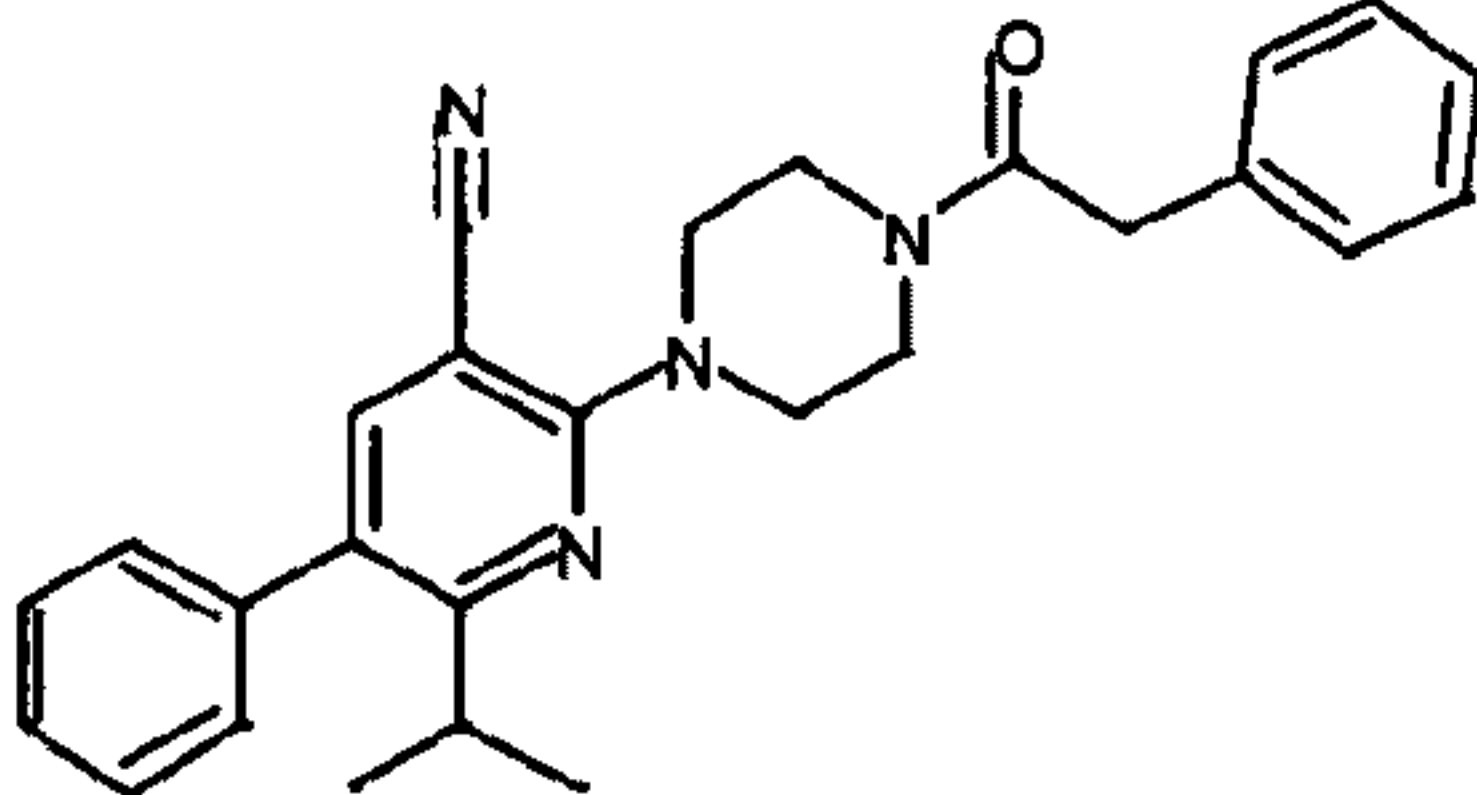
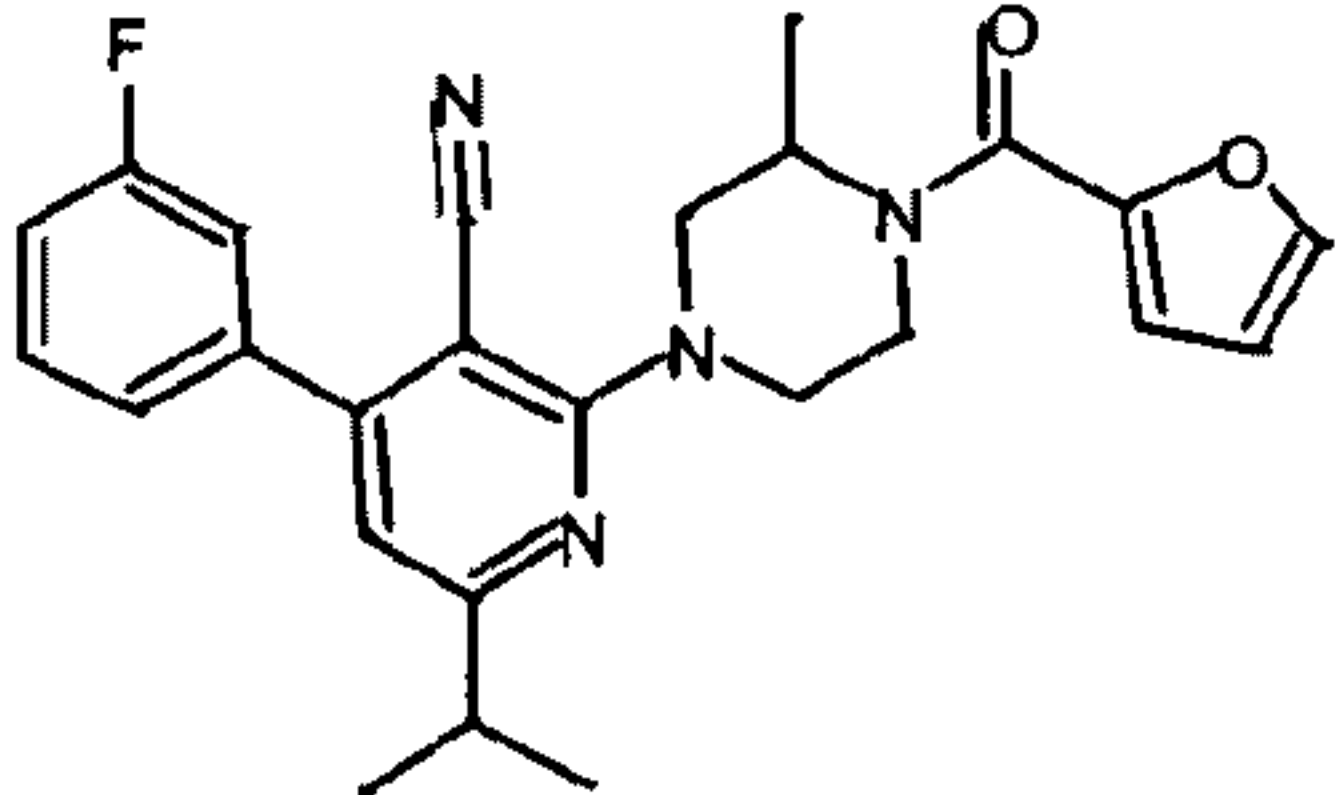
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110	
111	

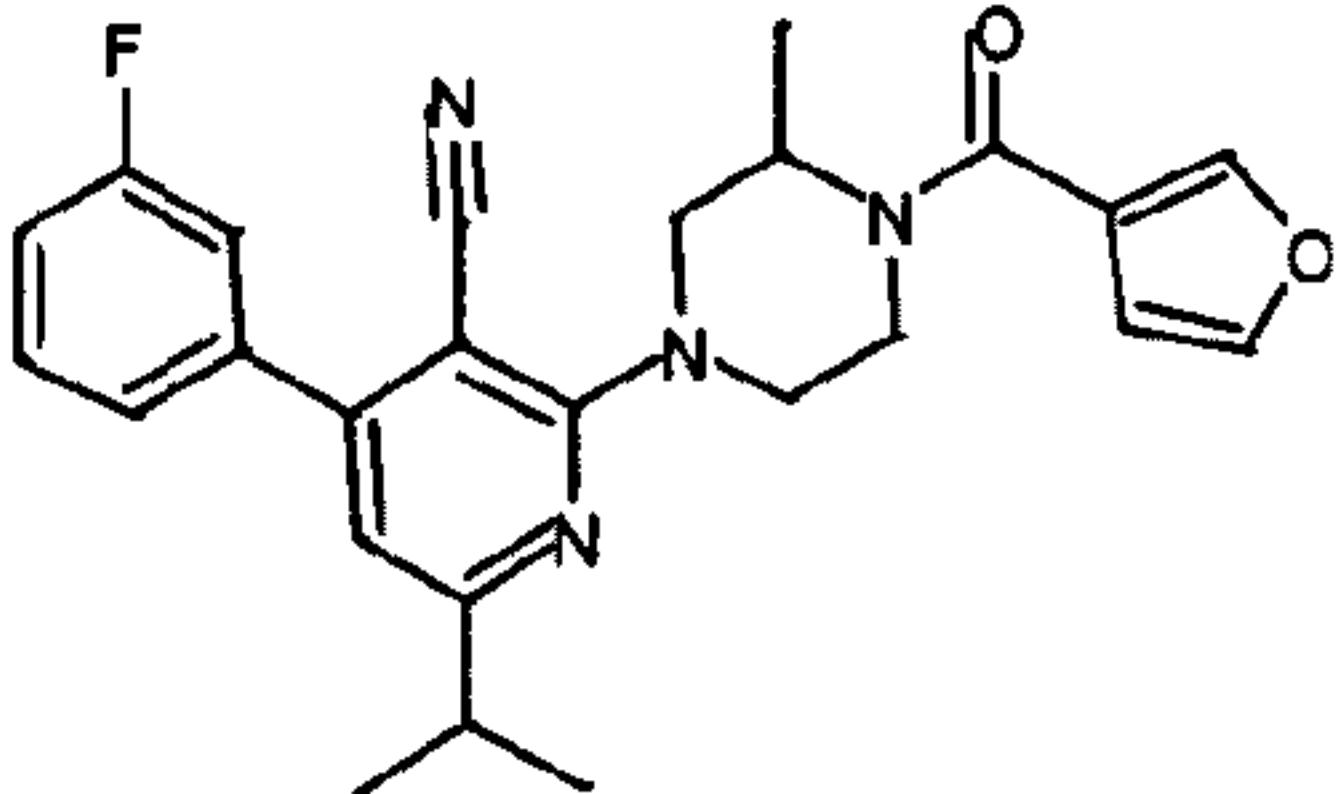
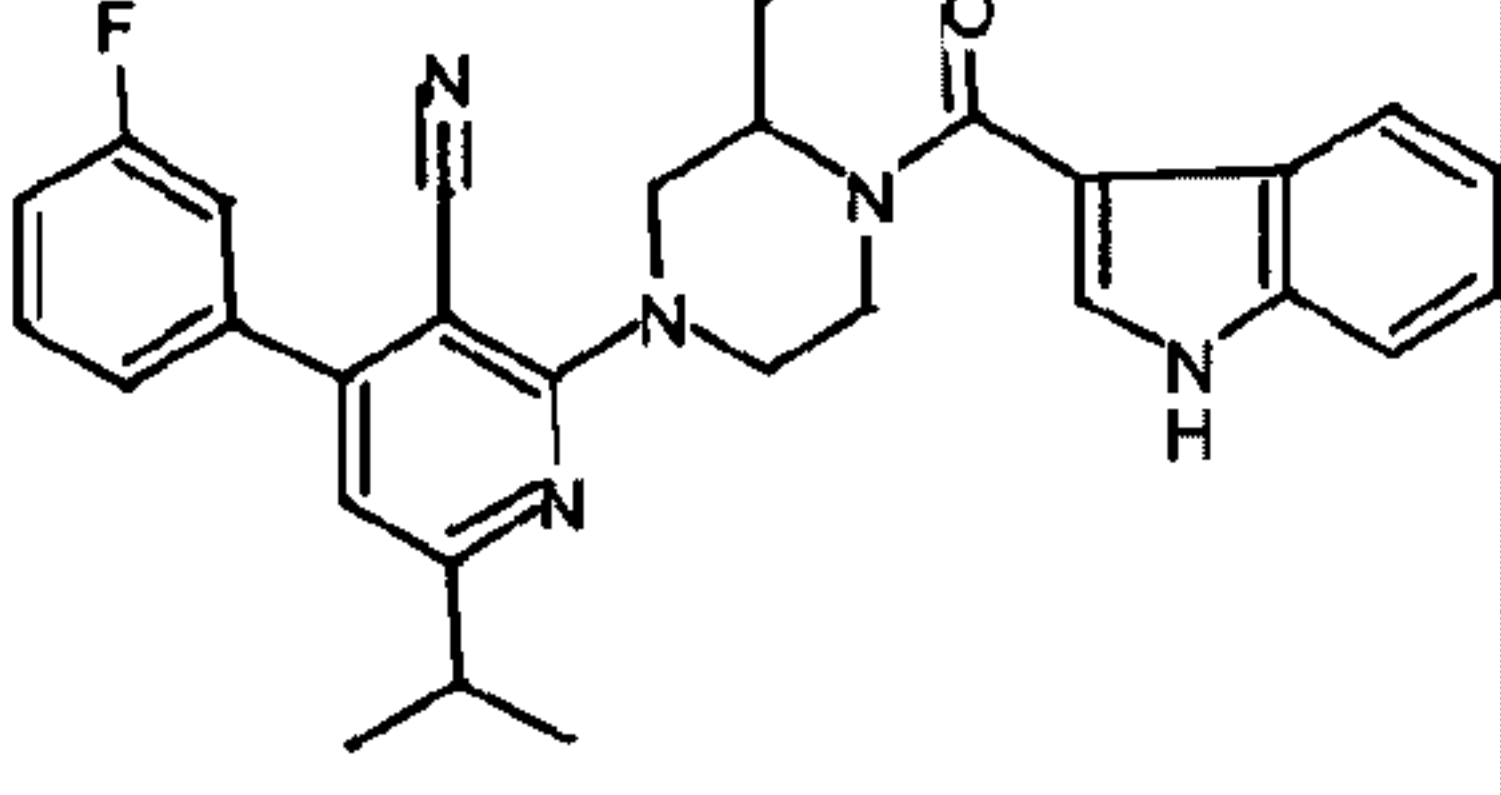
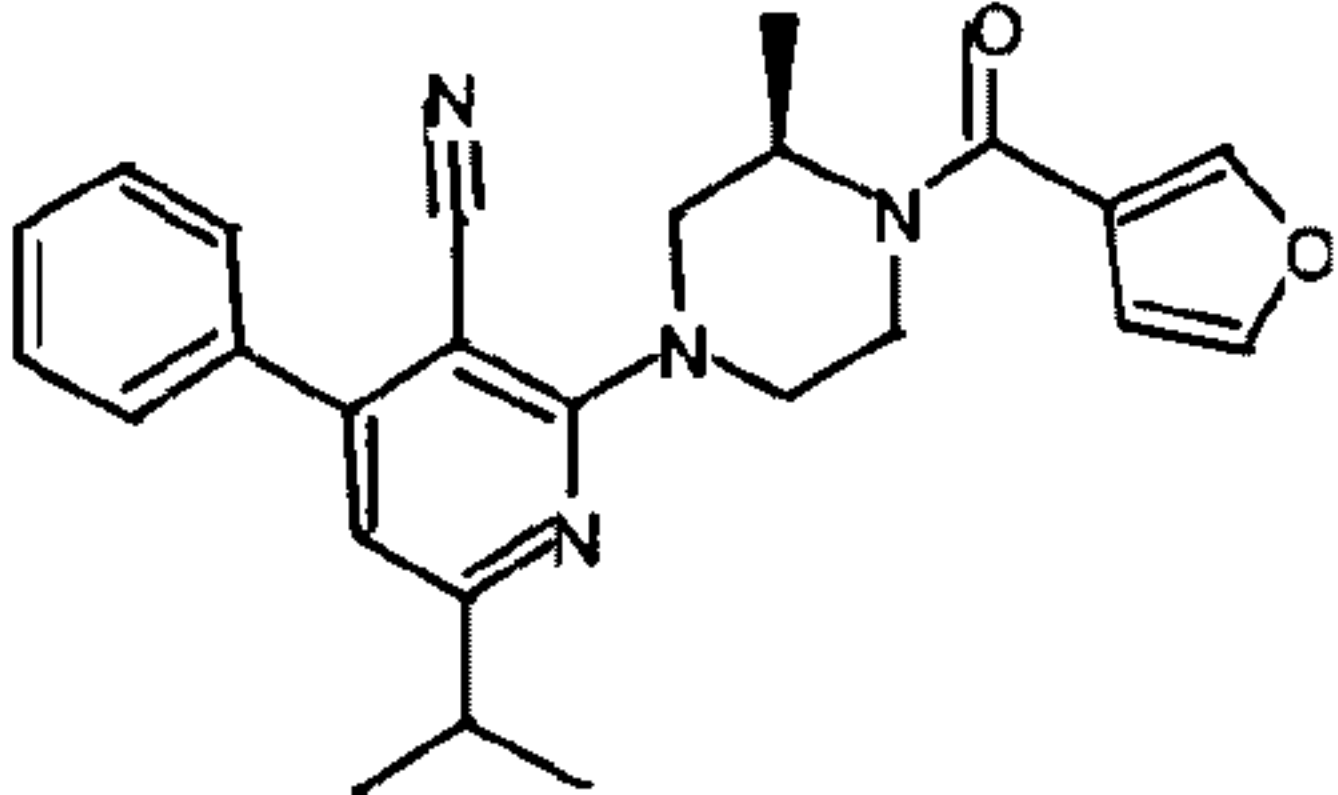
Cmpd No.	Structure
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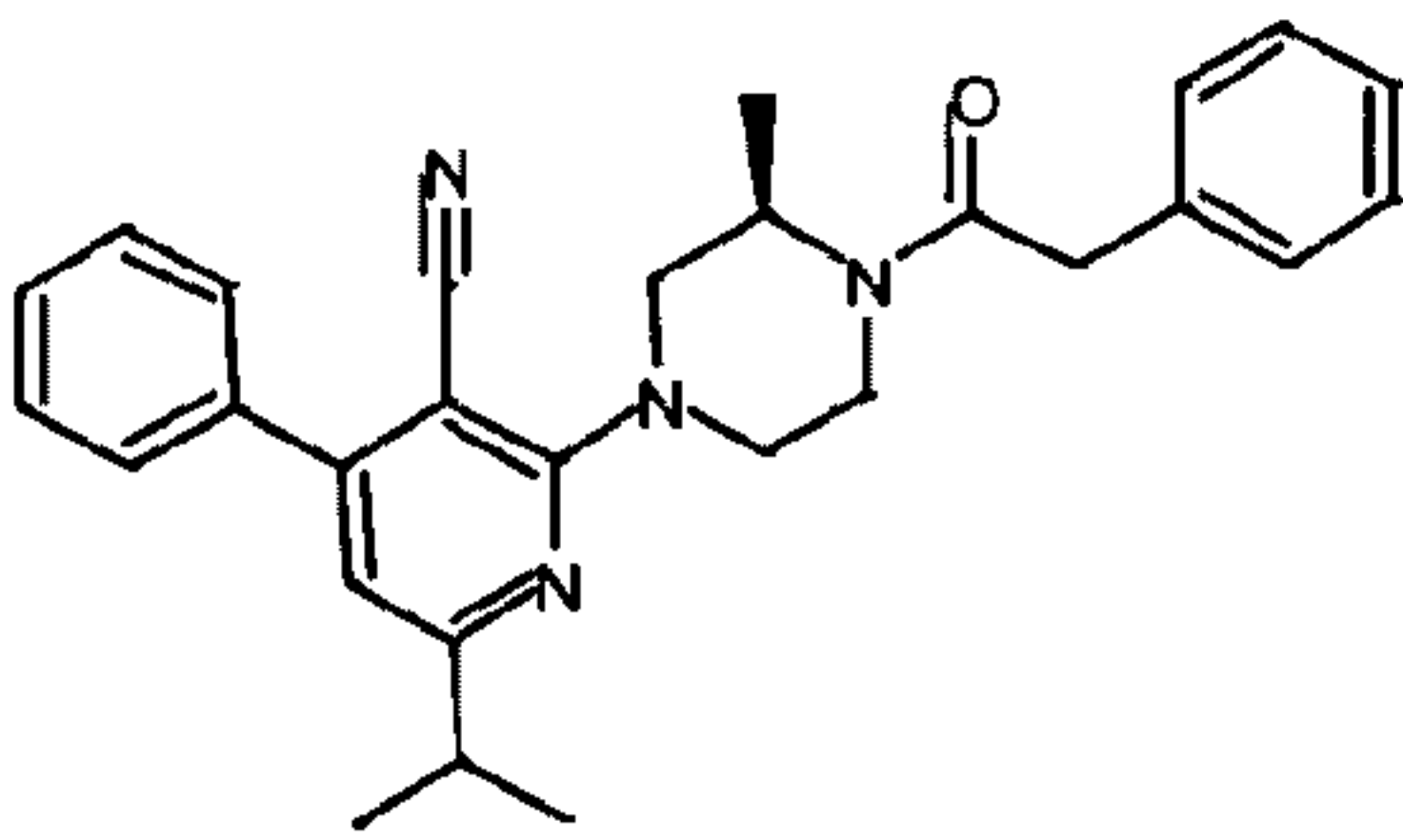
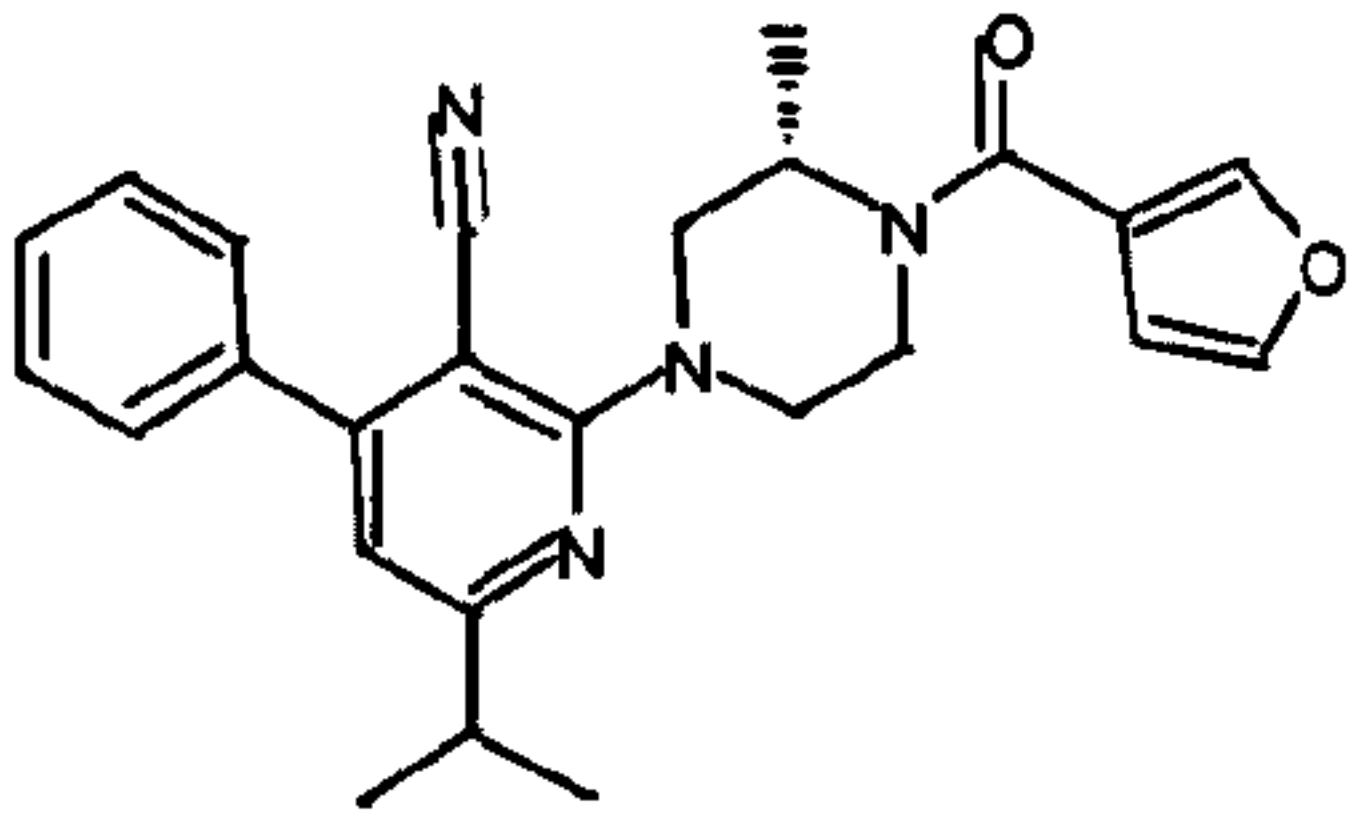
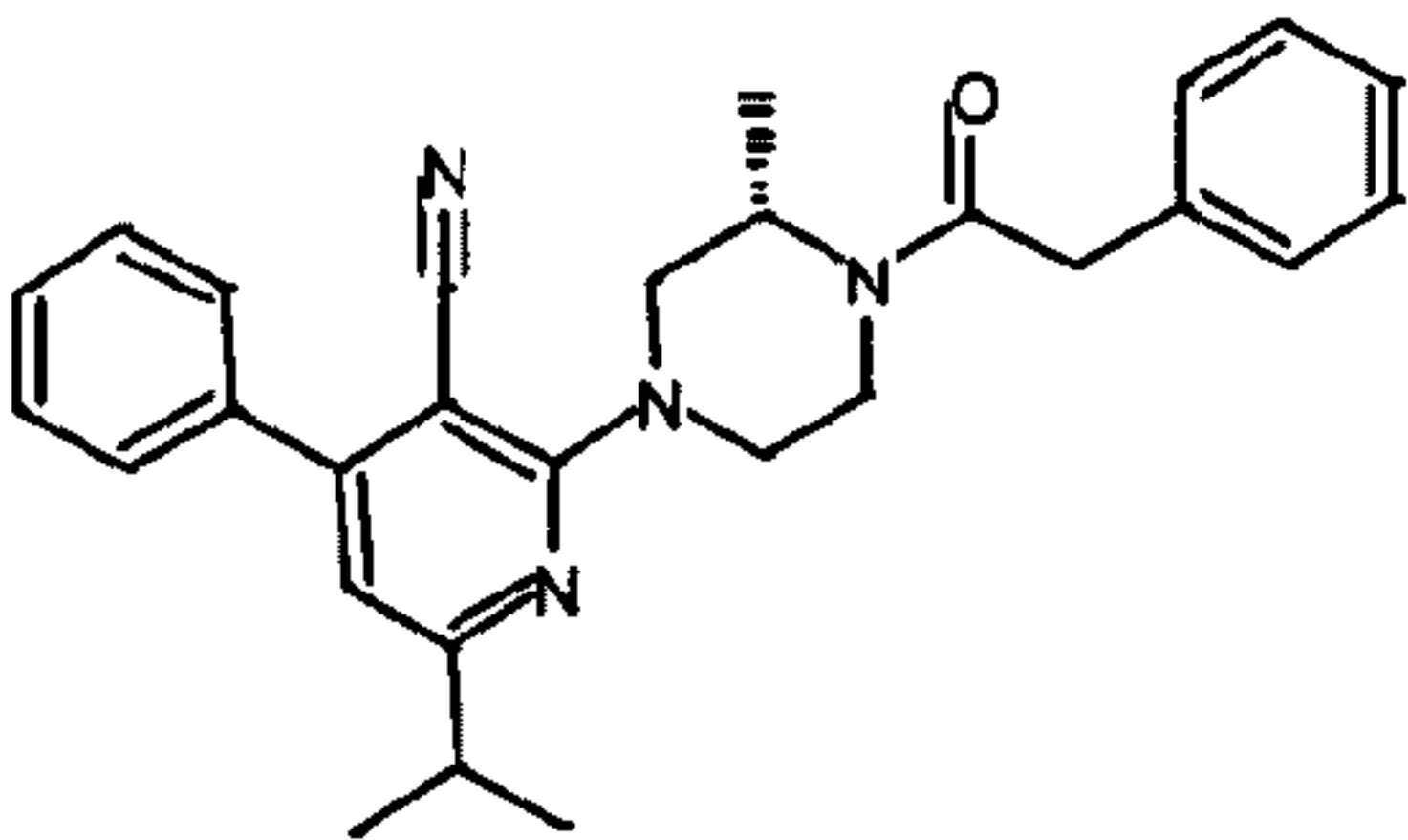
Cmpd No.	Structure
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118	

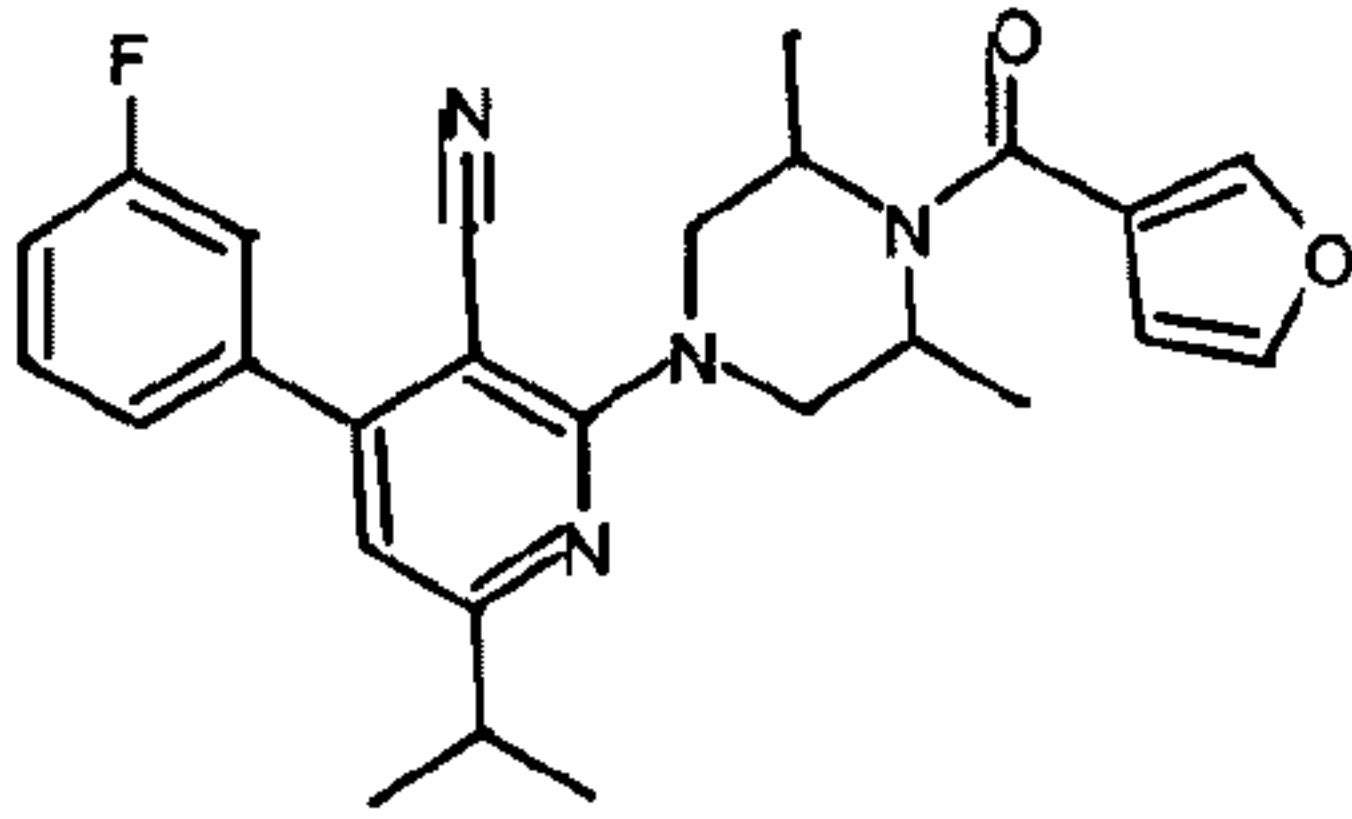
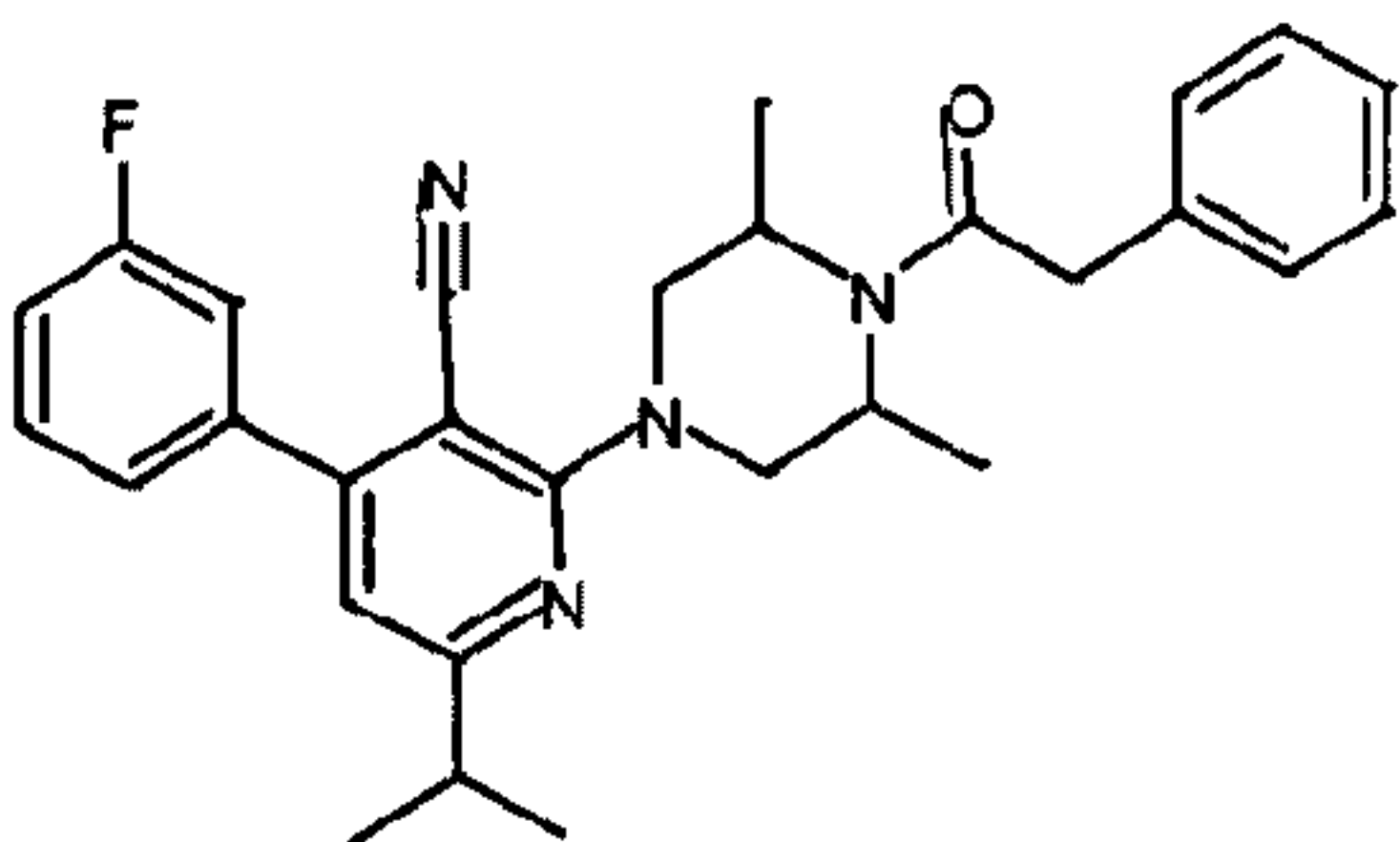
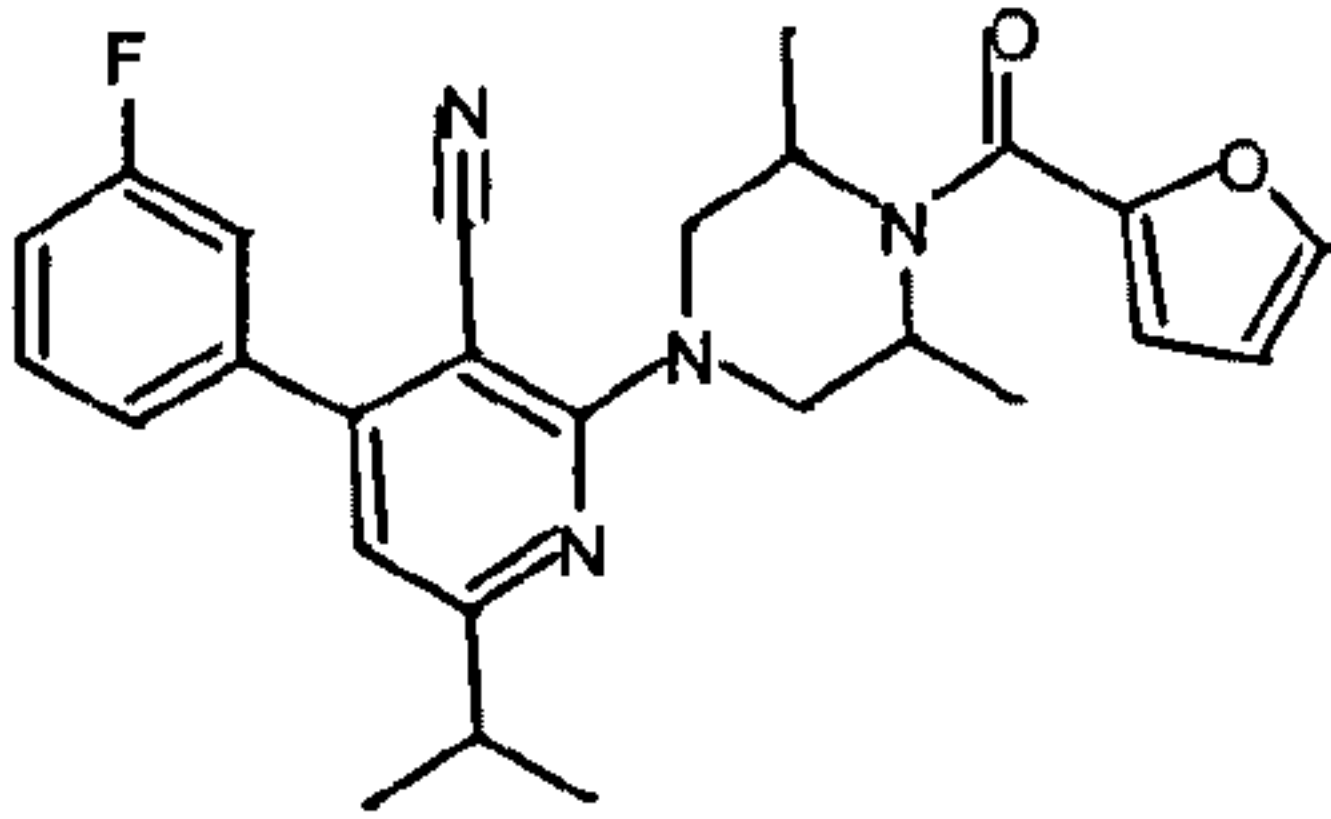
Cmpd No.	Structure
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121	

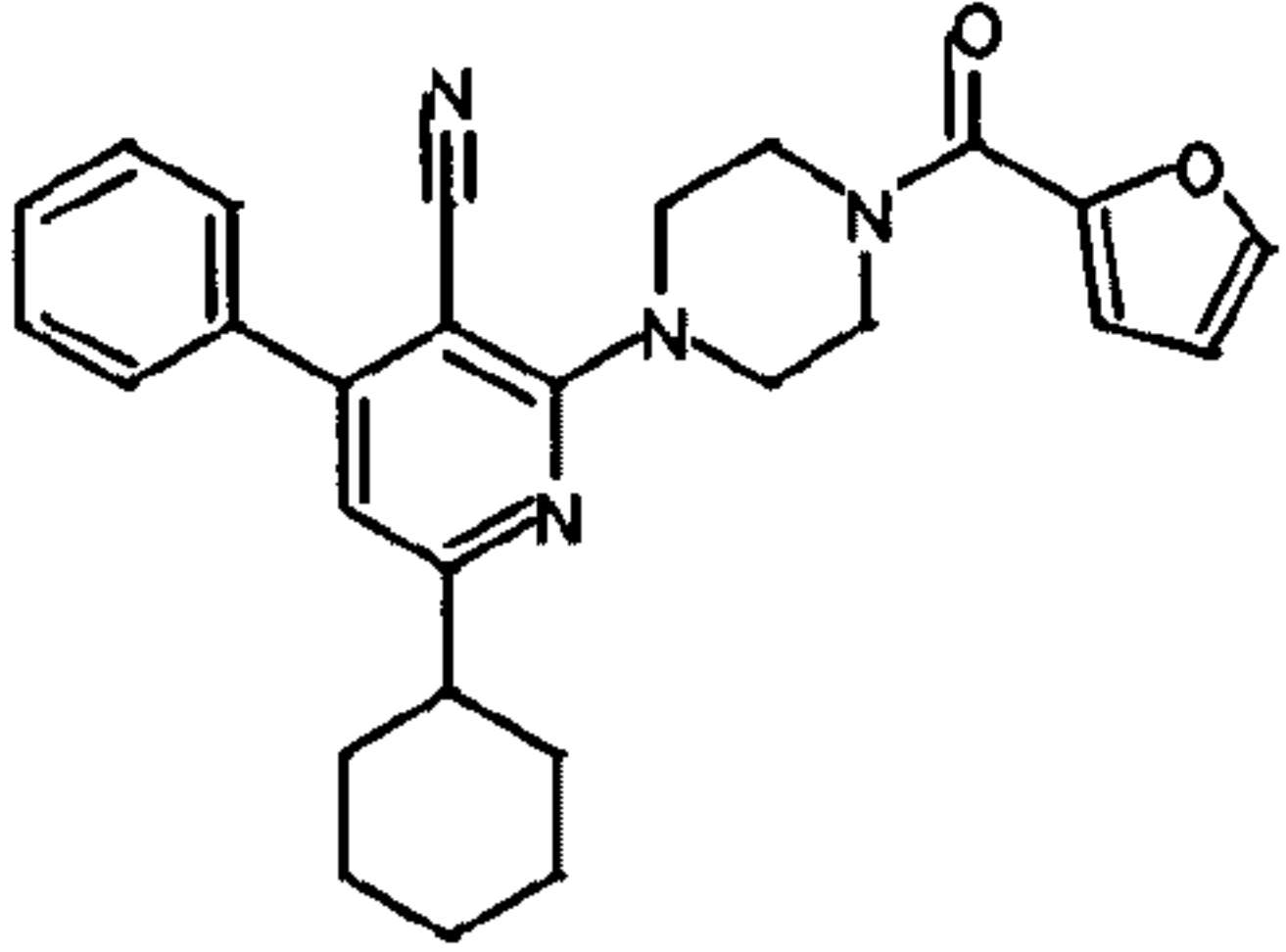
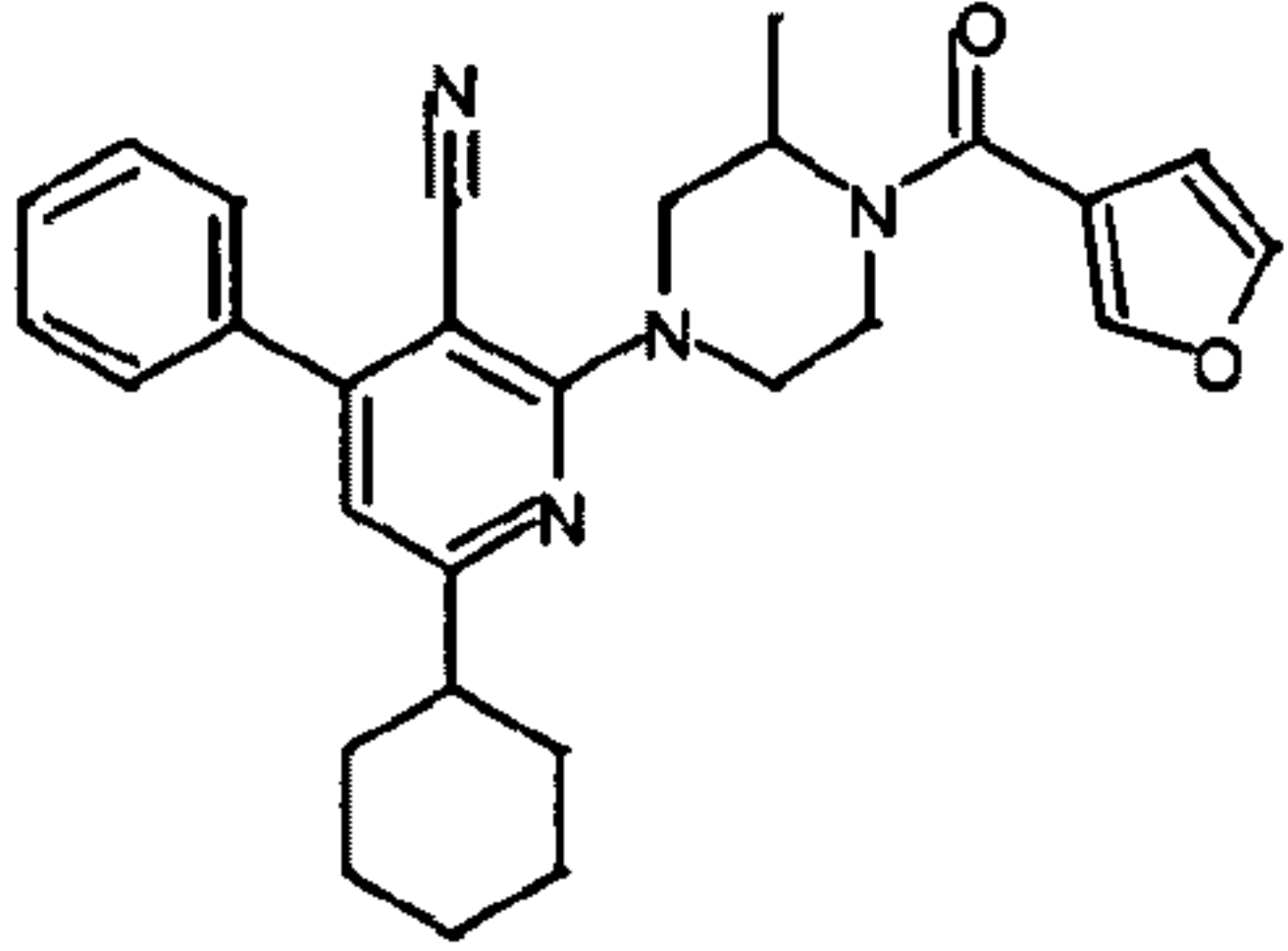
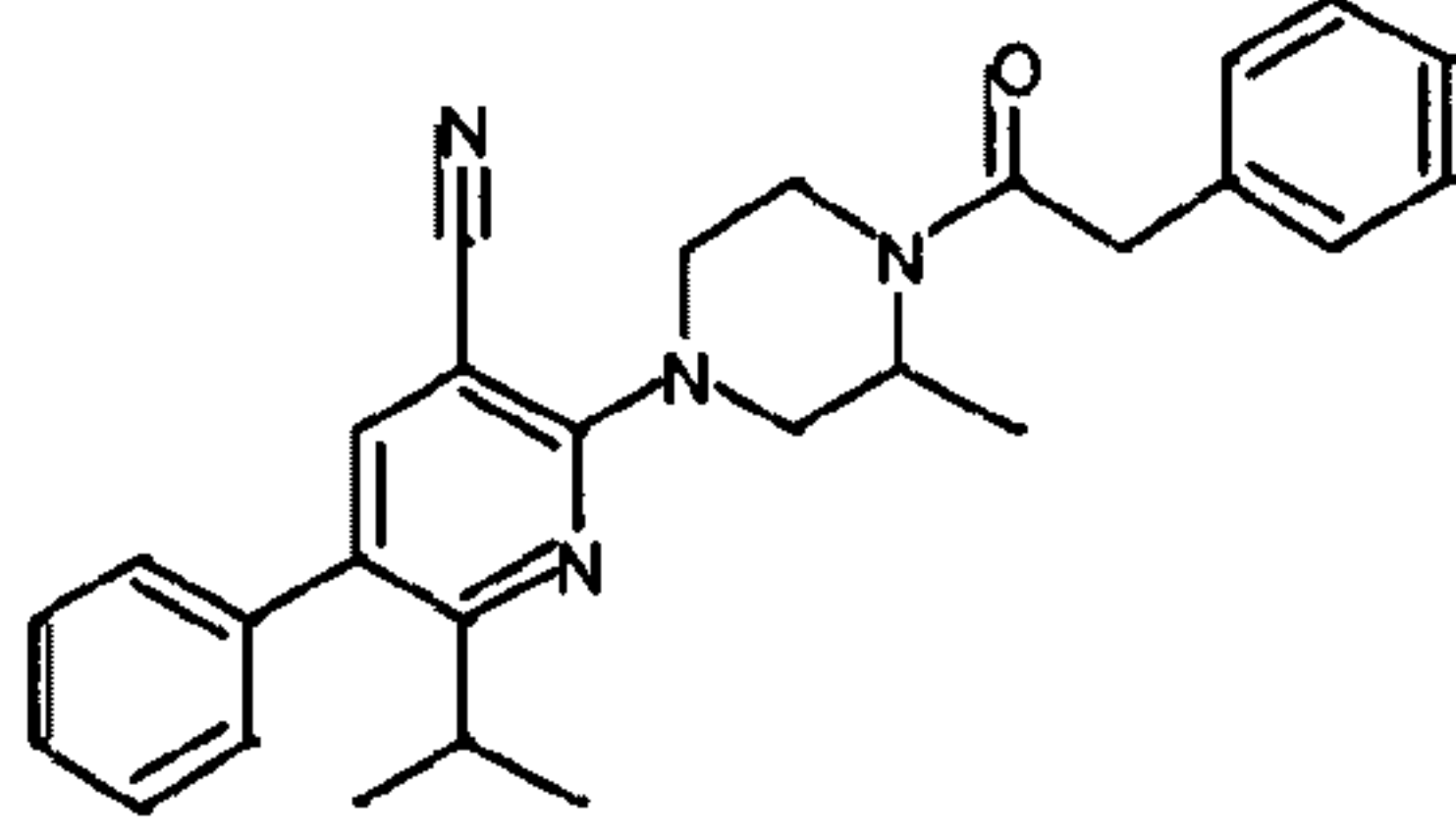
Cmpd No.	Structure
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123	
124	

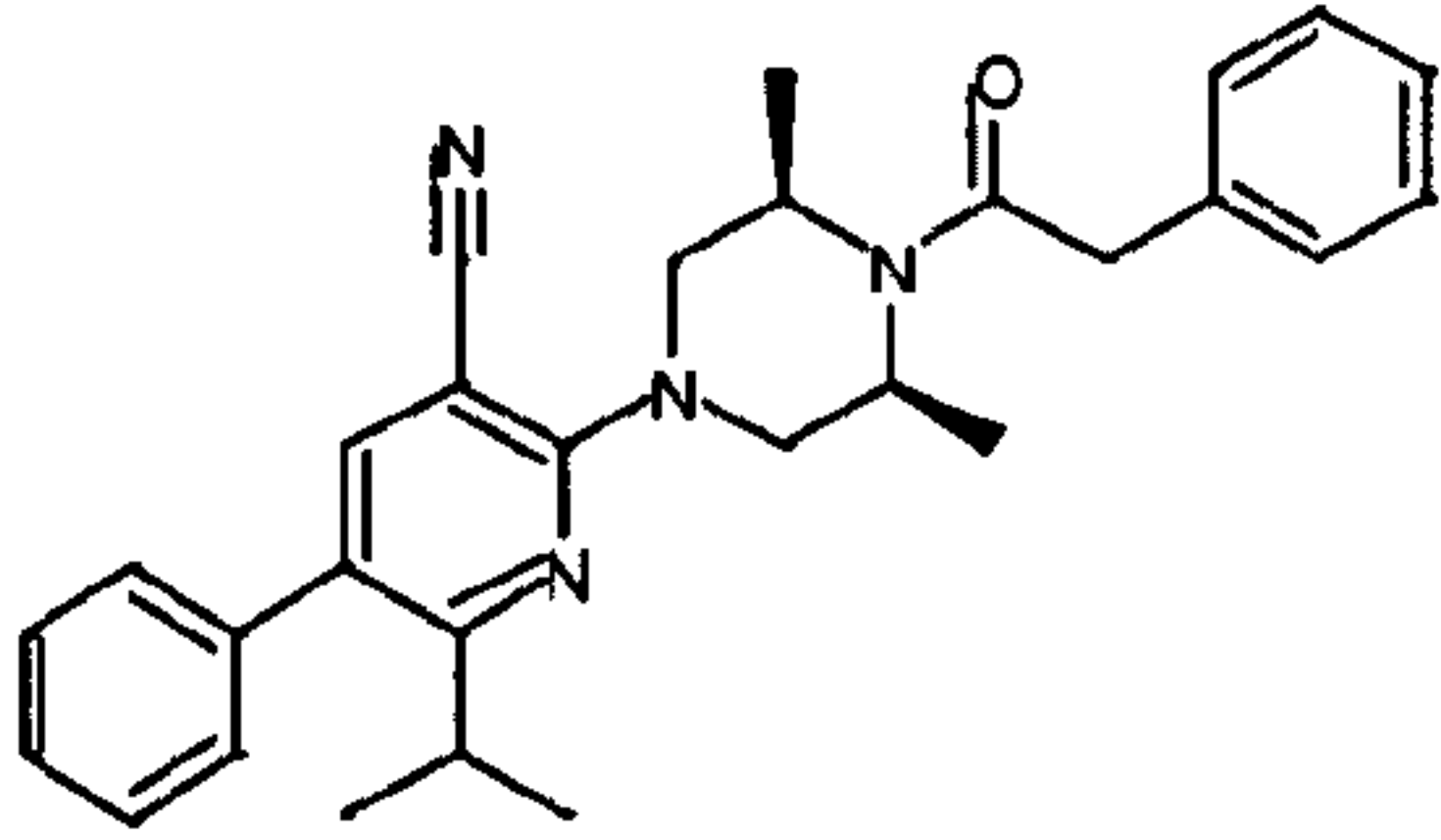
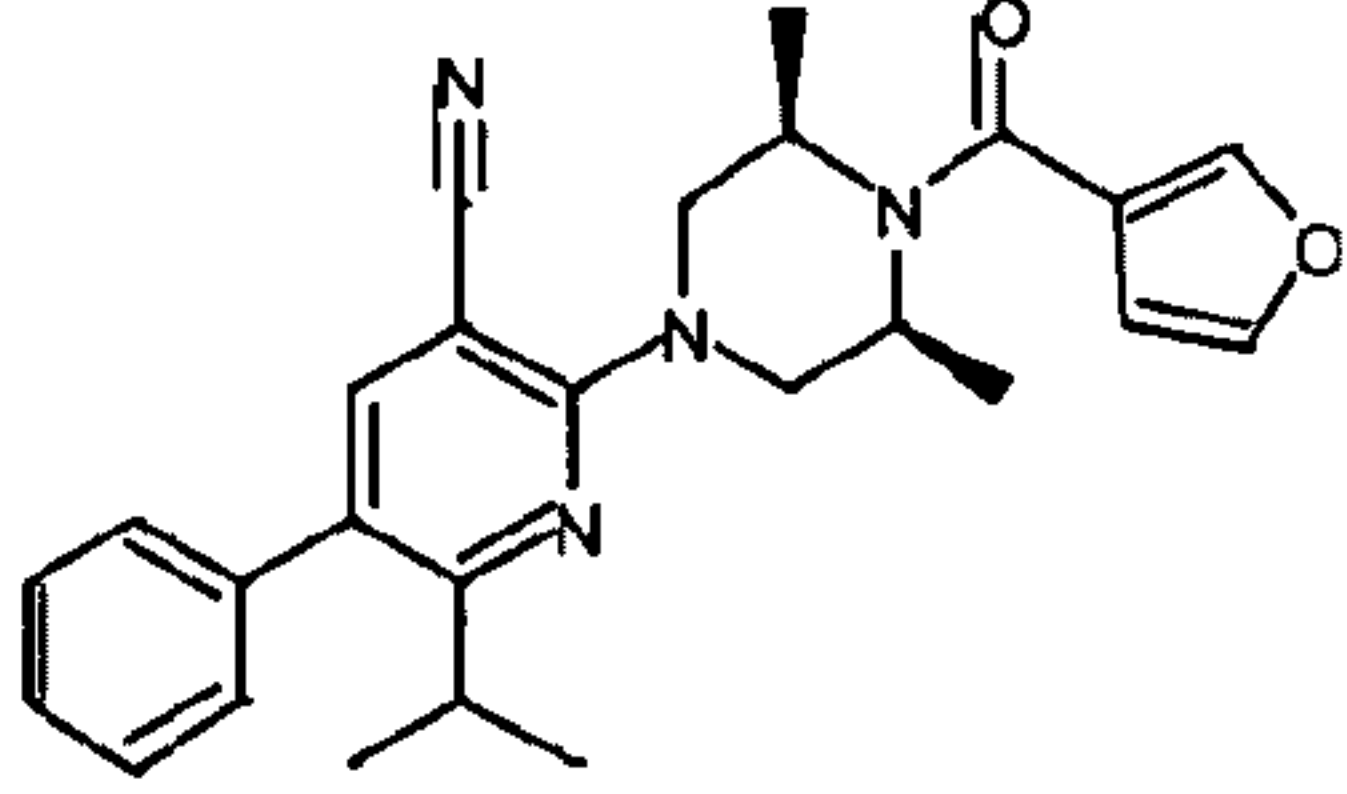
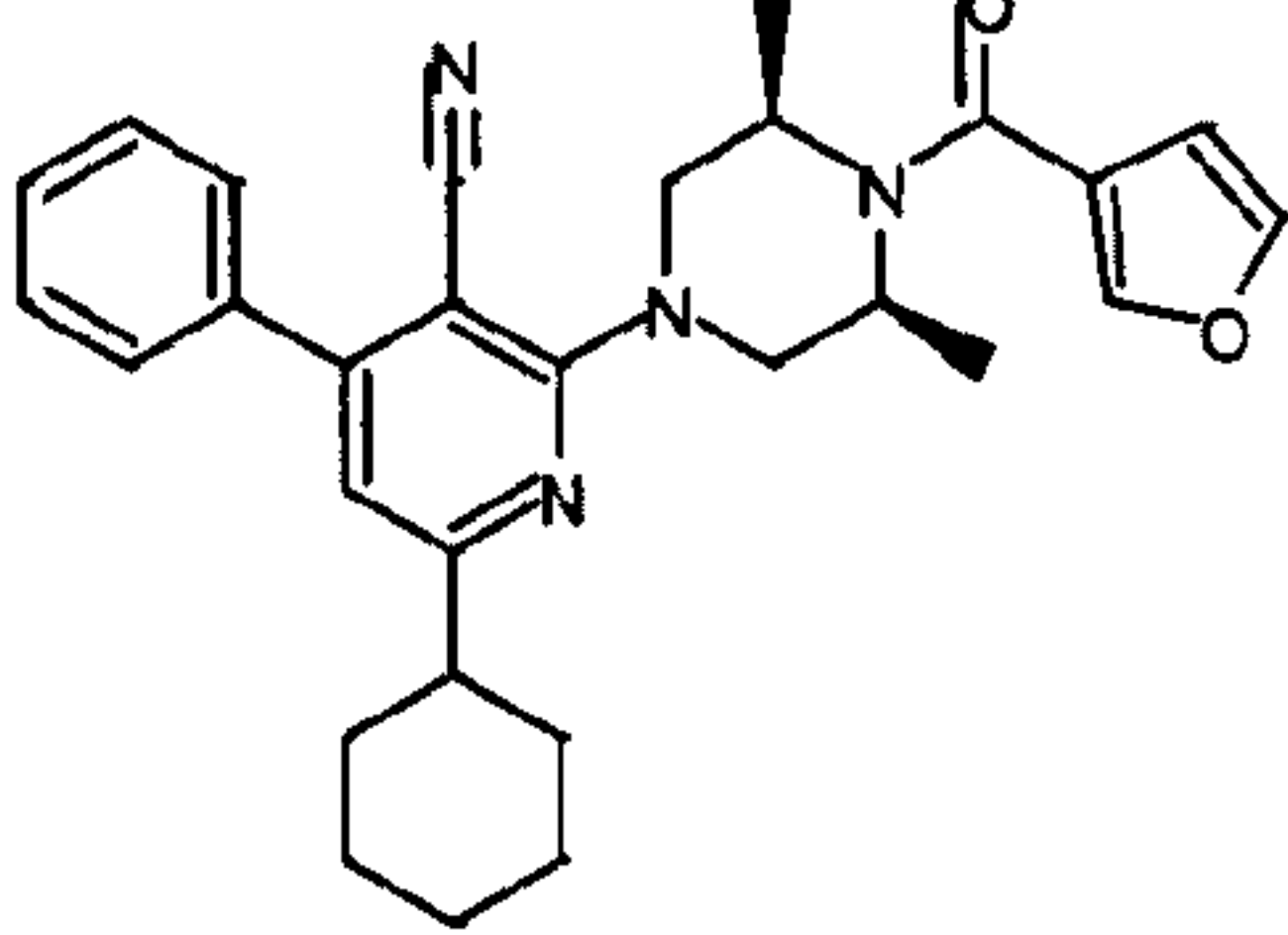
Cmpd No.	Structure
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126	
127	

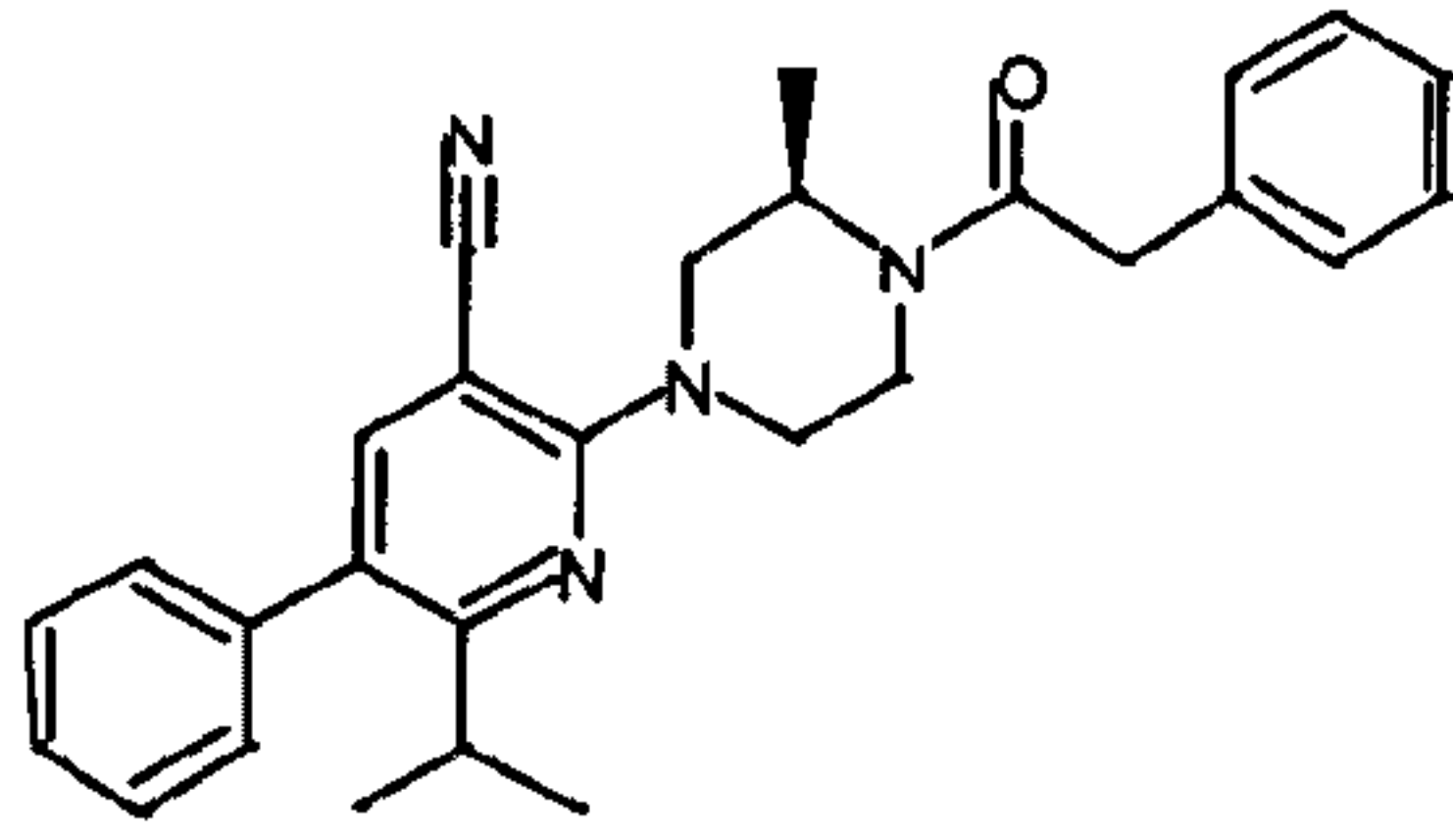
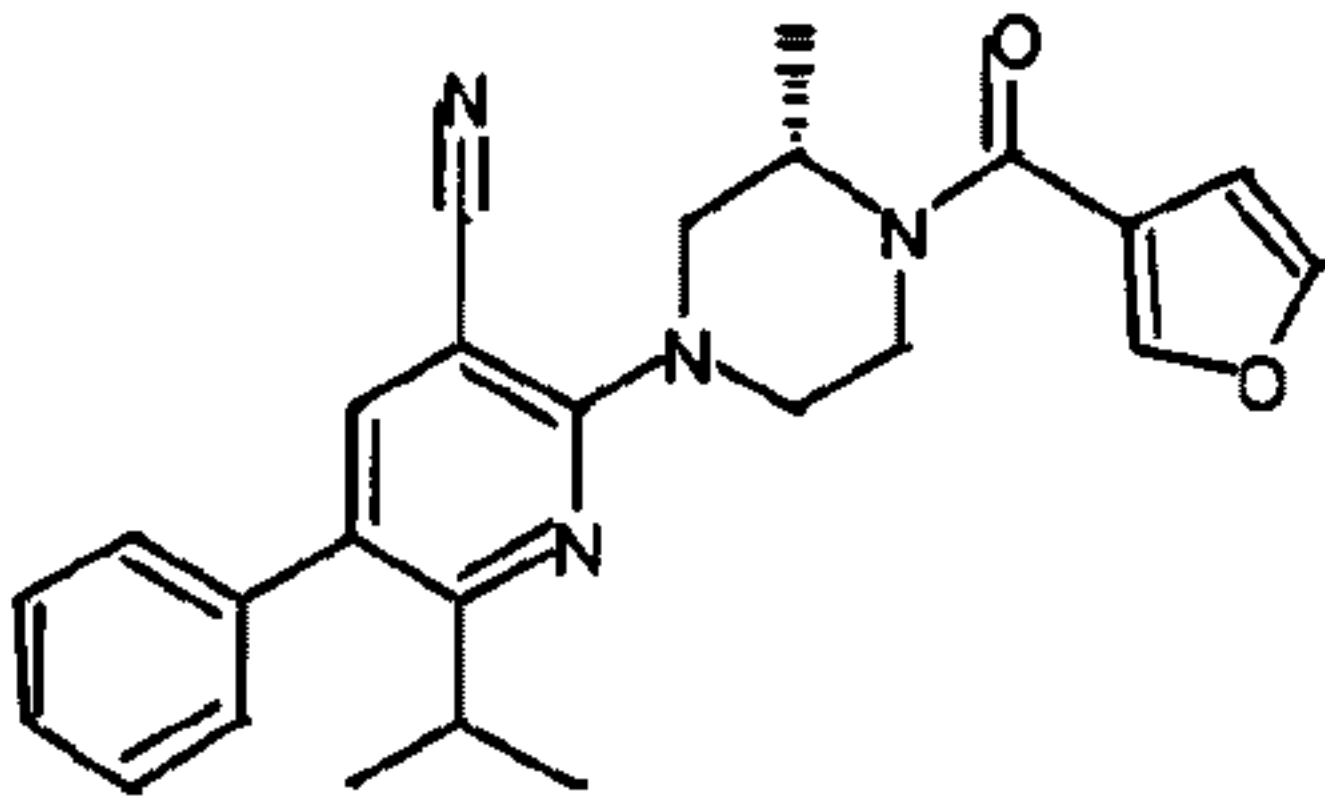
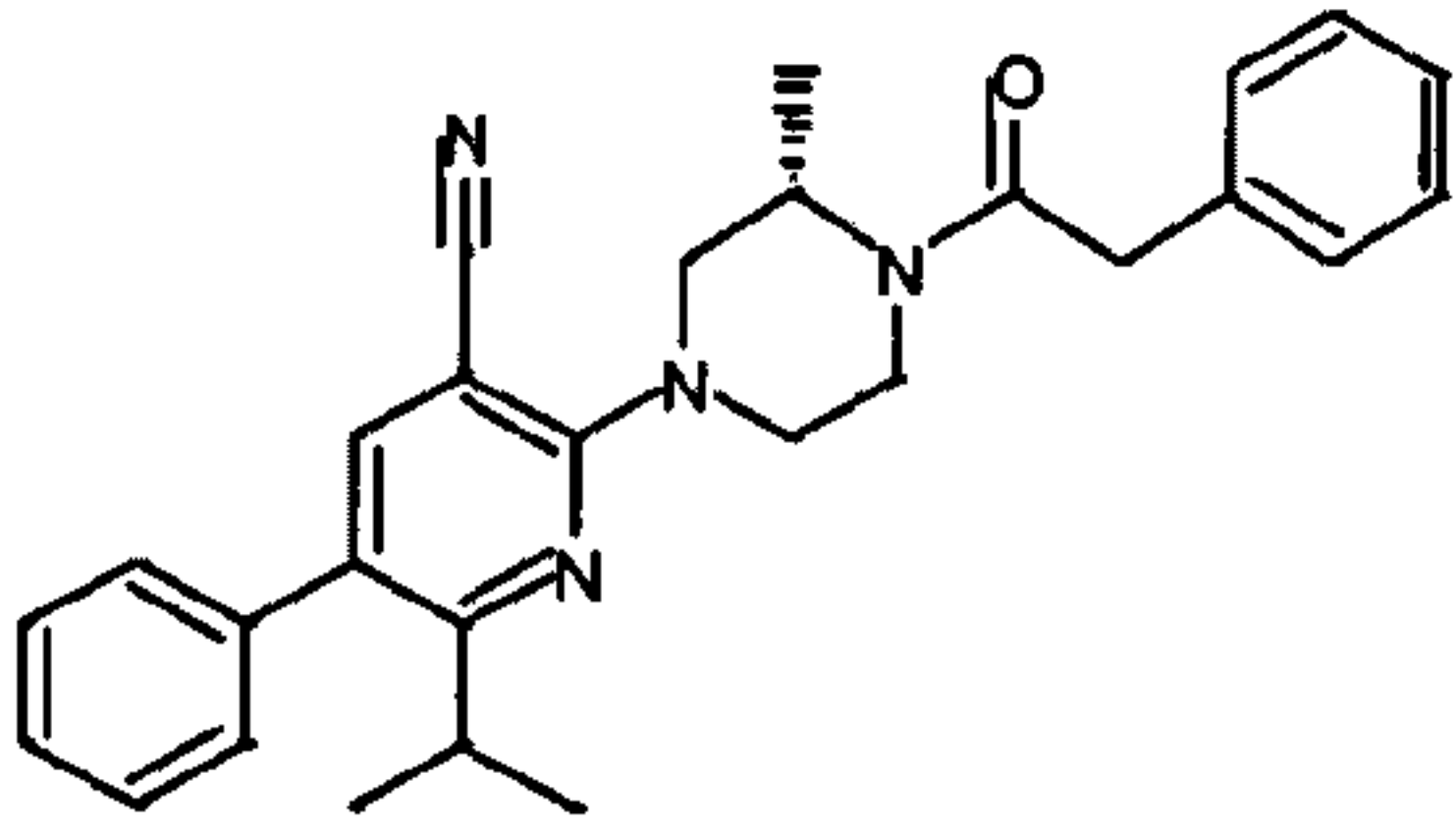
Cmpd No.	Structure
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129	
130	

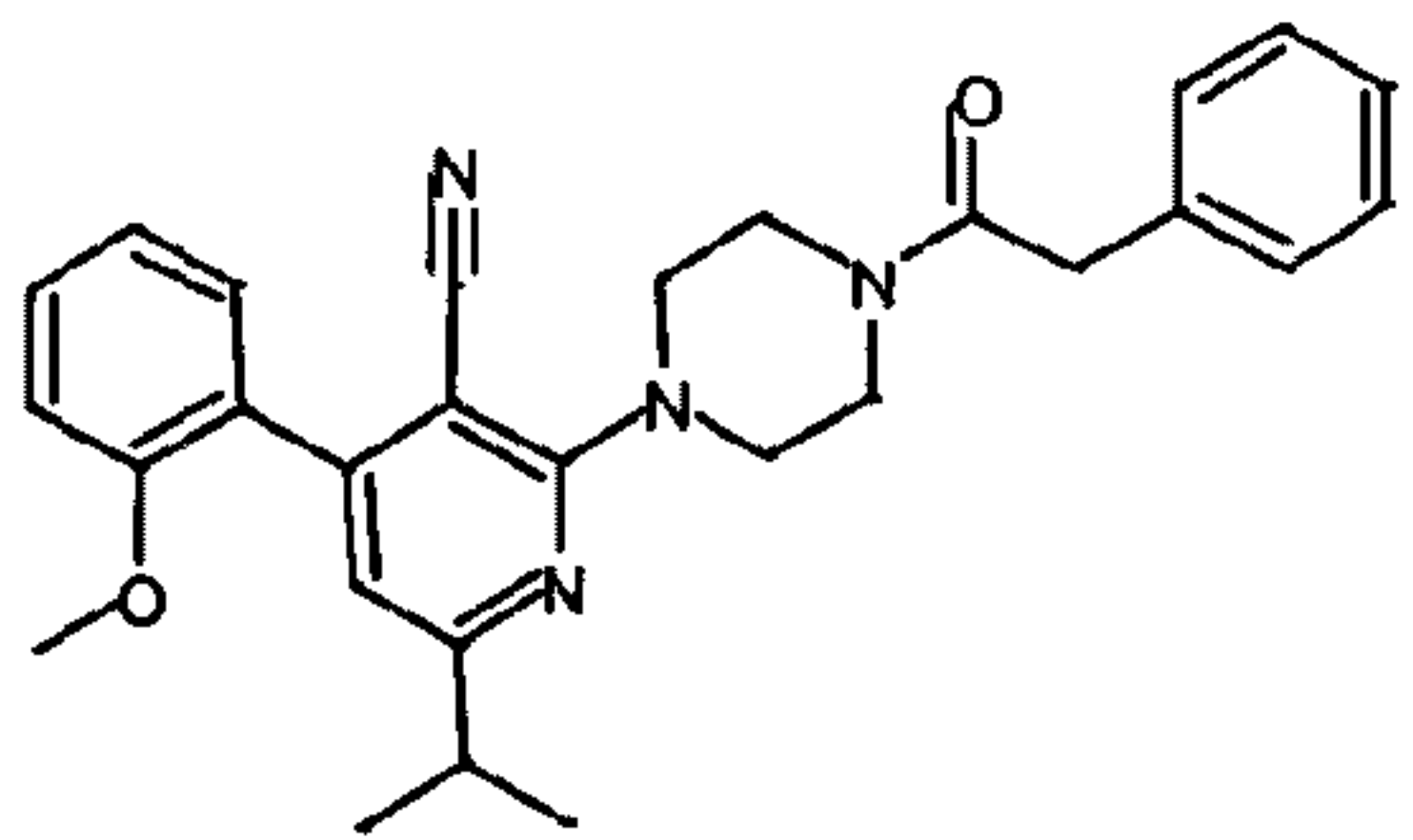
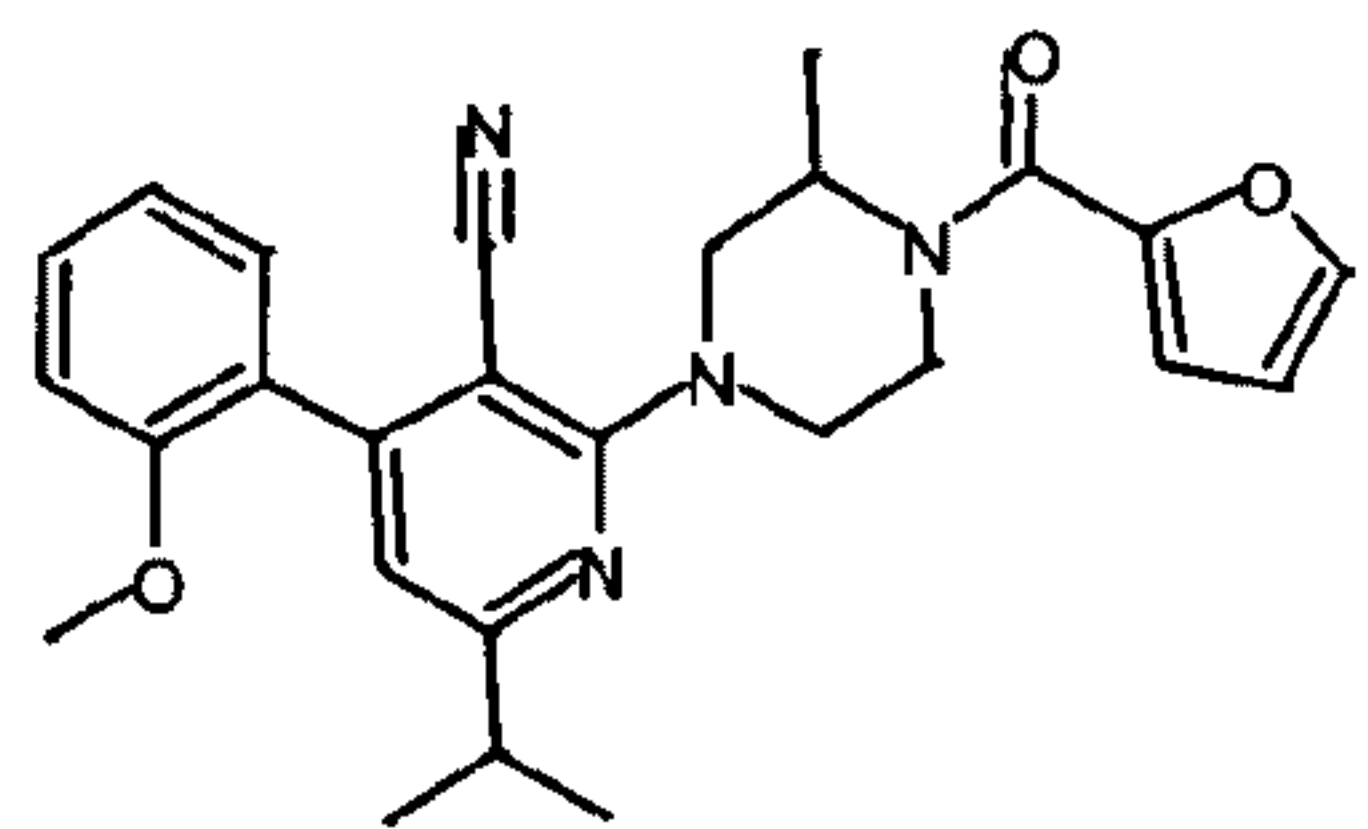
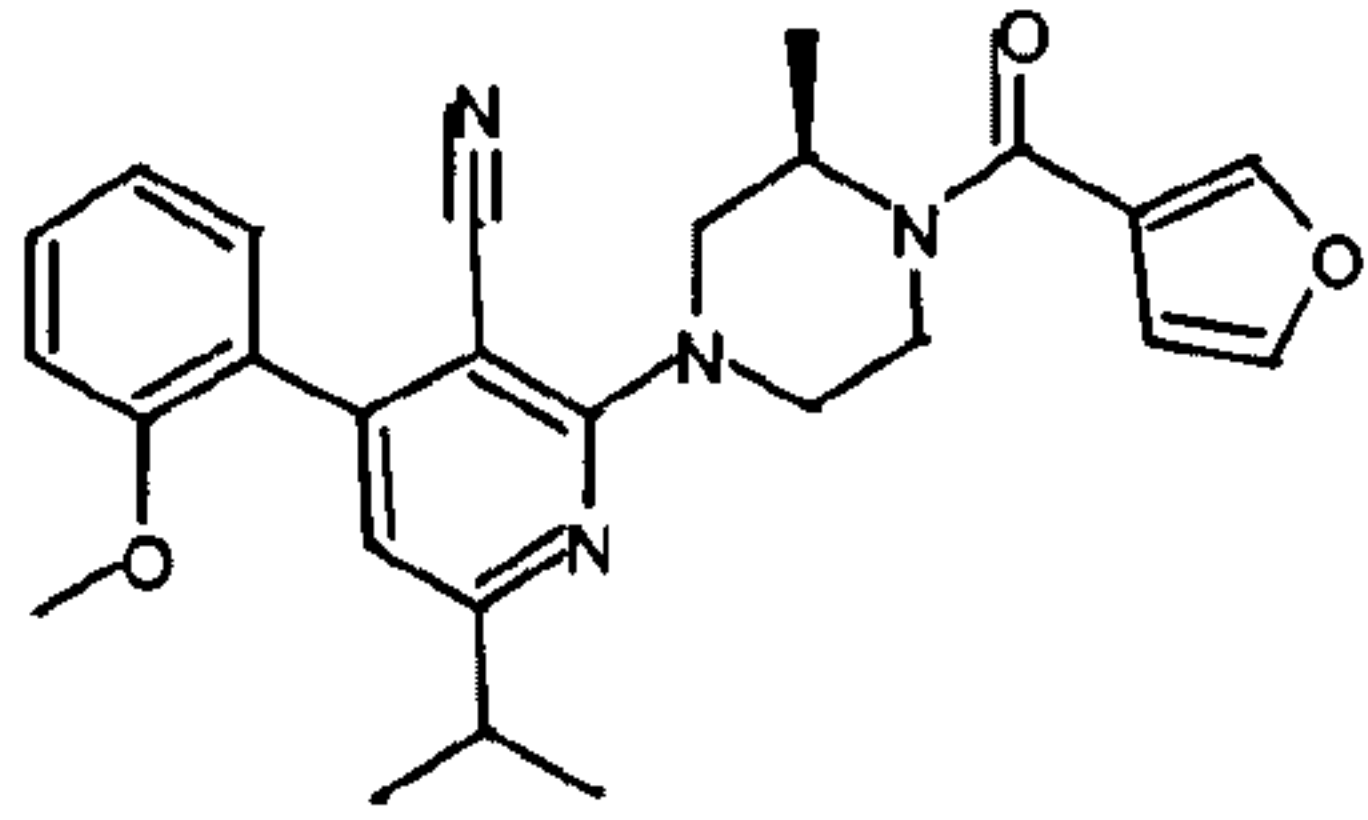
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132	
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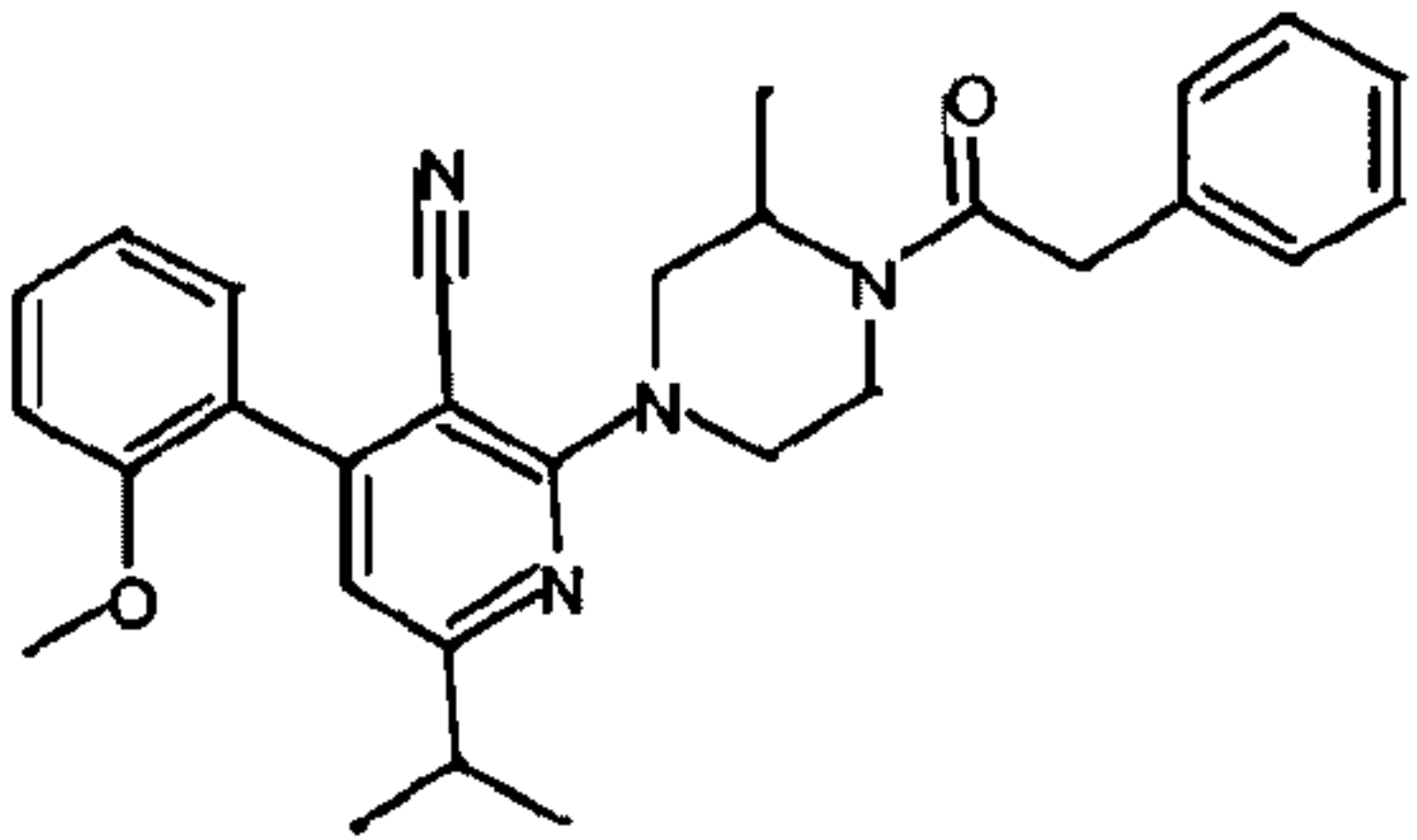
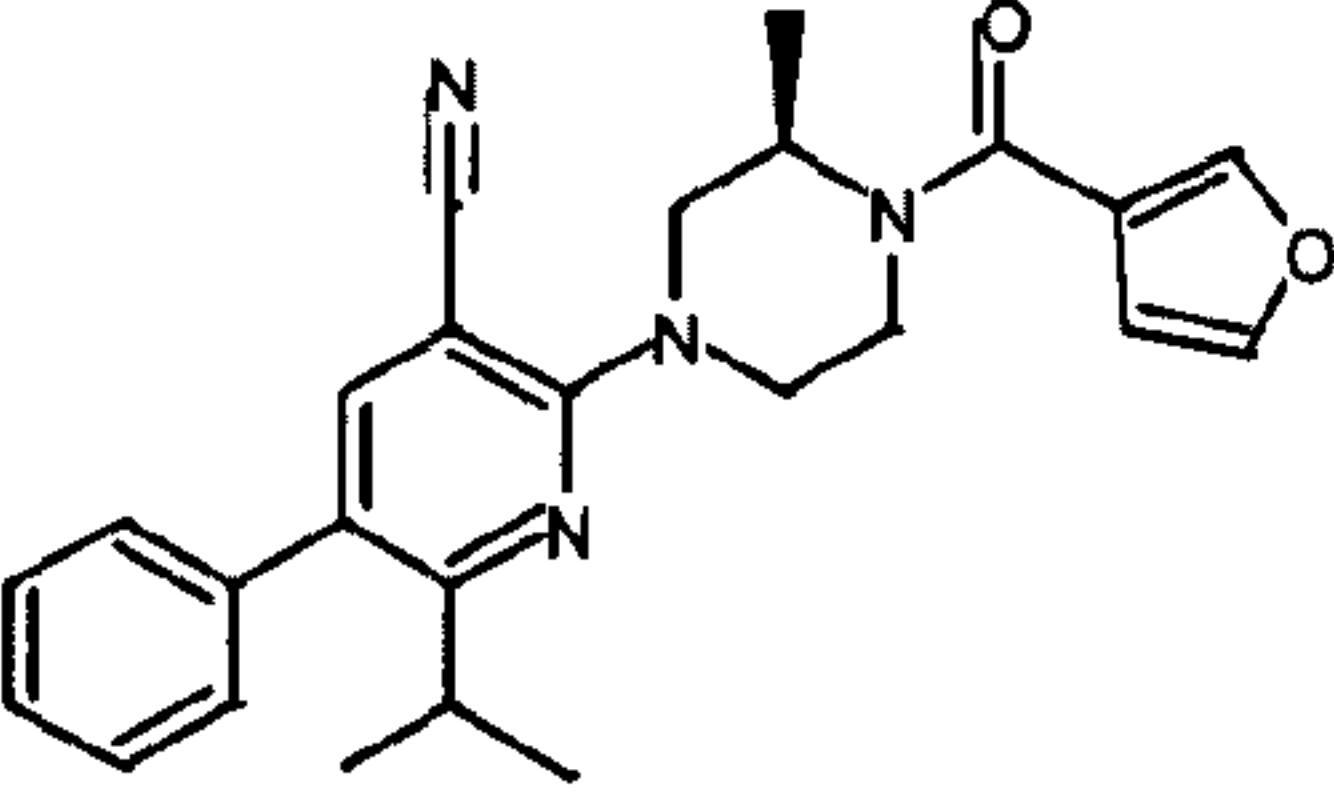
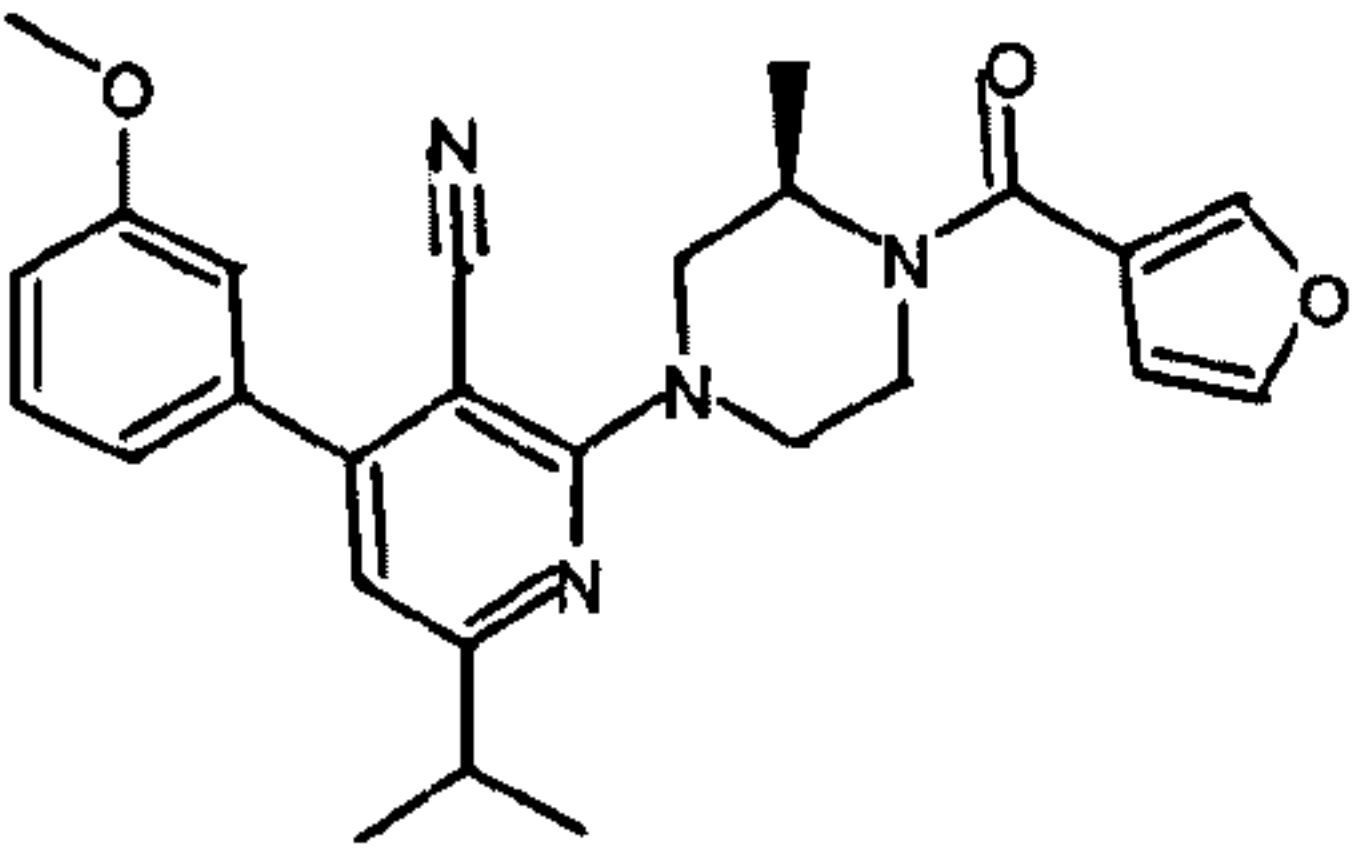
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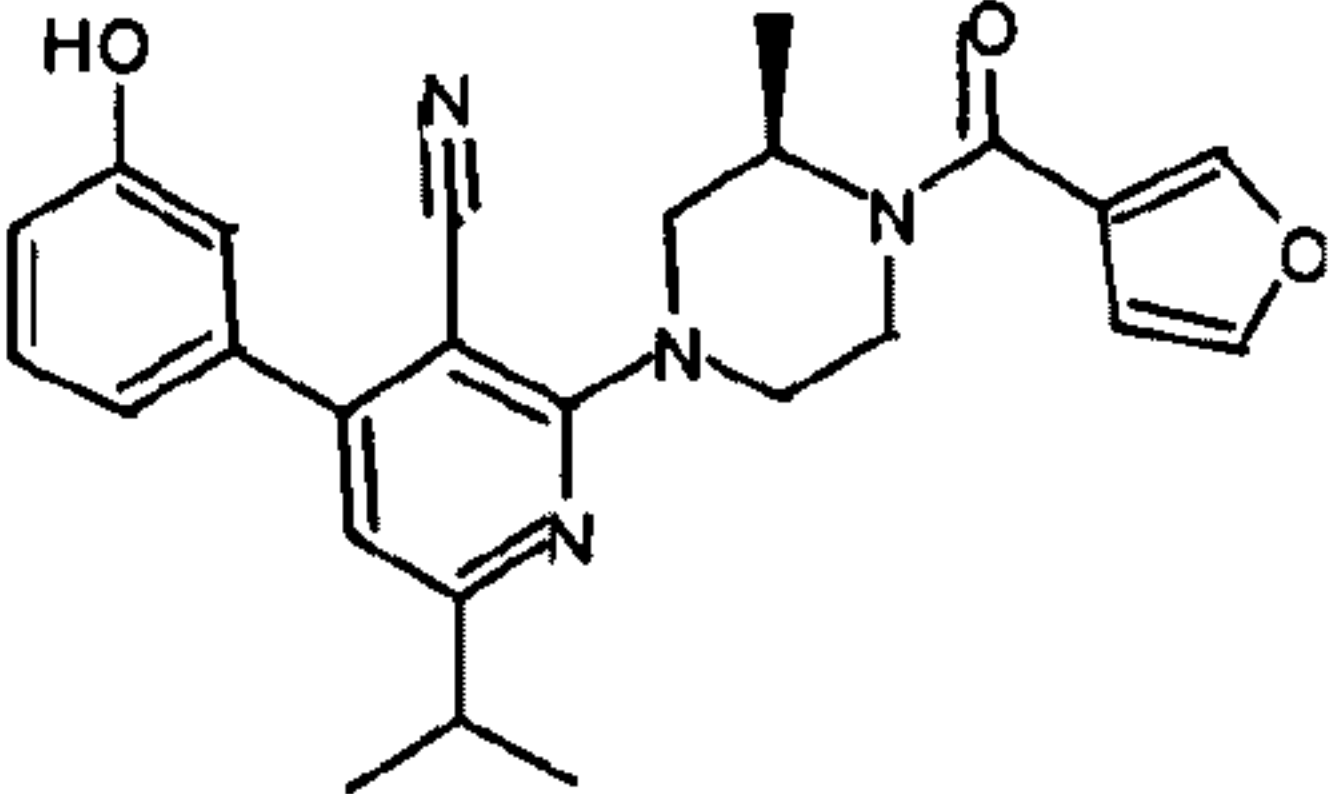
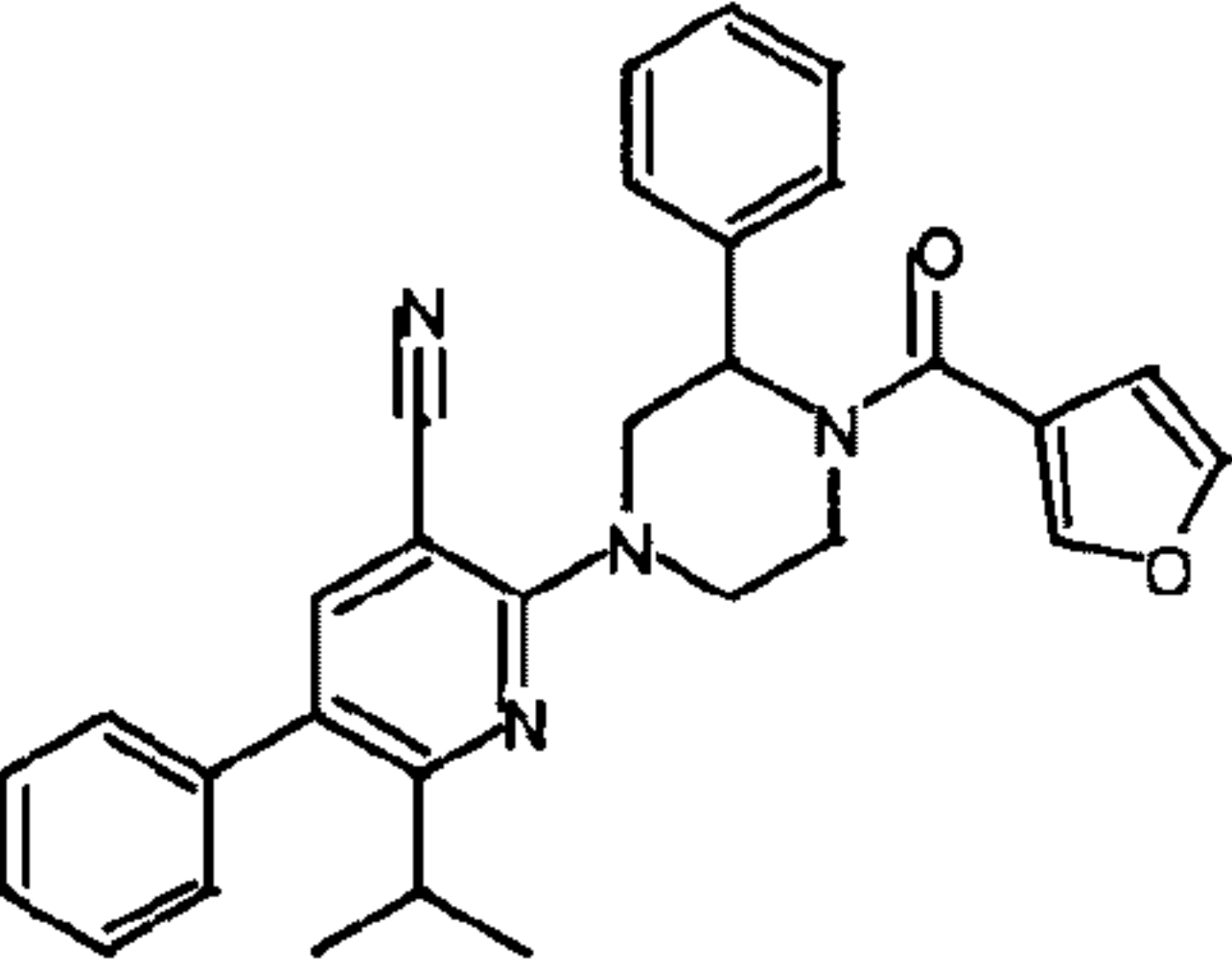
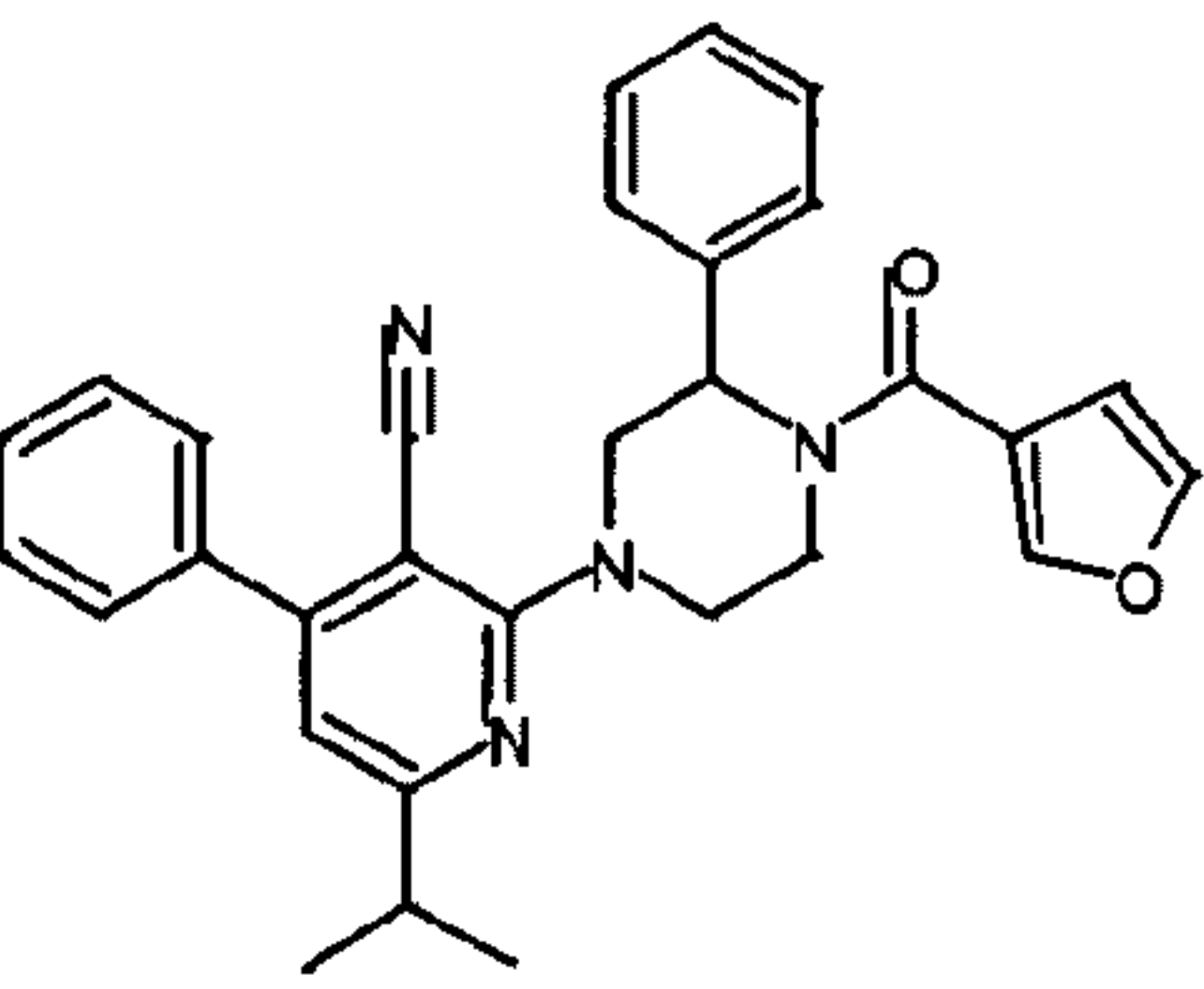
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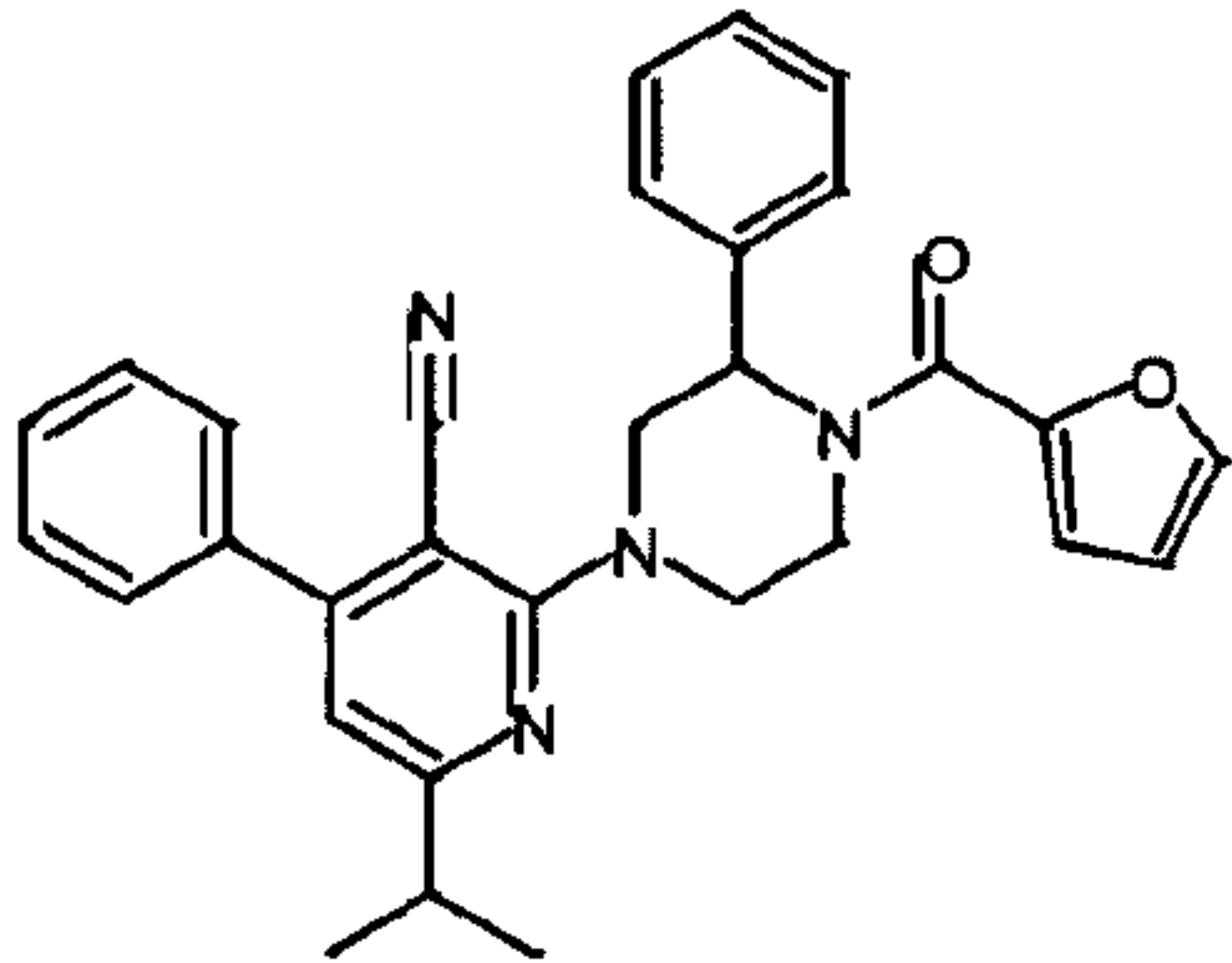
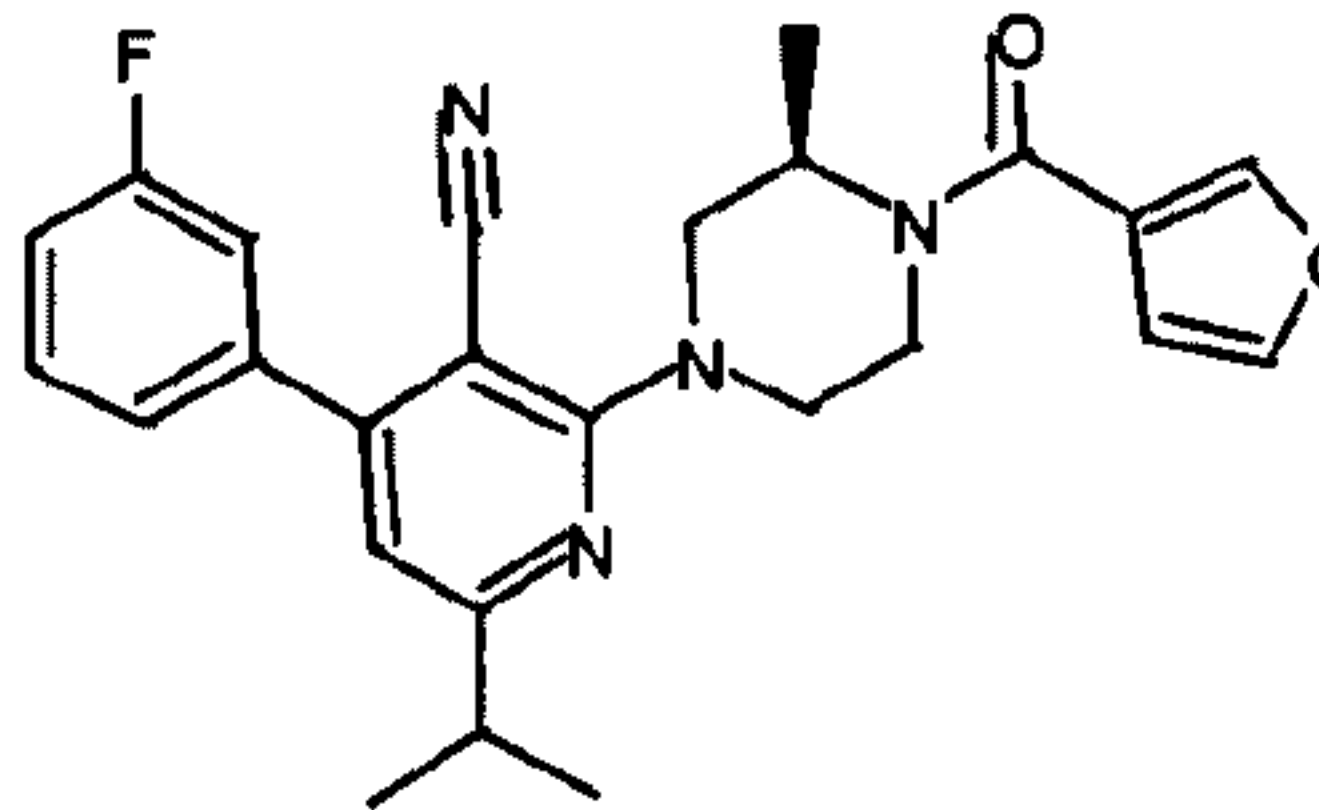
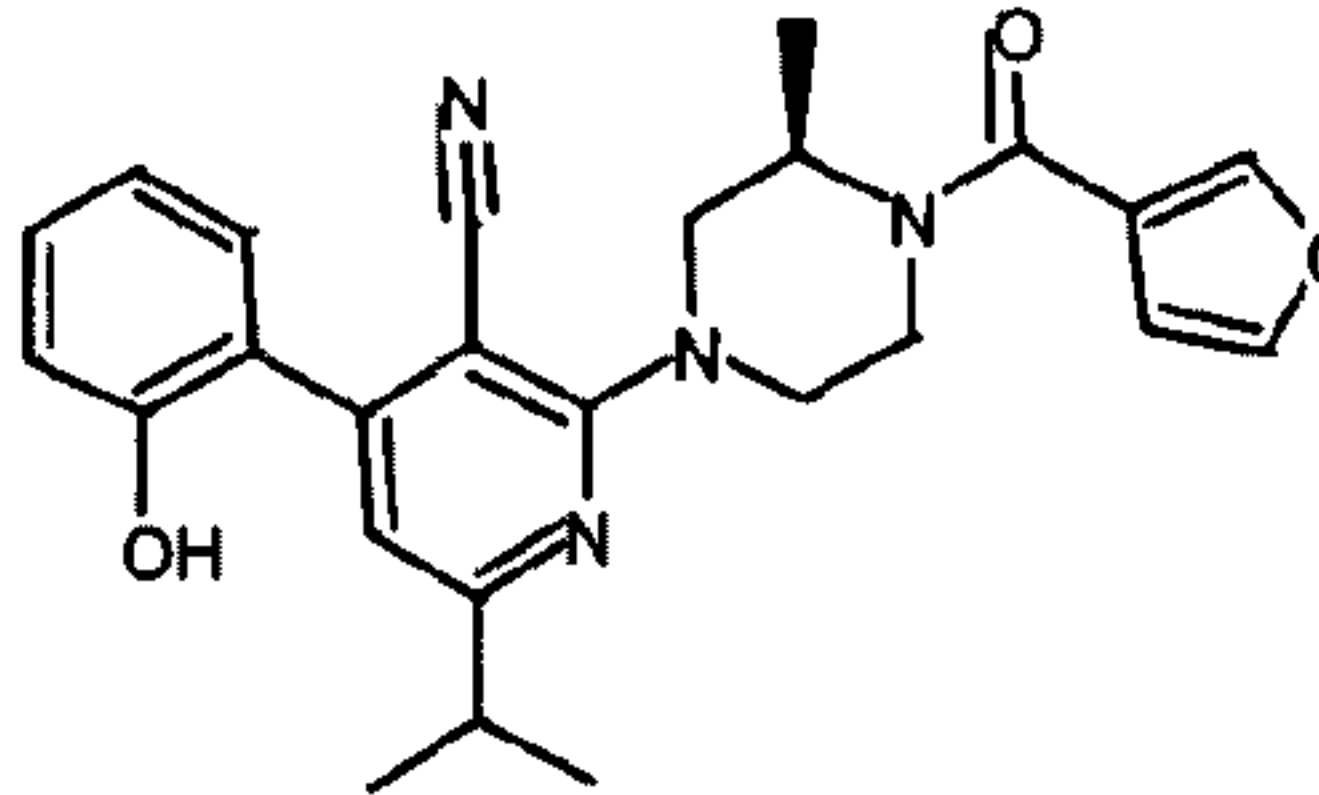
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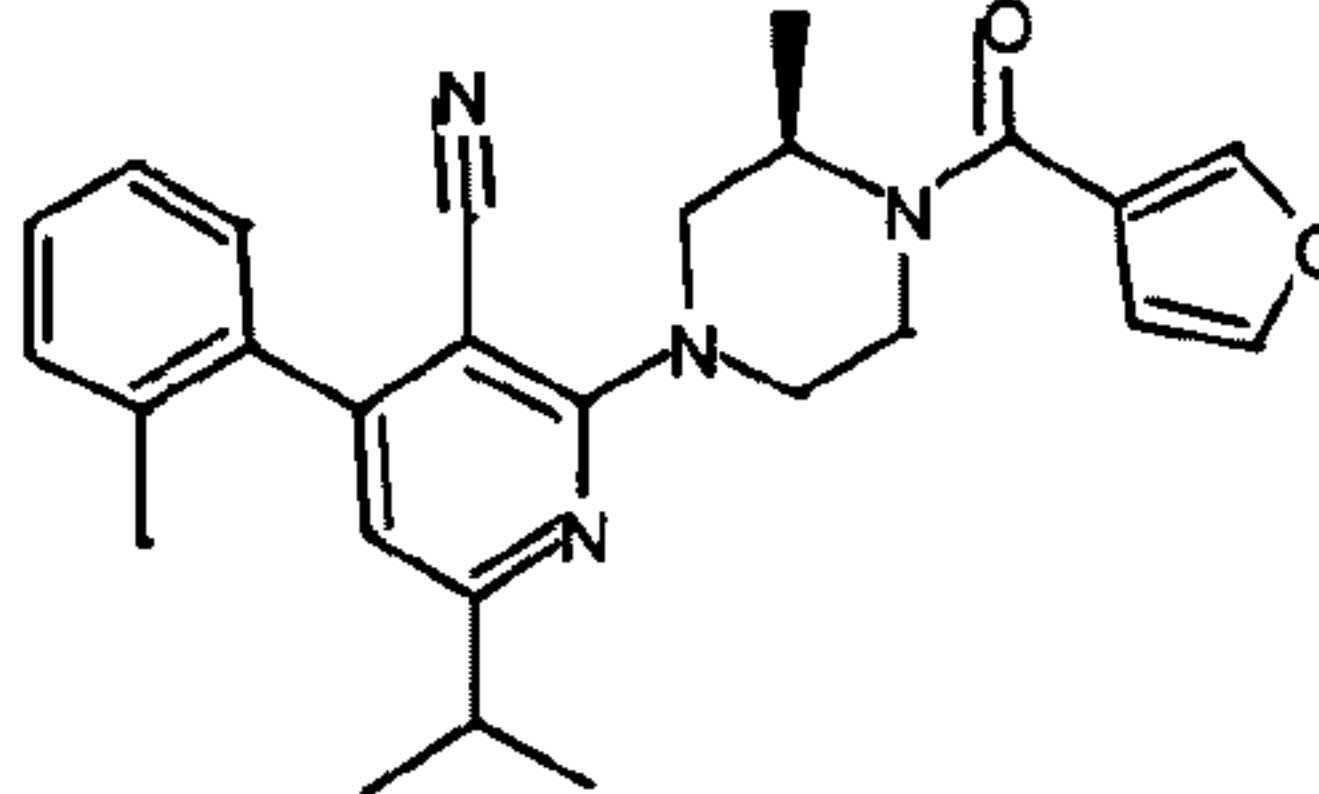
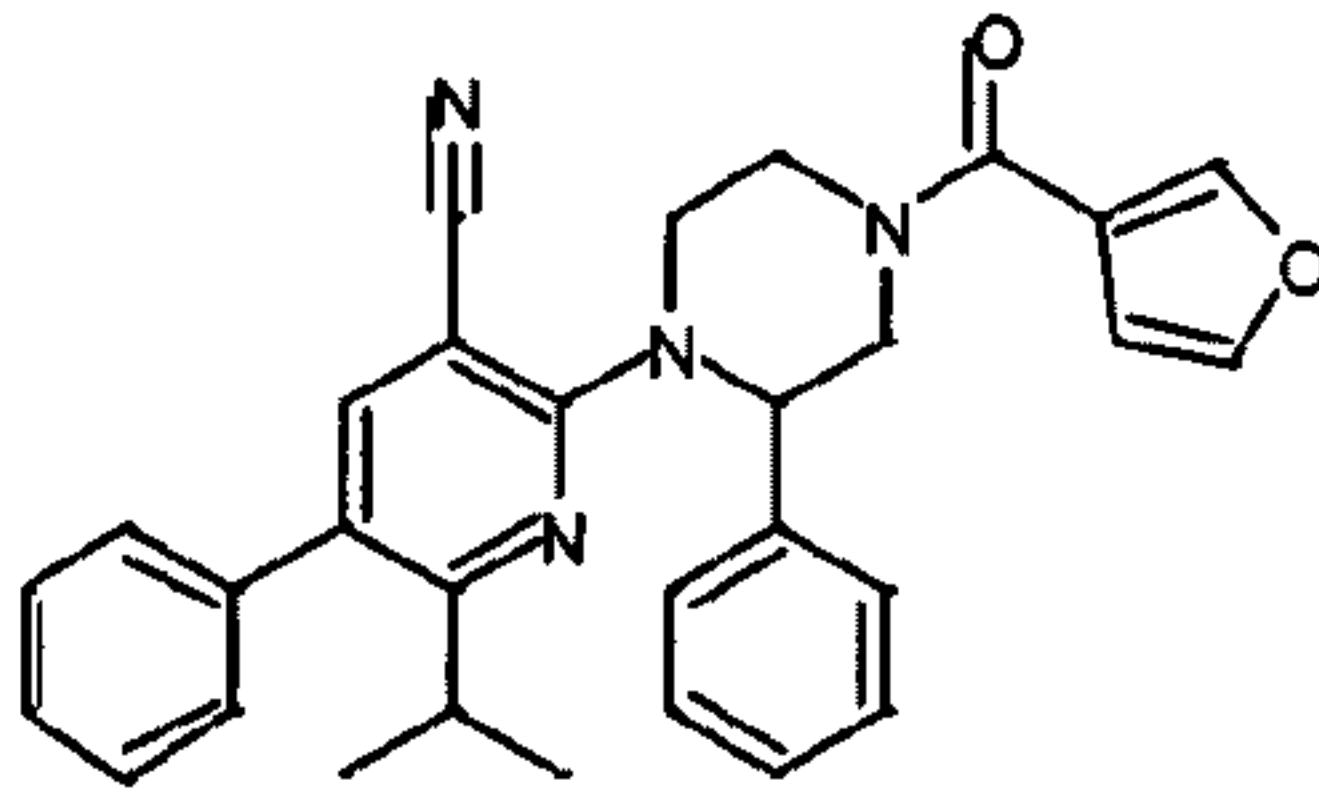
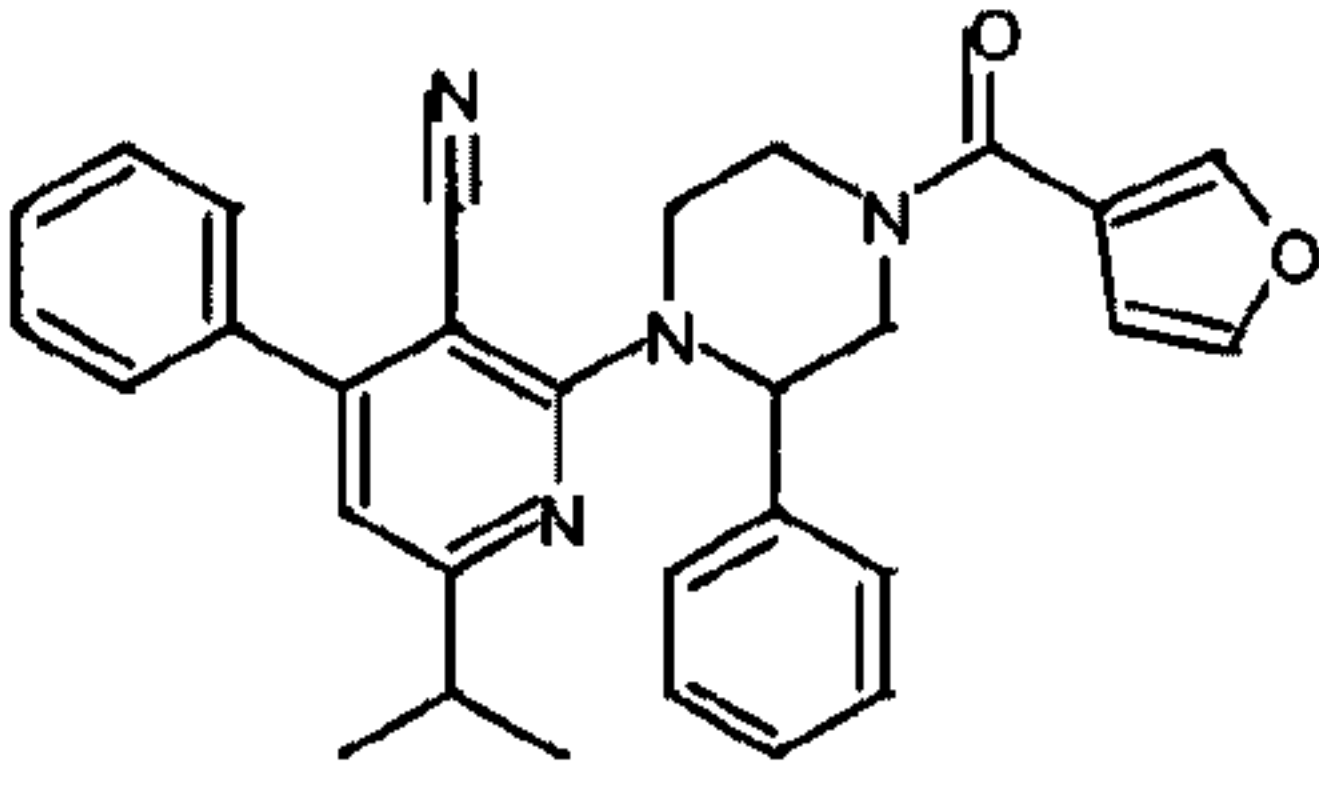
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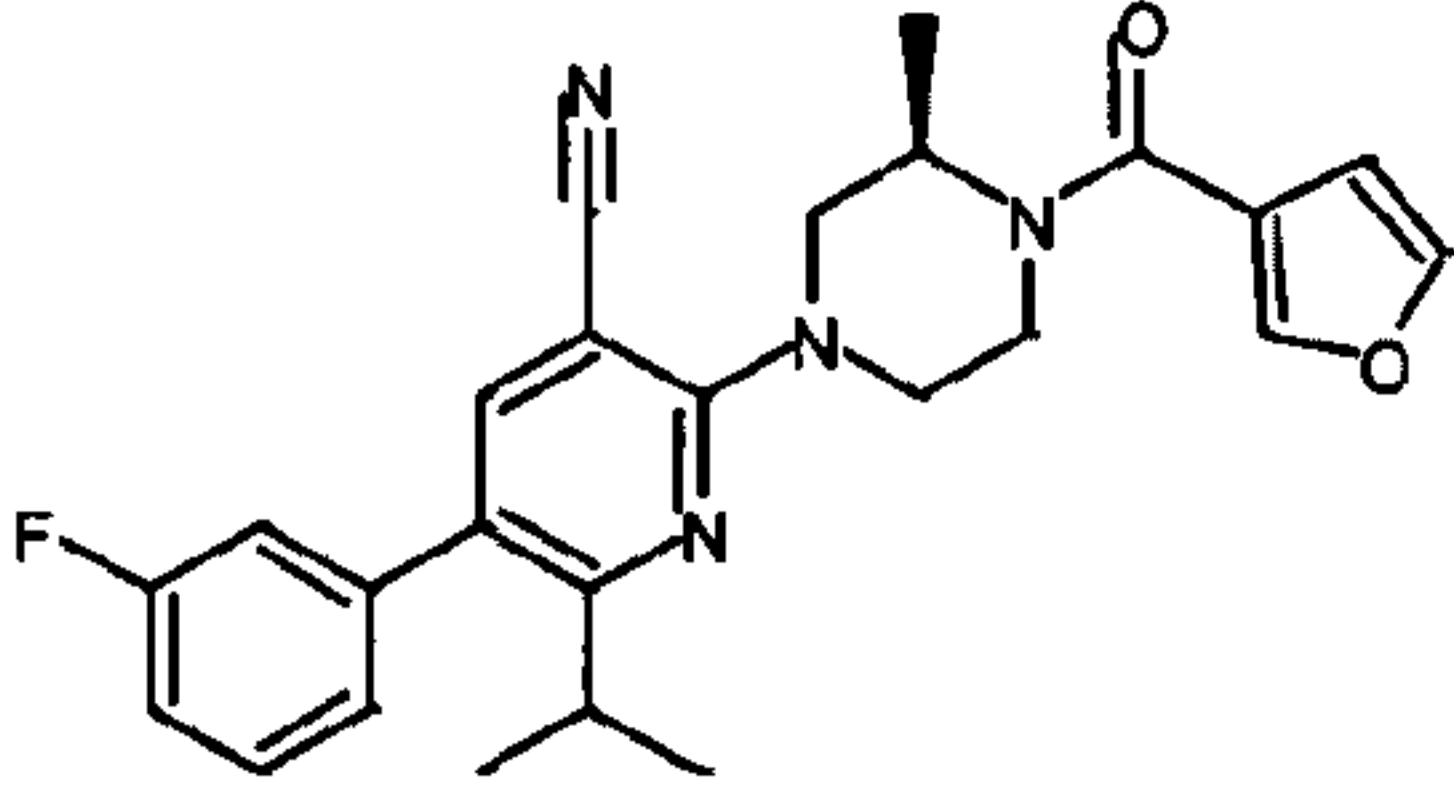
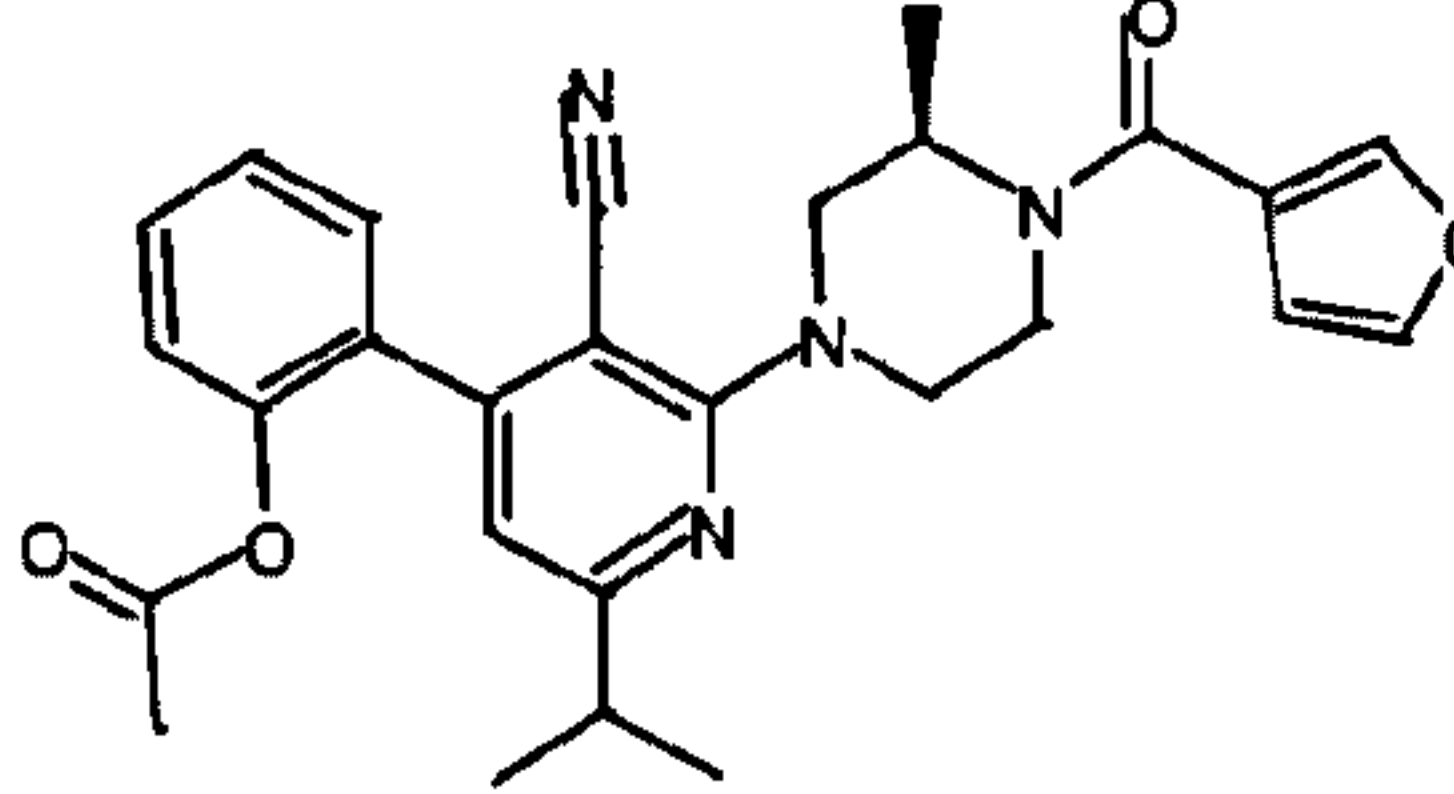
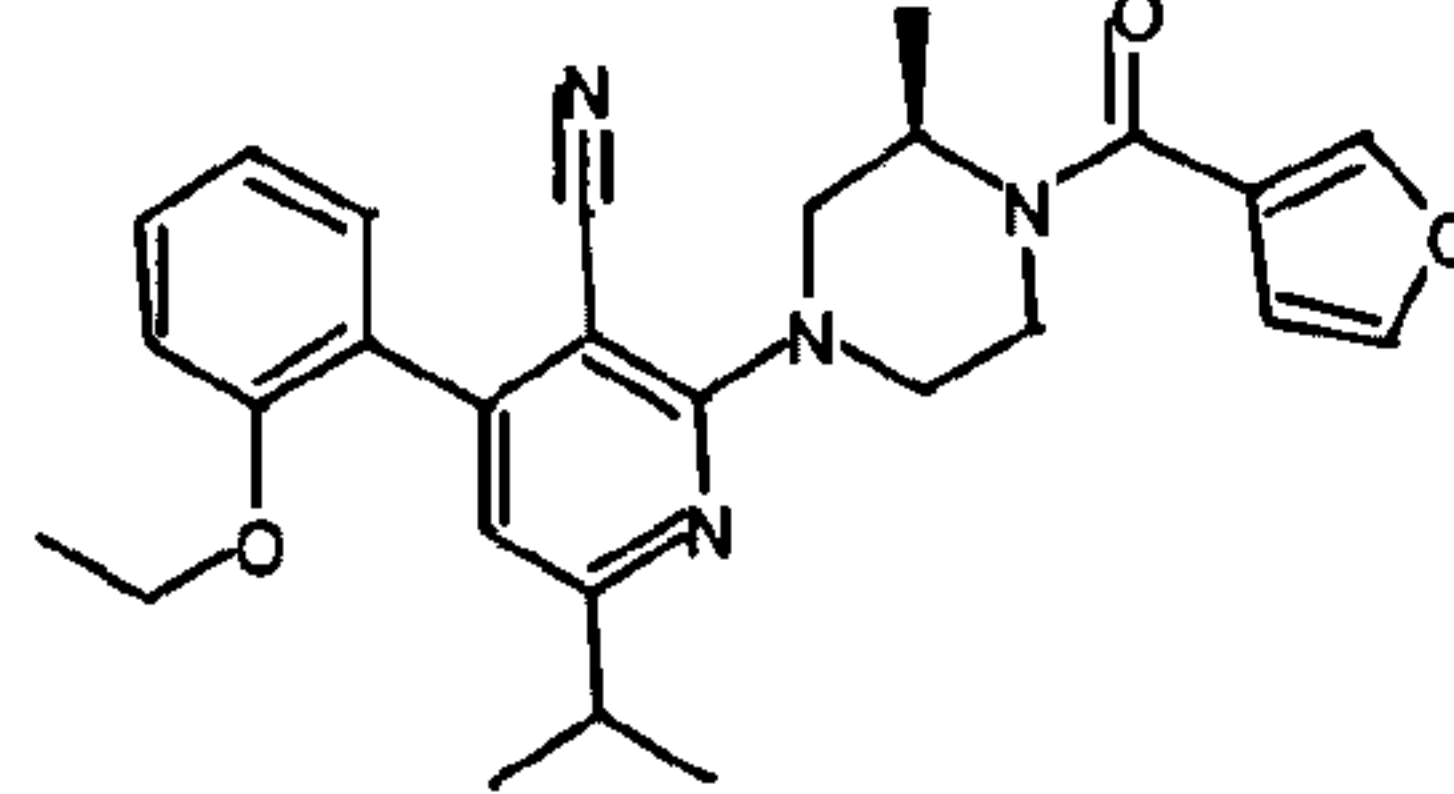
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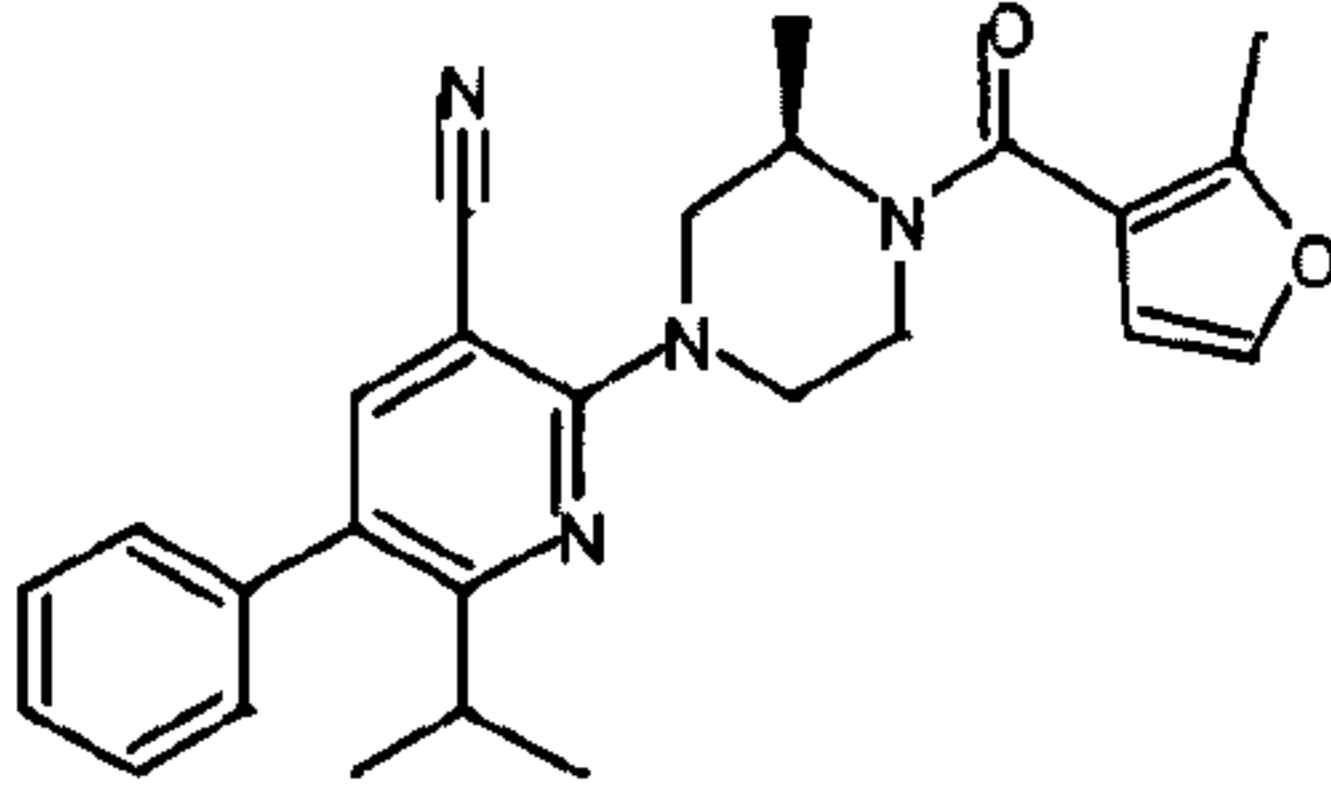
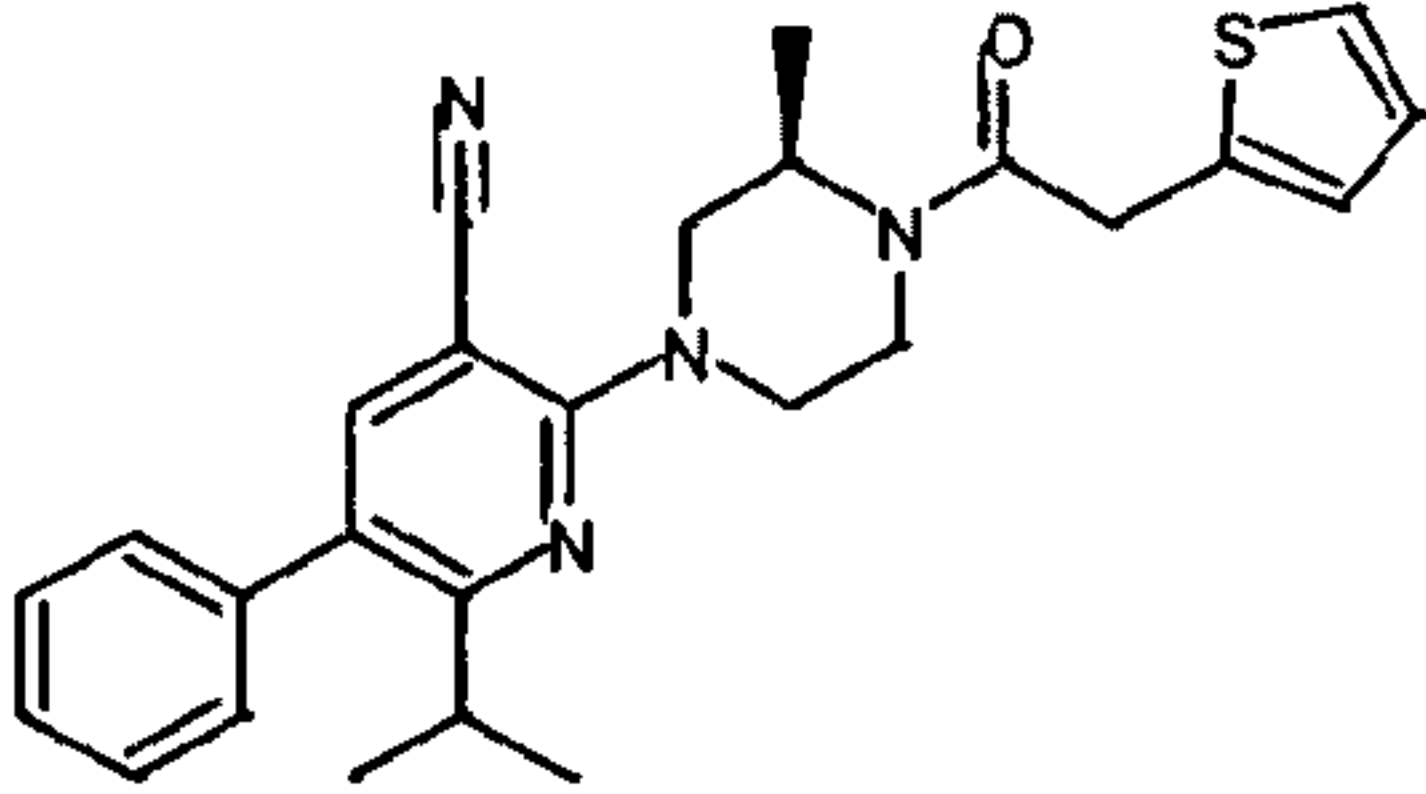
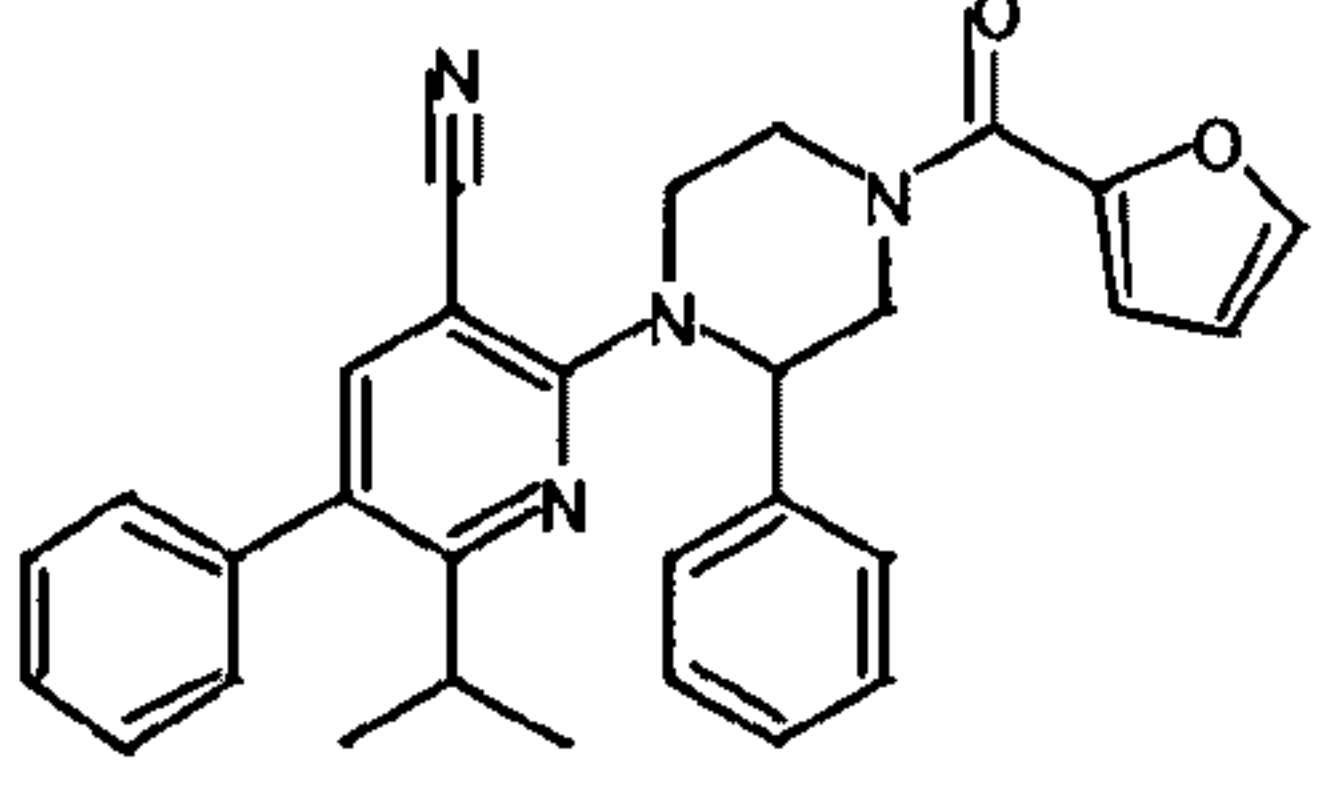
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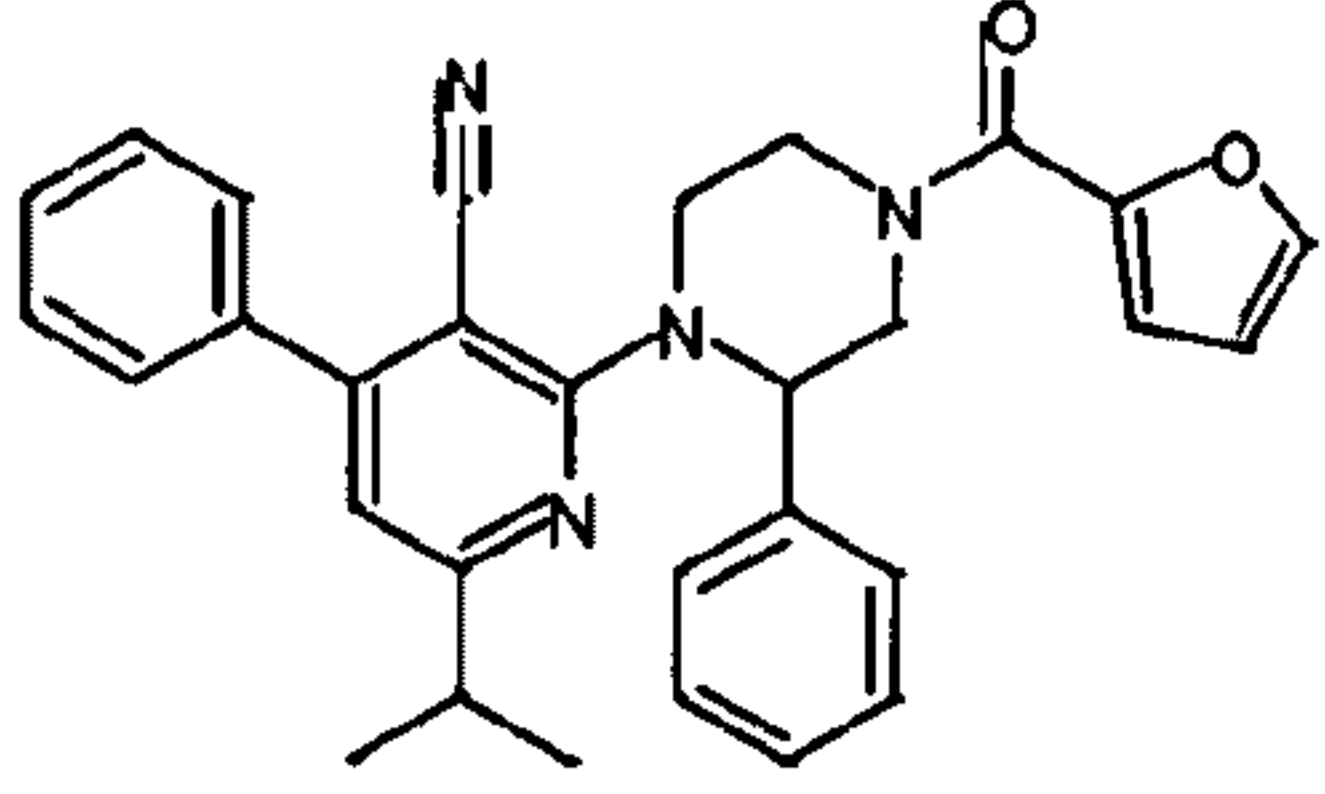
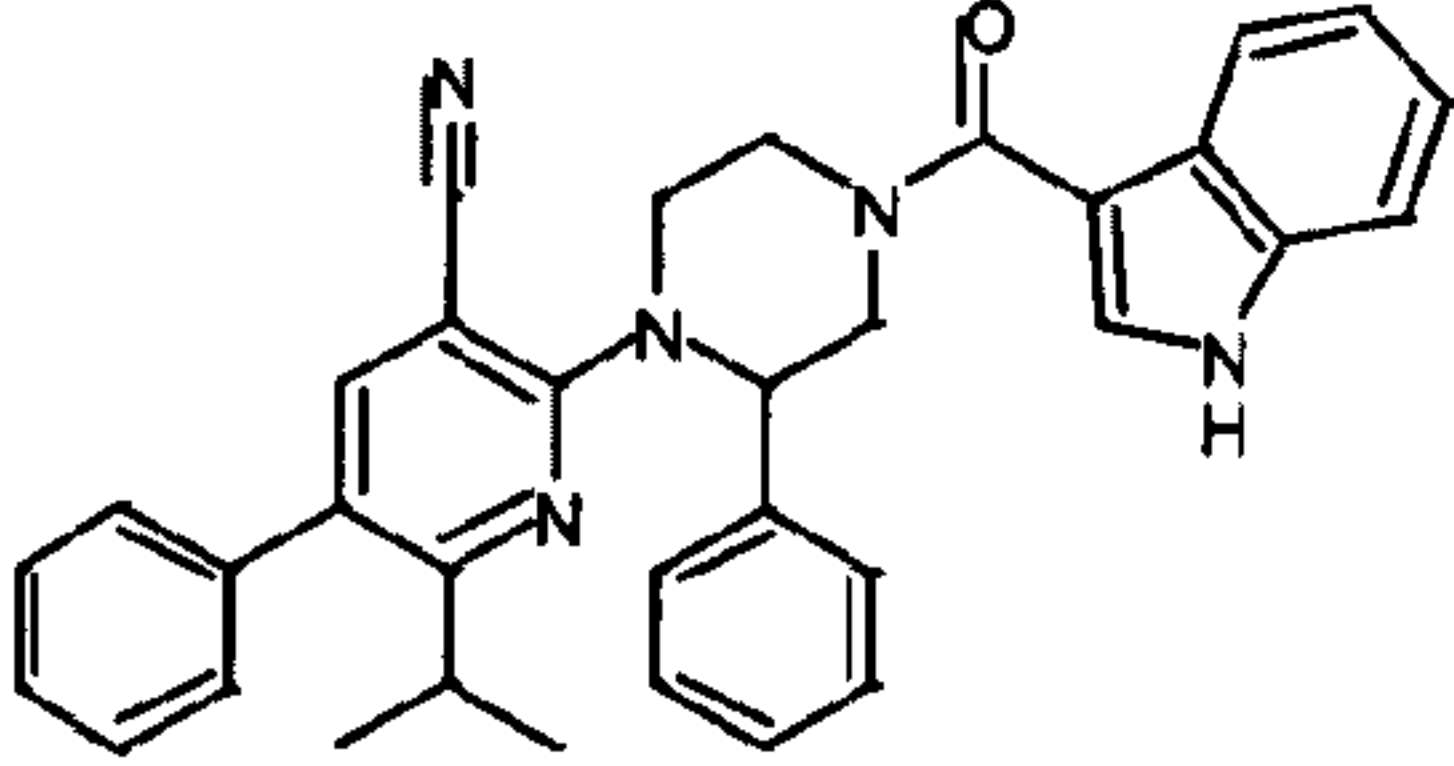
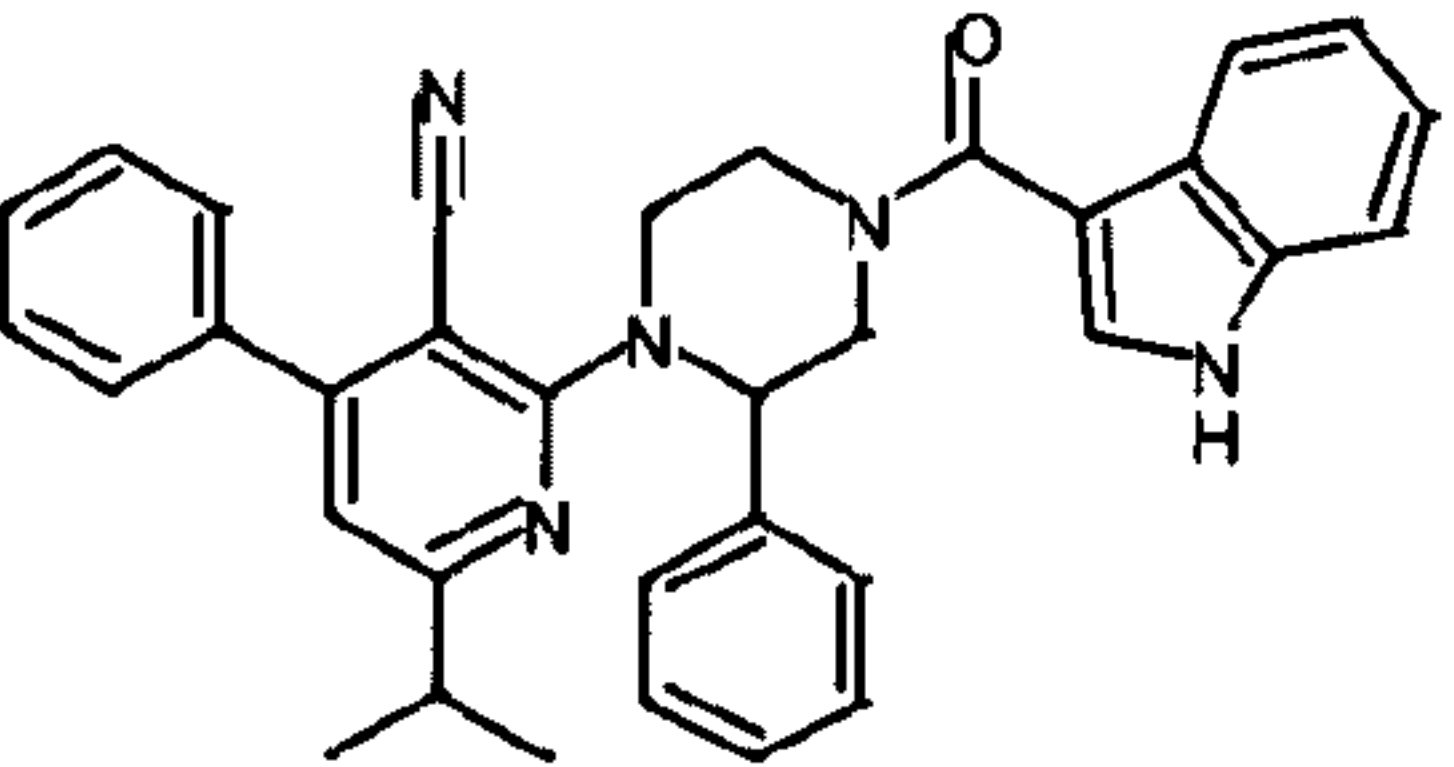
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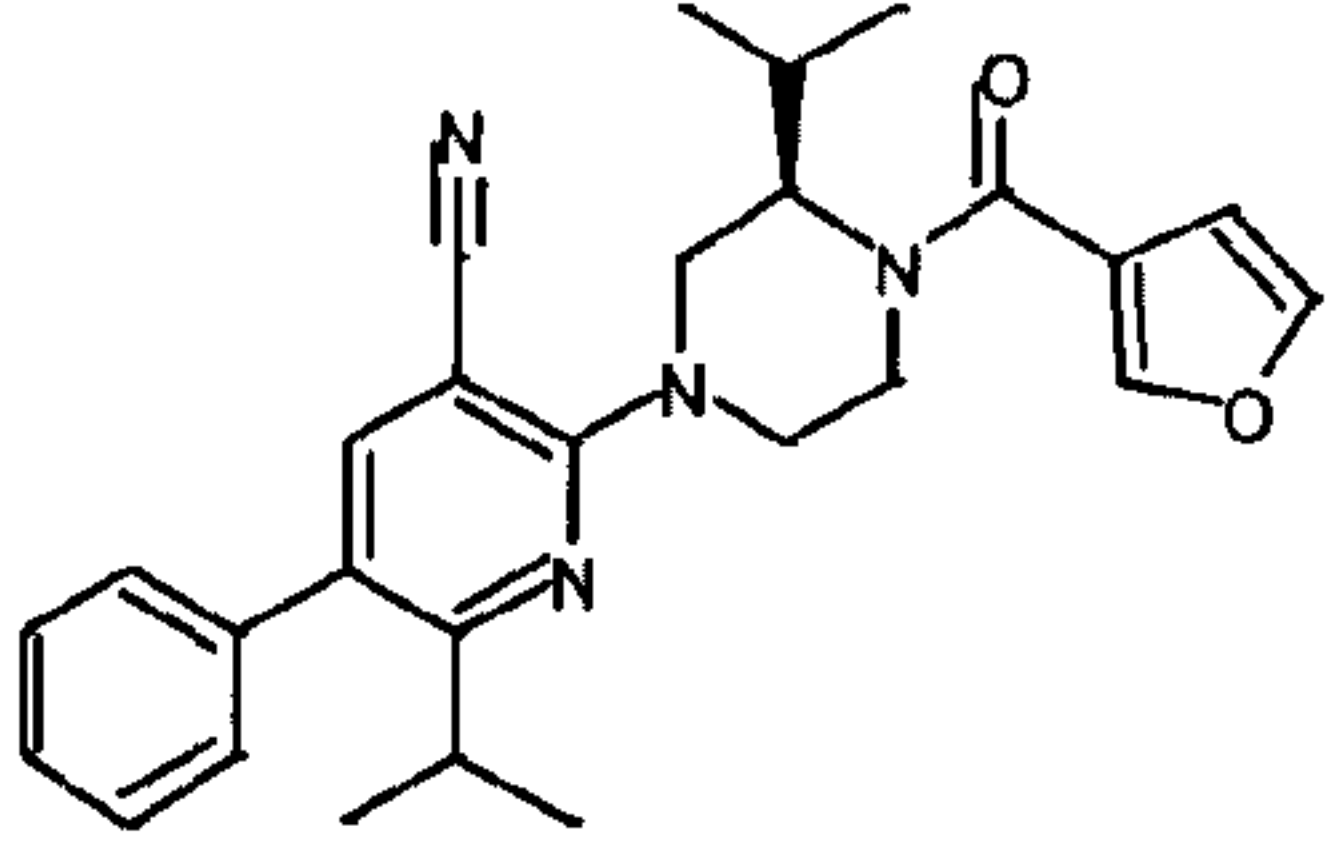
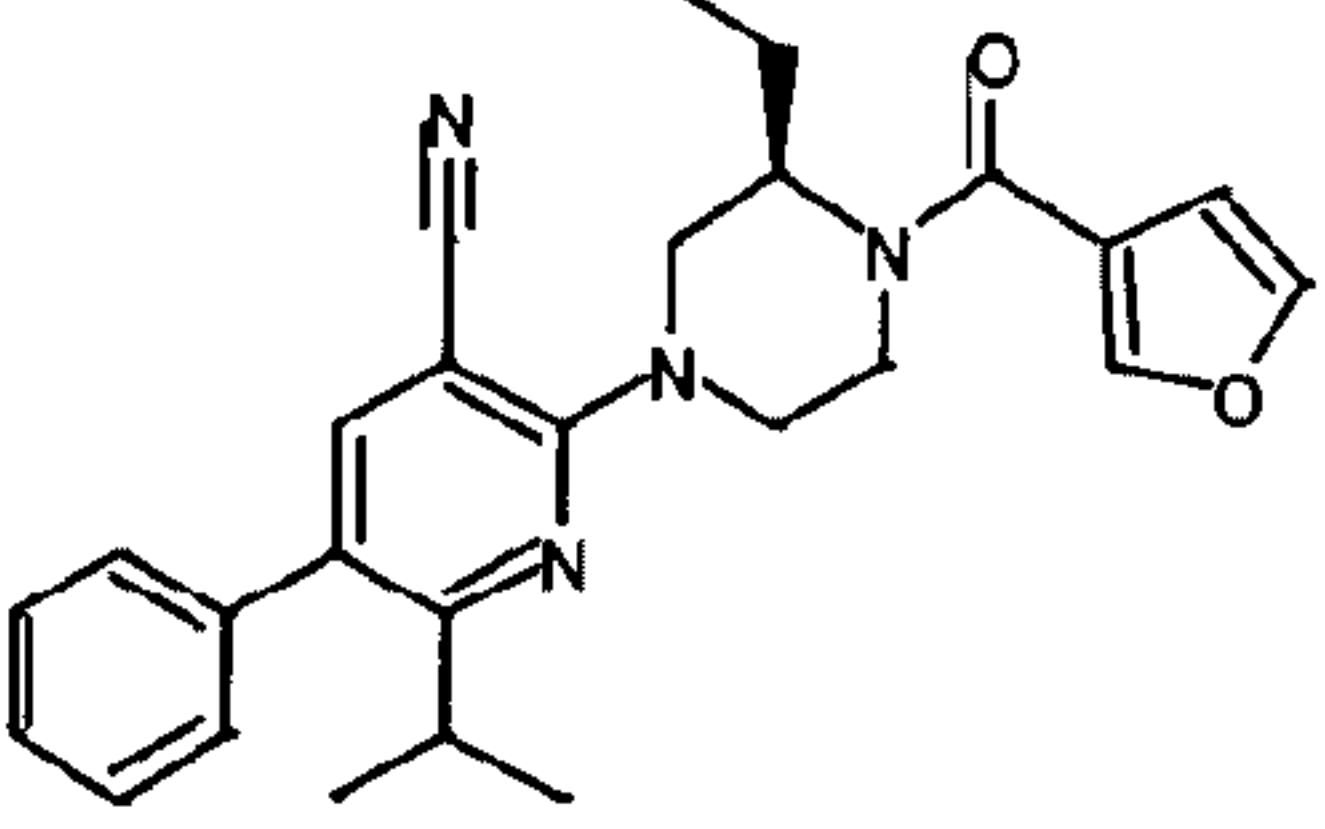
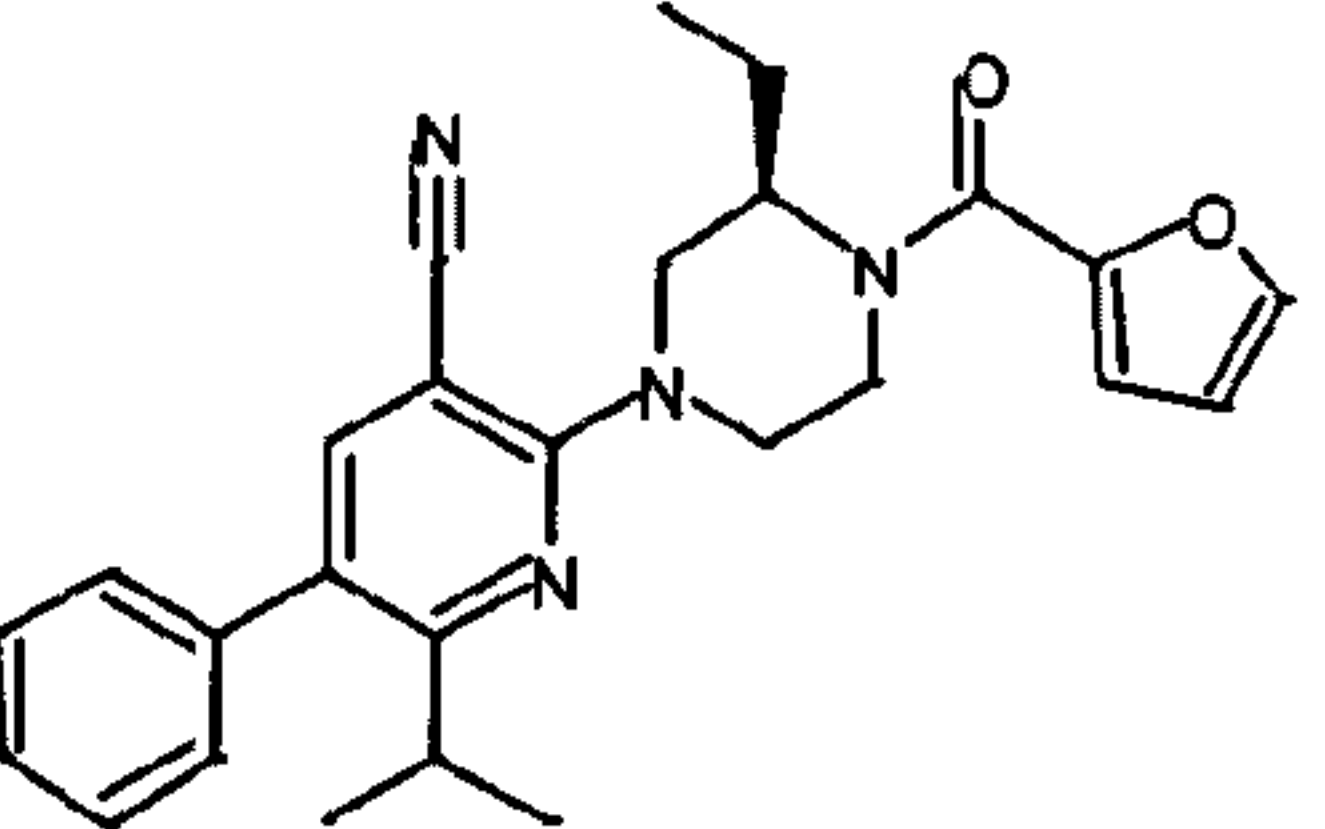
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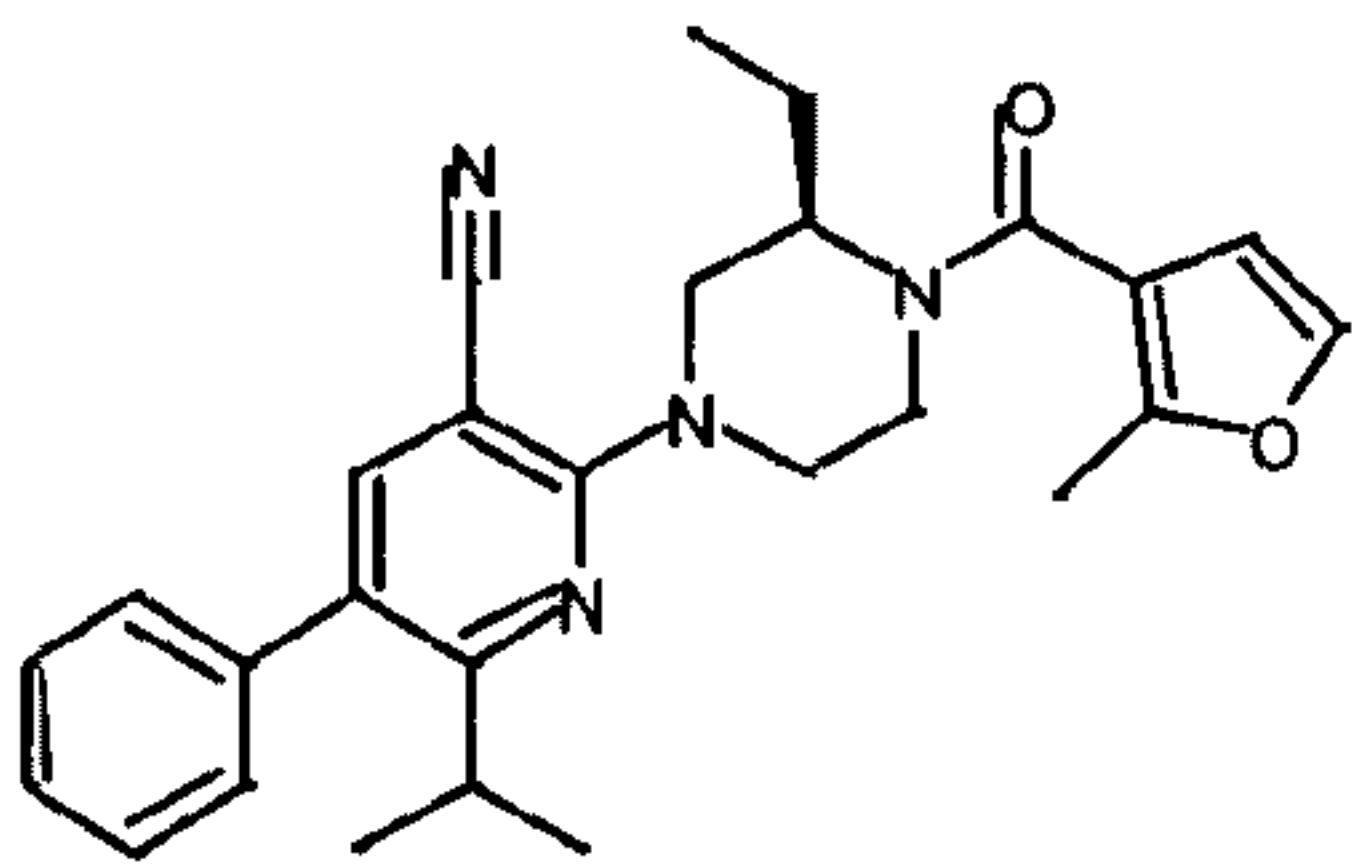
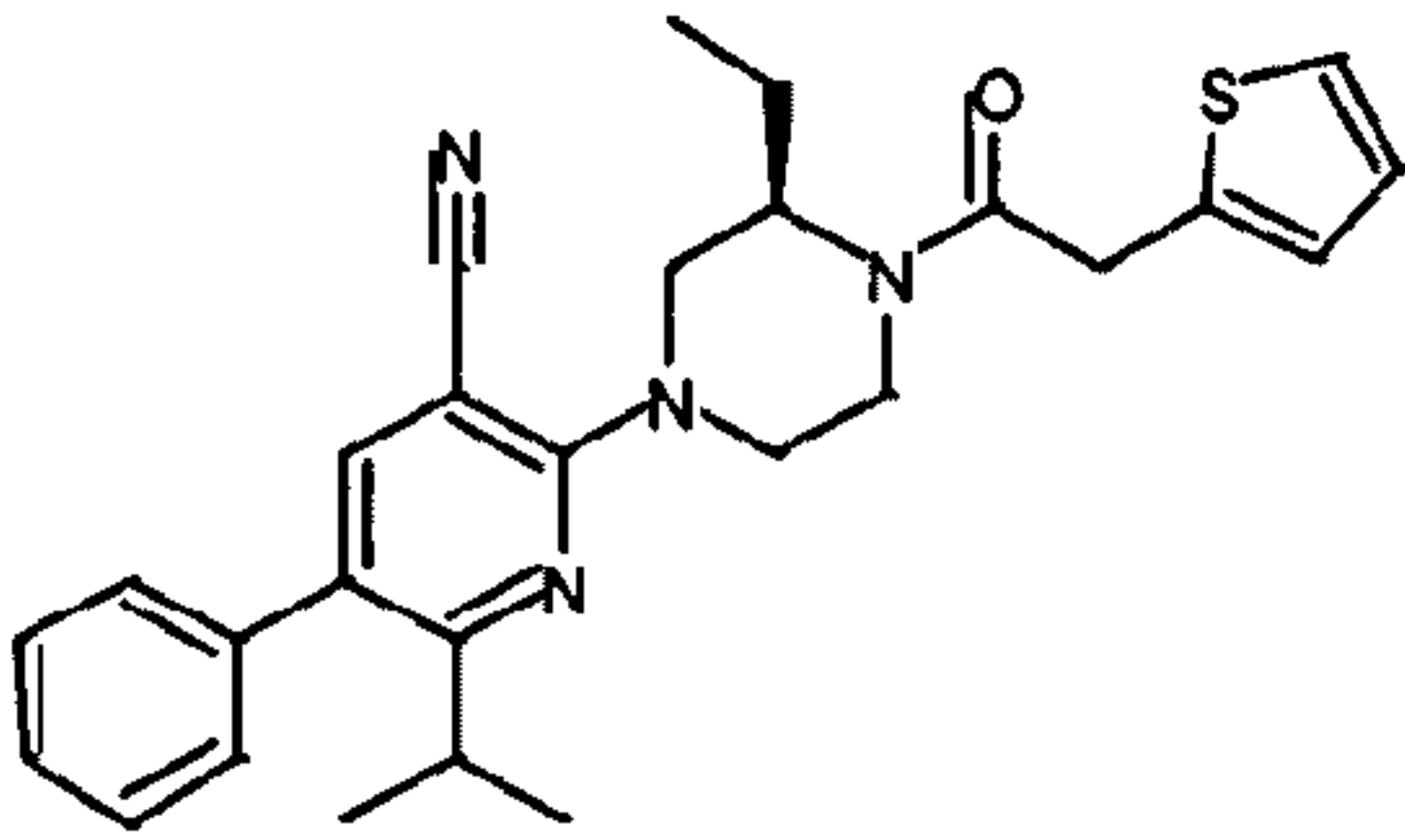
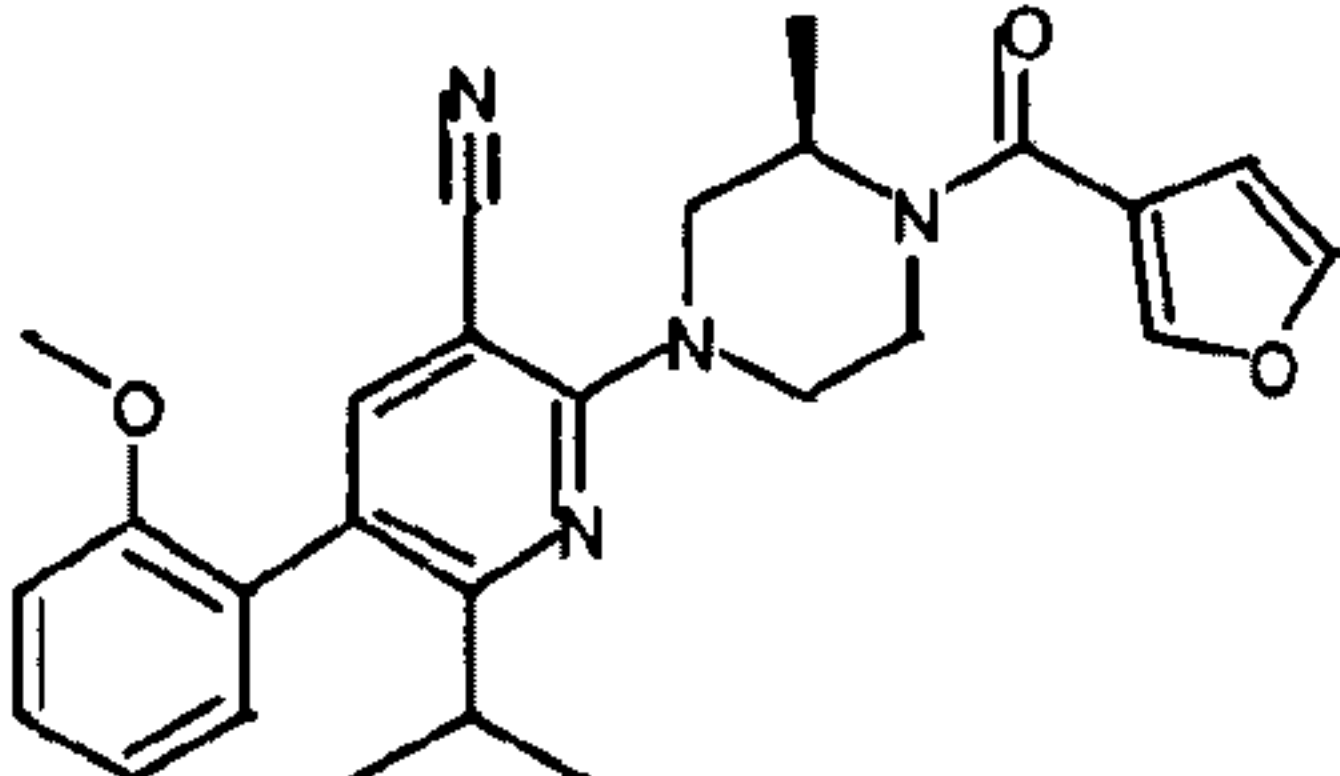
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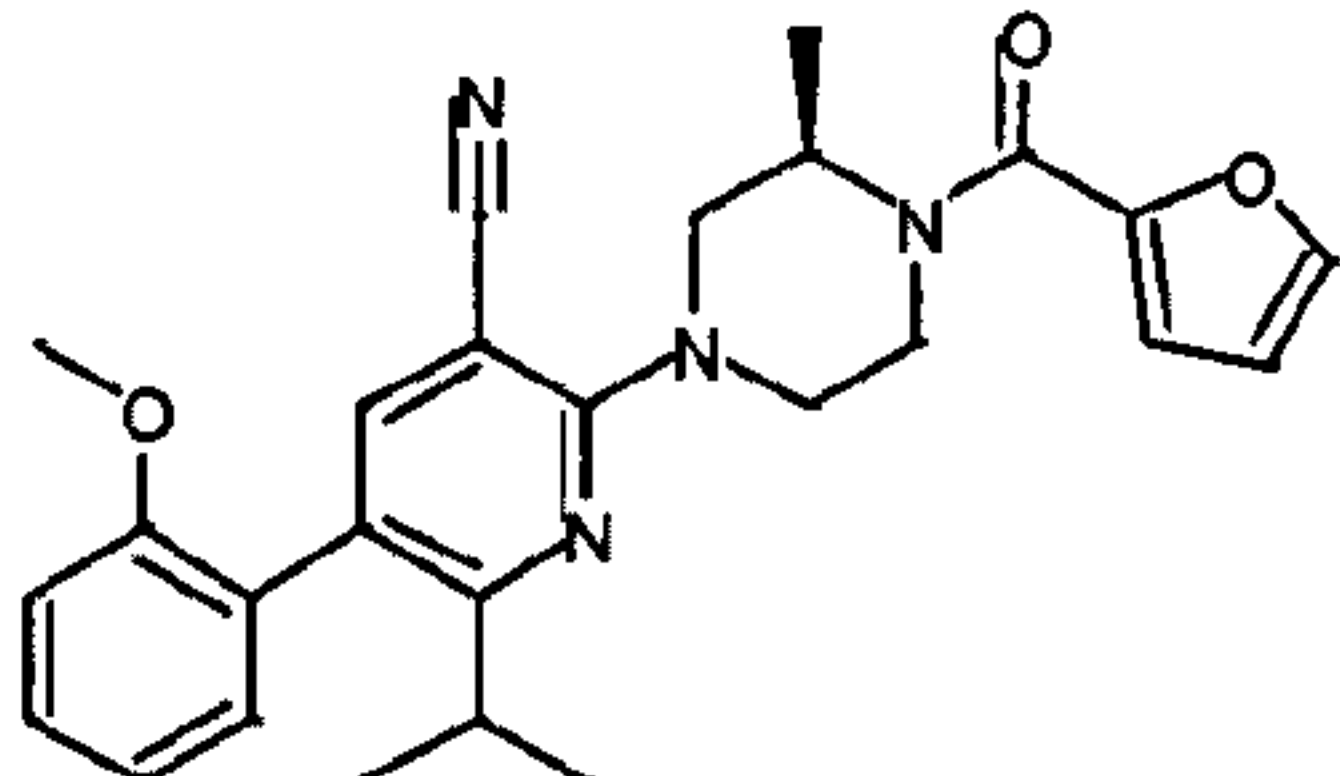
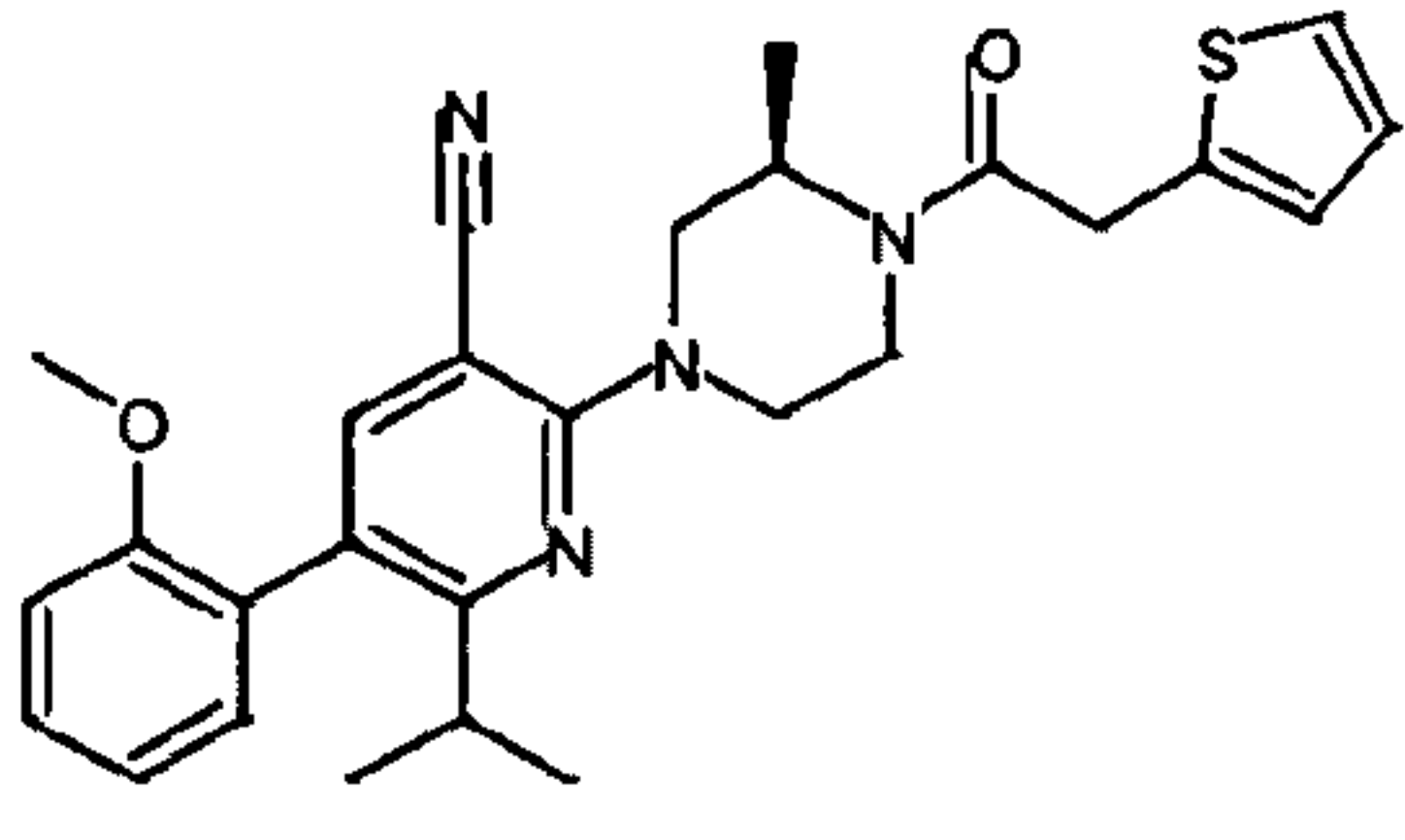
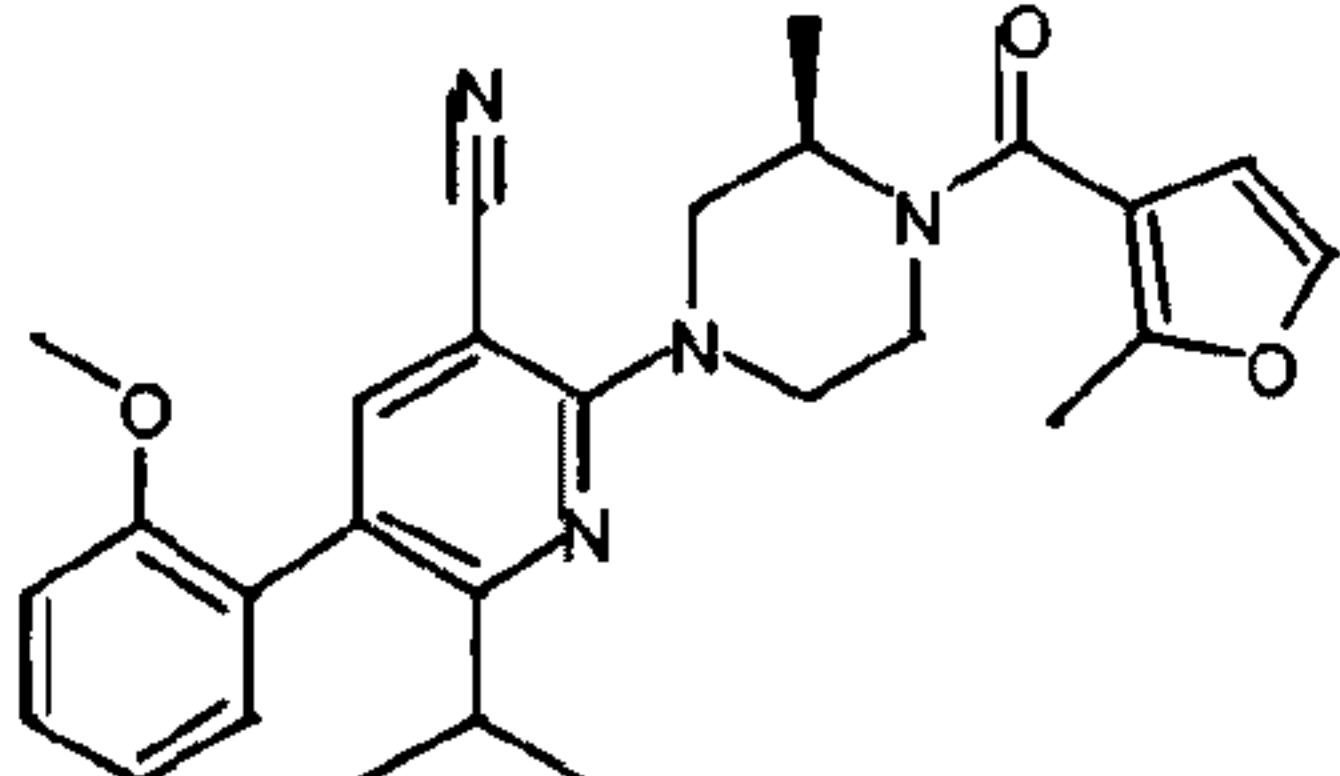
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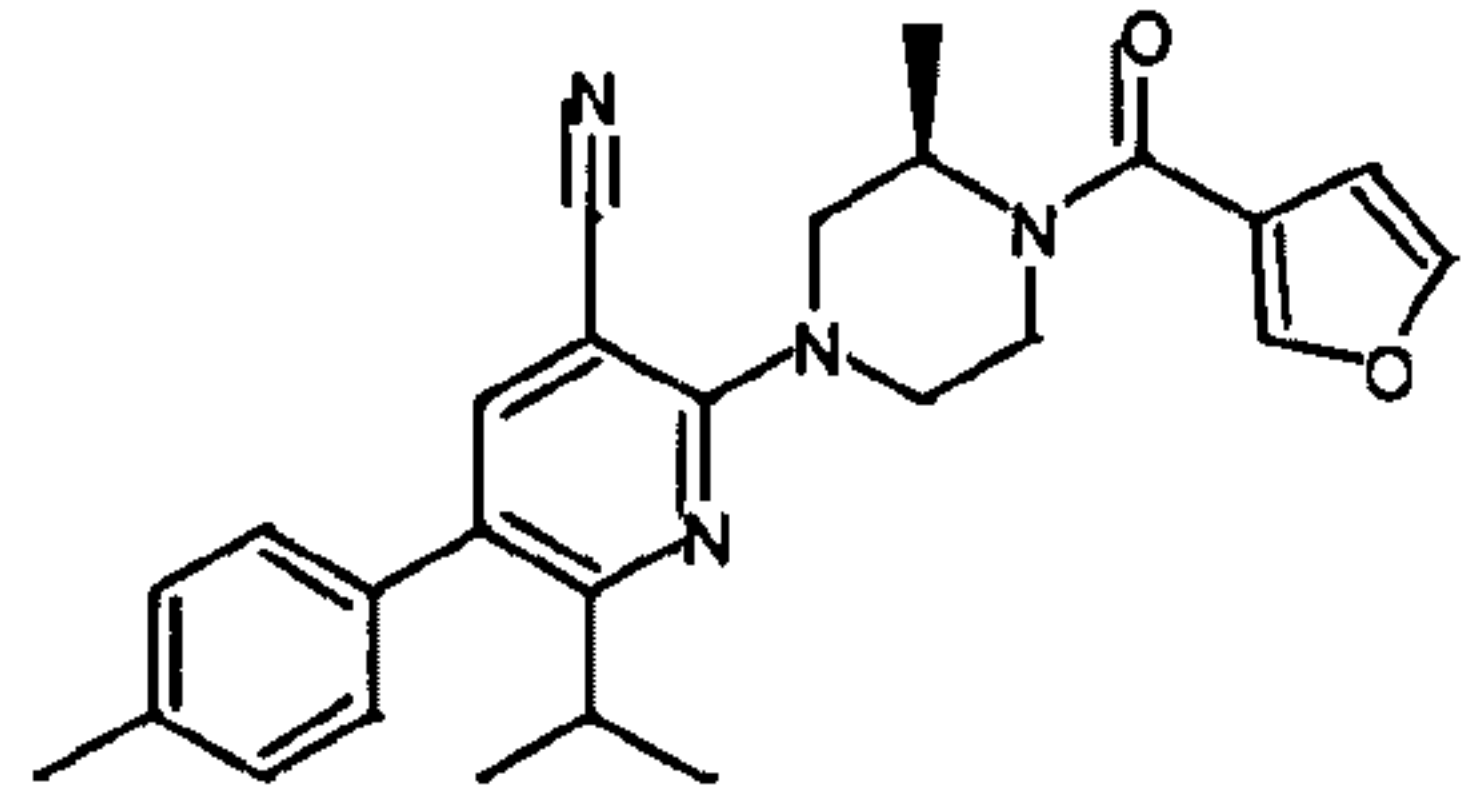
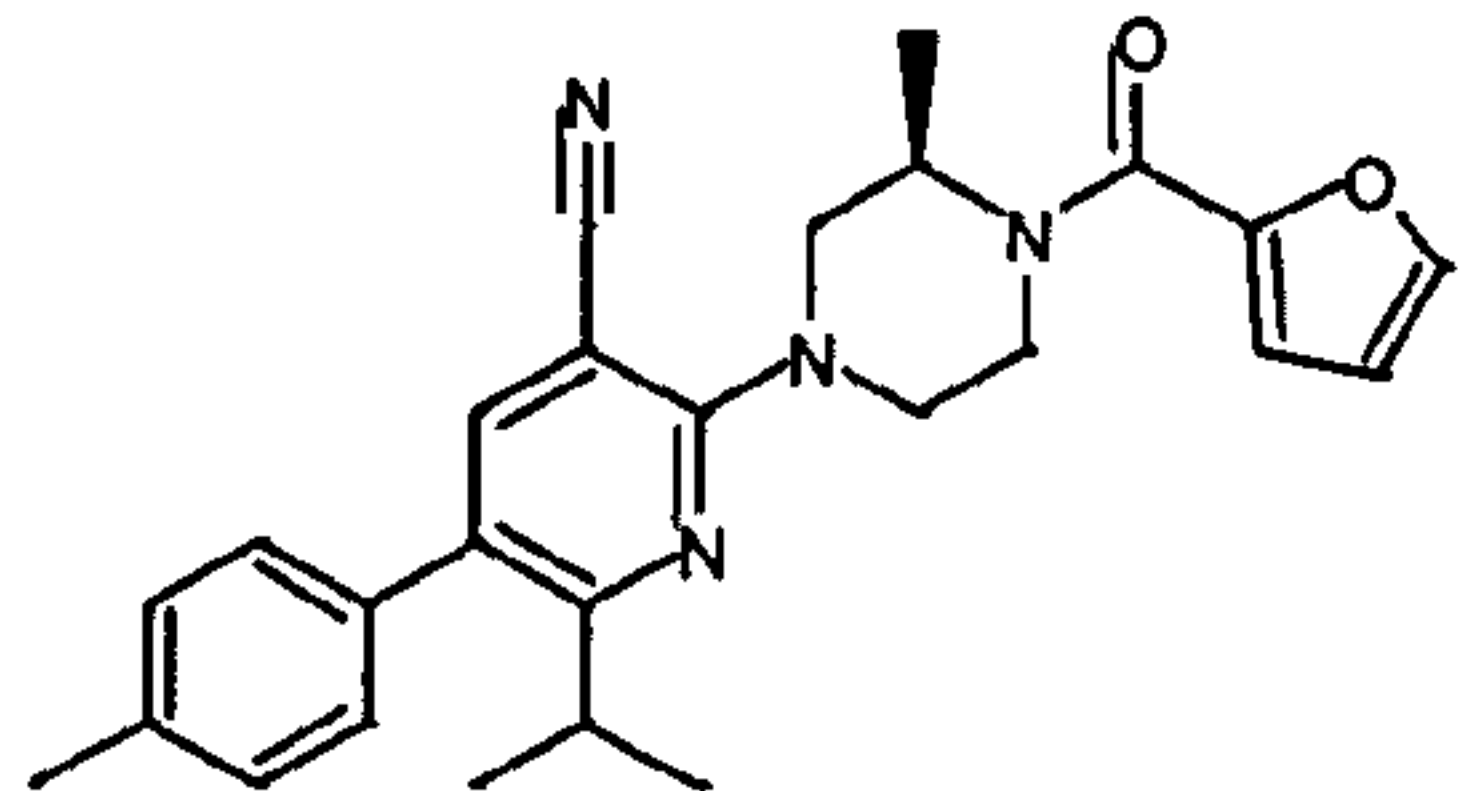
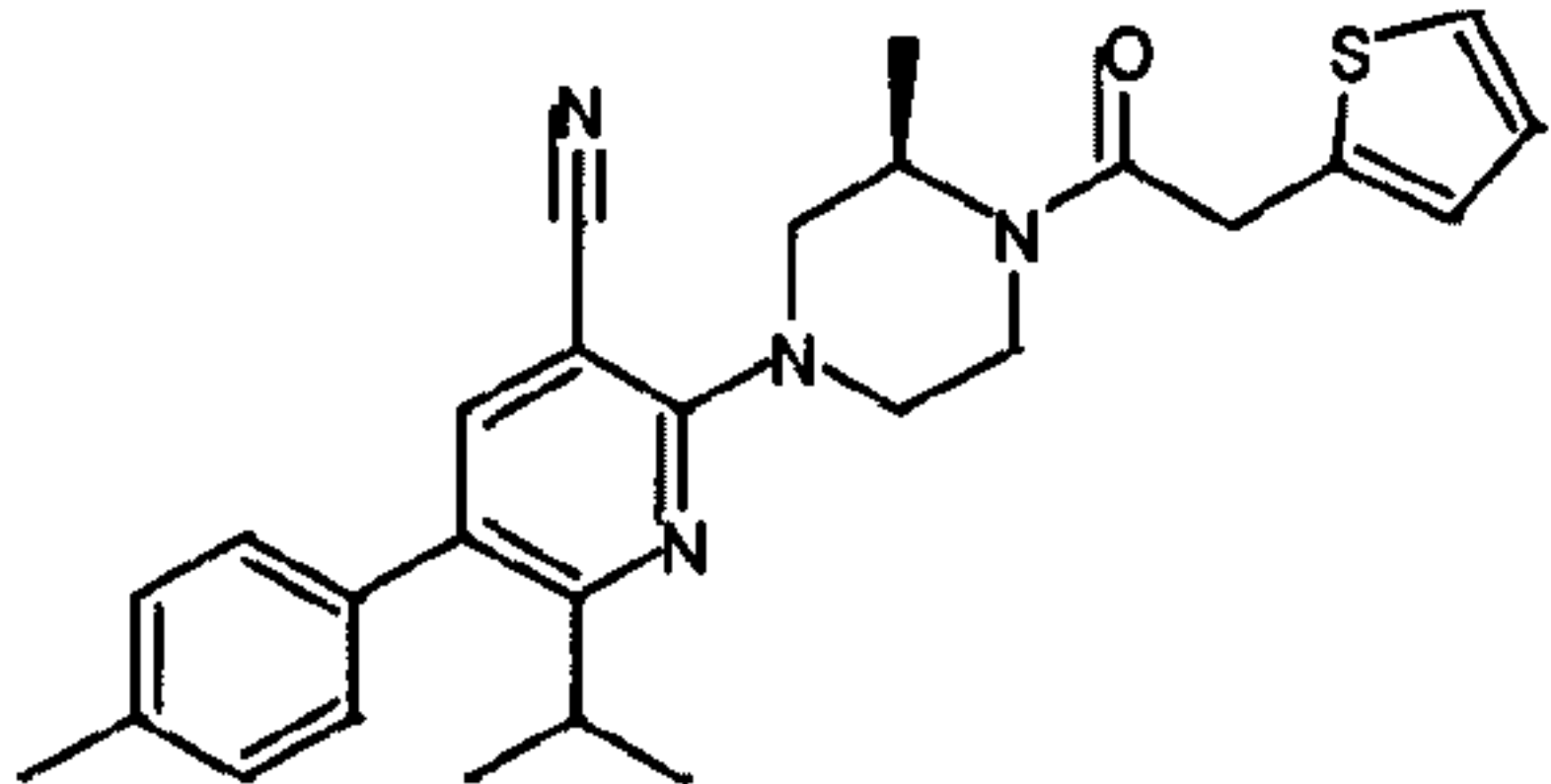
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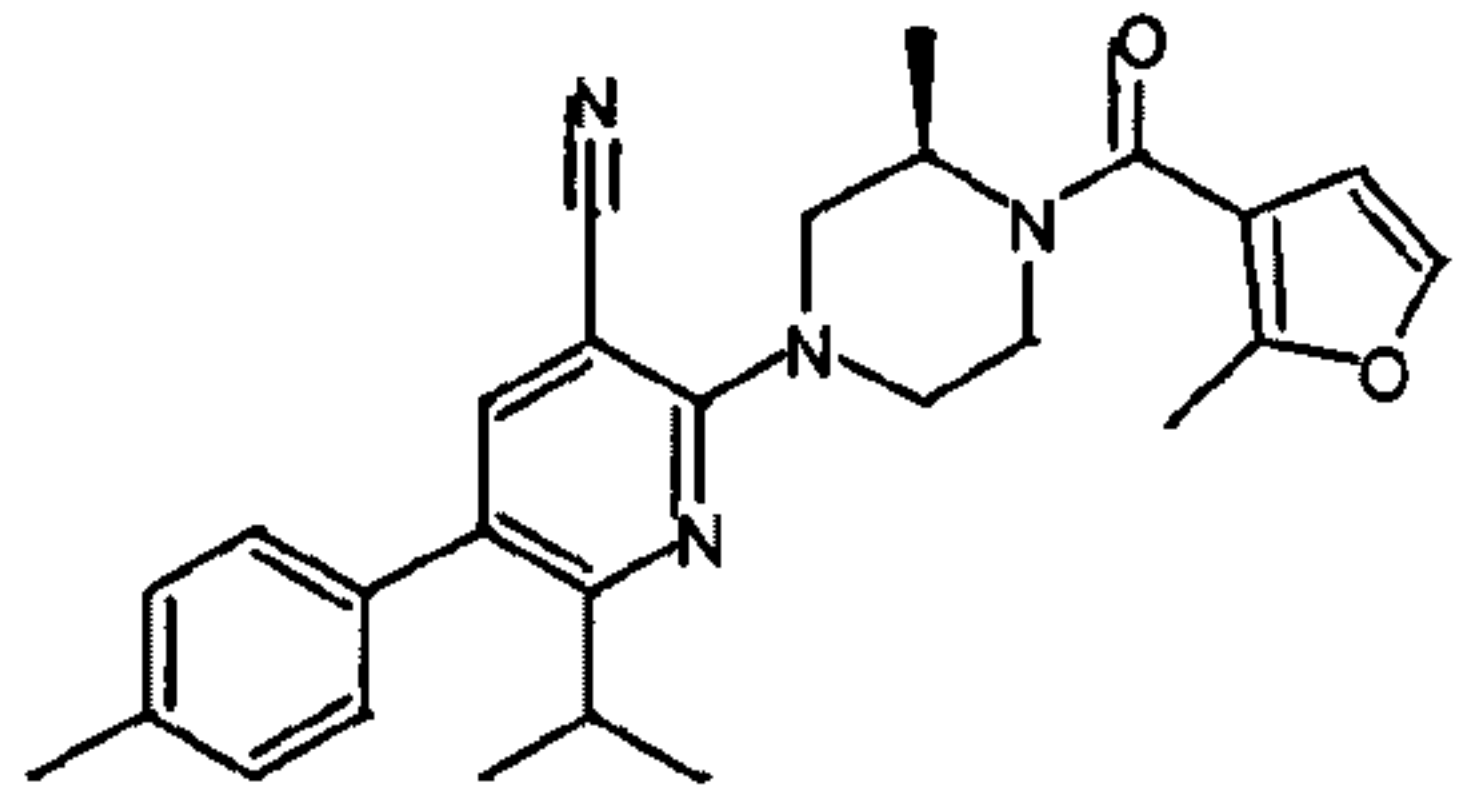
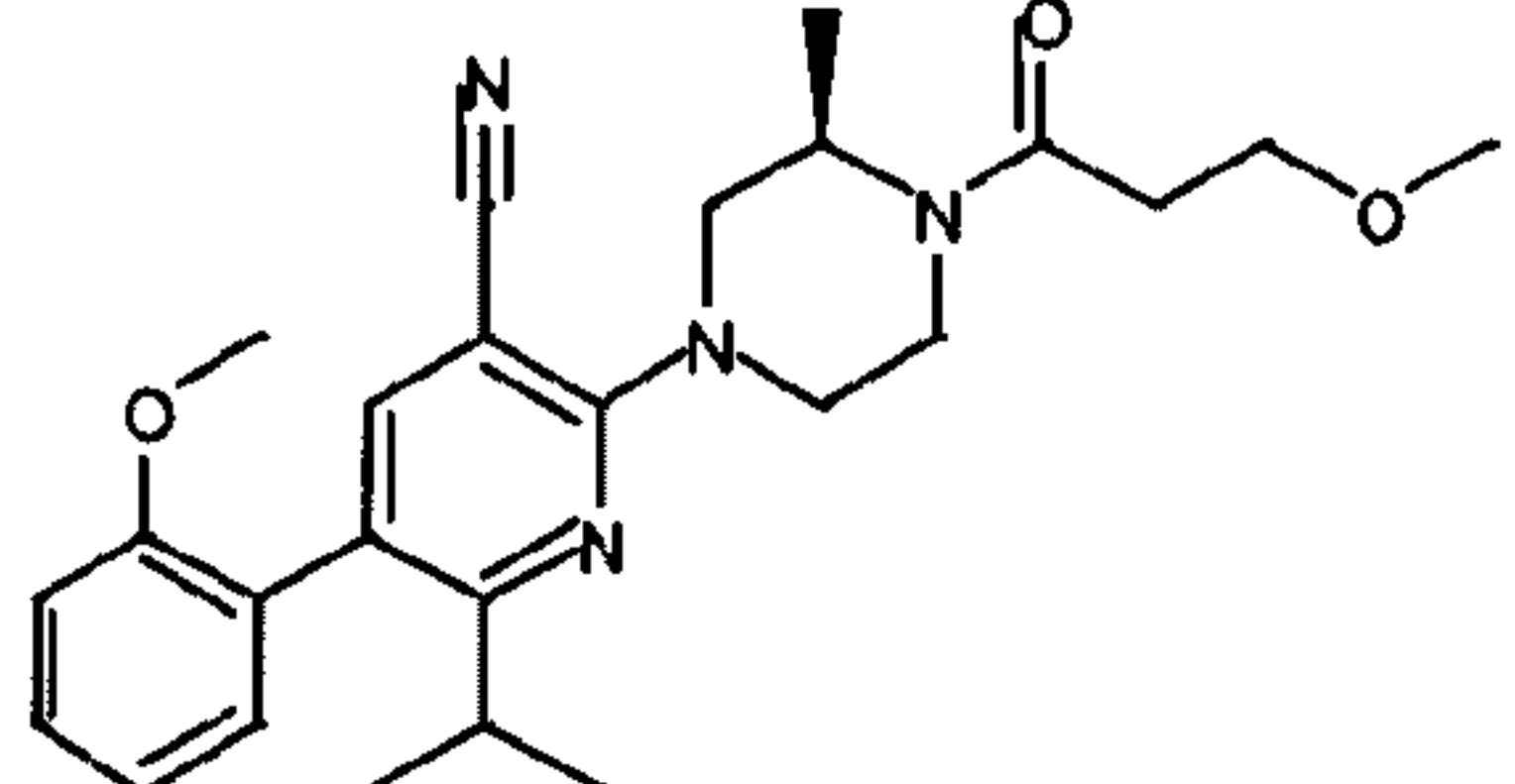
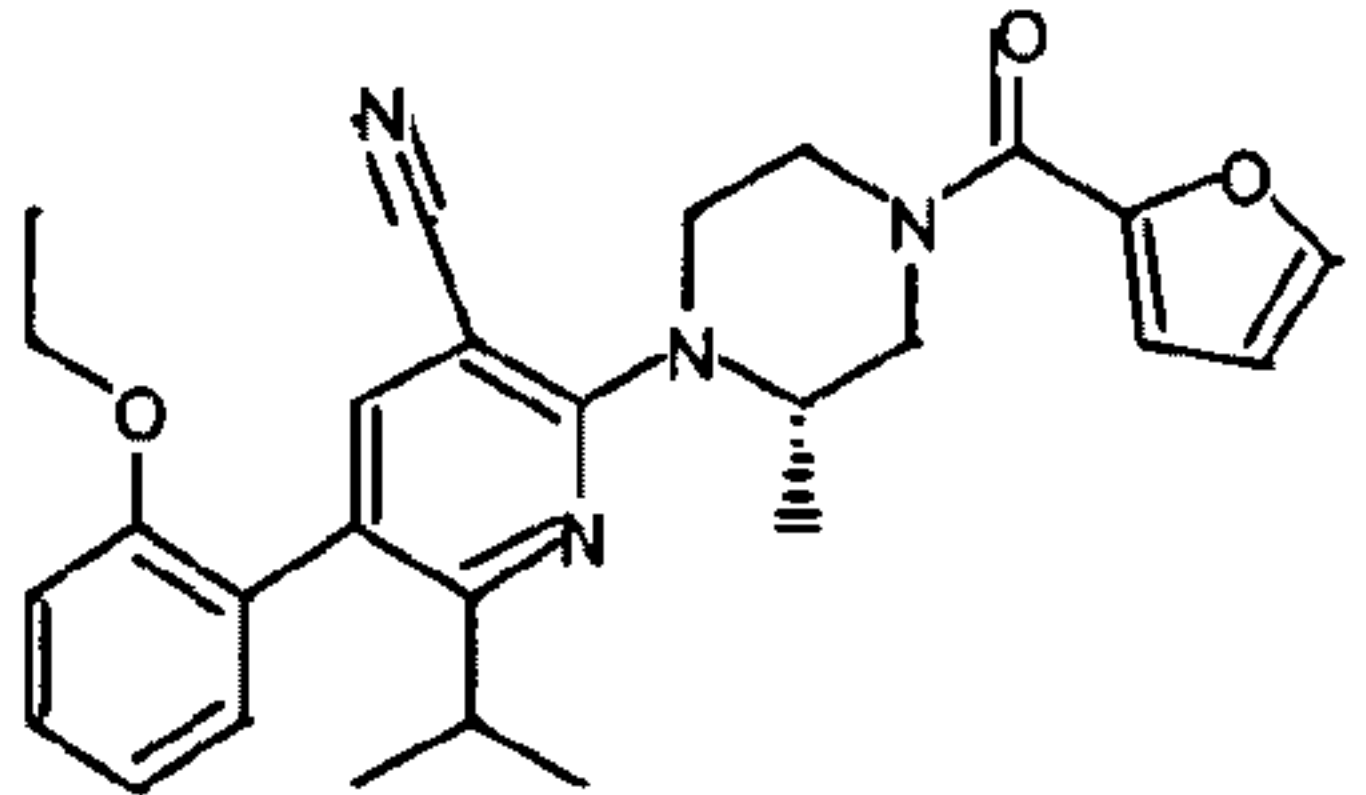
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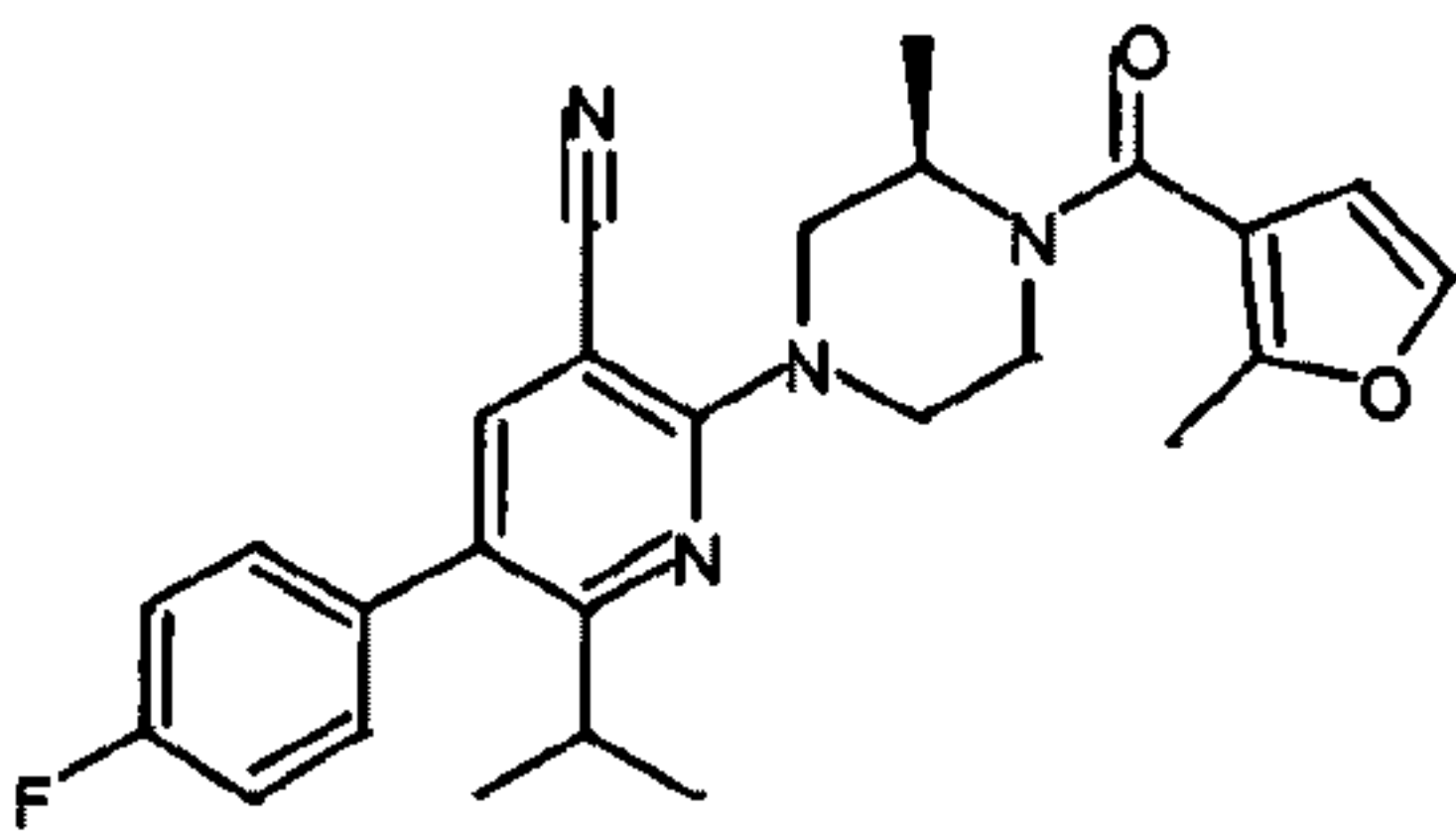
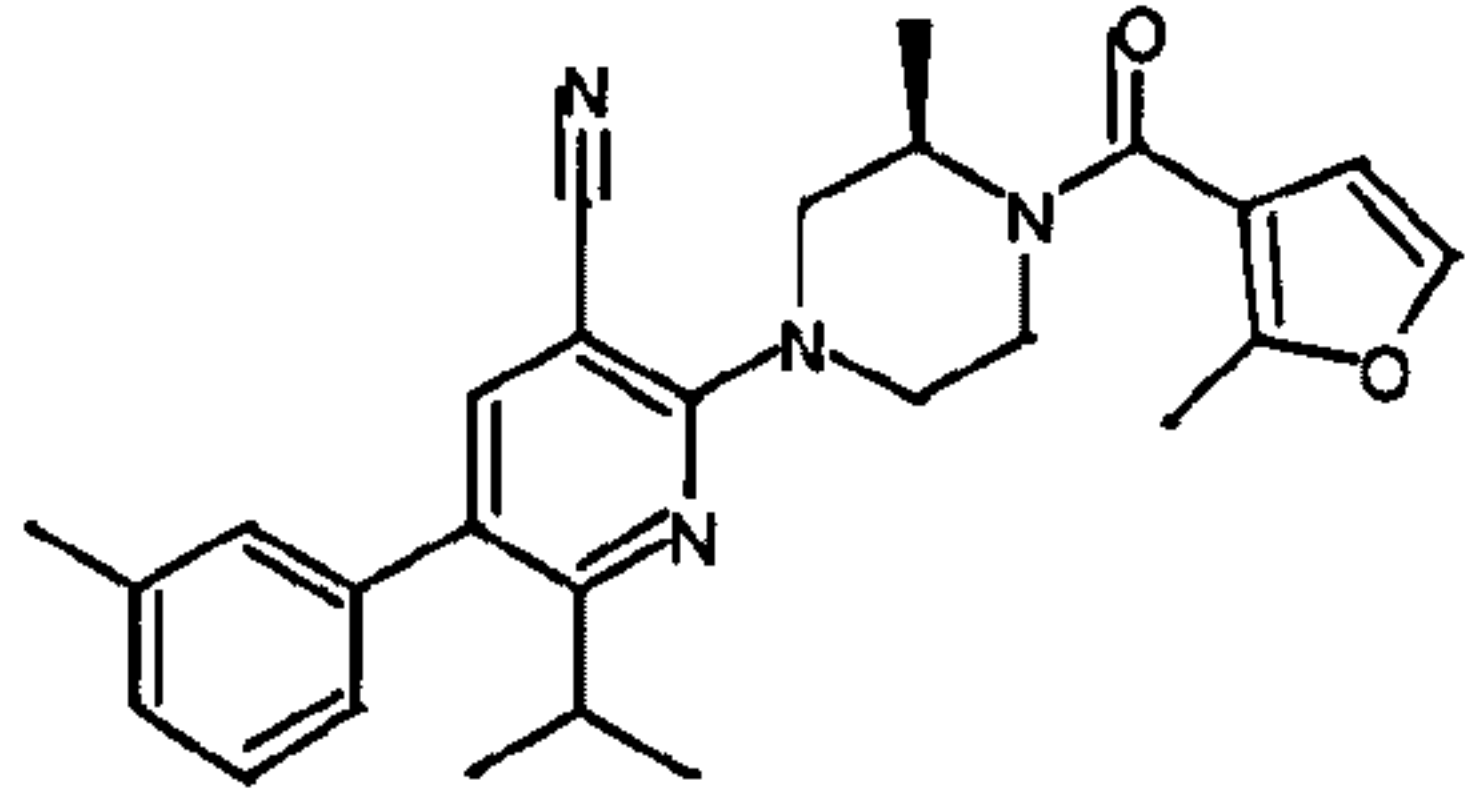
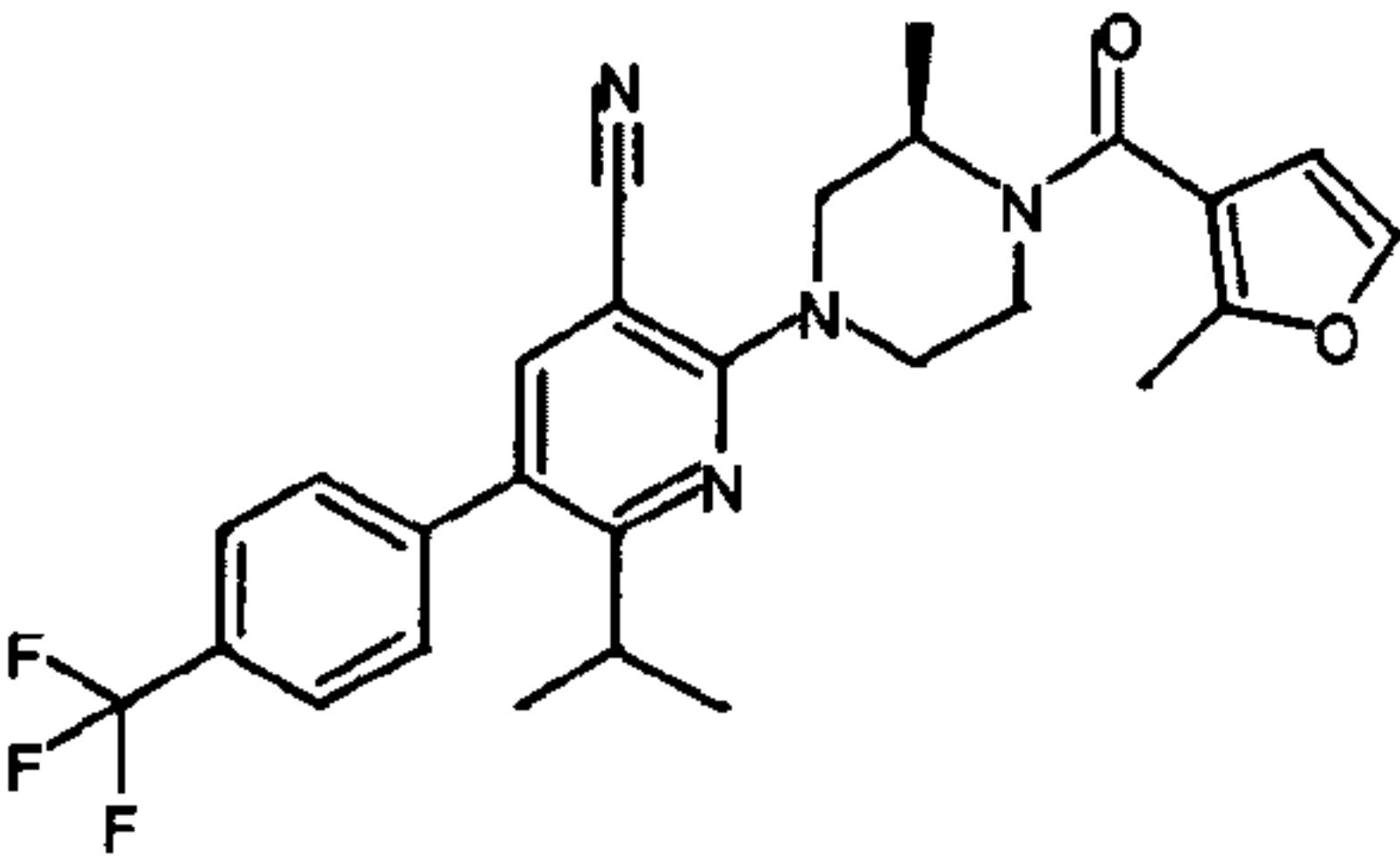
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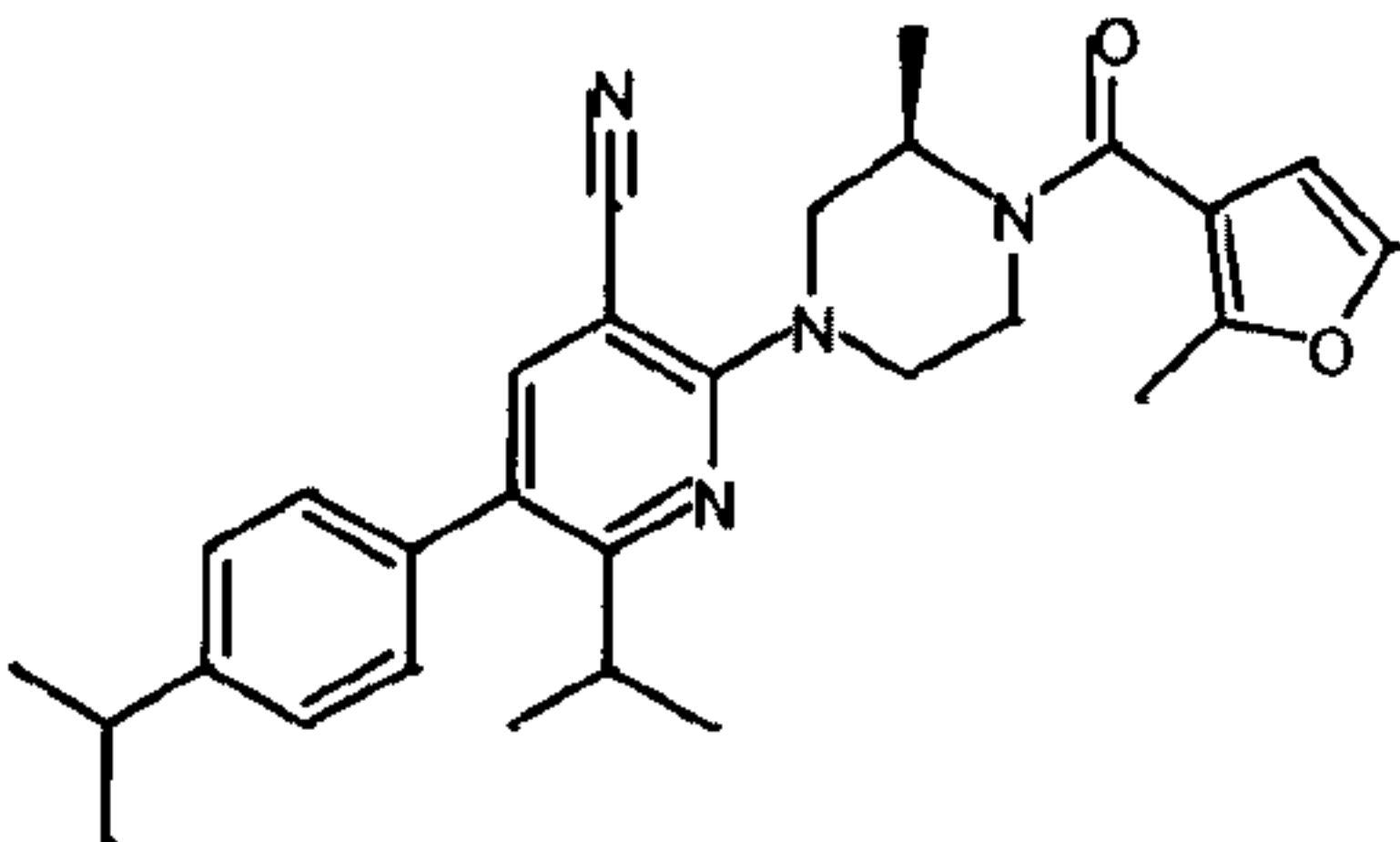
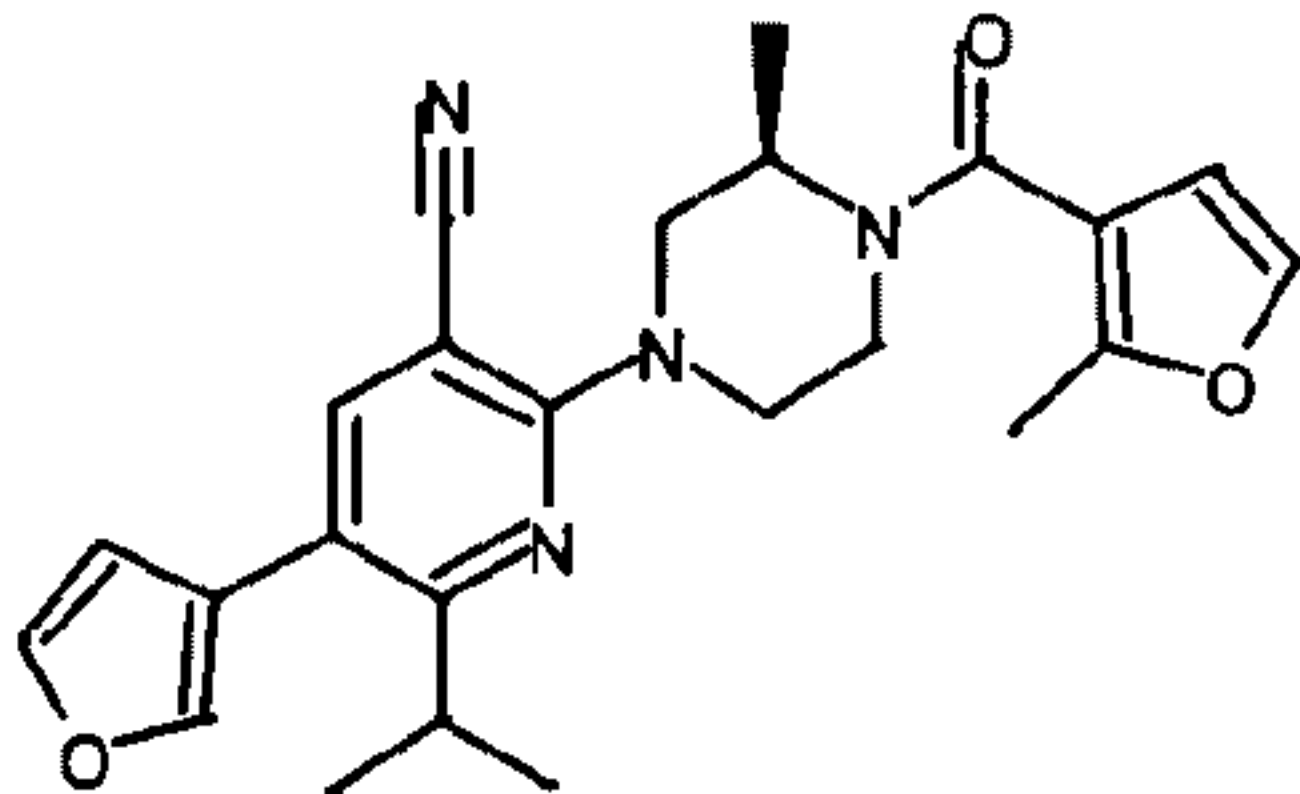
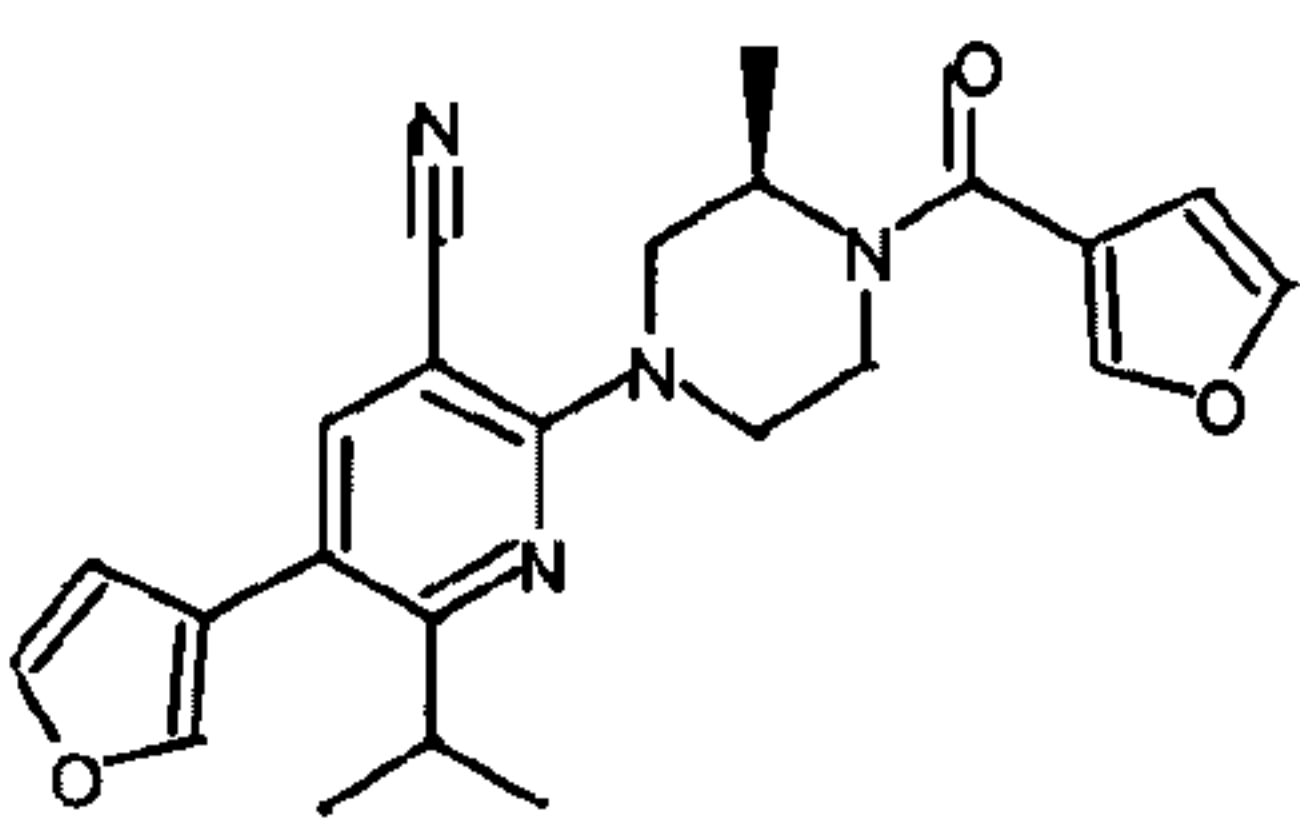
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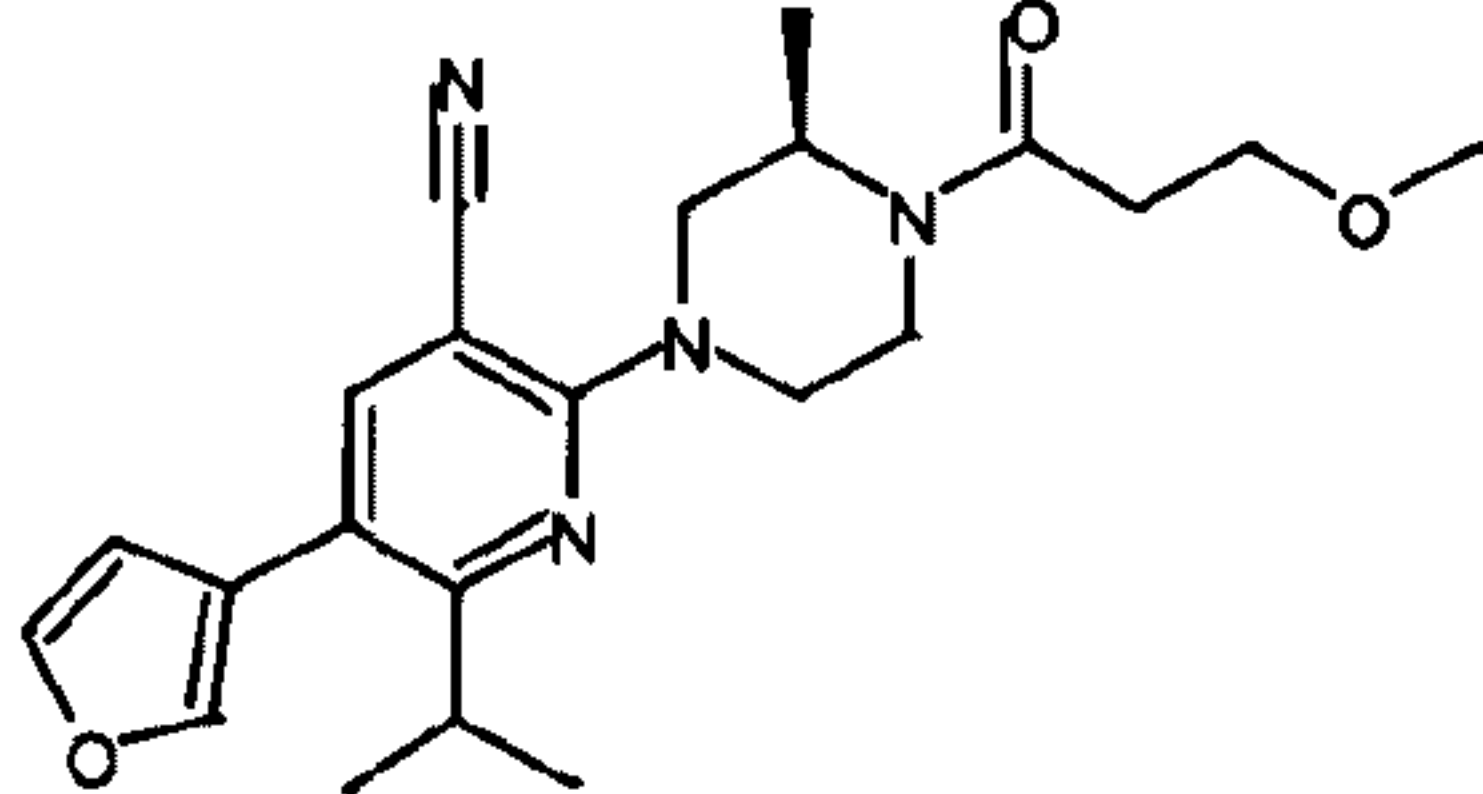
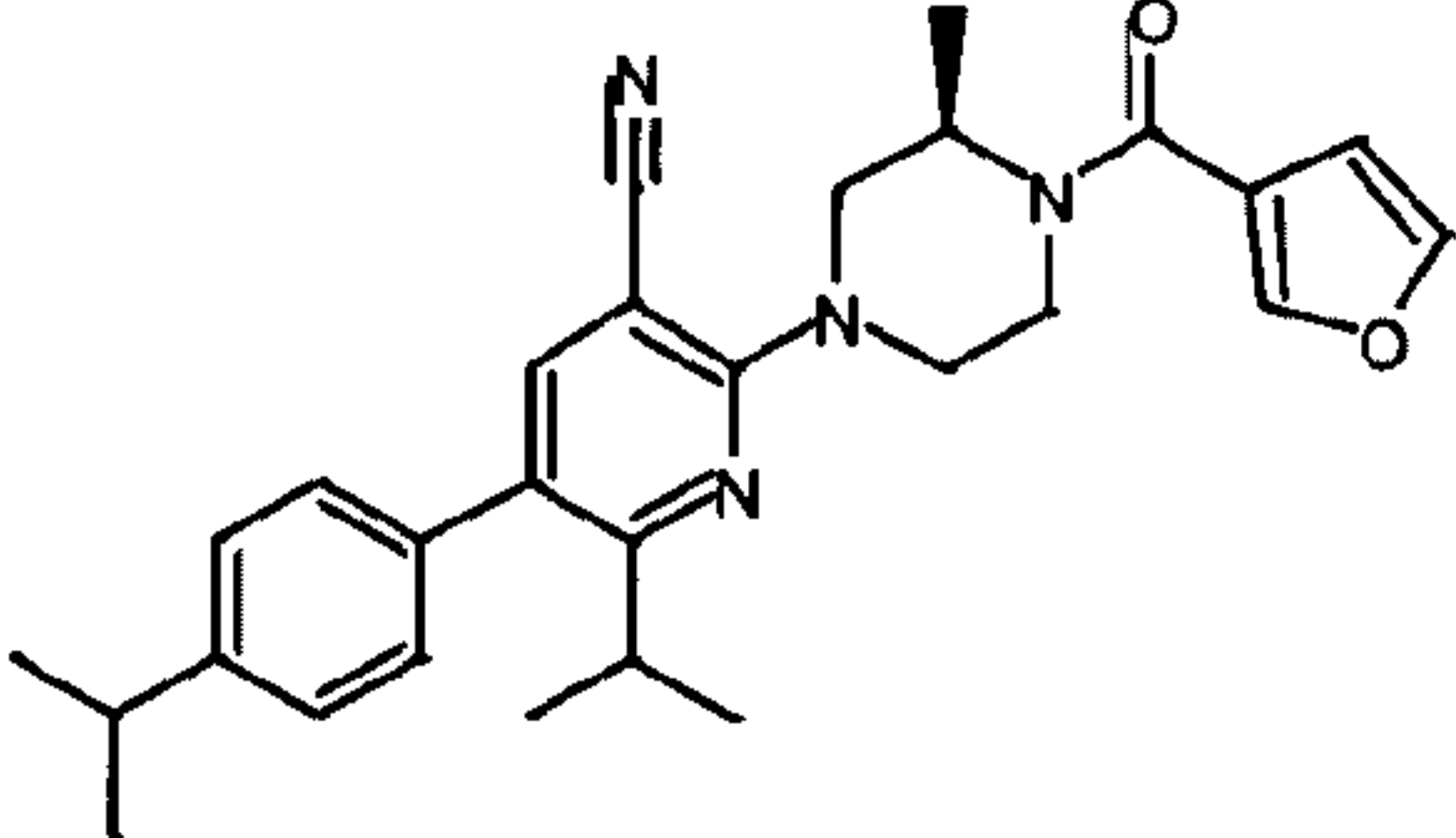
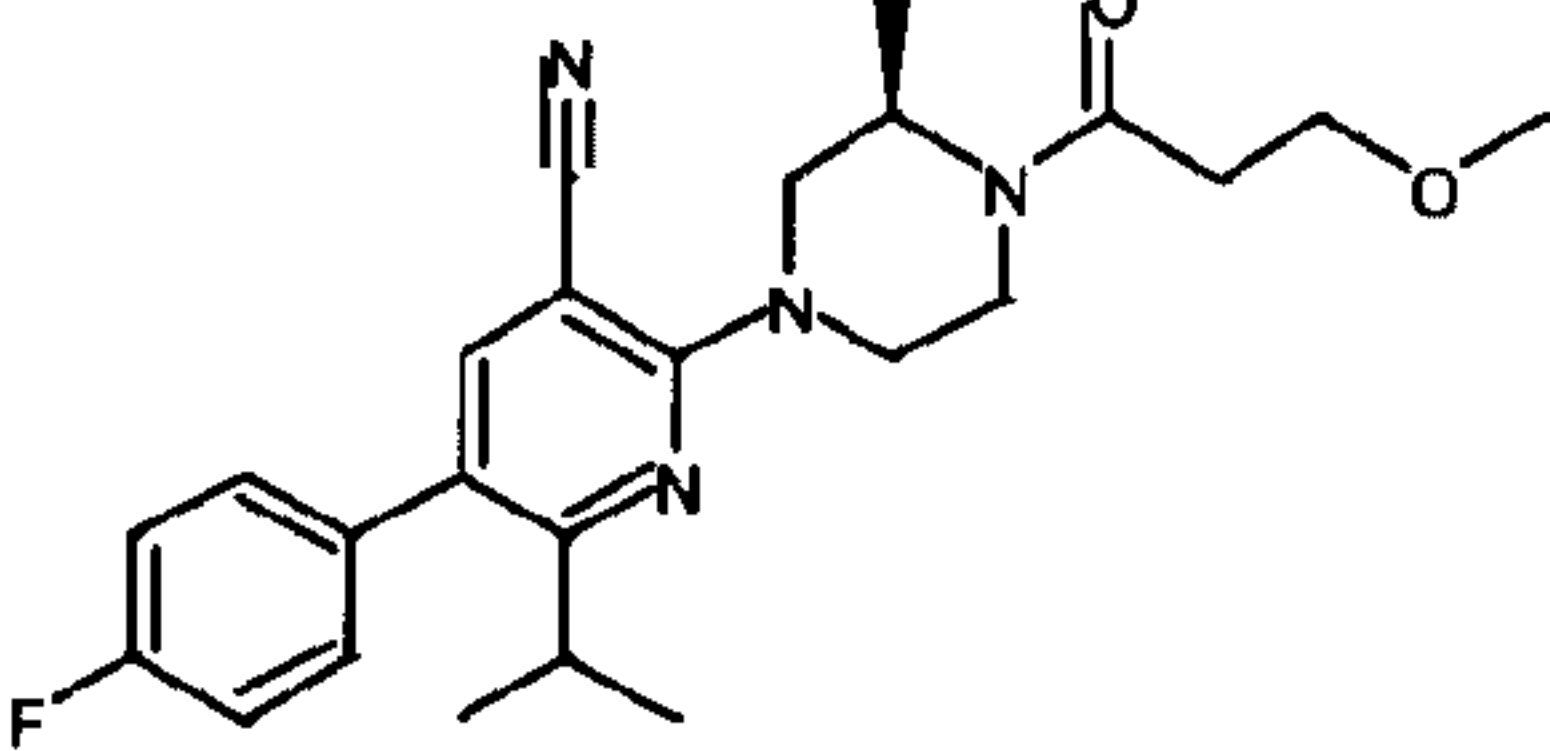
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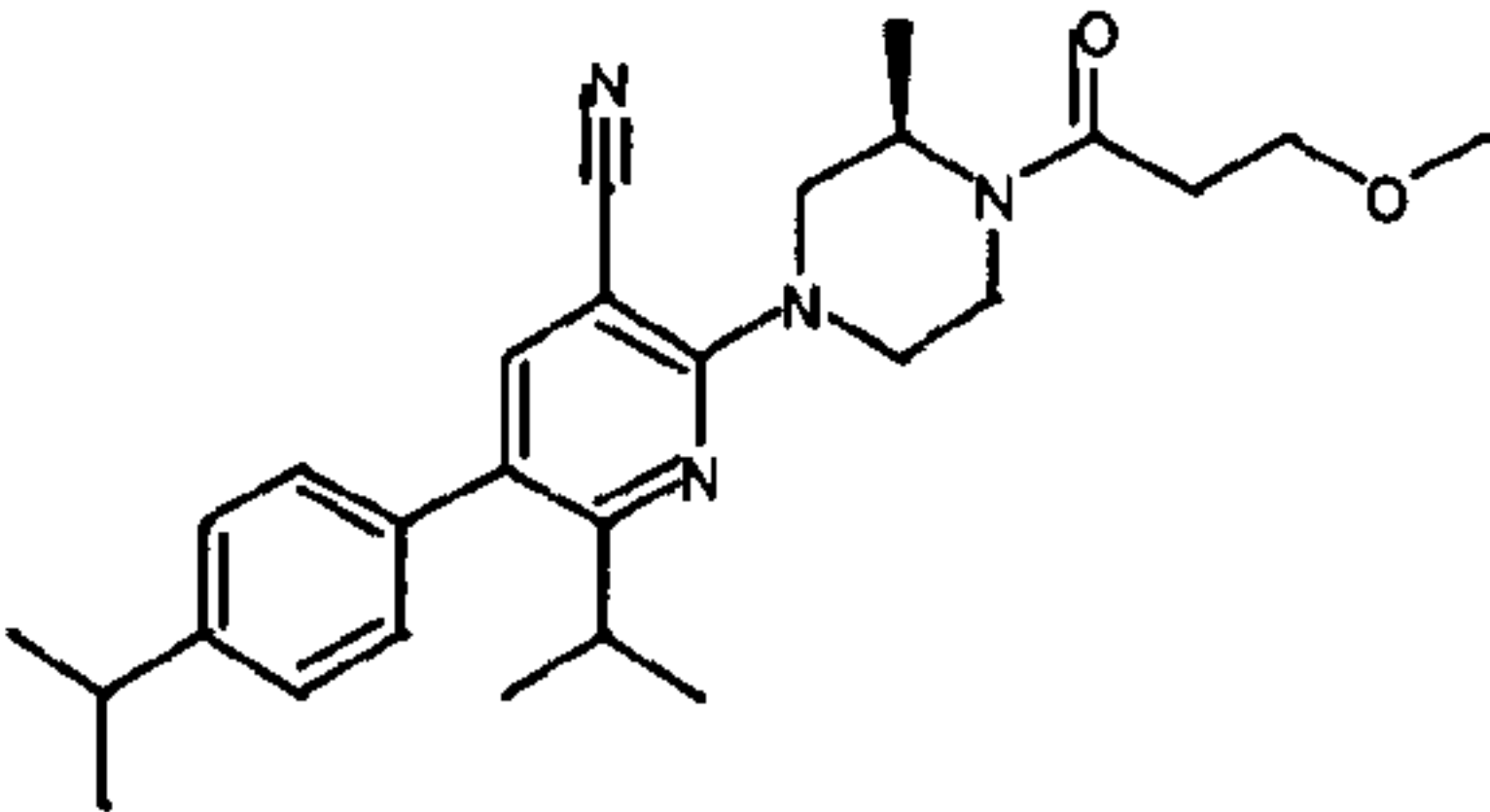
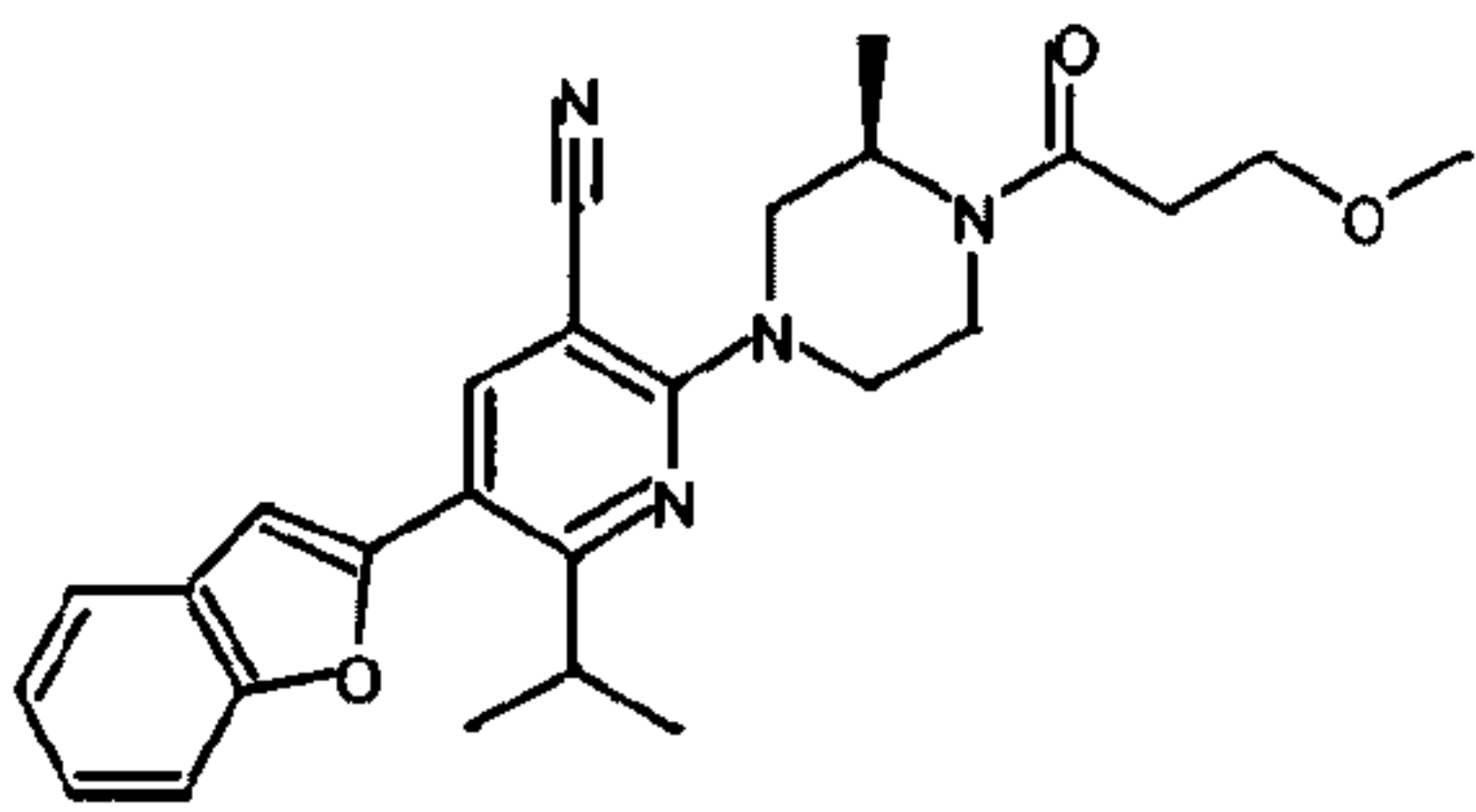
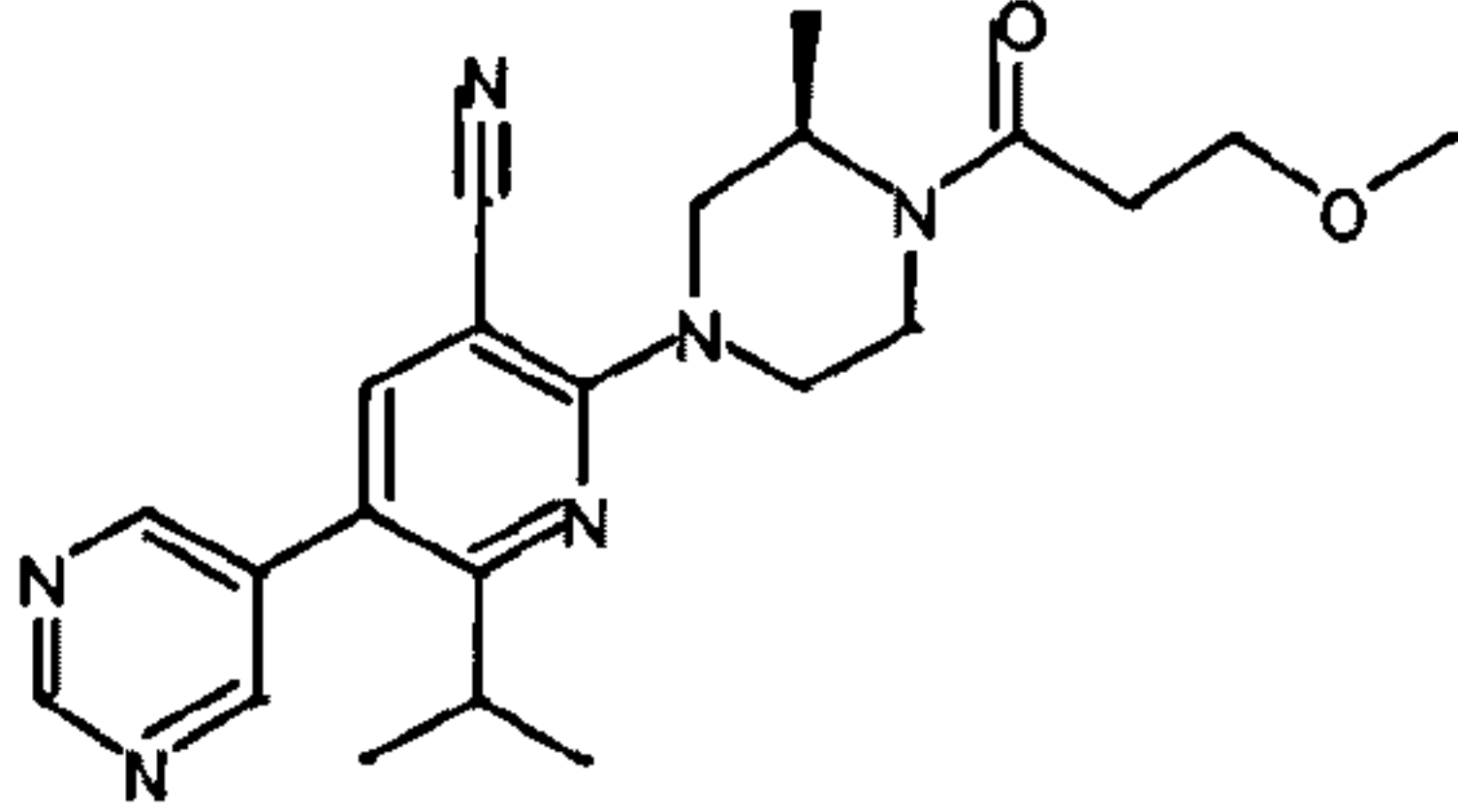
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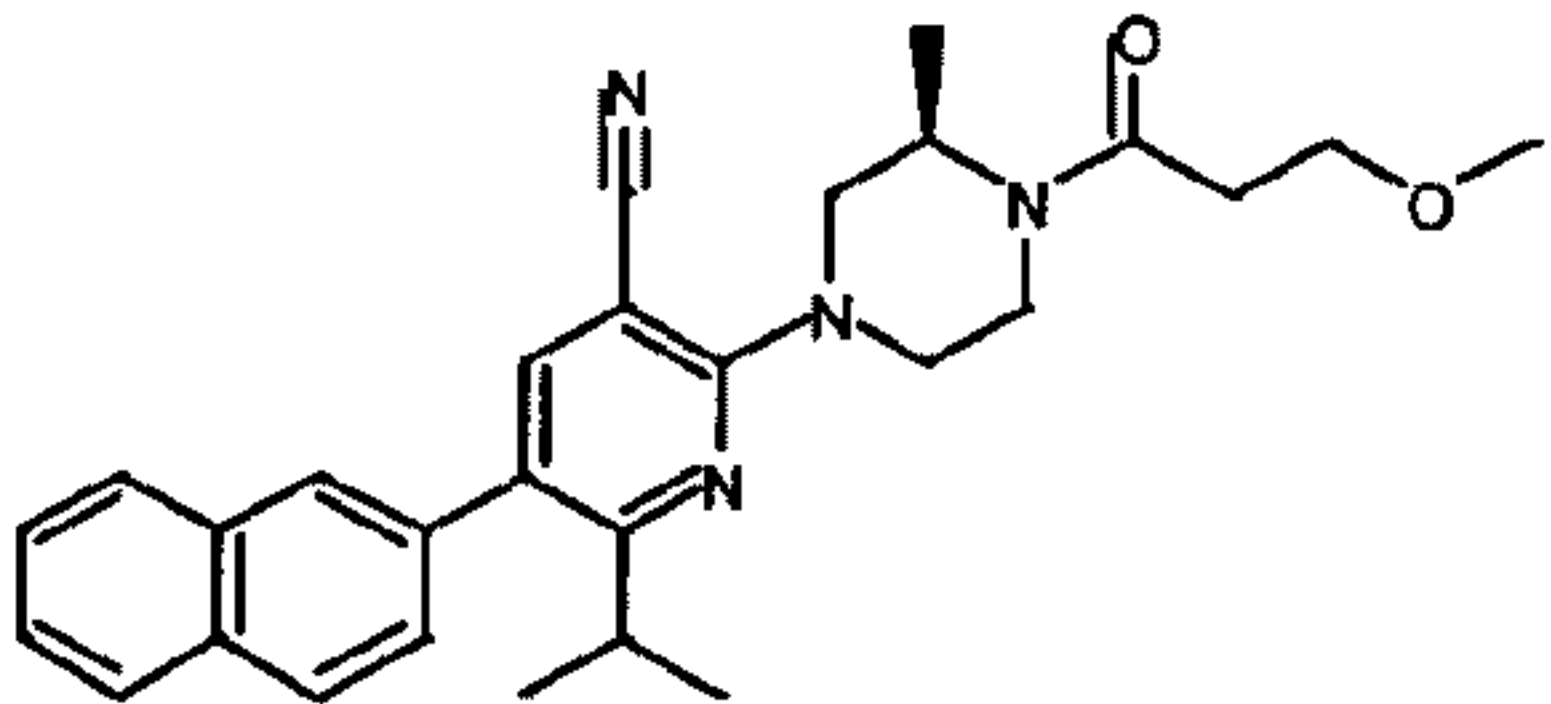
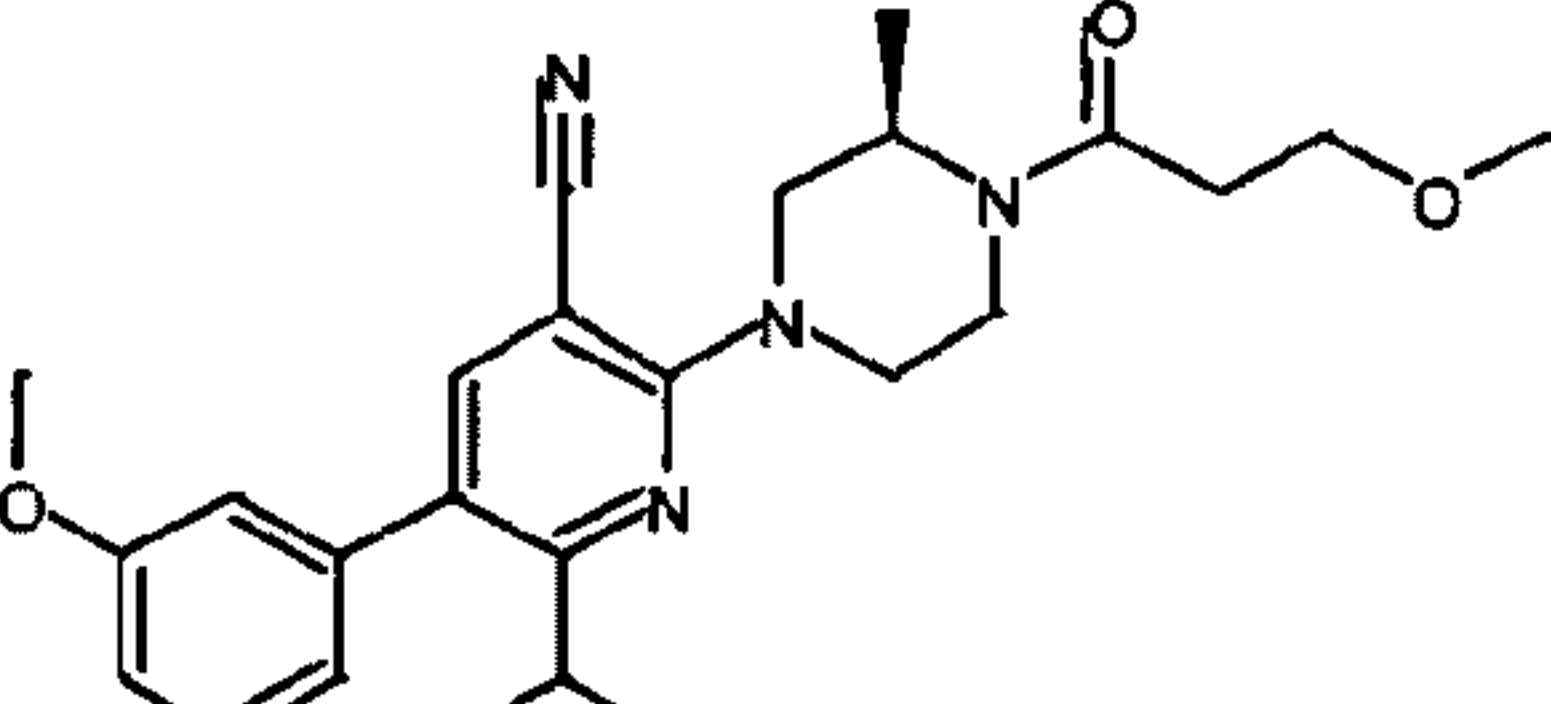
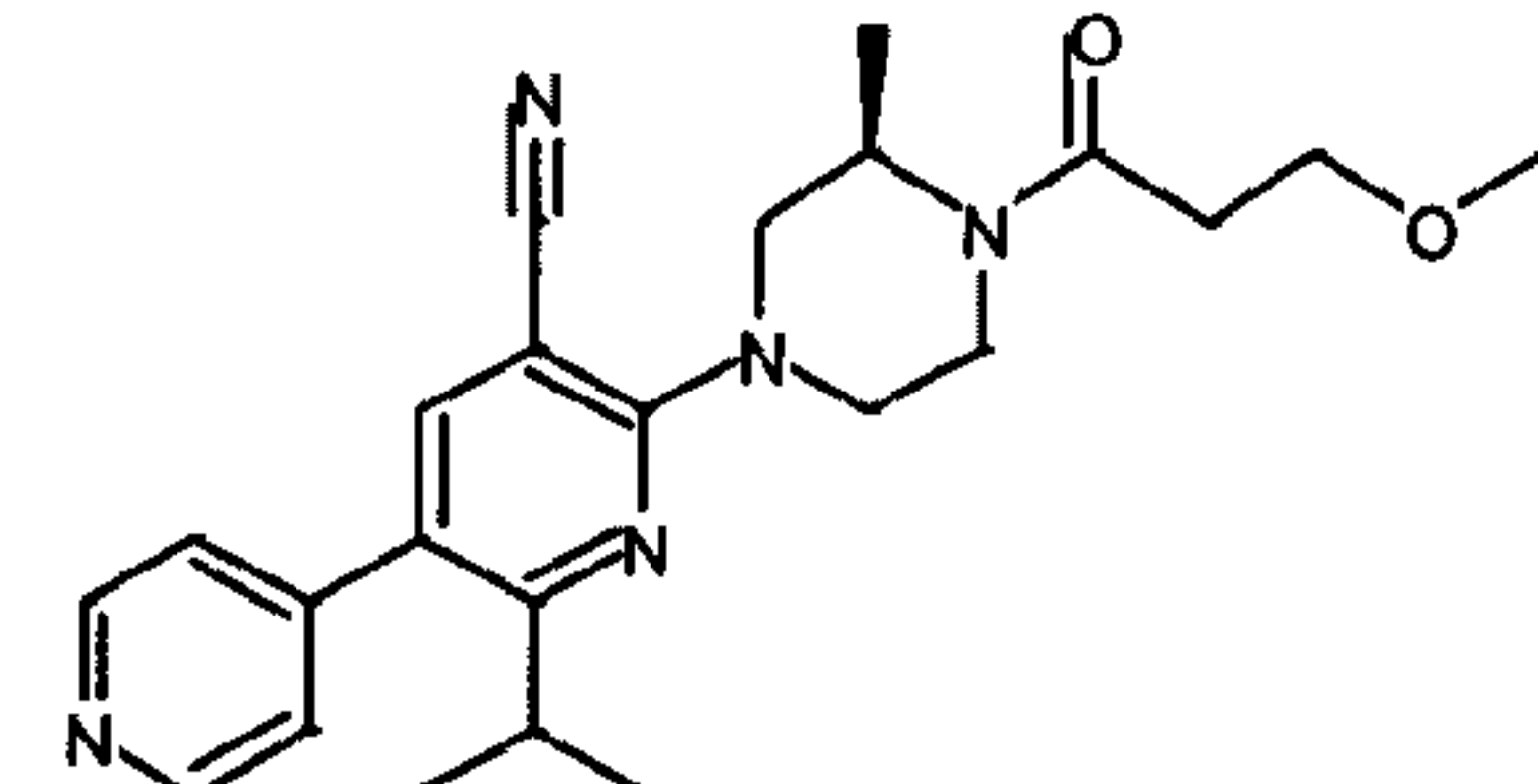
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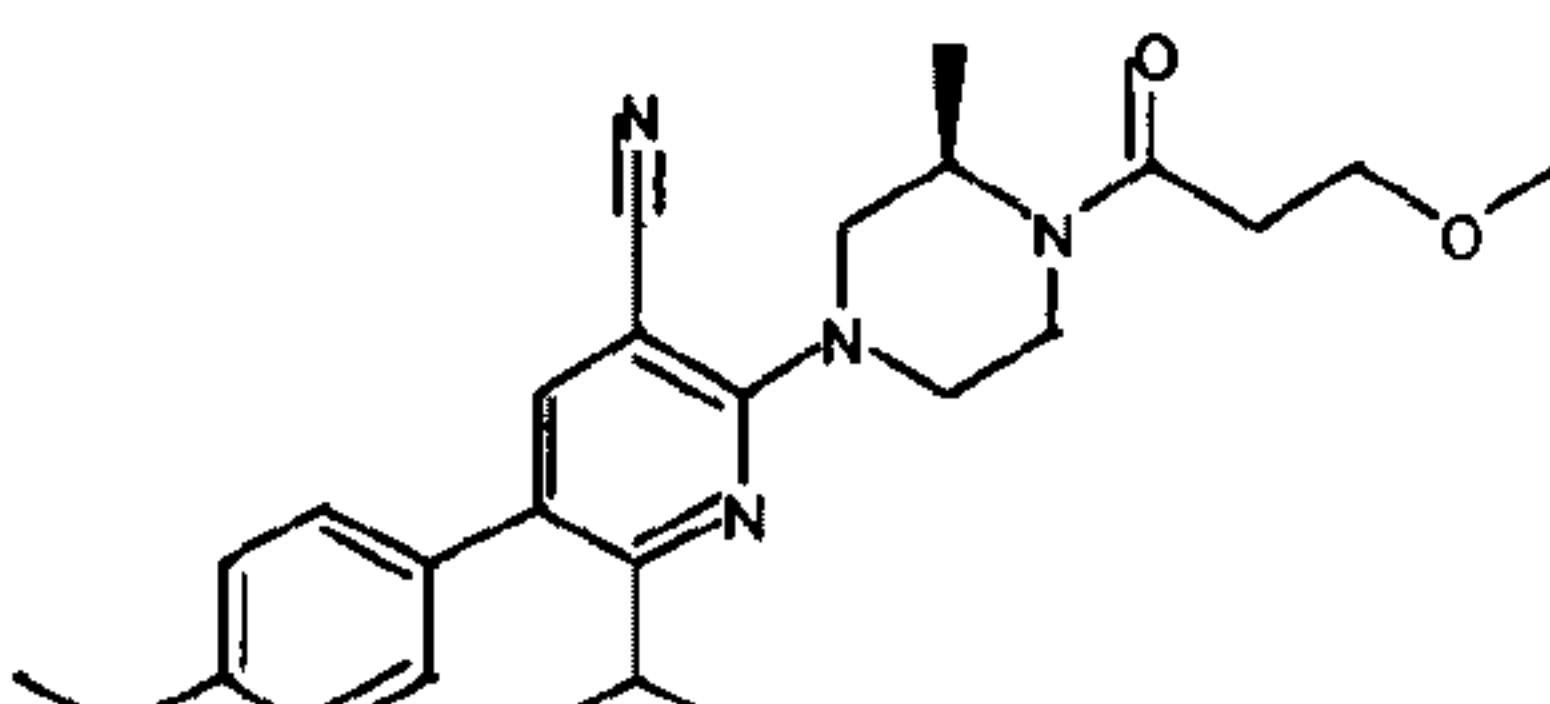
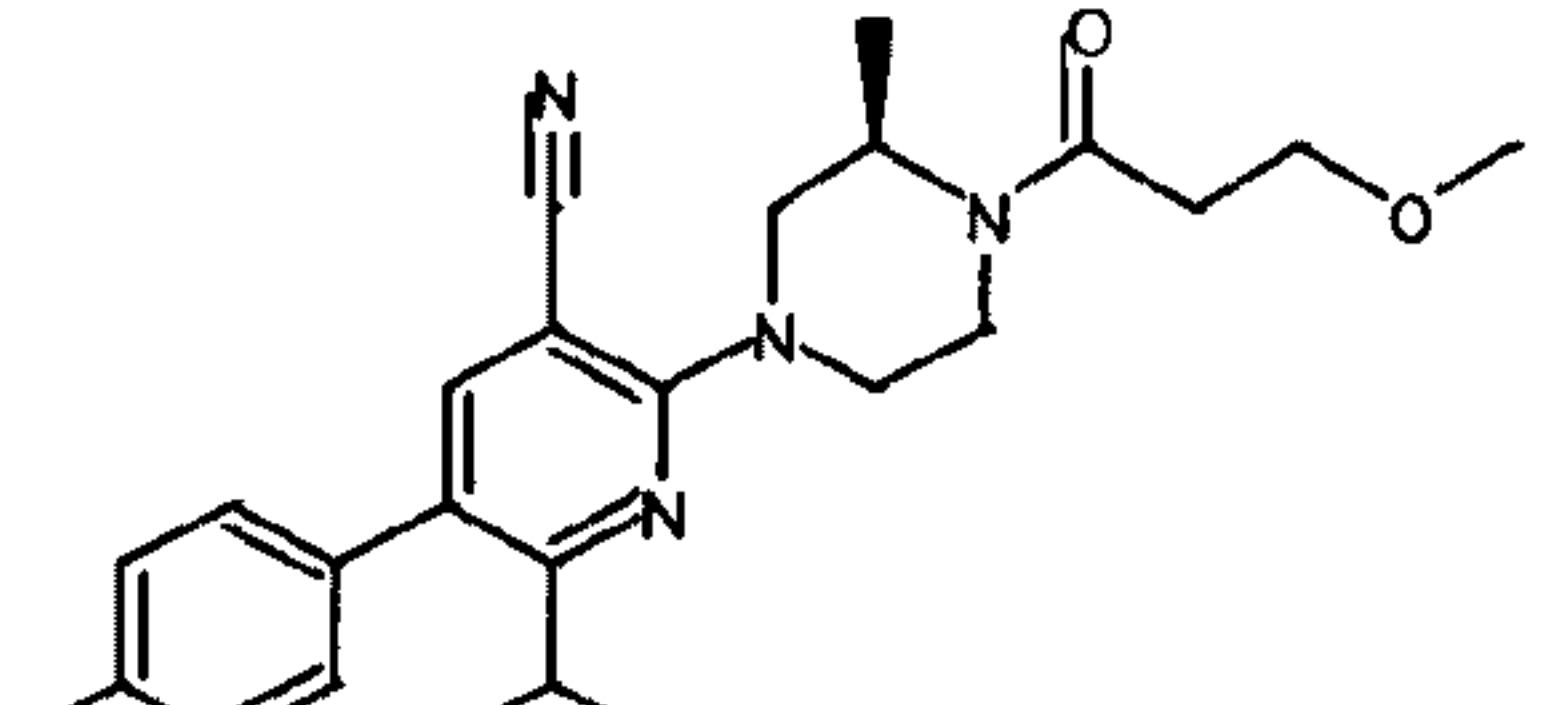
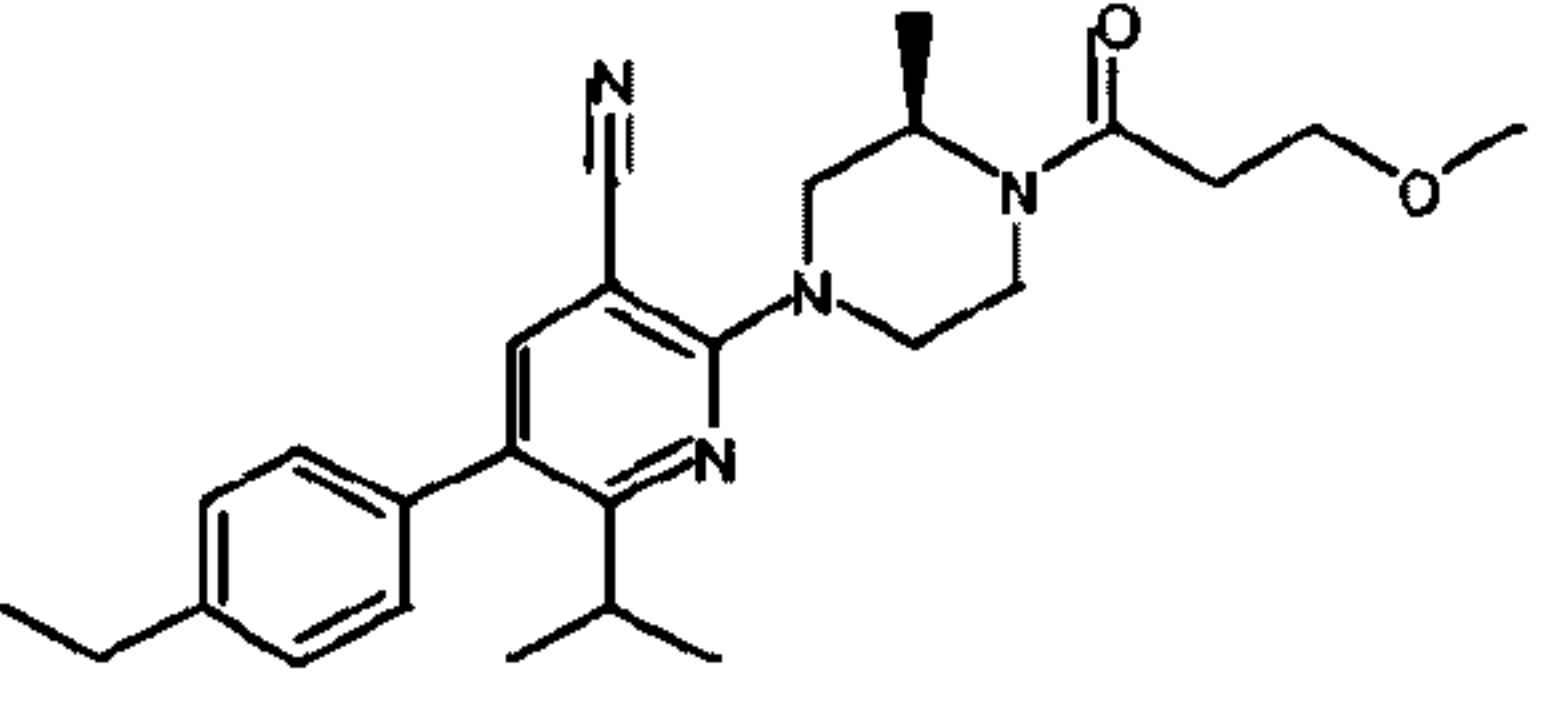
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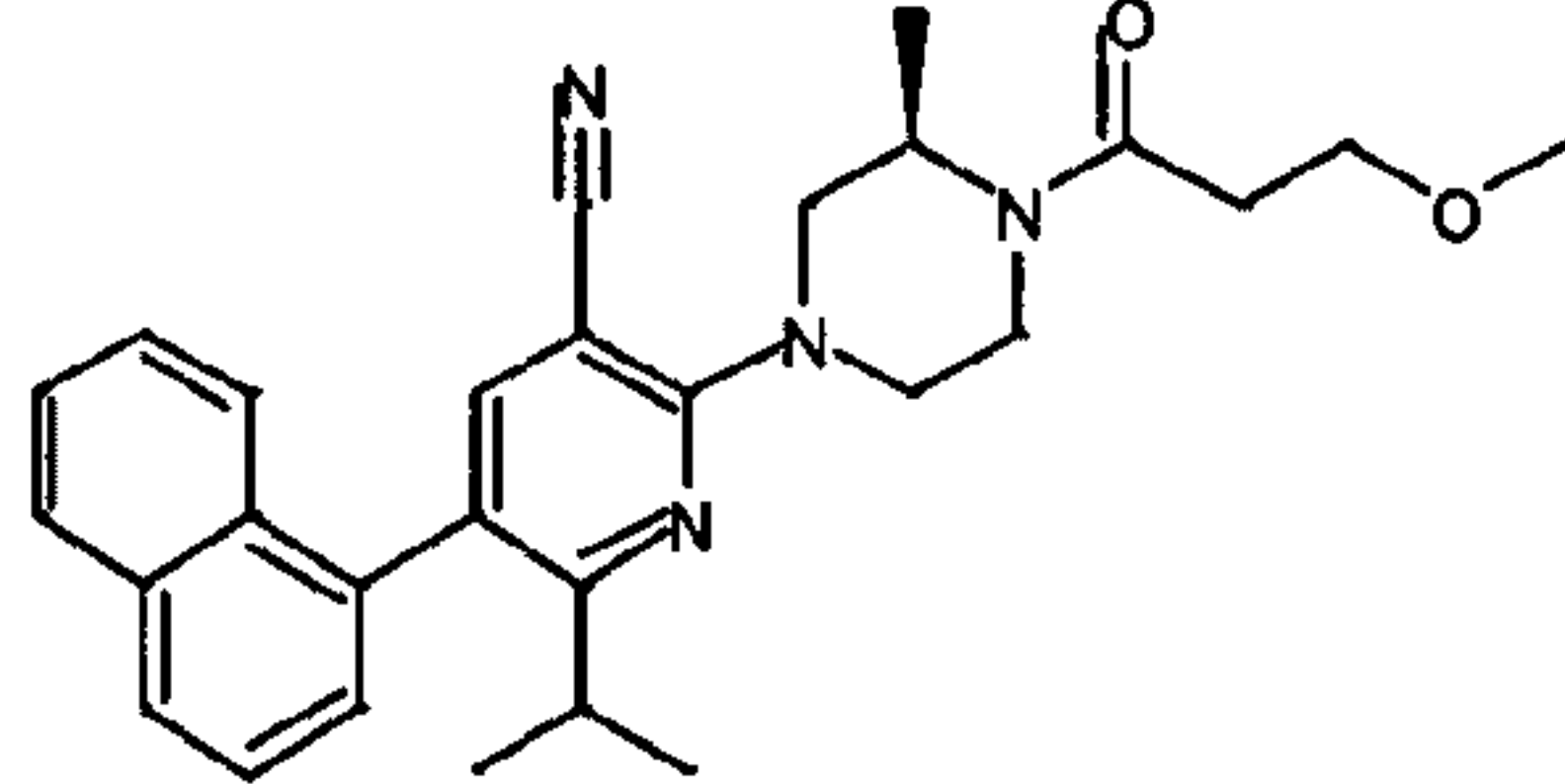
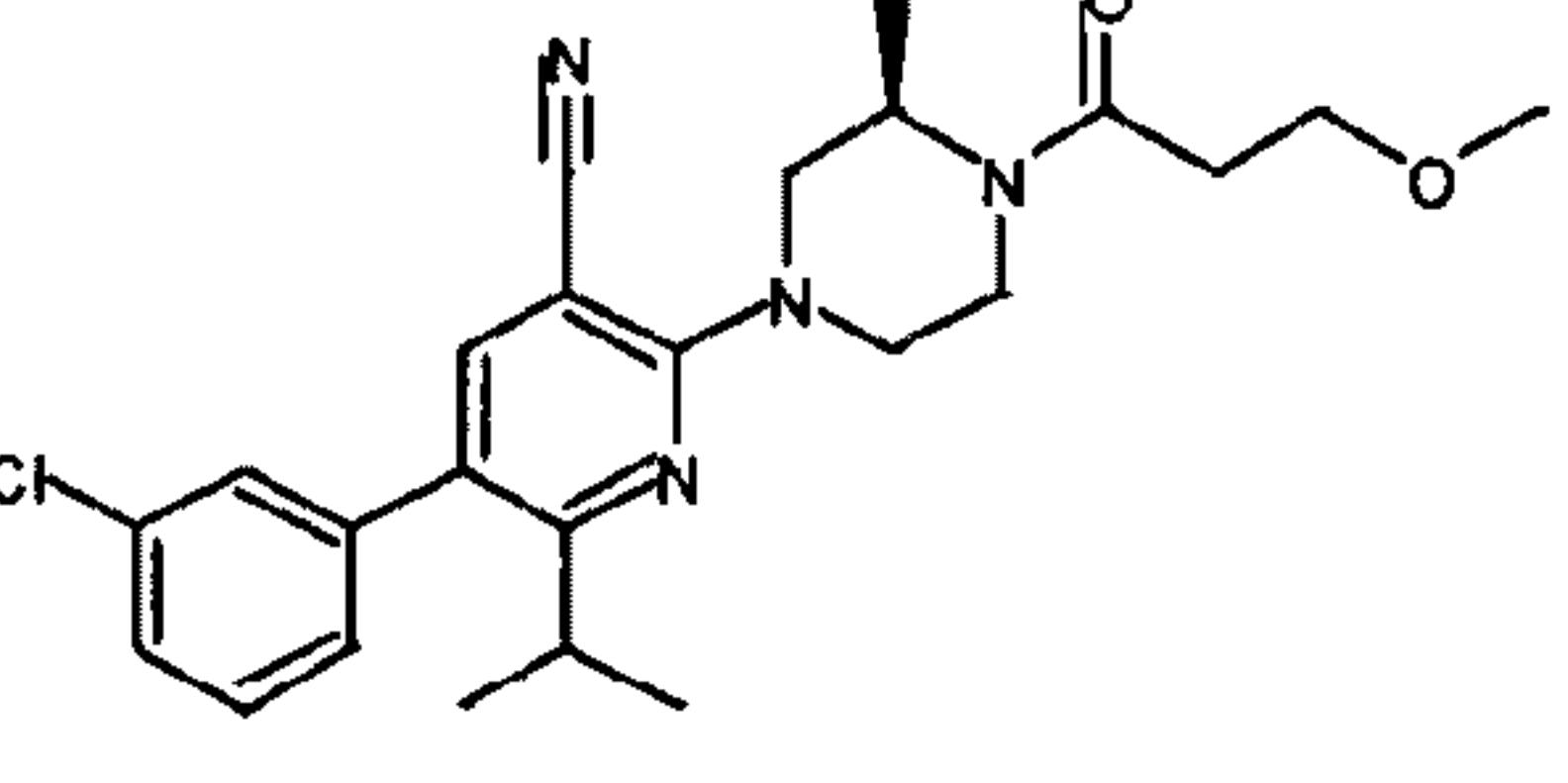
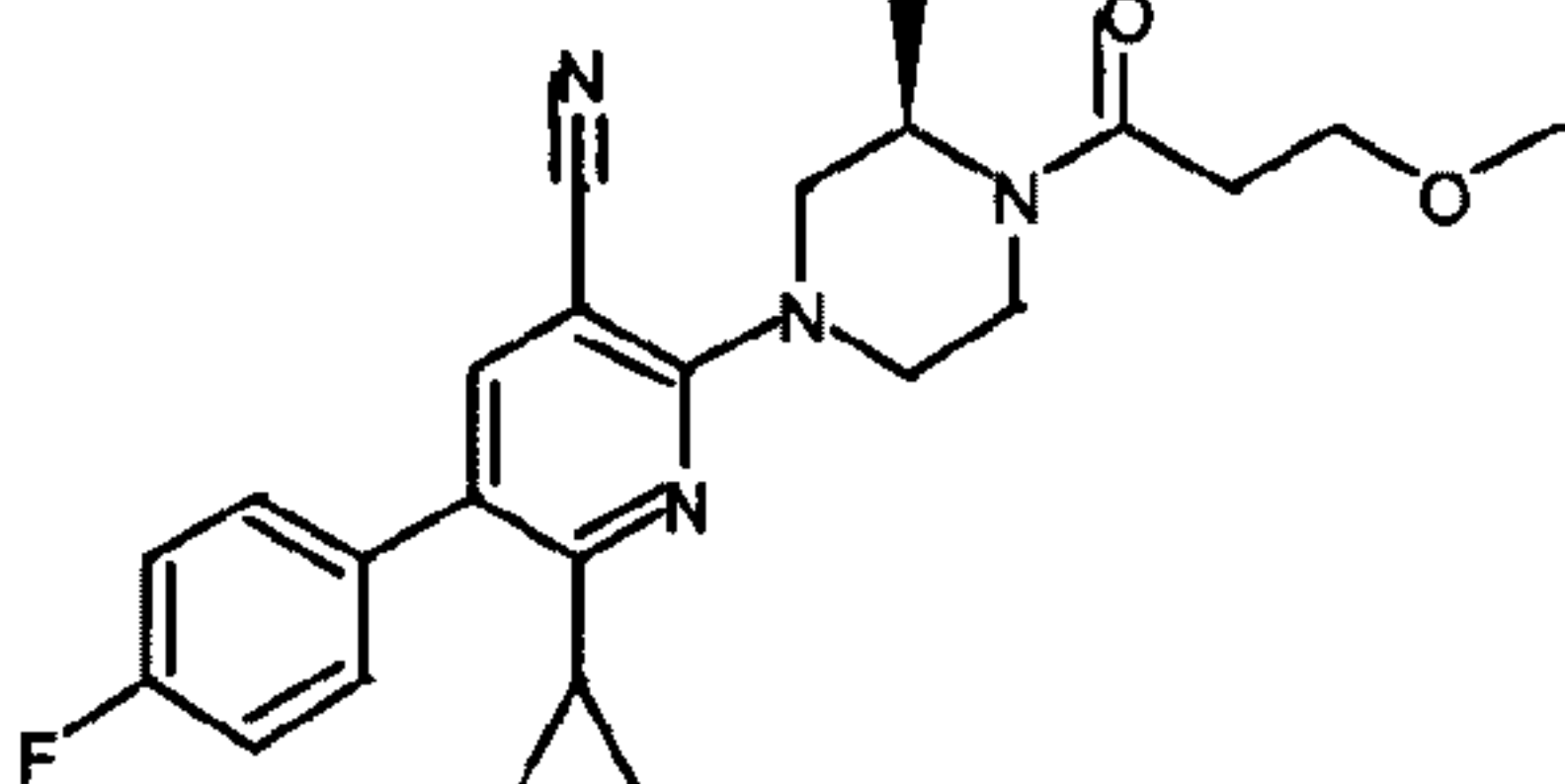
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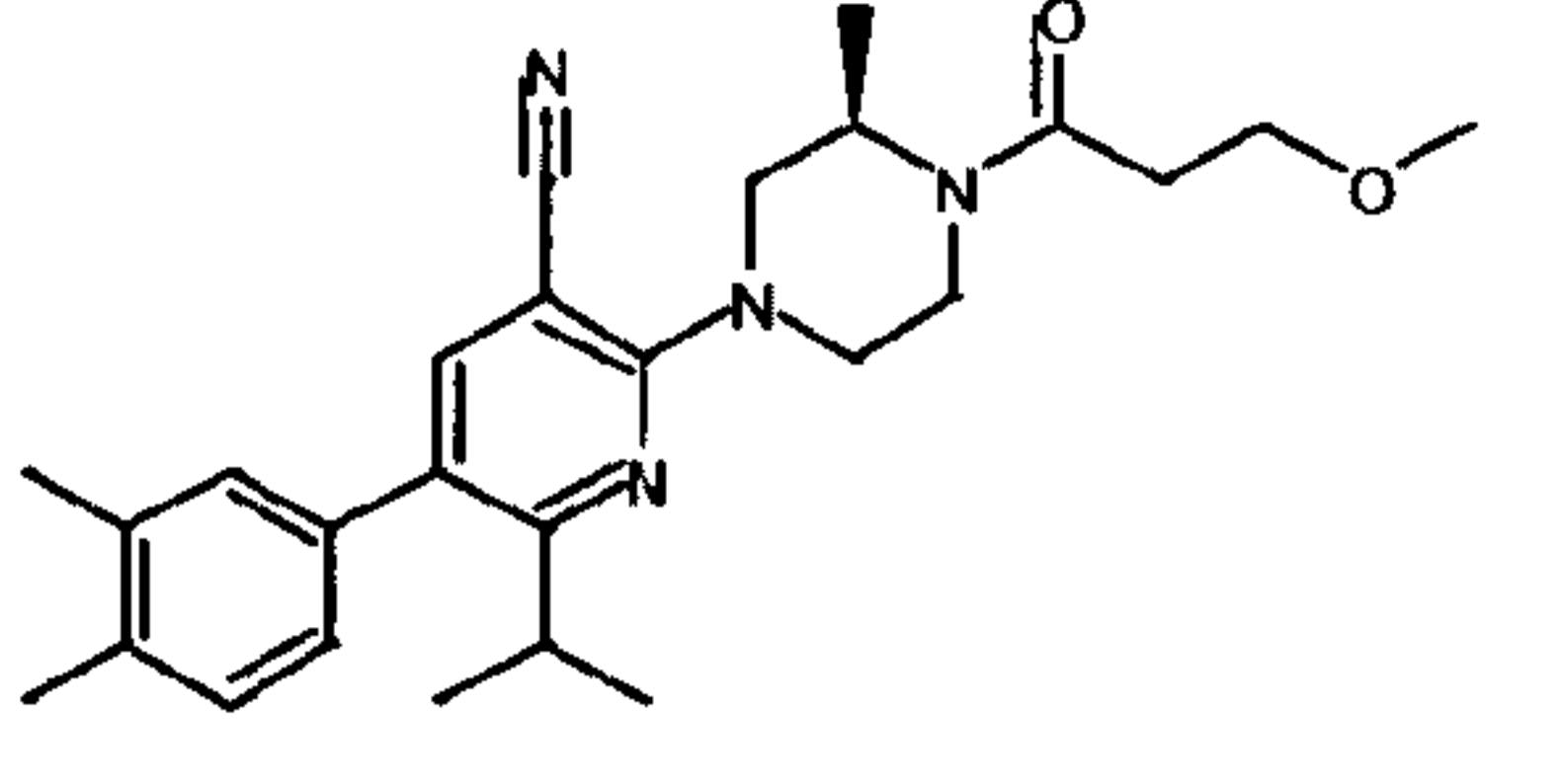
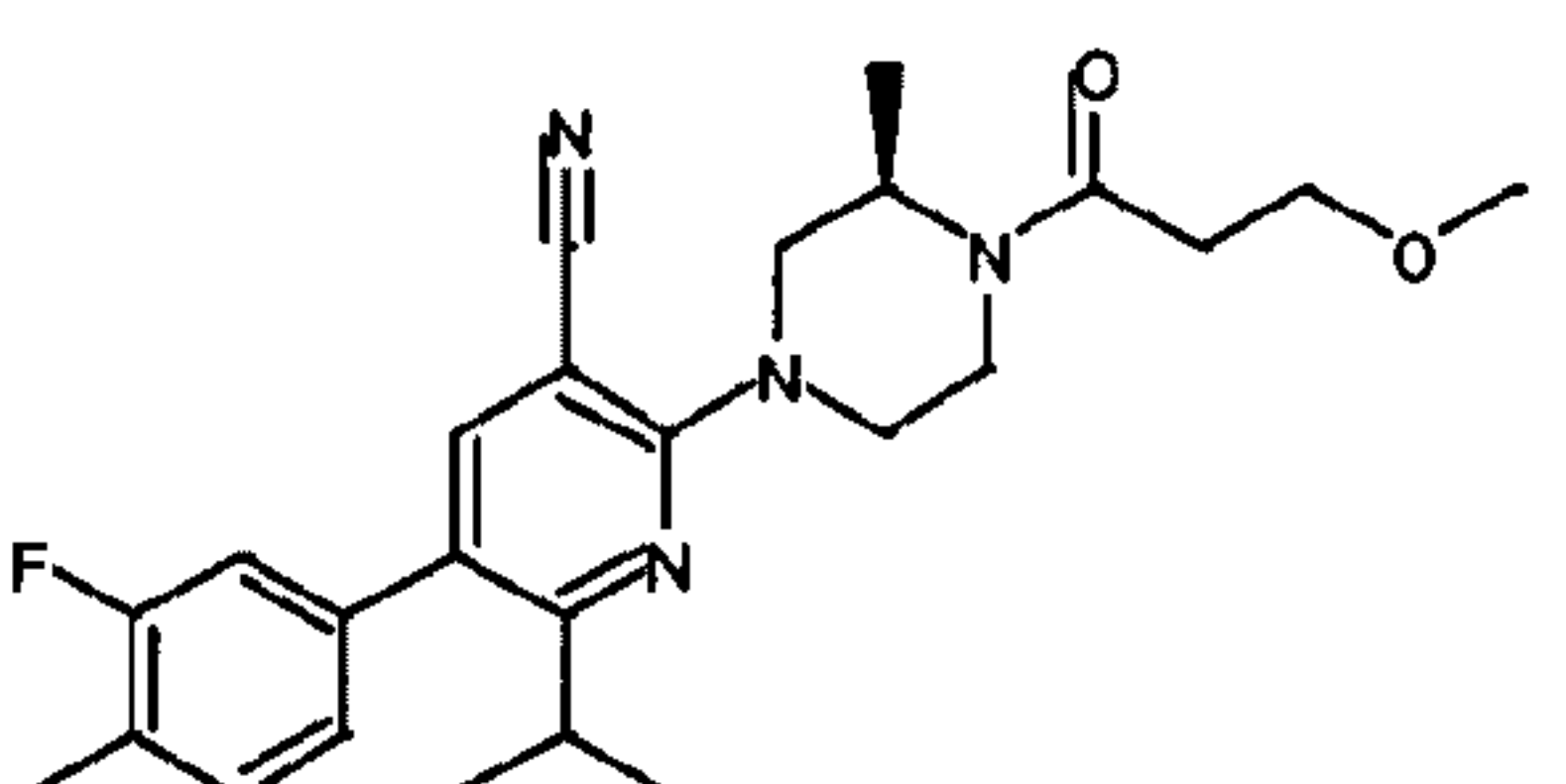
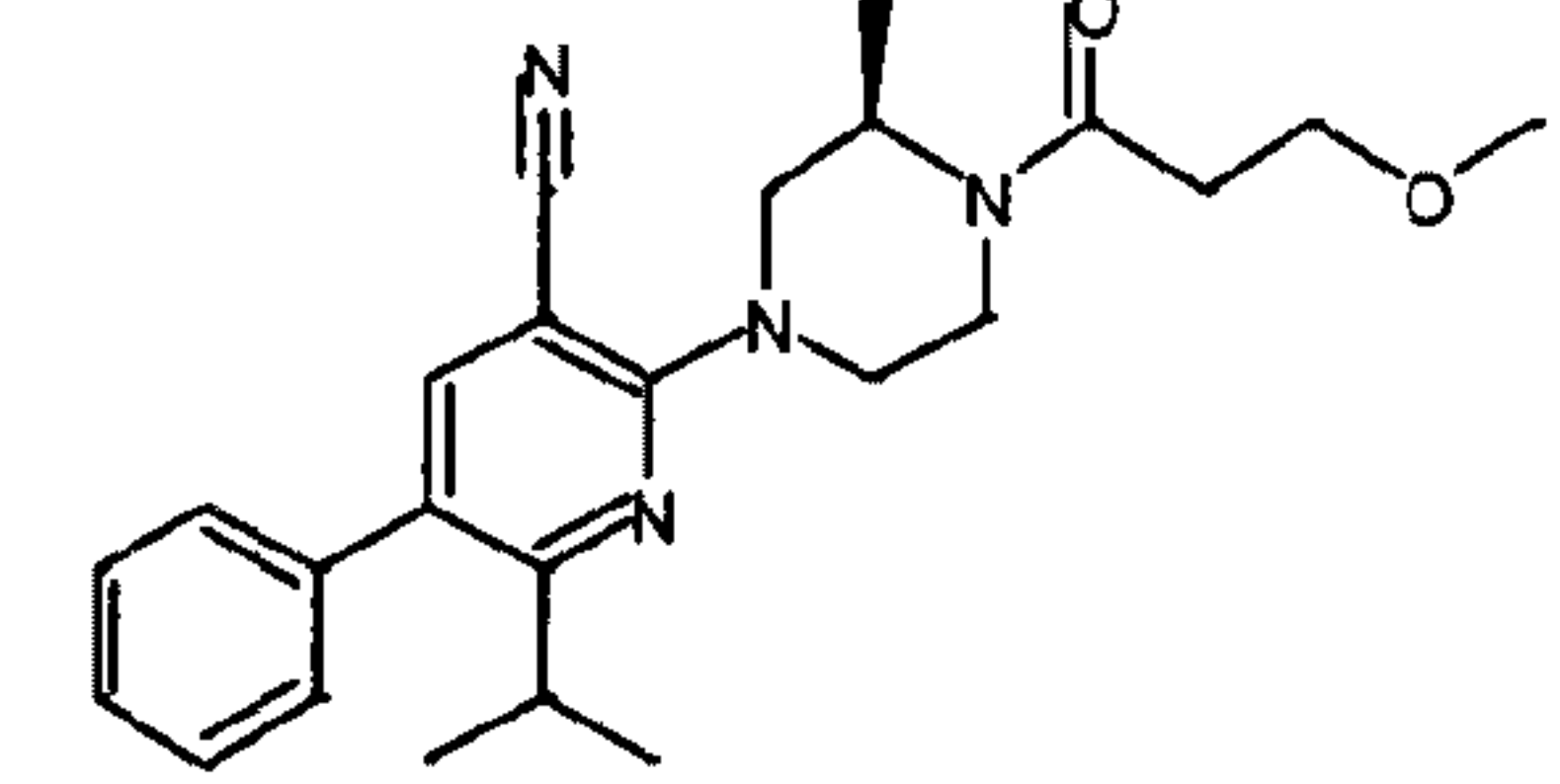
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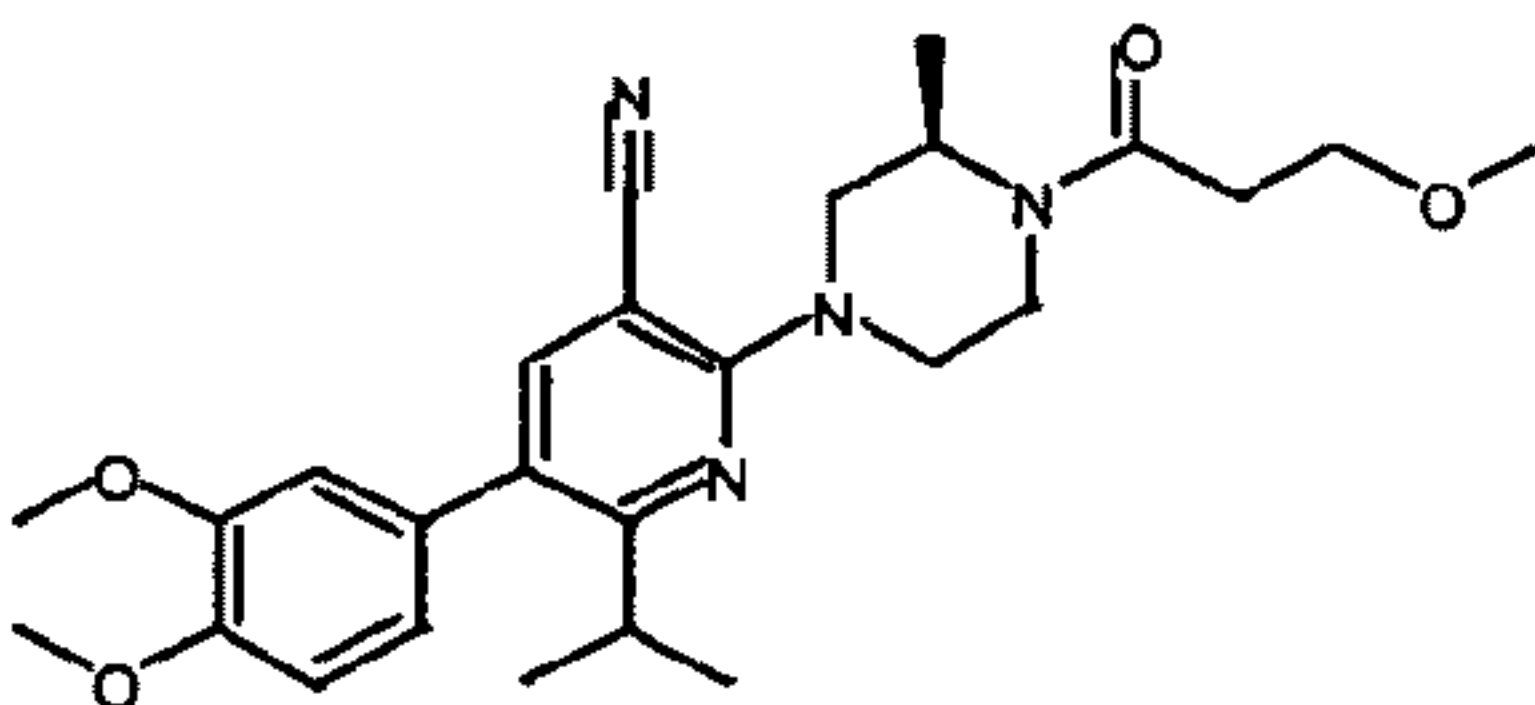
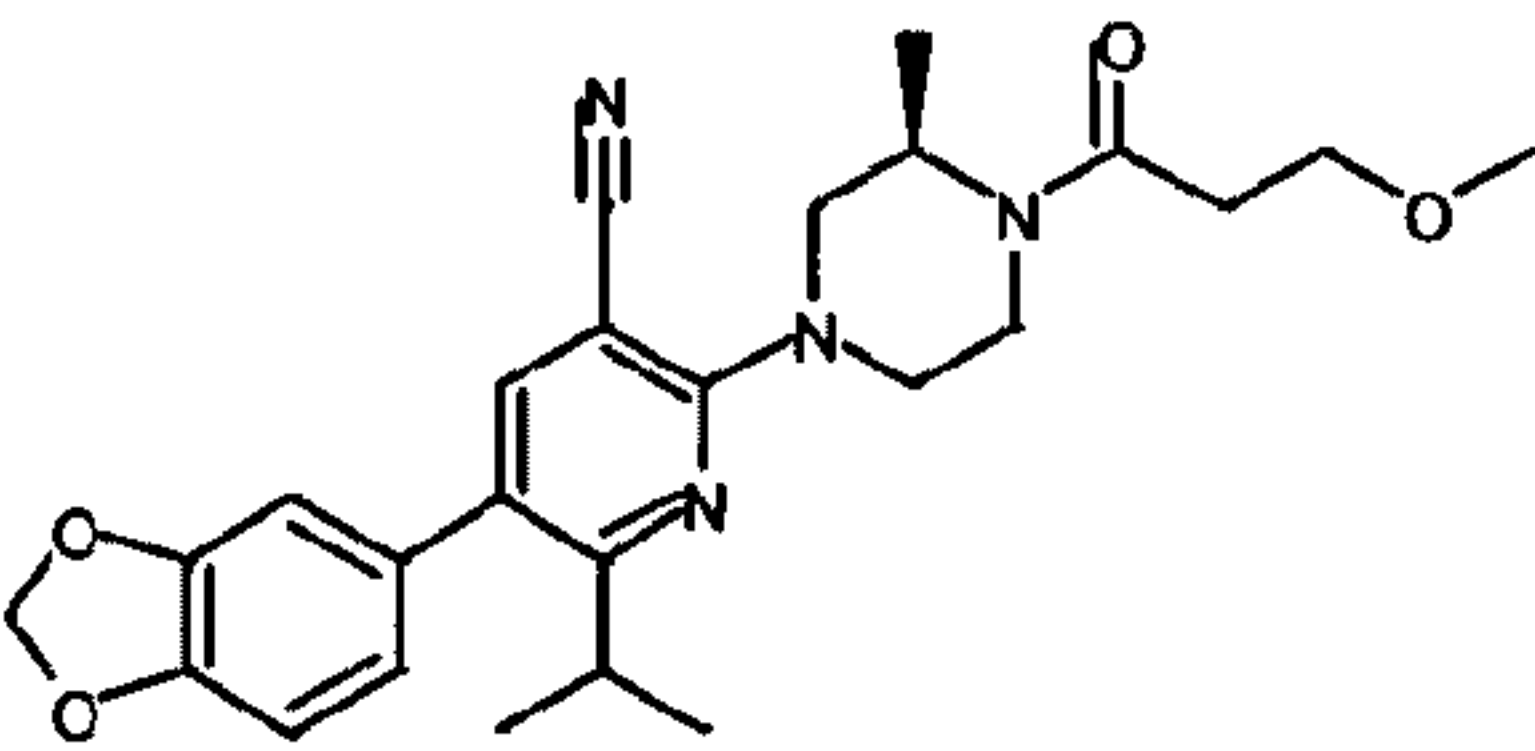
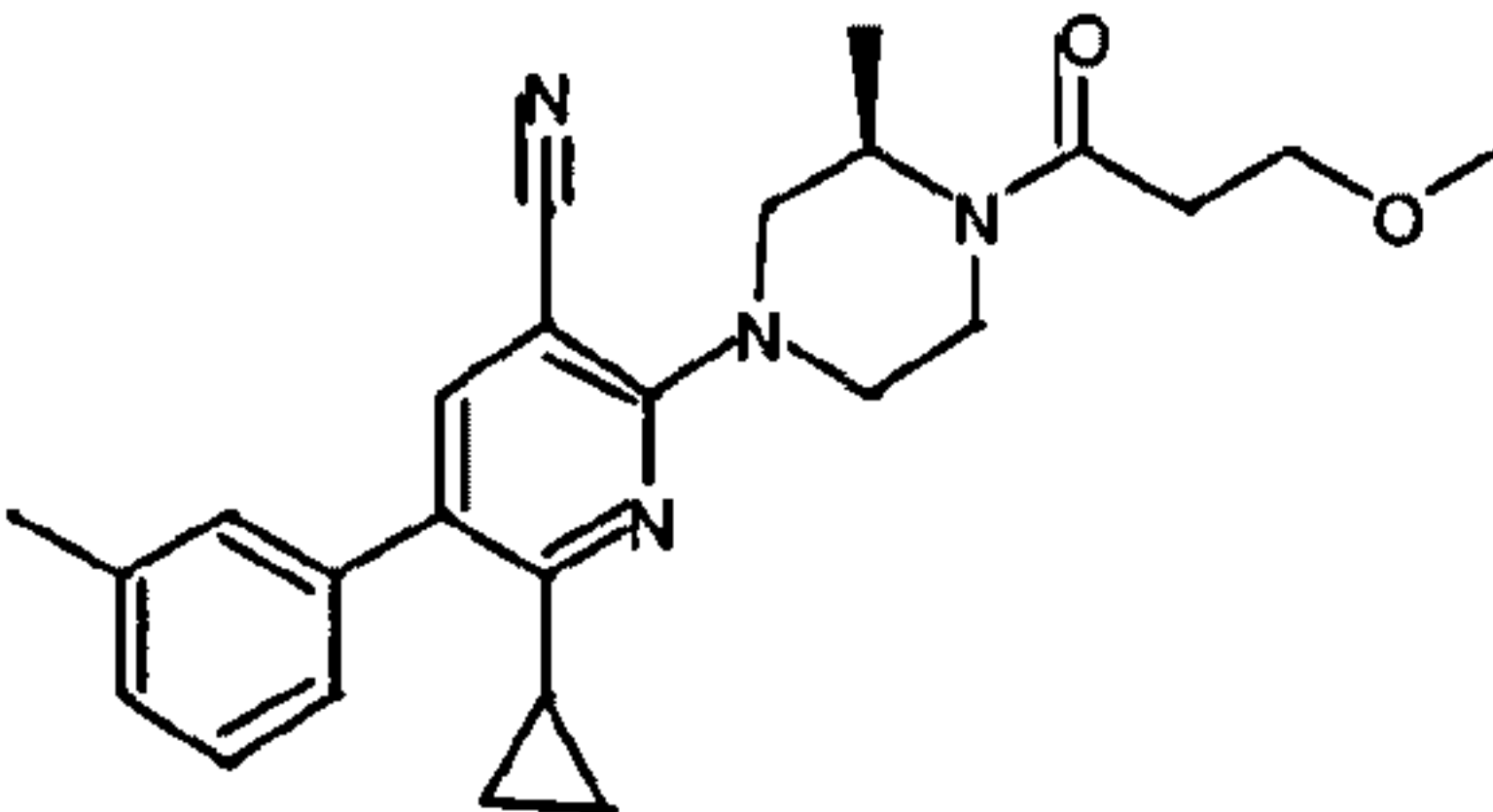
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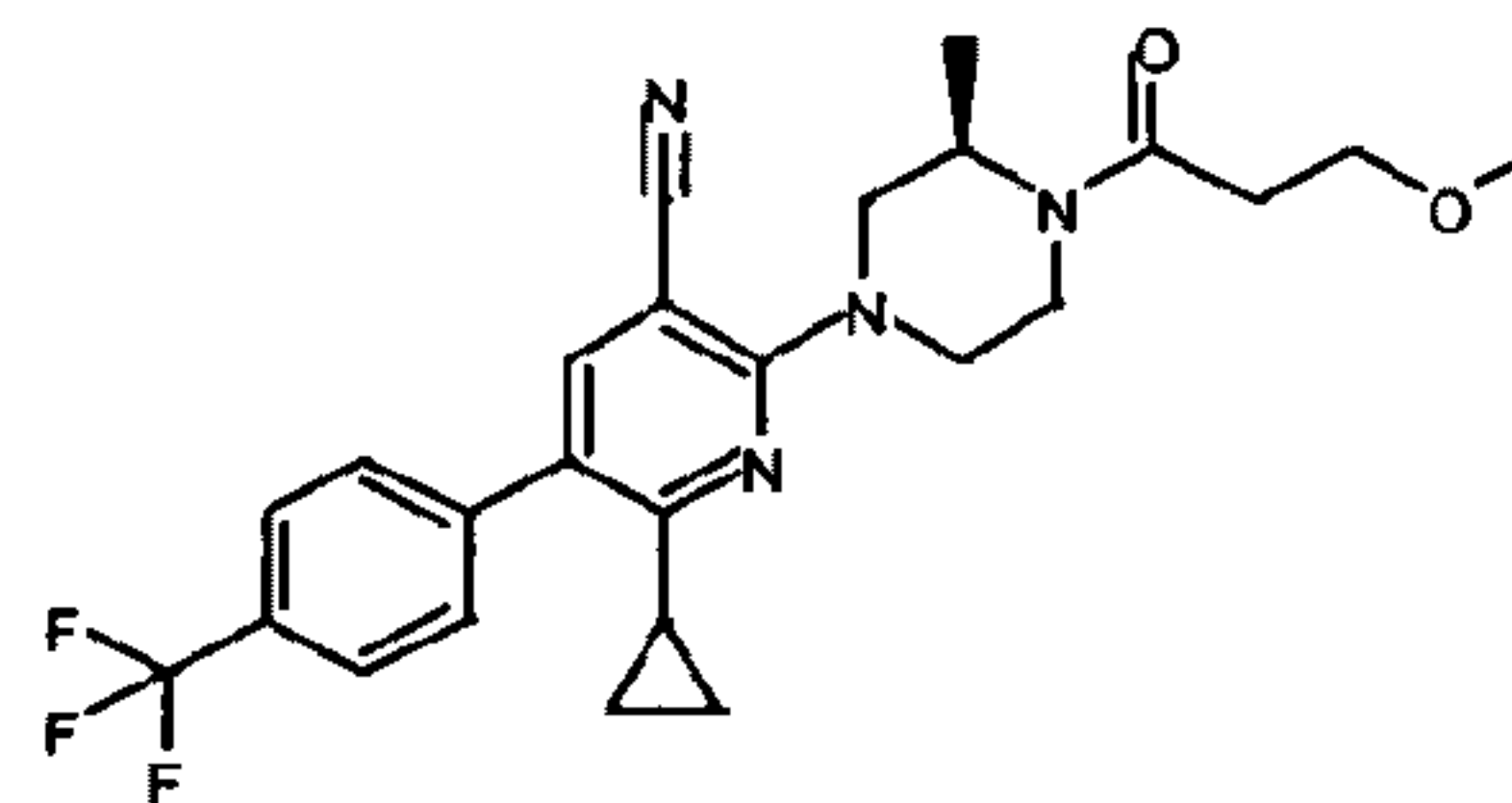
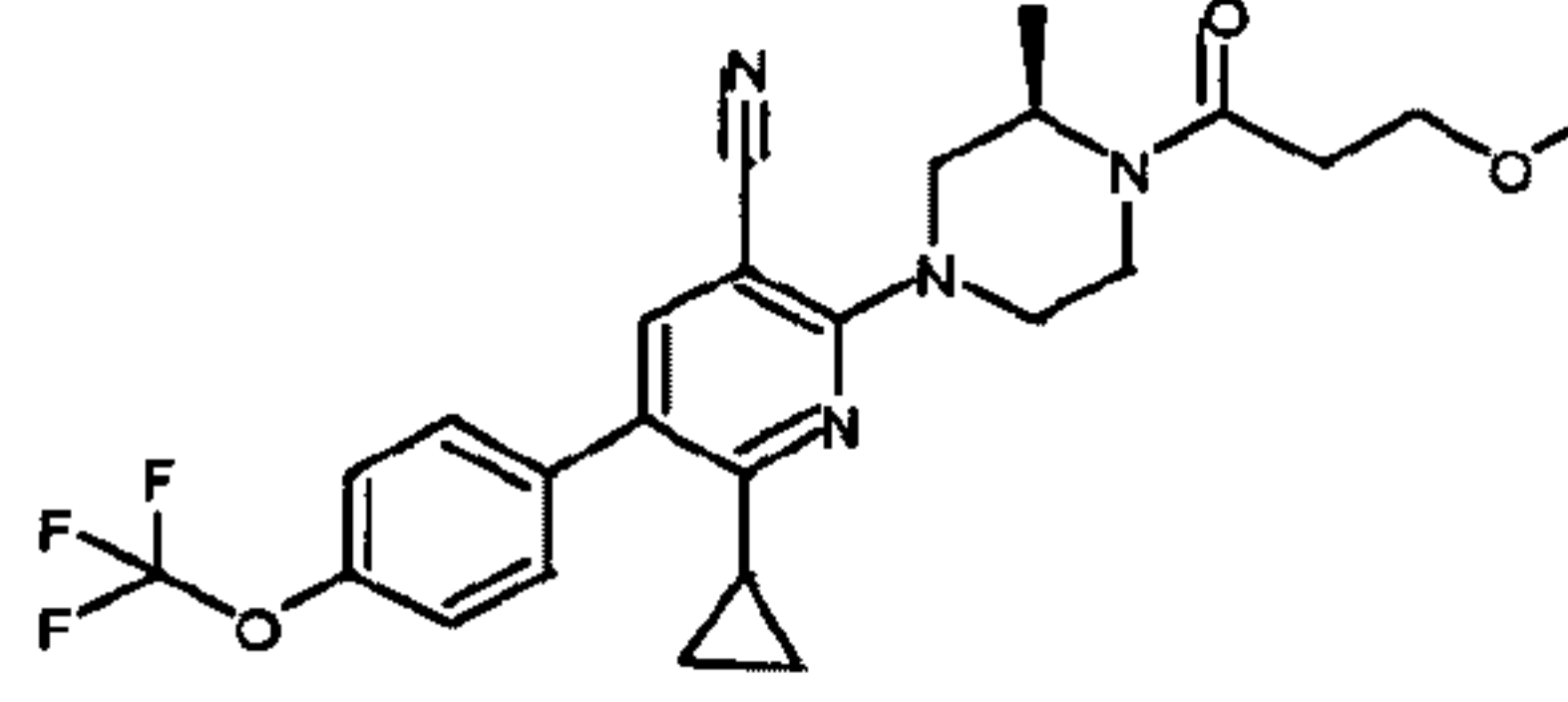
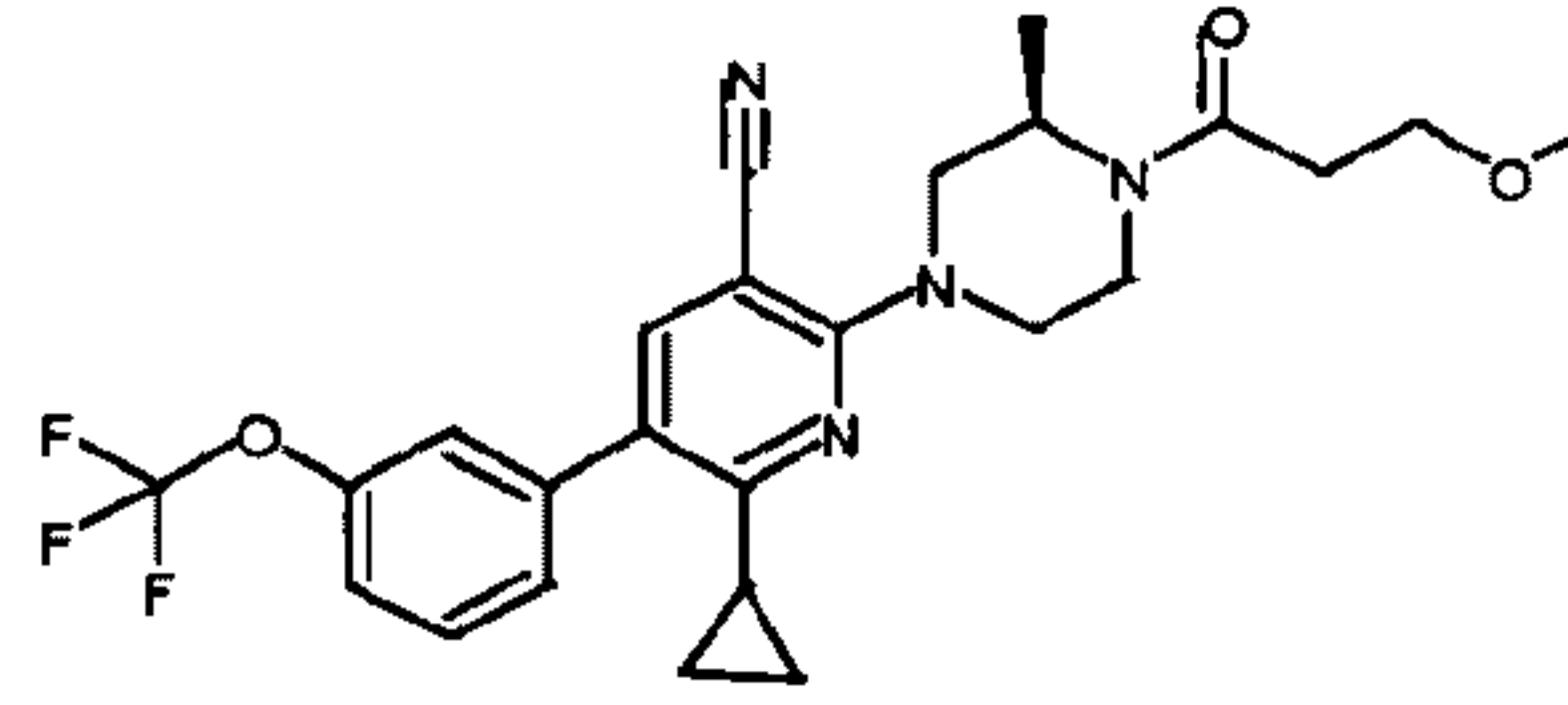
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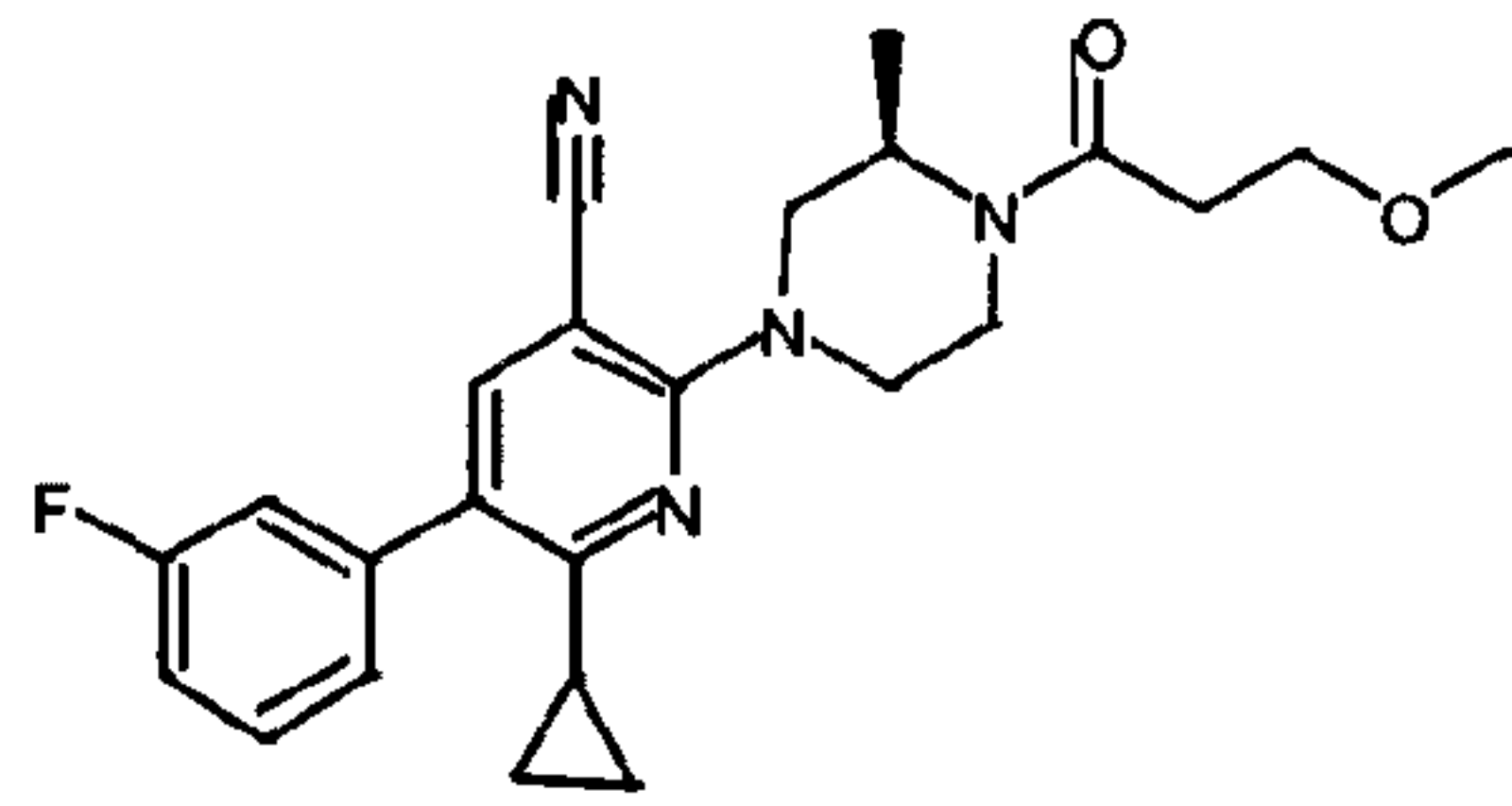
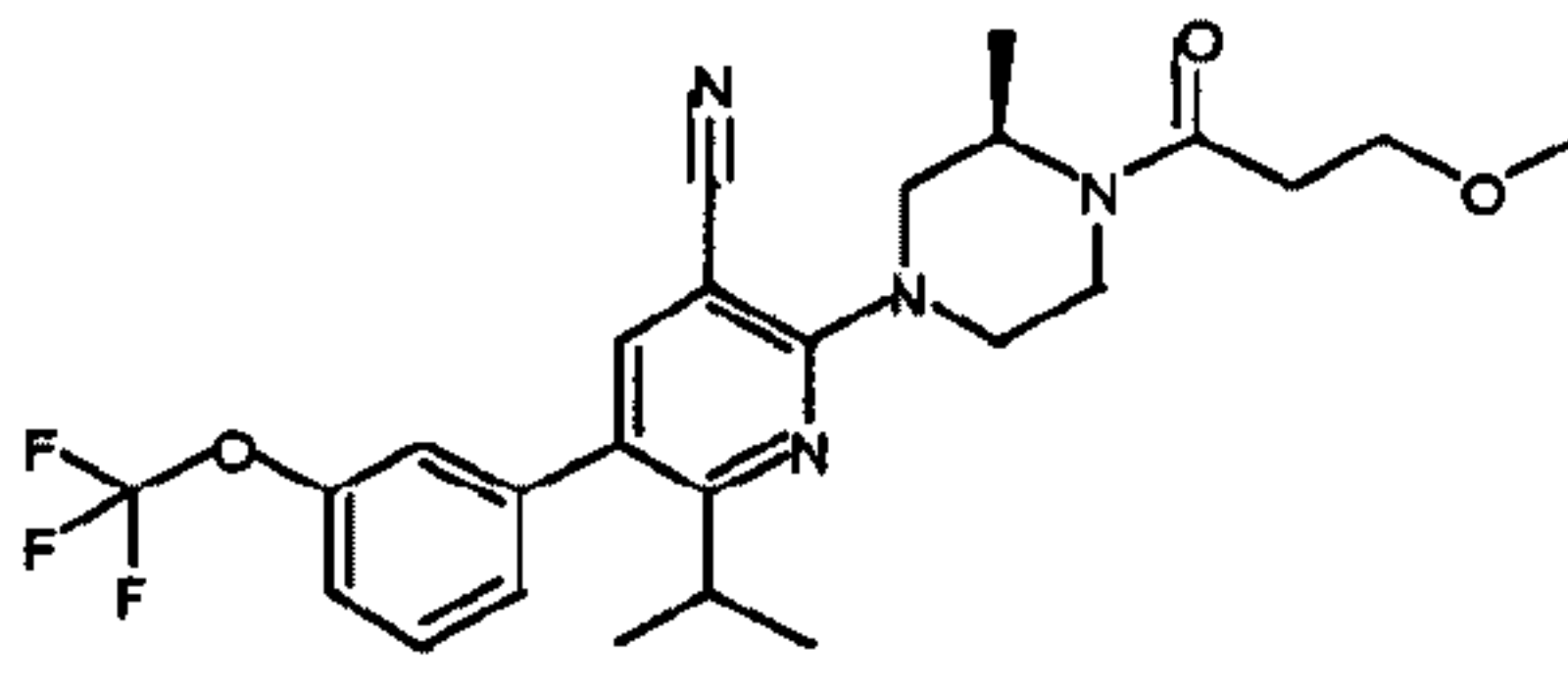
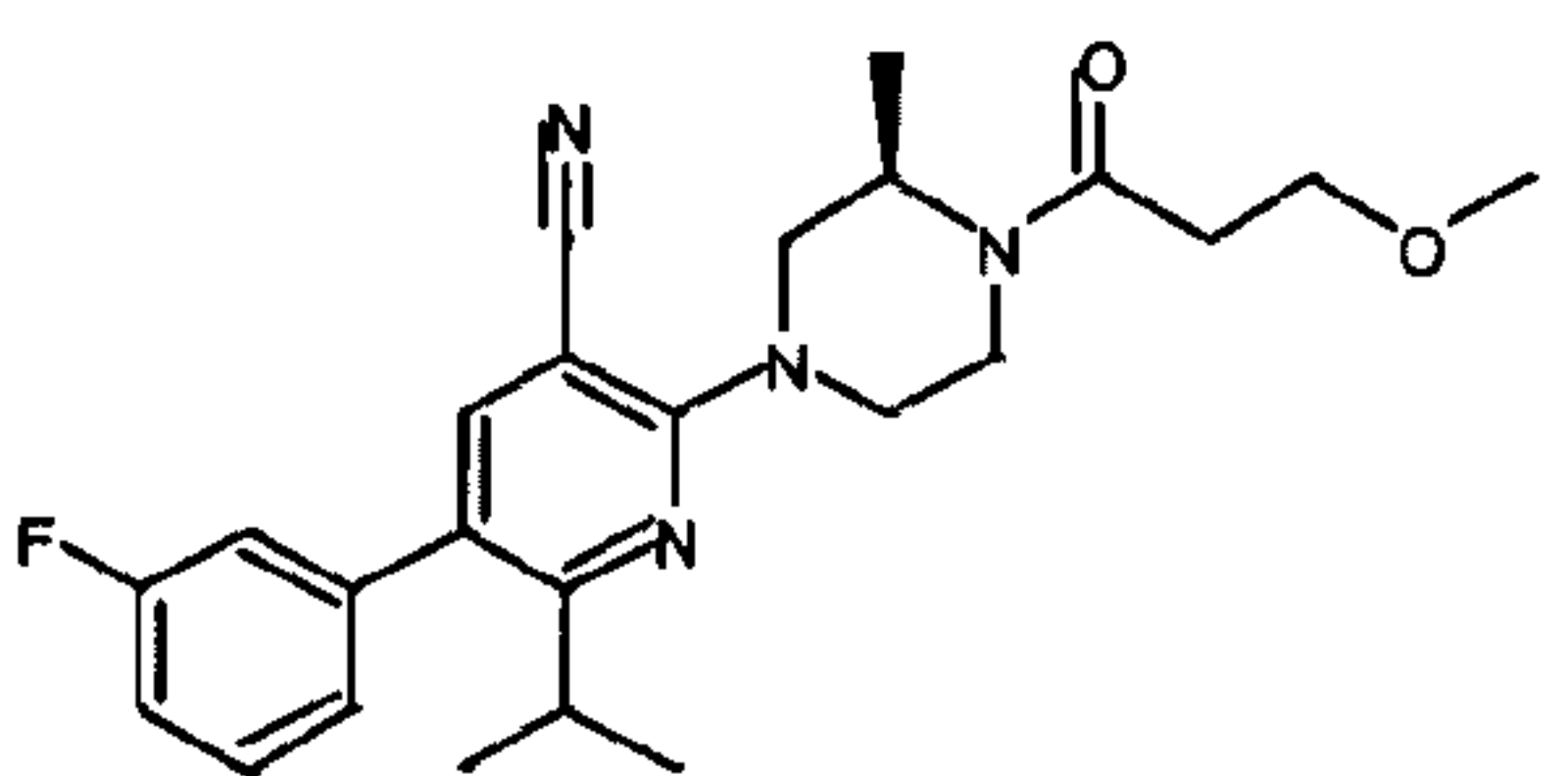
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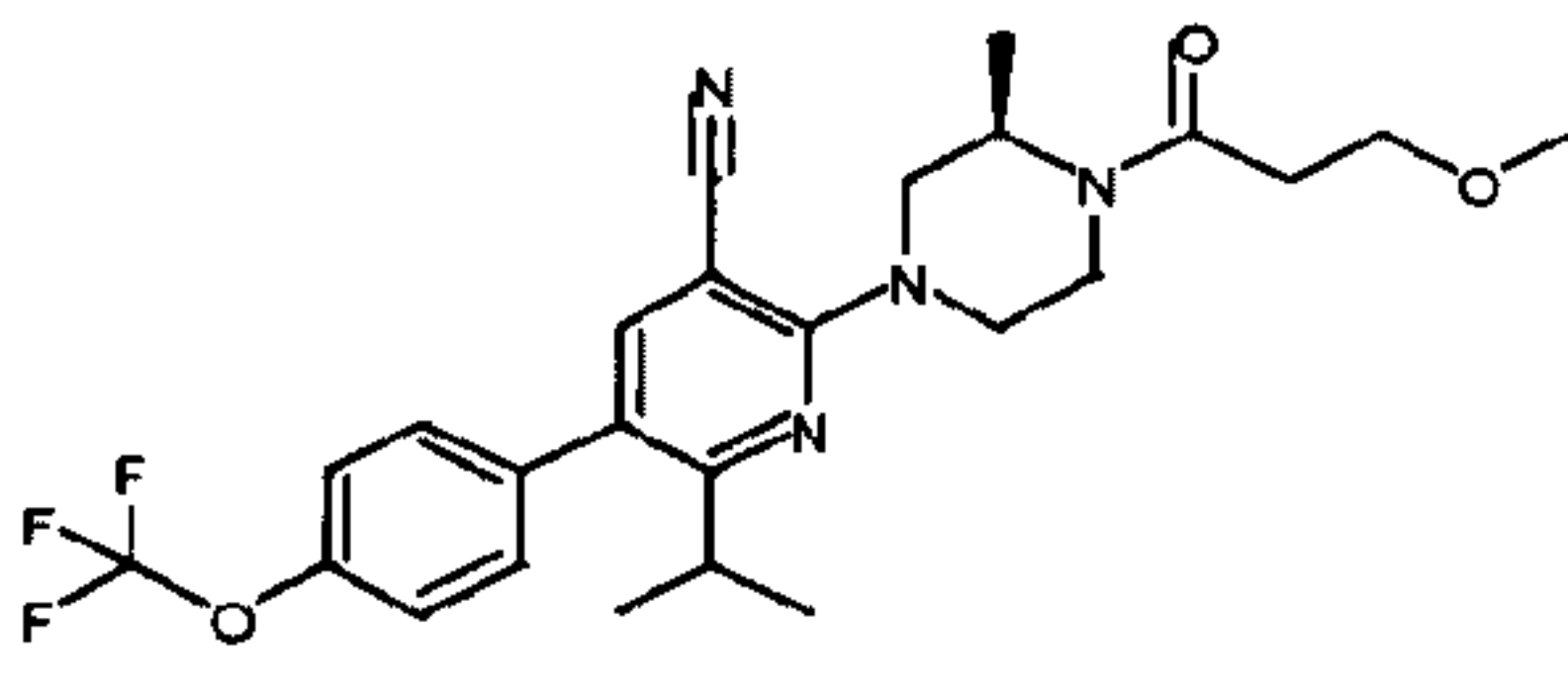
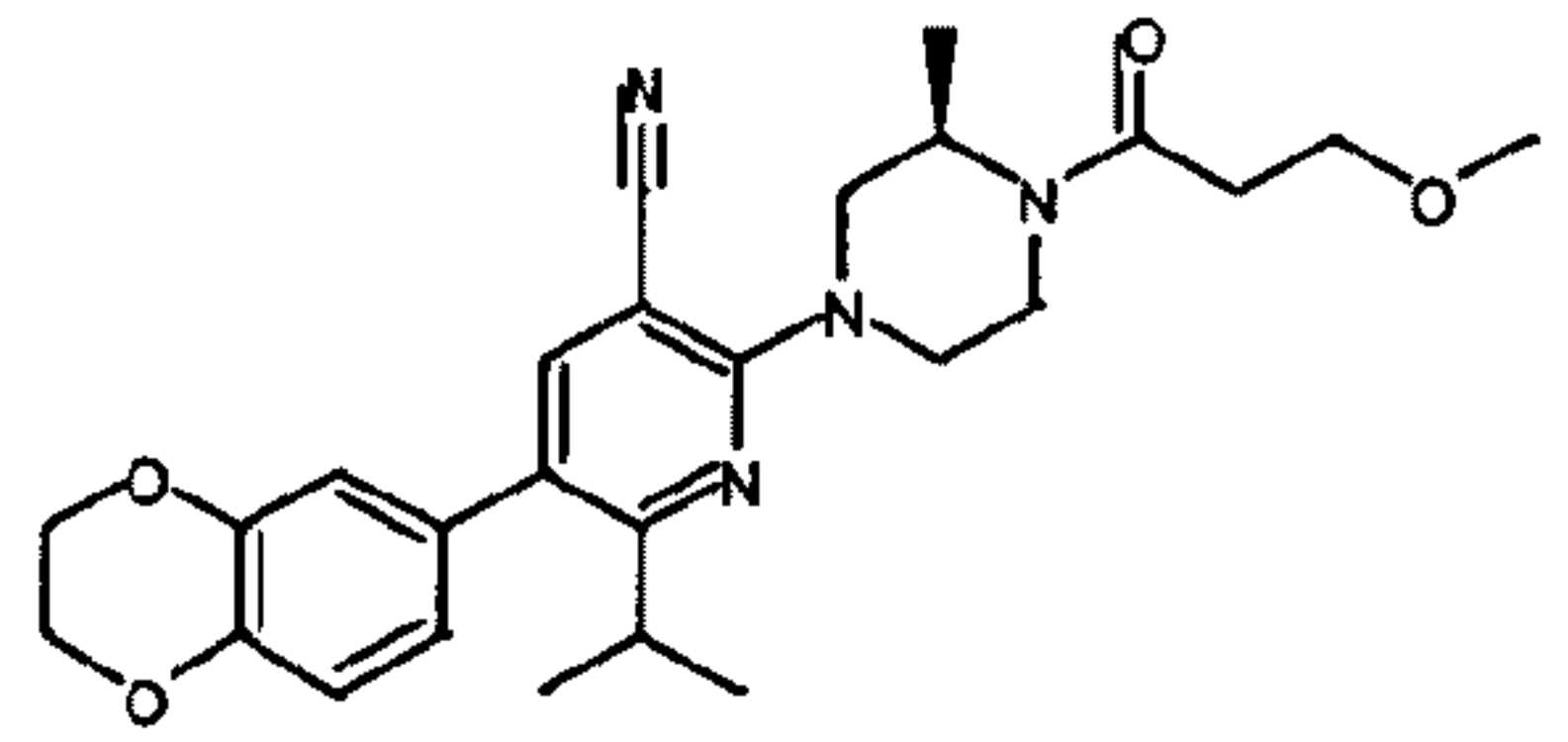
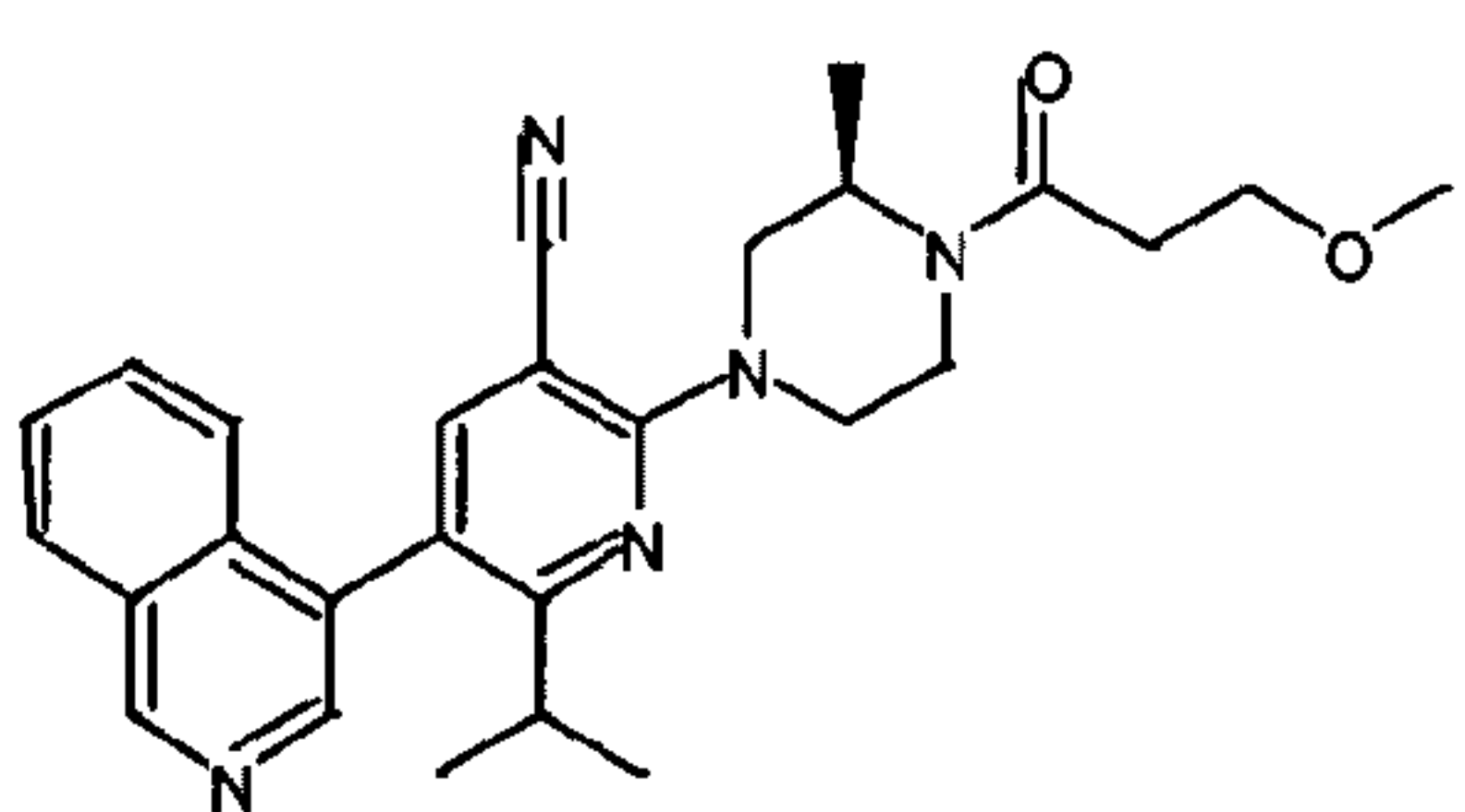
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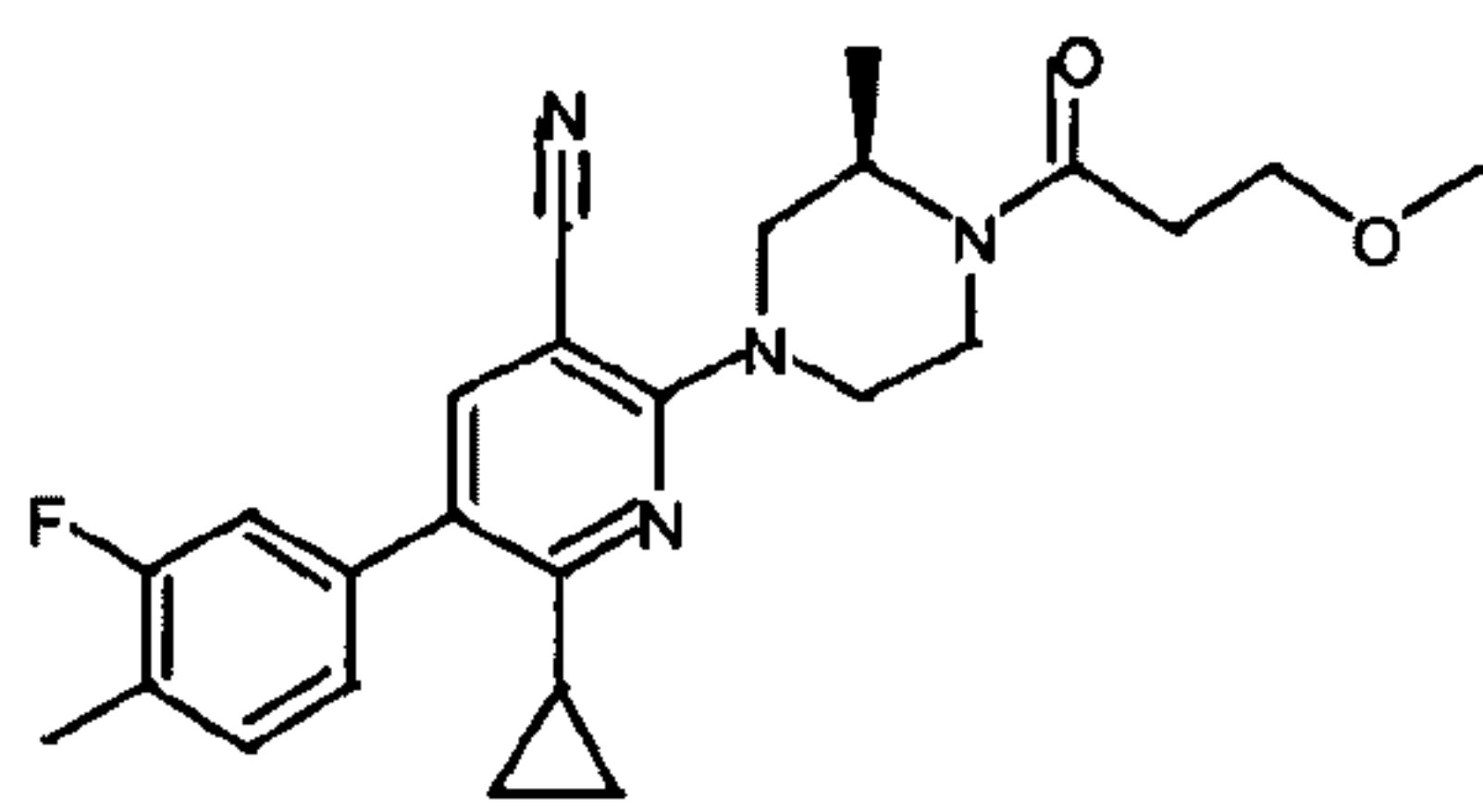
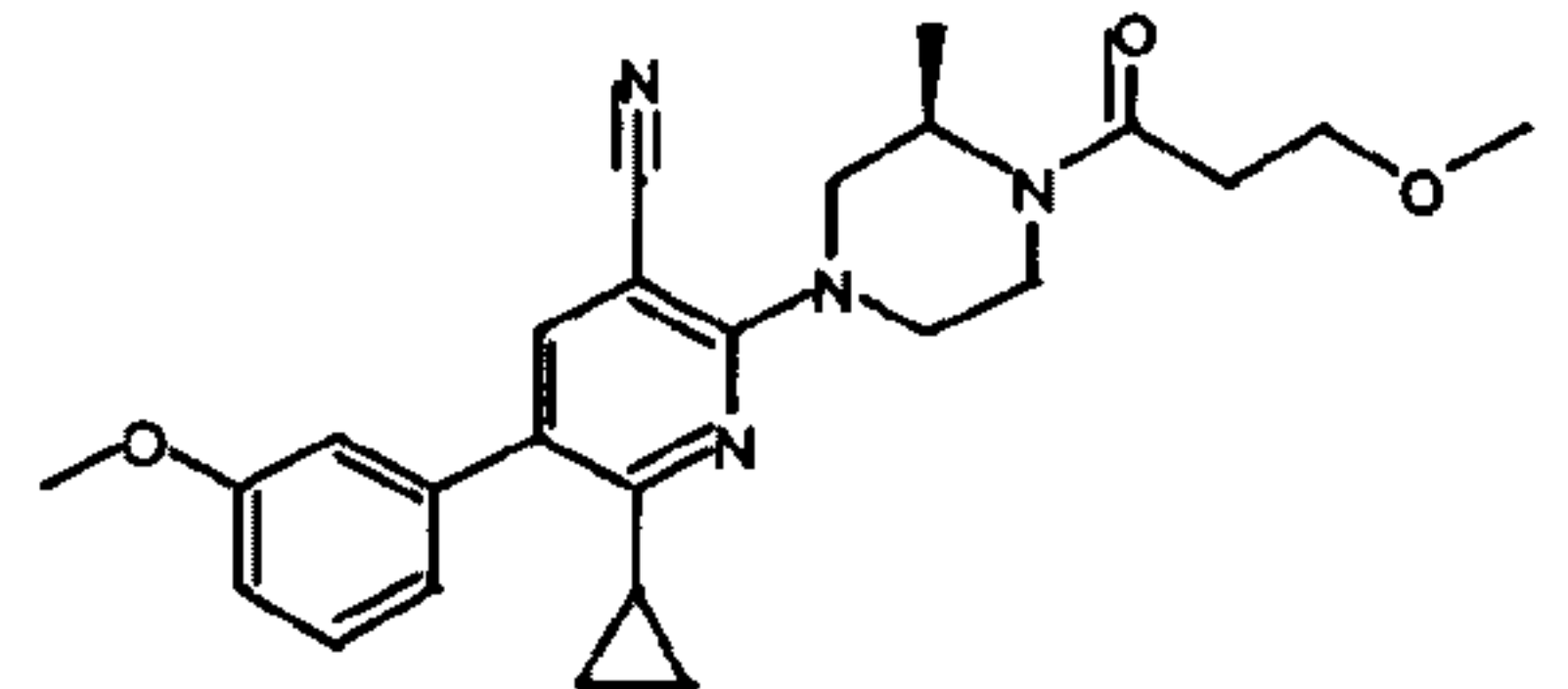
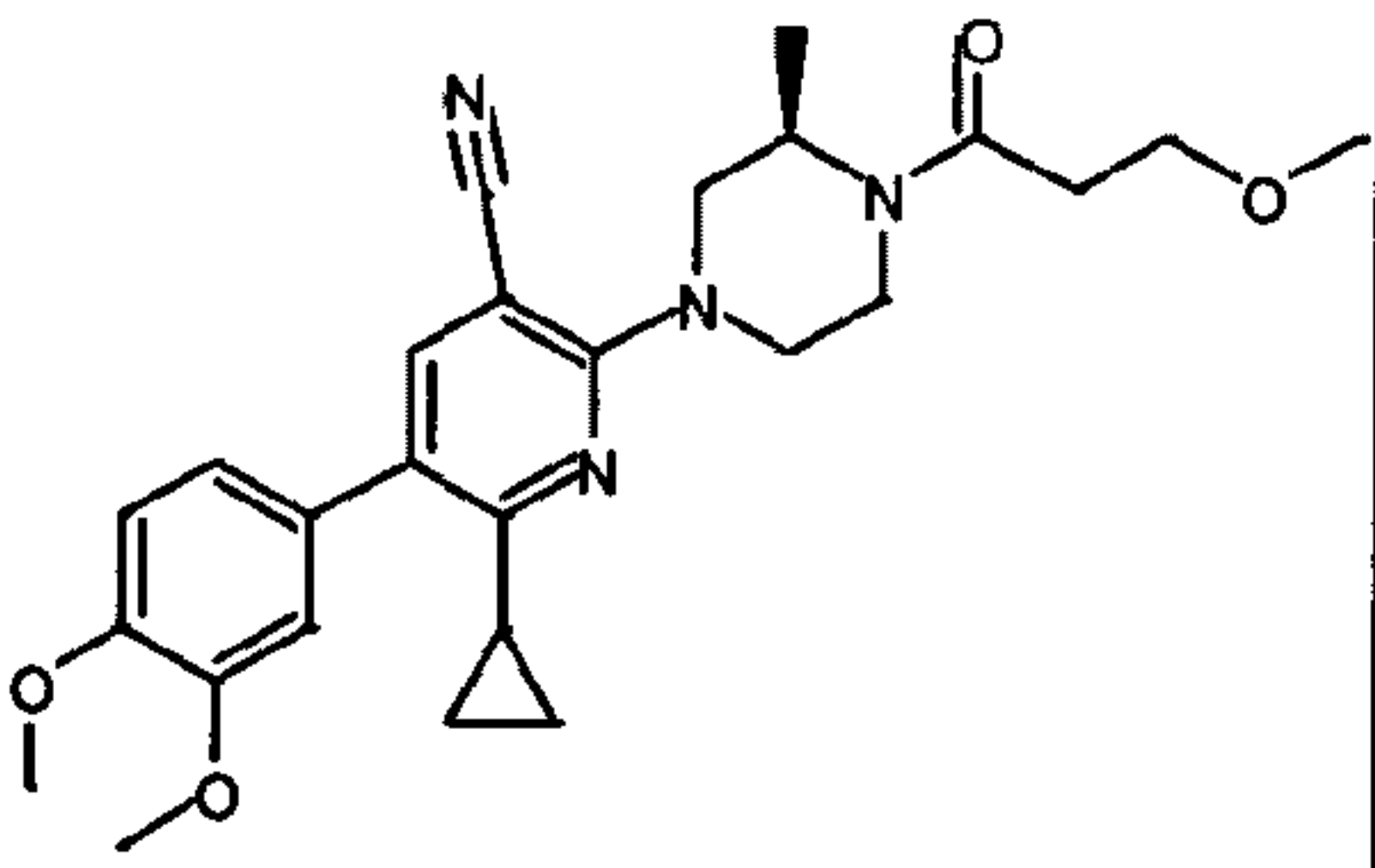
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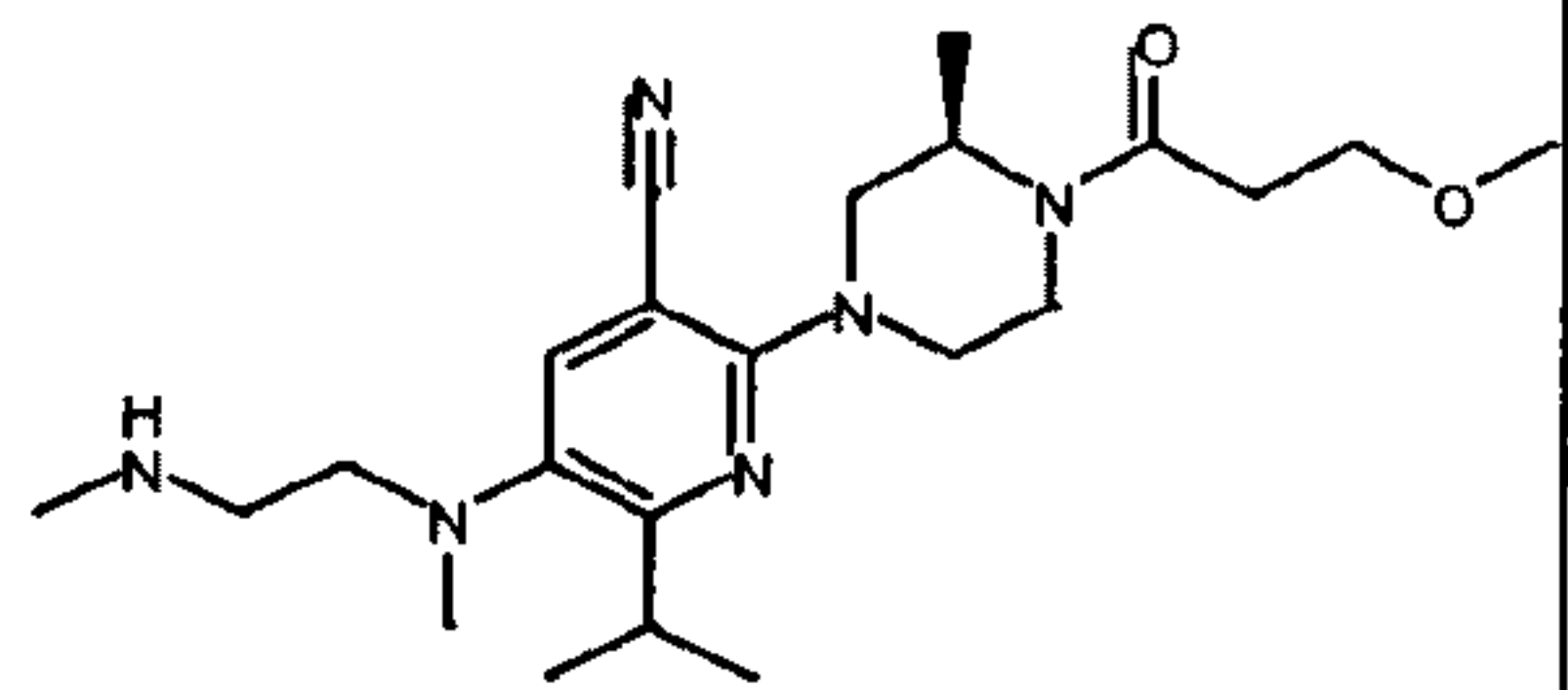
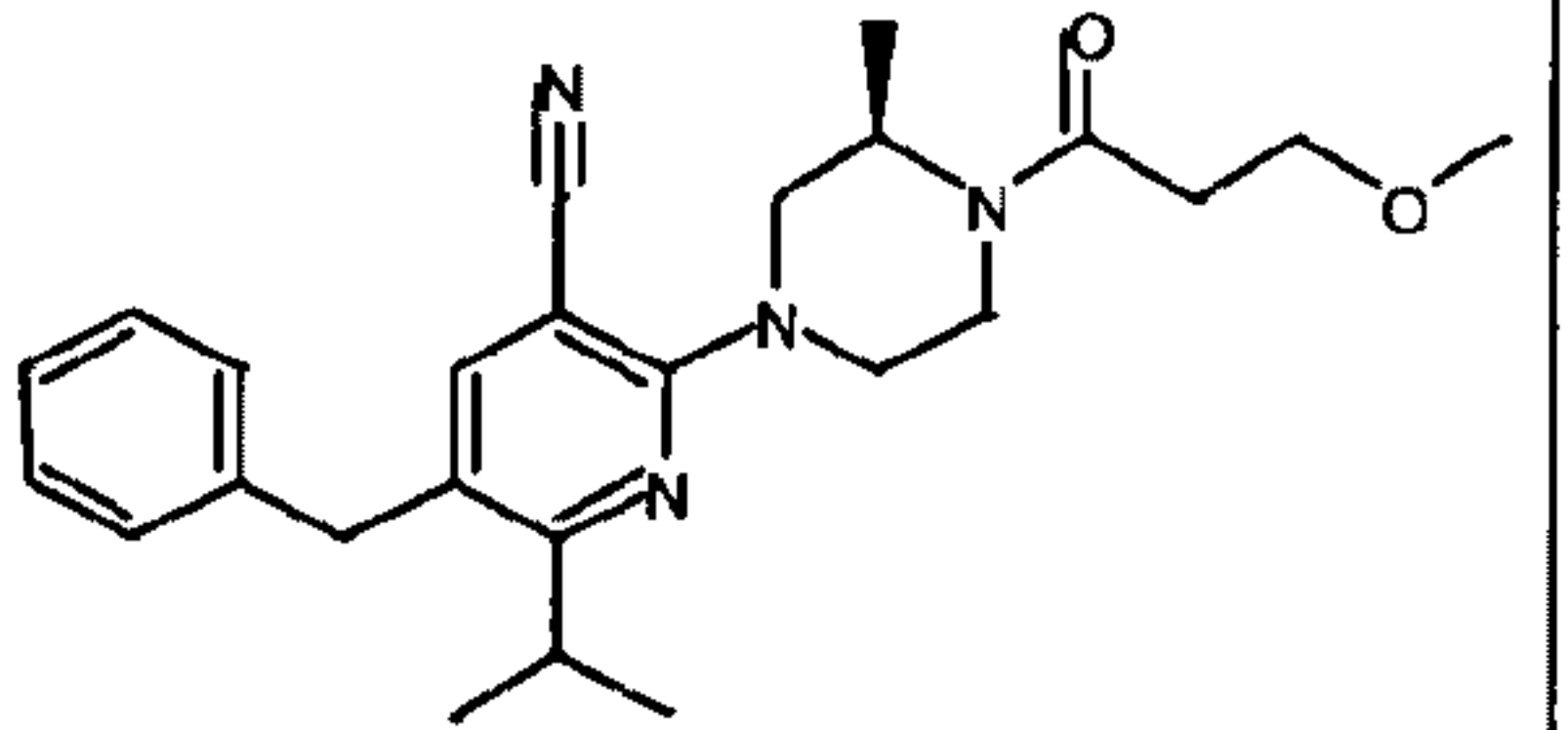
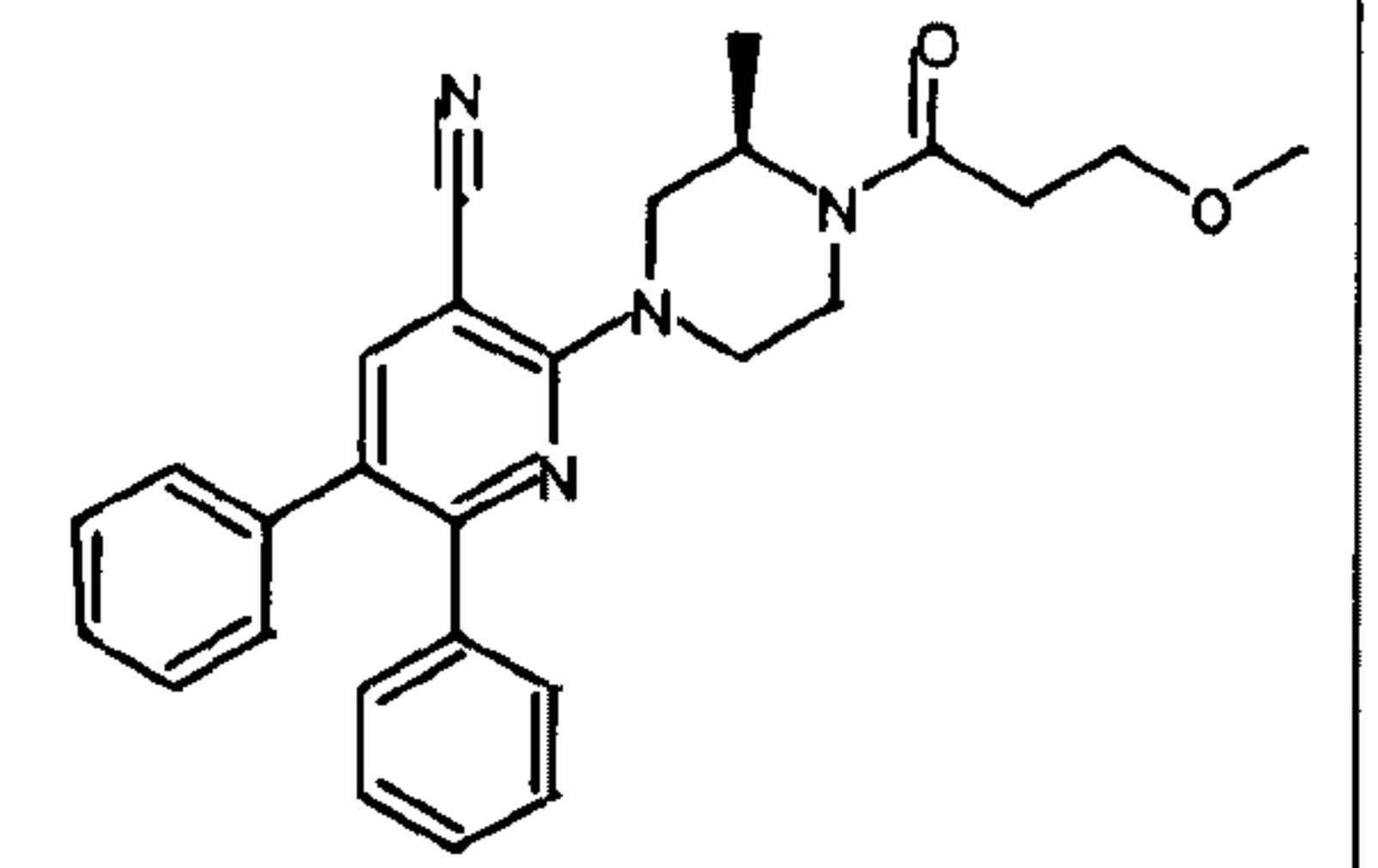
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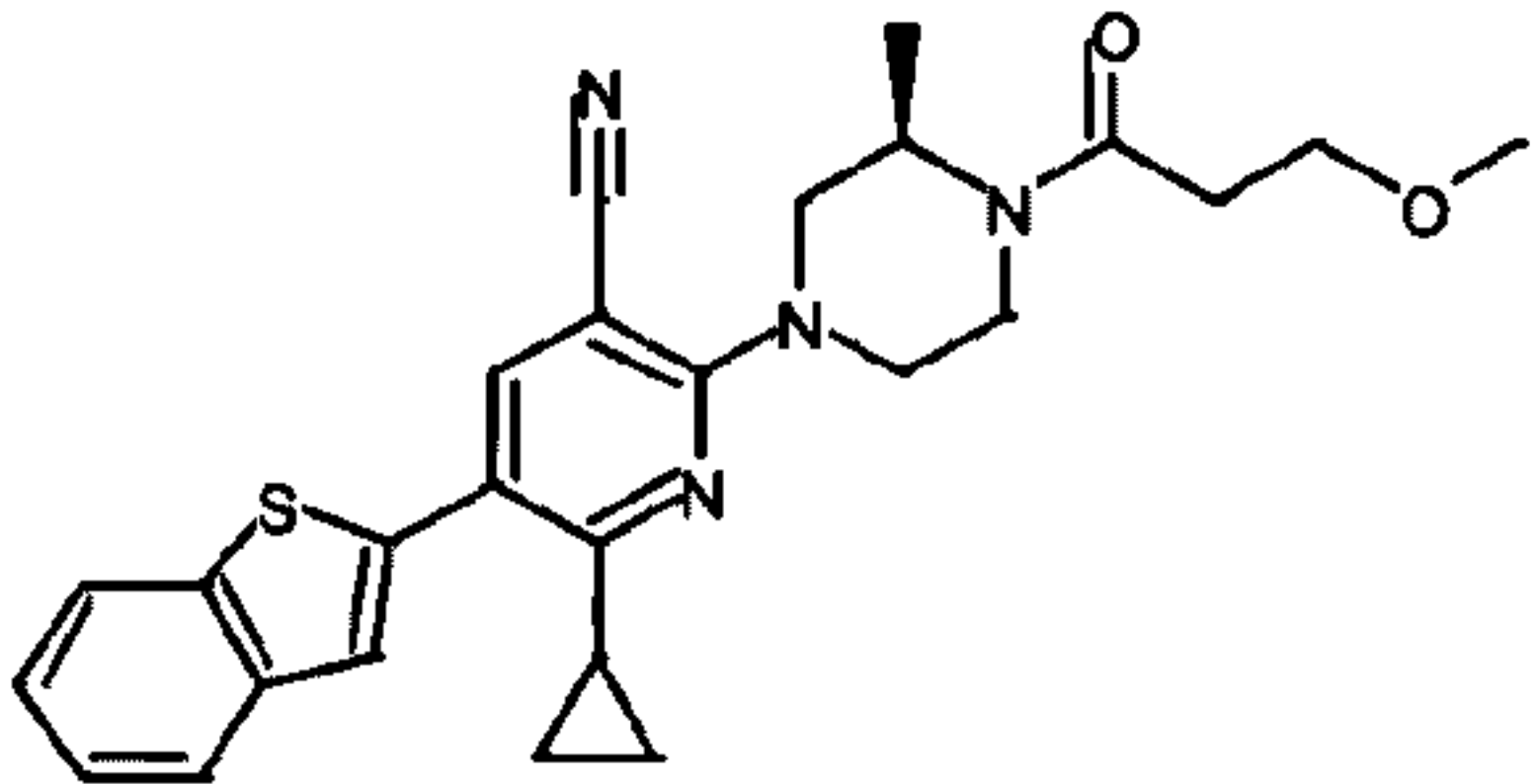
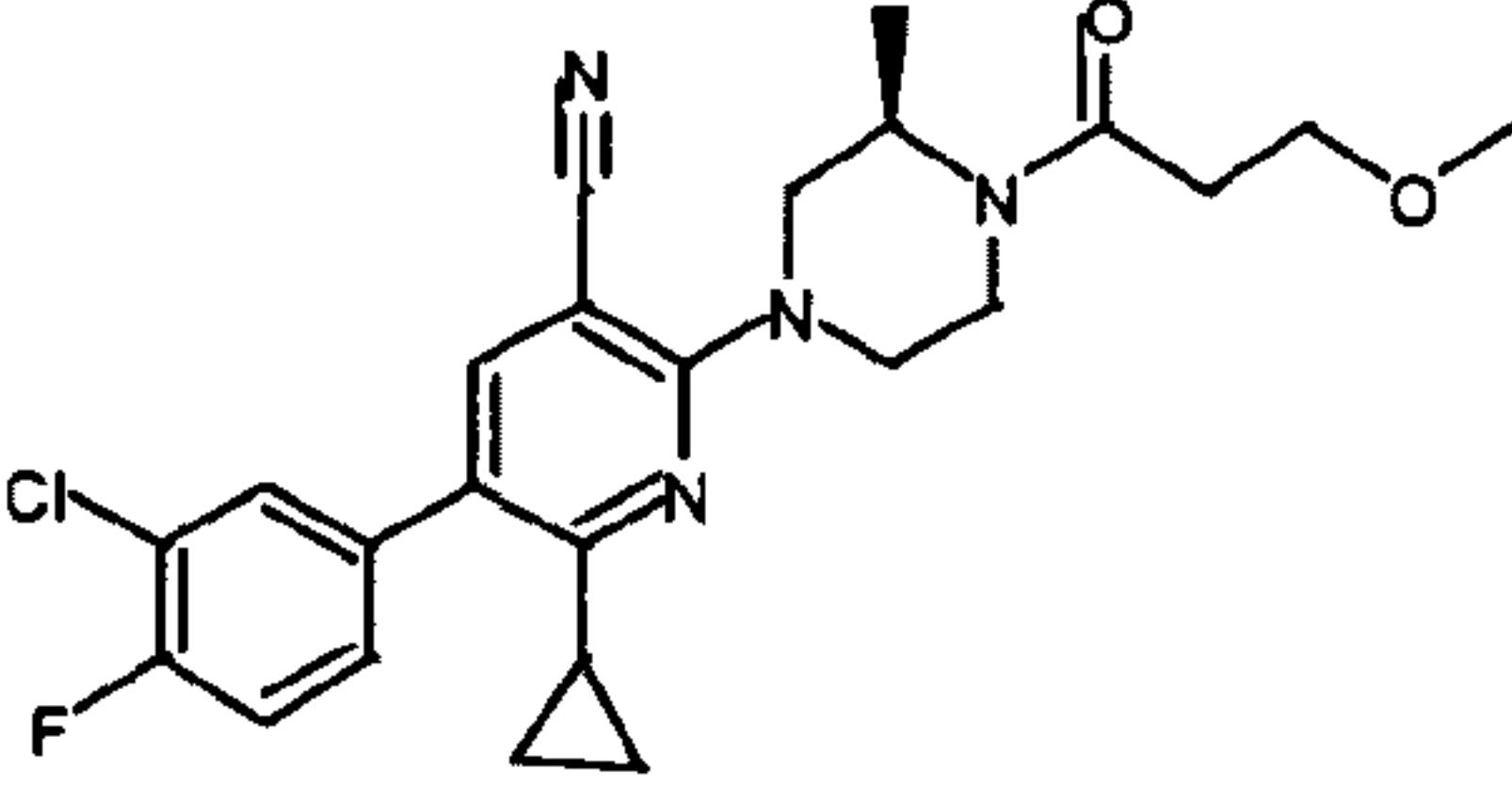
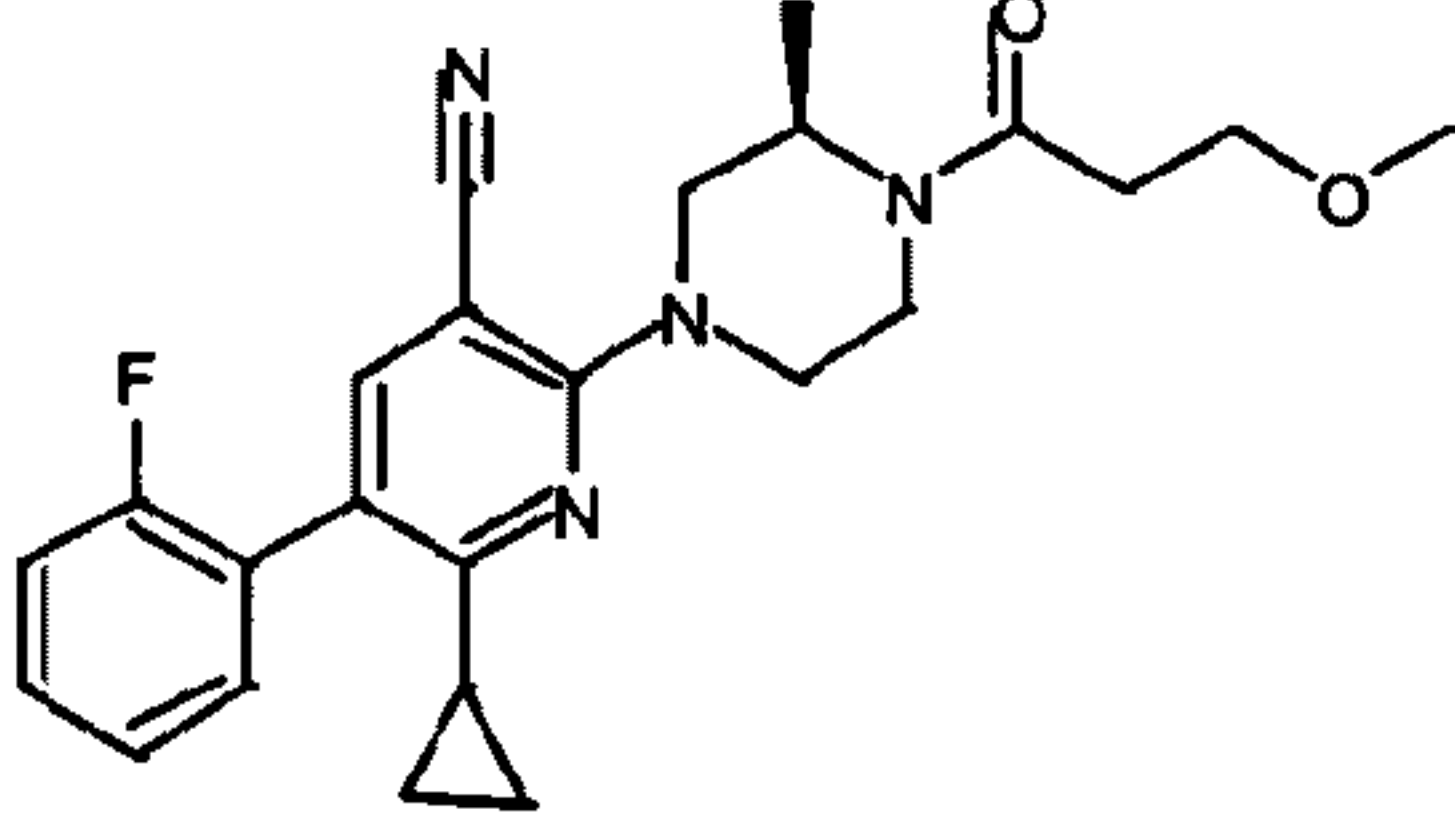
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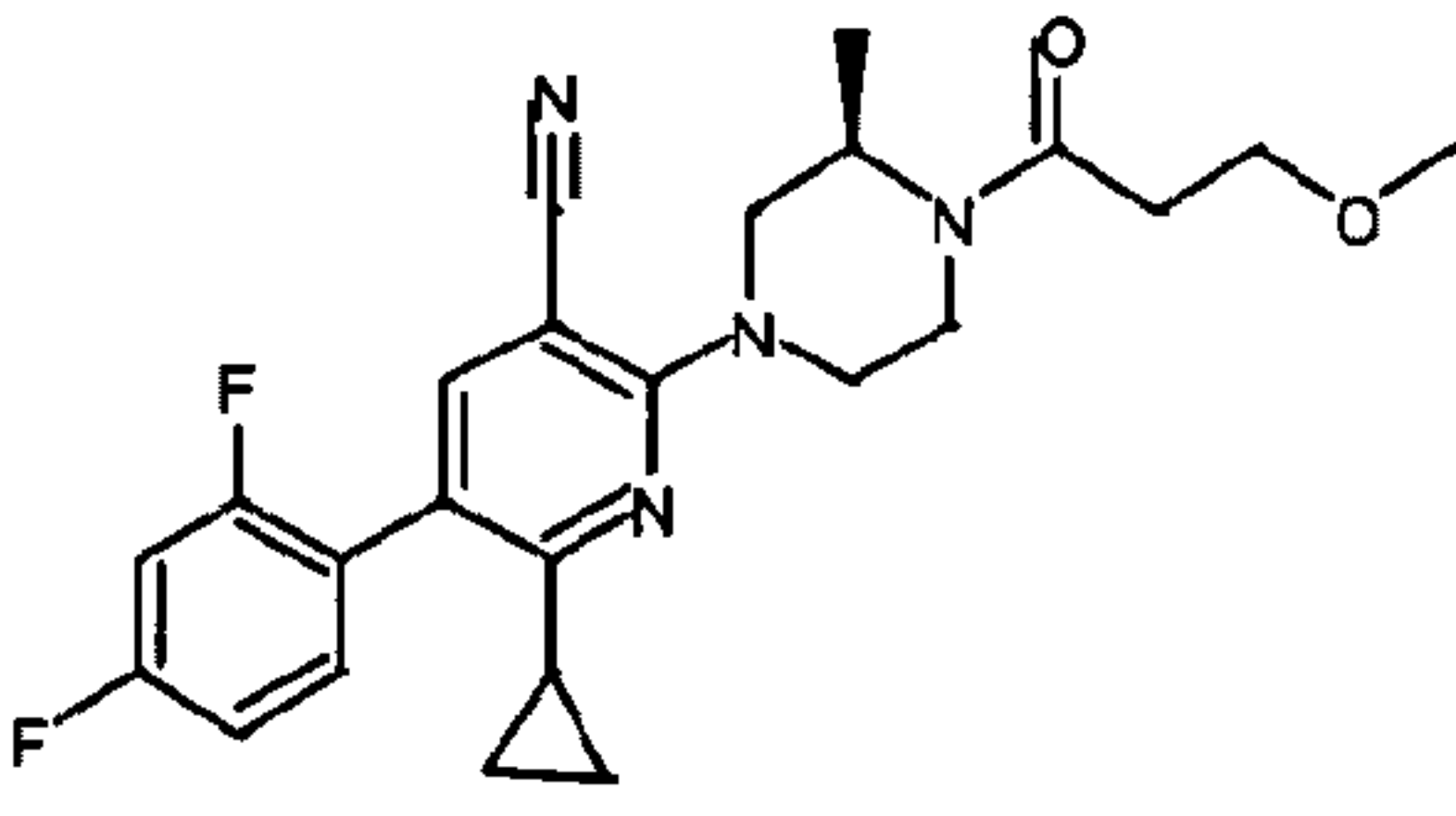
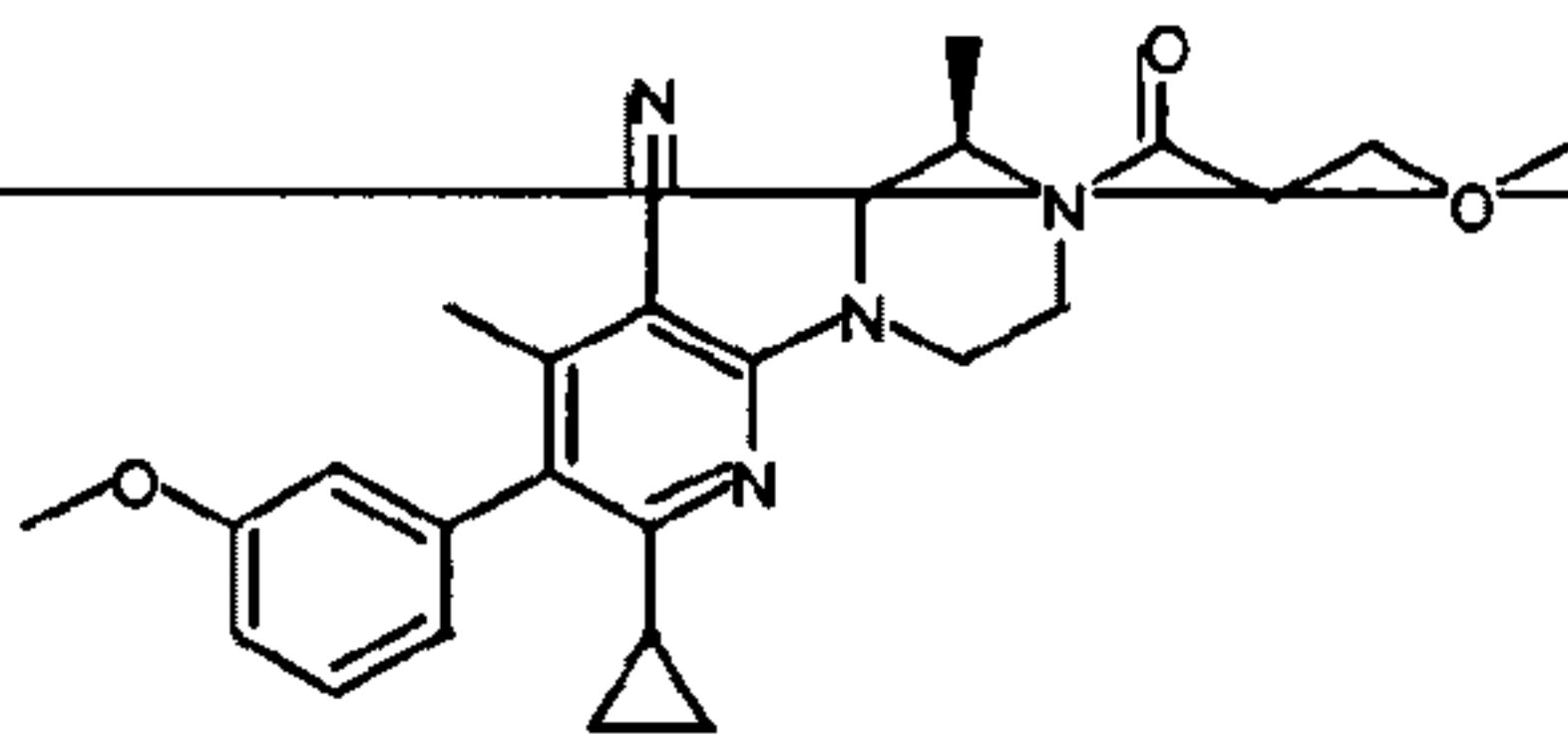
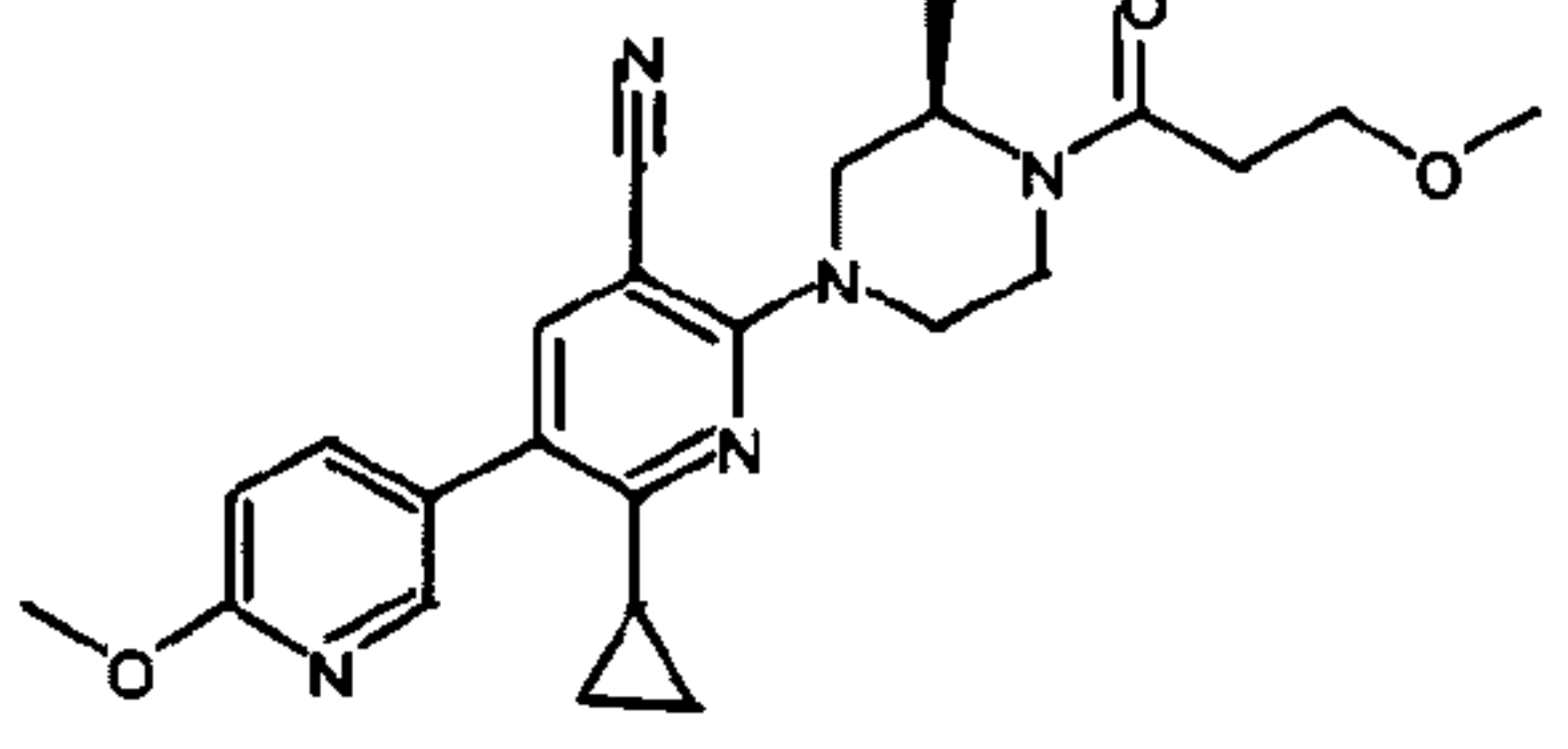
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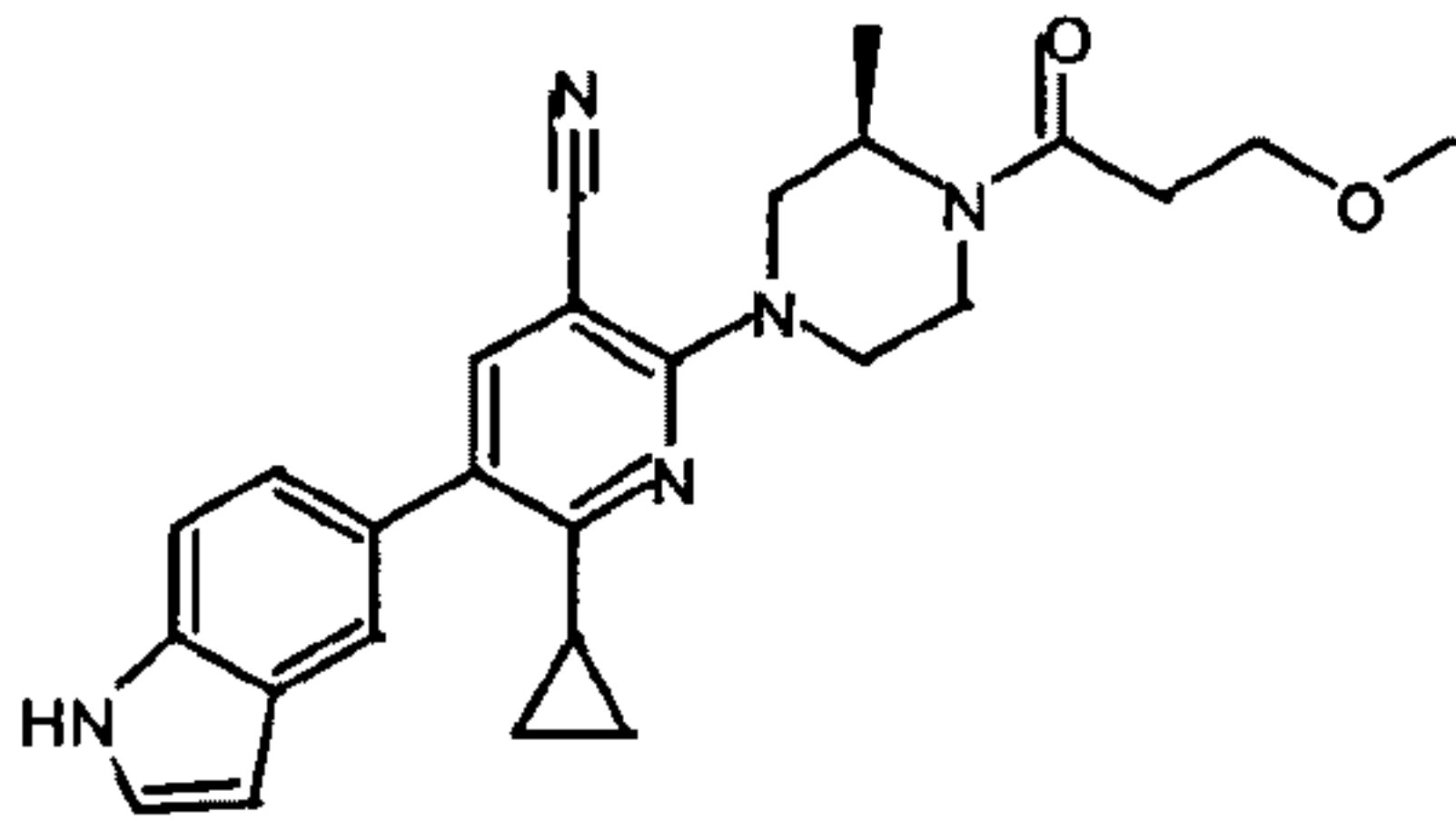
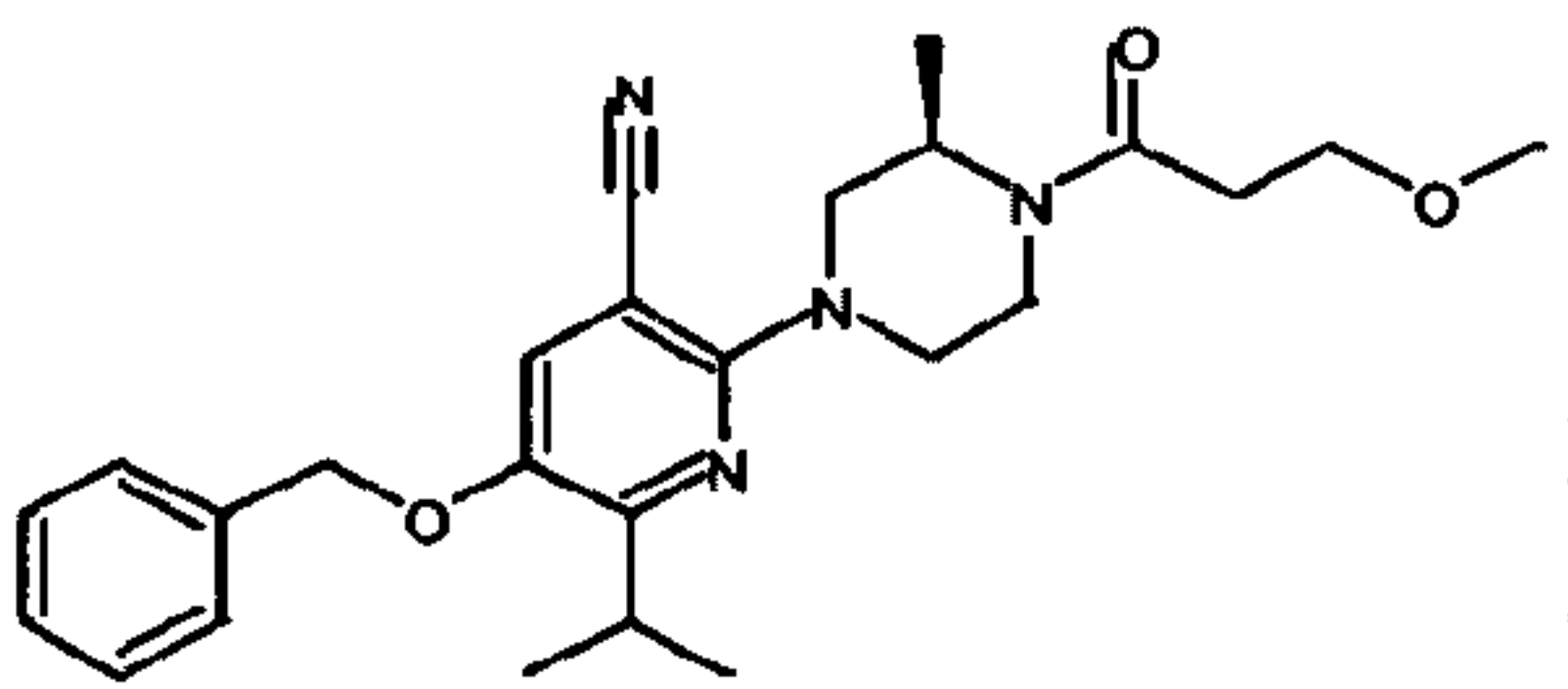
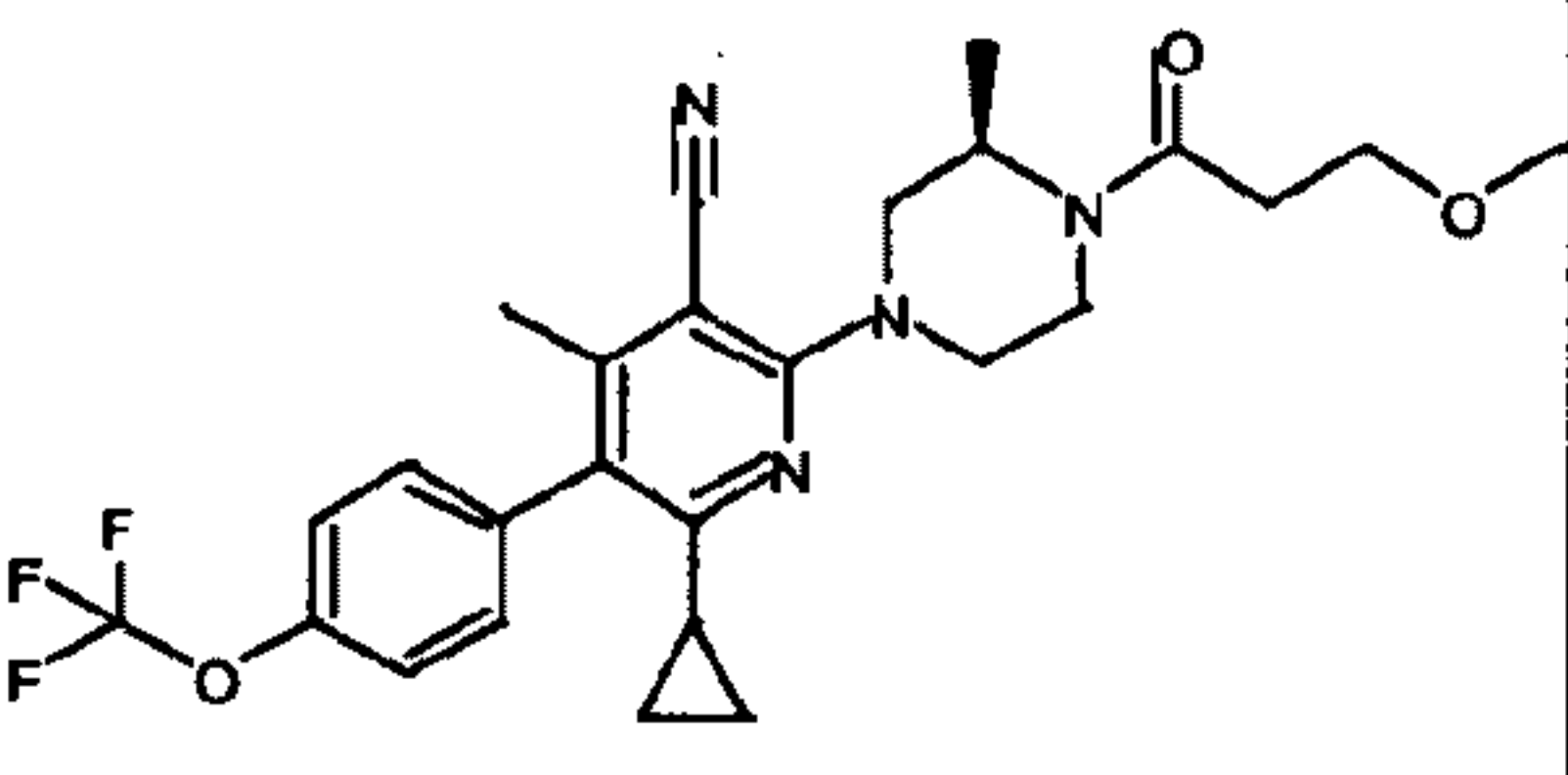
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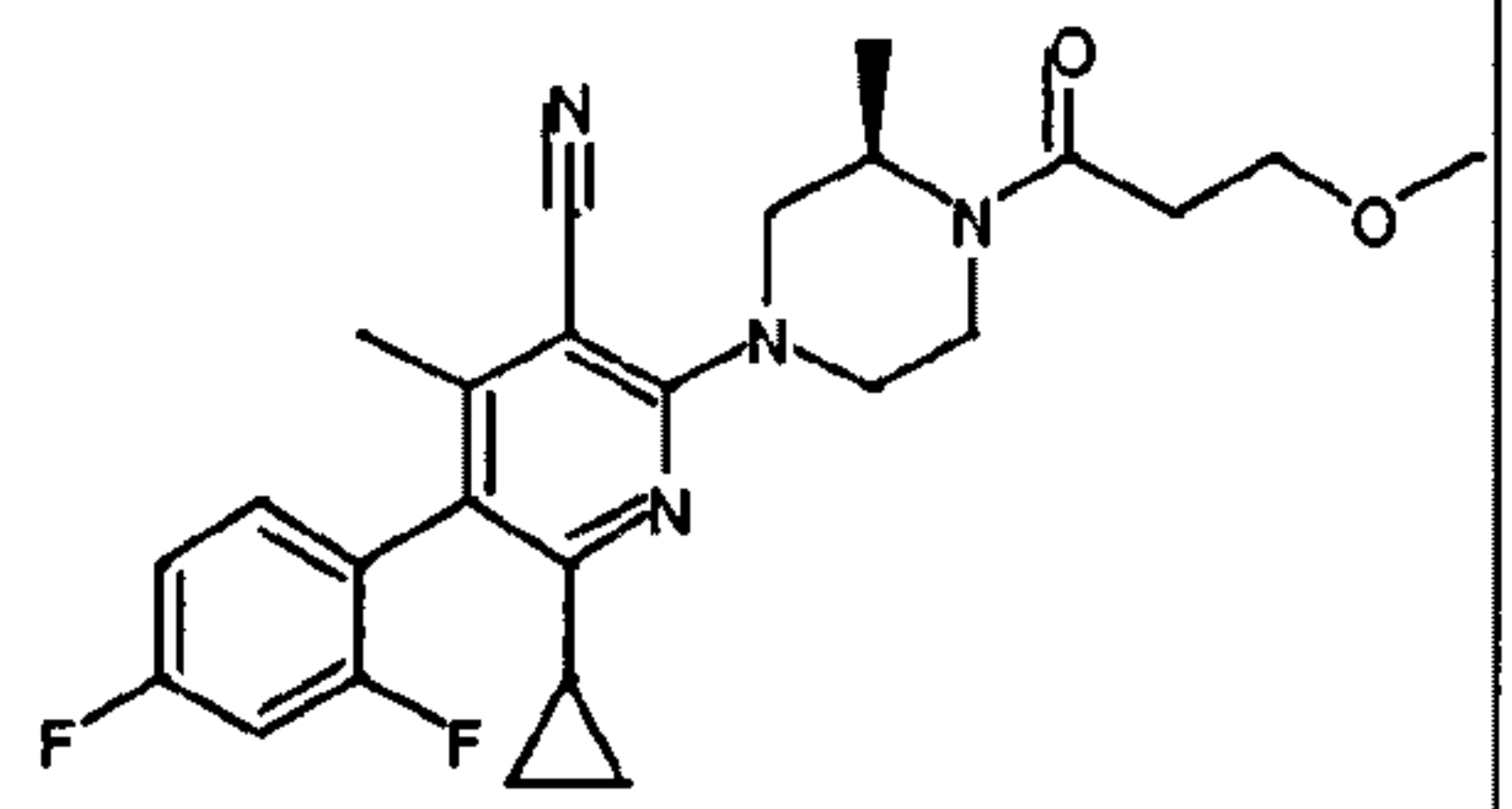
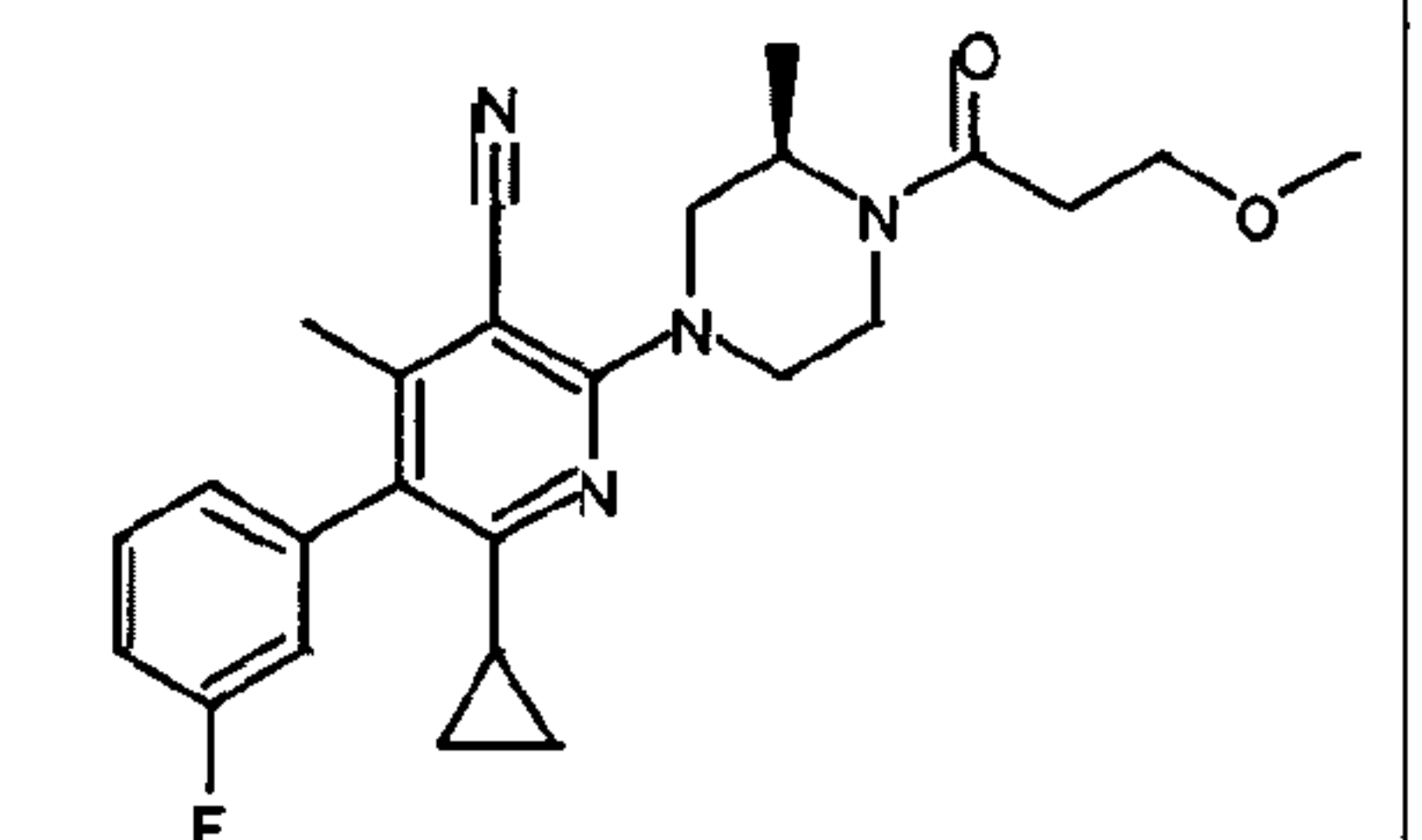
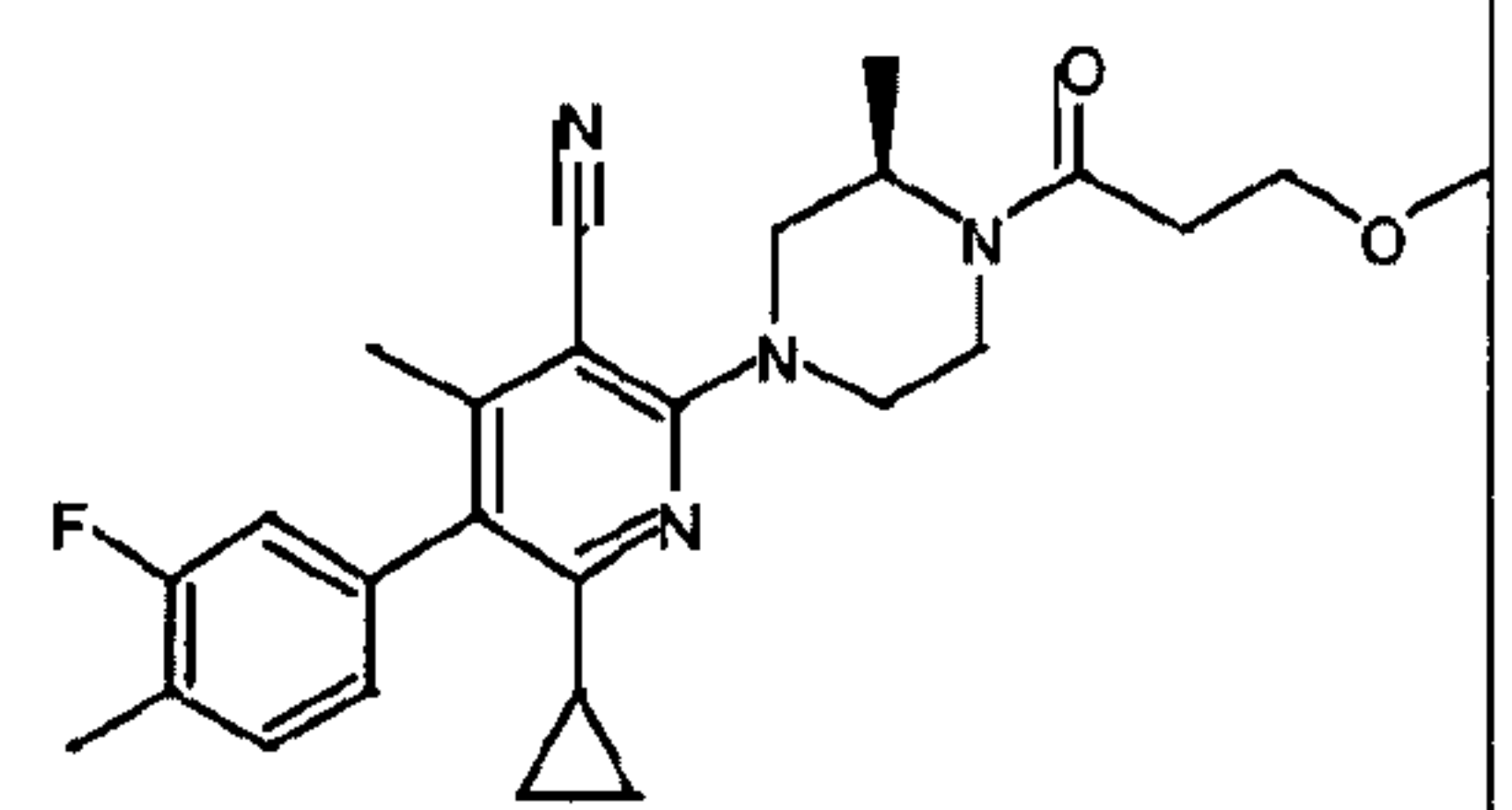
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249	

Cmpd No.	Structure
250	
251	
252	

Cmpd No.	Structure
253	
254	
255	

Cmpd No.	Structure
256	
257	
258	

Cmpd No.	Structure
259	
260	
261	

Cmpd No.	Structure
262	
59	
60	
61	

In another embodiment, the compound is selected from any one of the compounds set forth in Table 5, below.

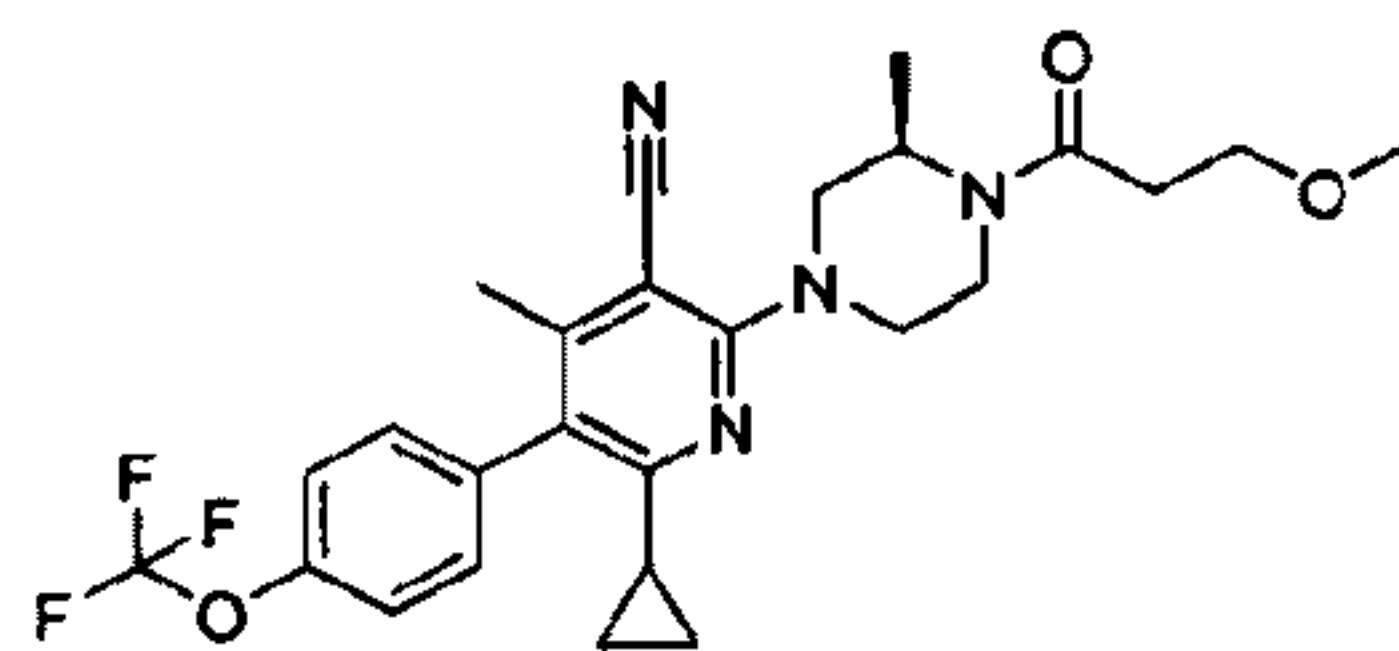
Table 5. Exemplary Compounds of Formula I.

Cpd

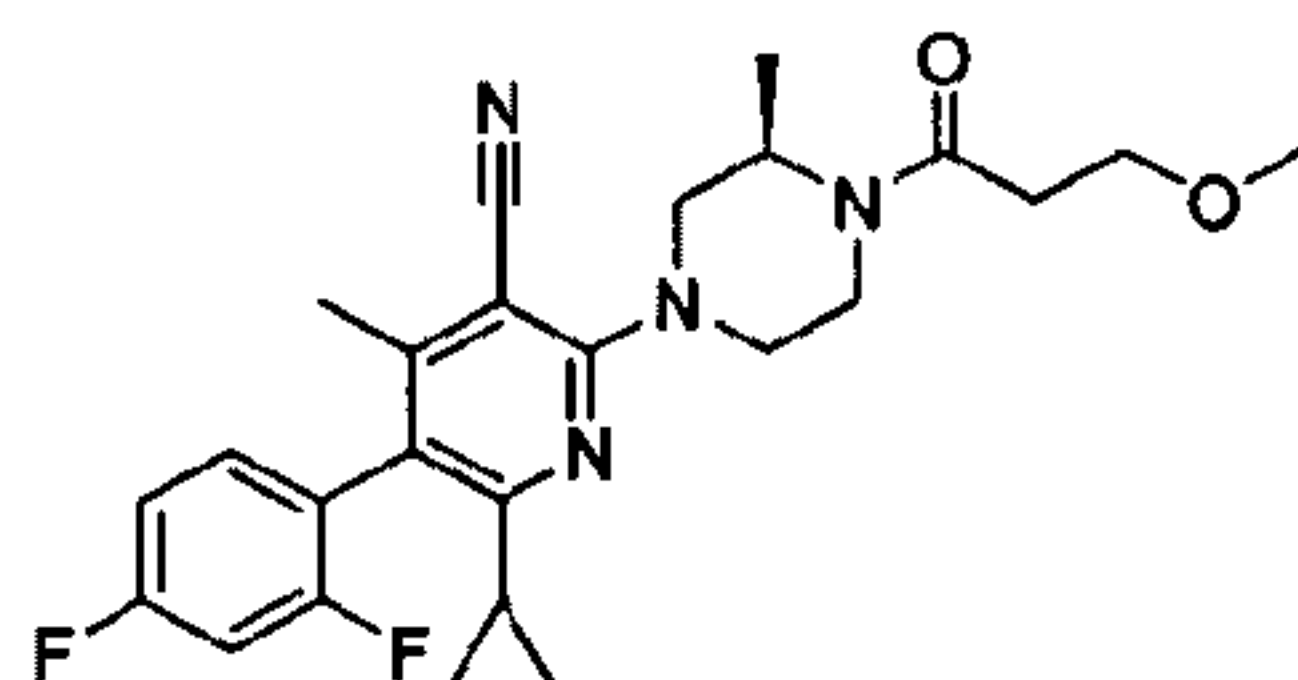
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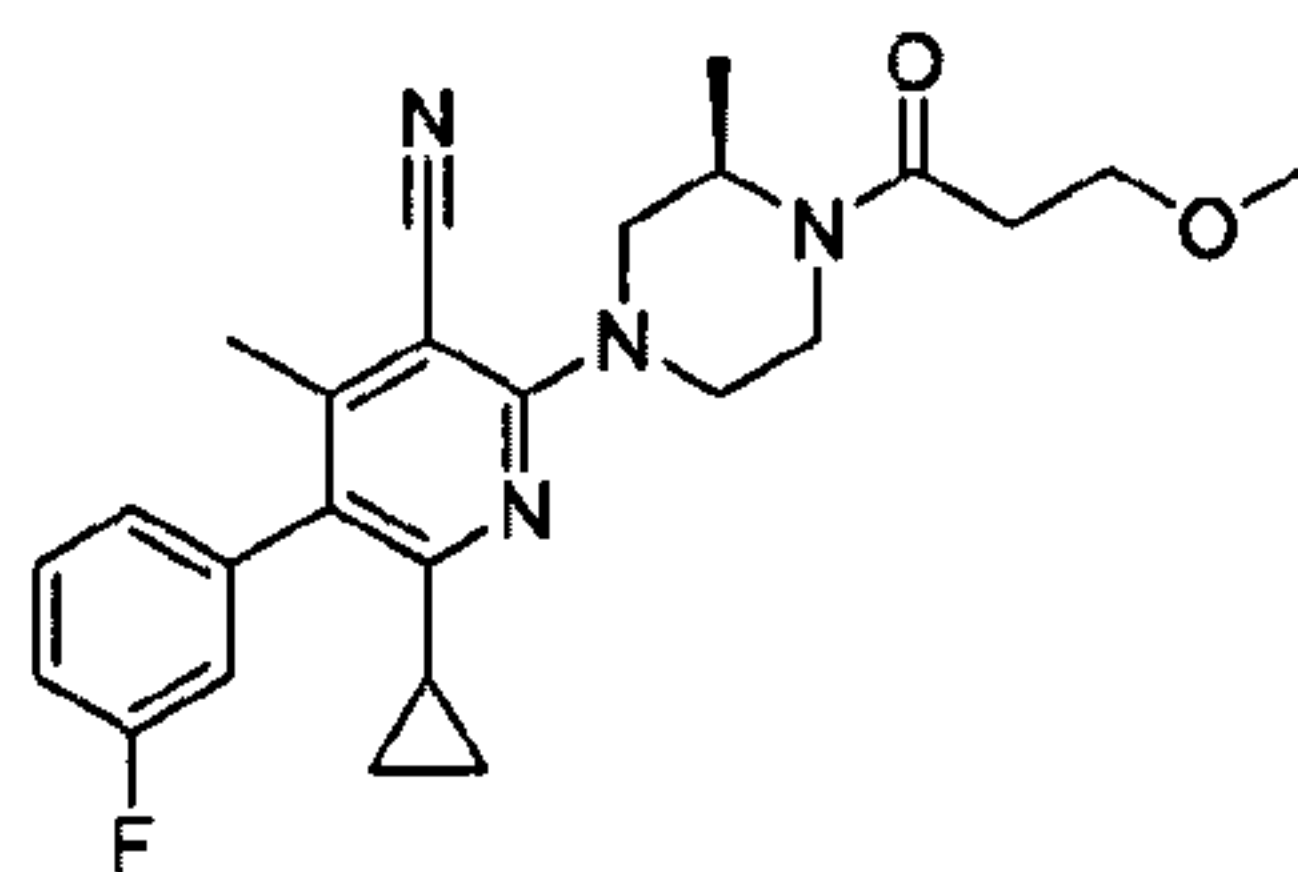
263



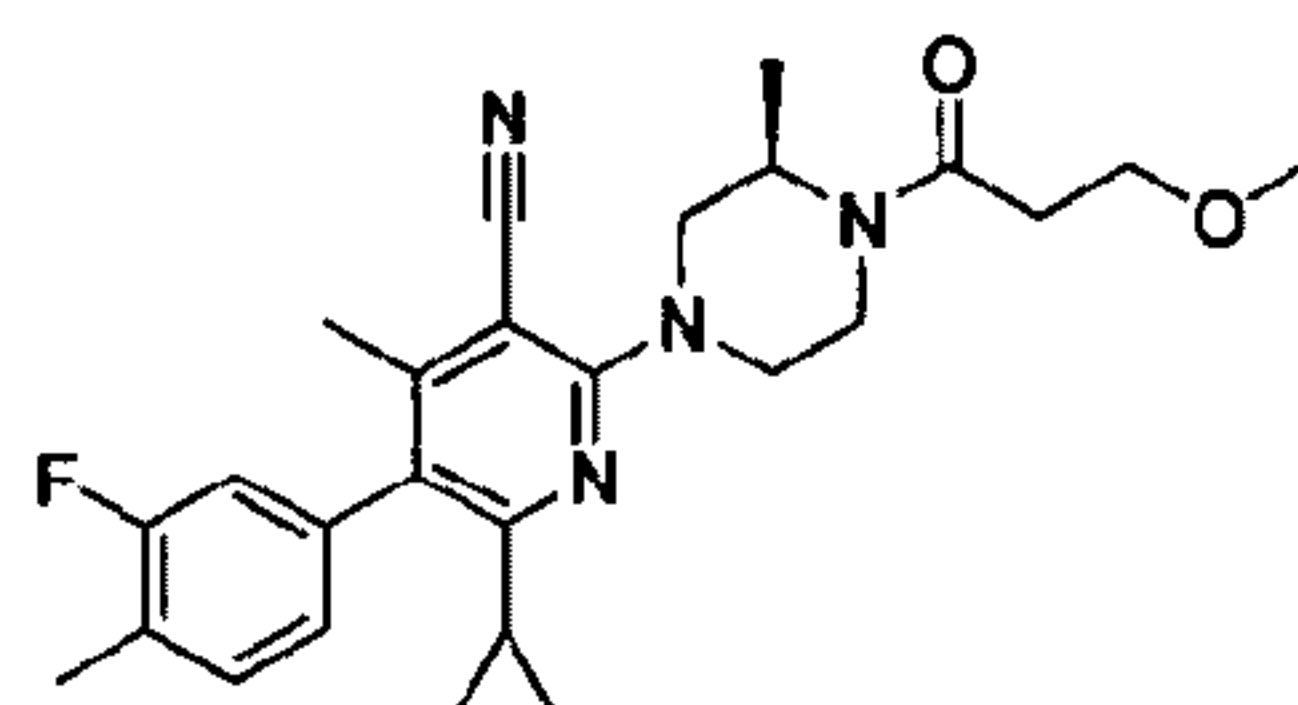
264



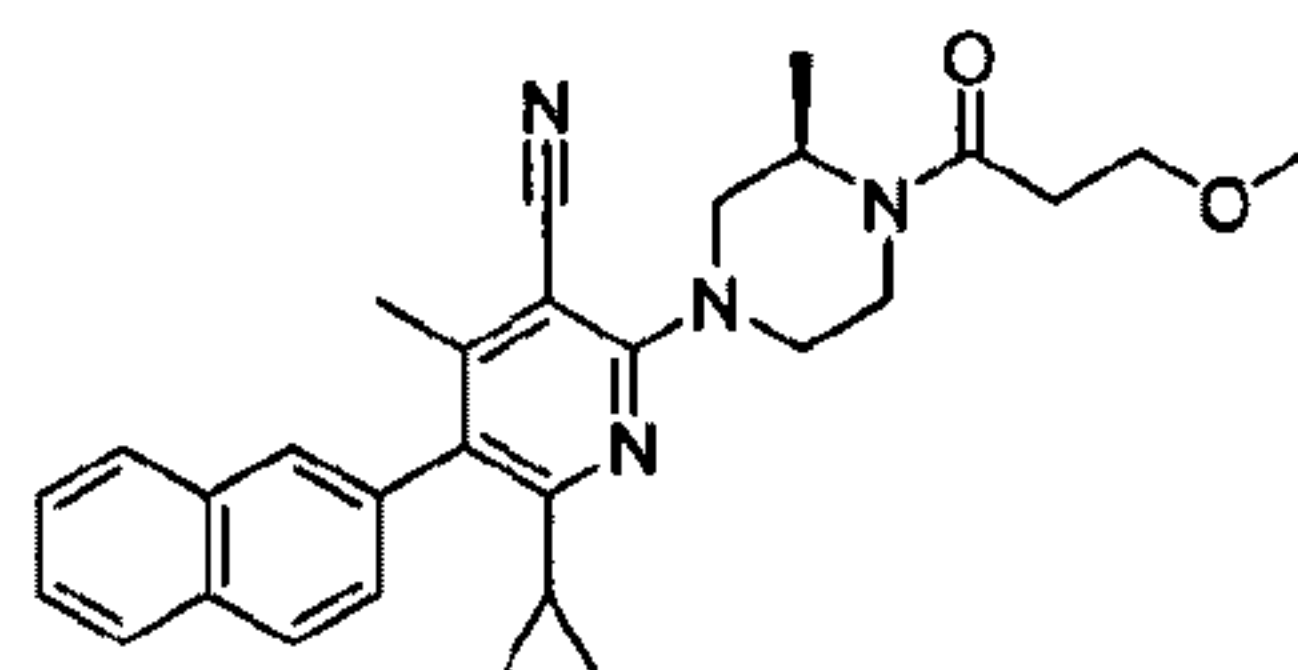
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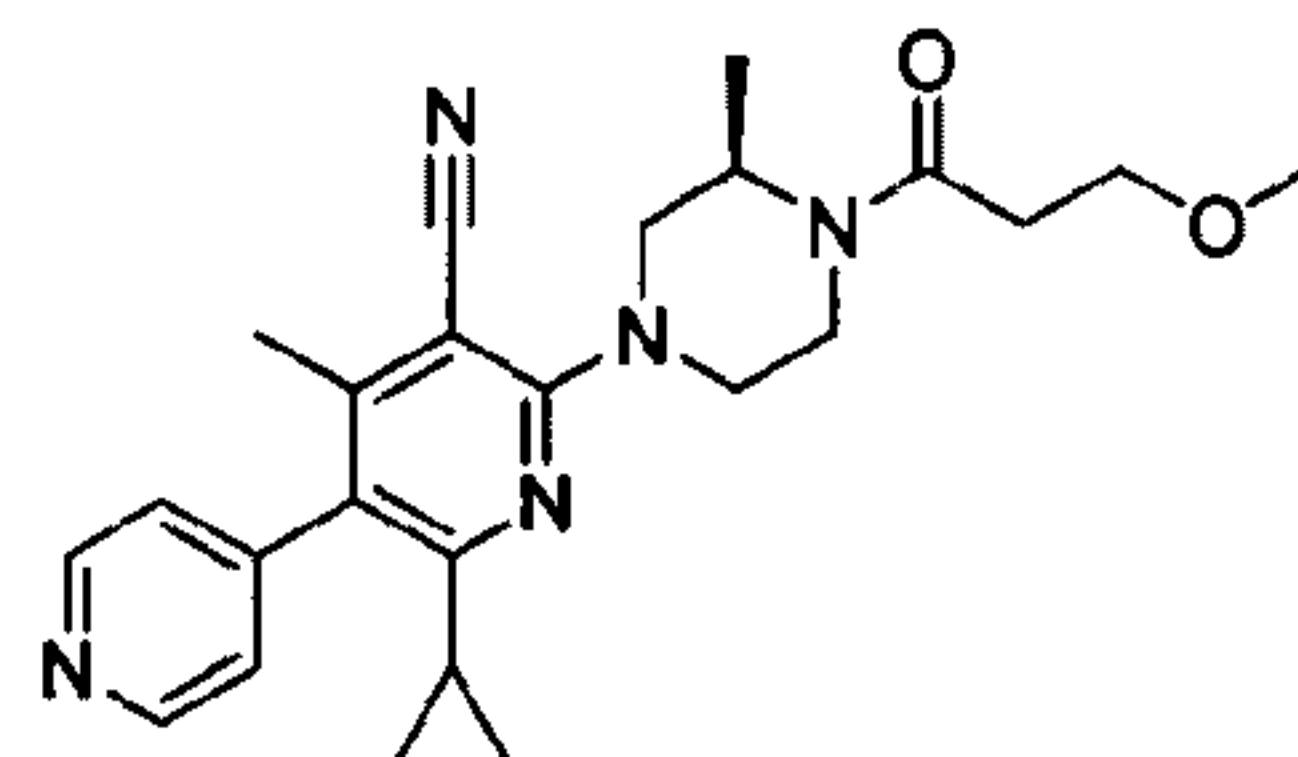
266



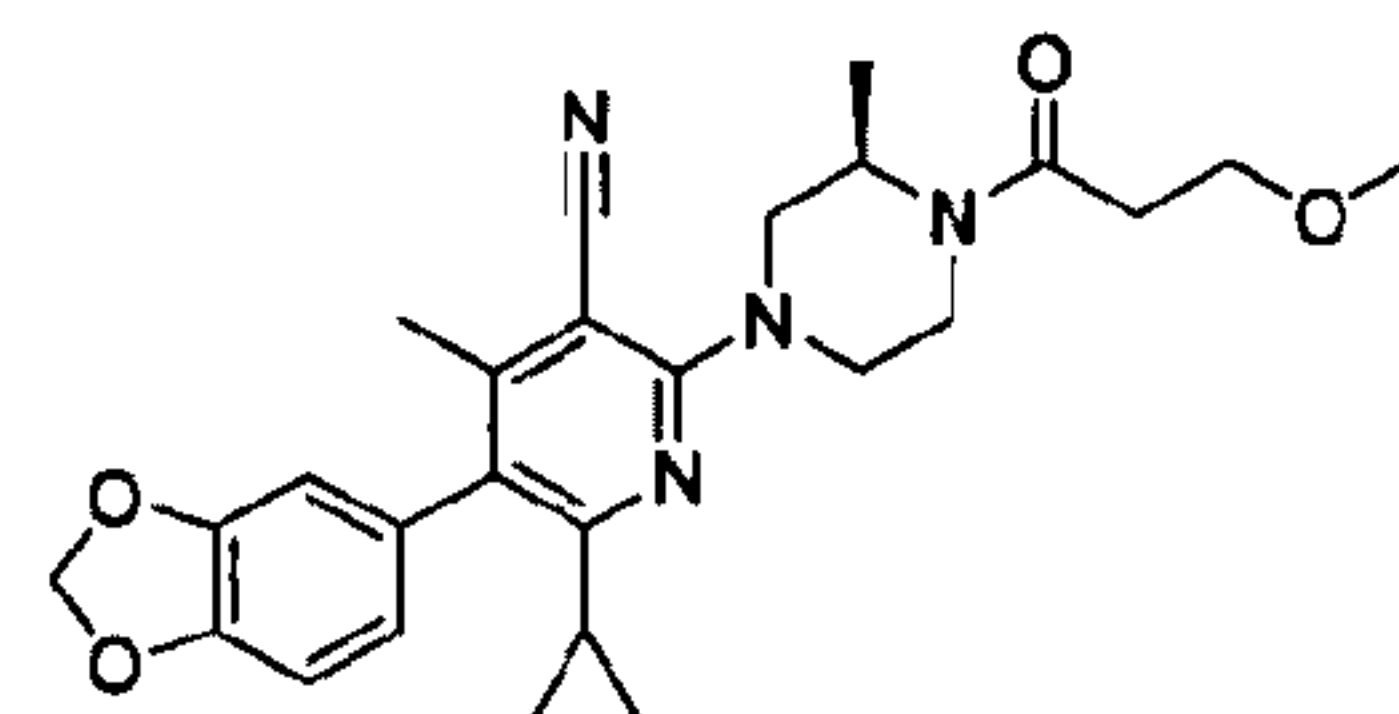
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268



269

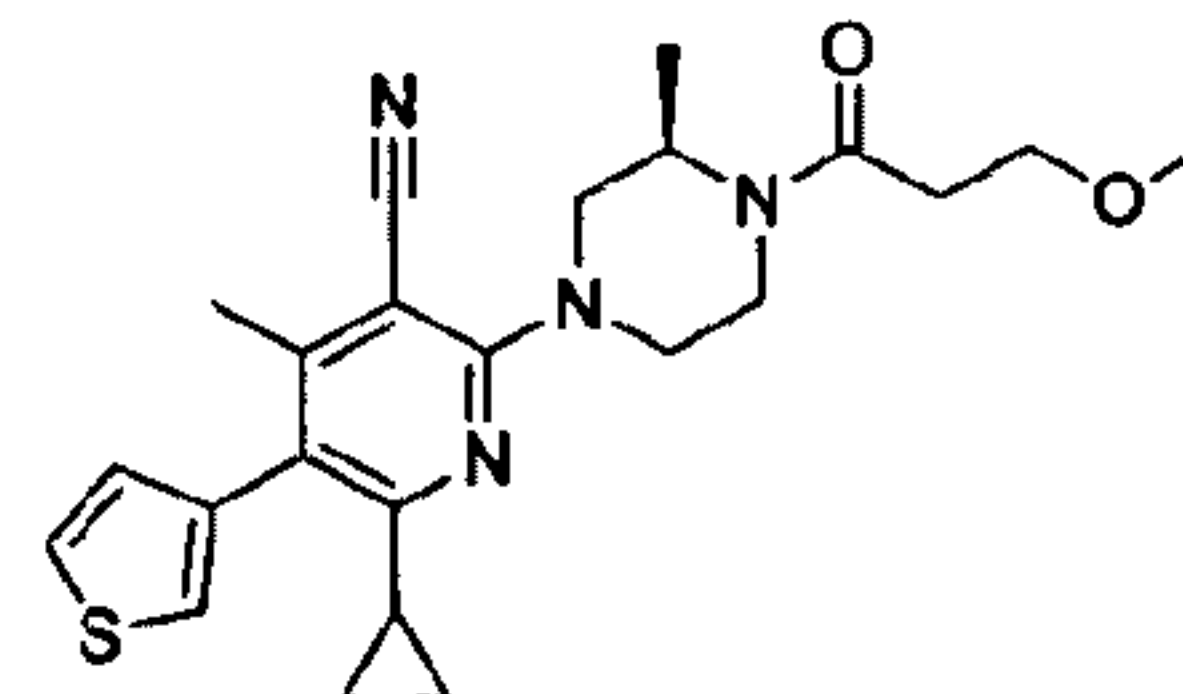


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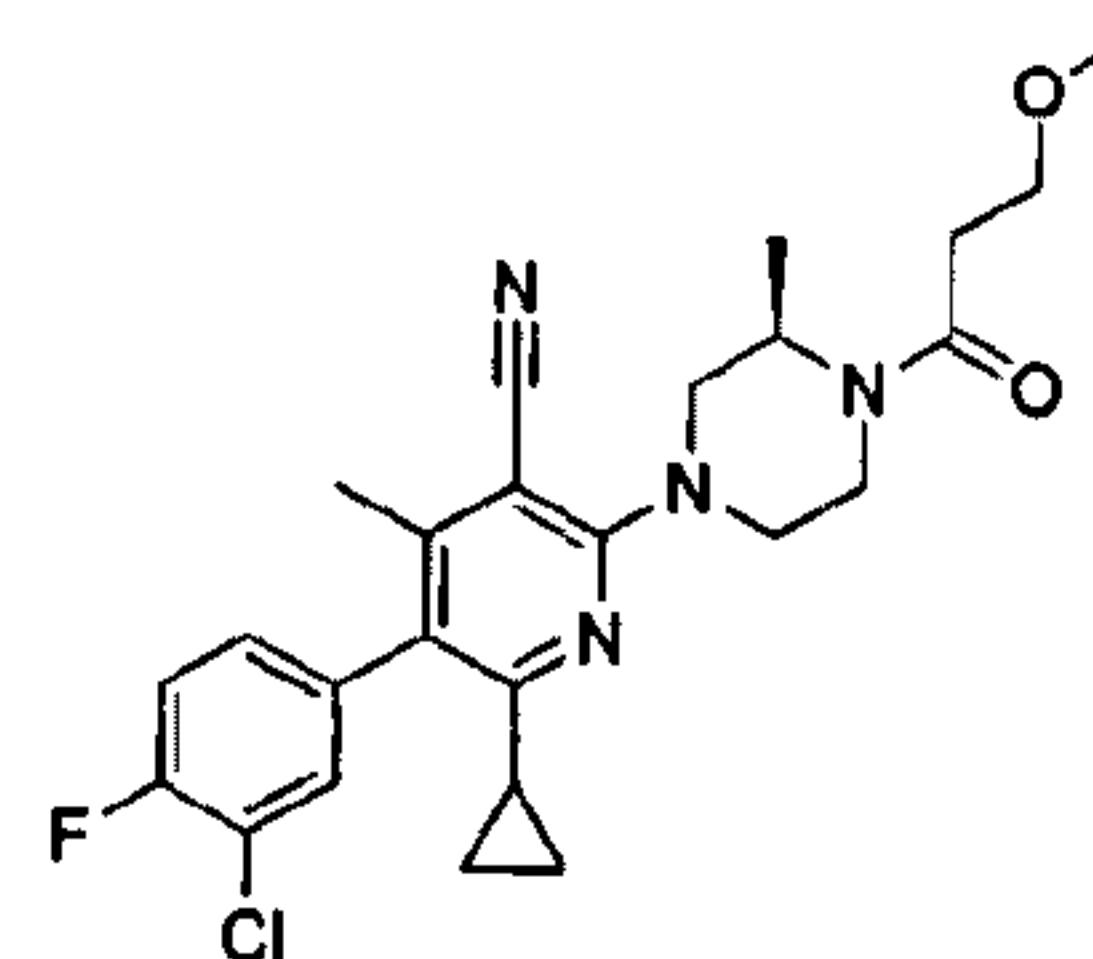
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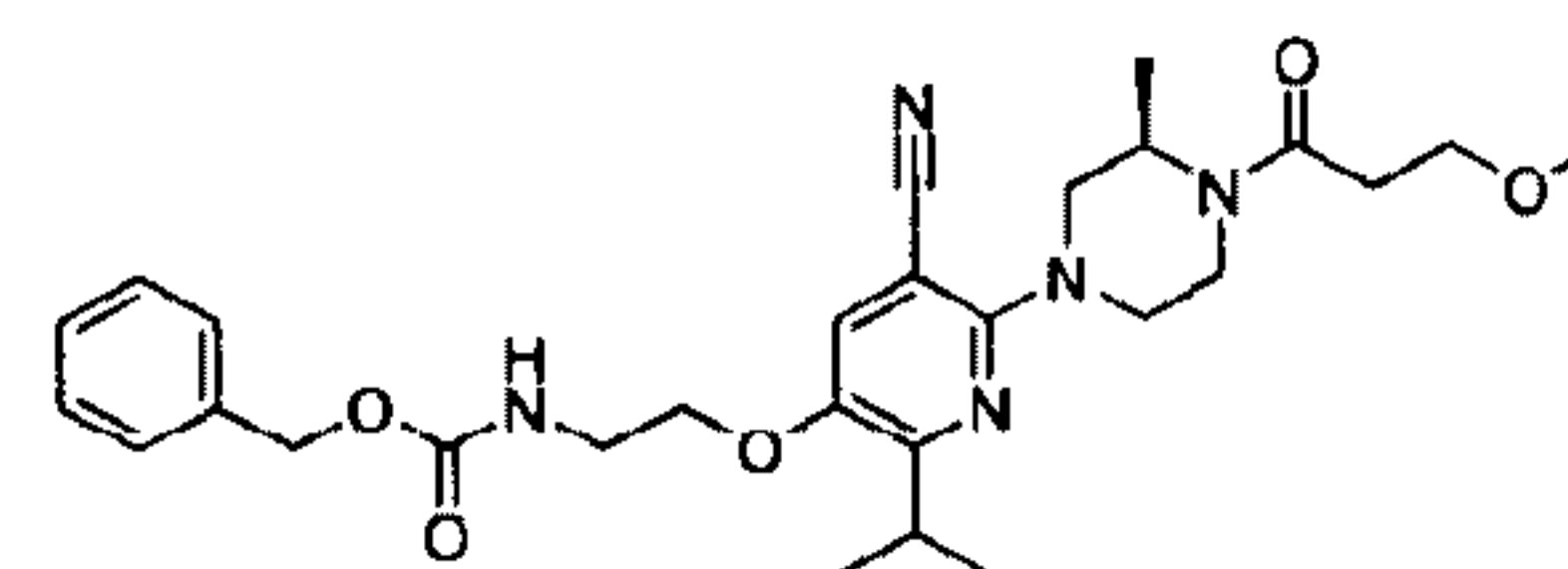
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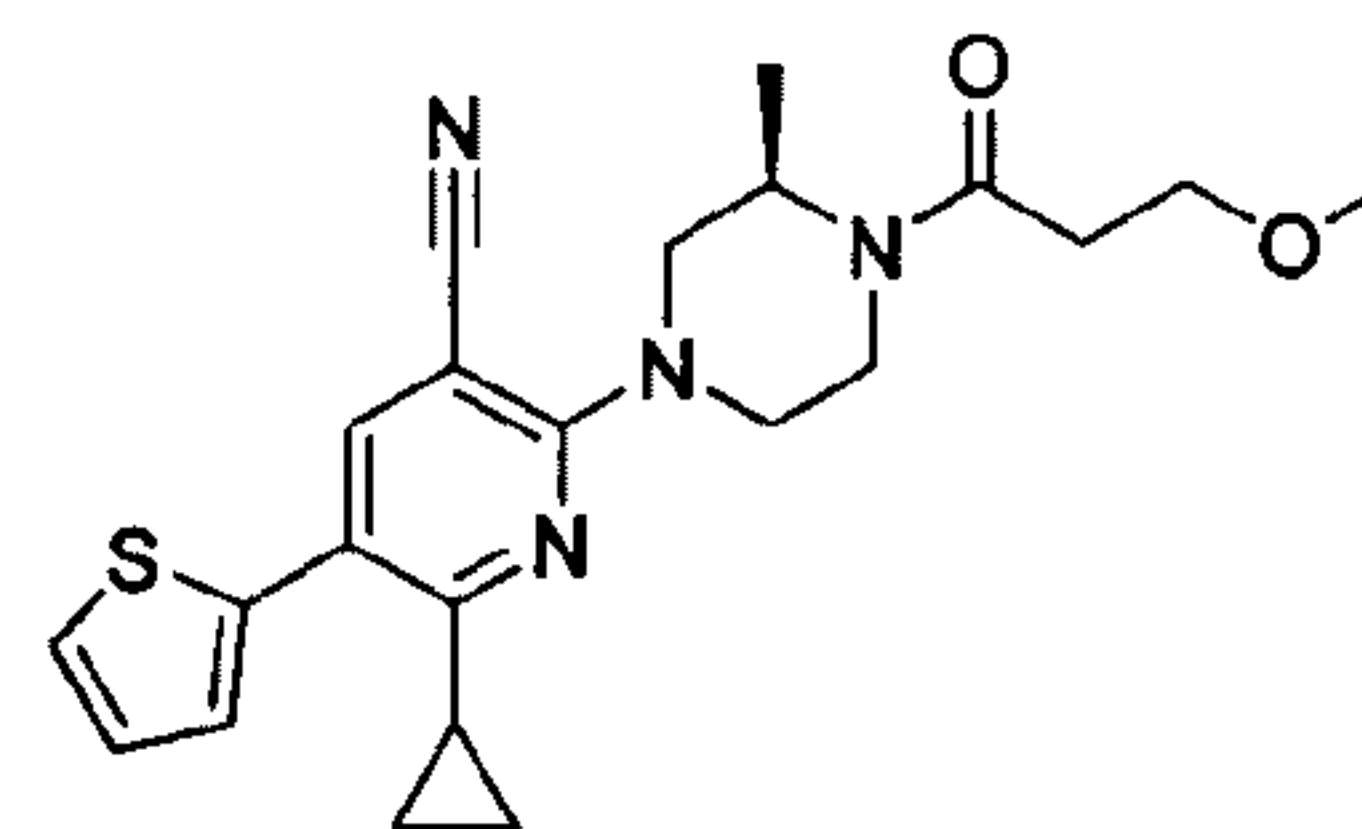
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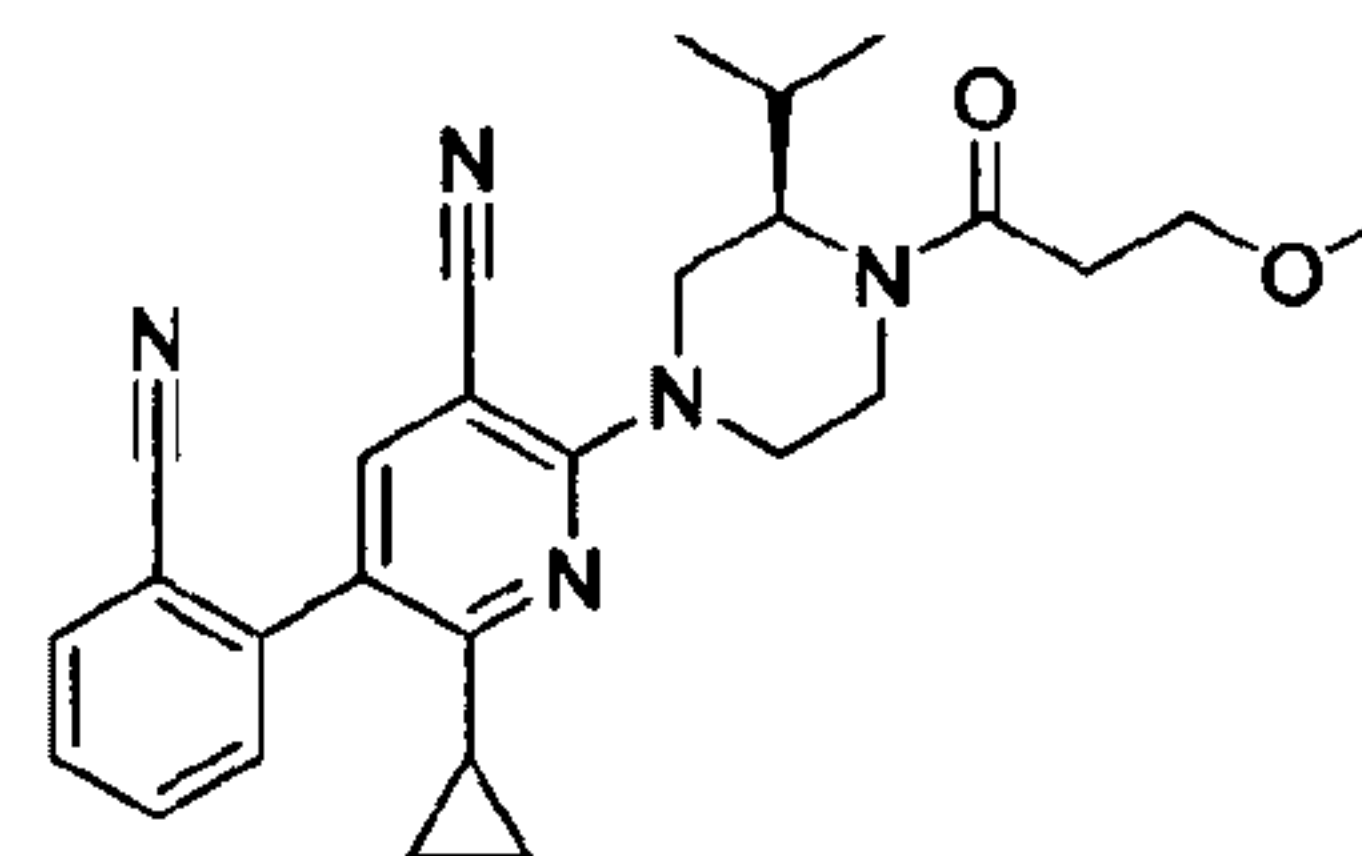
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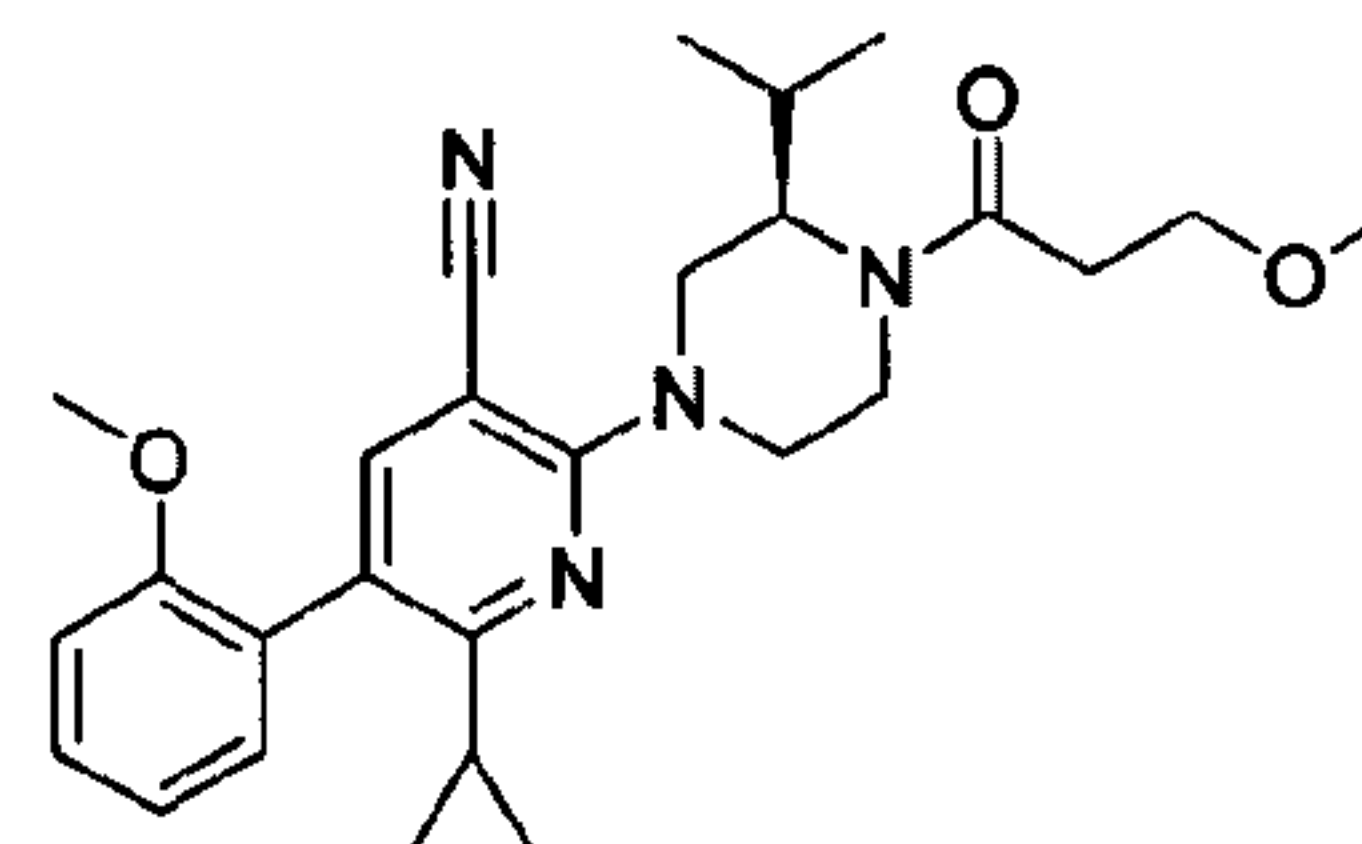
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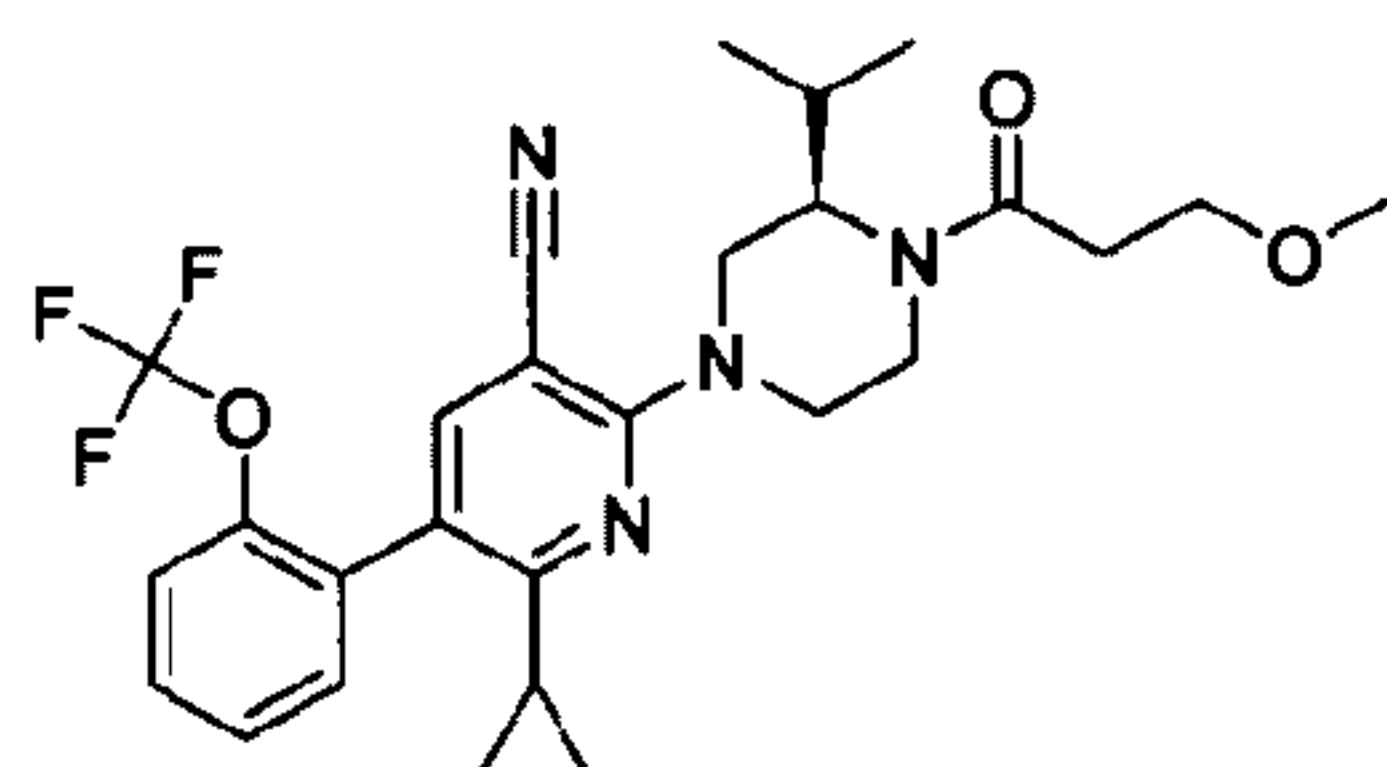


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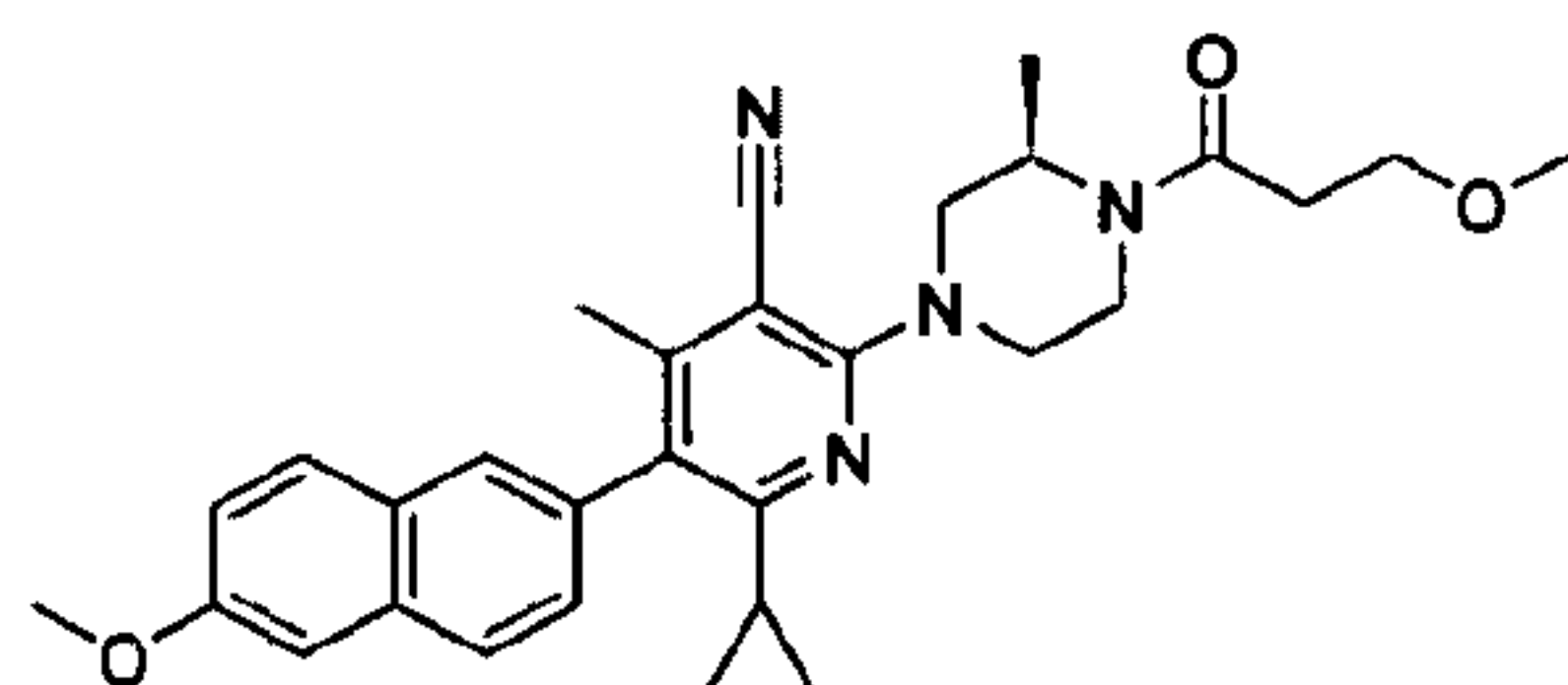


**Cpd
#****Structure**

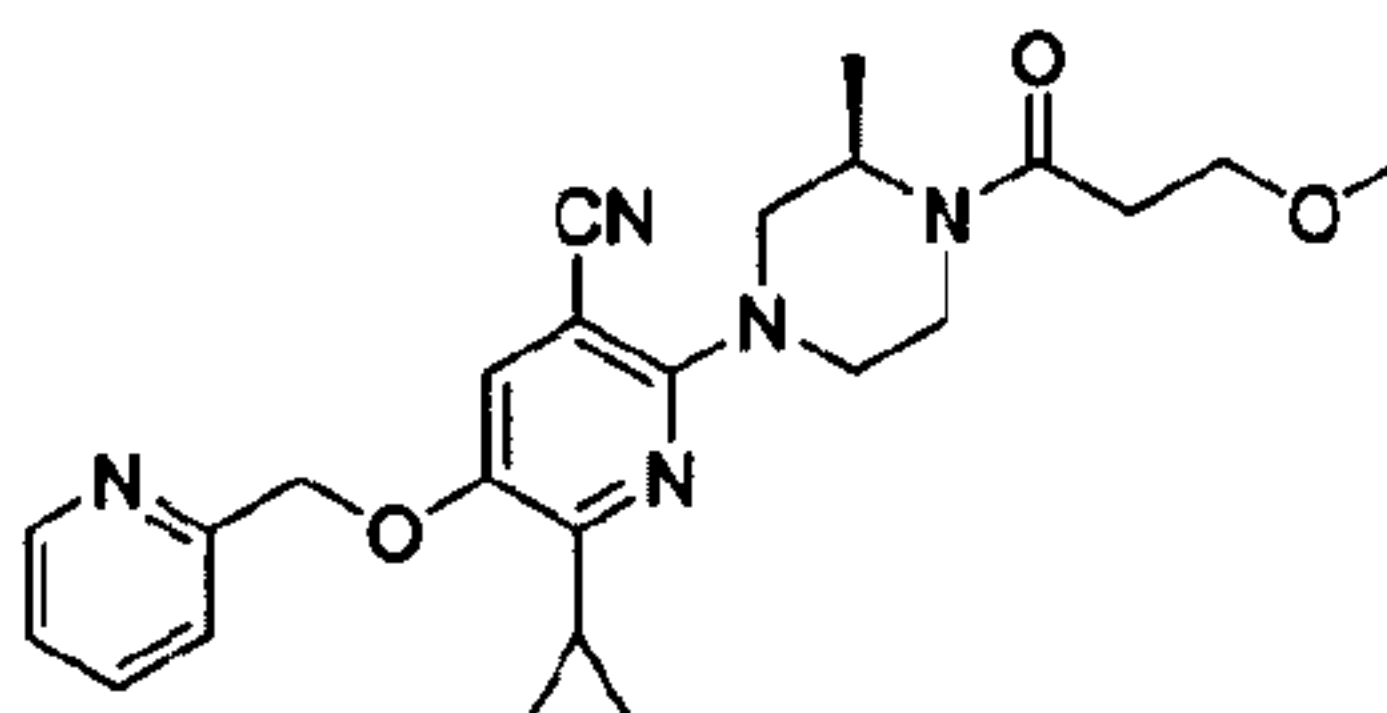
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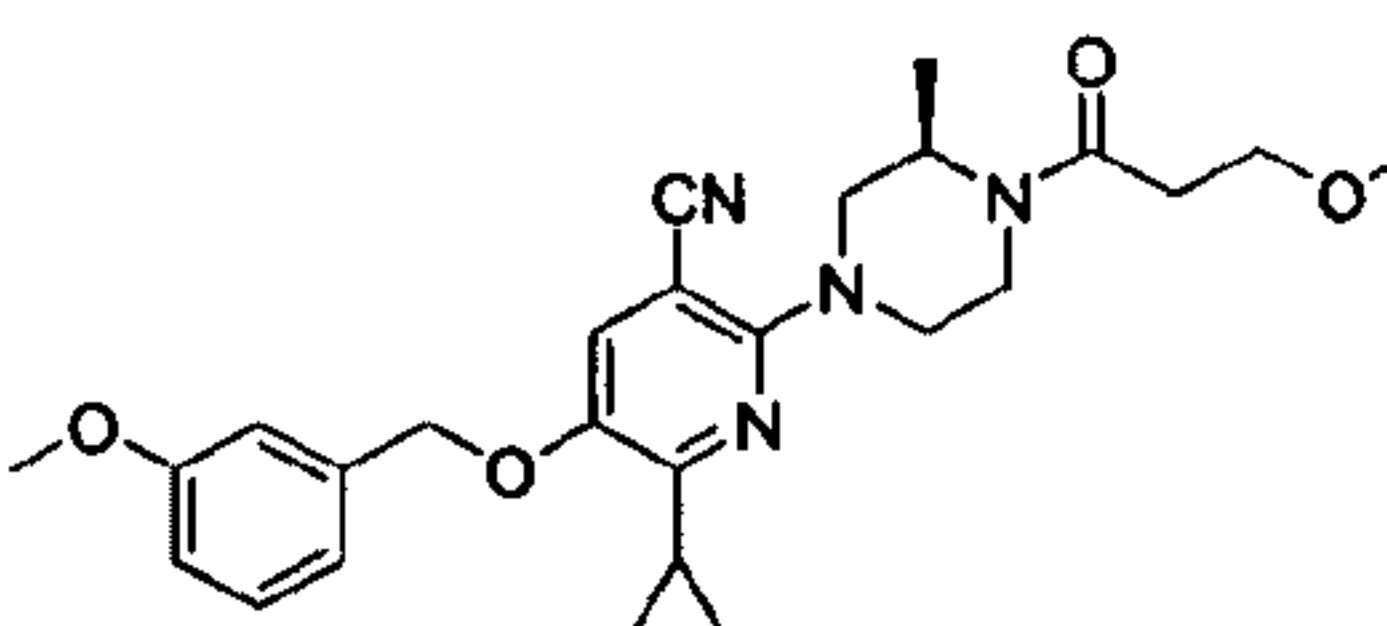
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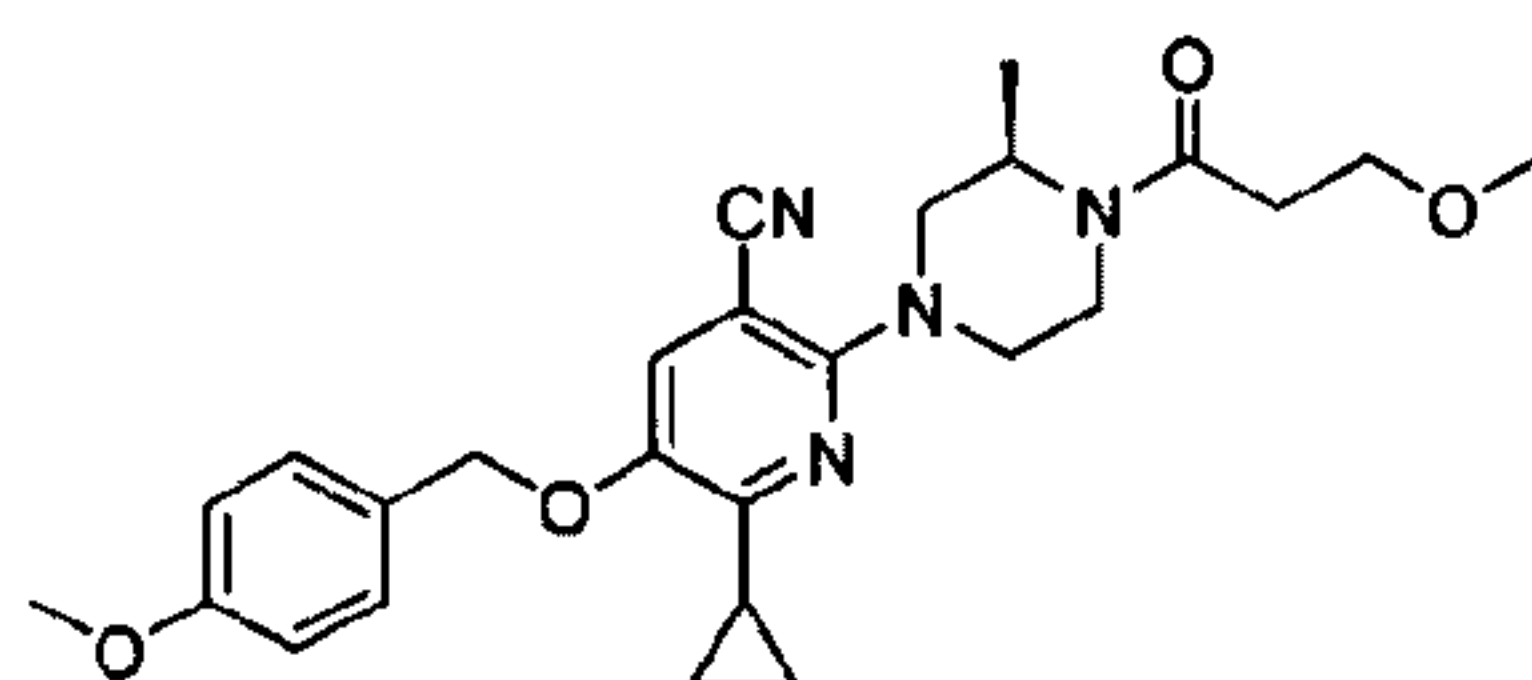
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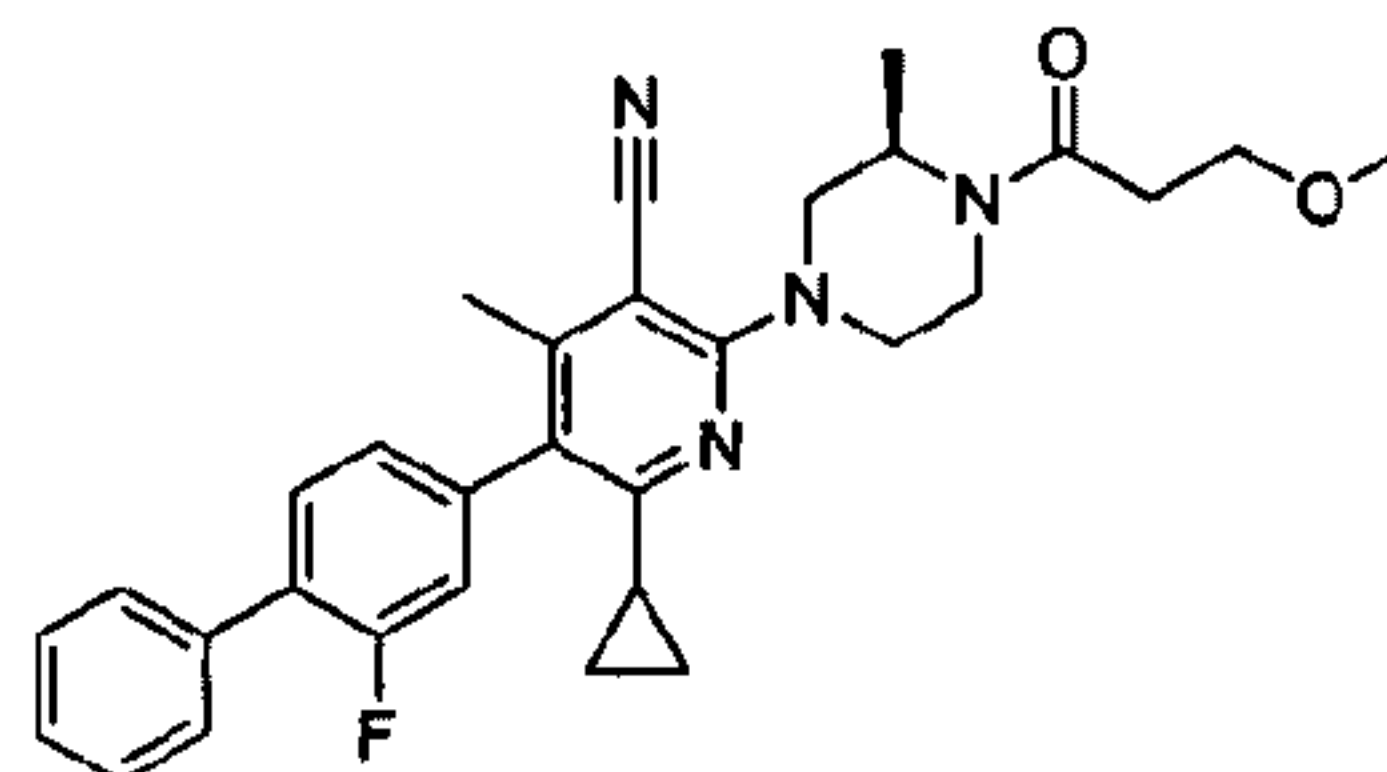
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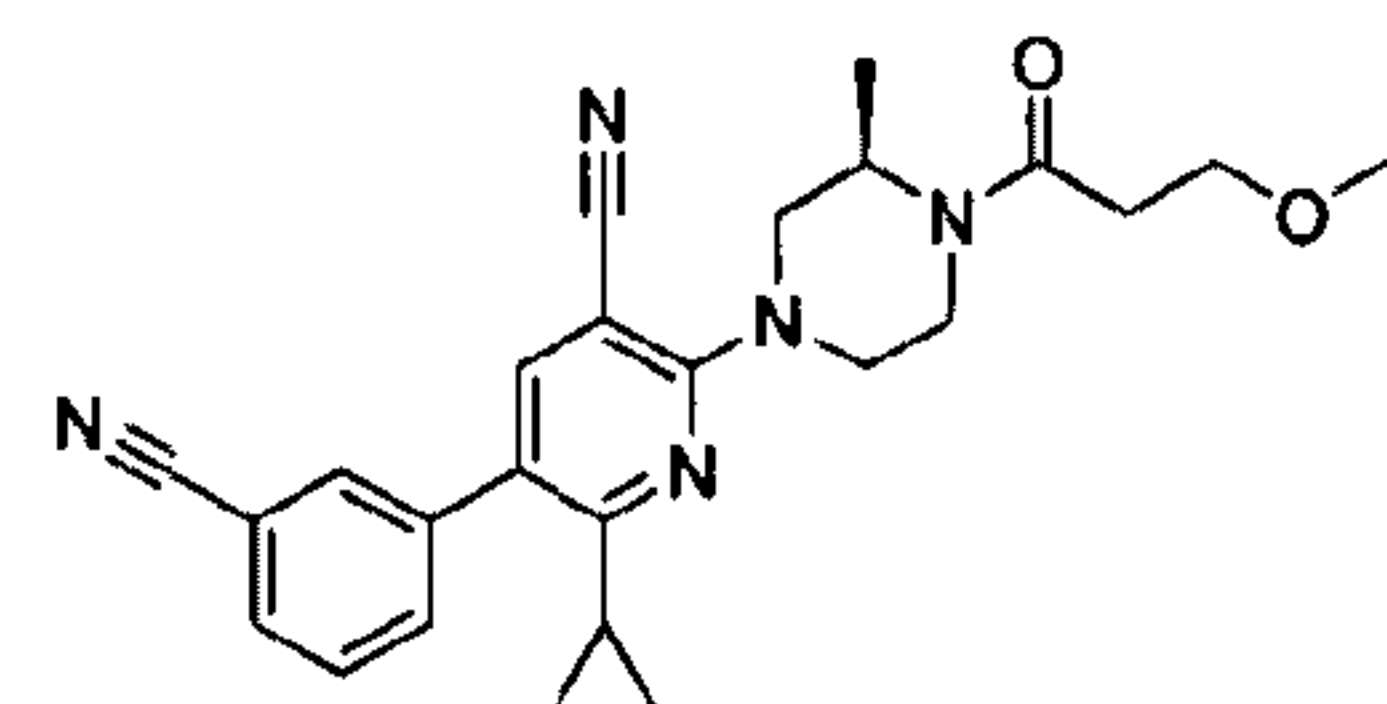
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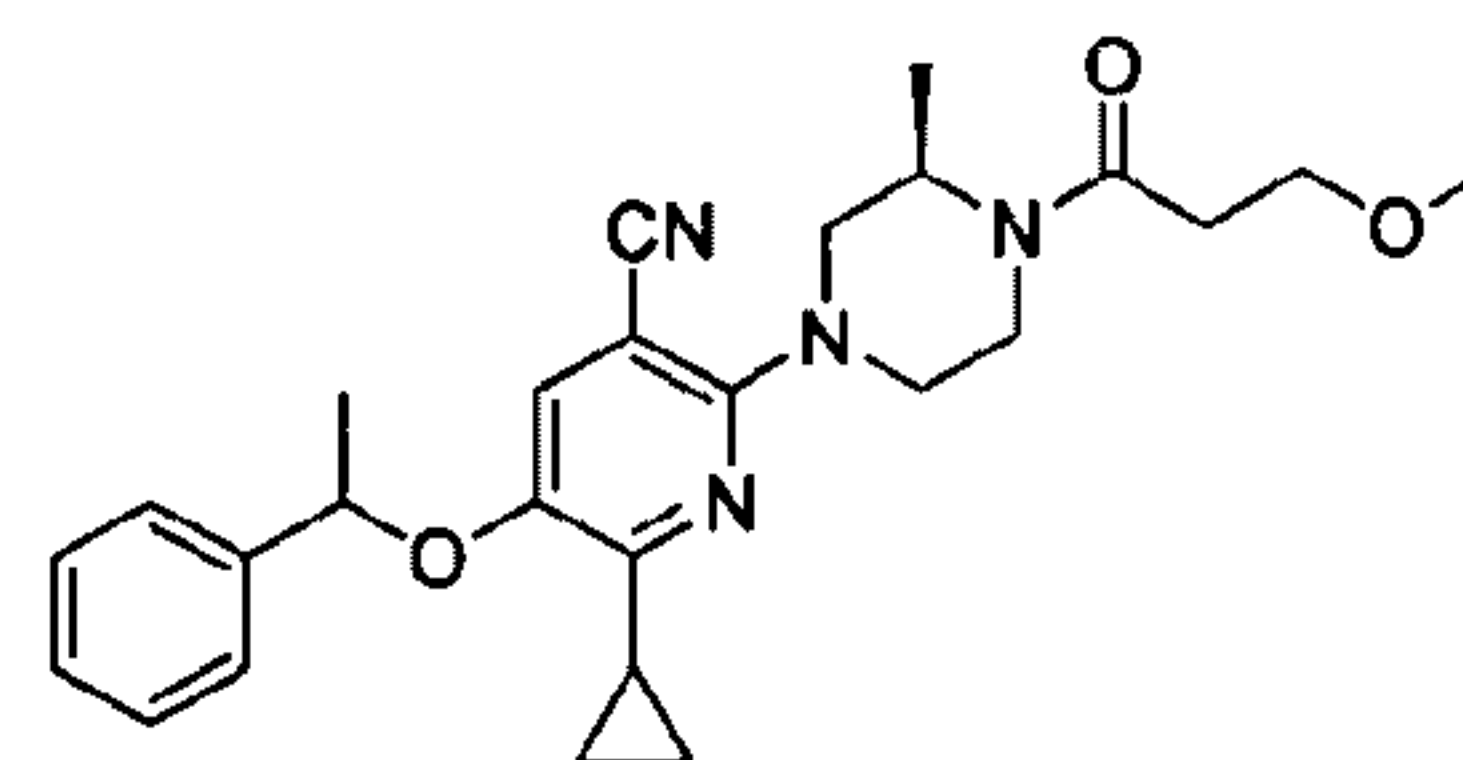
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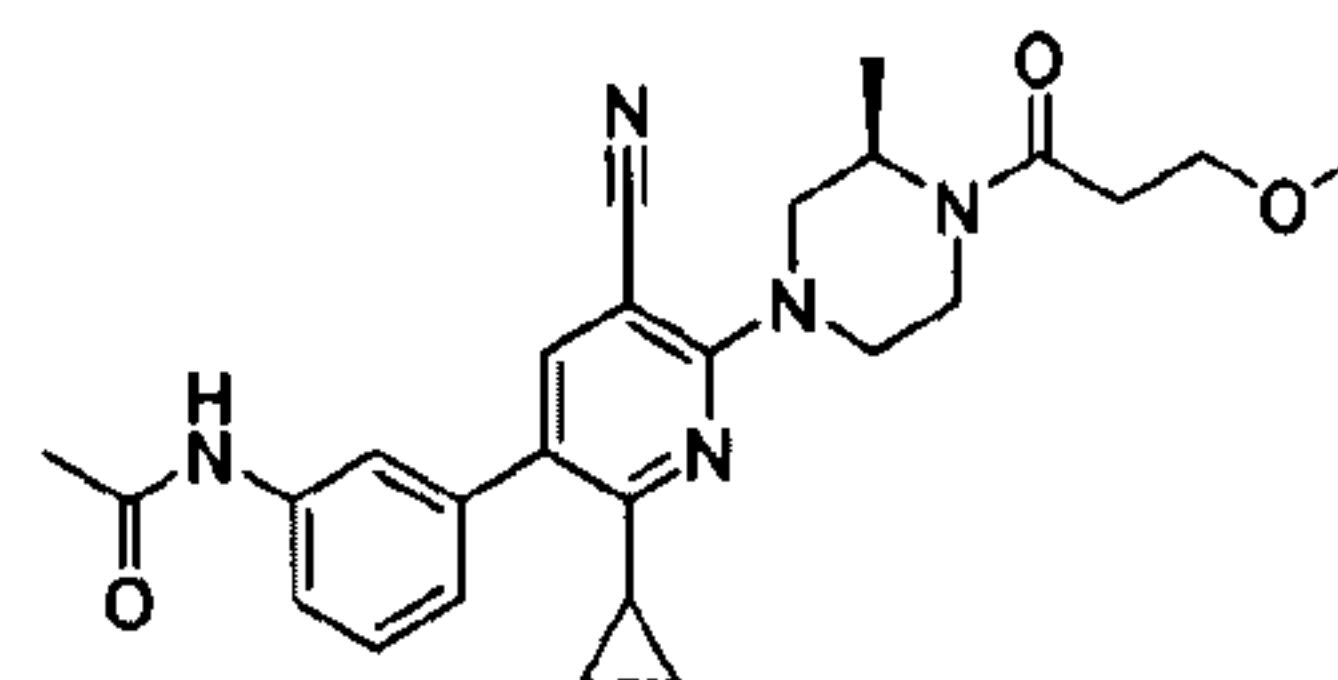
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**Cpd
#****Structure**

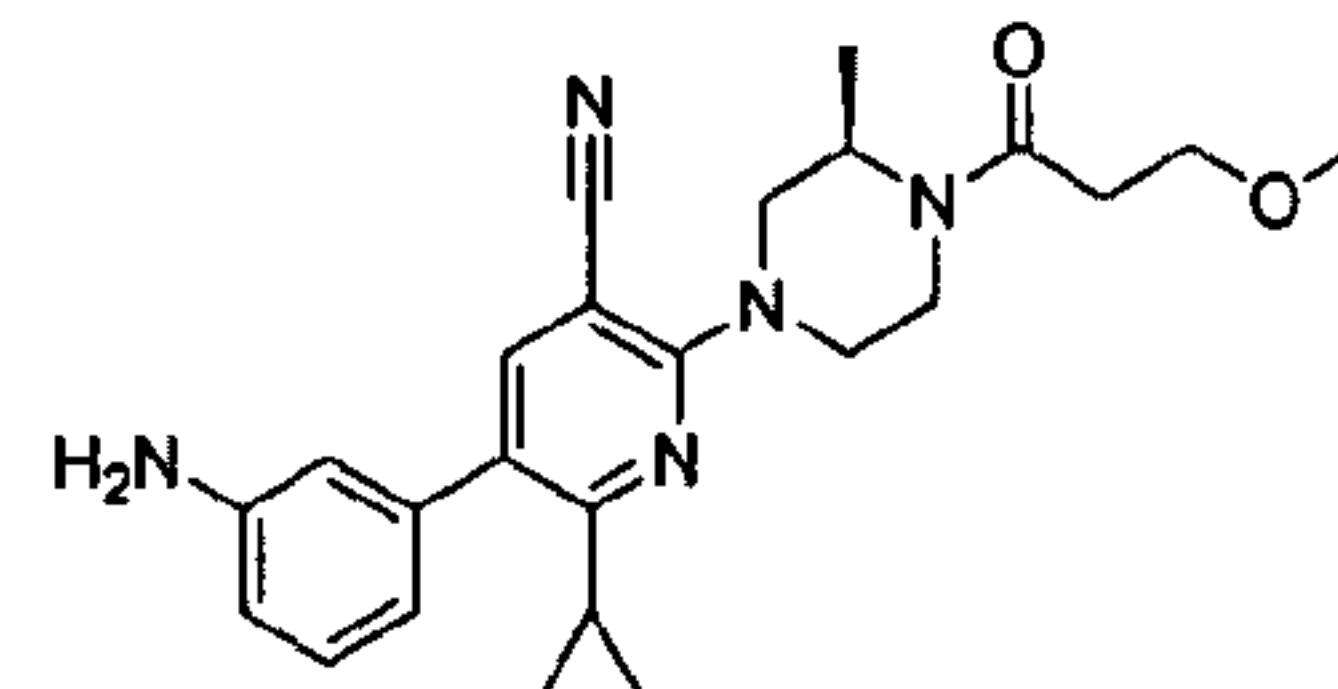
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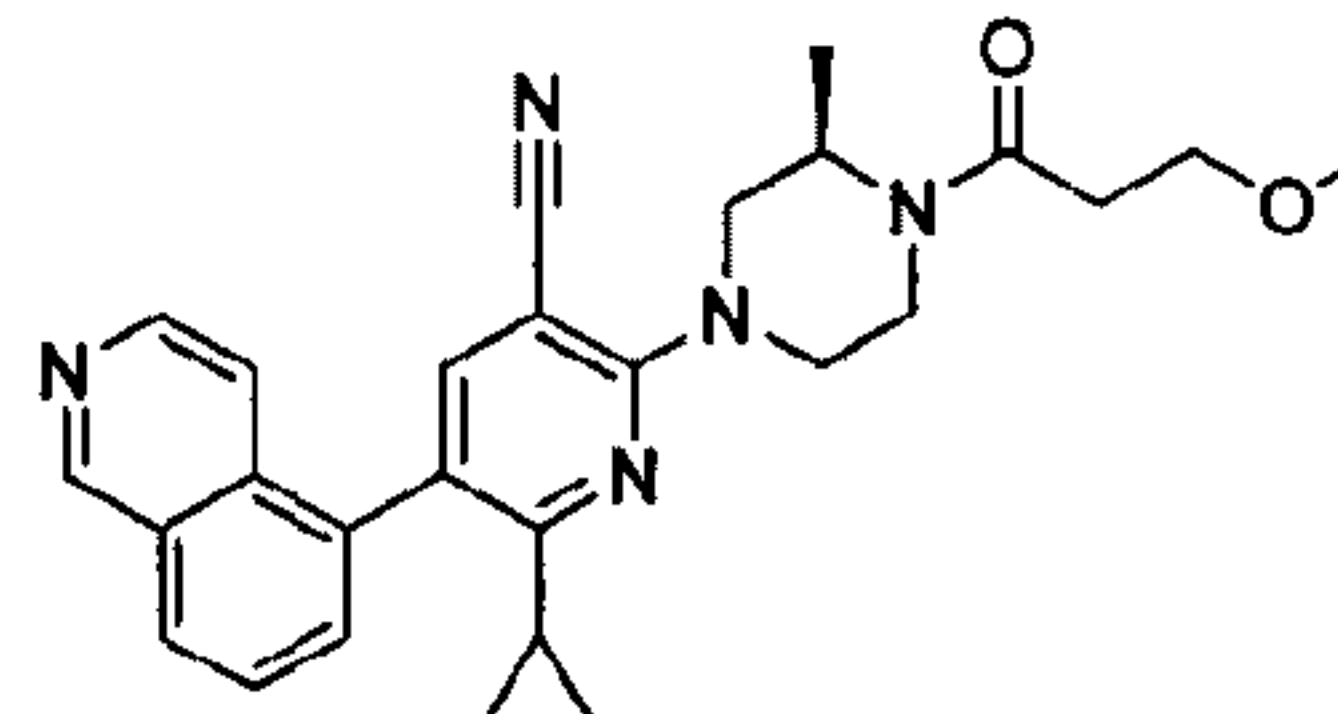
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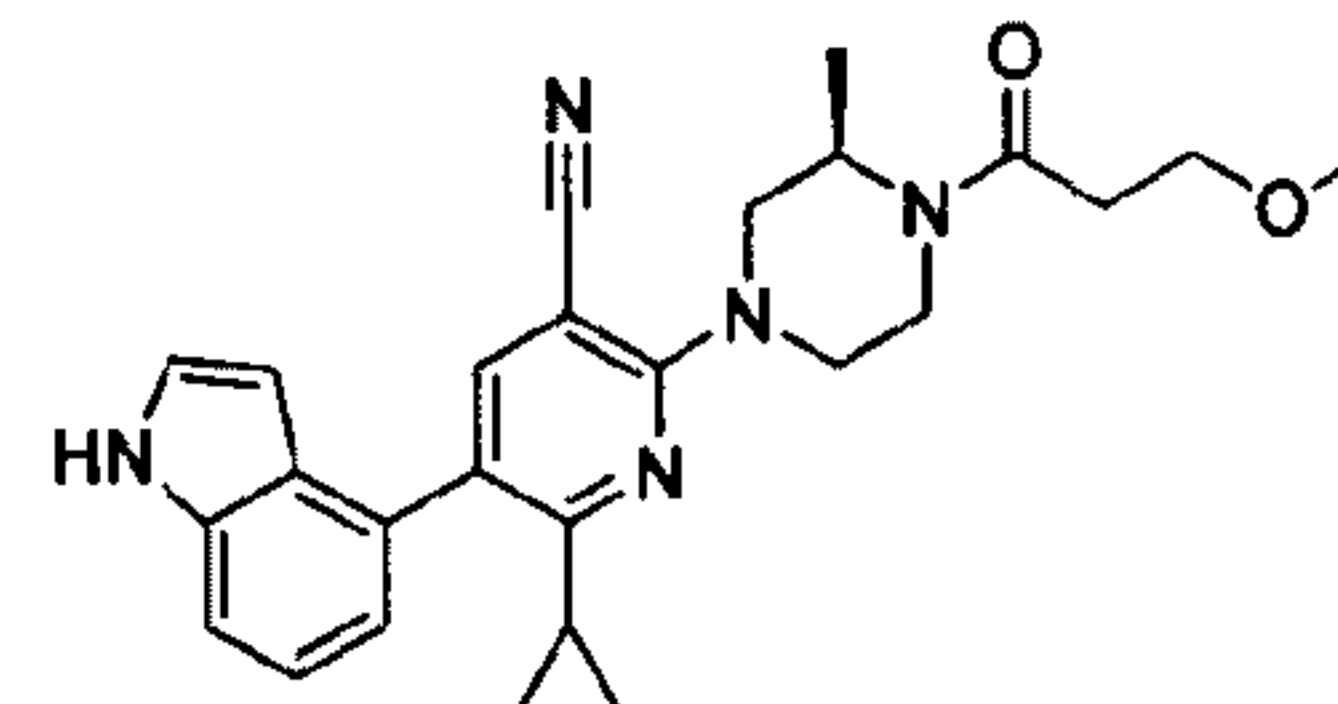
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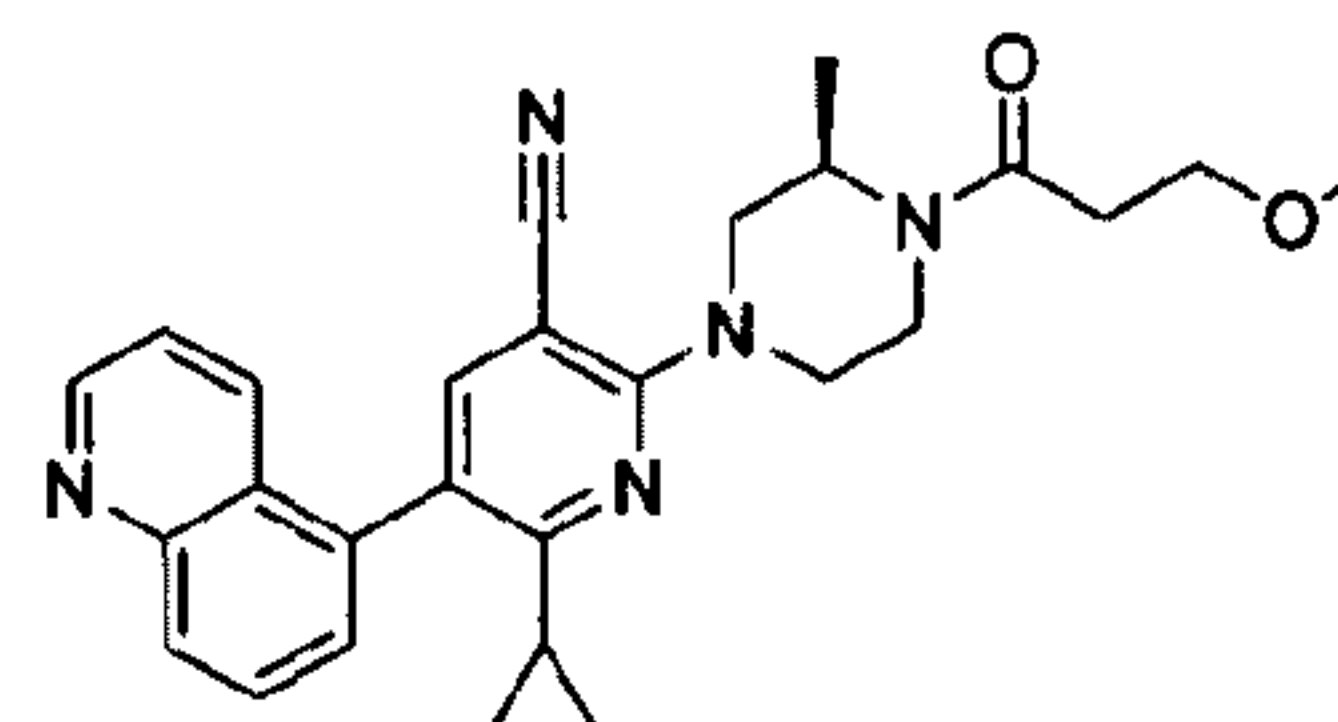
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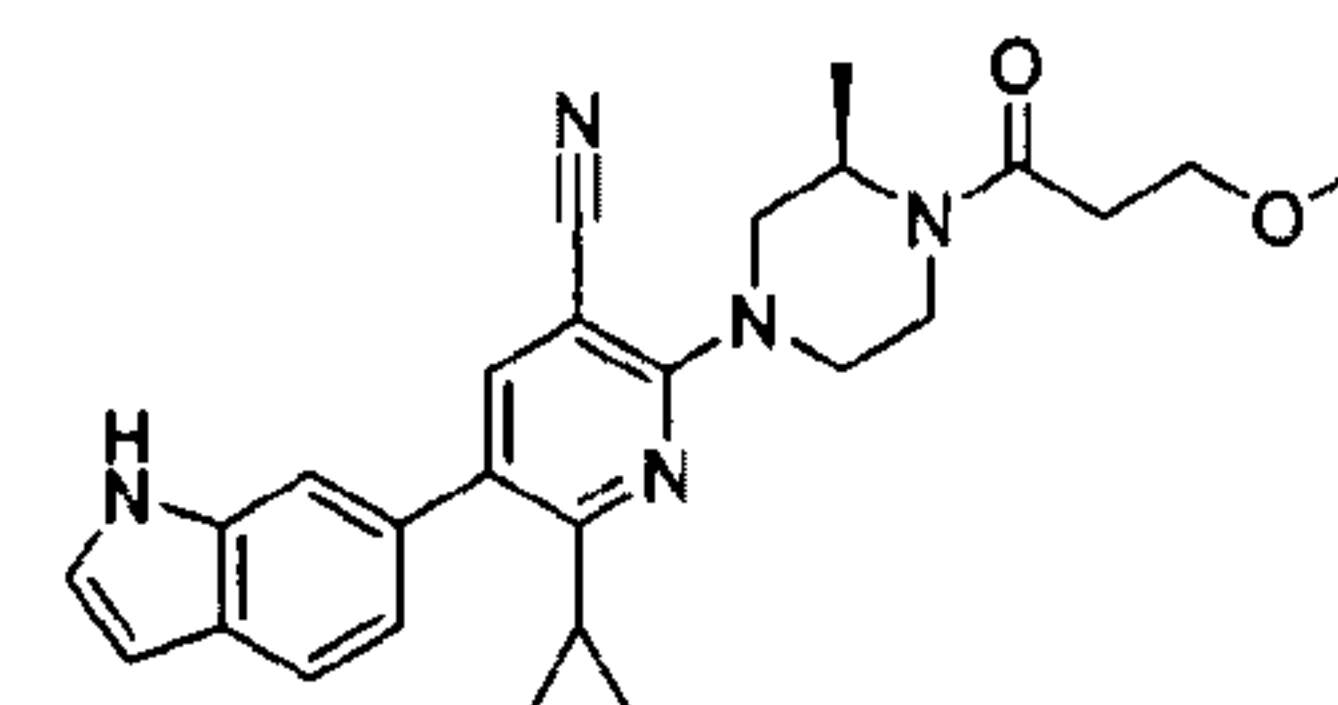
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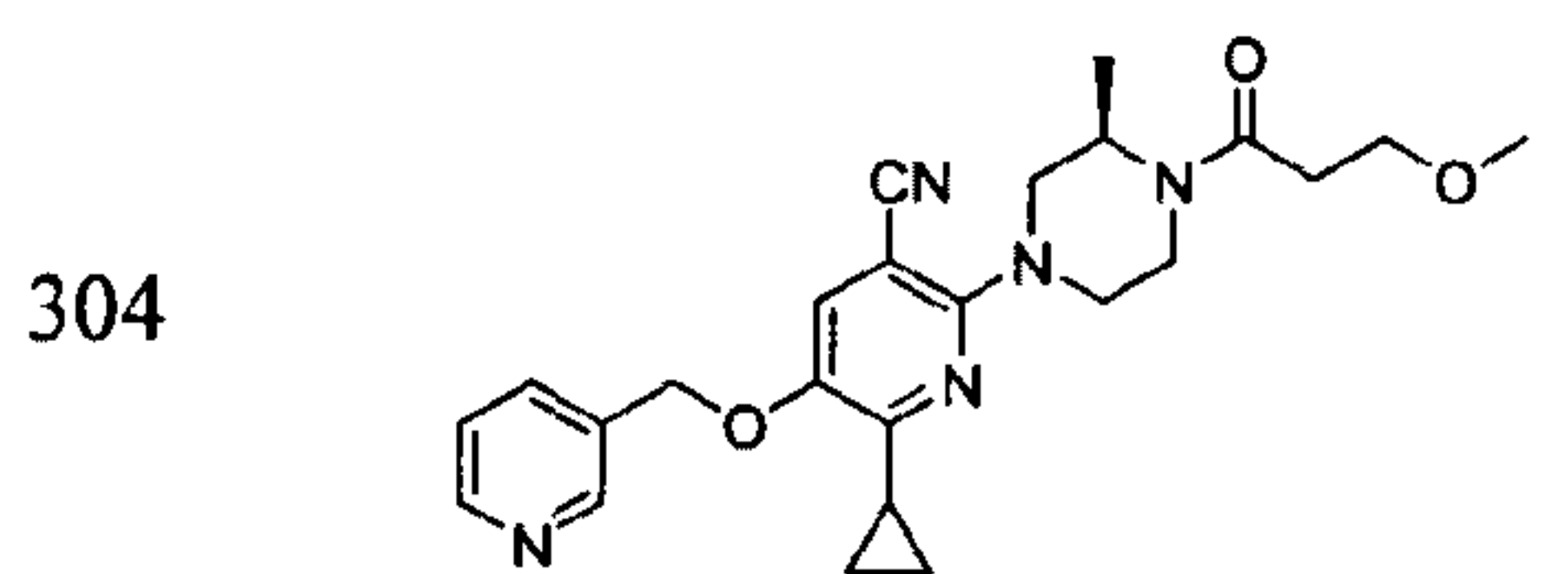
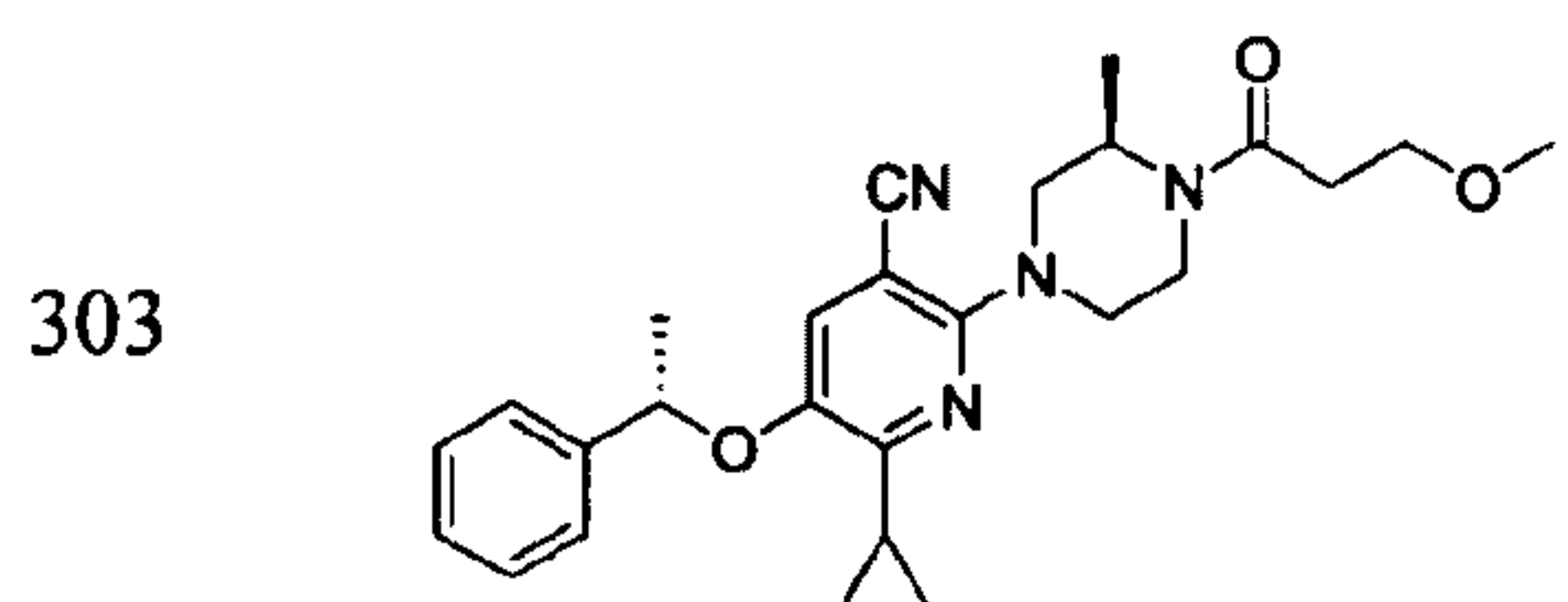
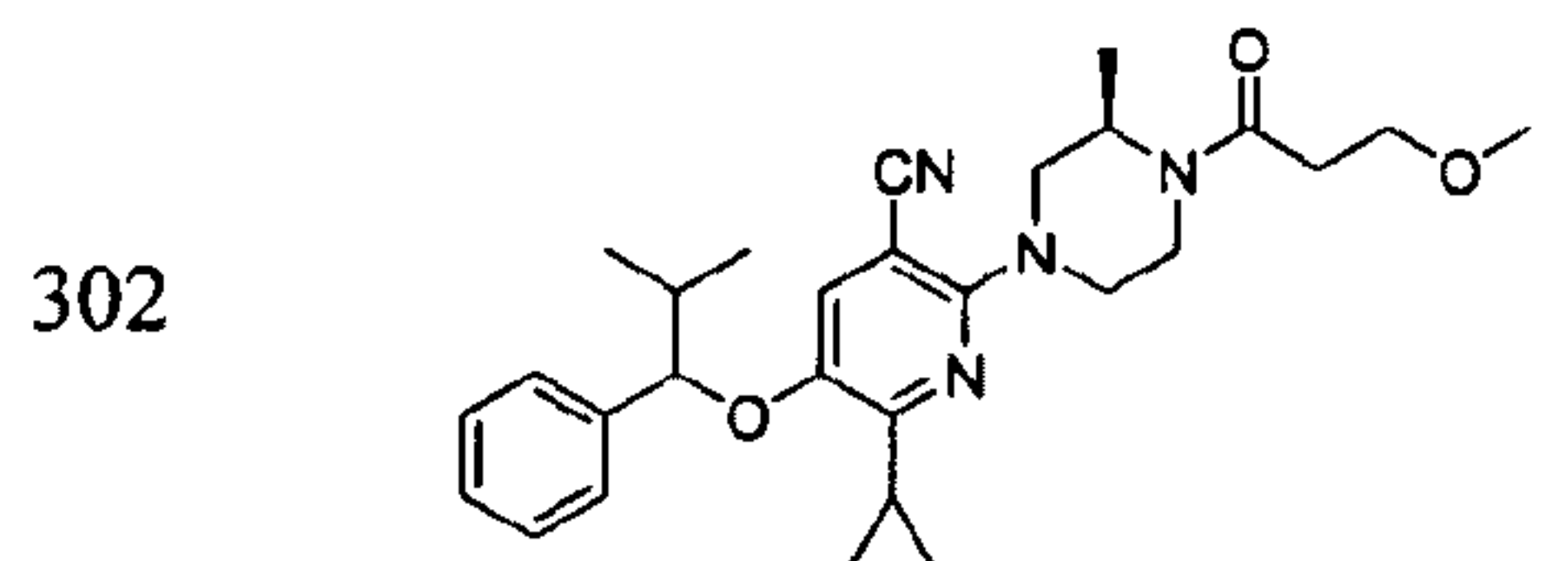
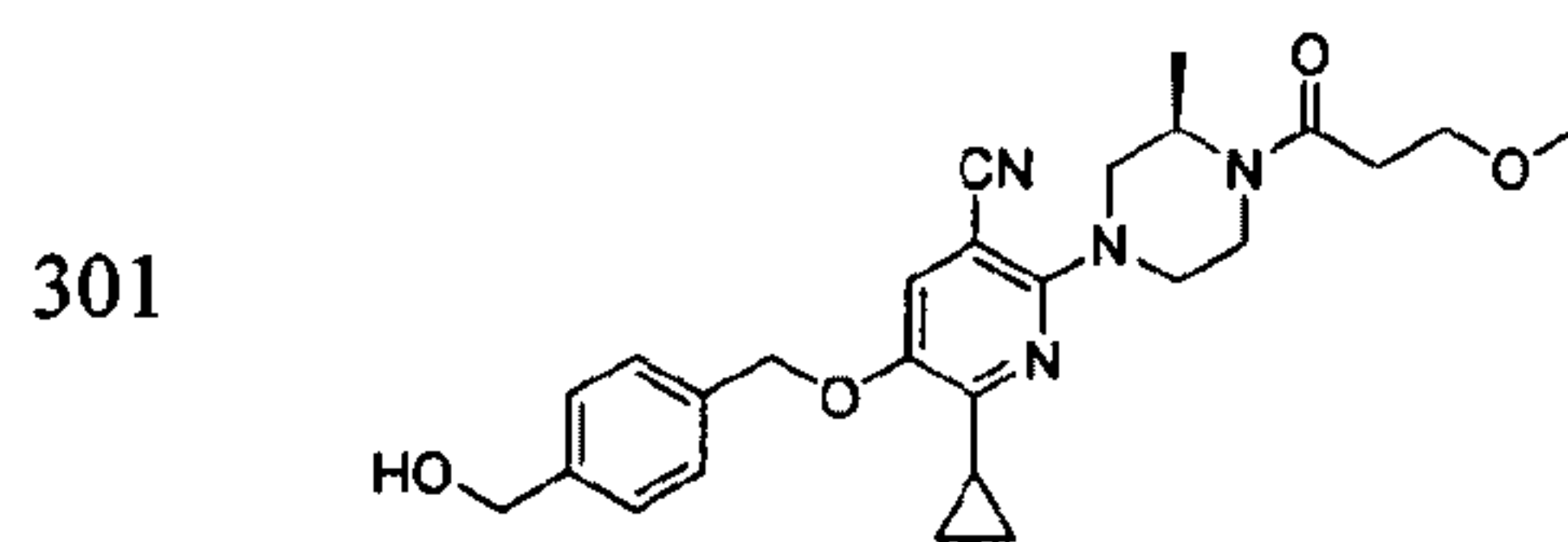
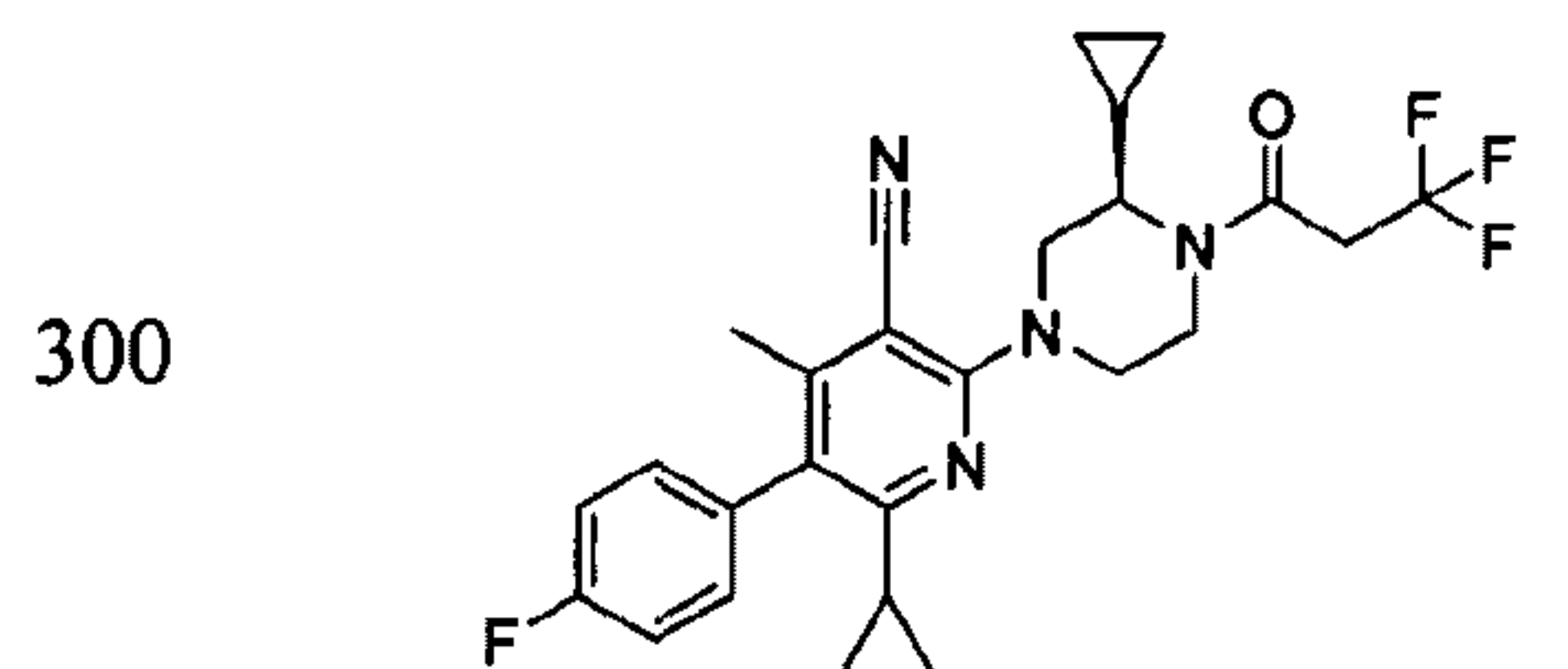
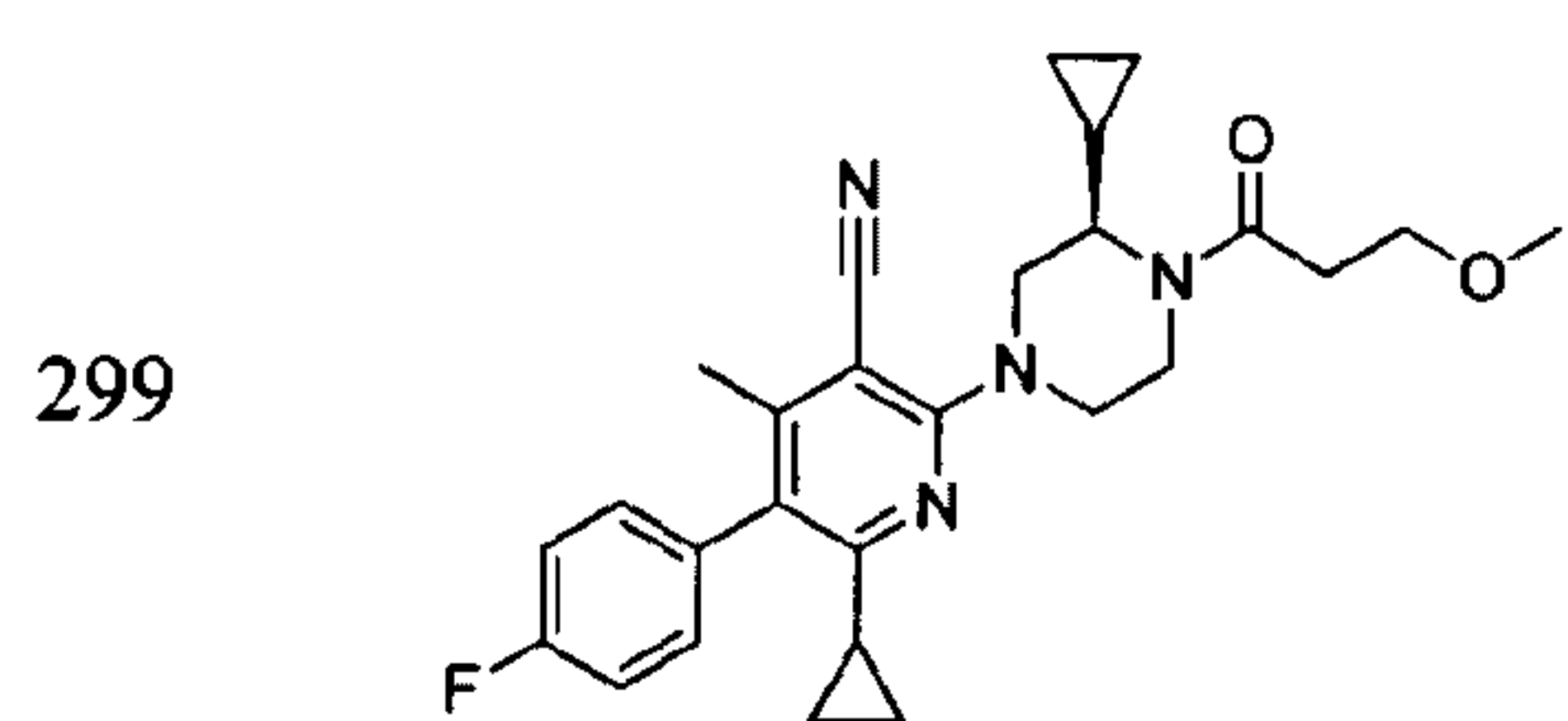
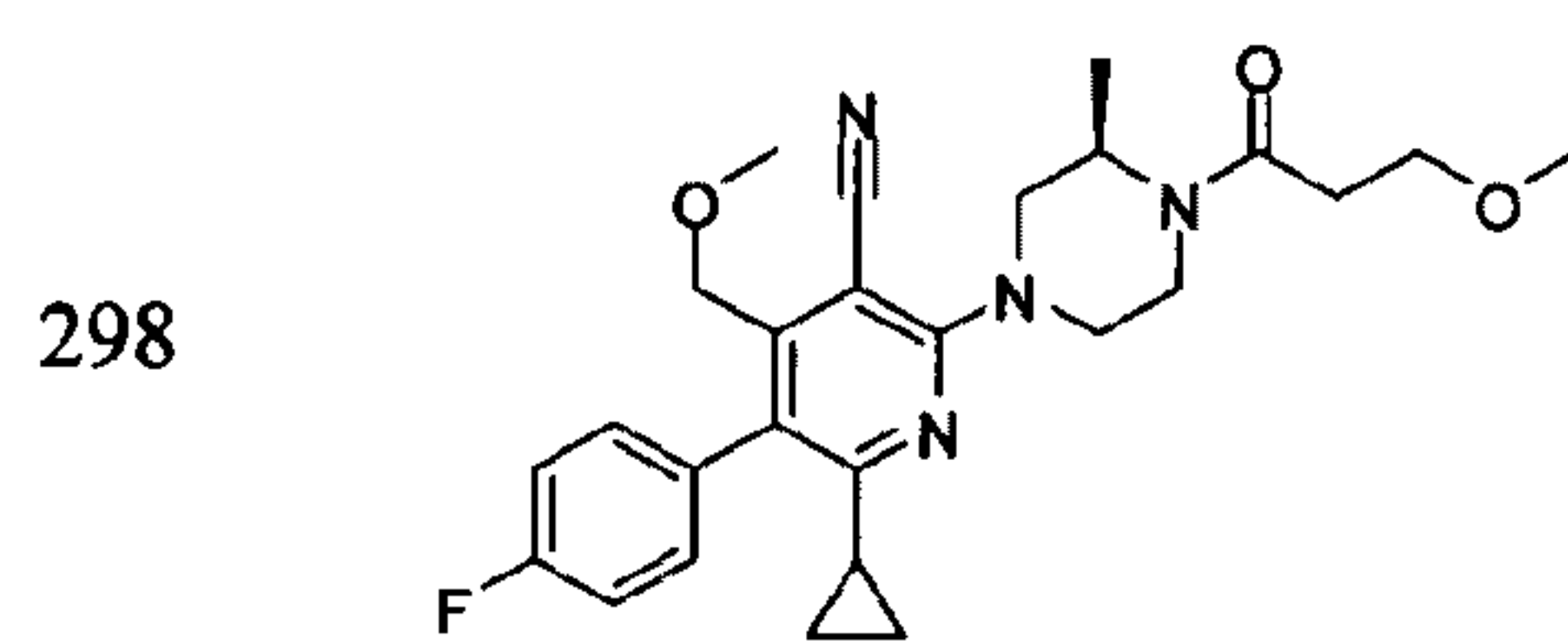
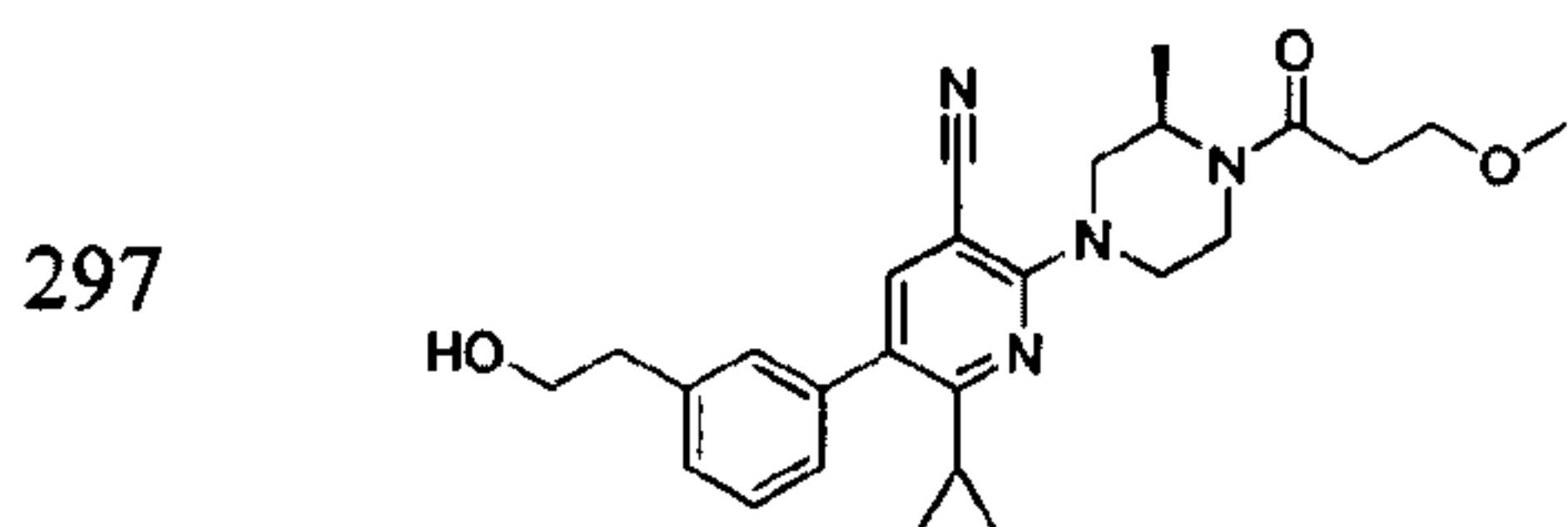
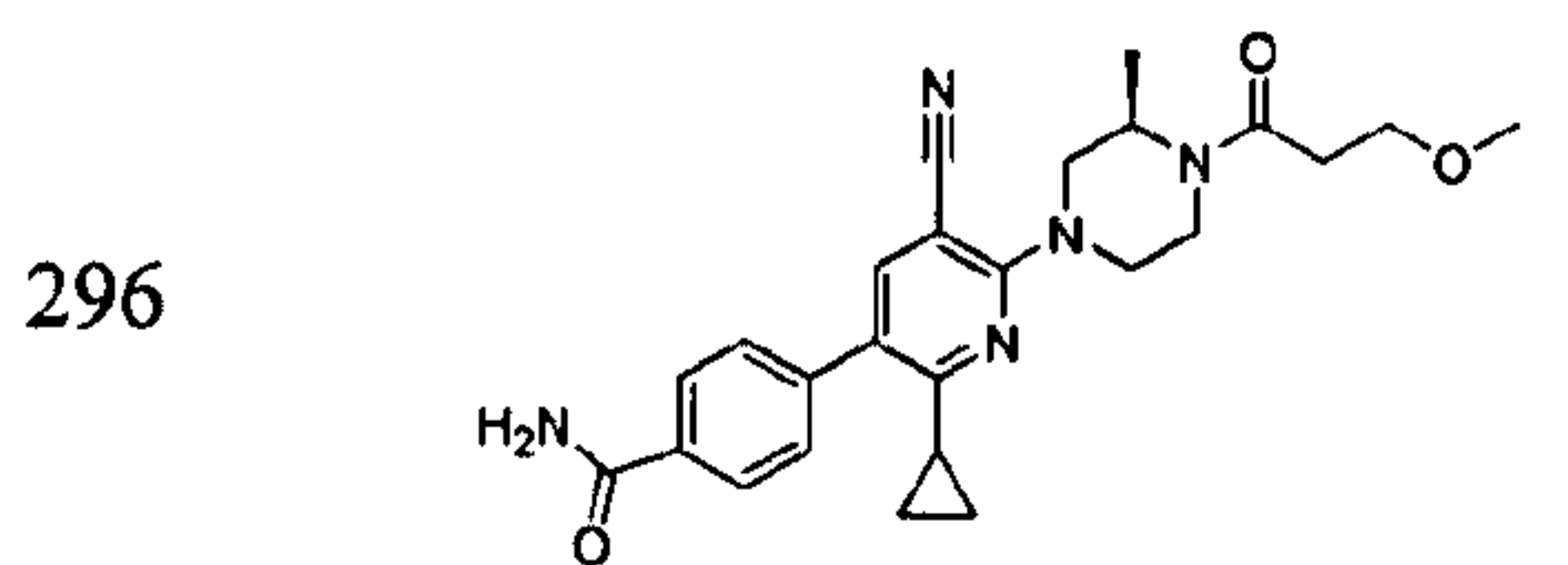
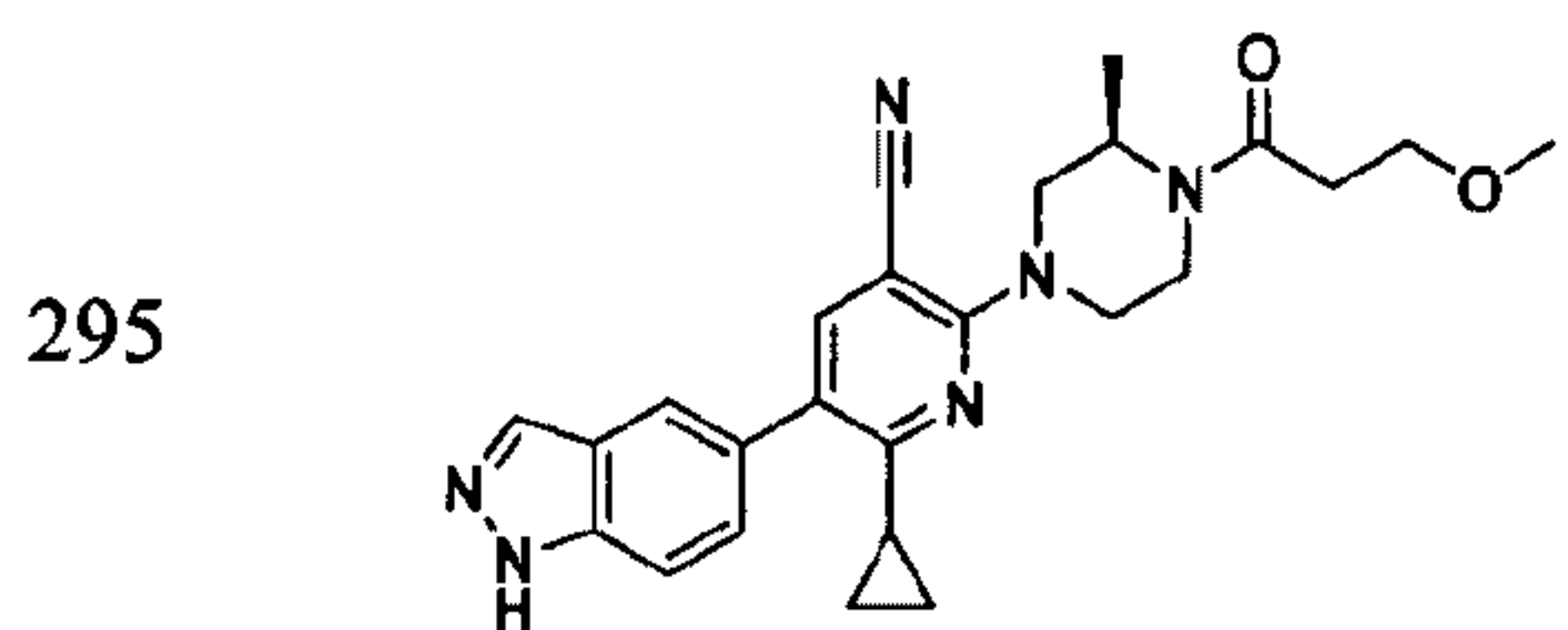
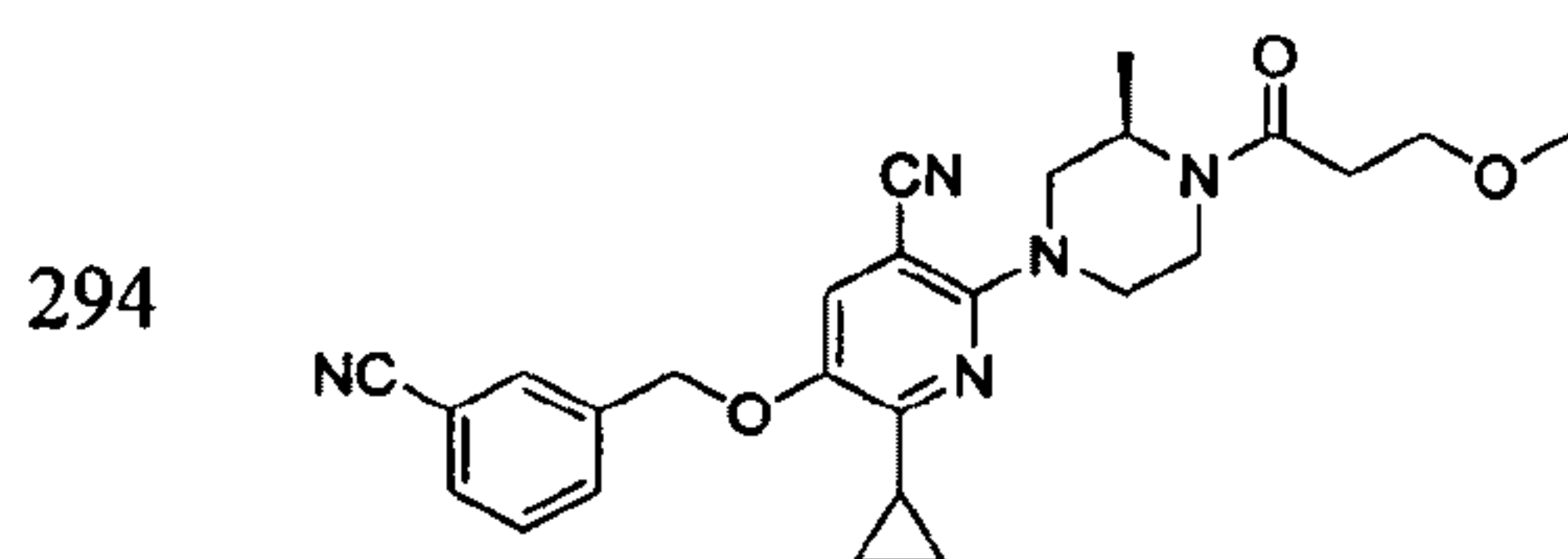
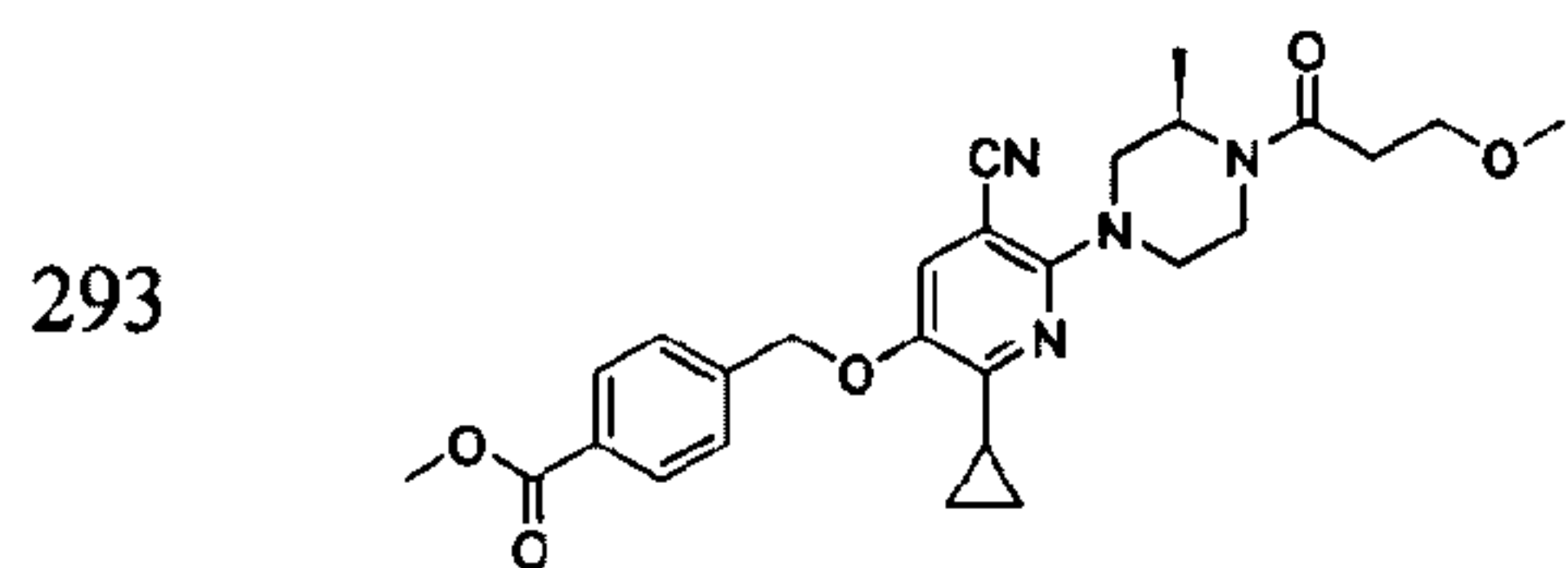
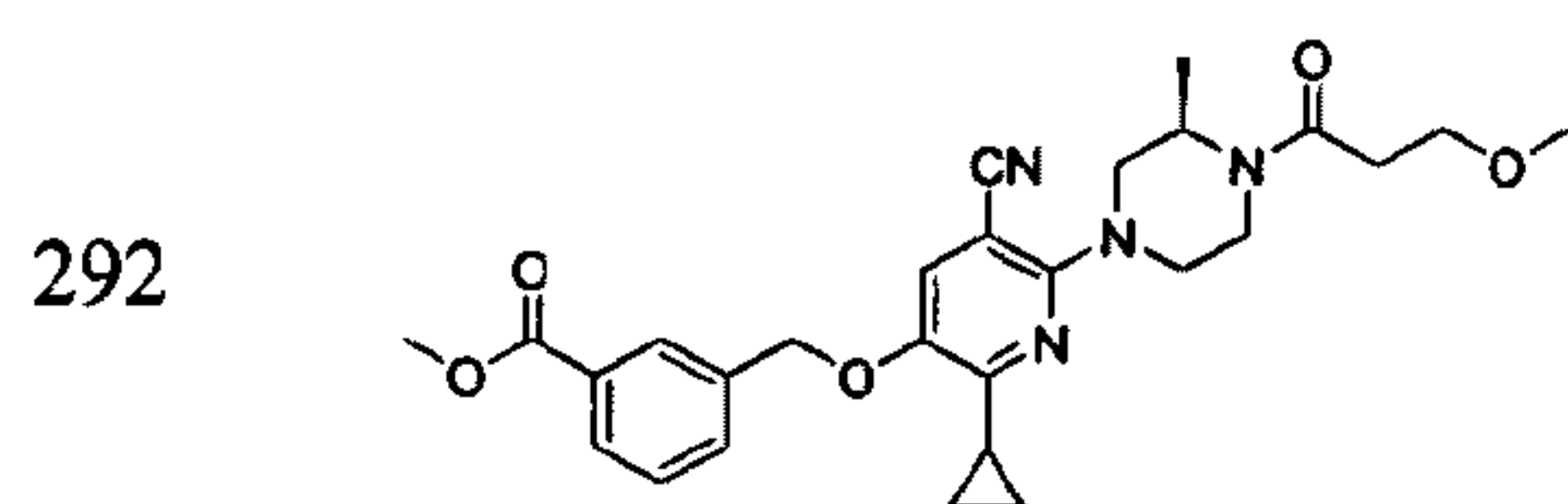
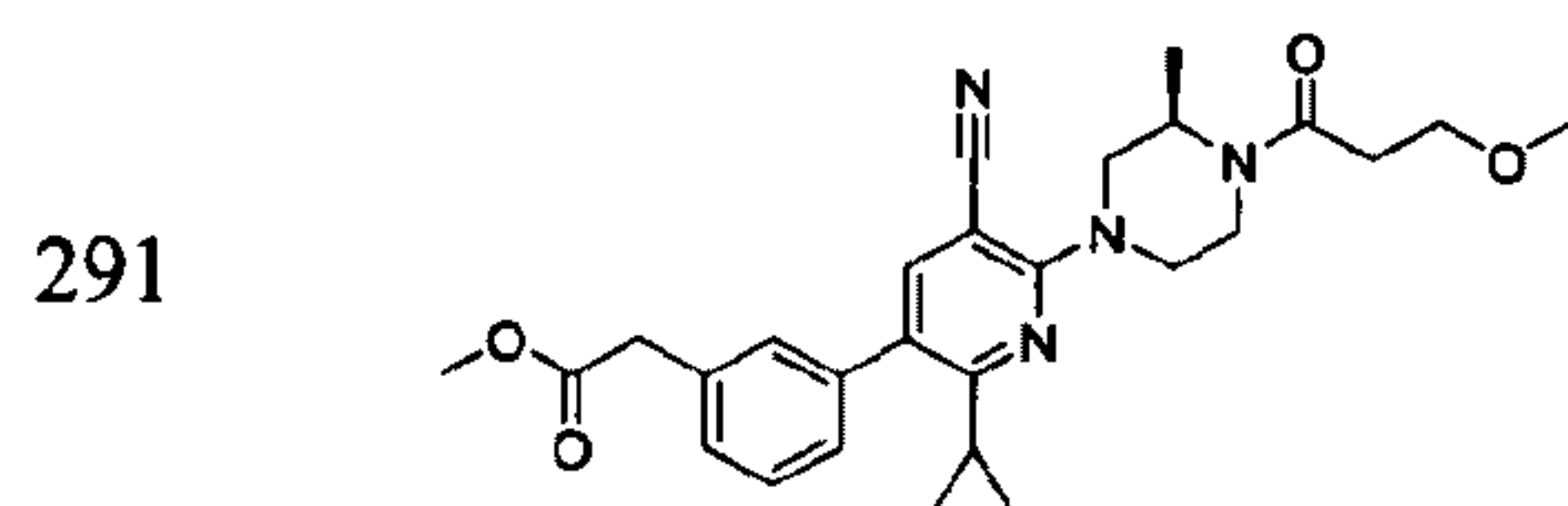
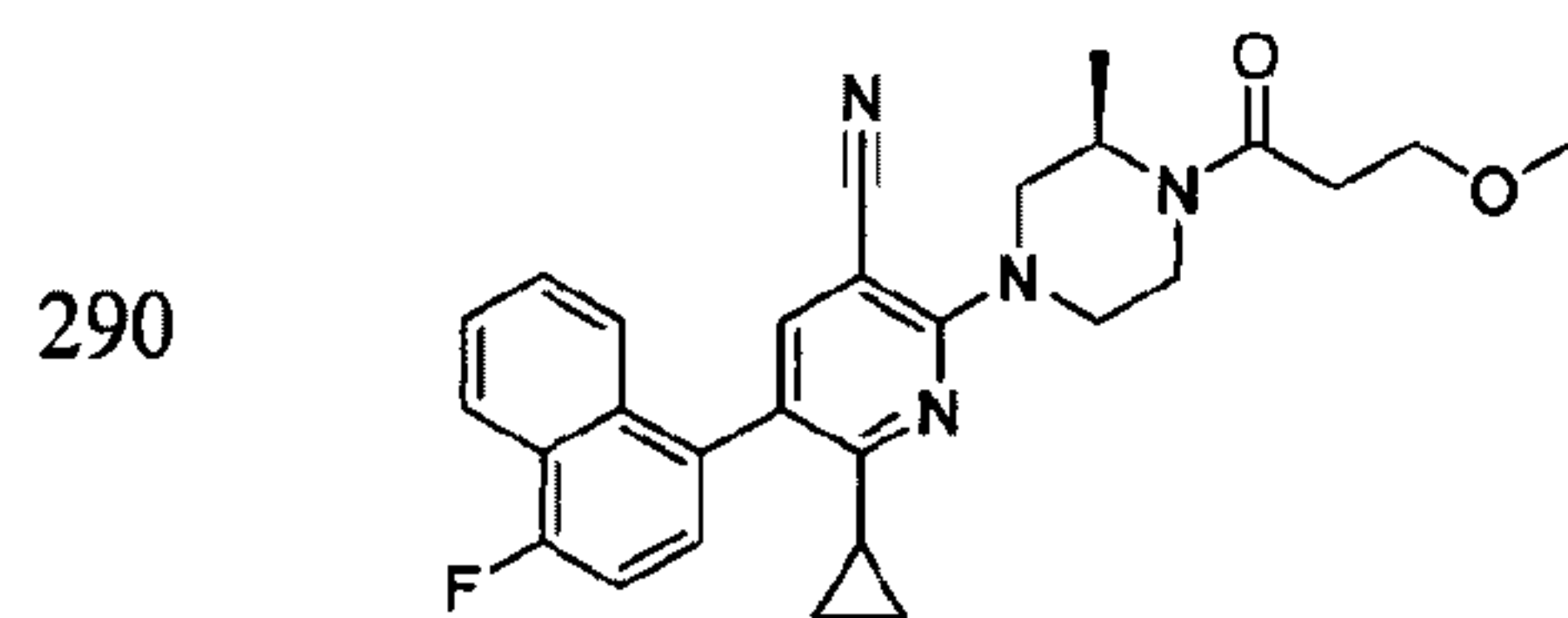


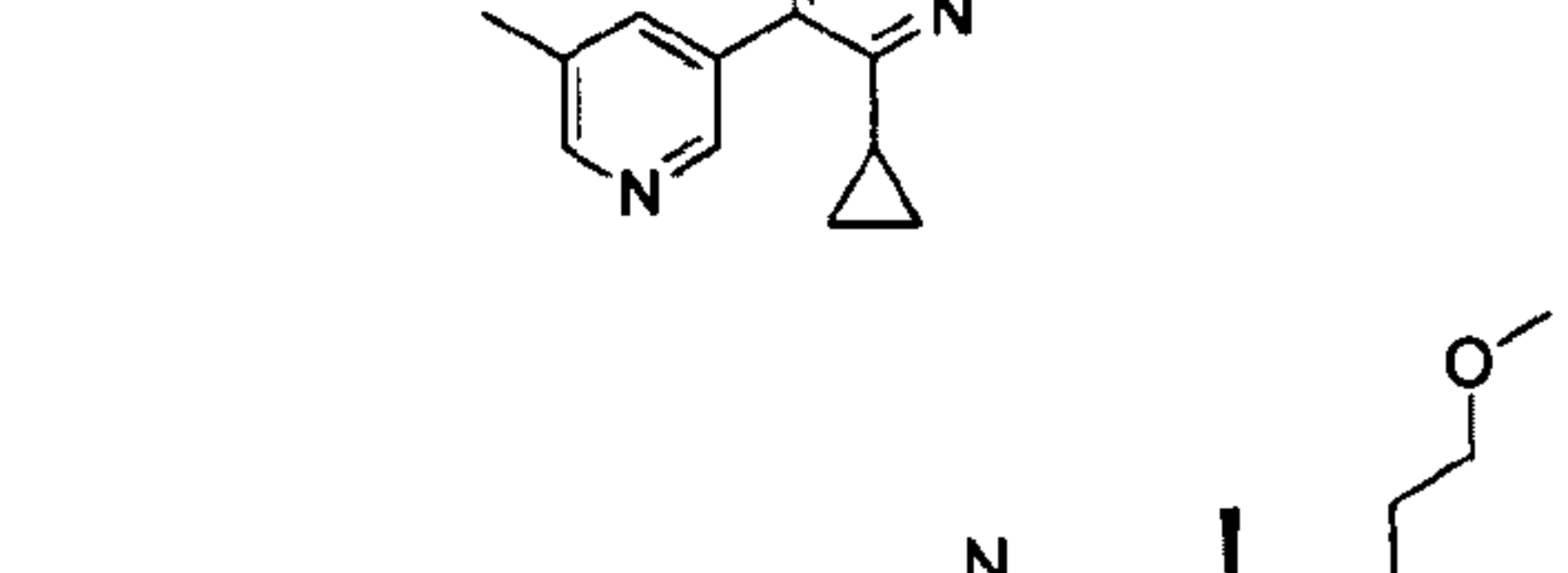
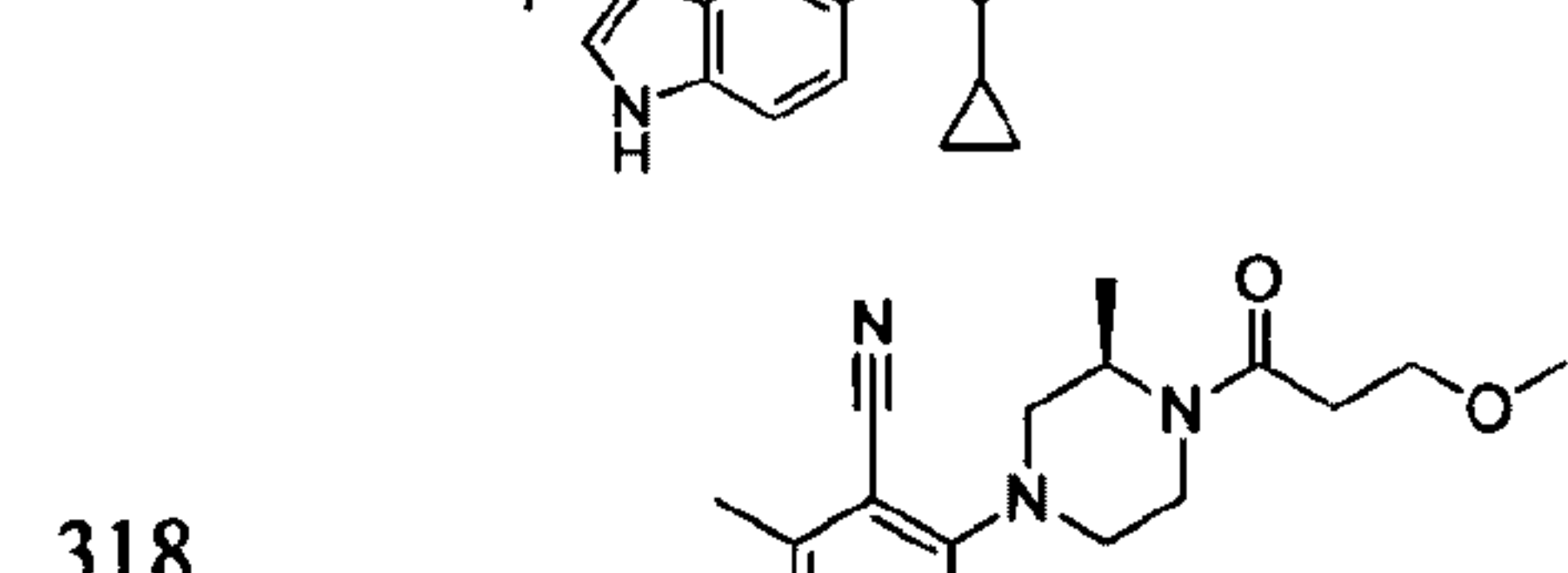
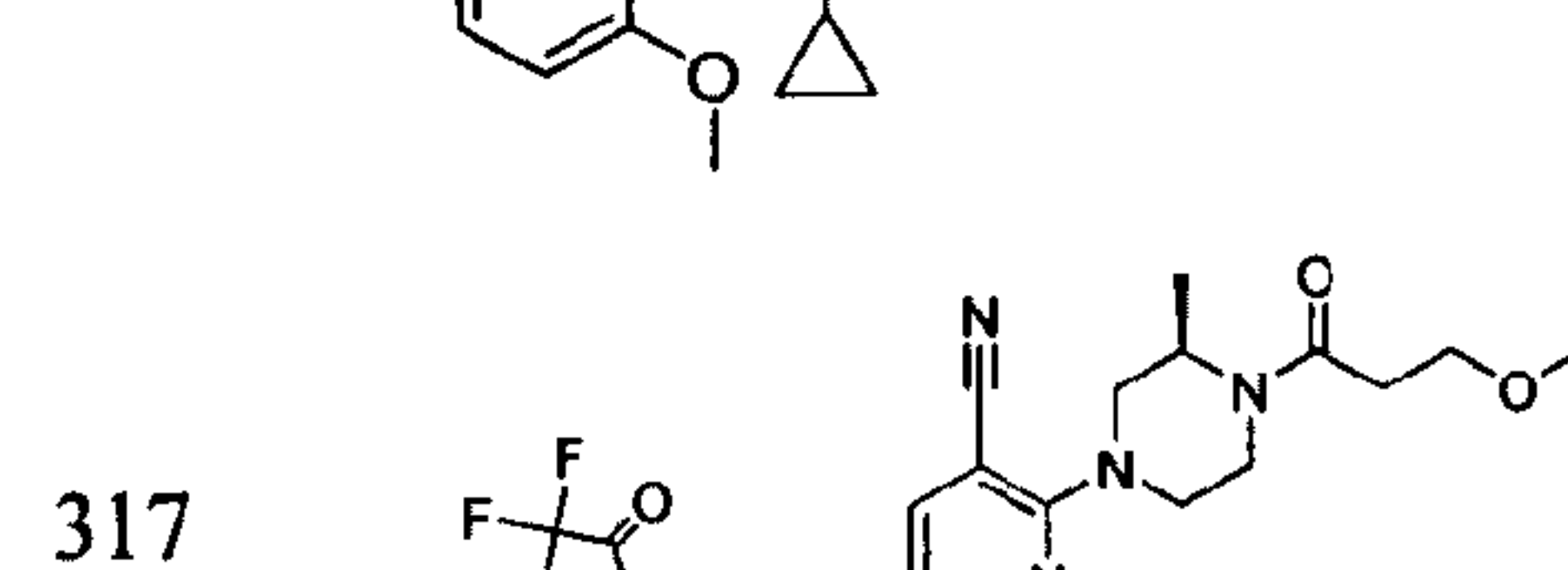
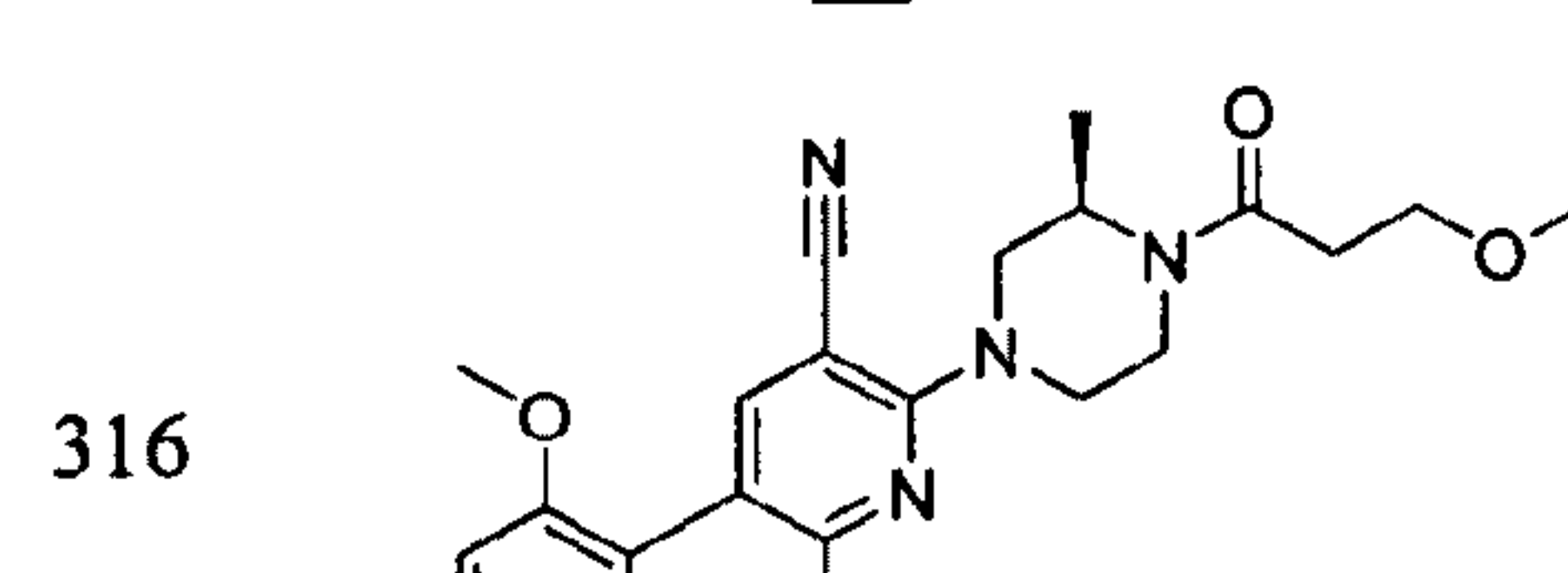
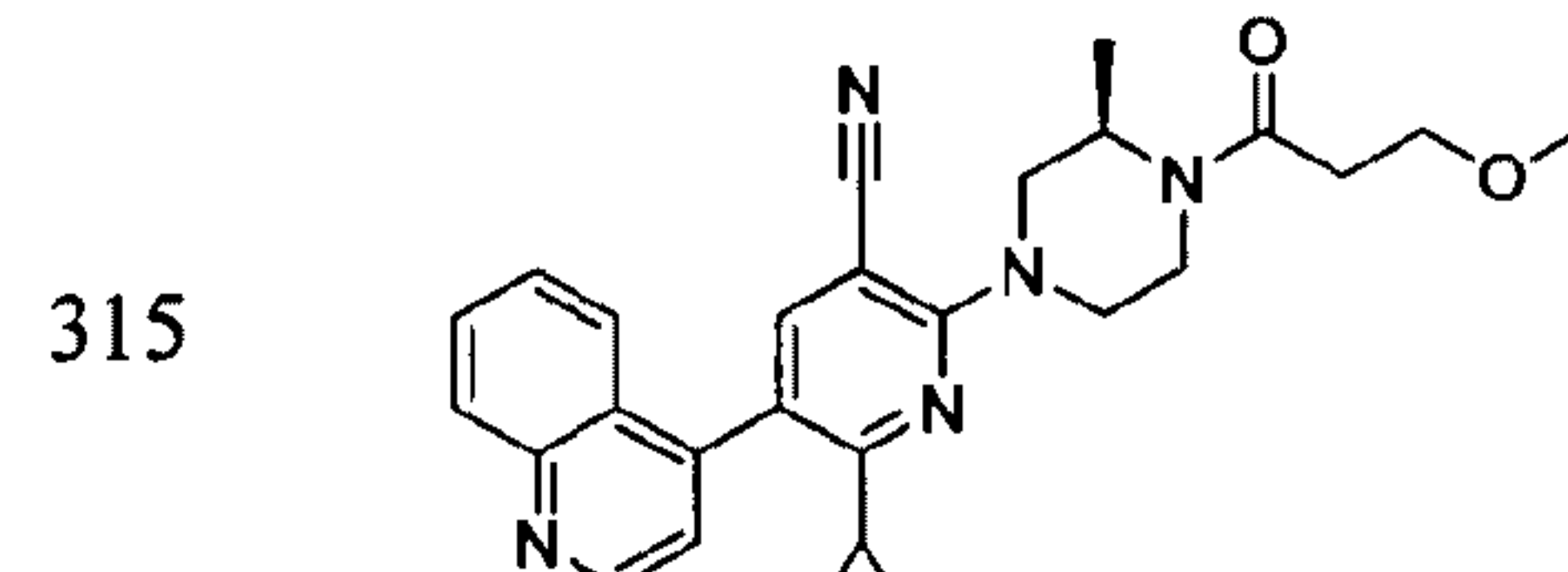
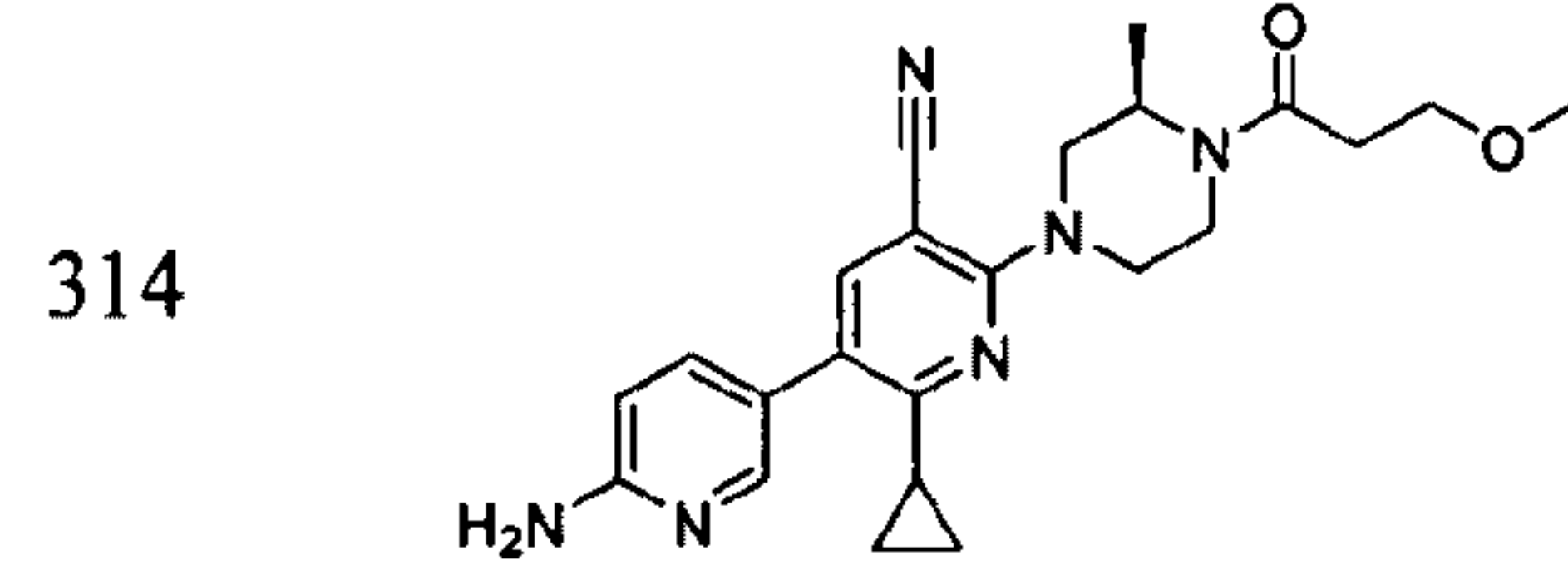
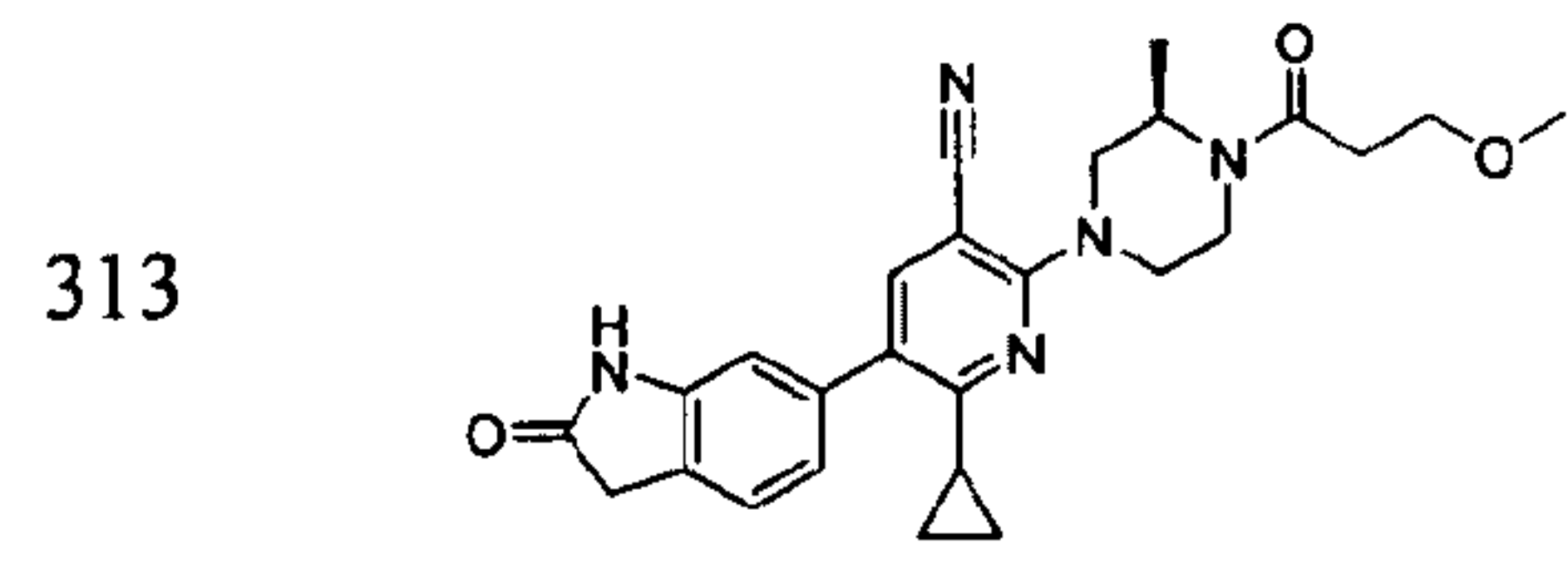
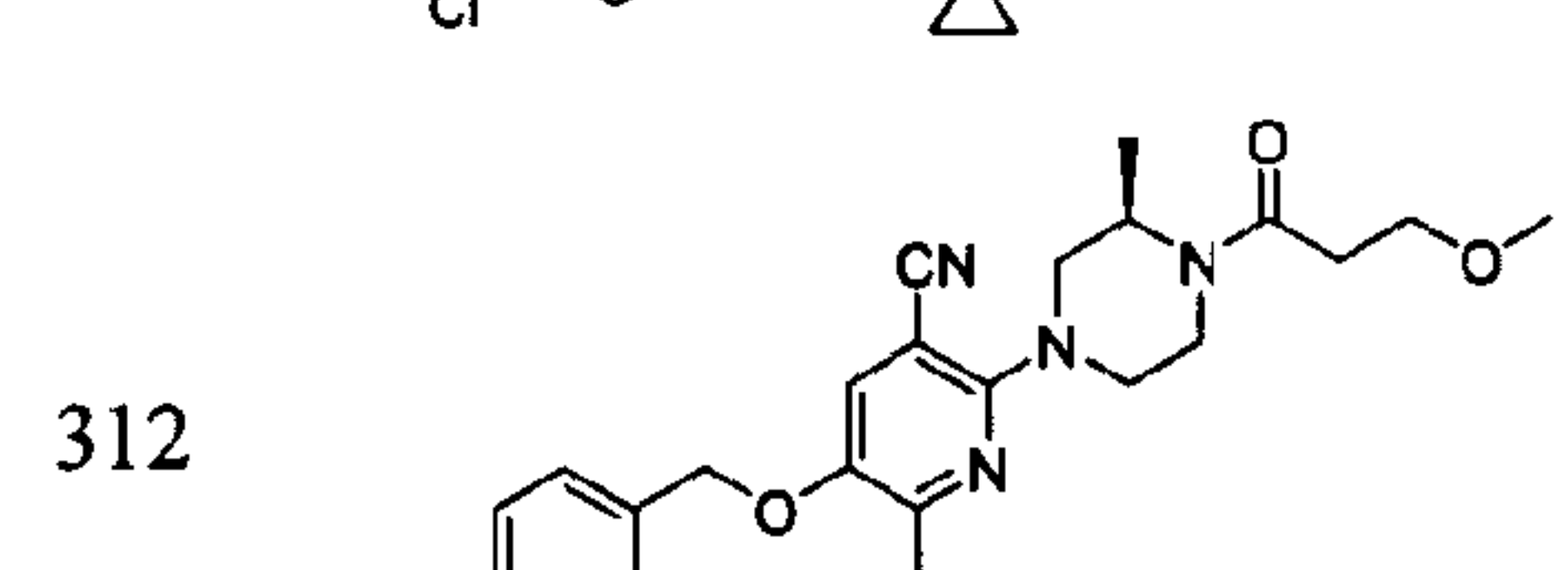
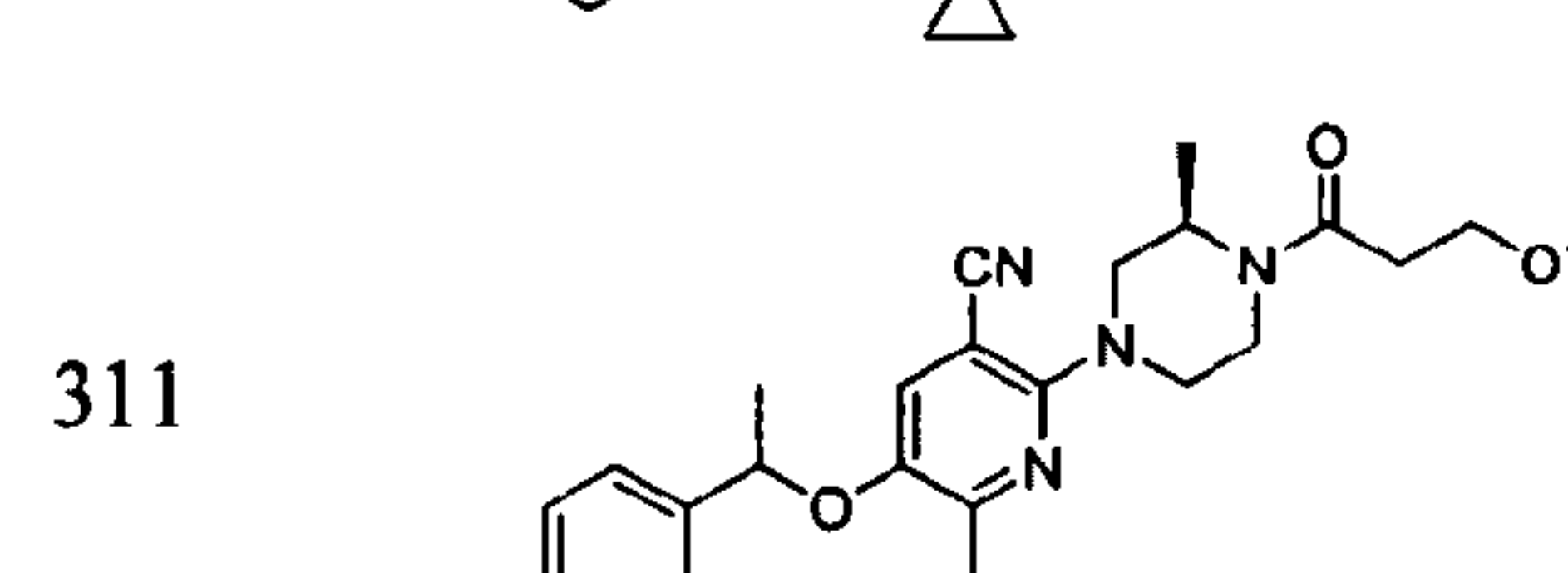
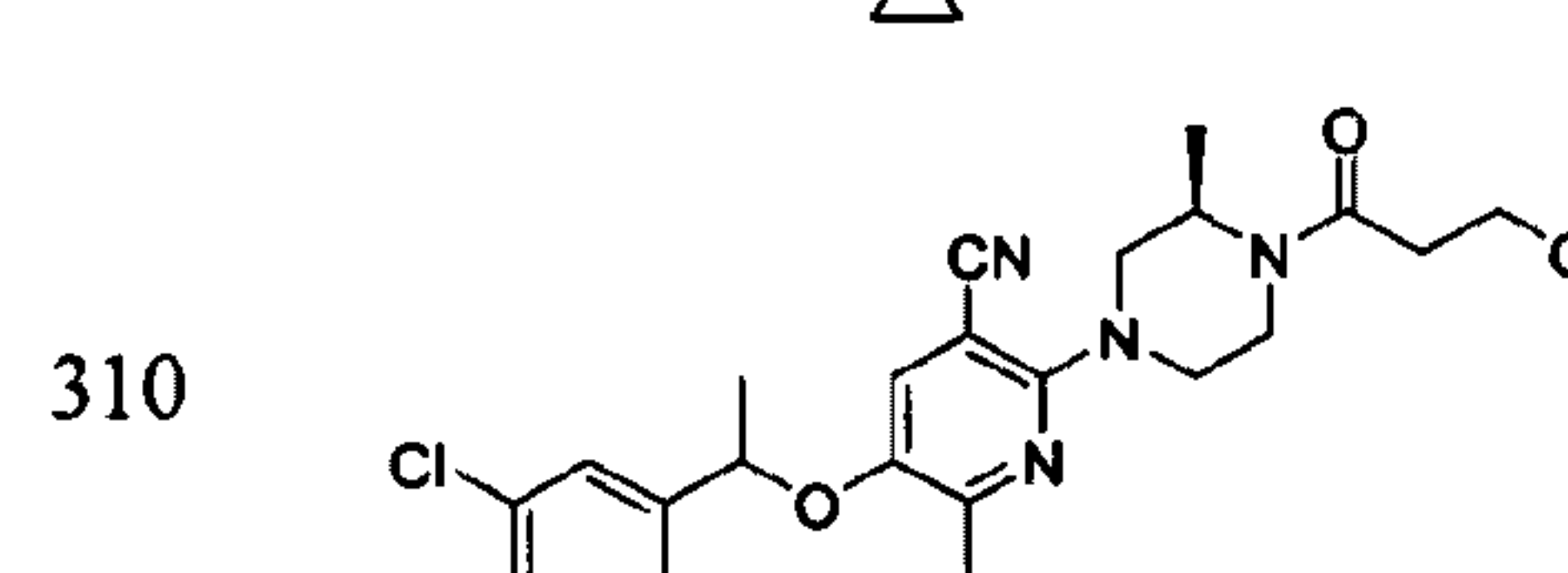
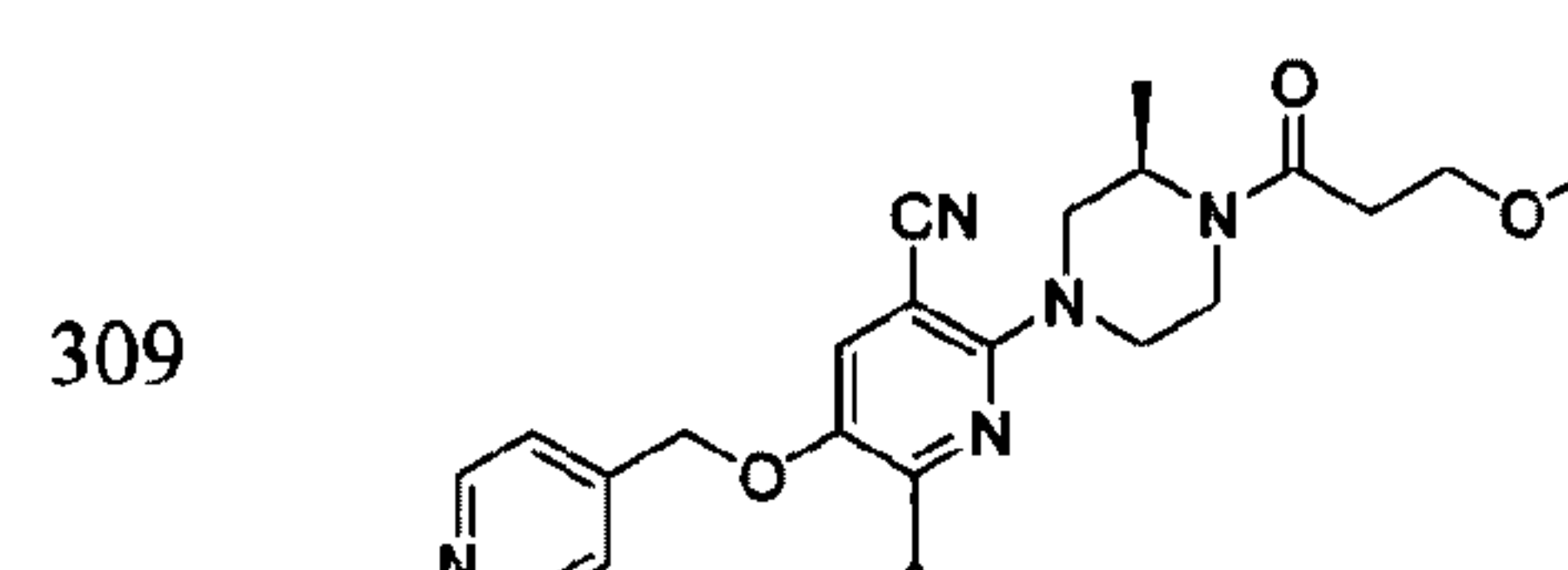
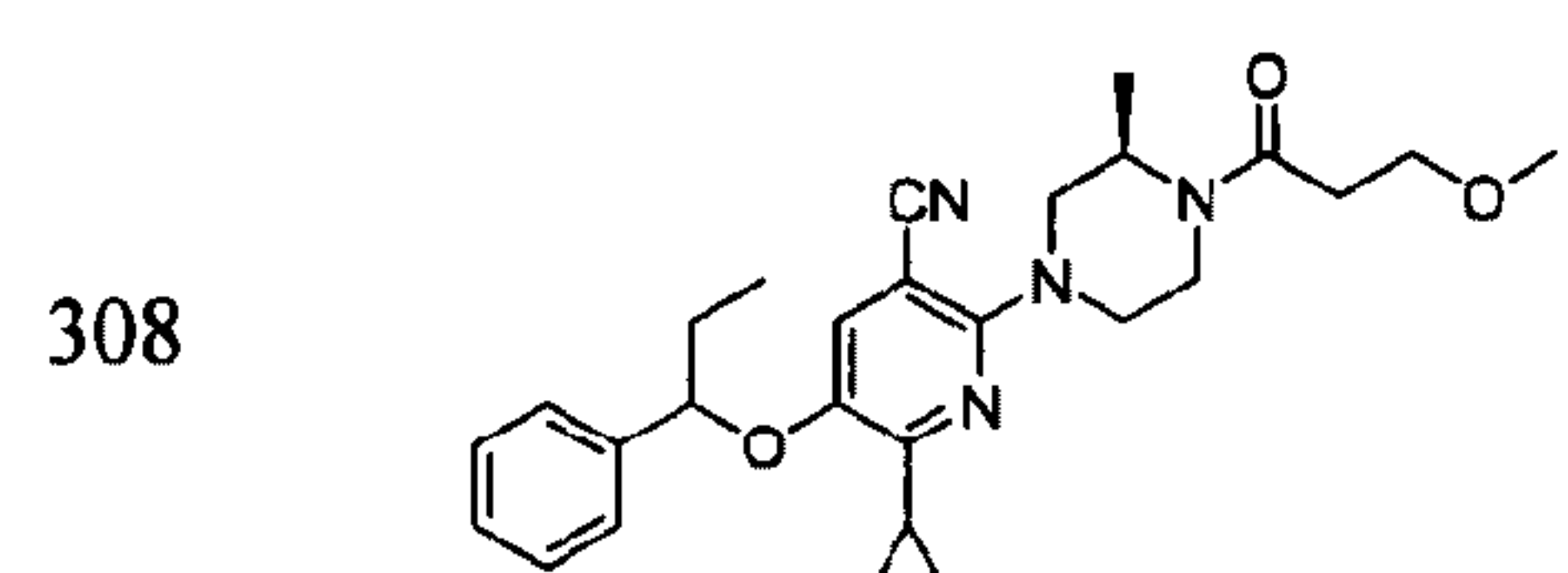
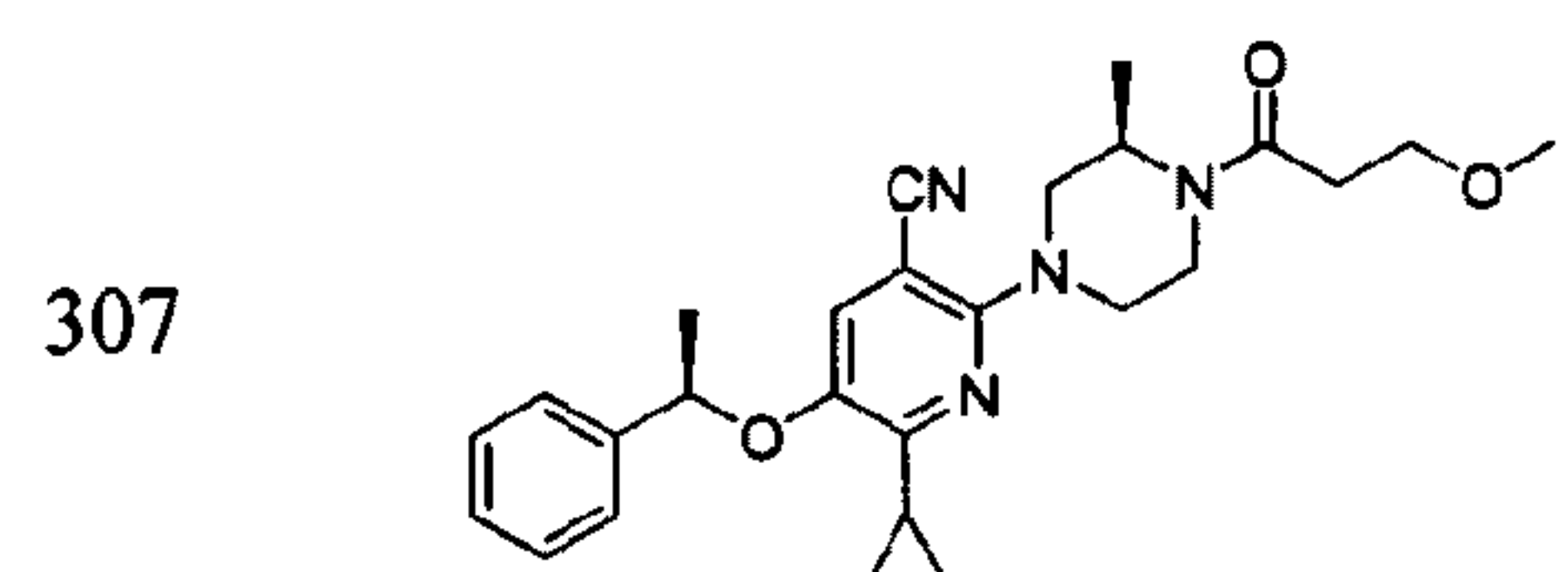
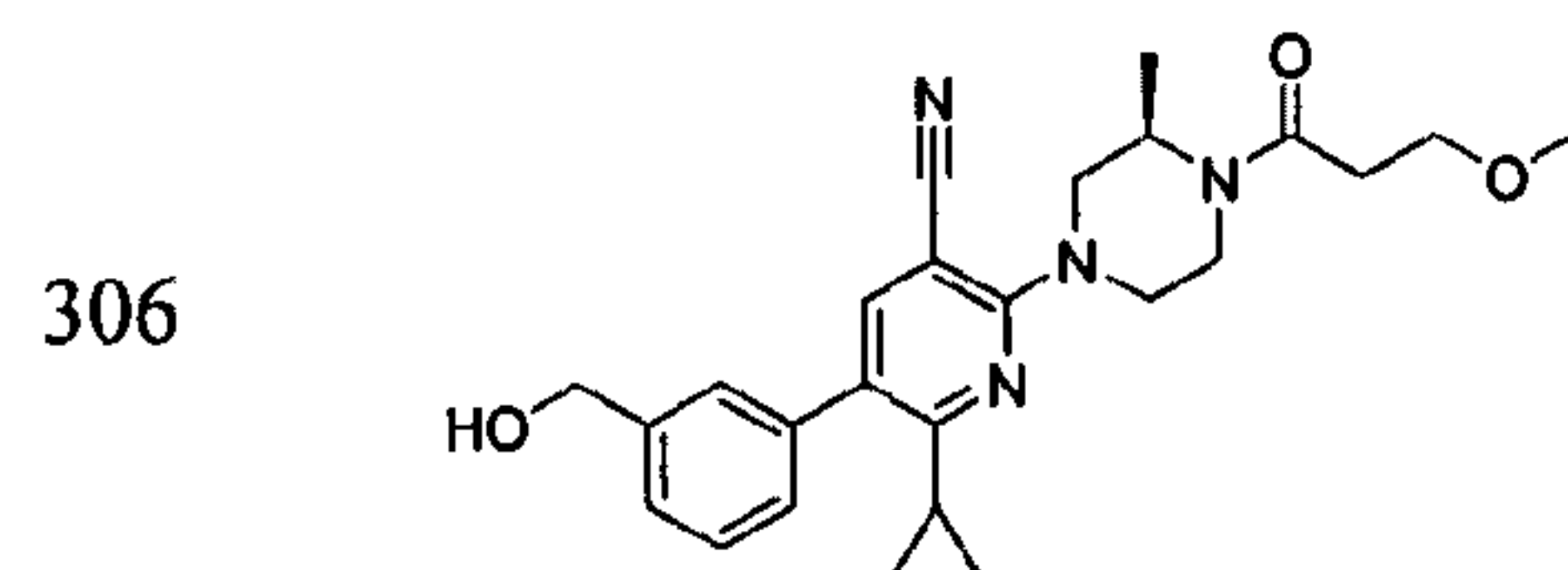
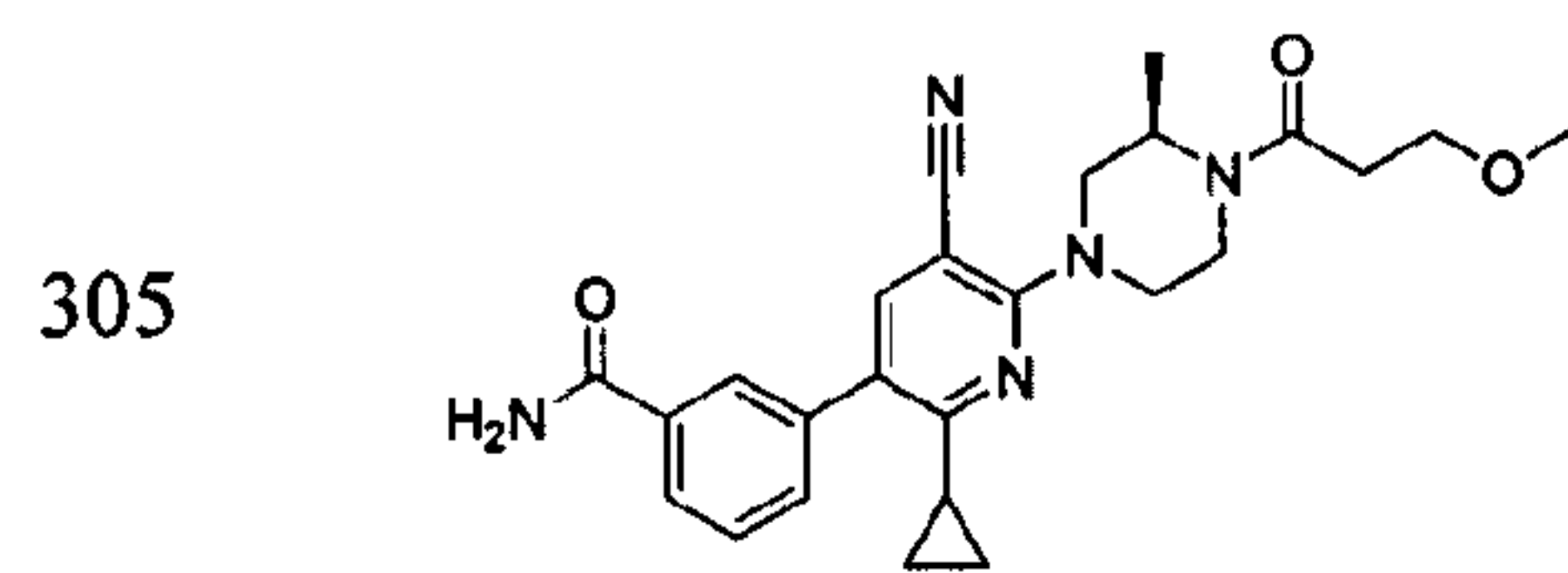
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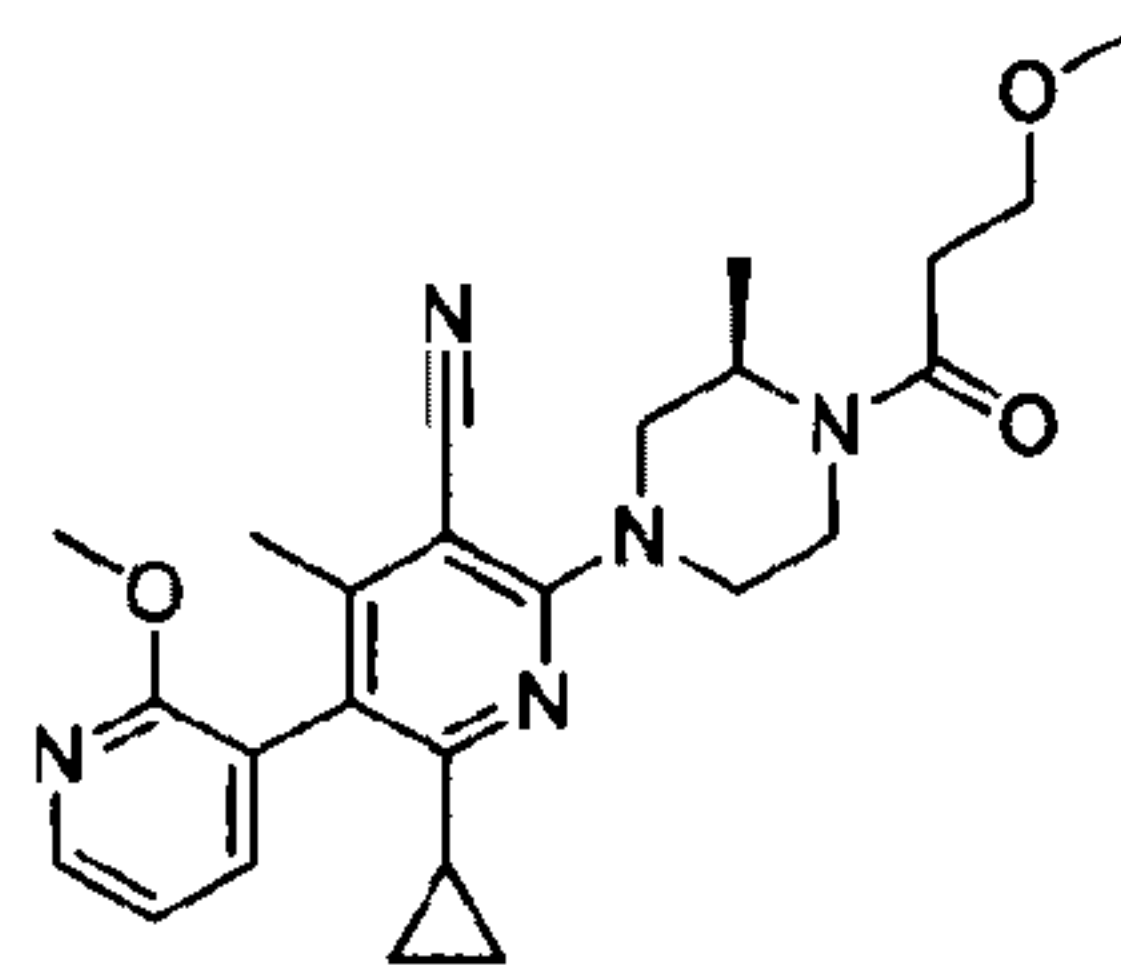
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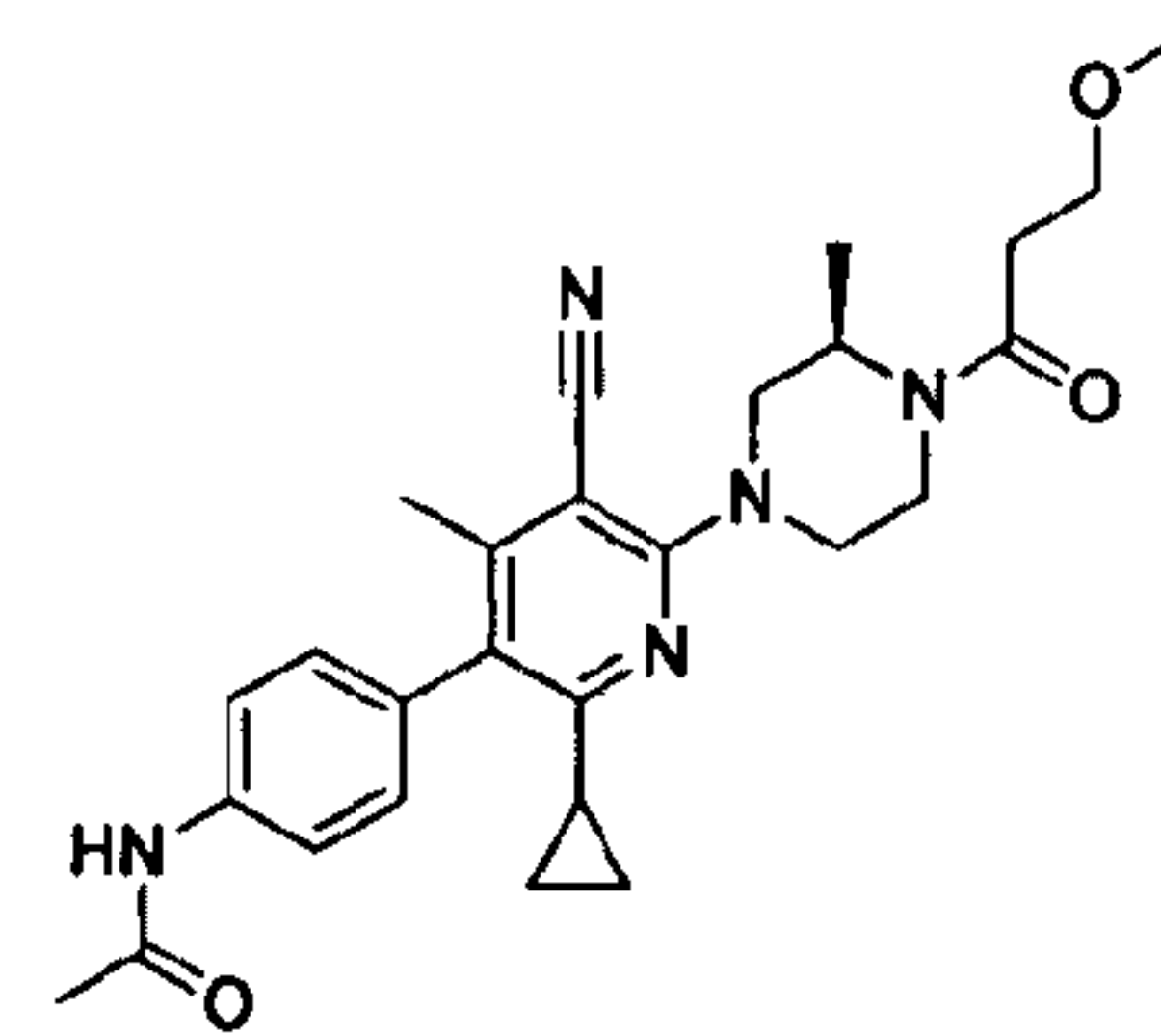




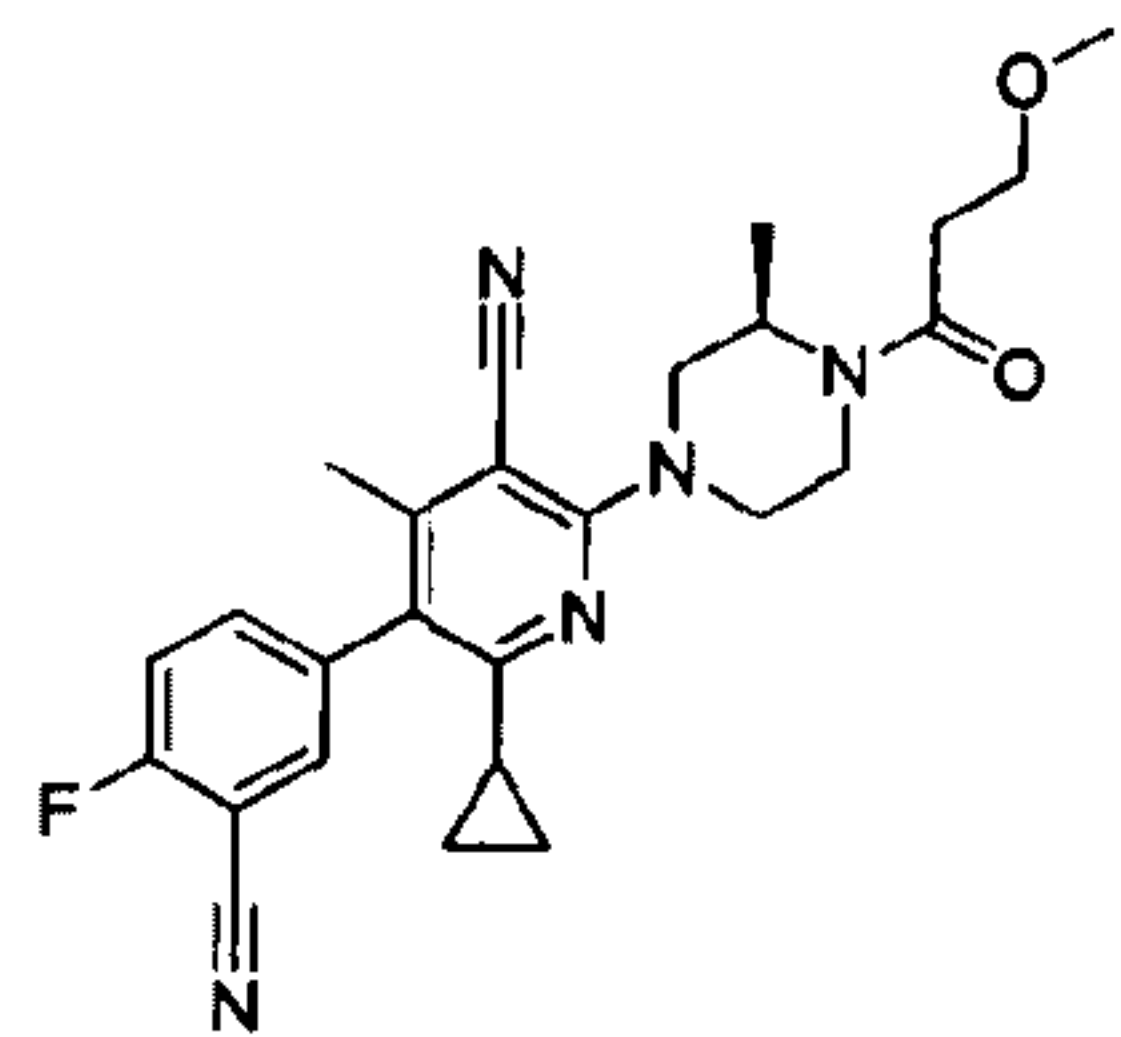
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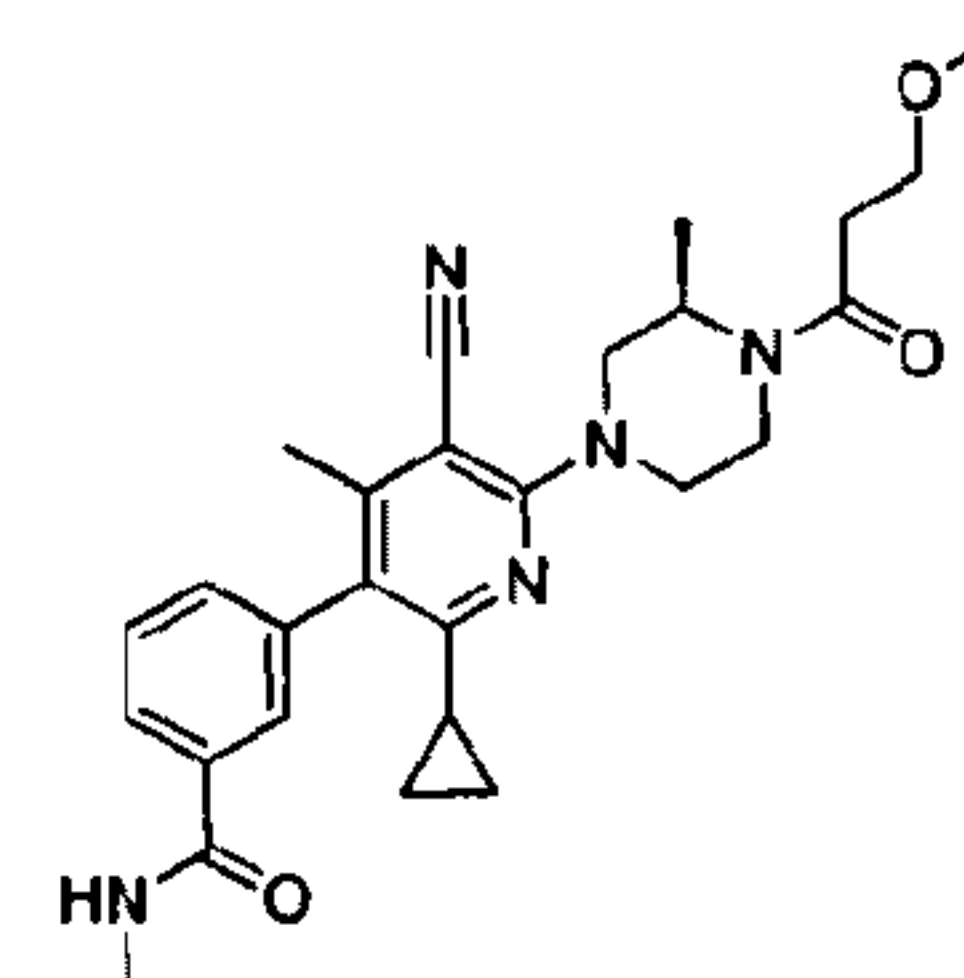
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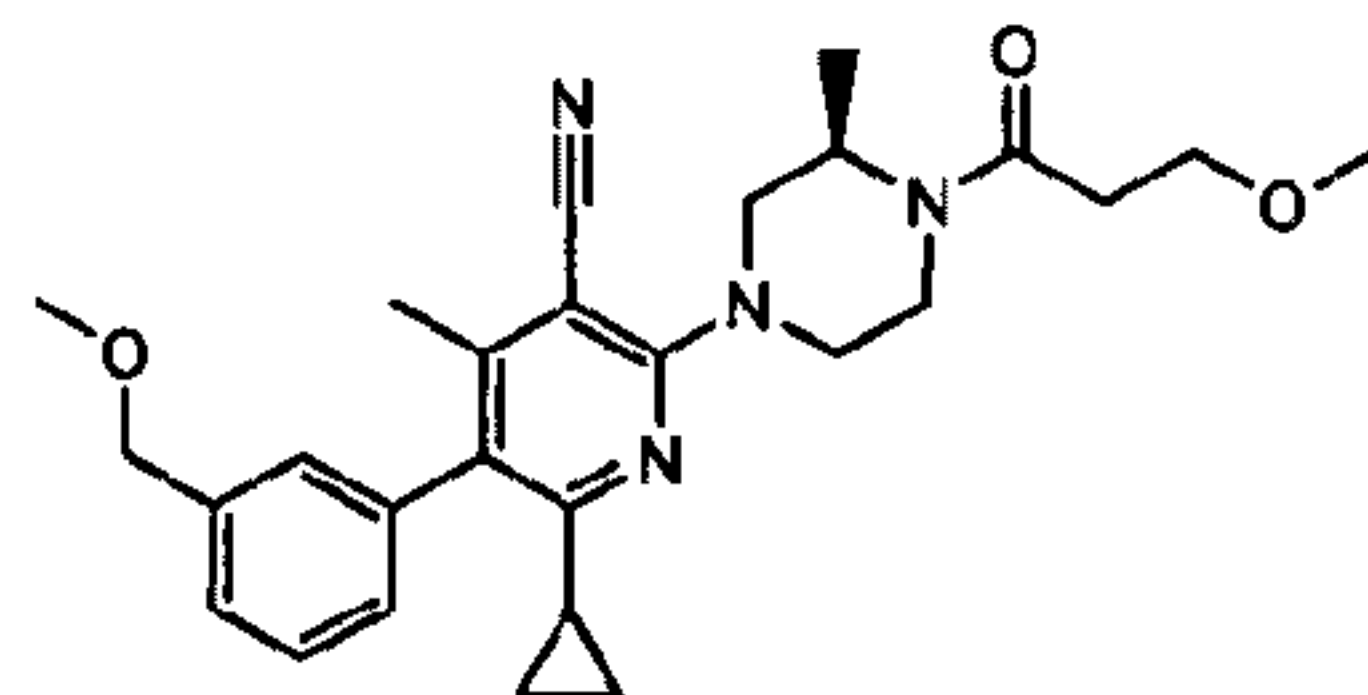
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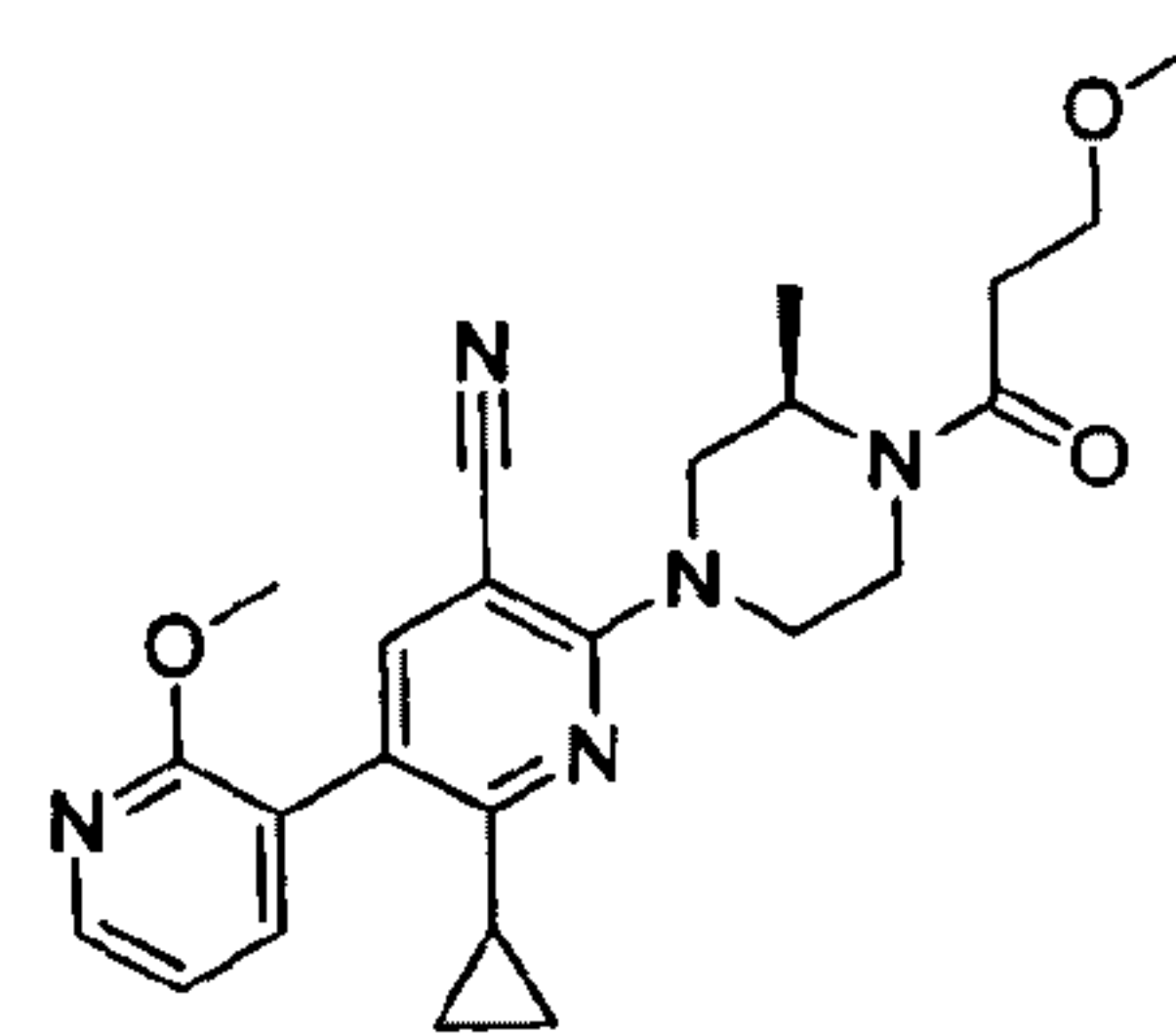
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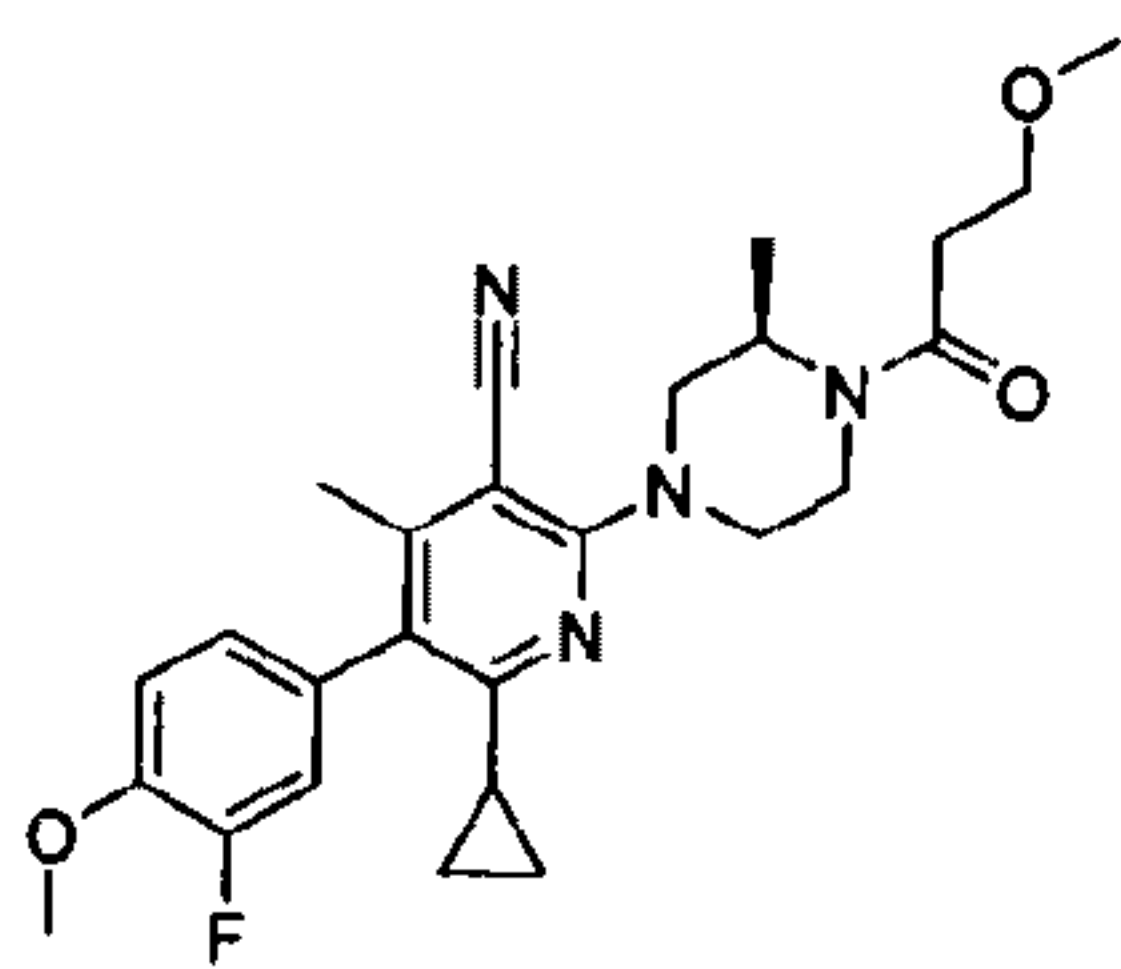
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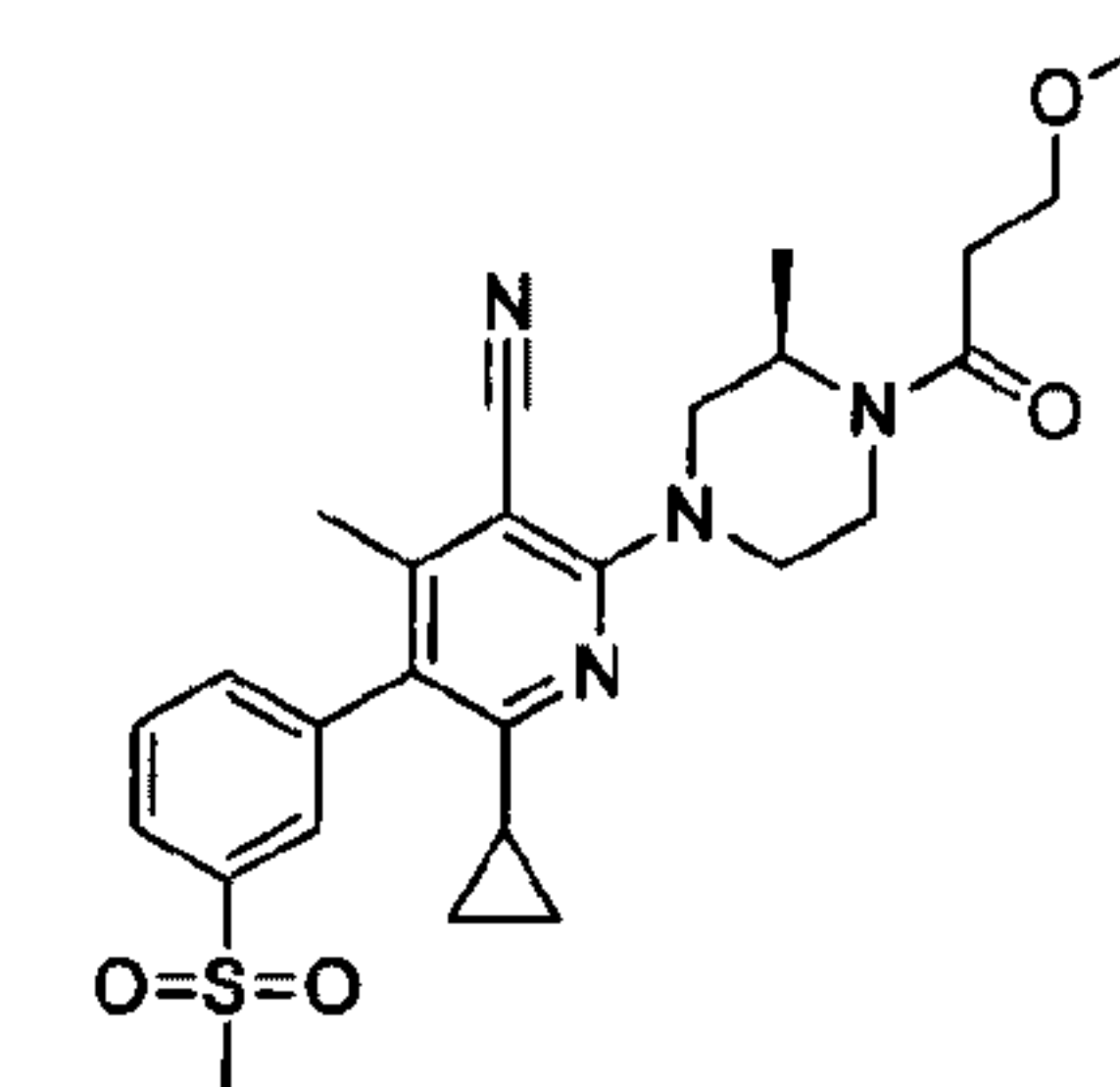
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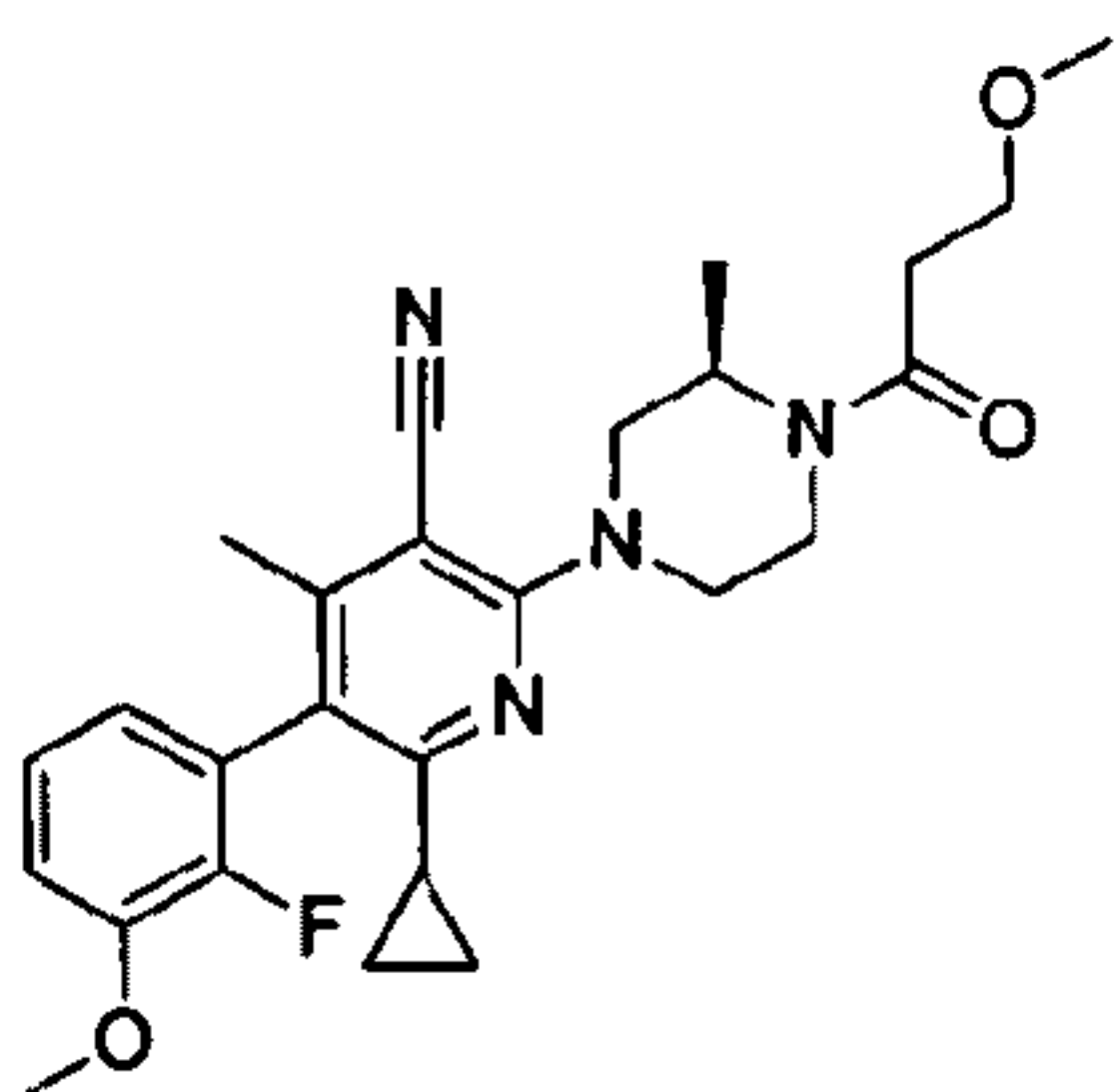
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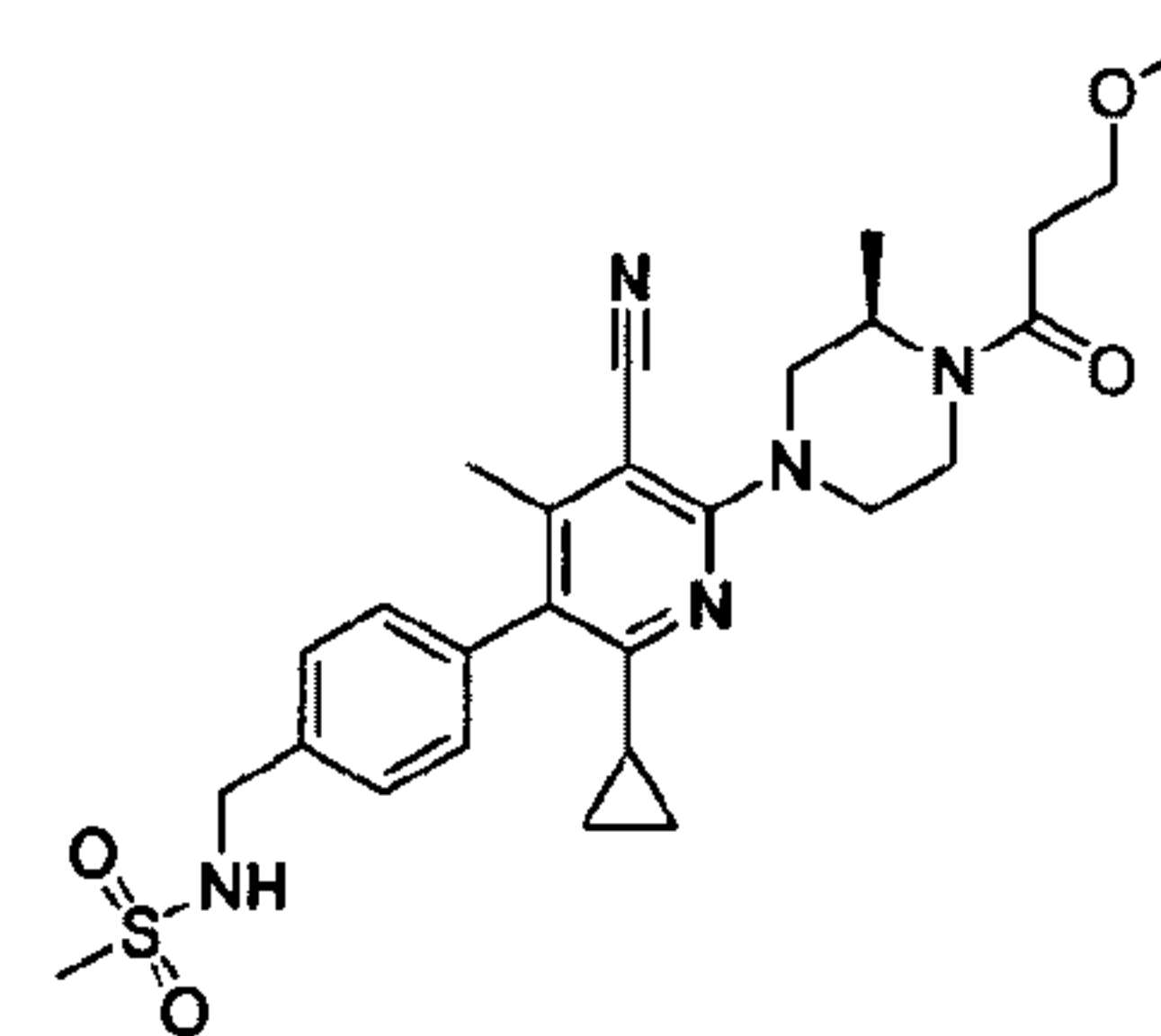
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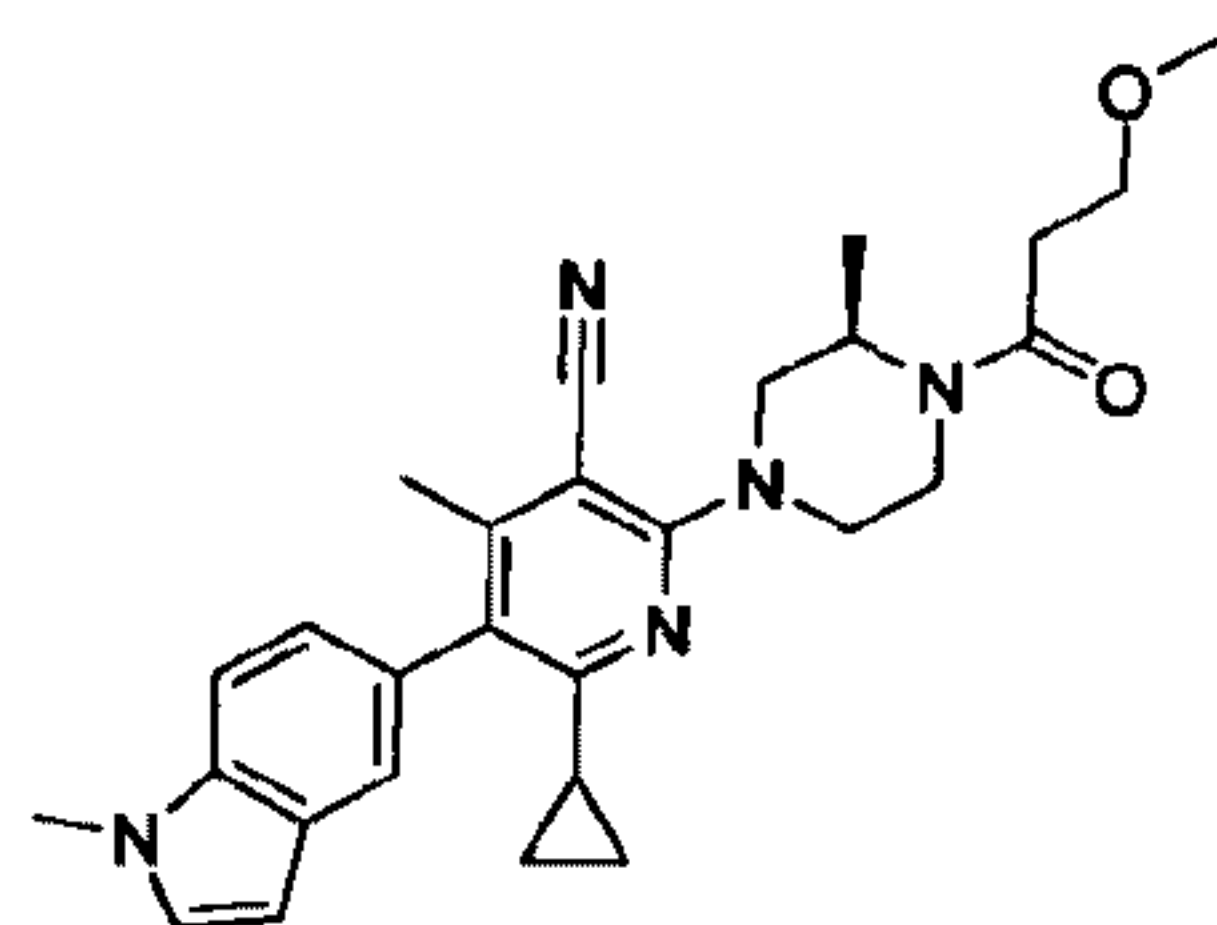
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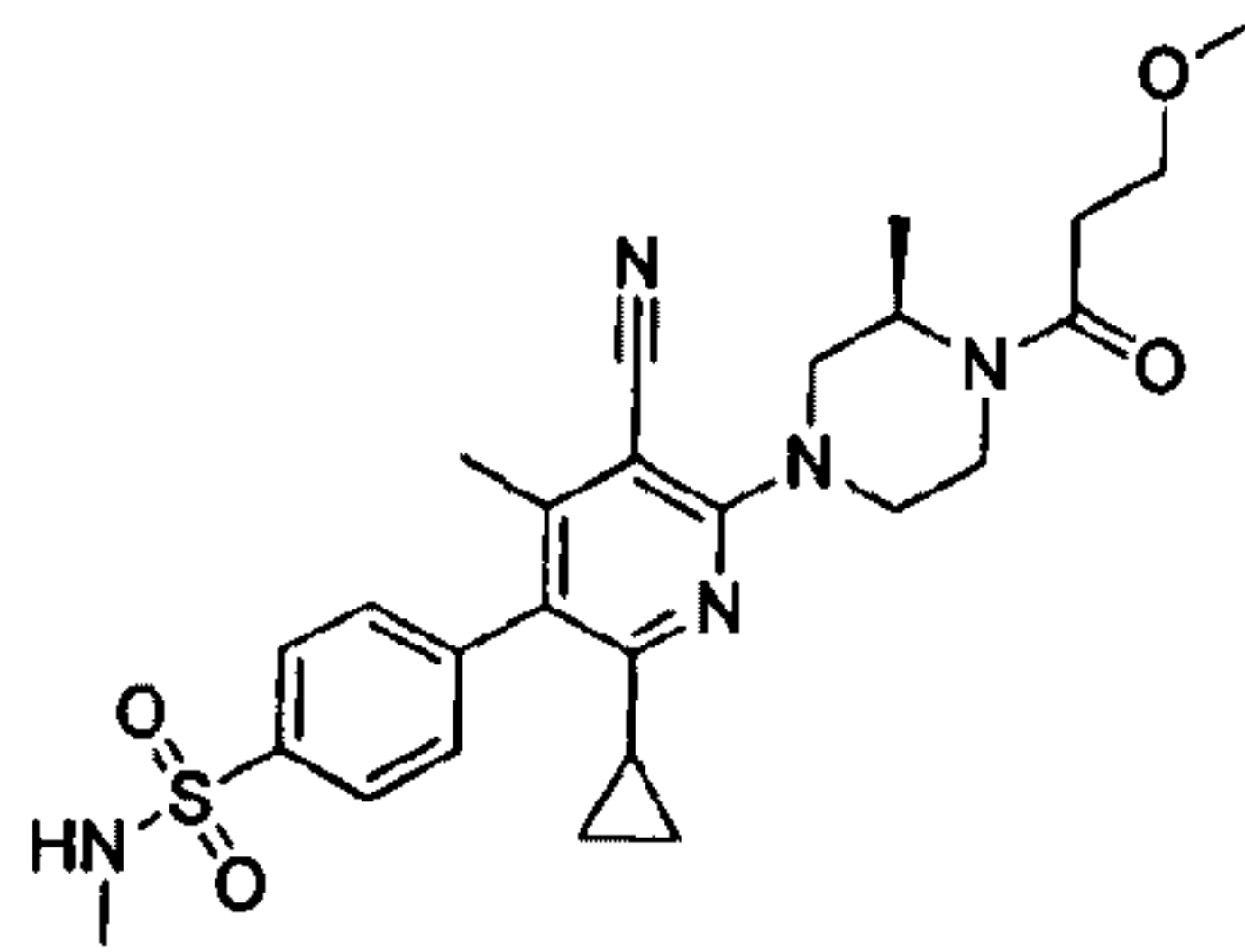
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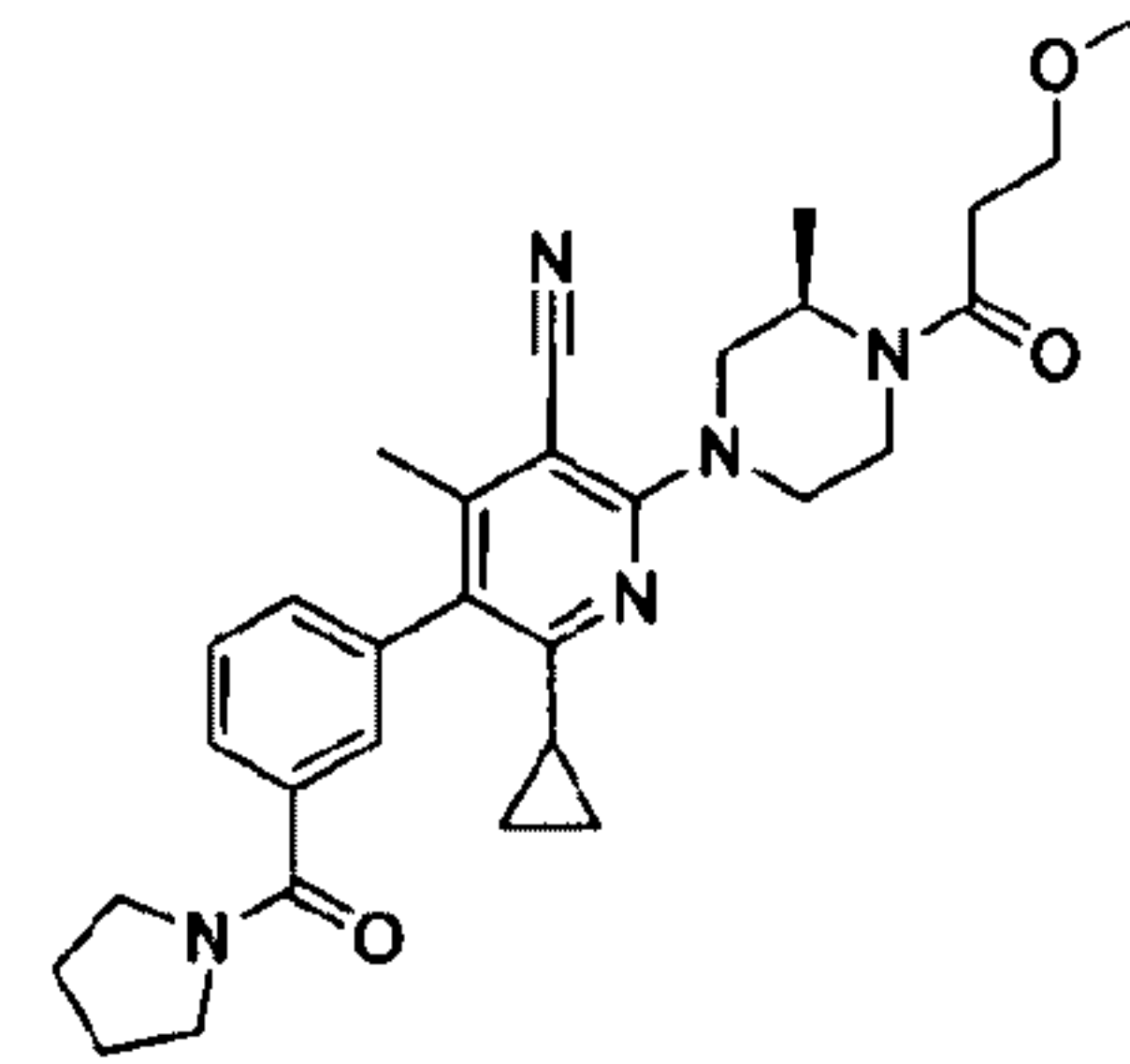
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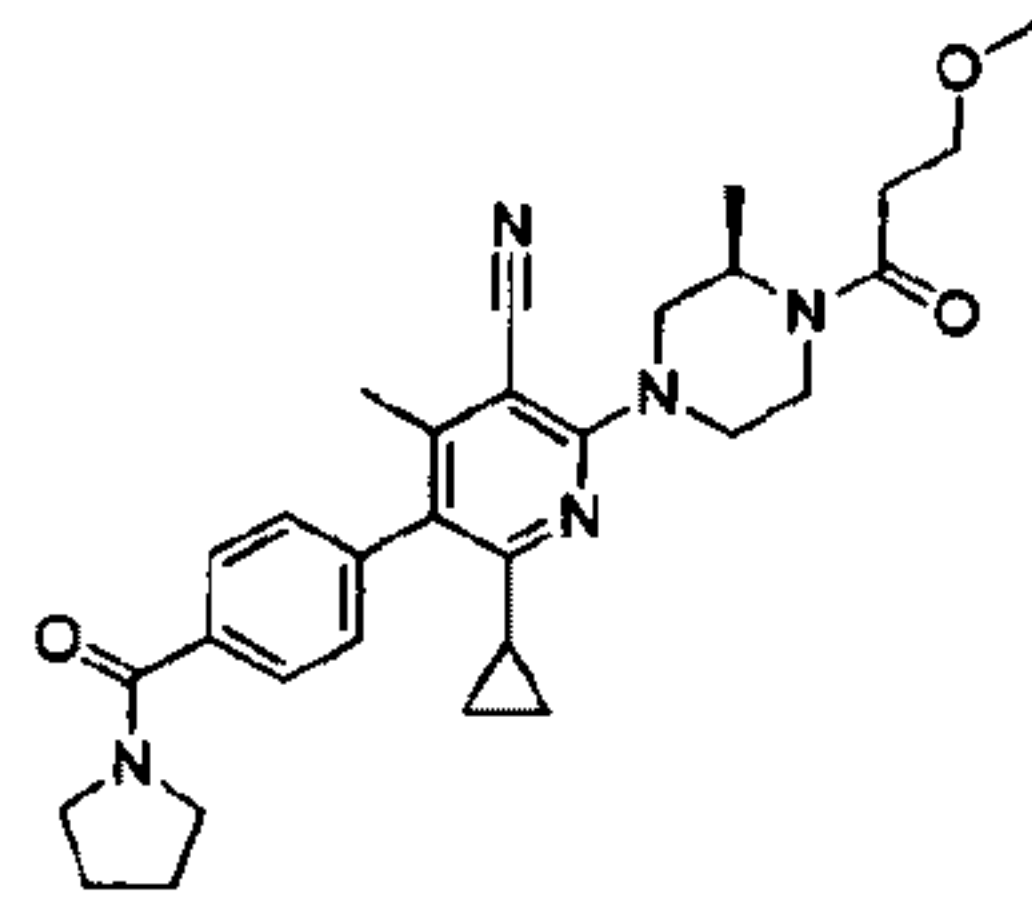
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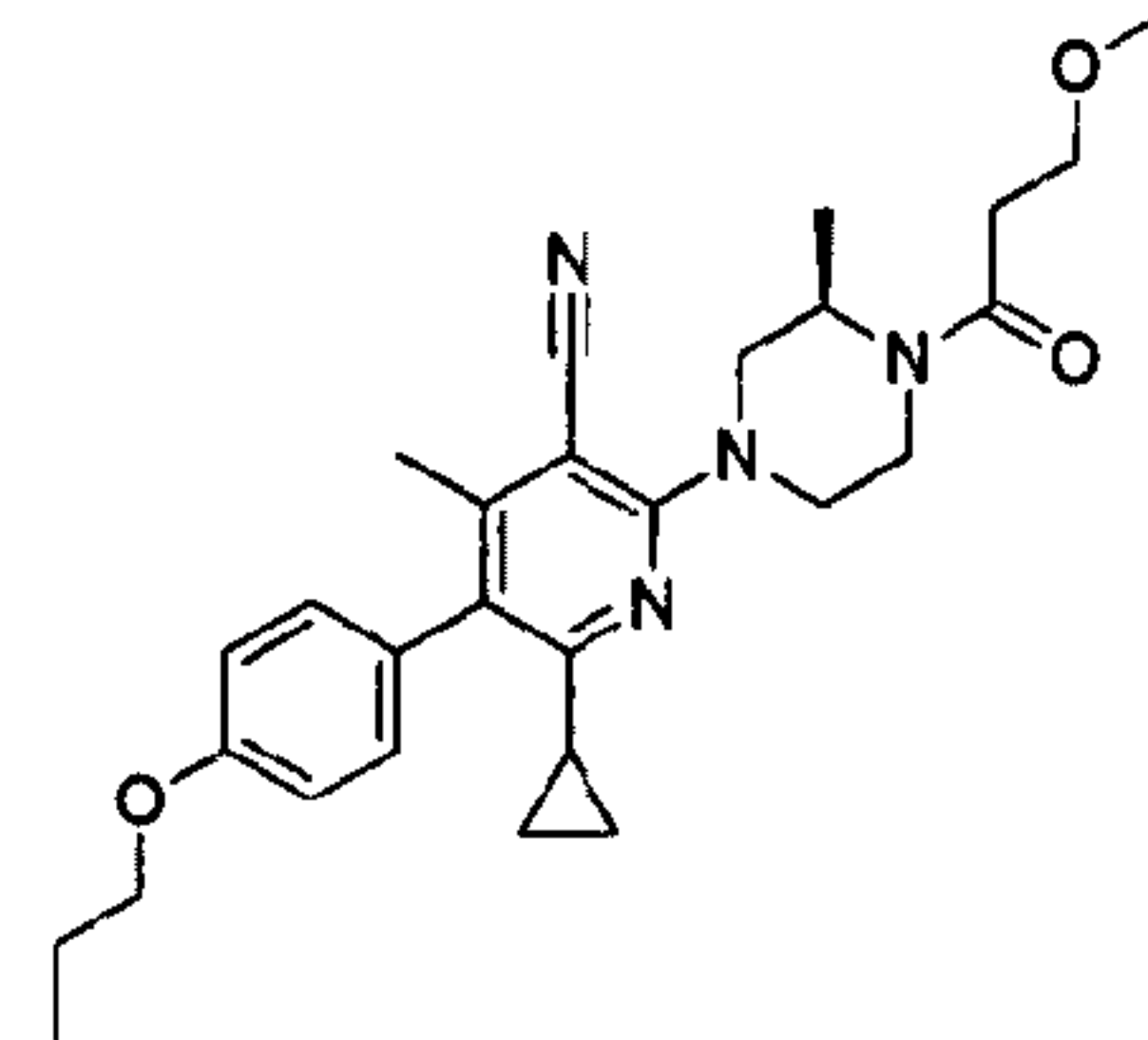
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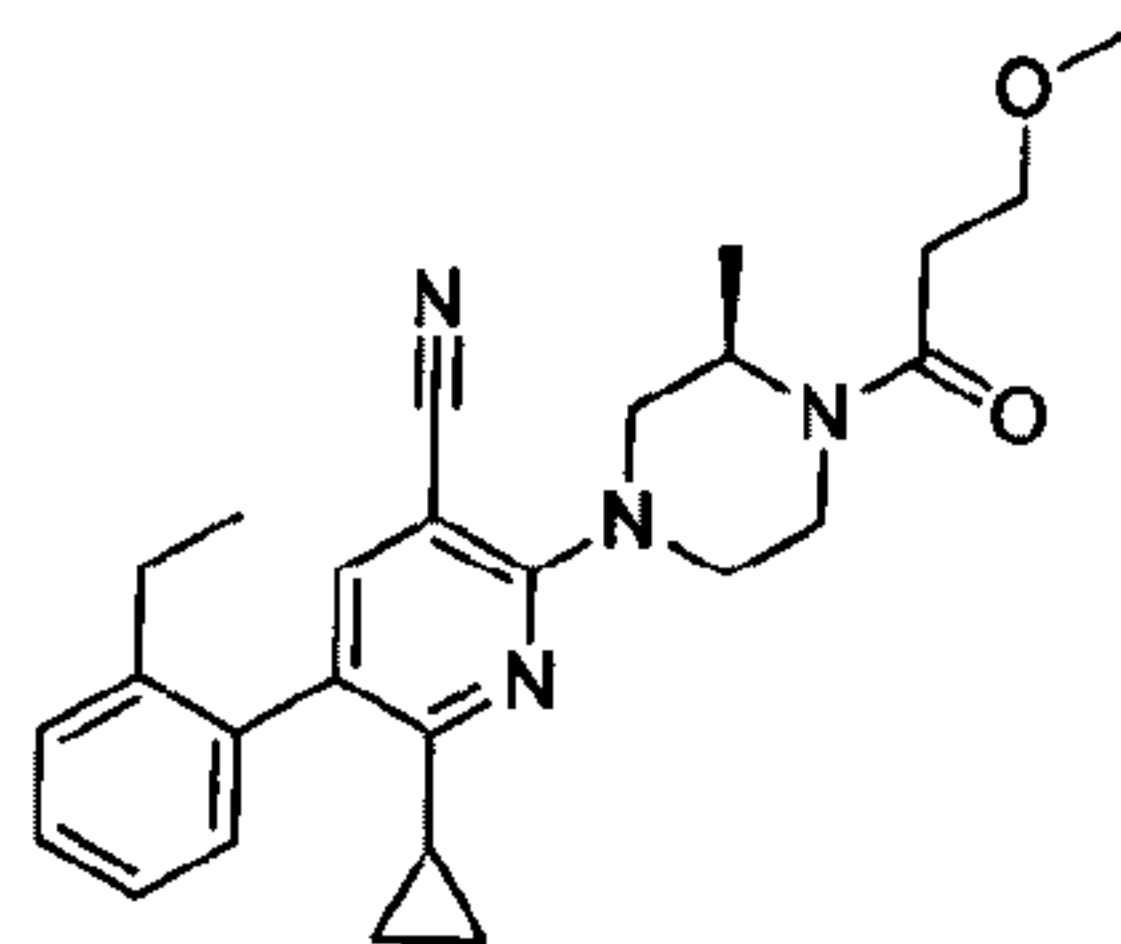
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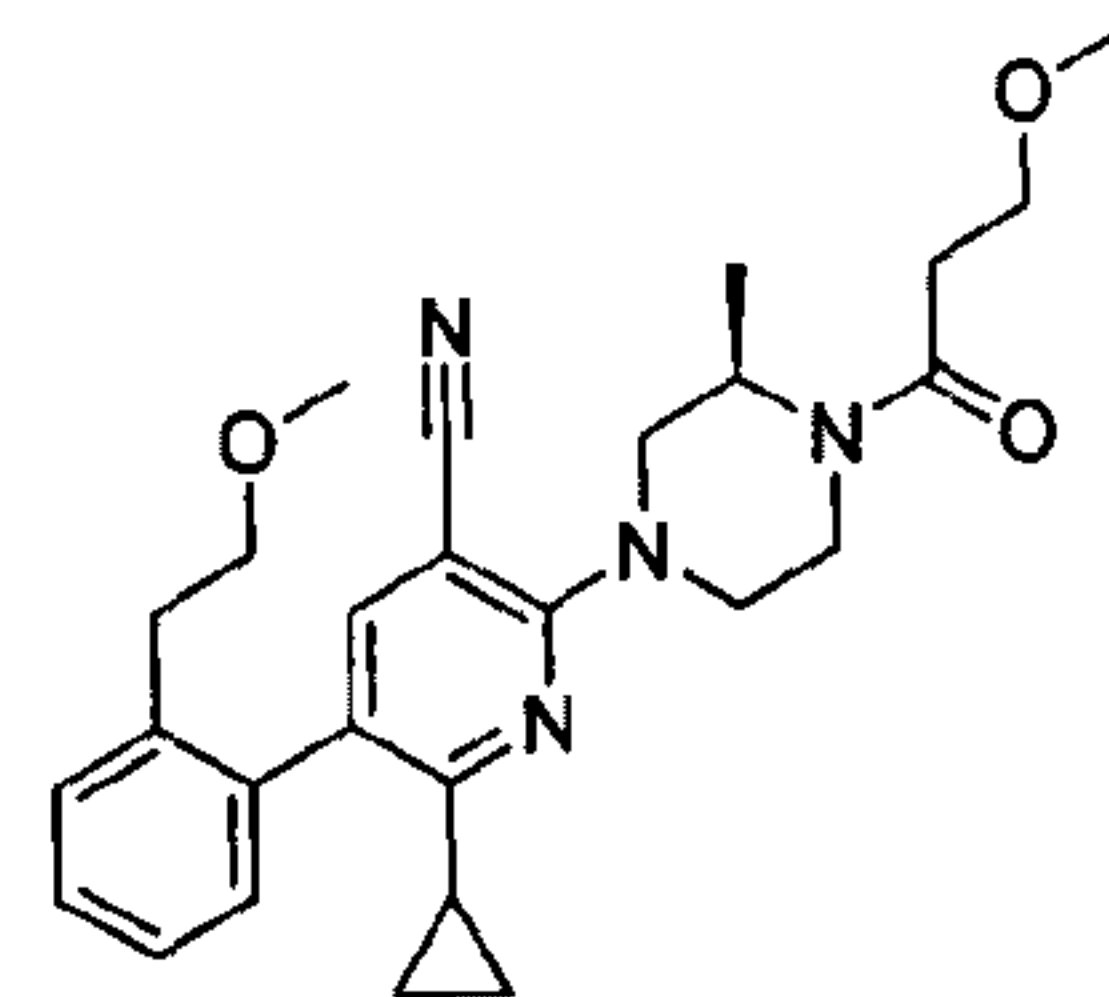
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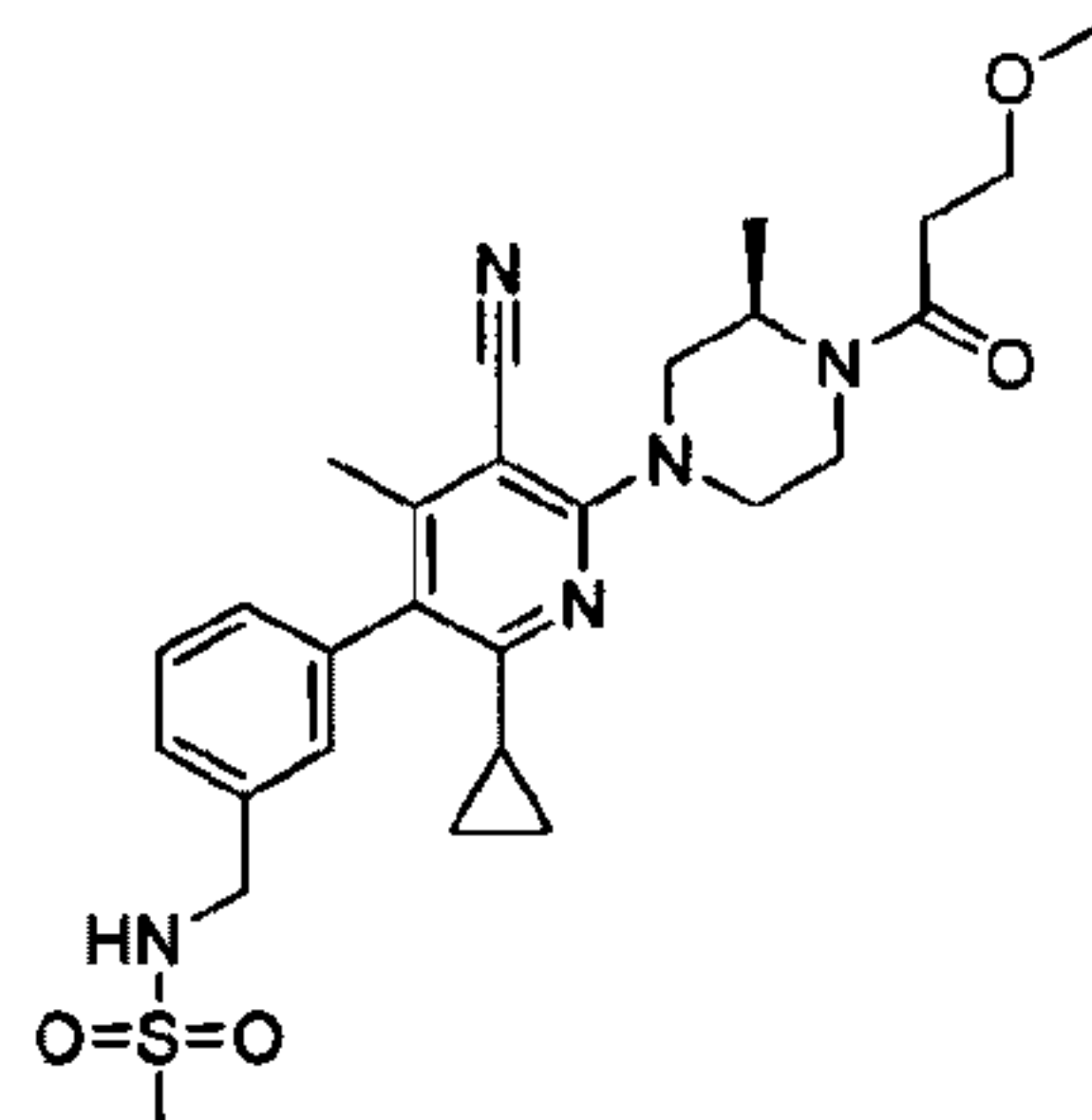
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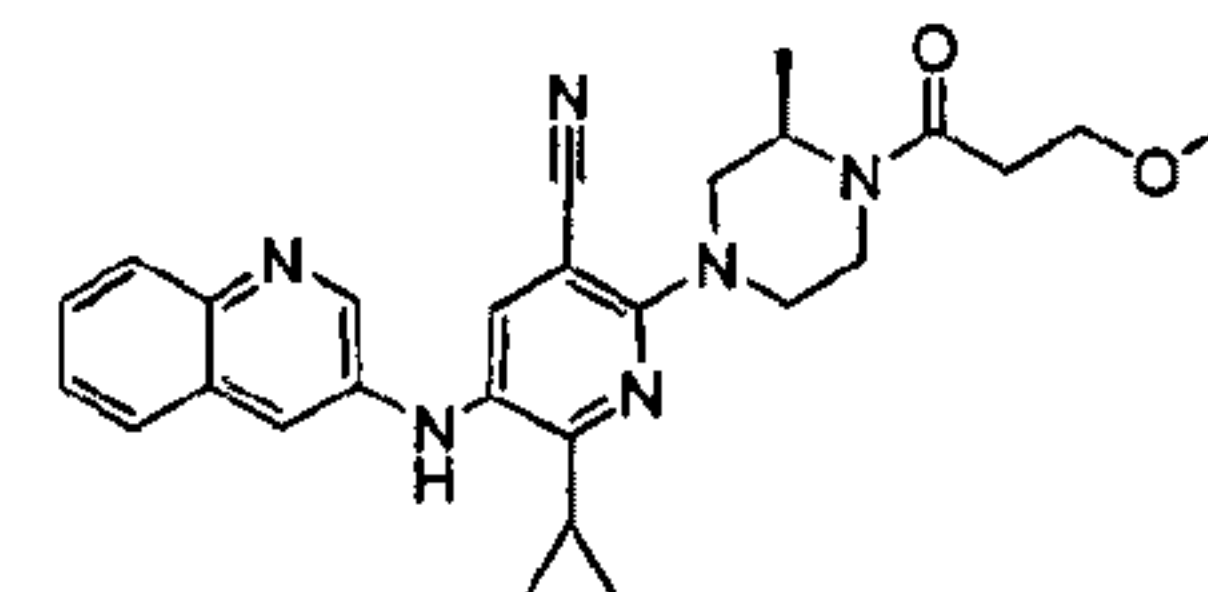
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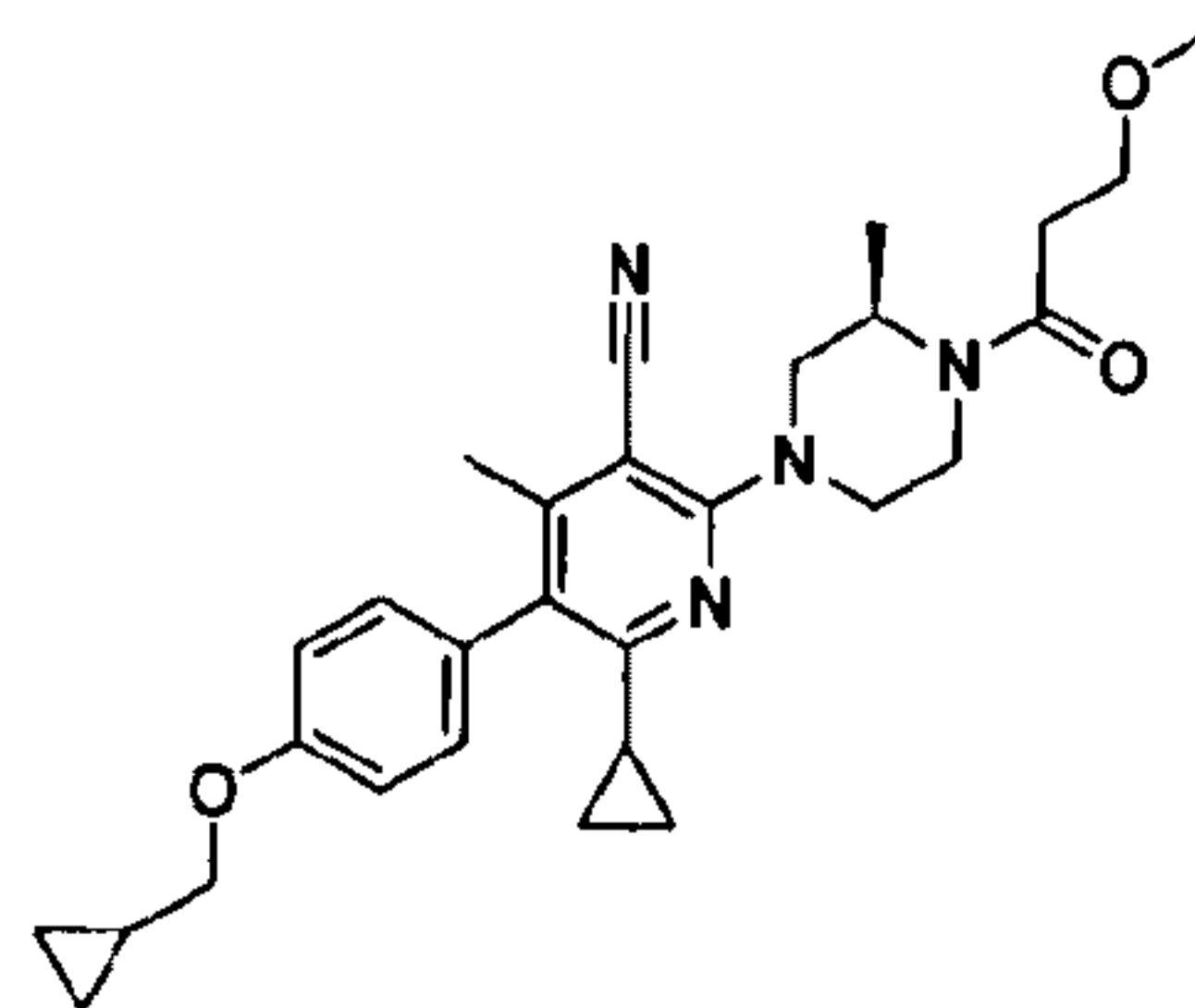
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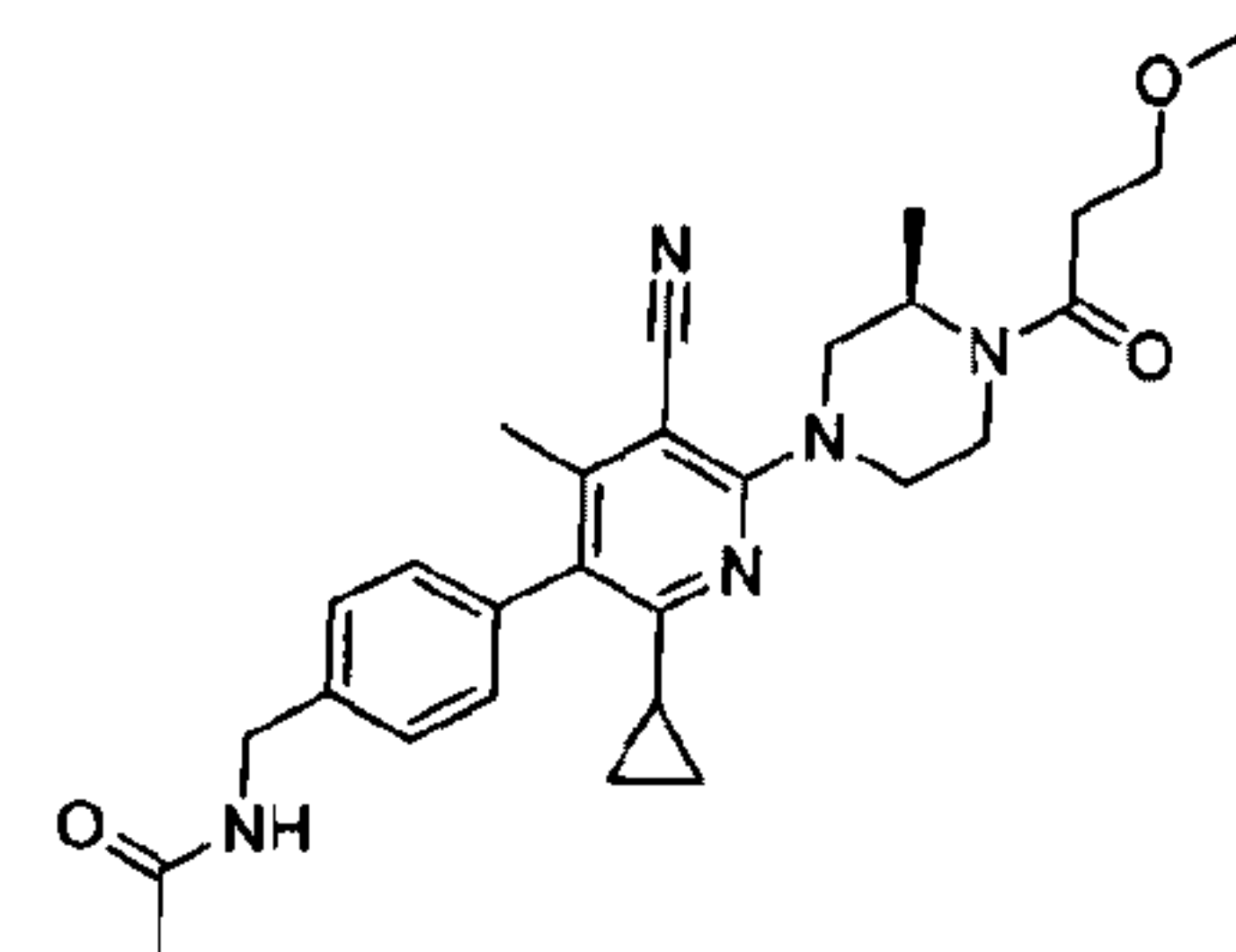
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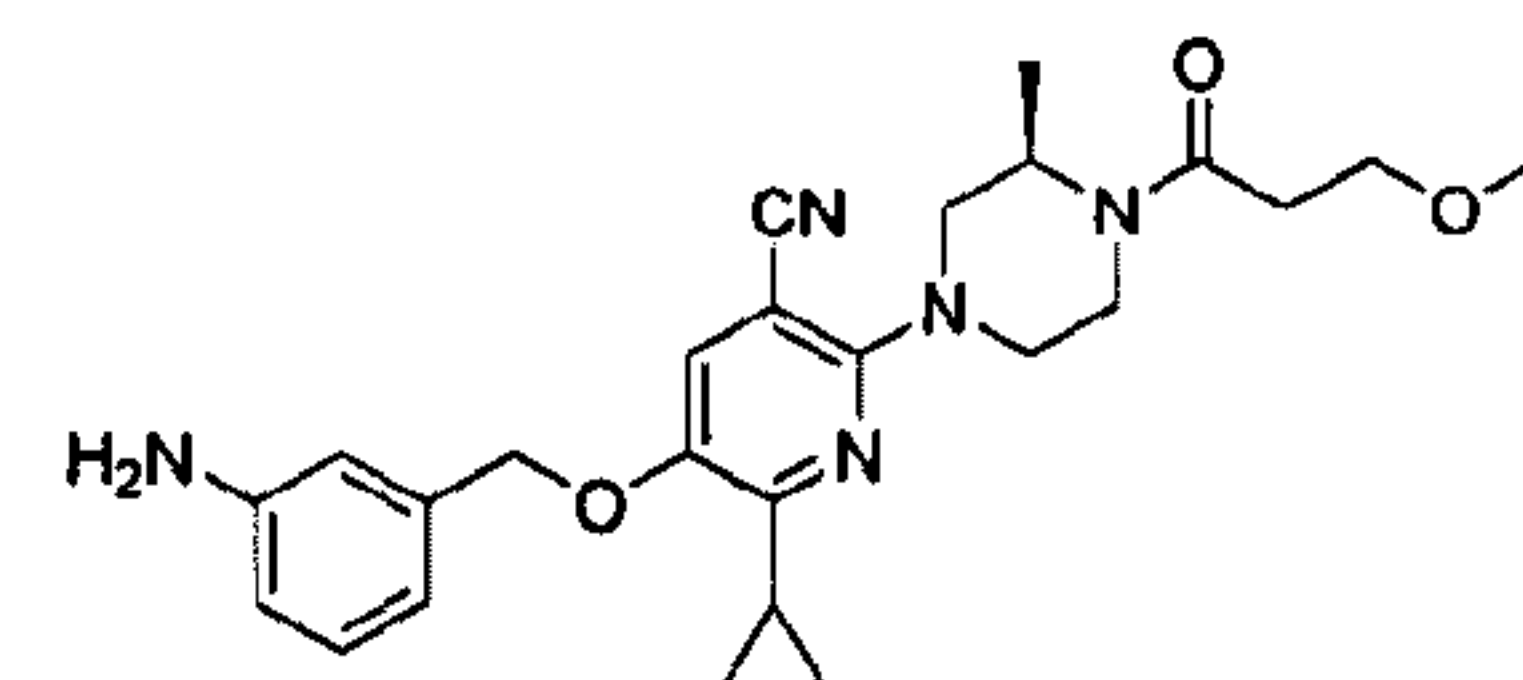
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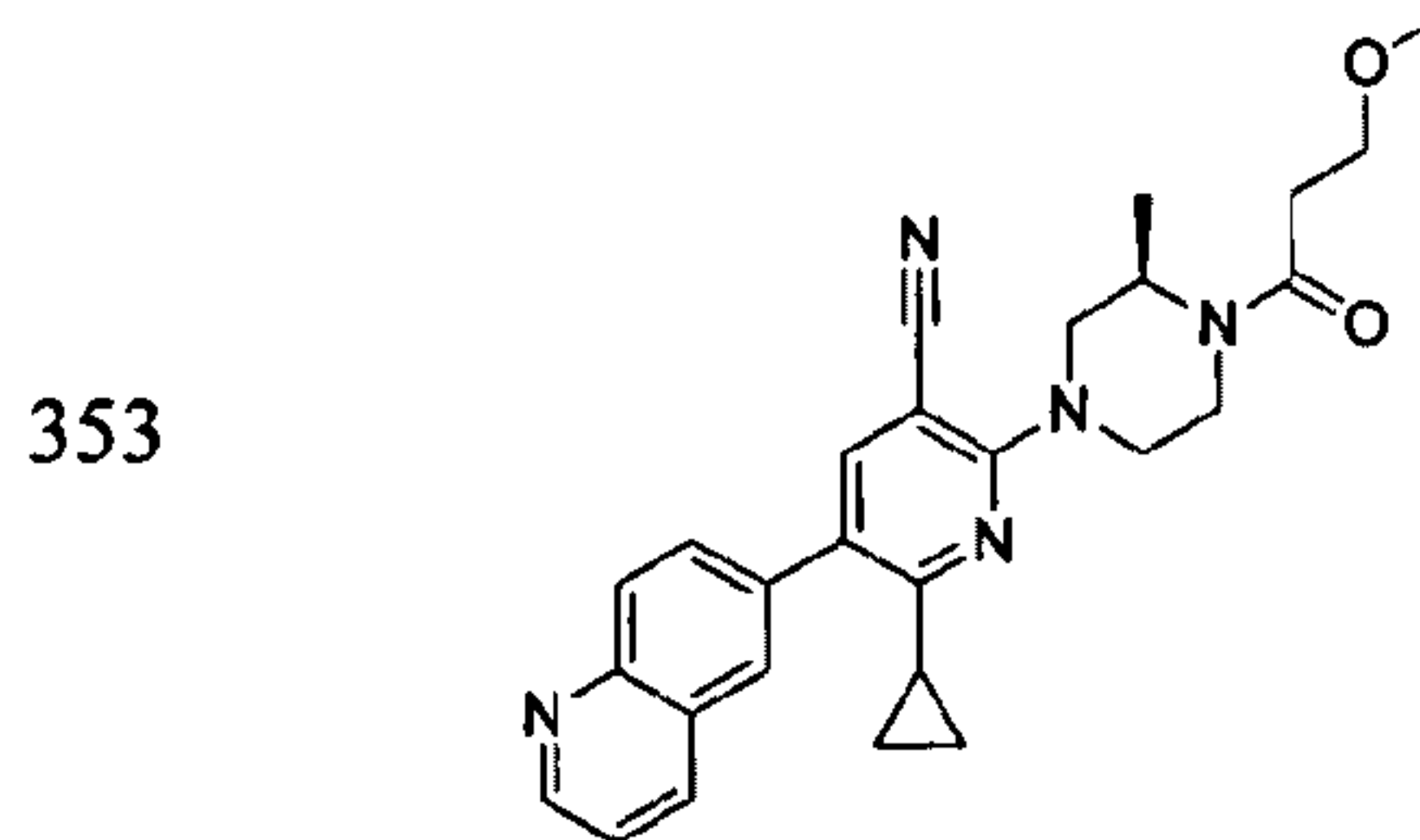
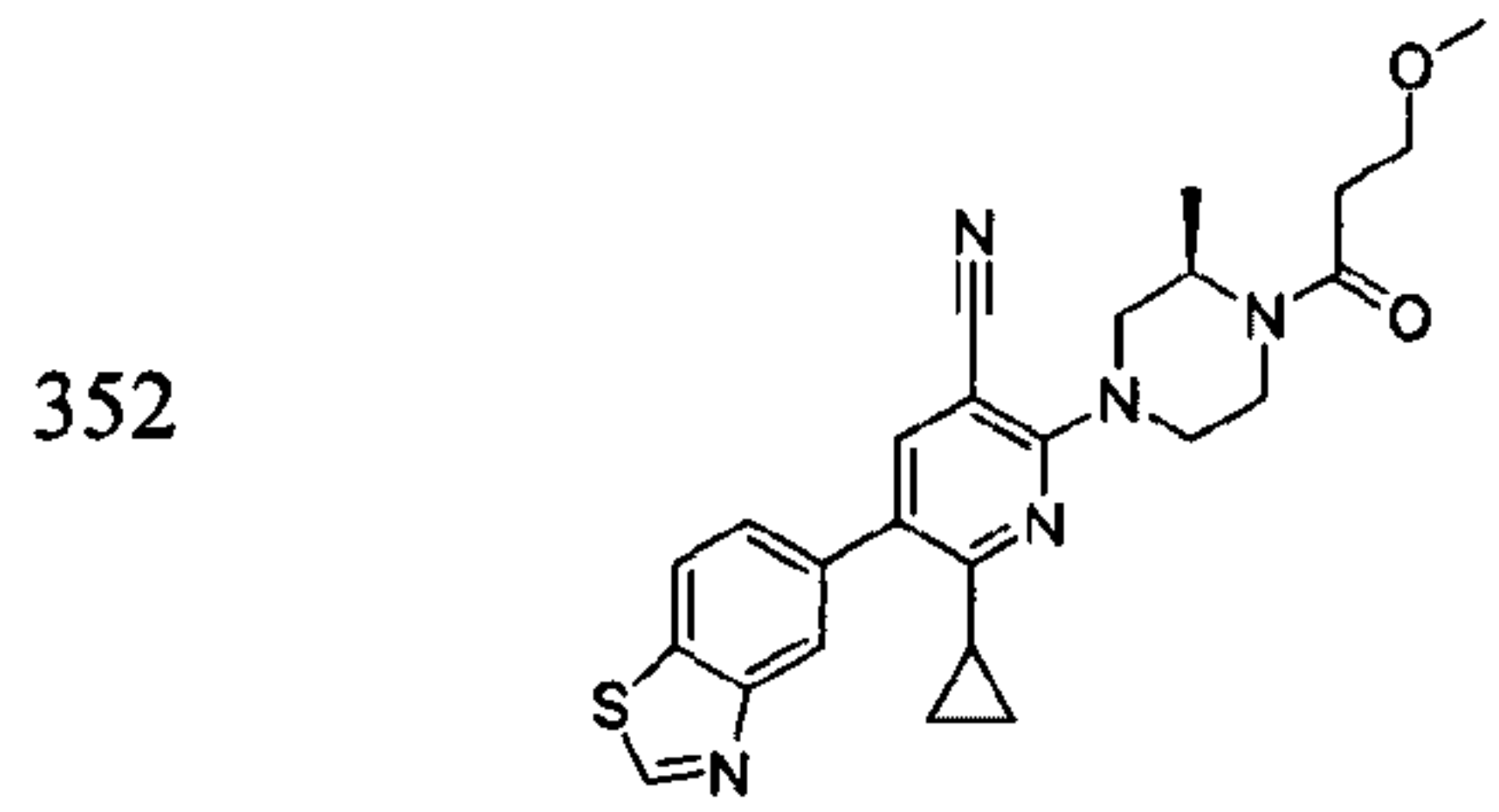
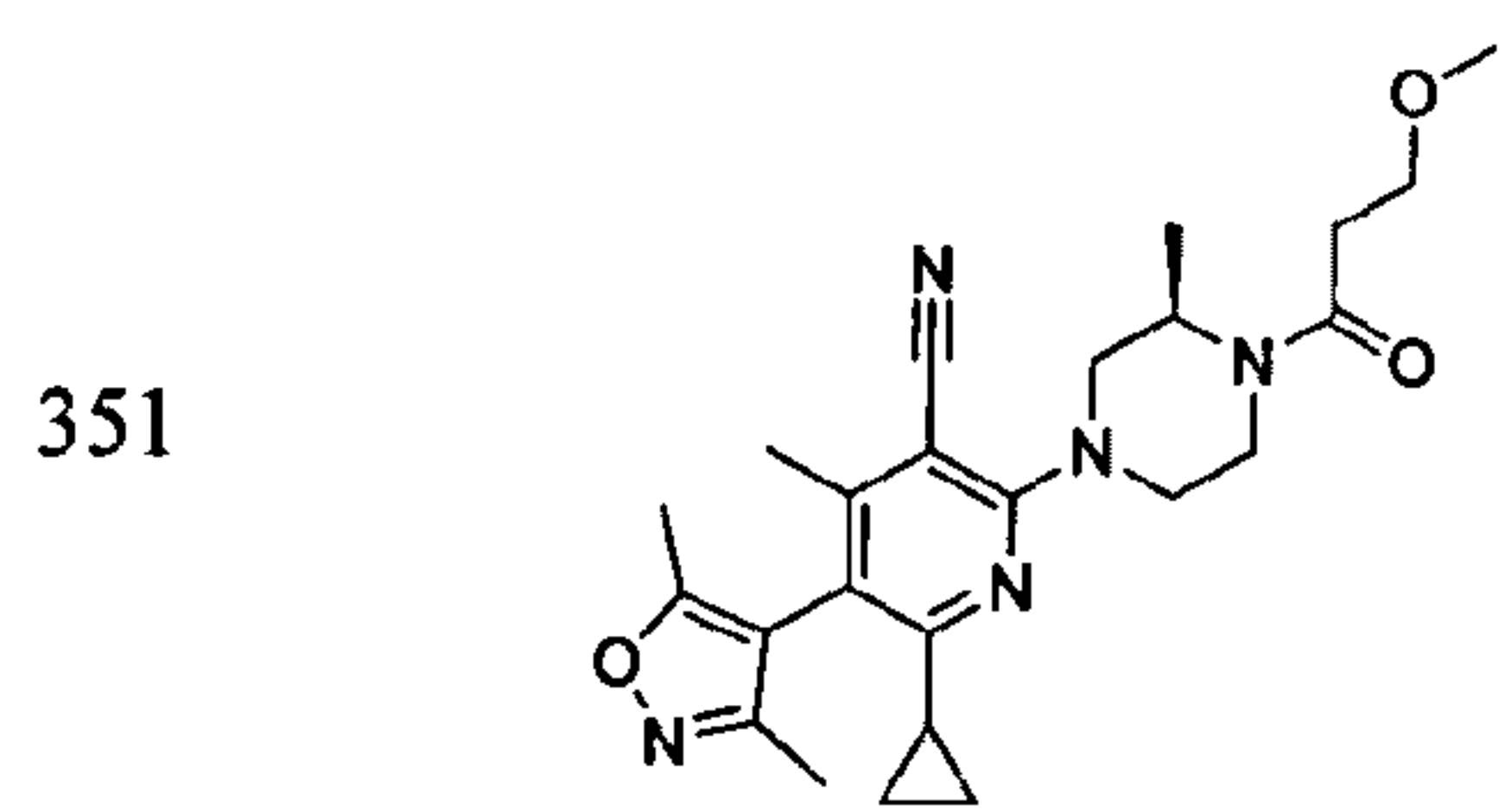
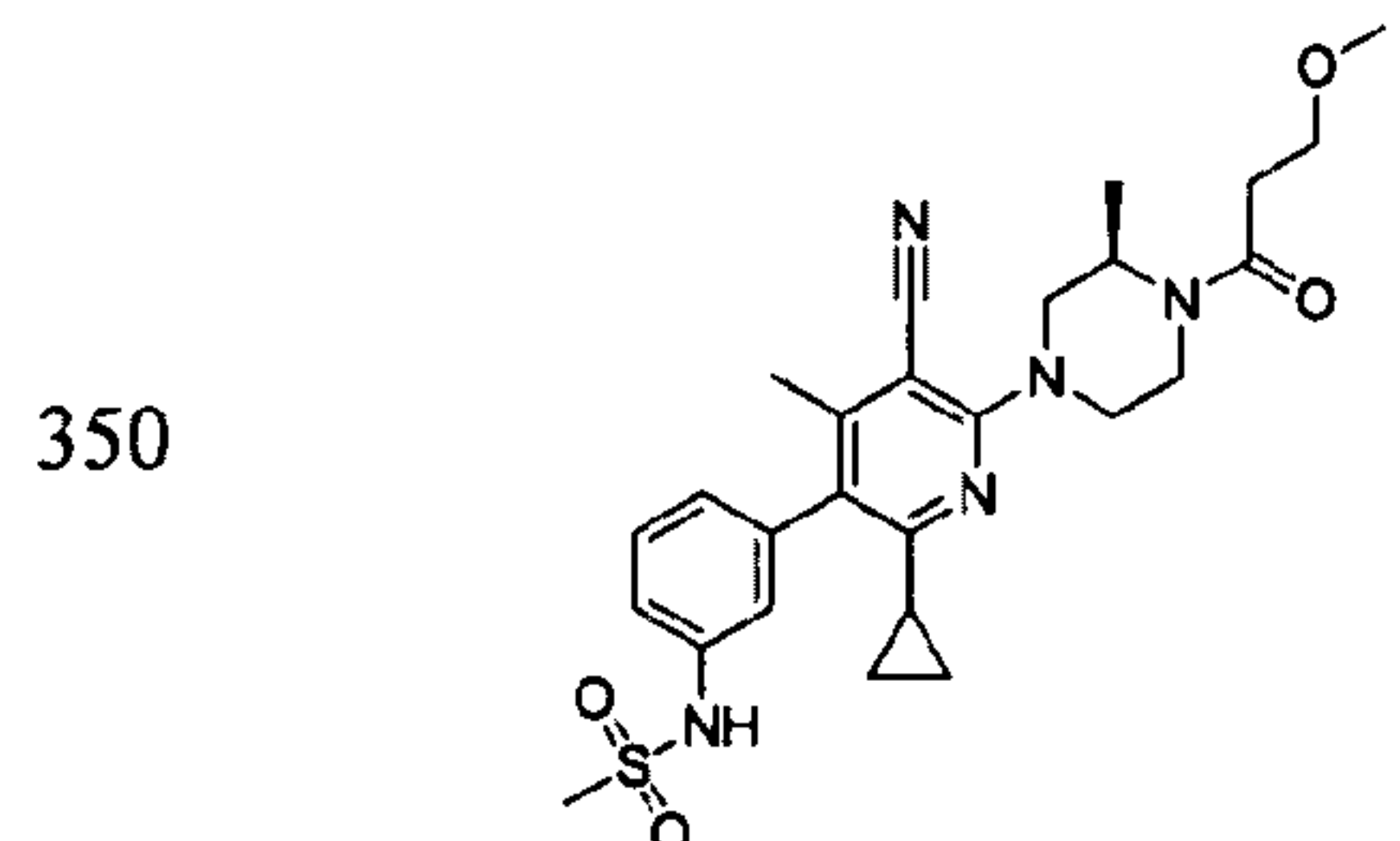
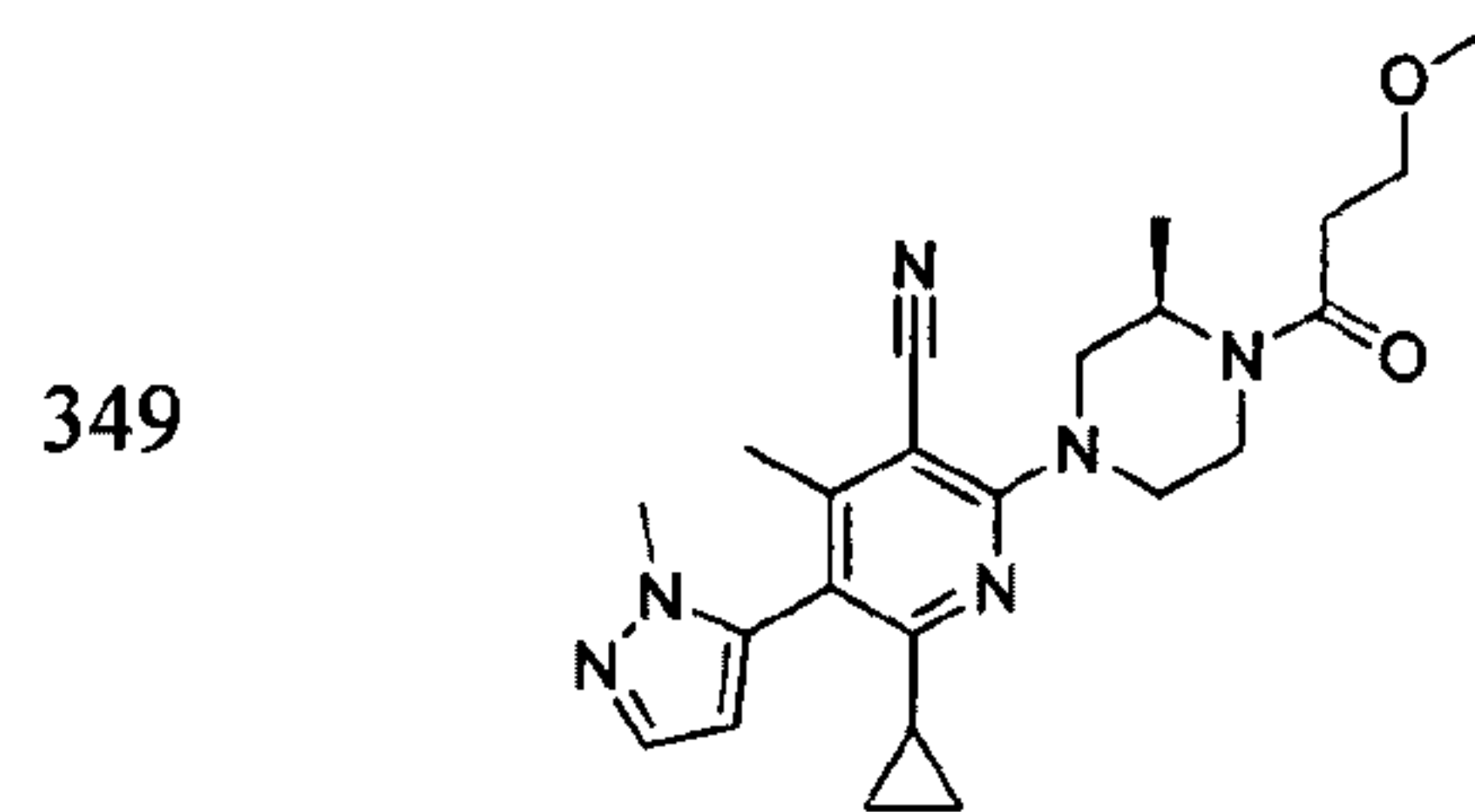
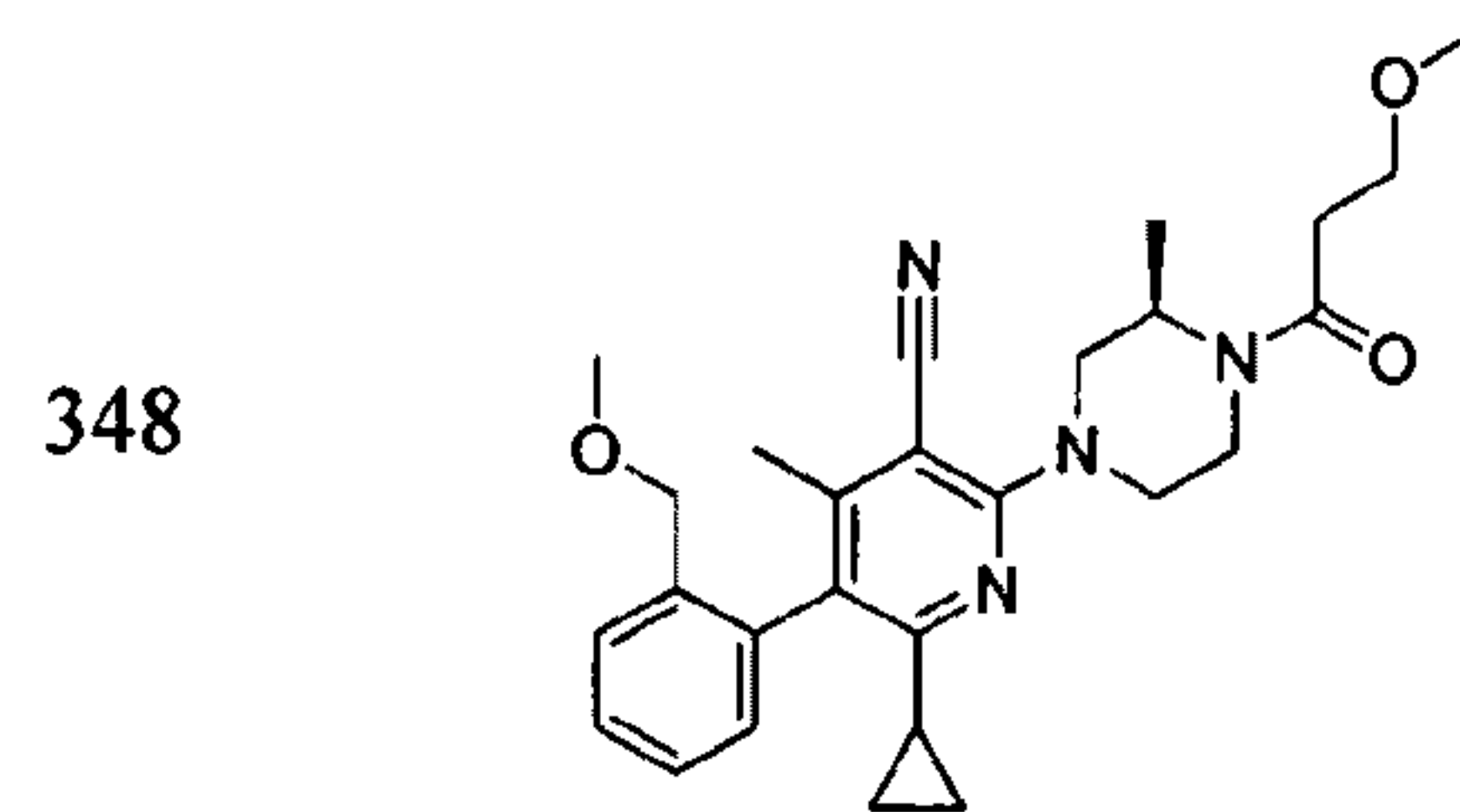
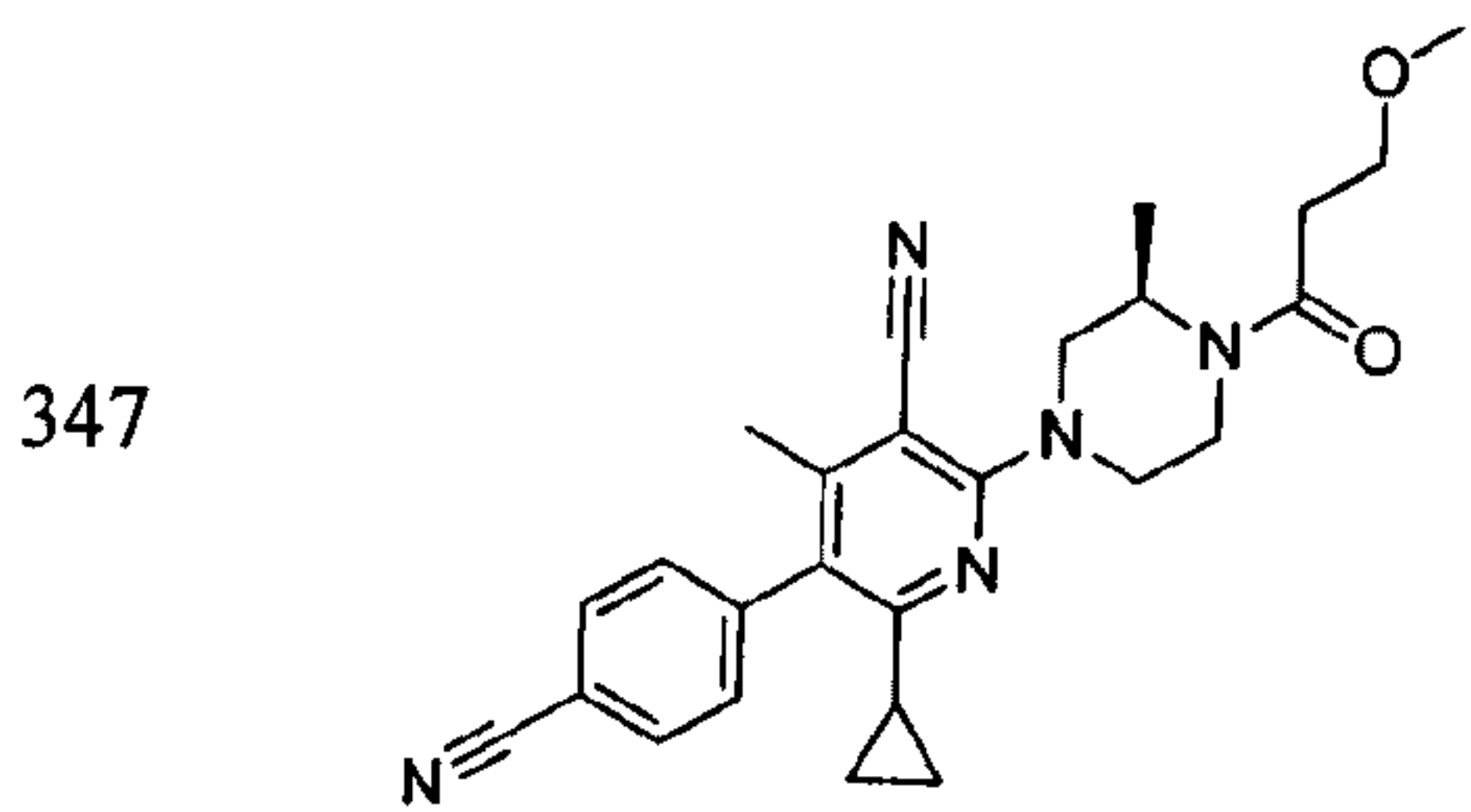
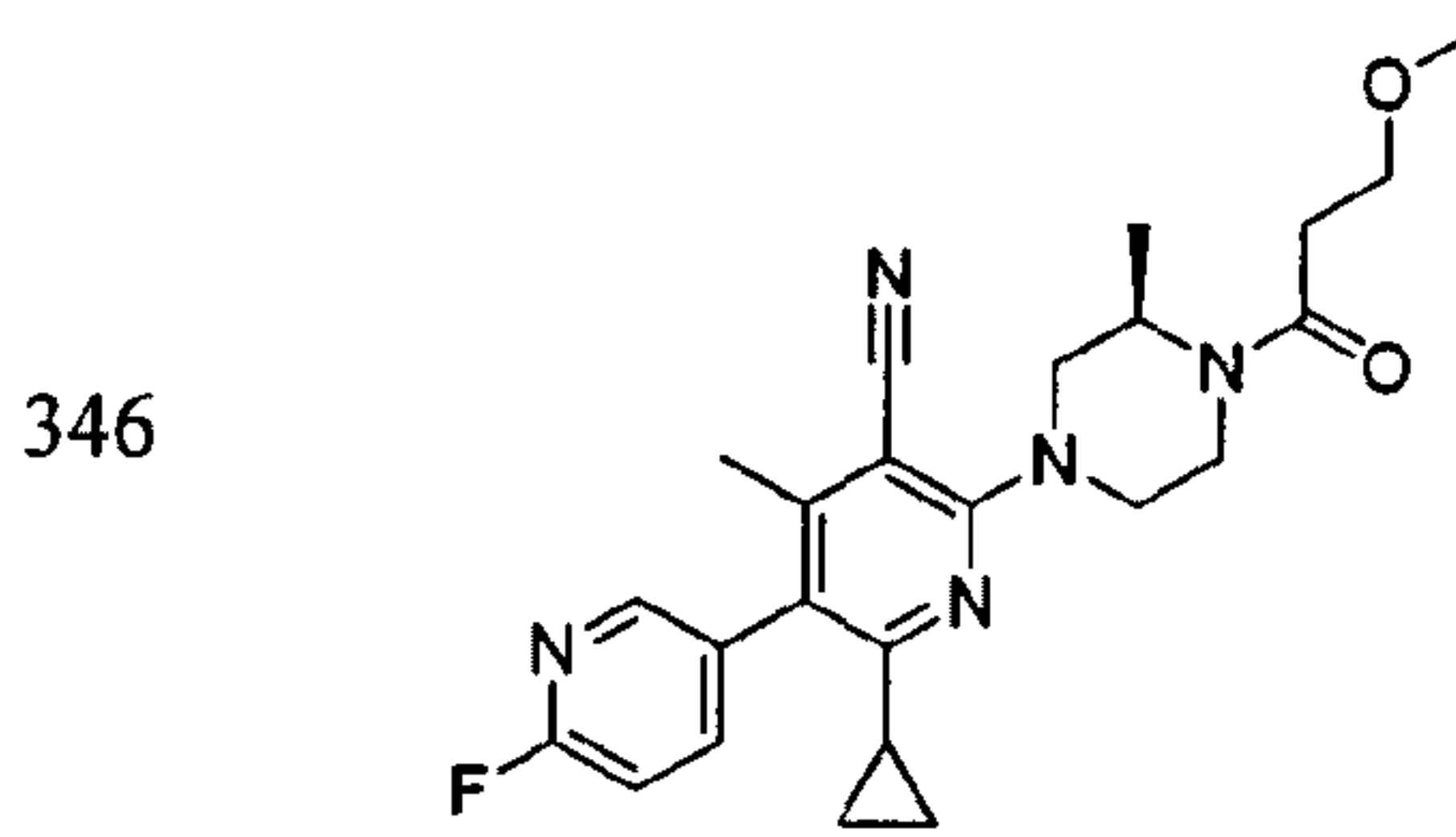
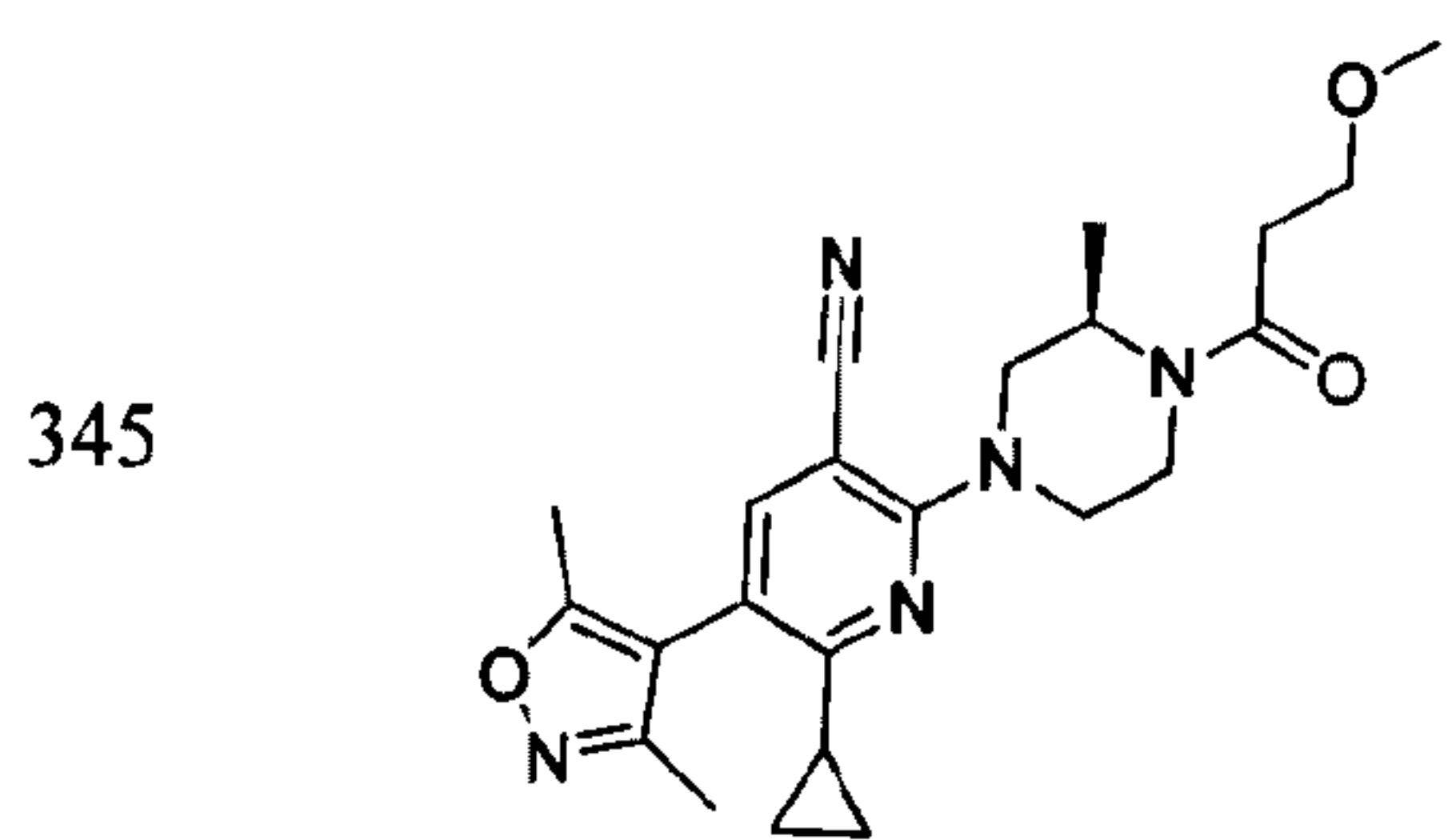
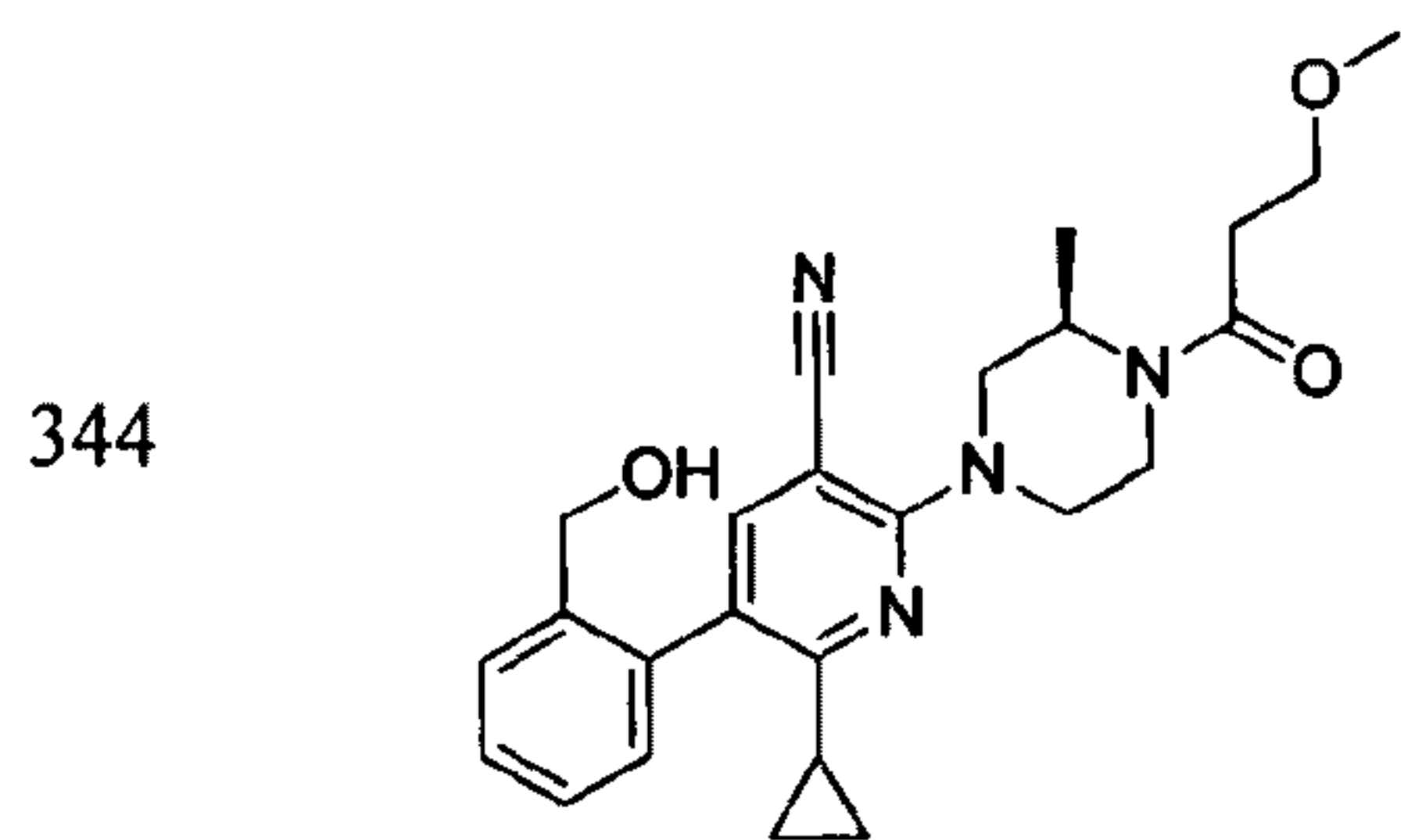
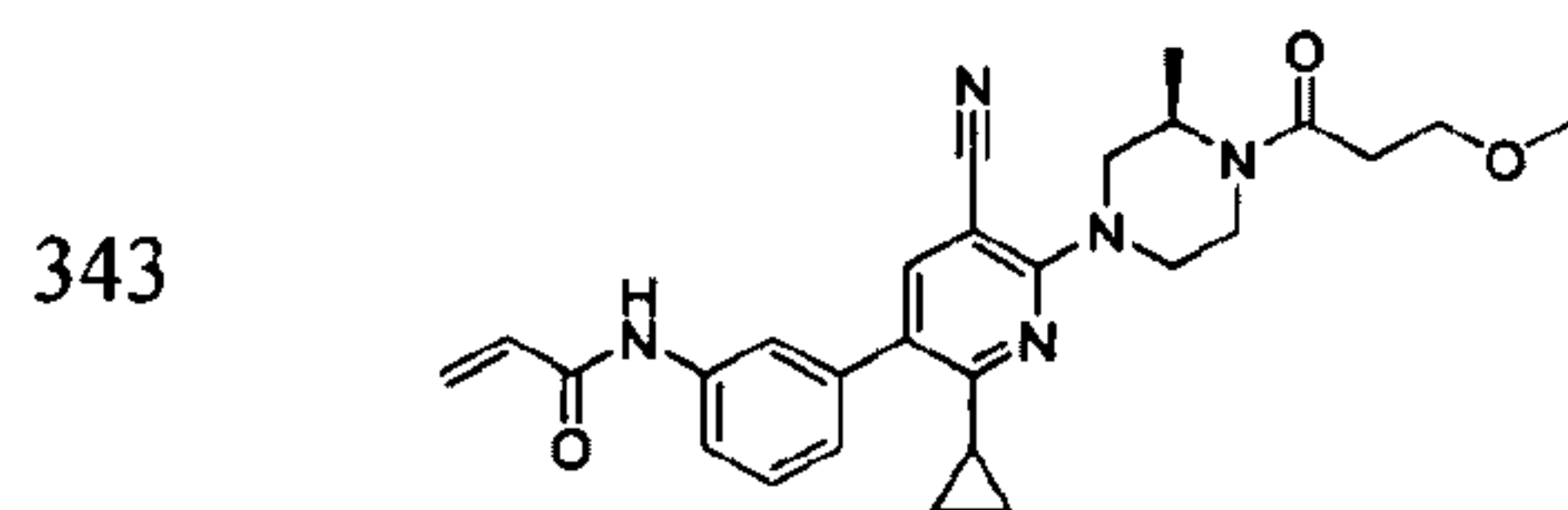
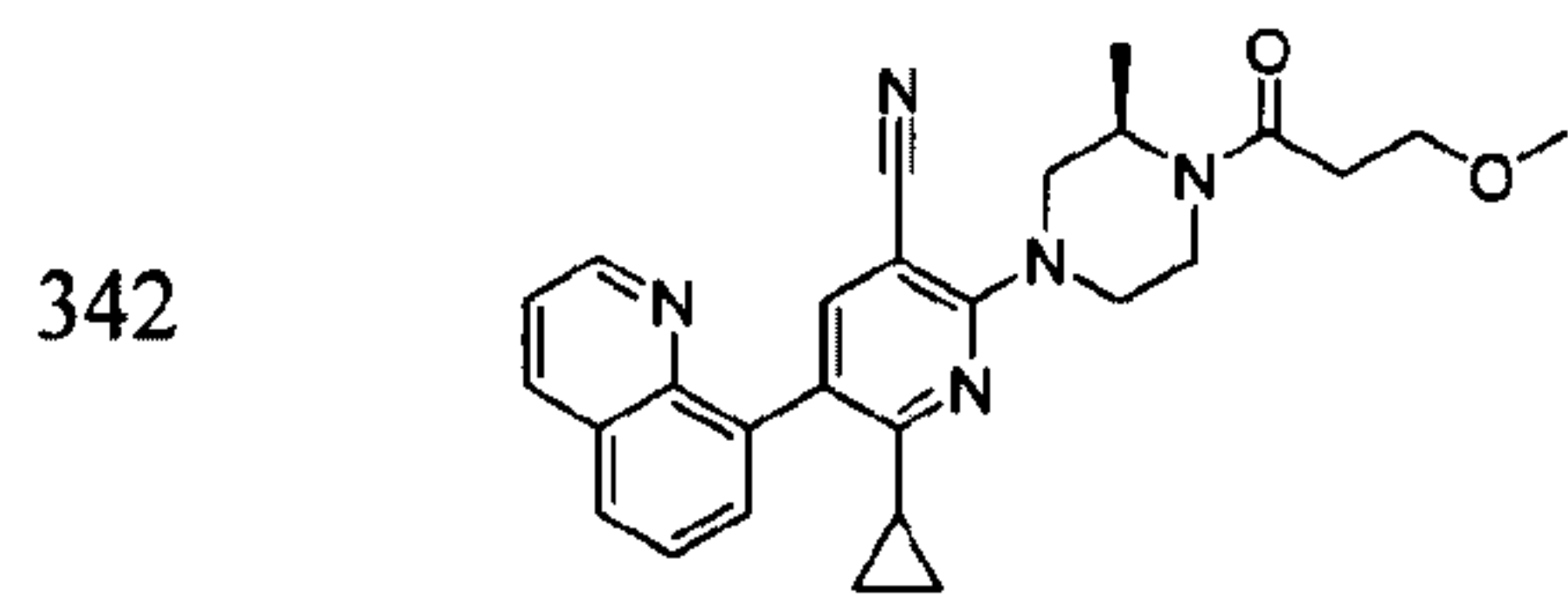


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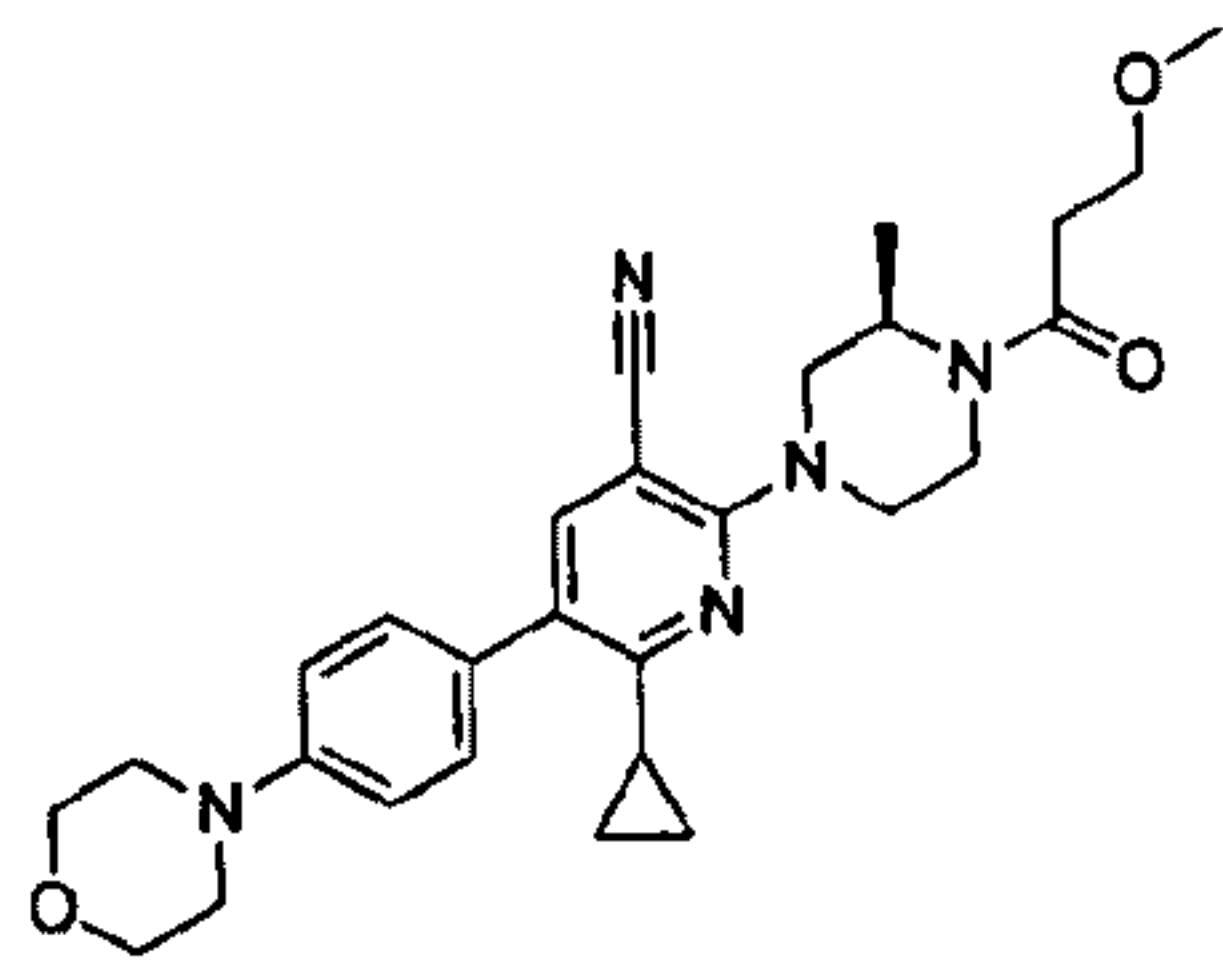


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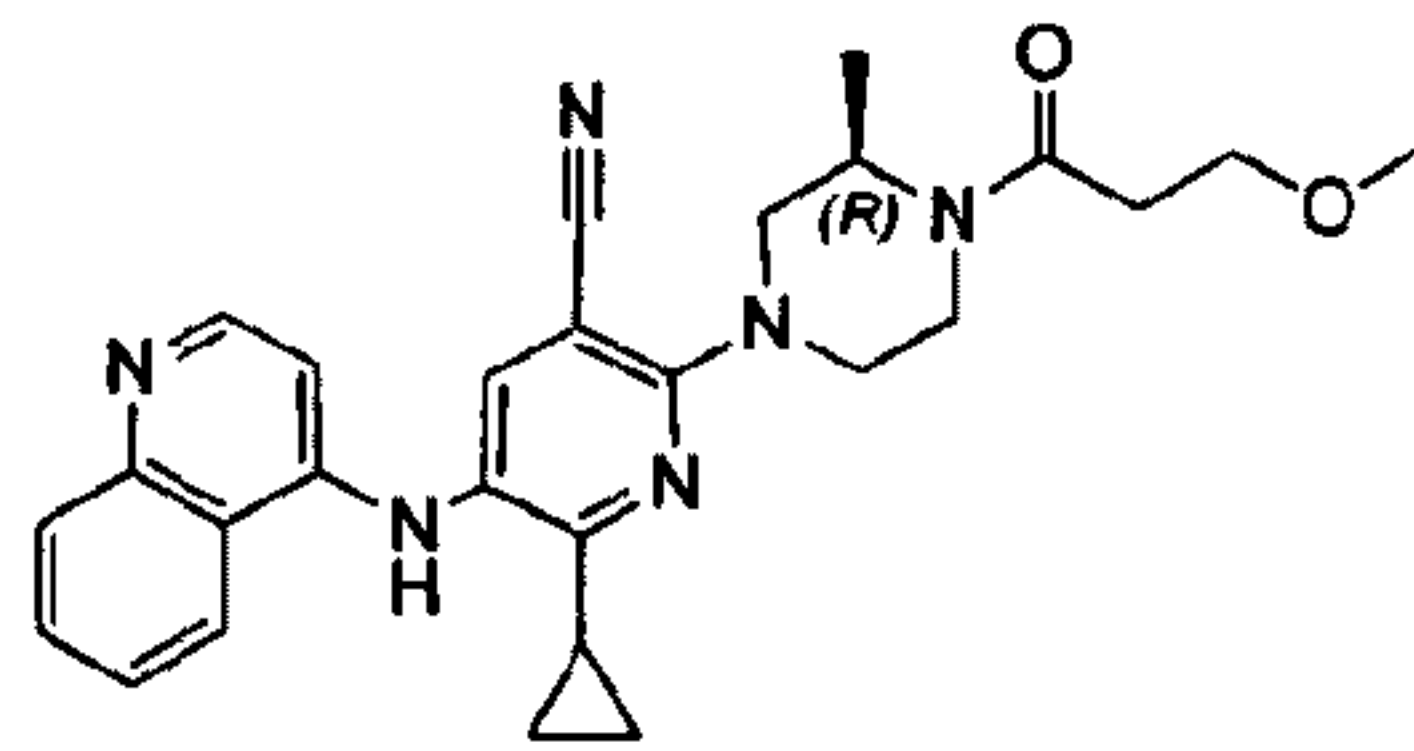




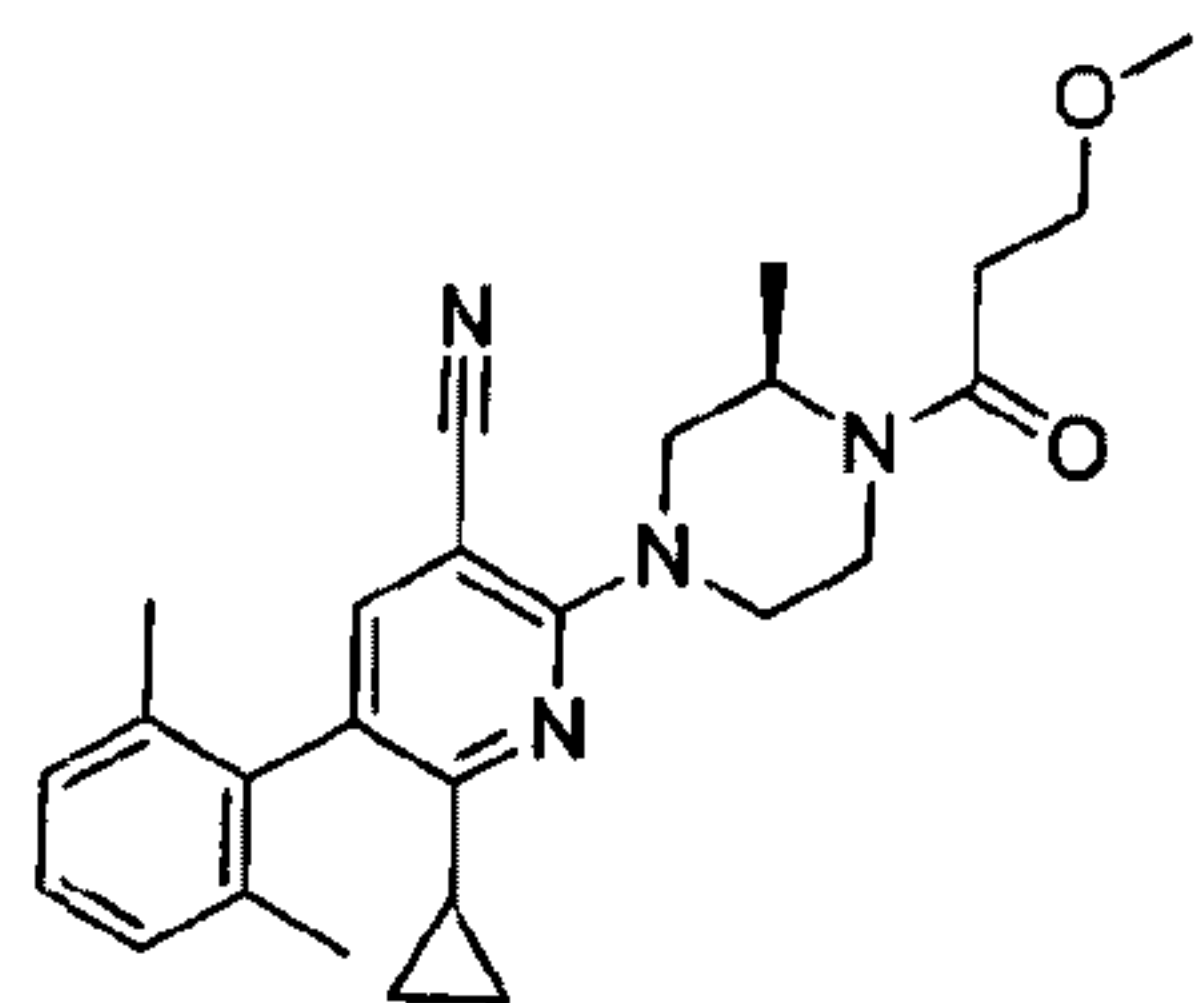
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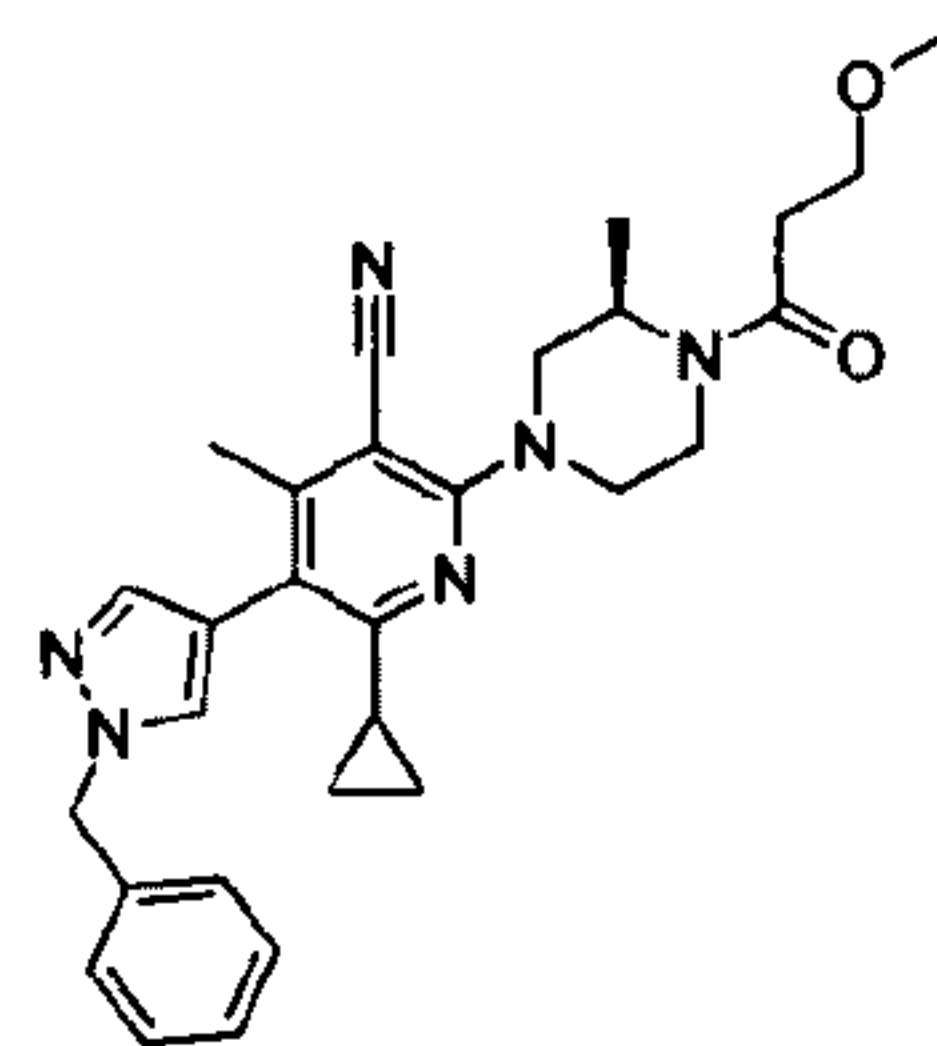
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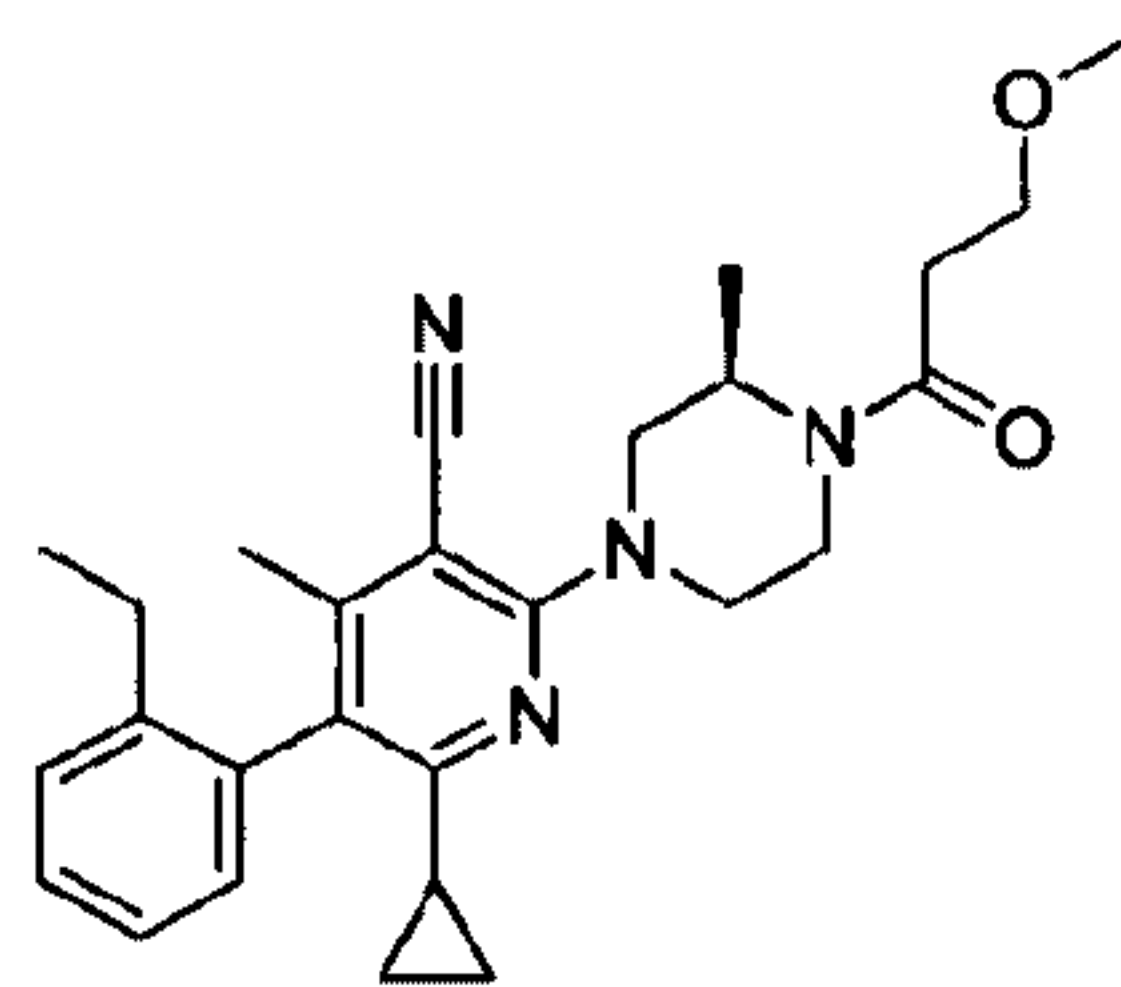
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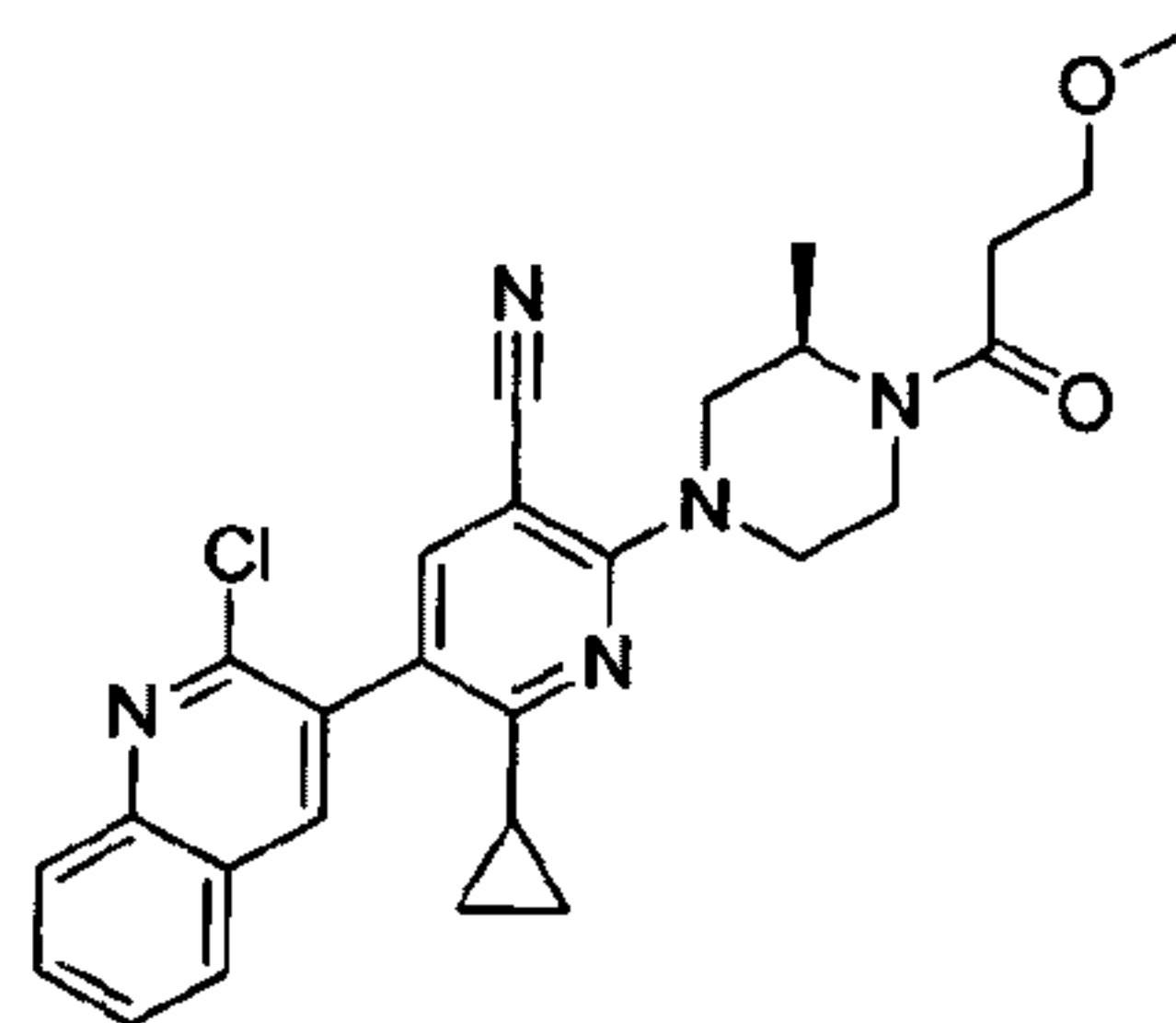
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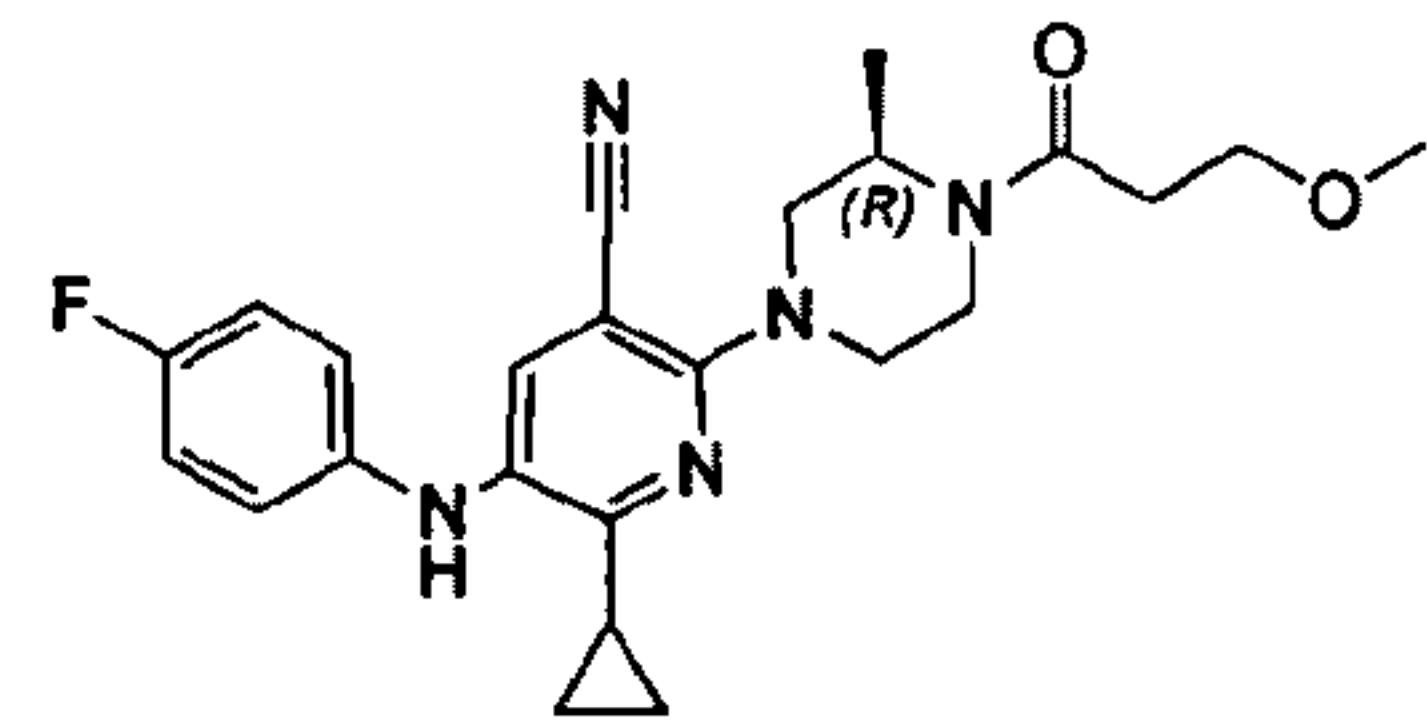
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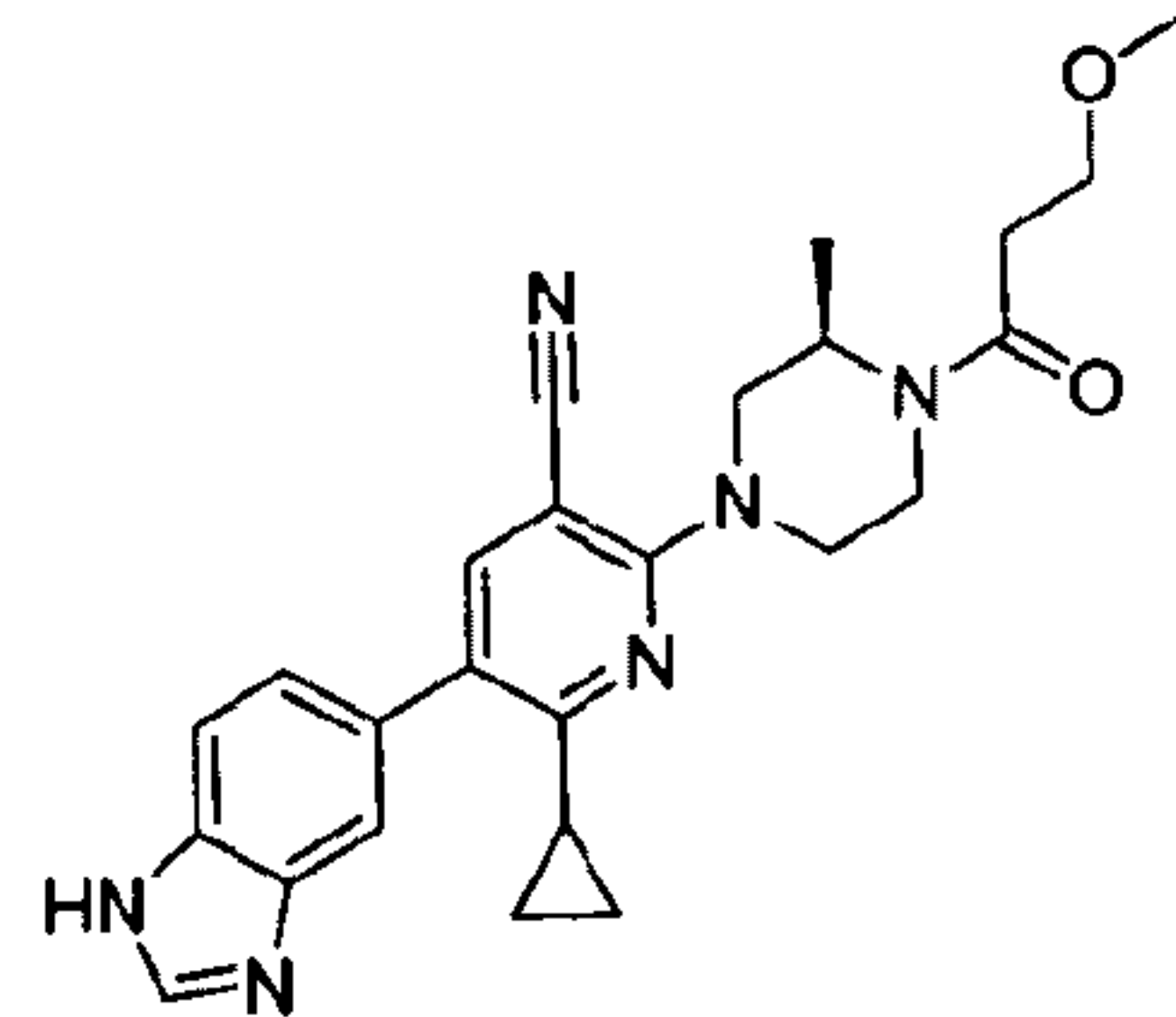
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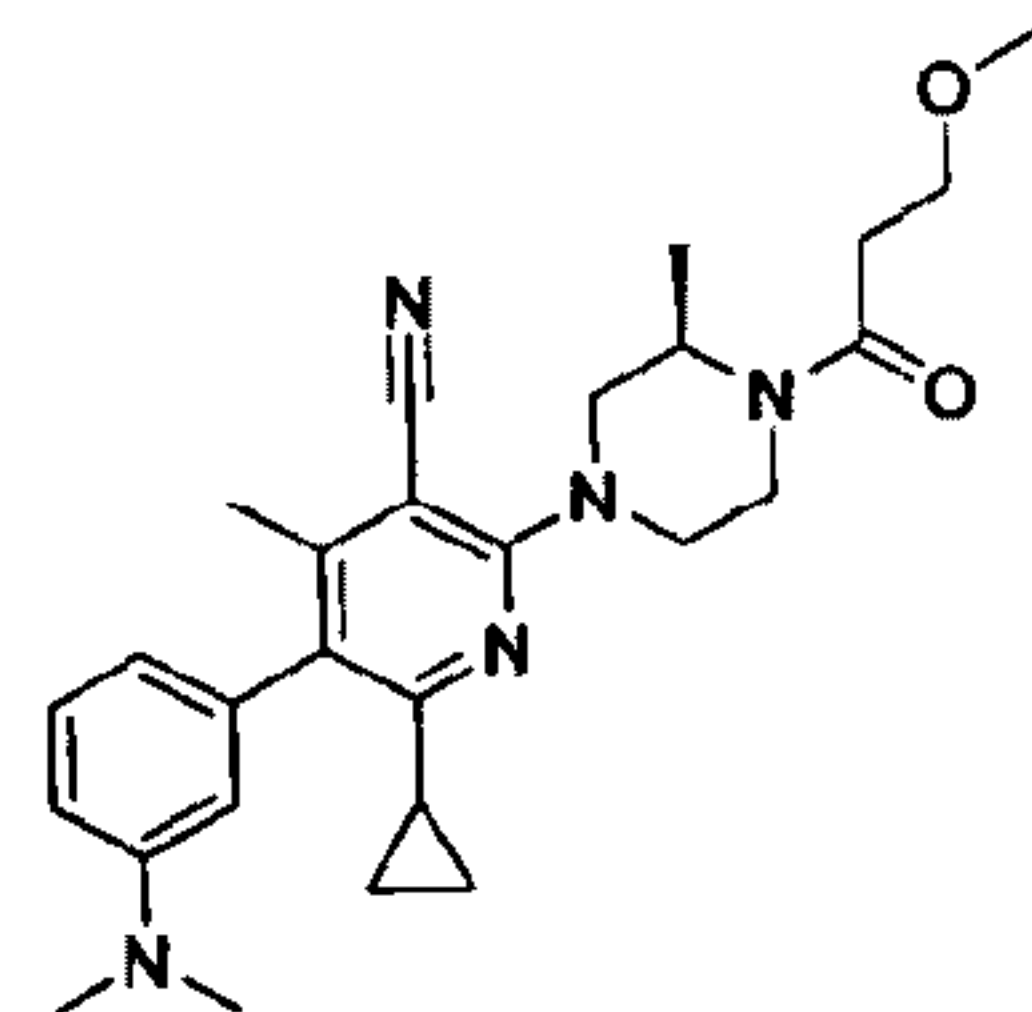
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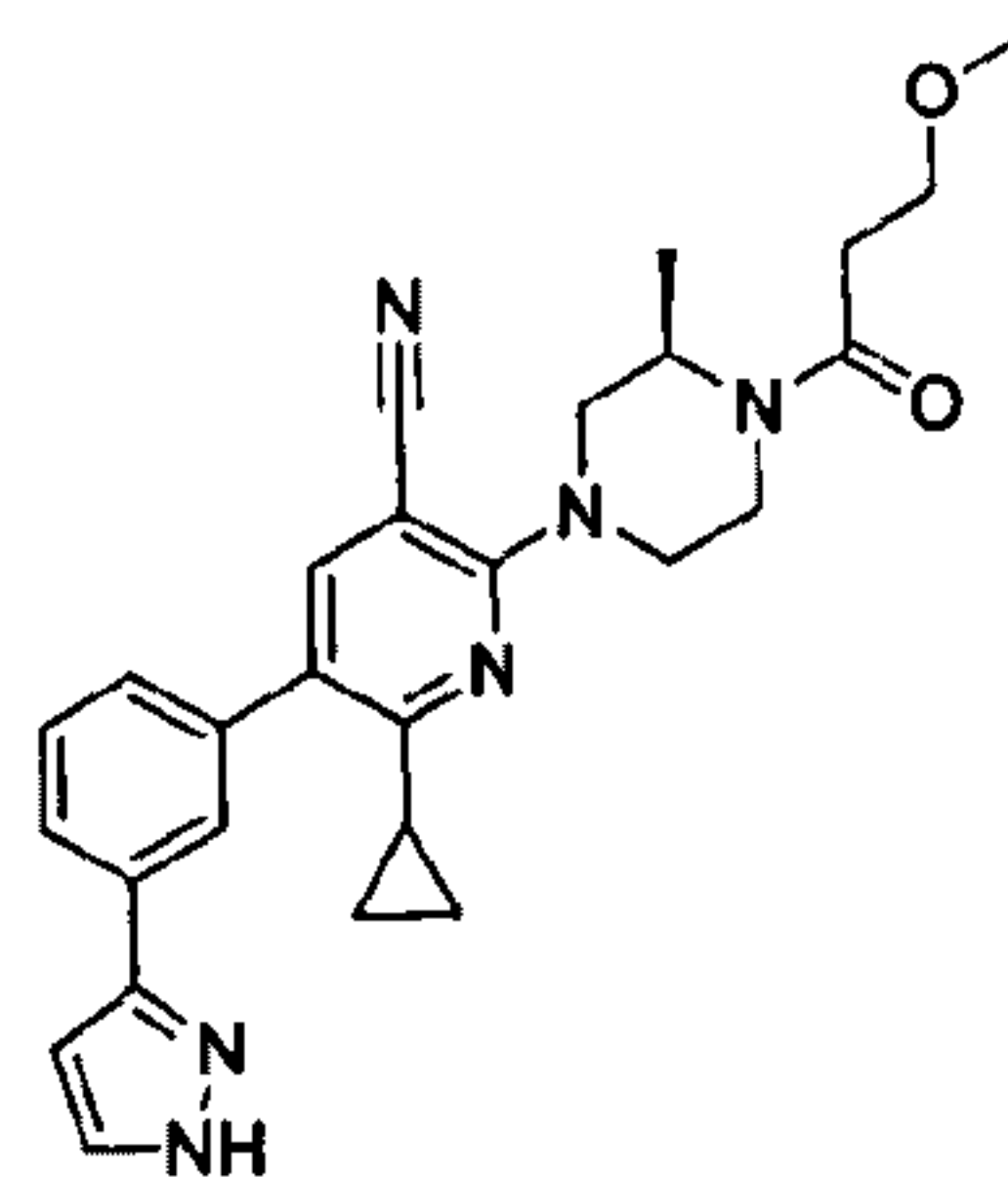
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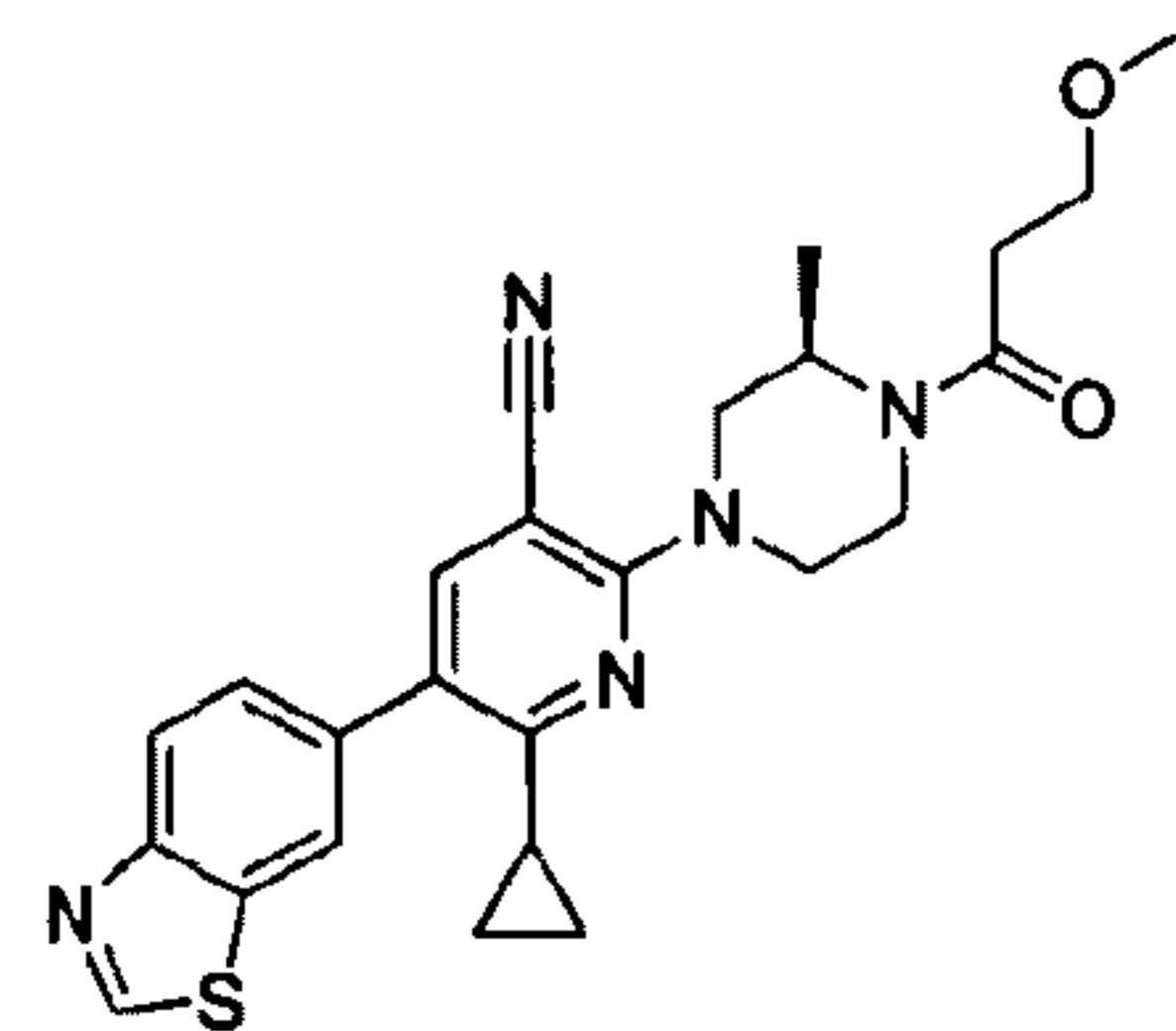
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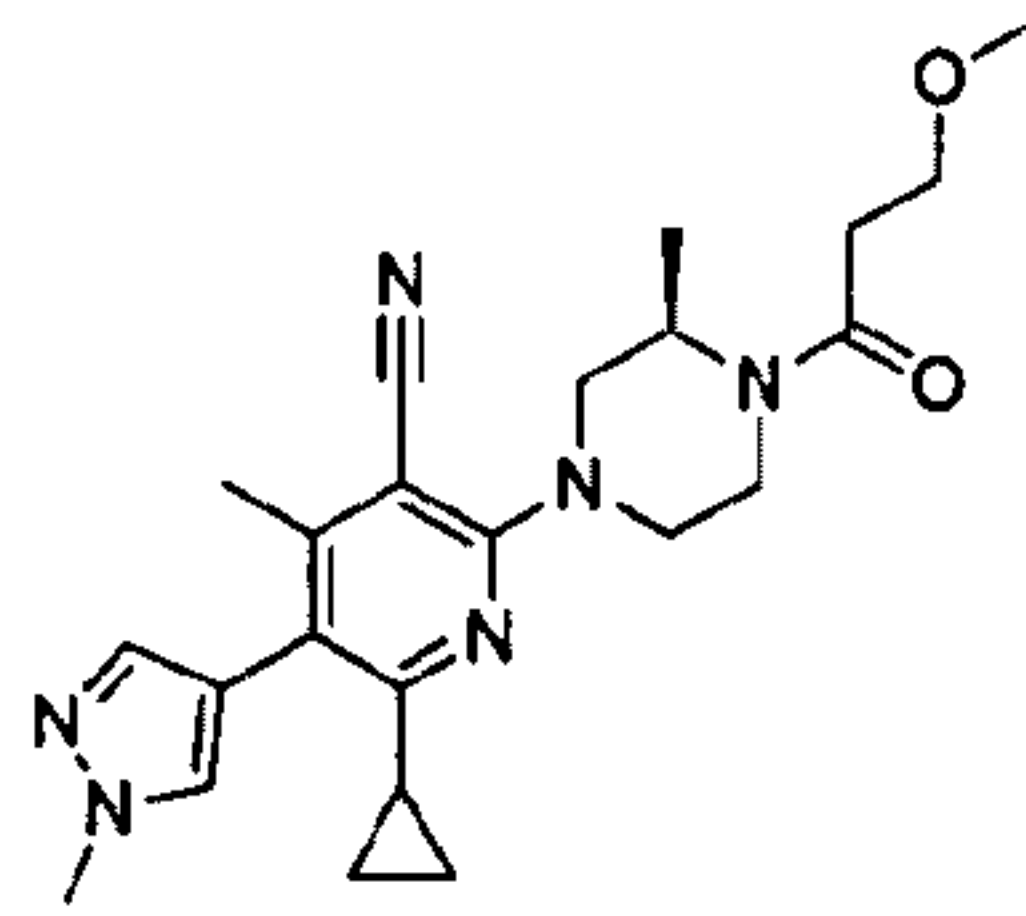
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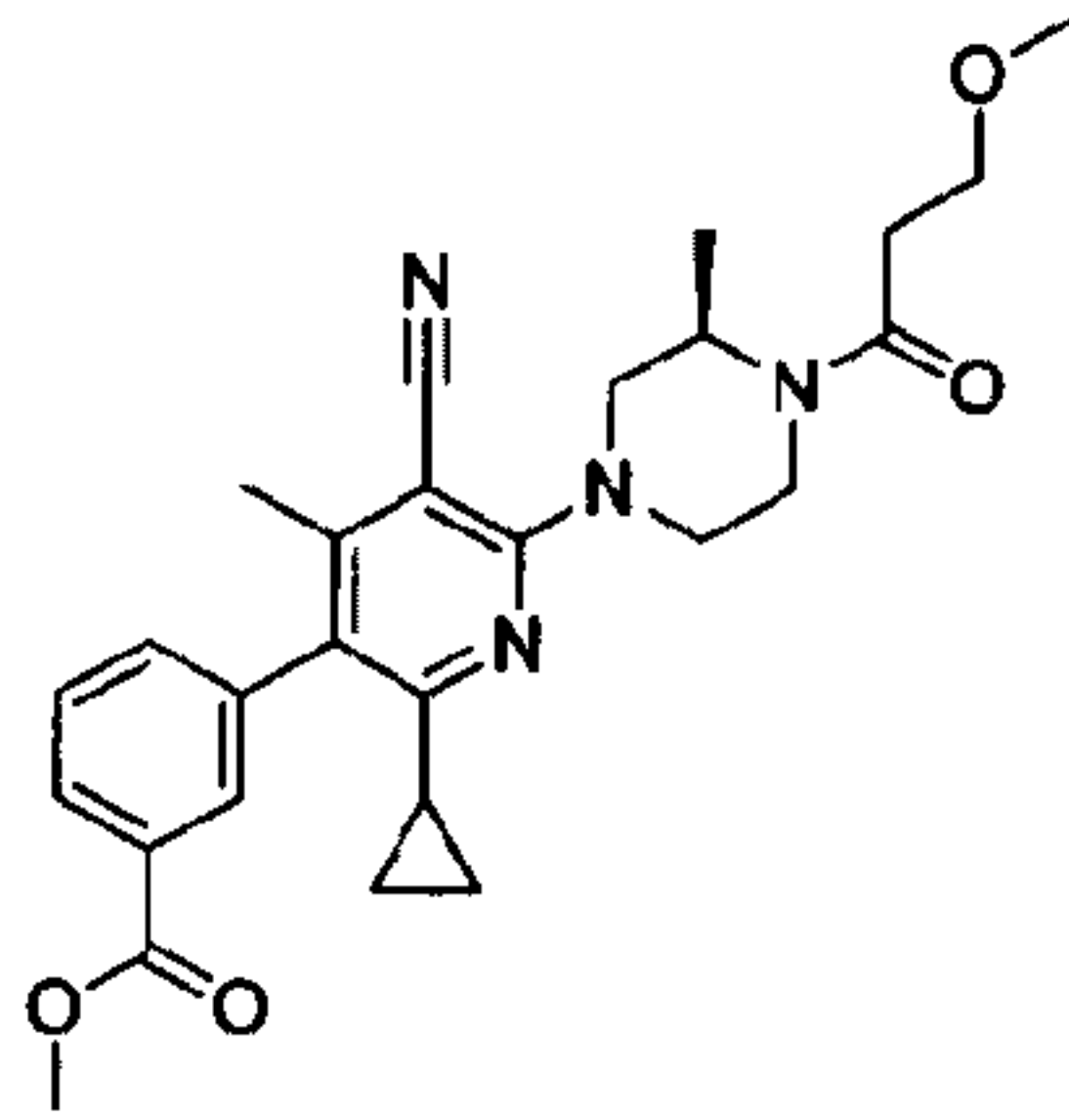
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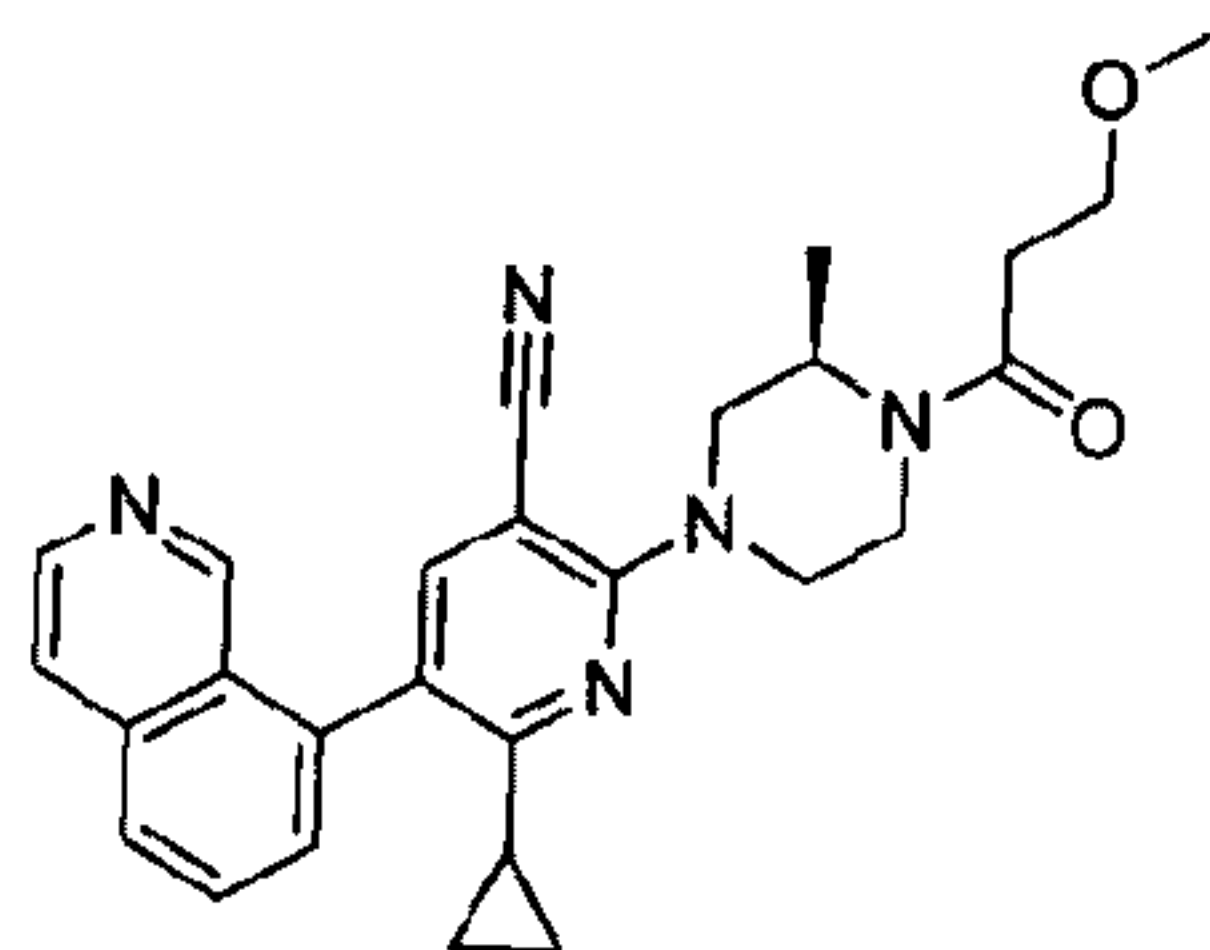
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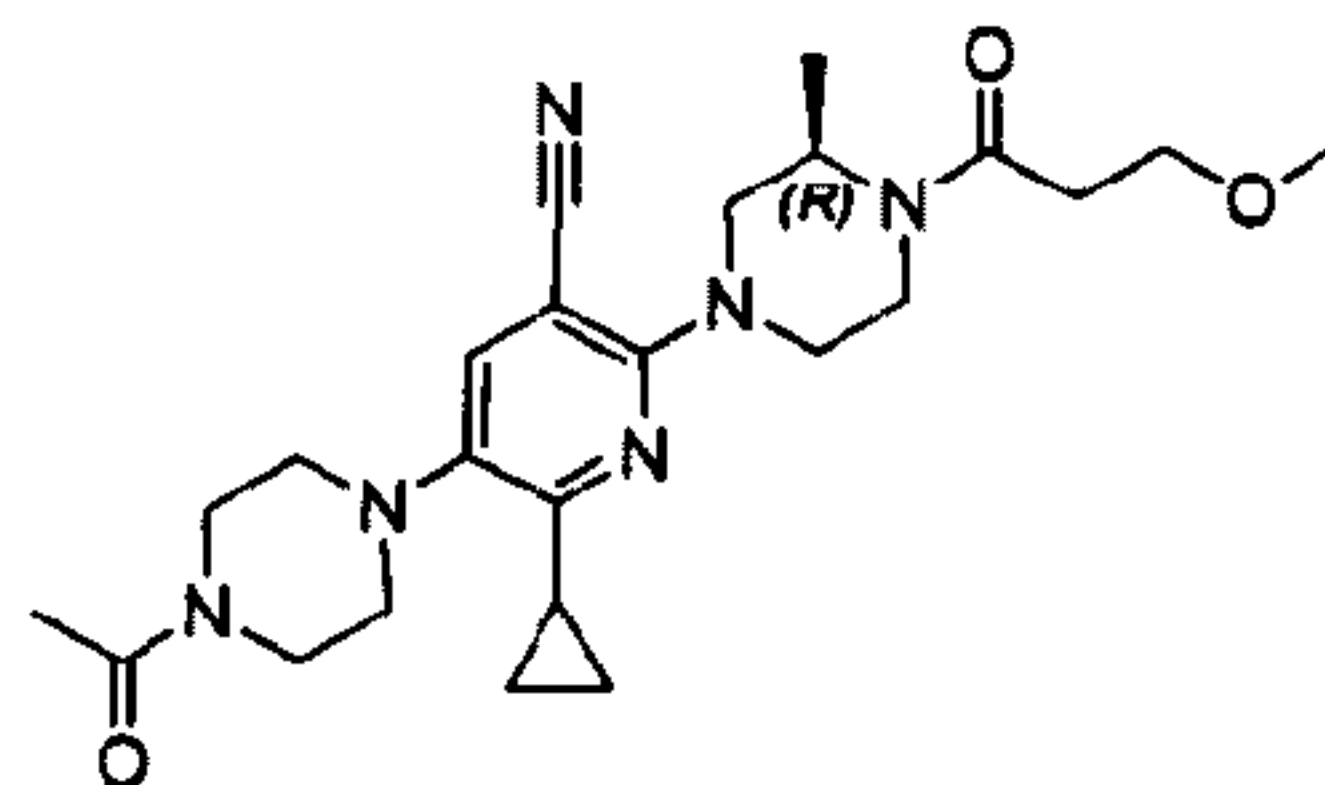
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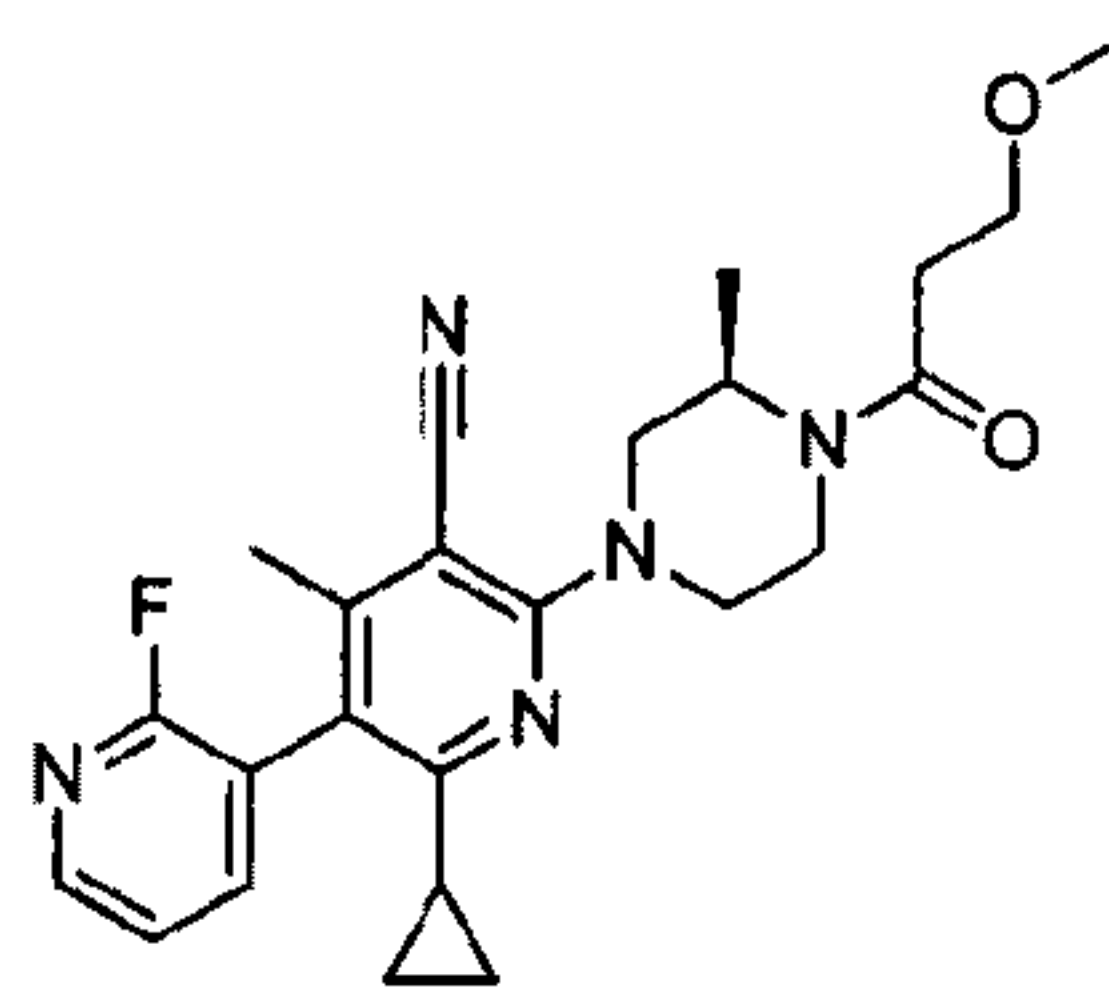
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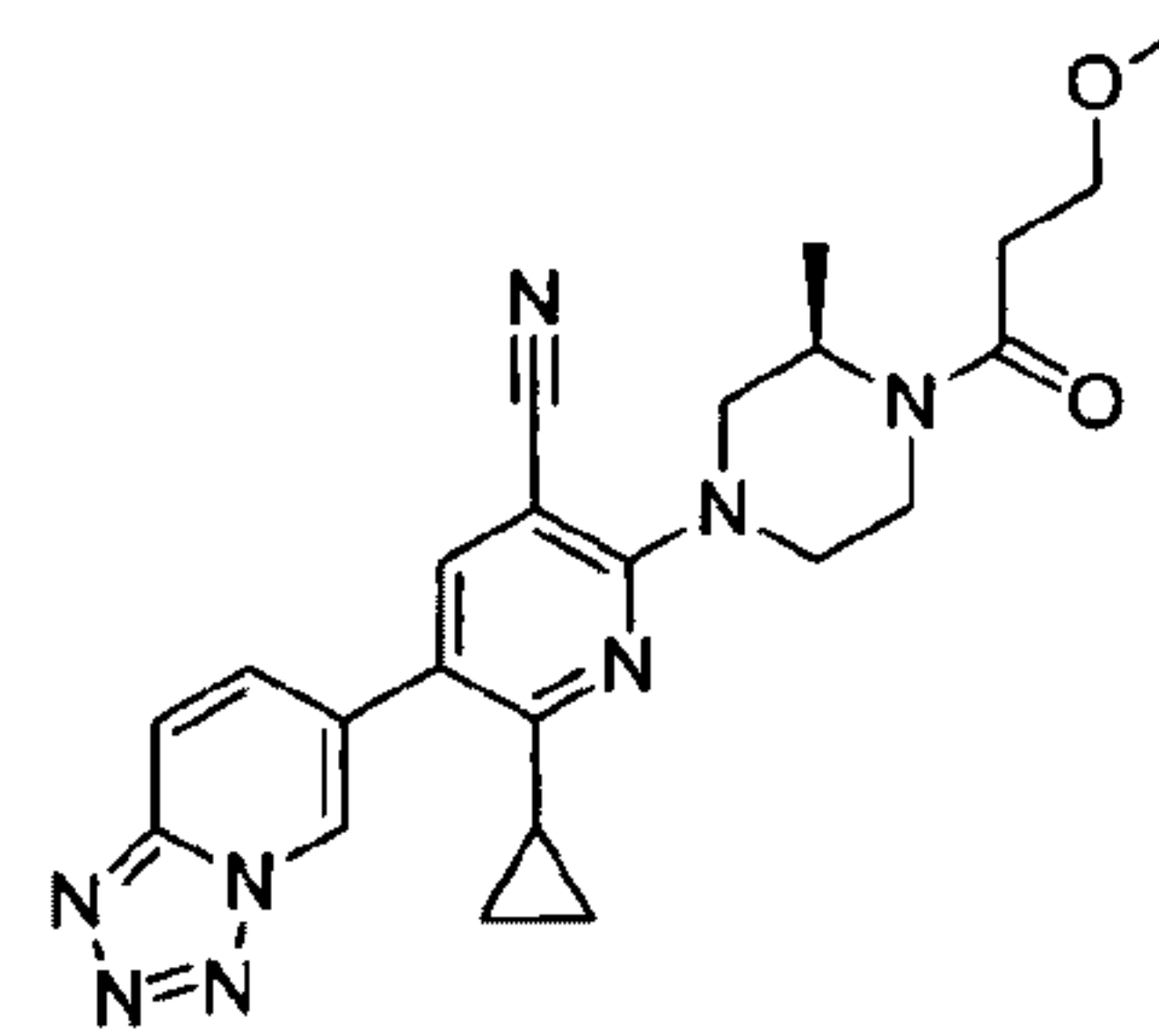
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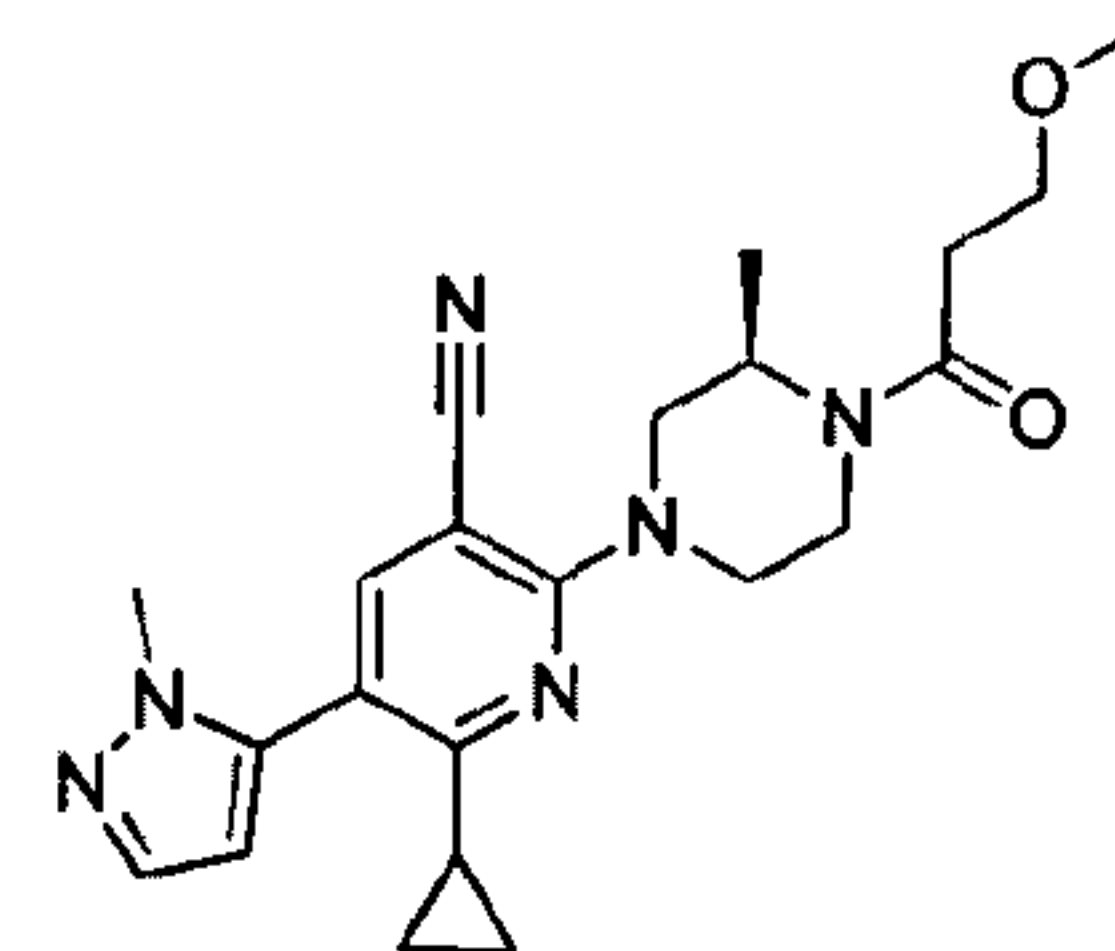
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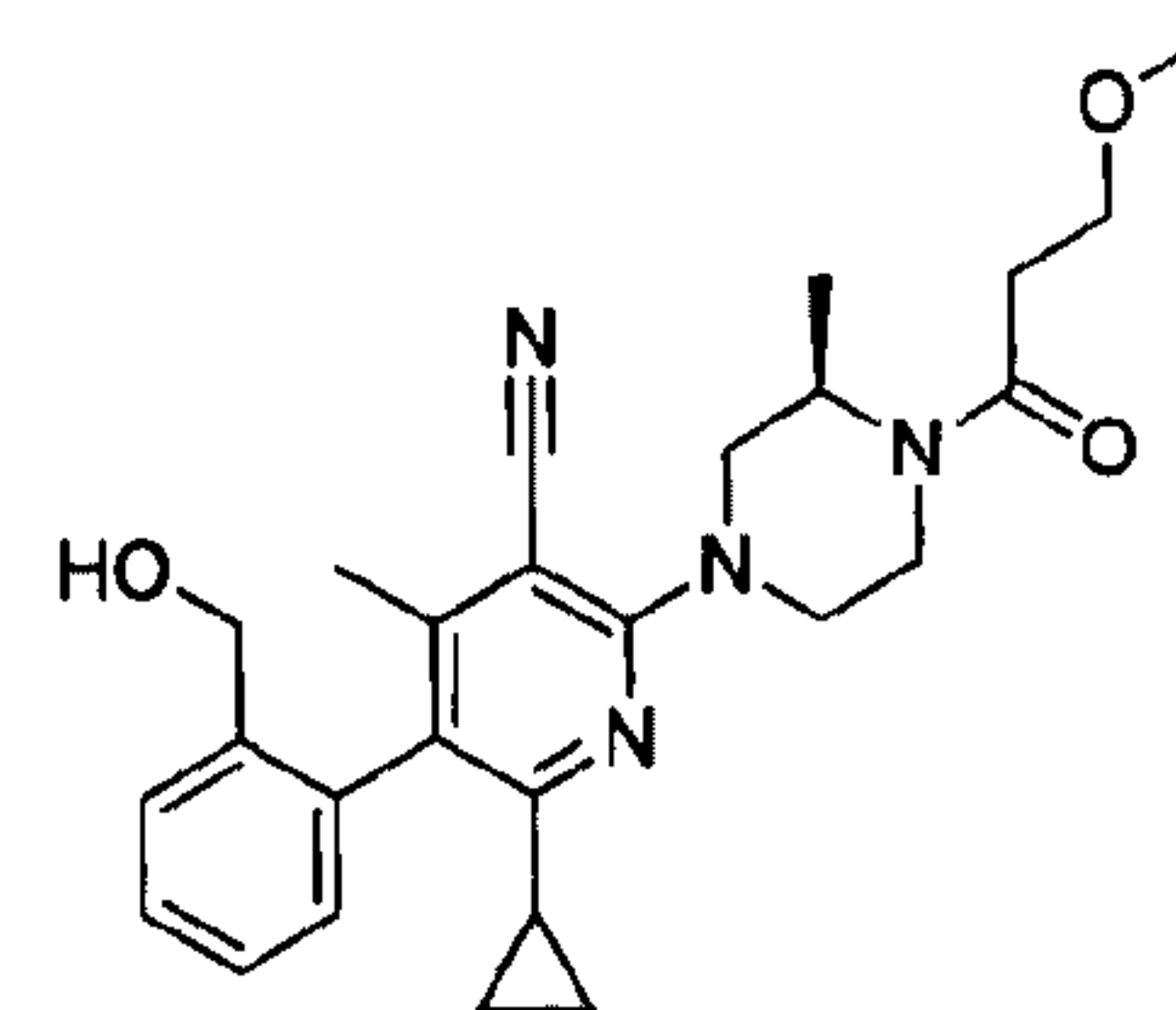
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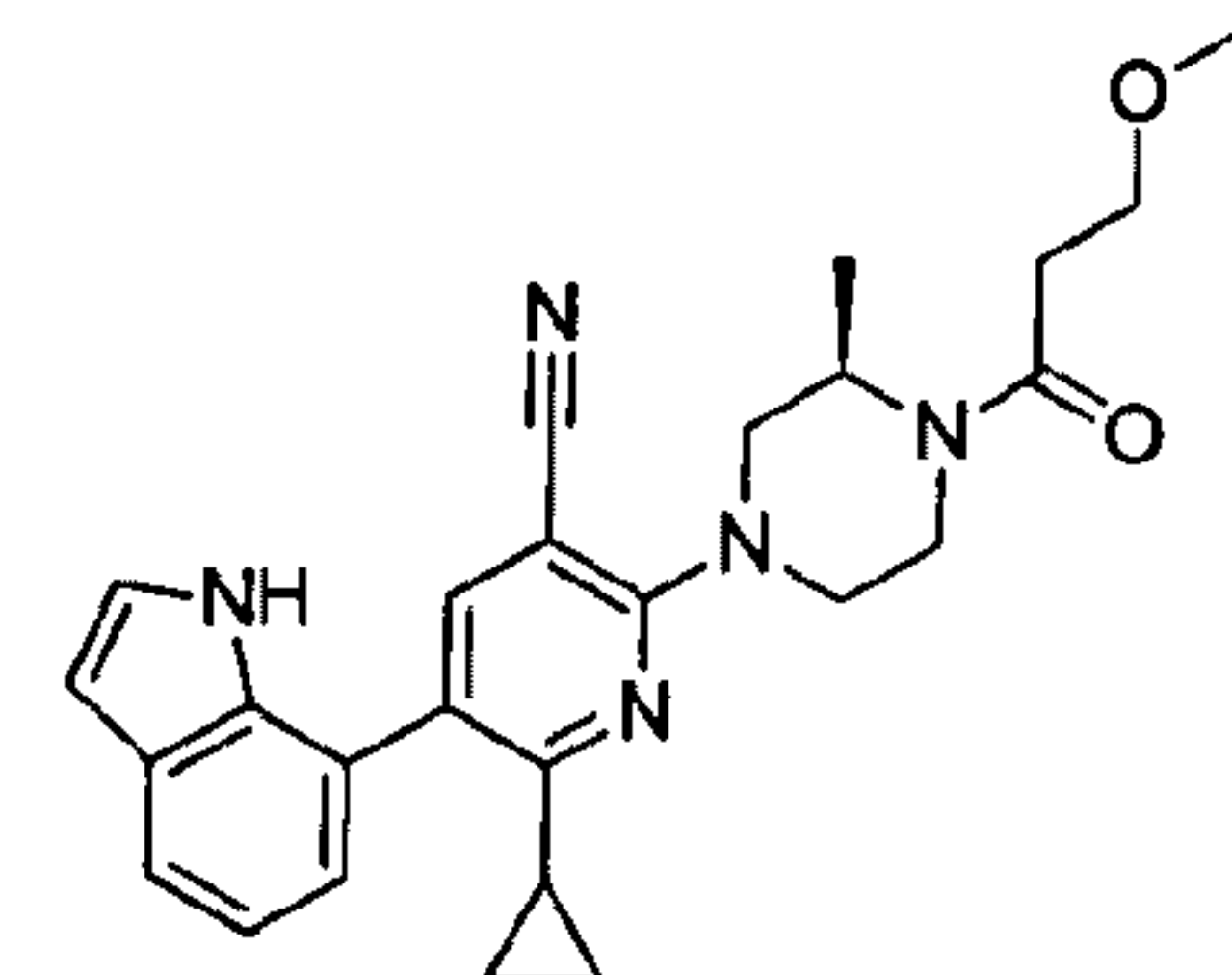
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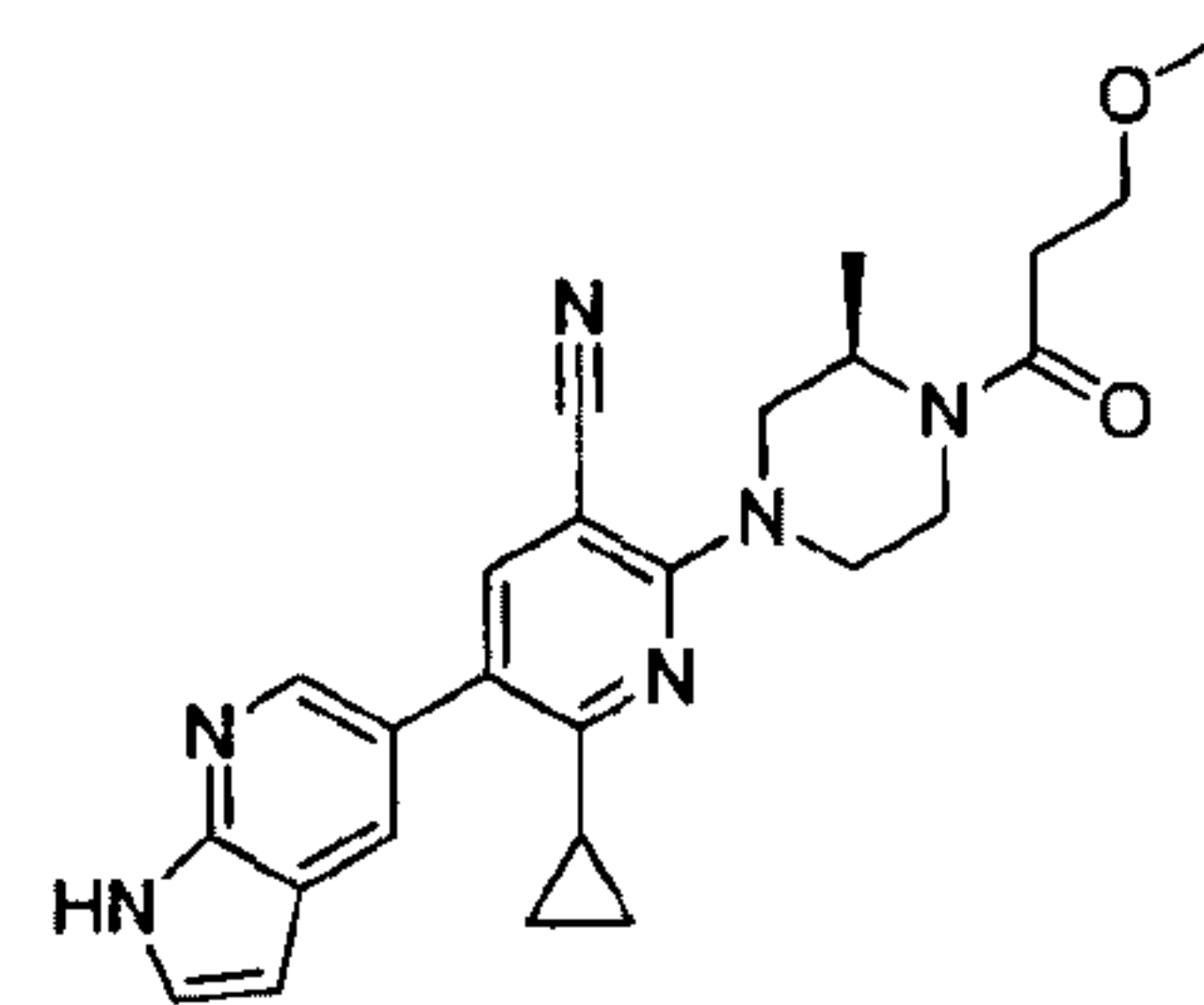
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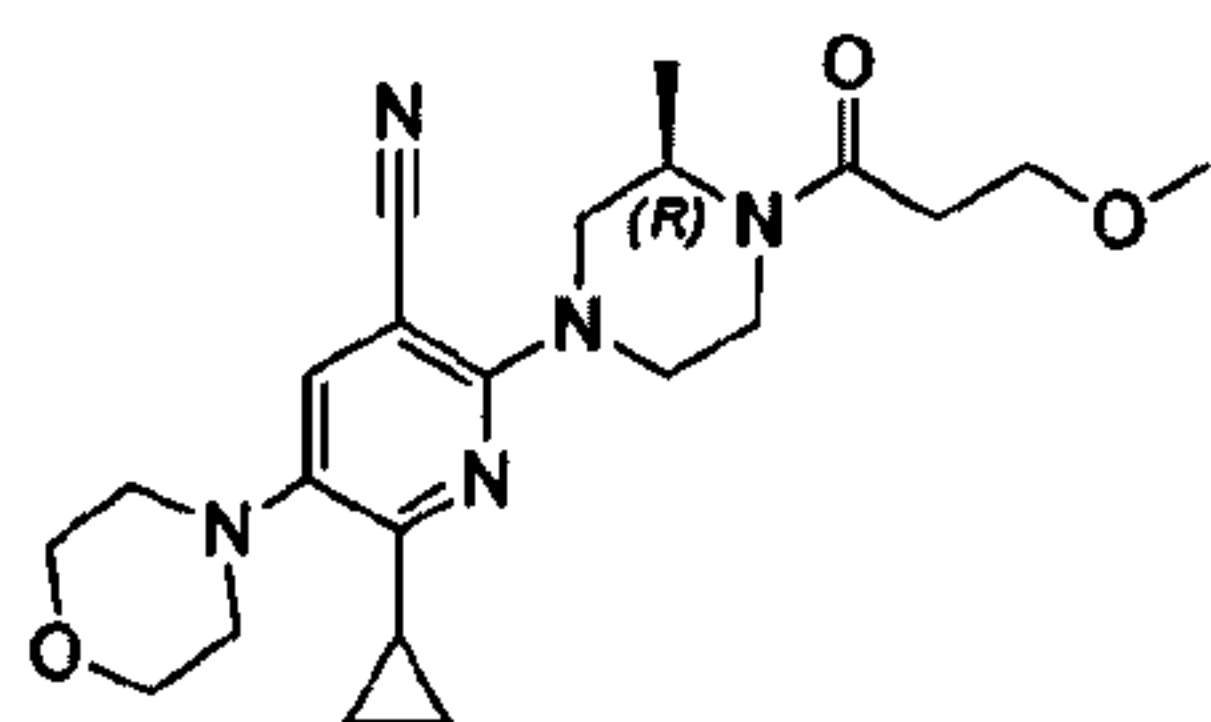
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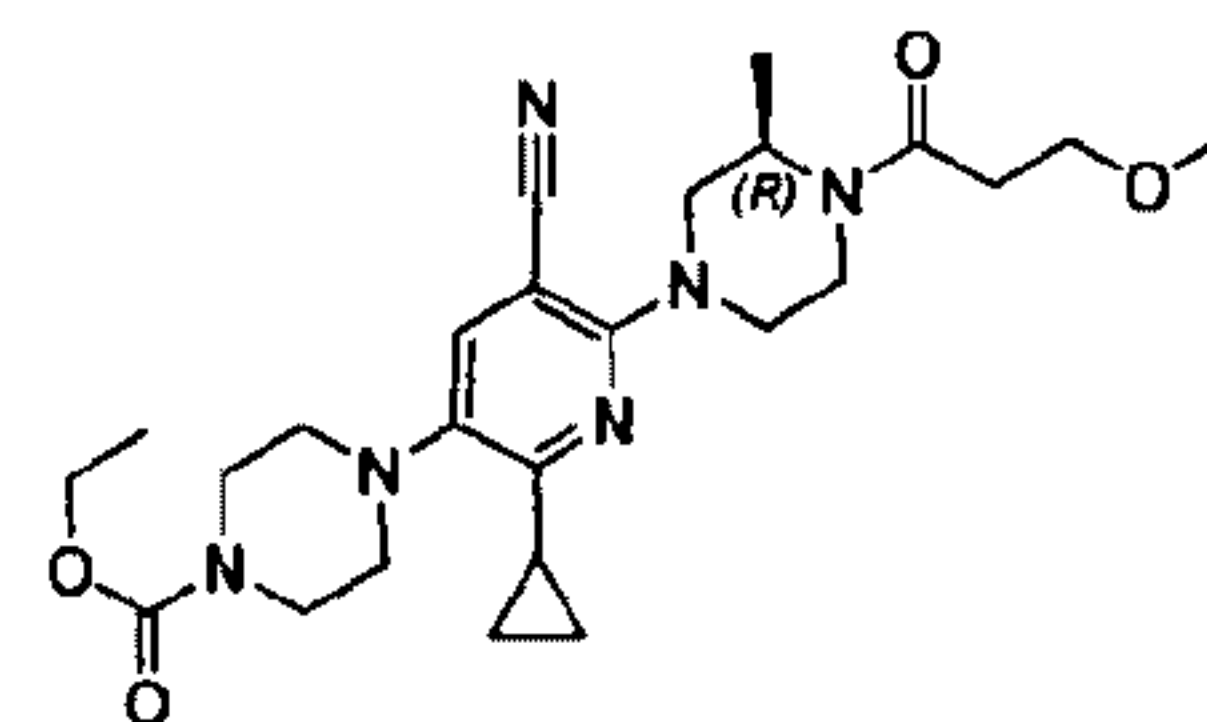
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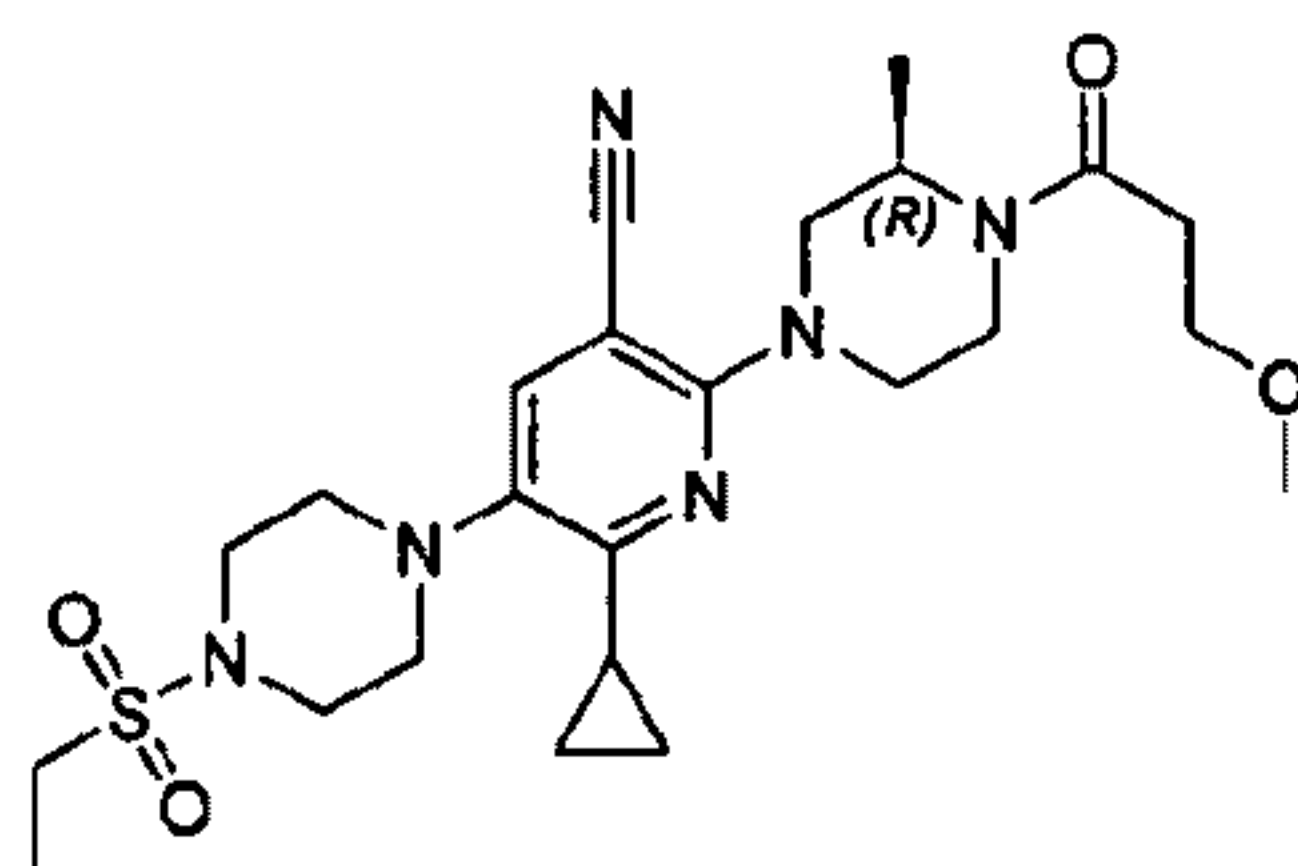
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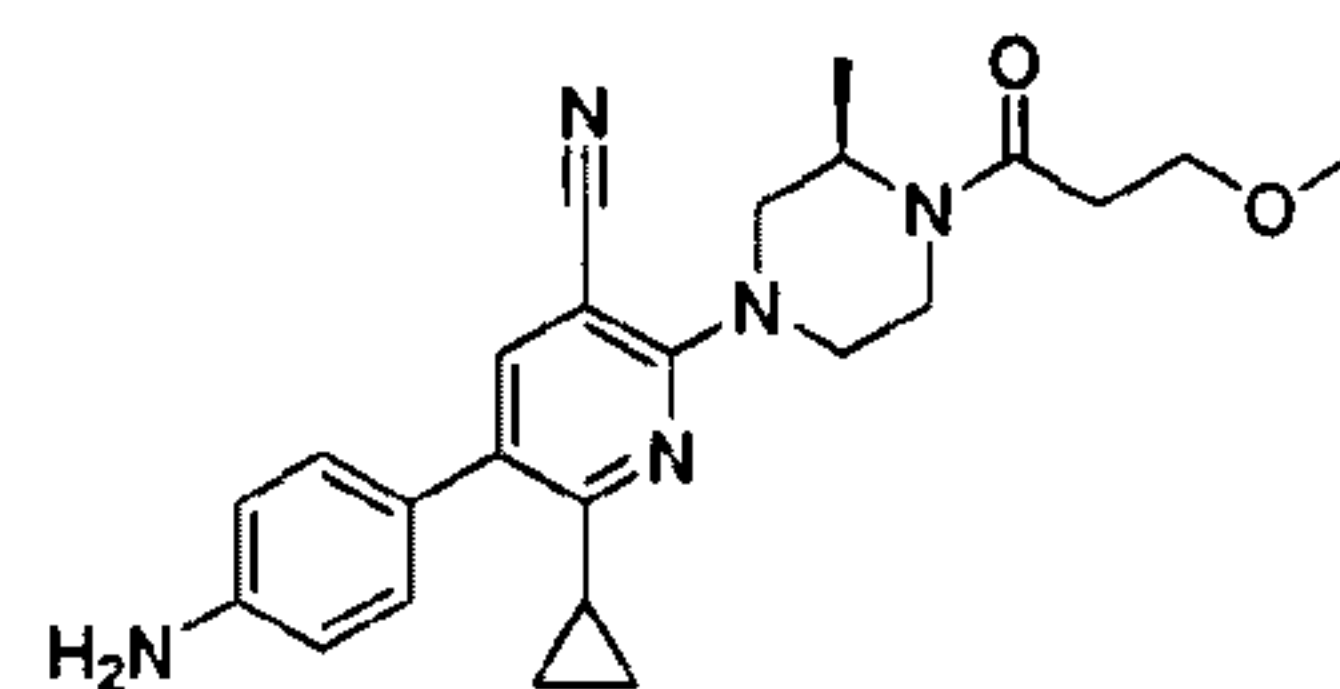
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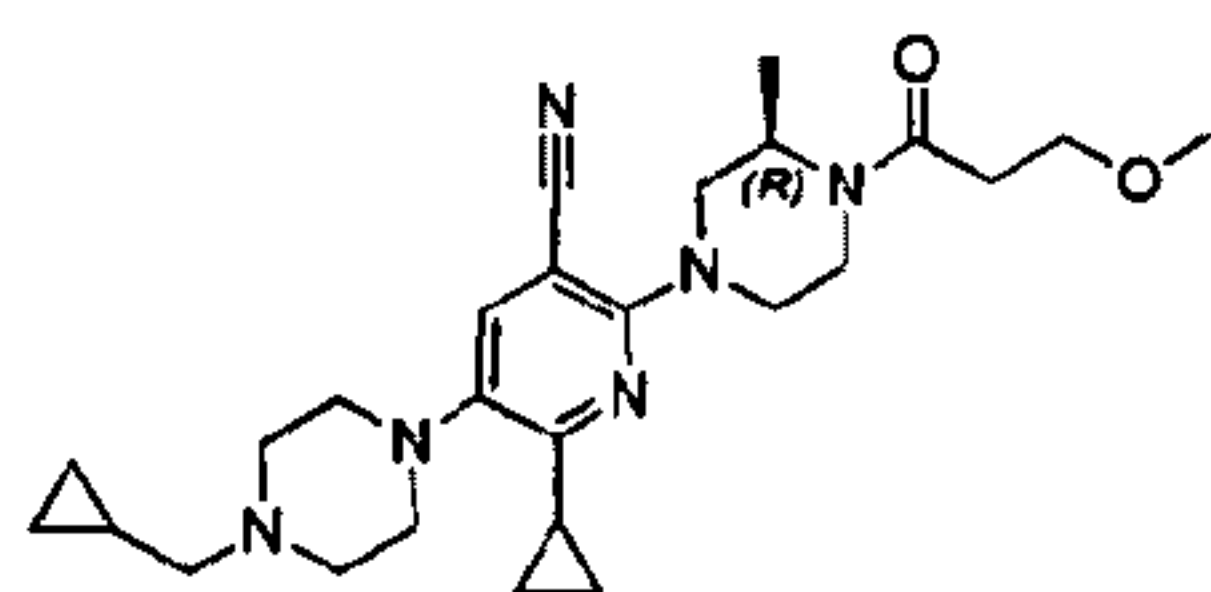
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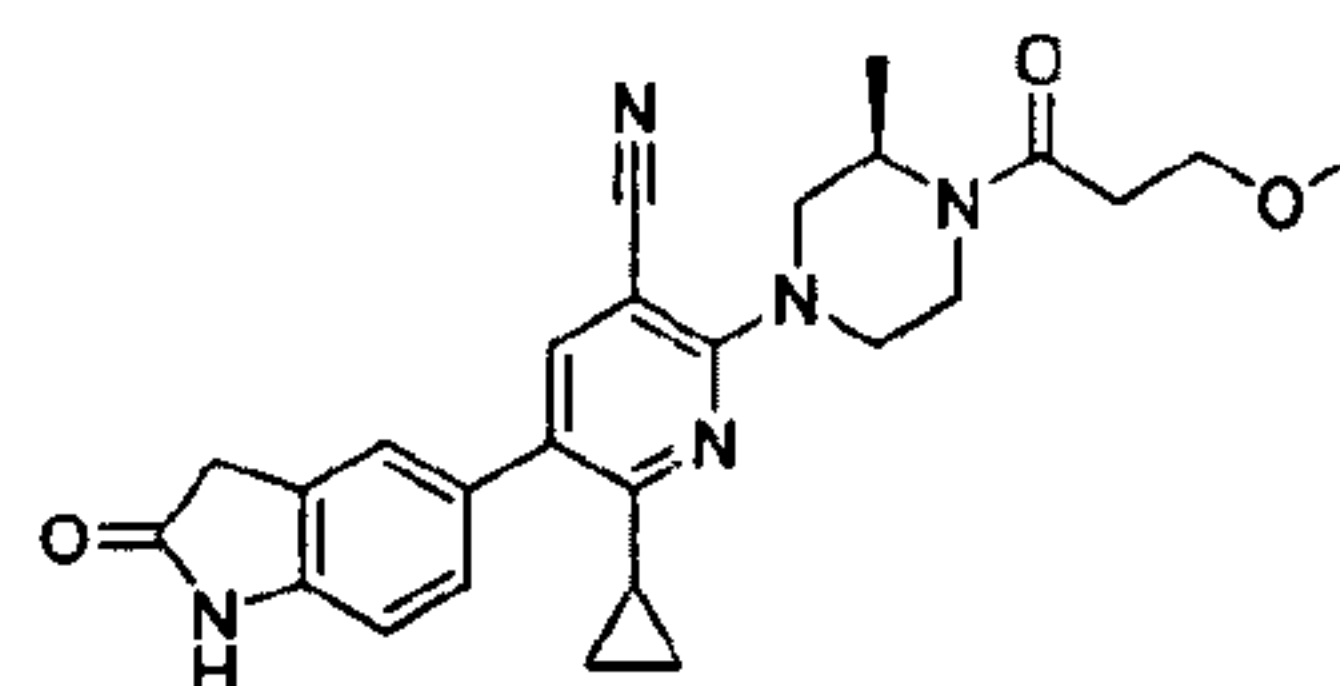
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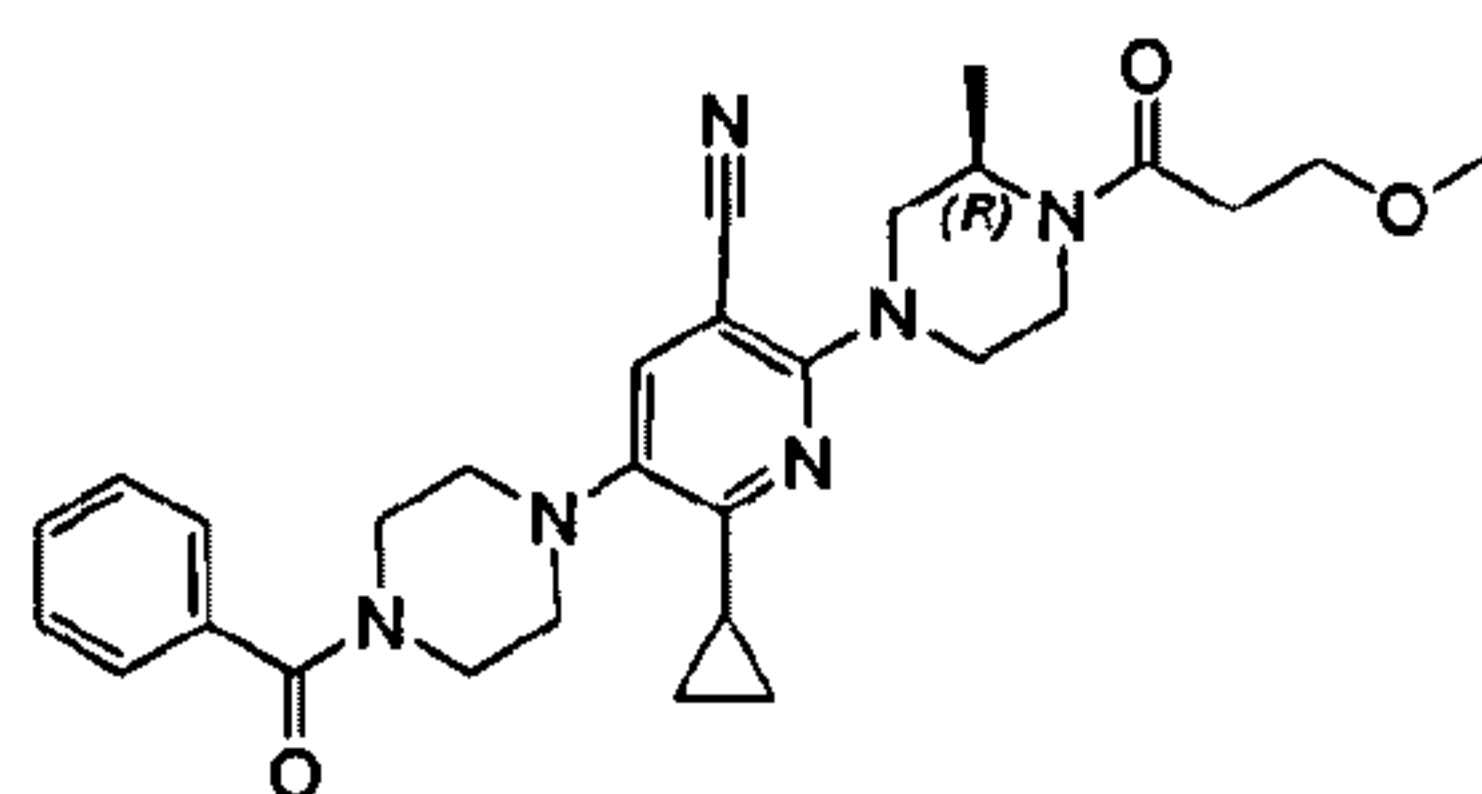
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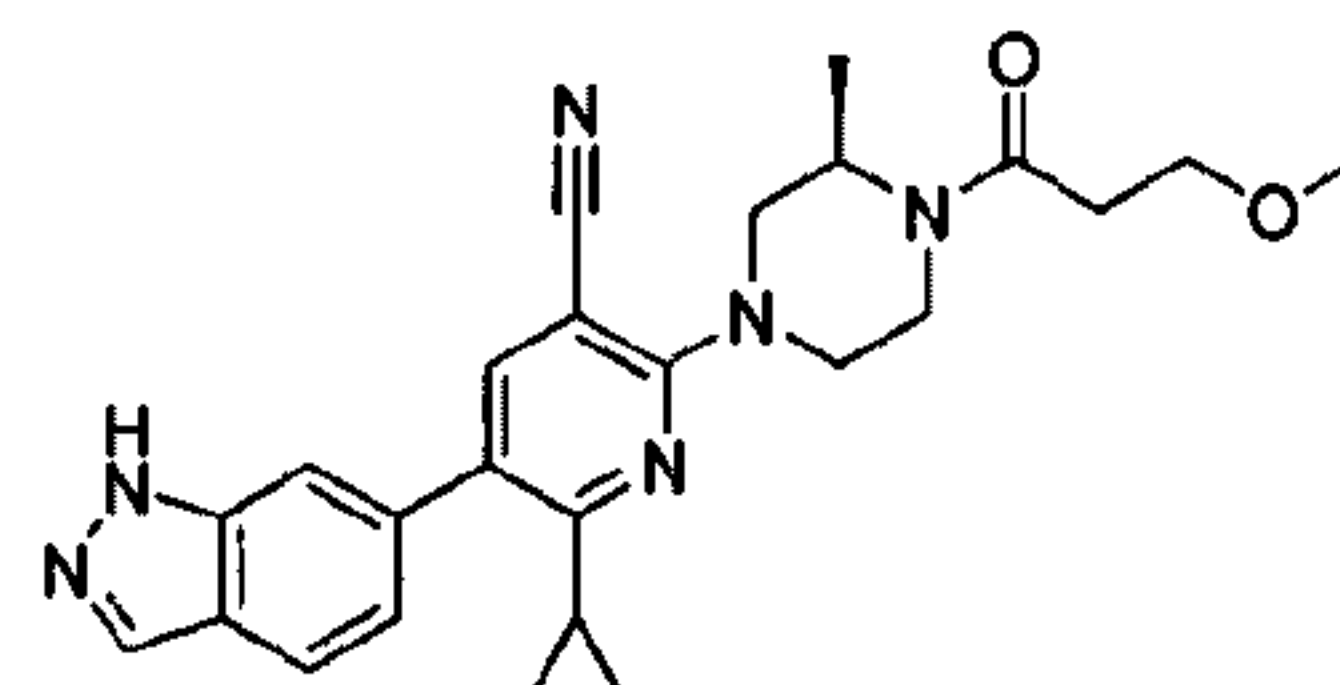
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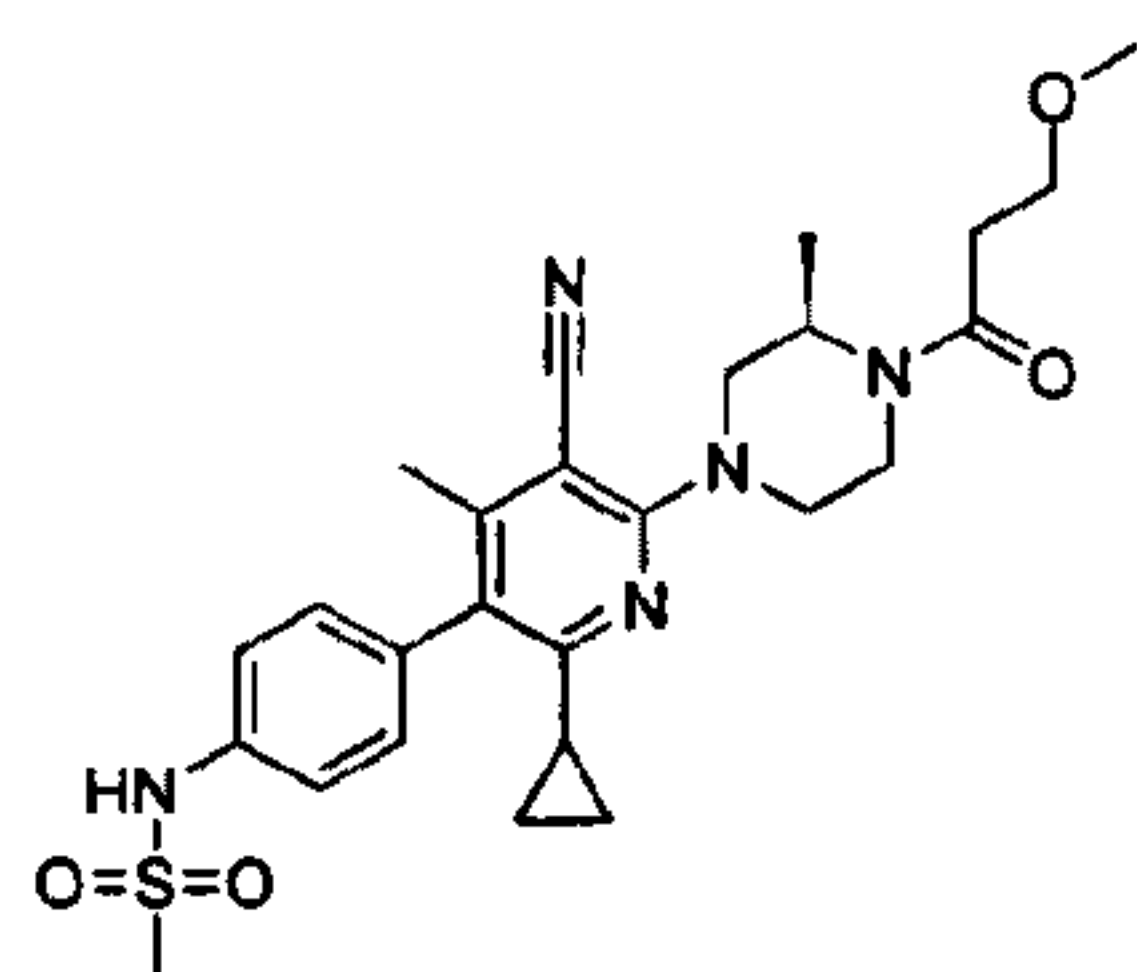
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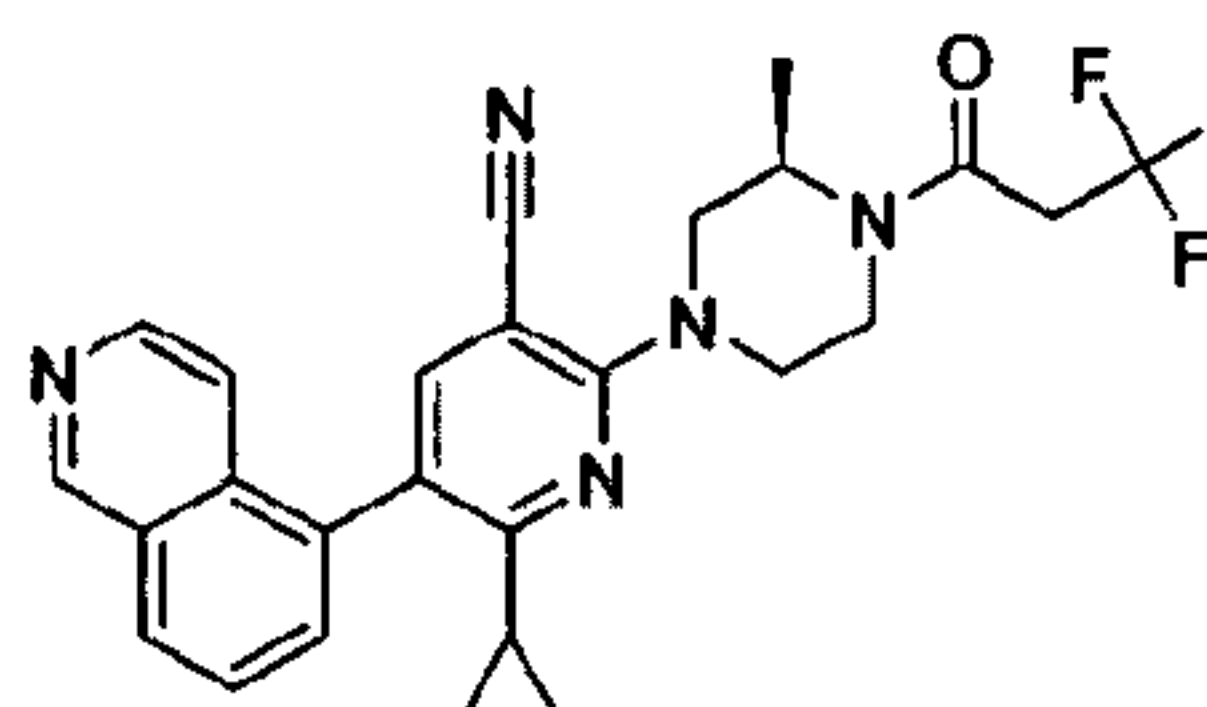
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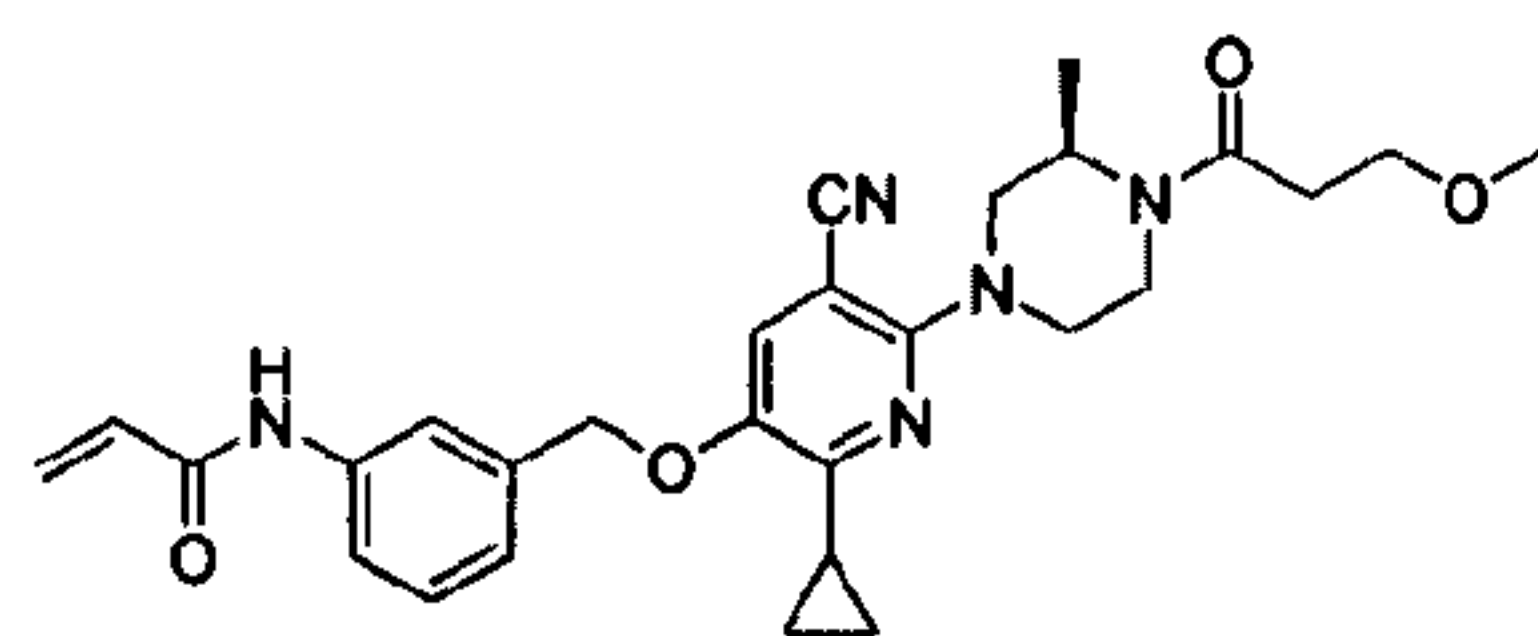
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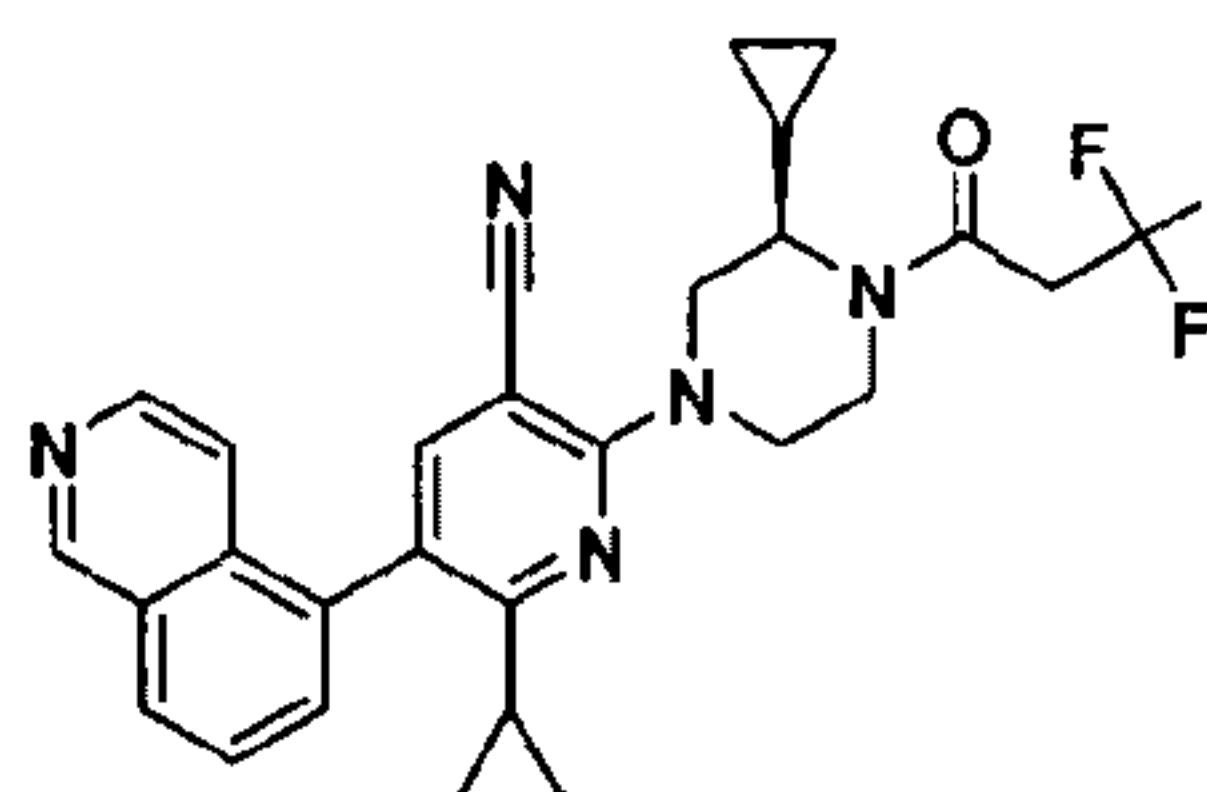
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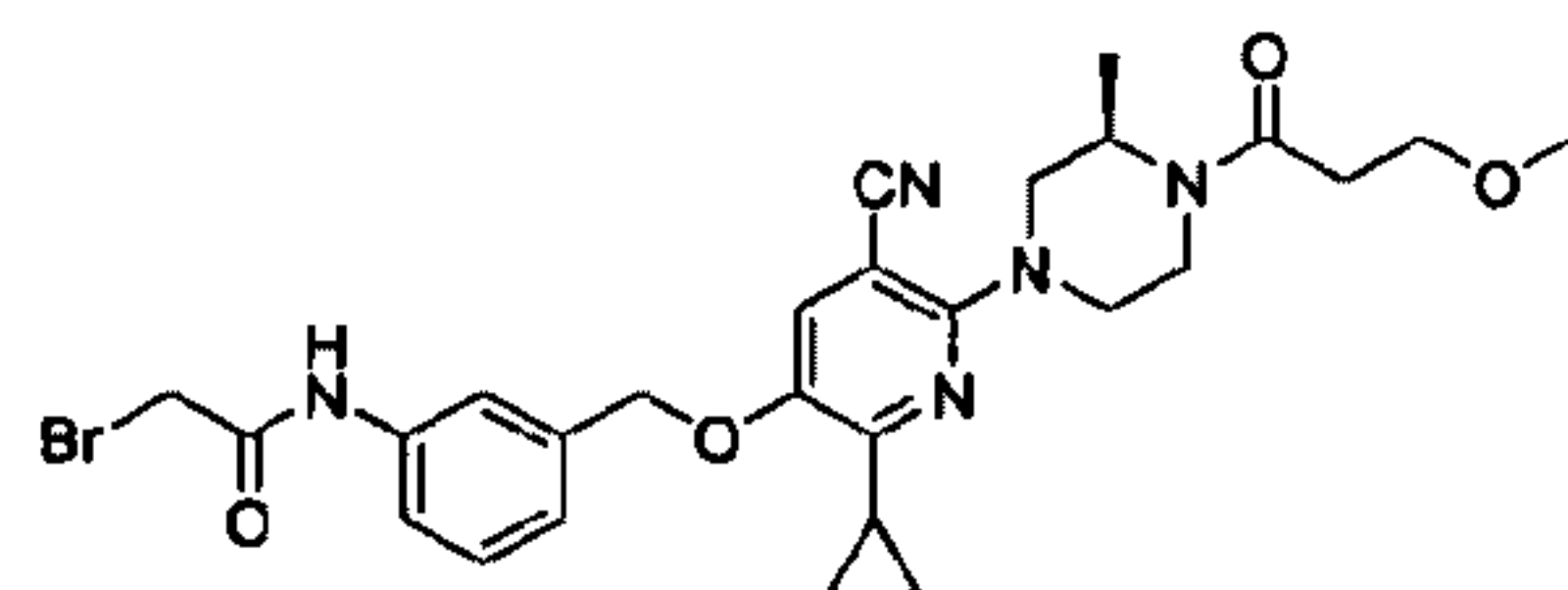
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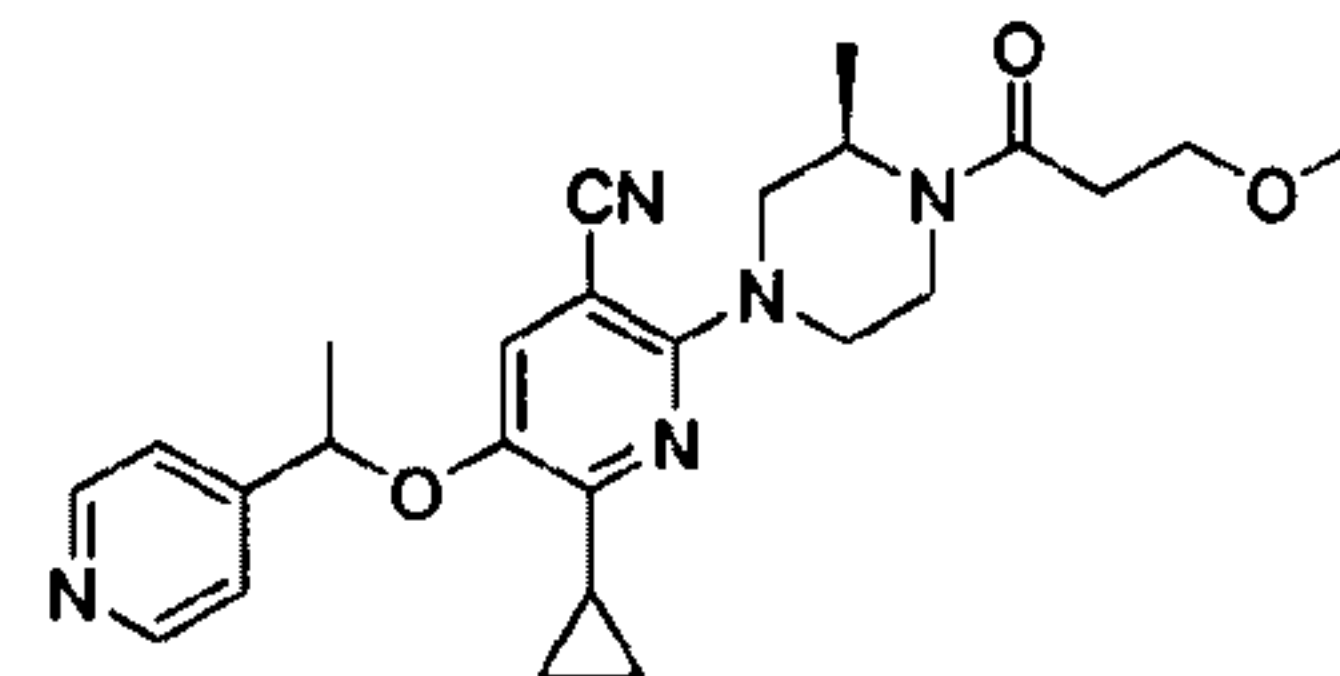
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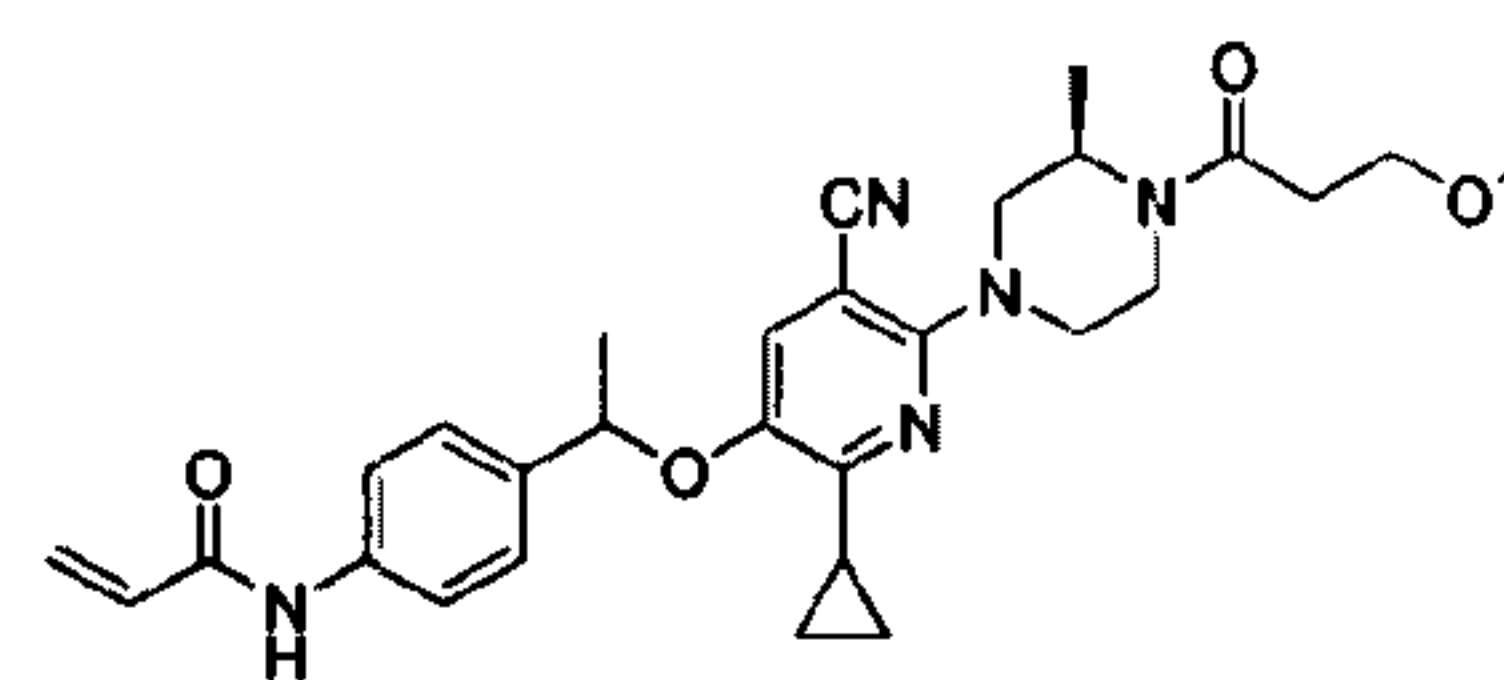
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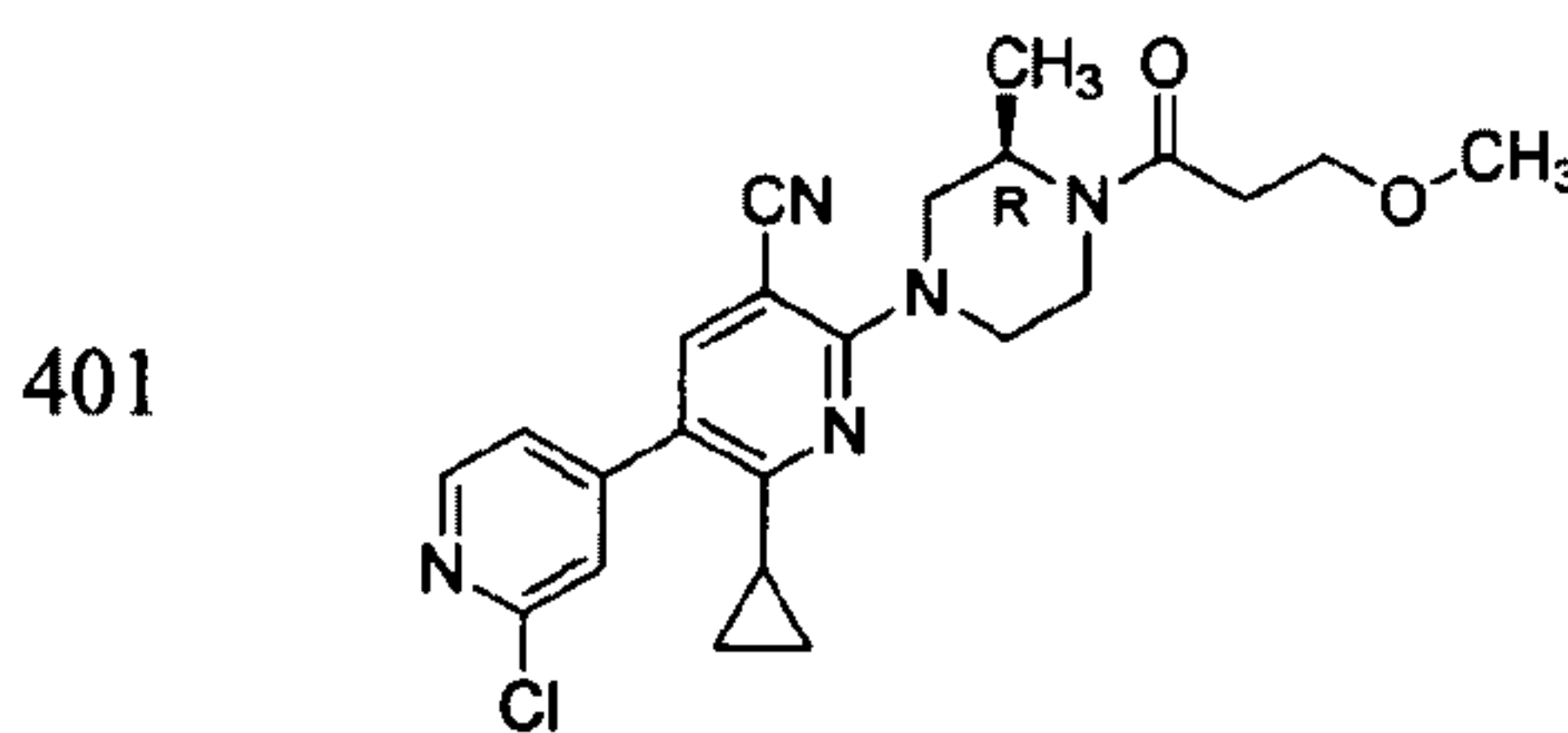
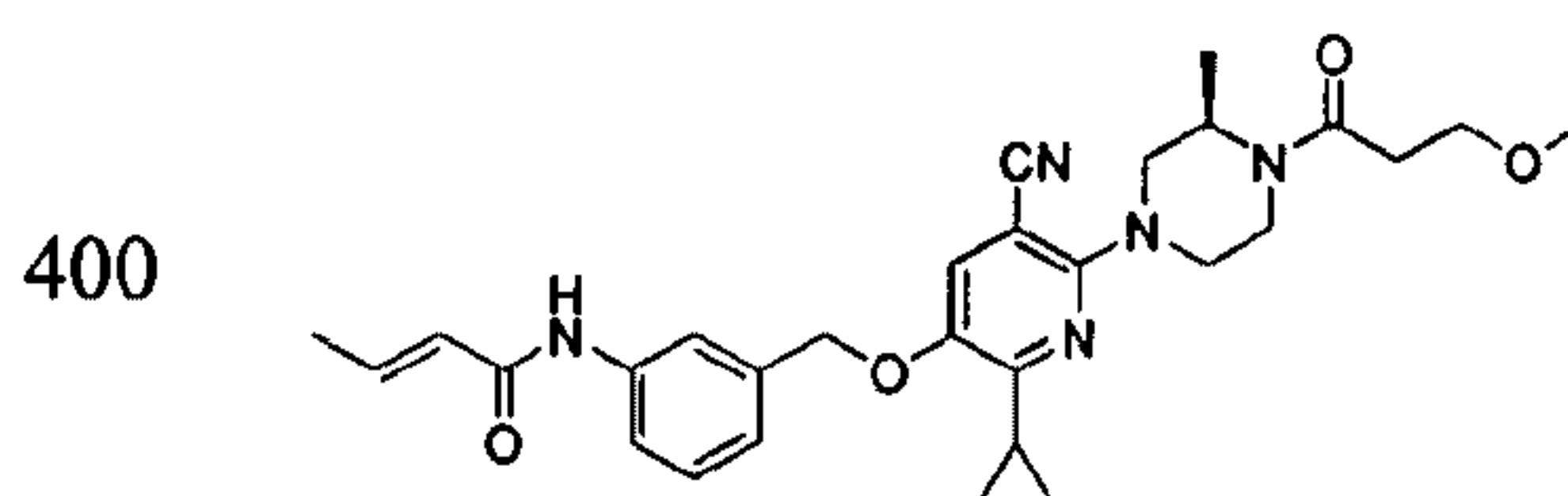
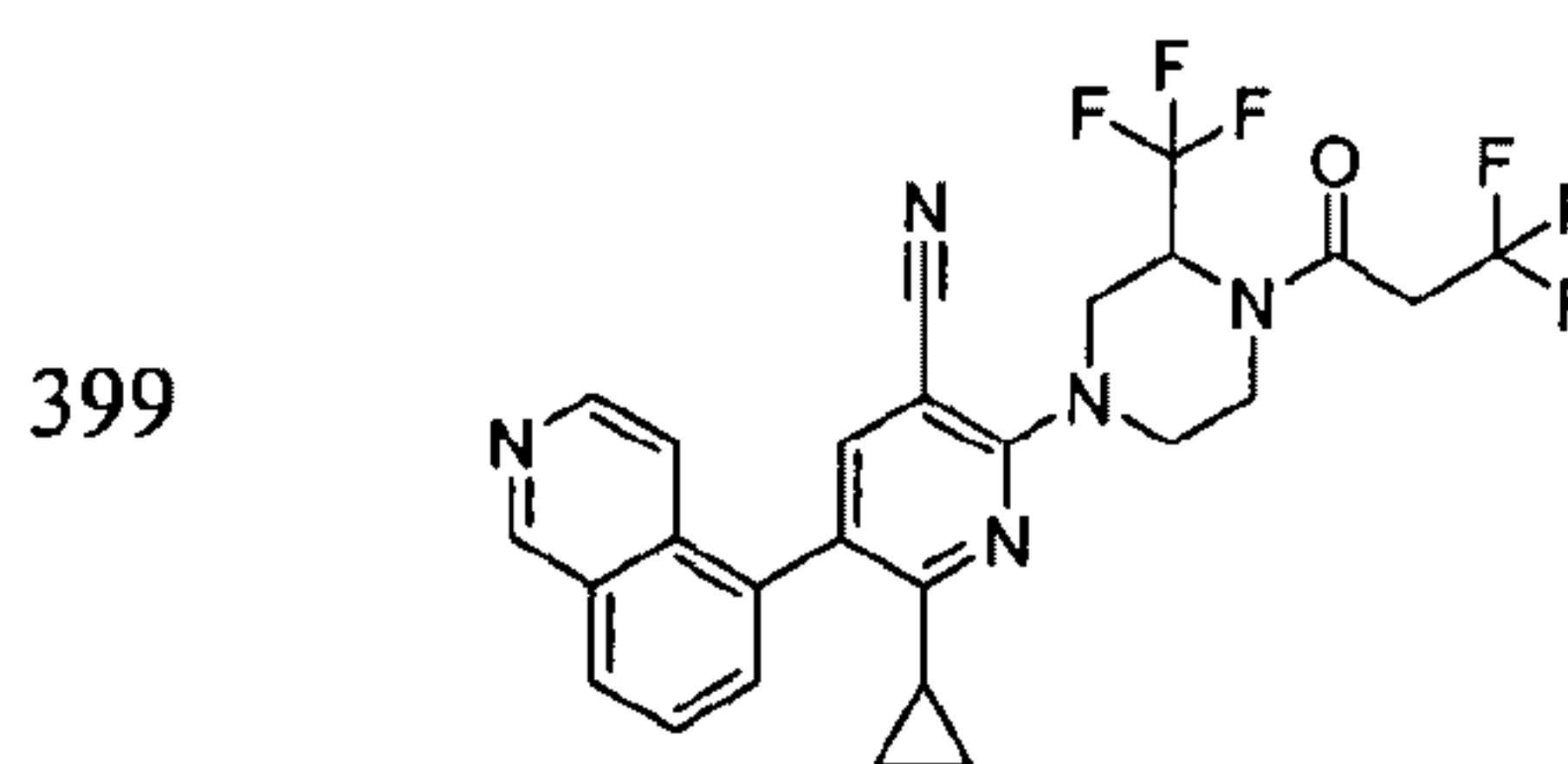
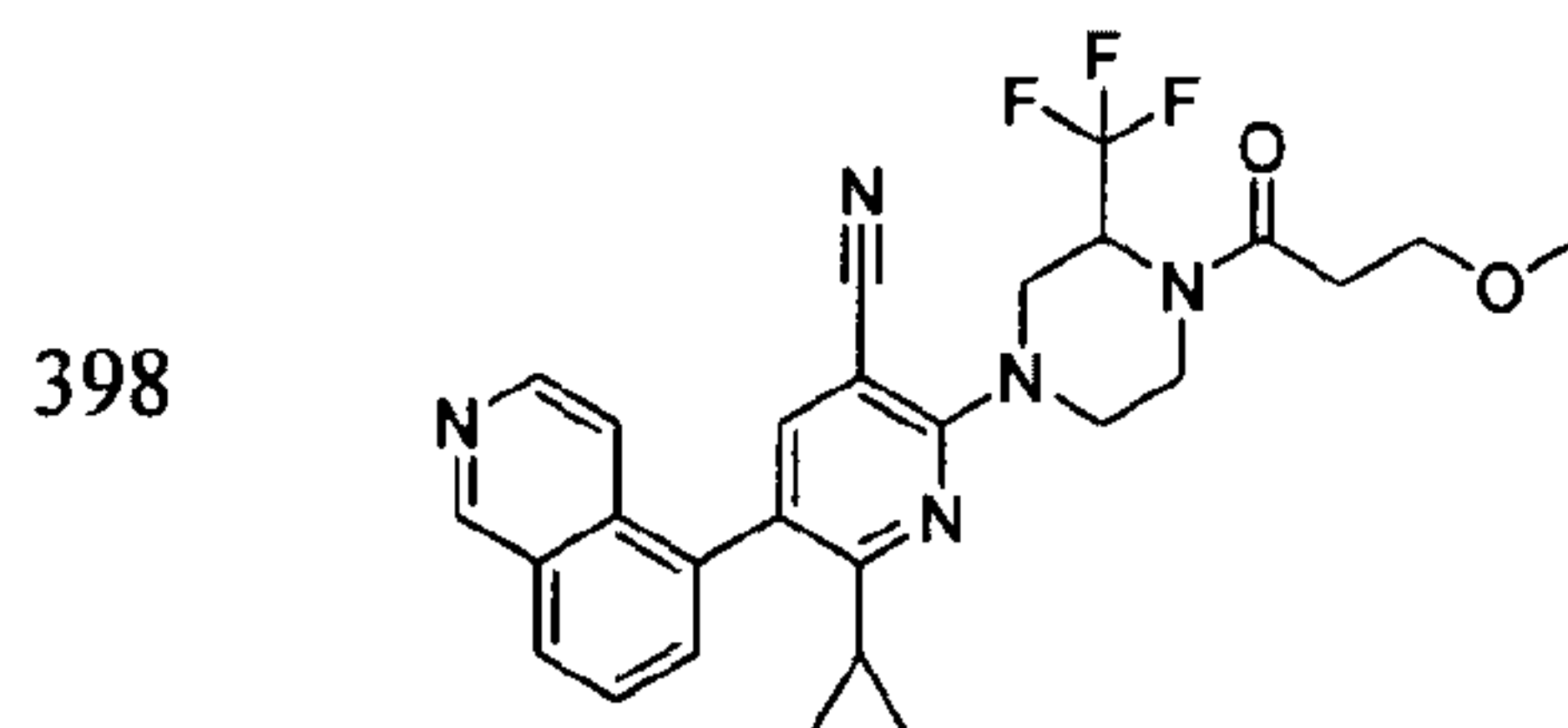
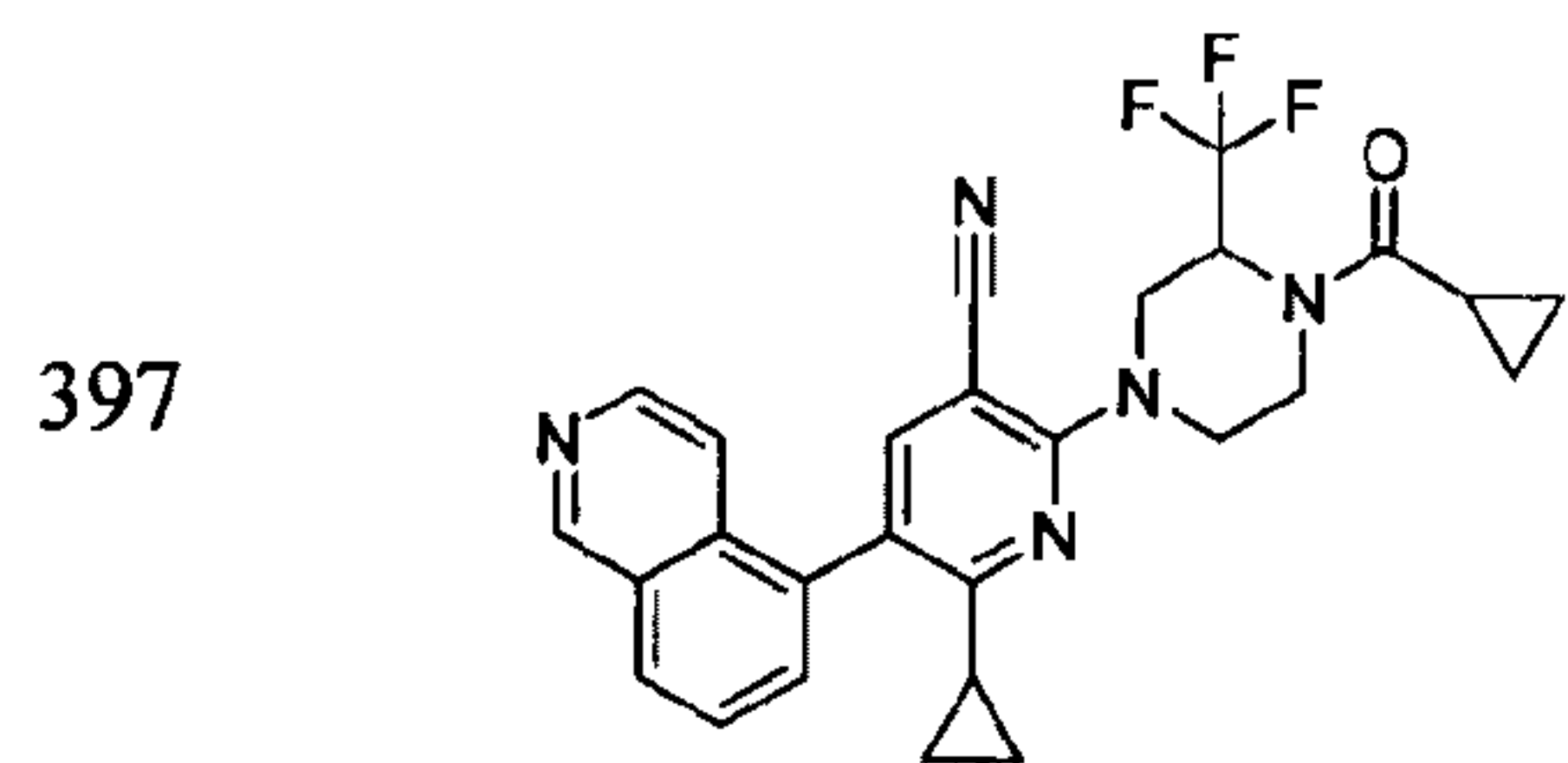
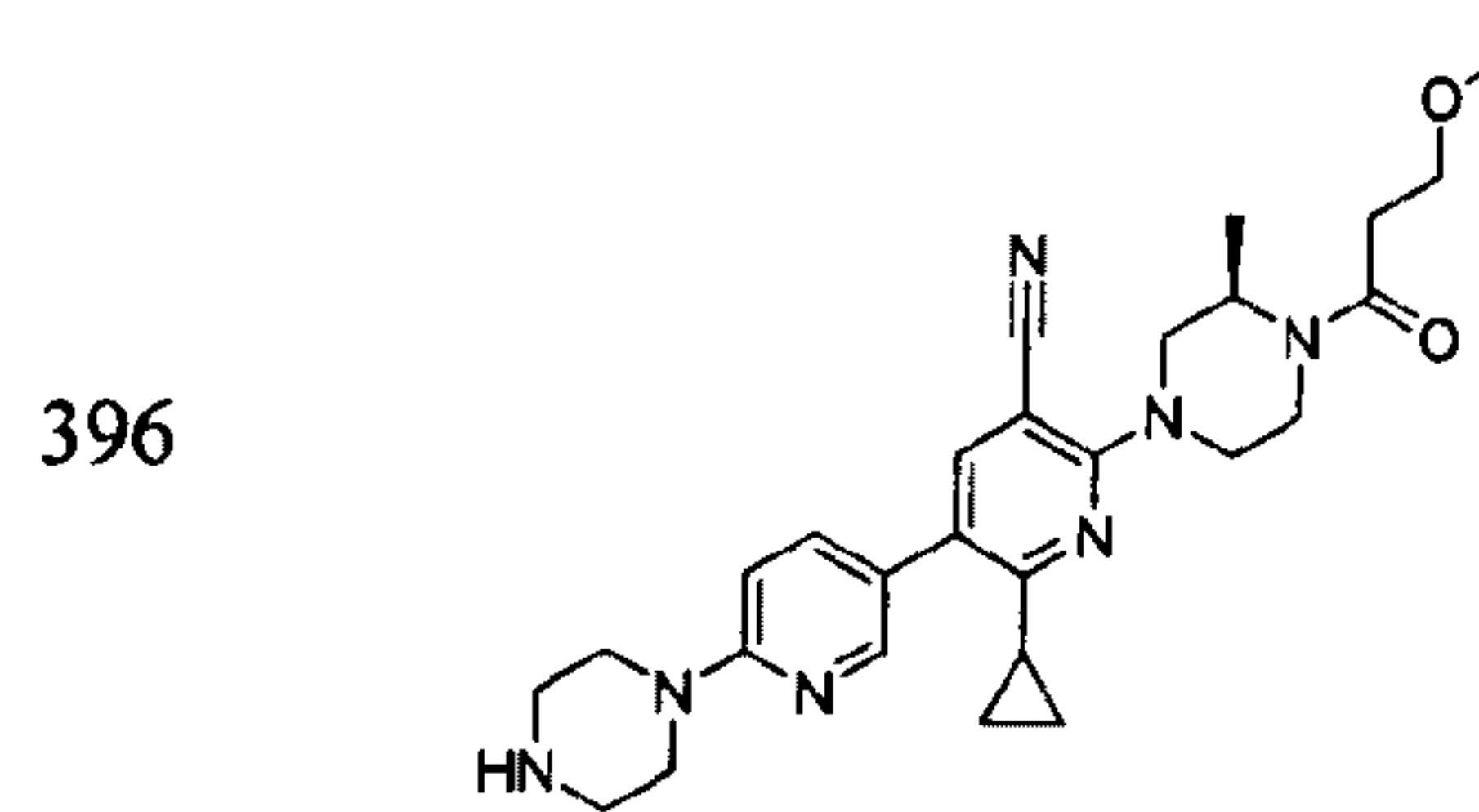
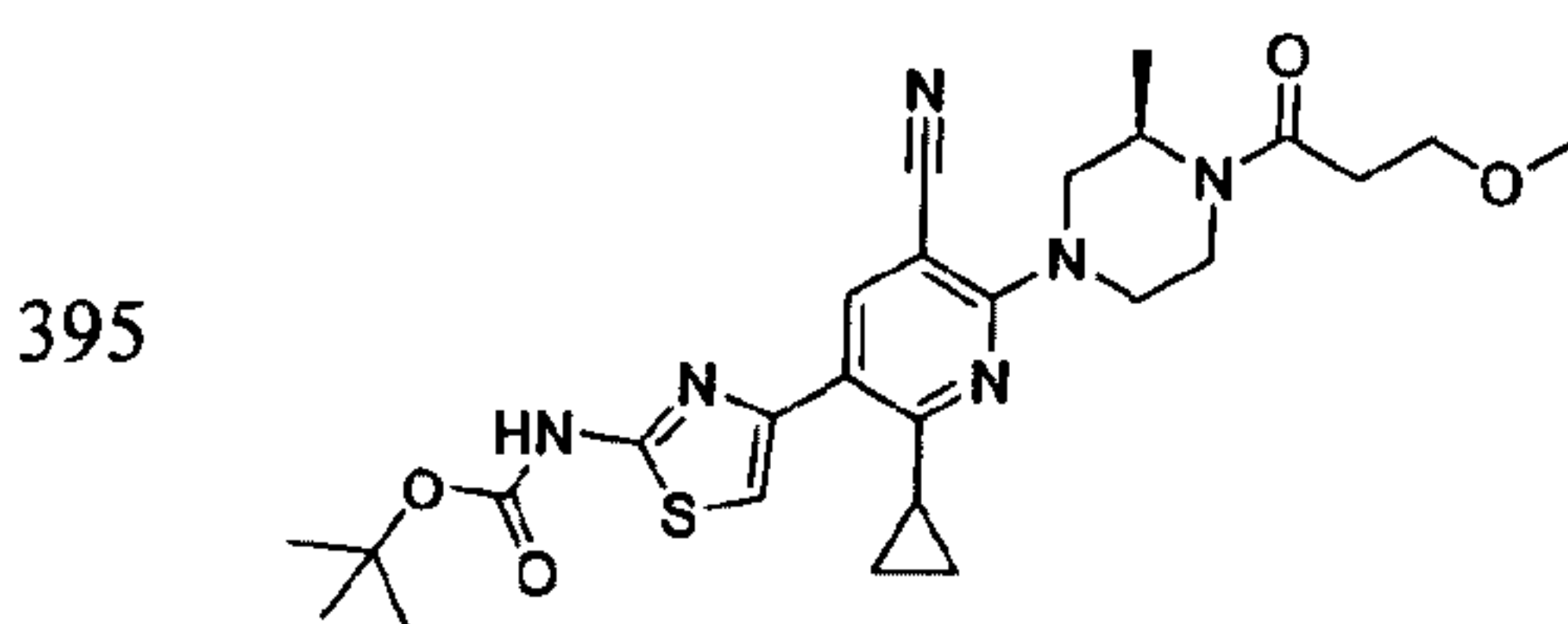
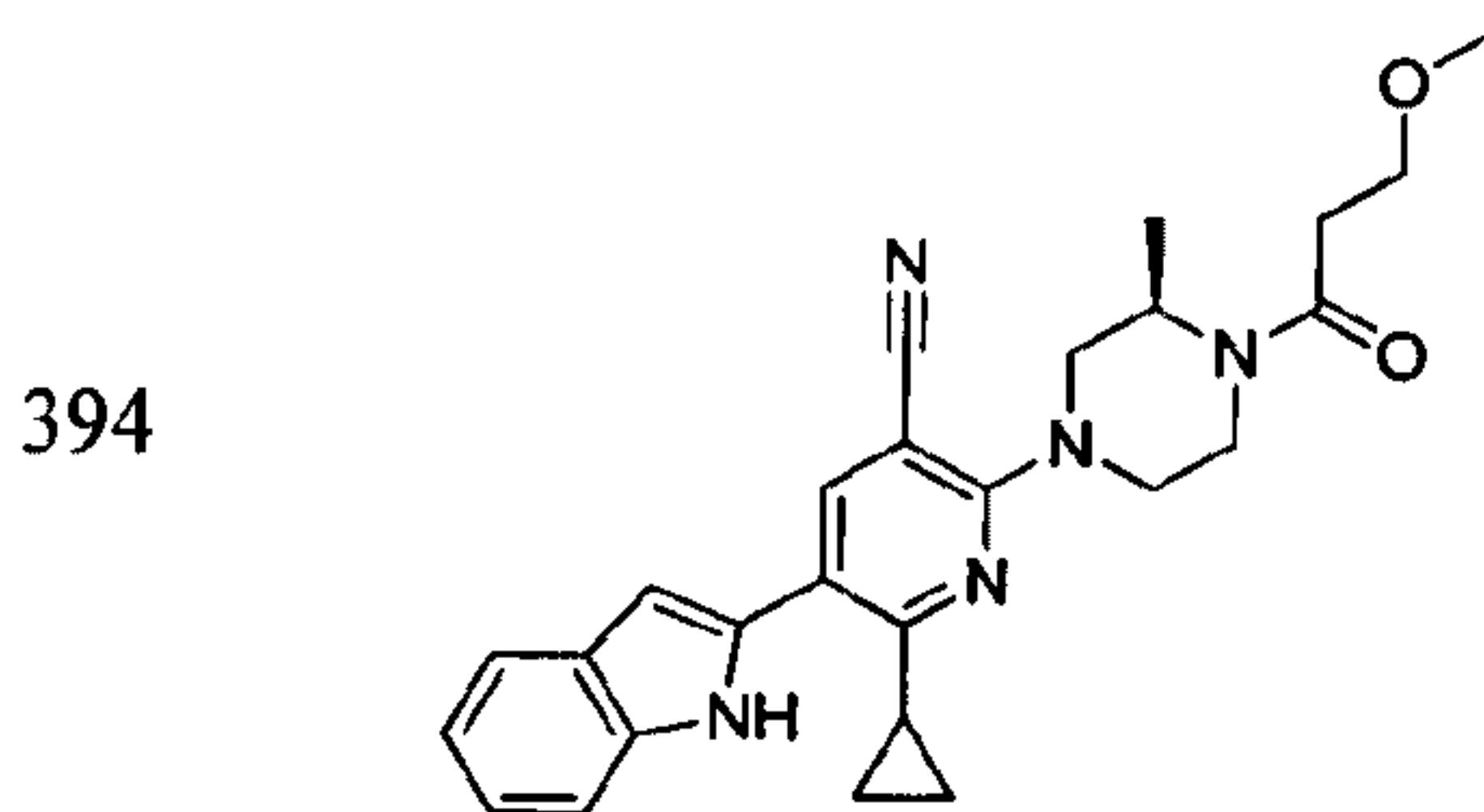
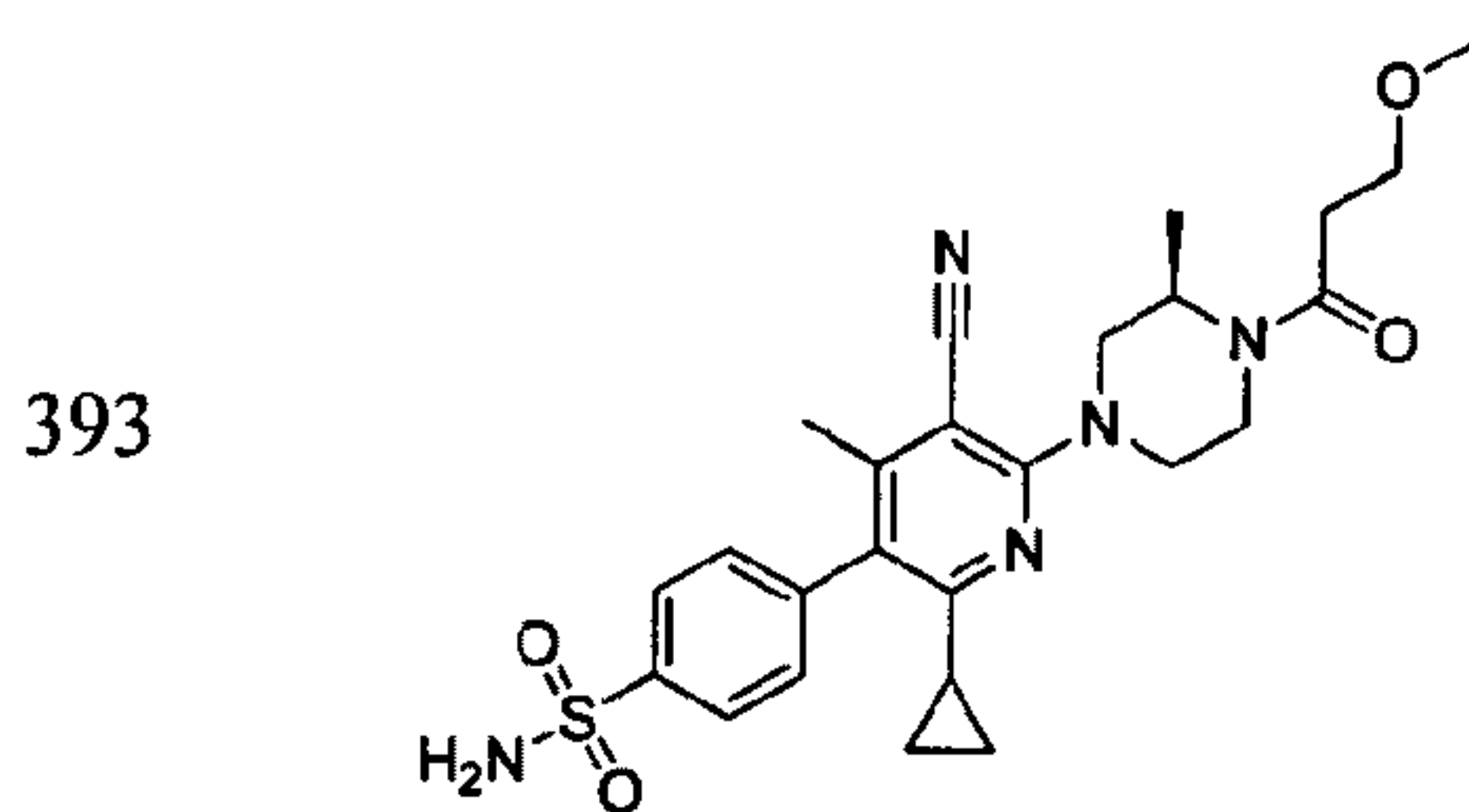
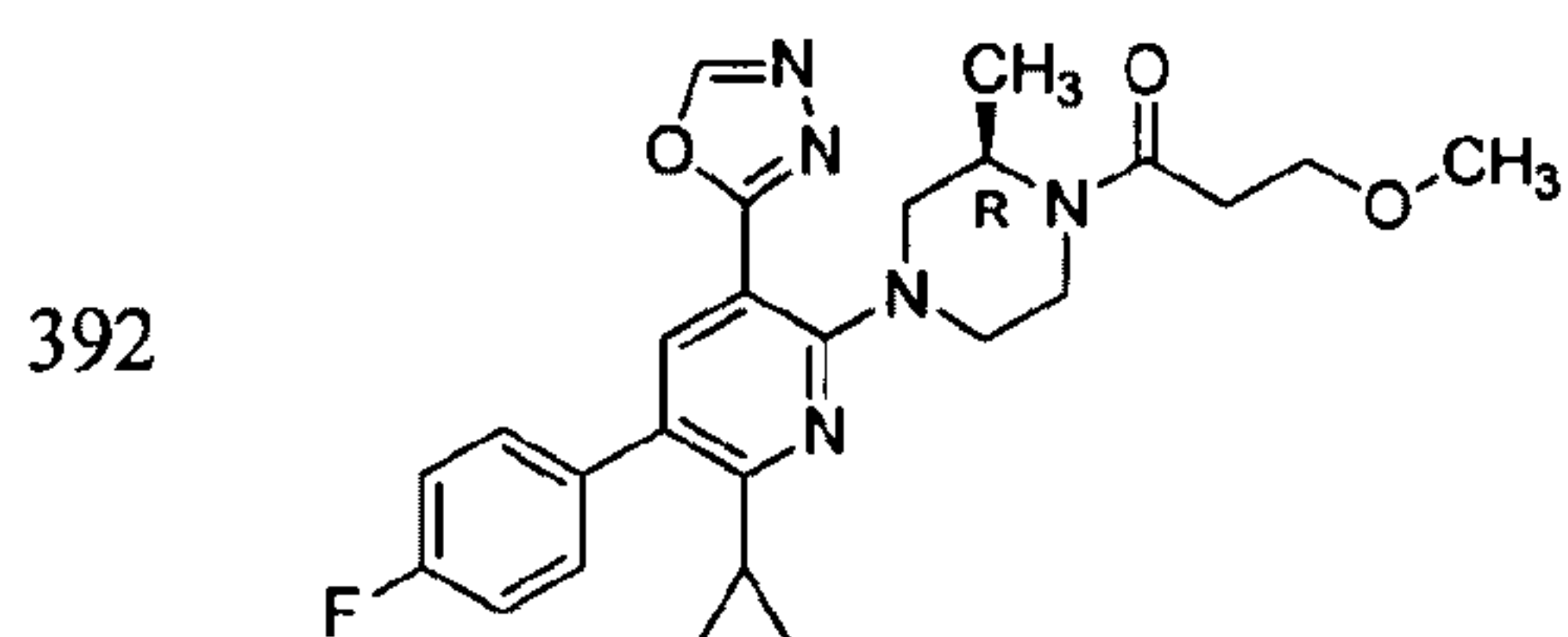
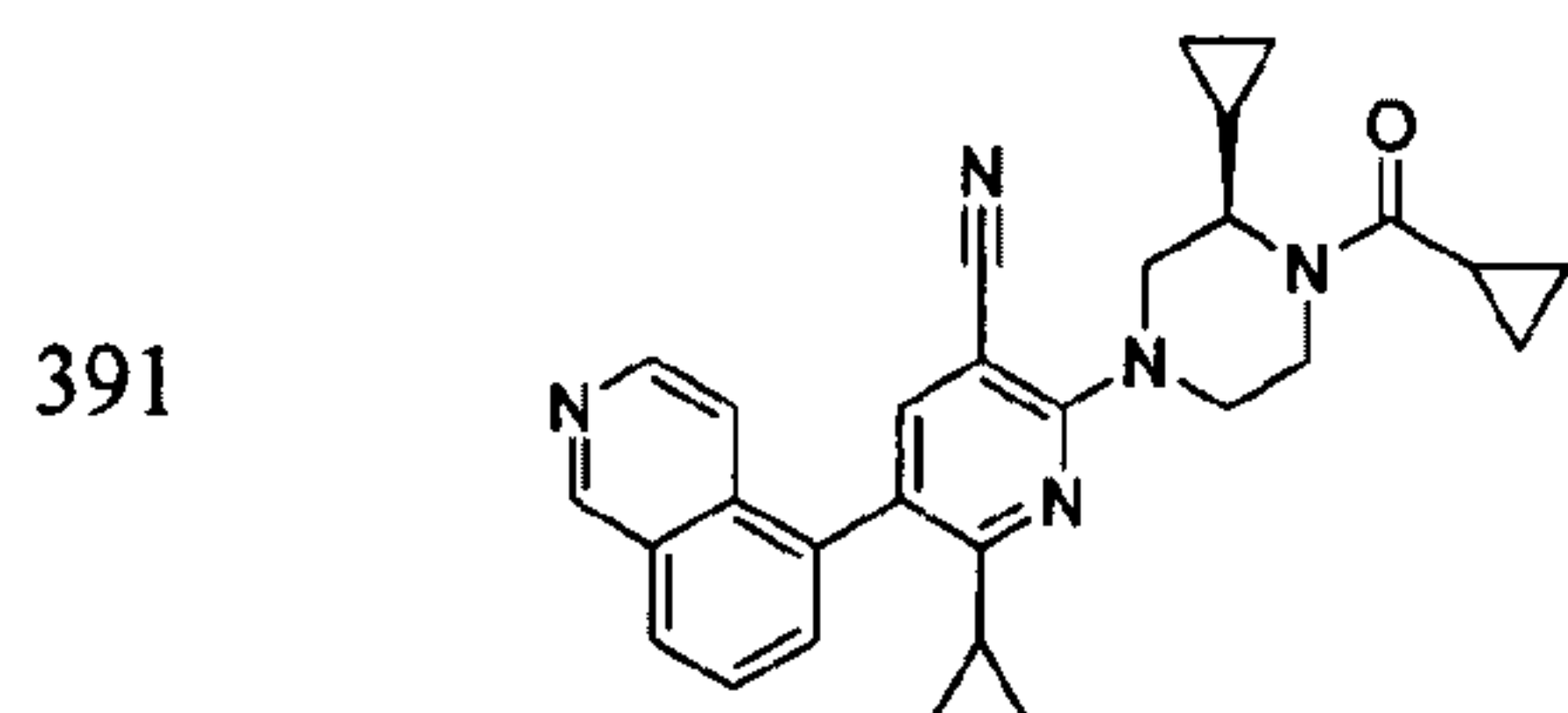
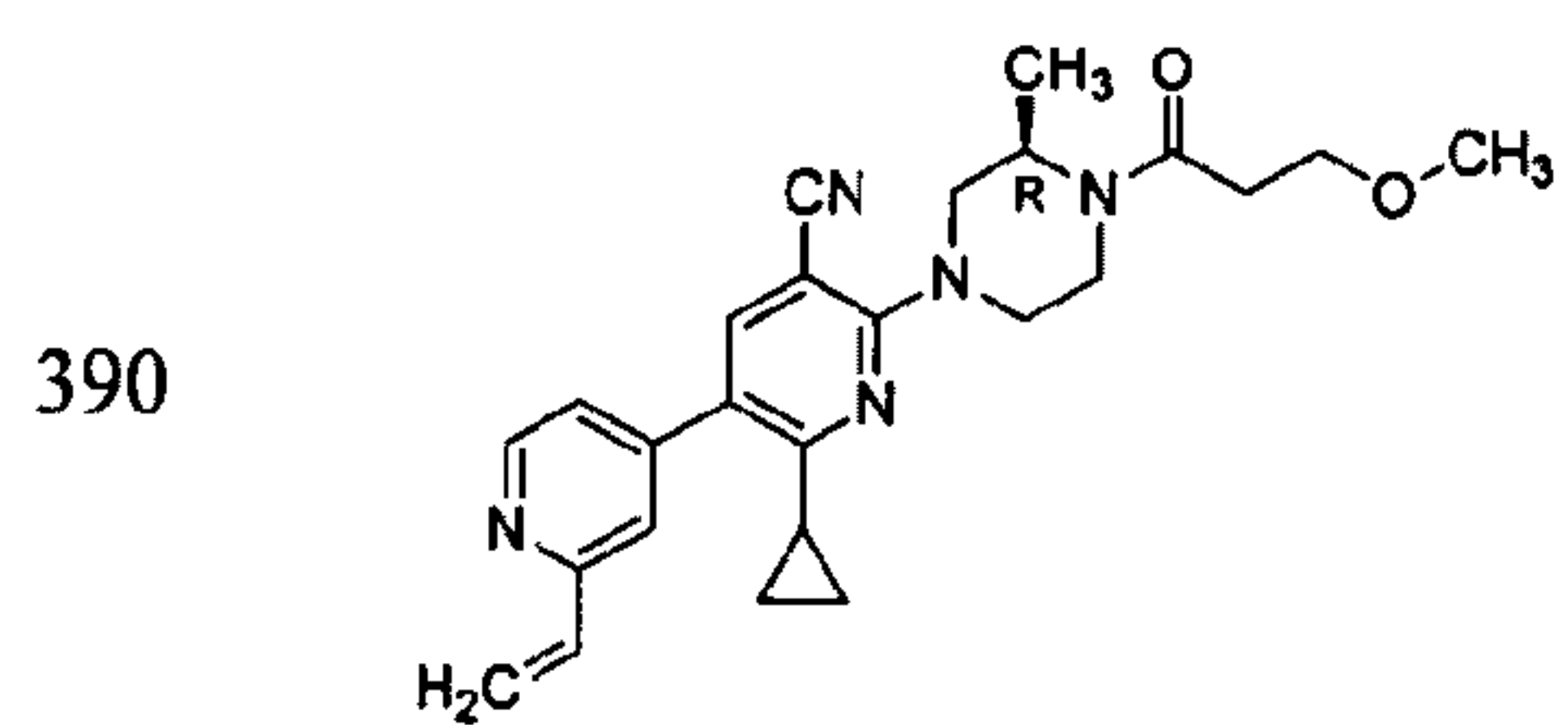


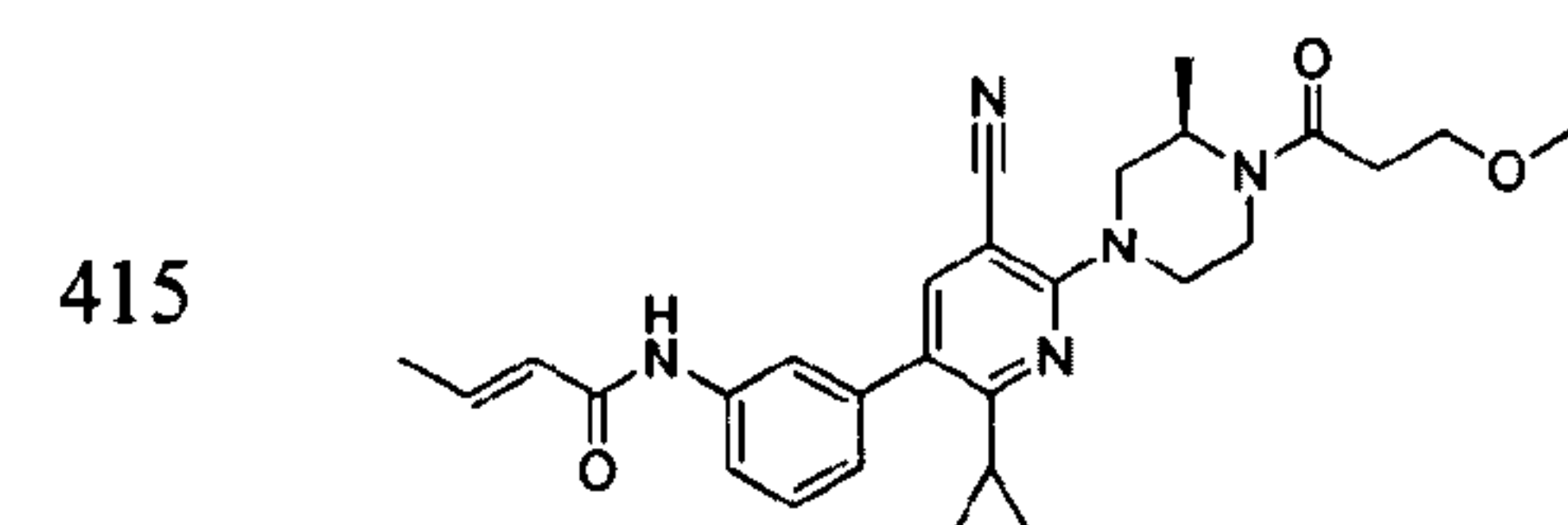
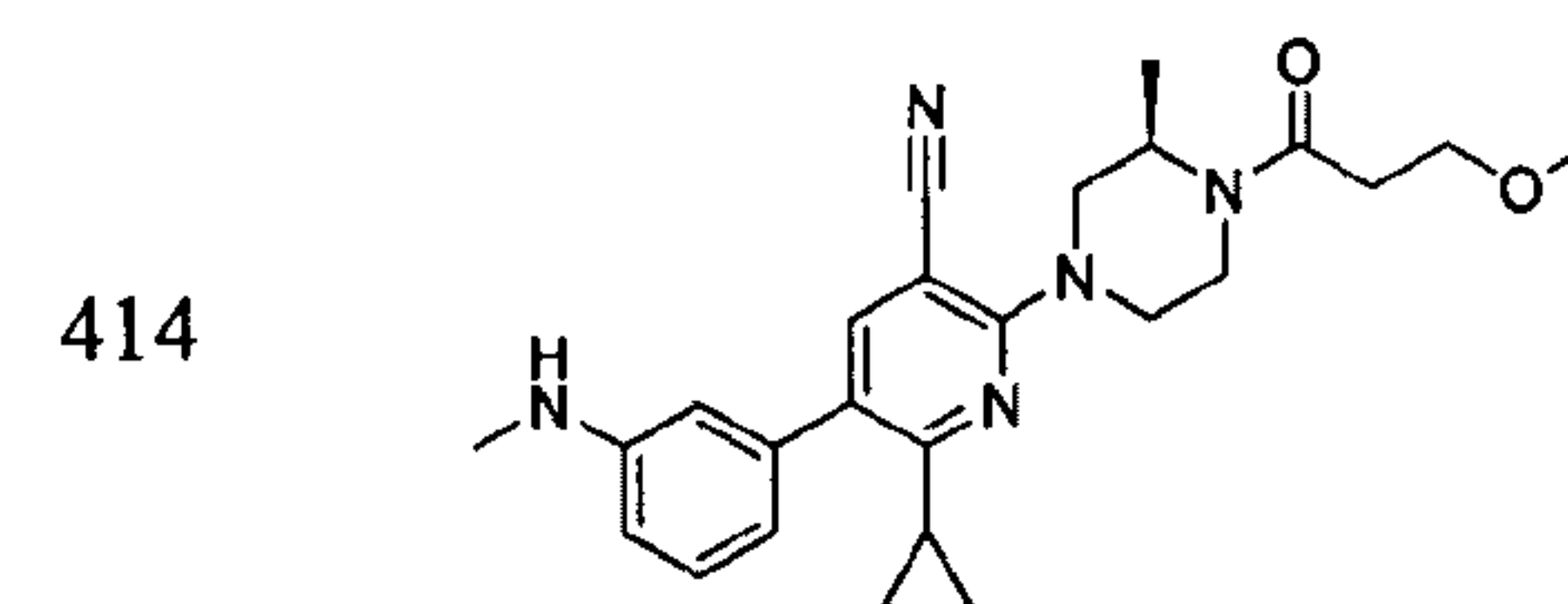
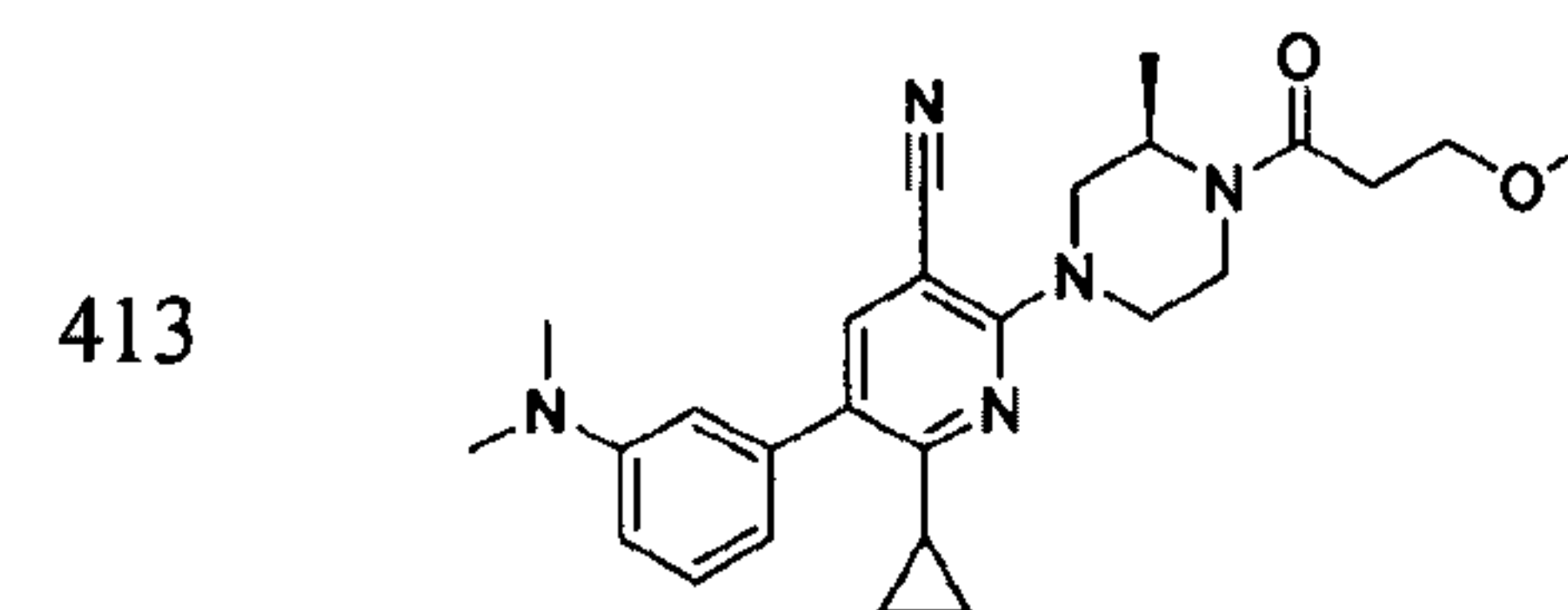
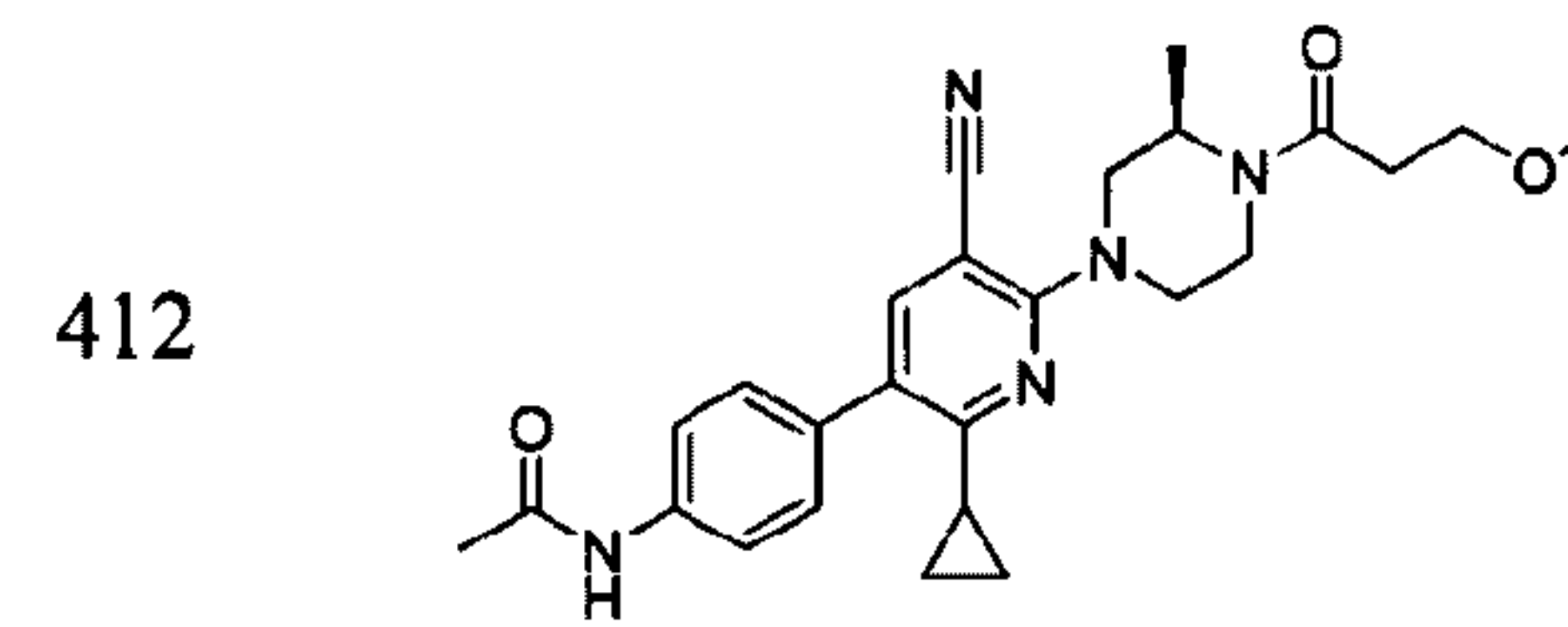
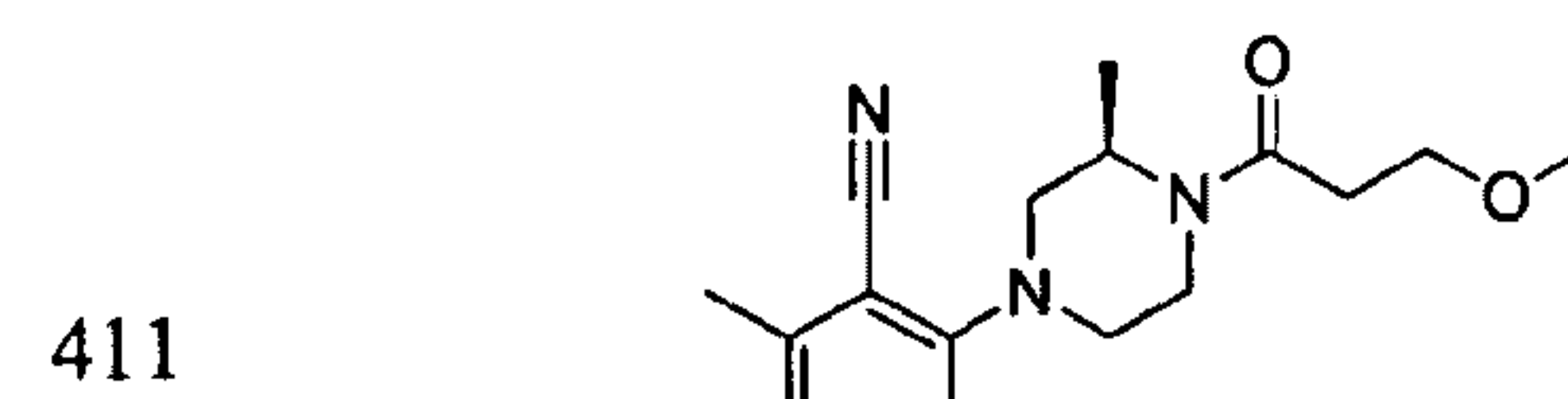
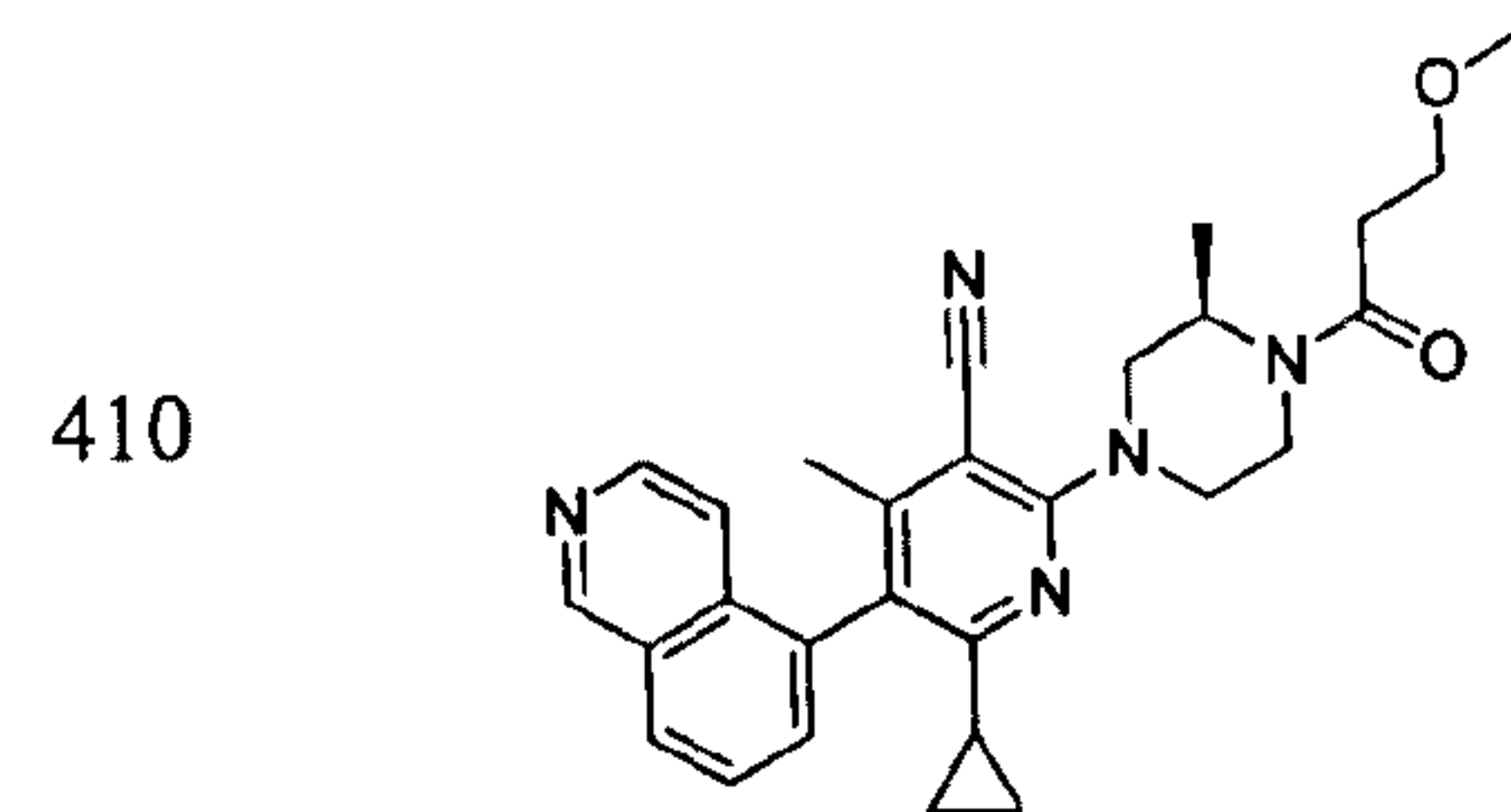
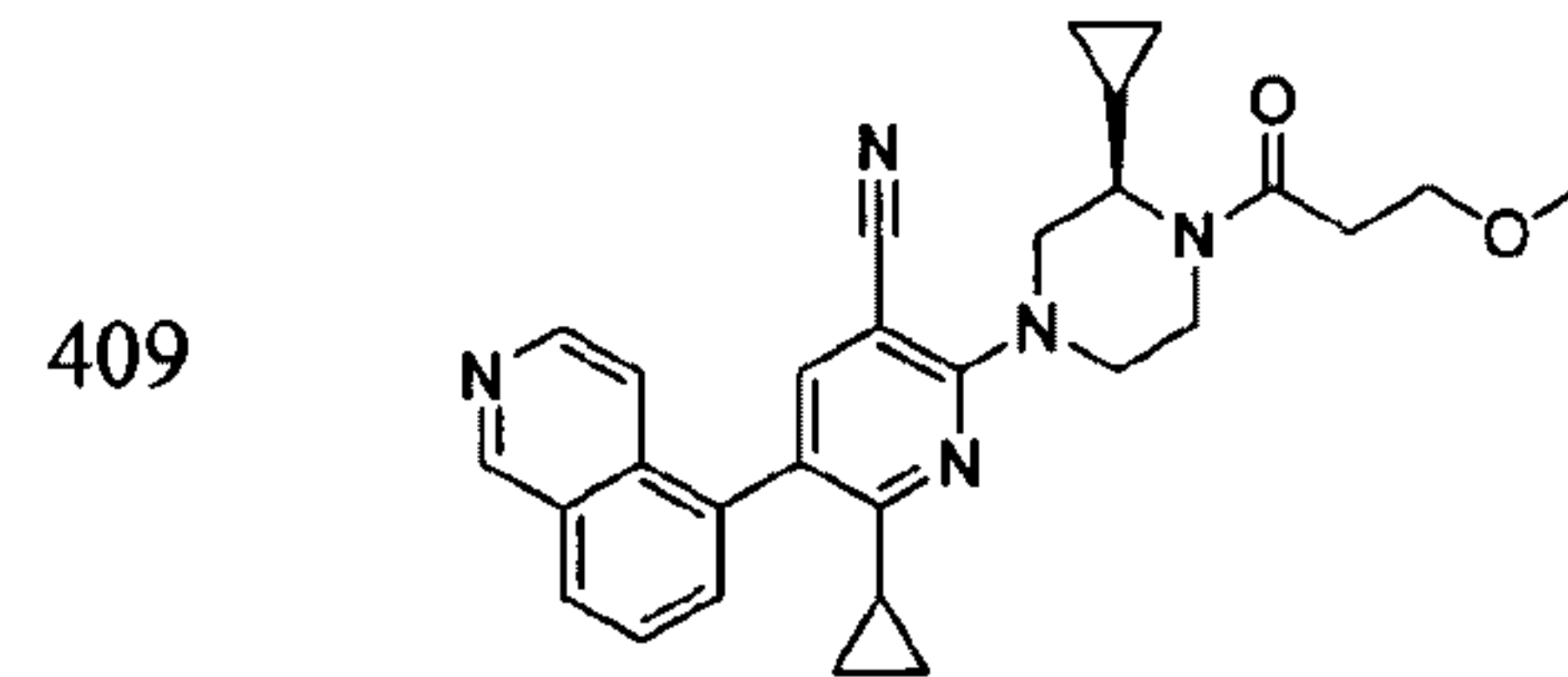
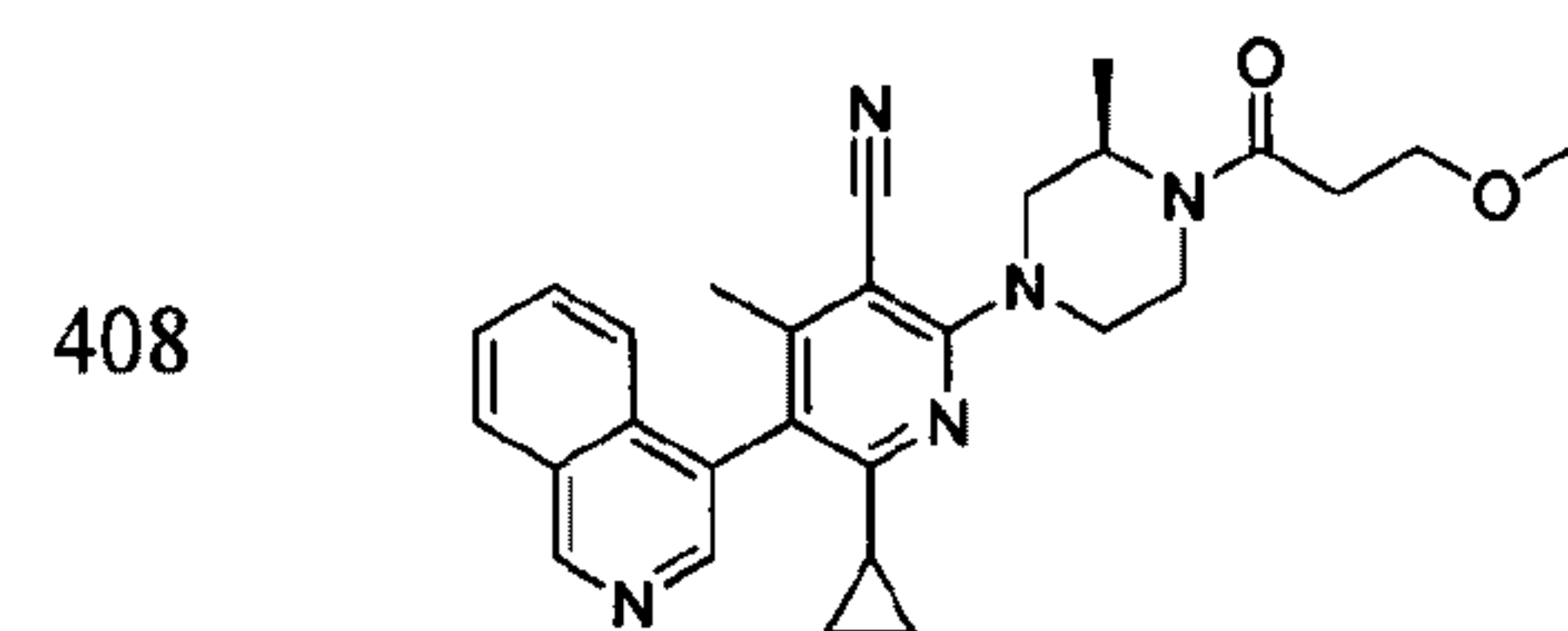
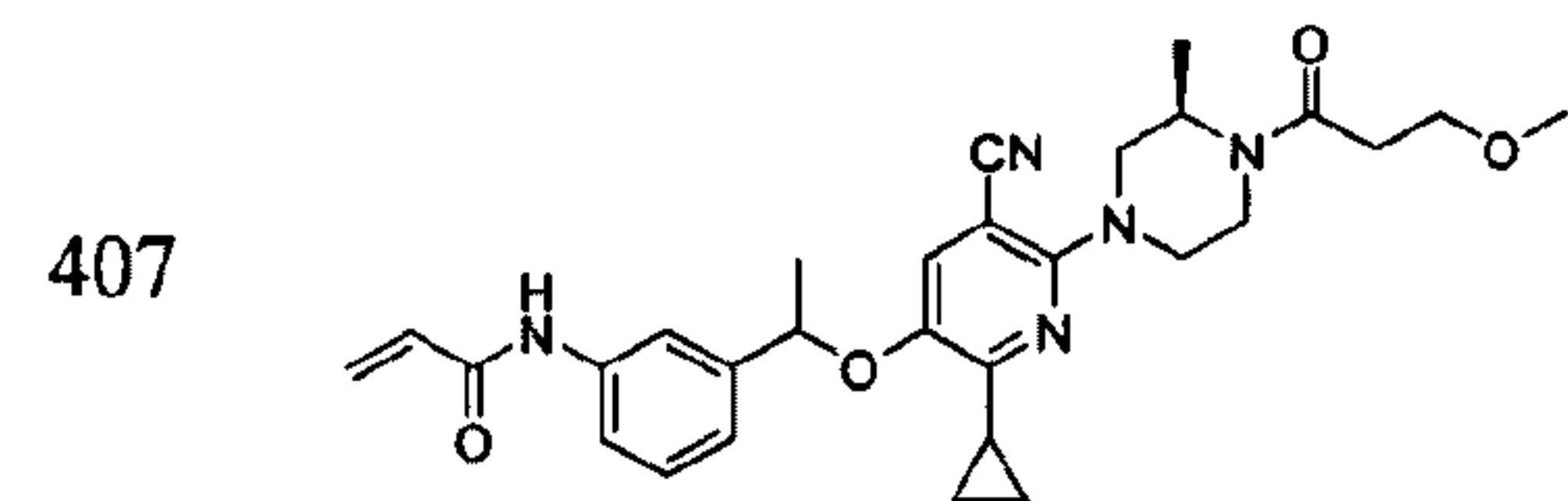
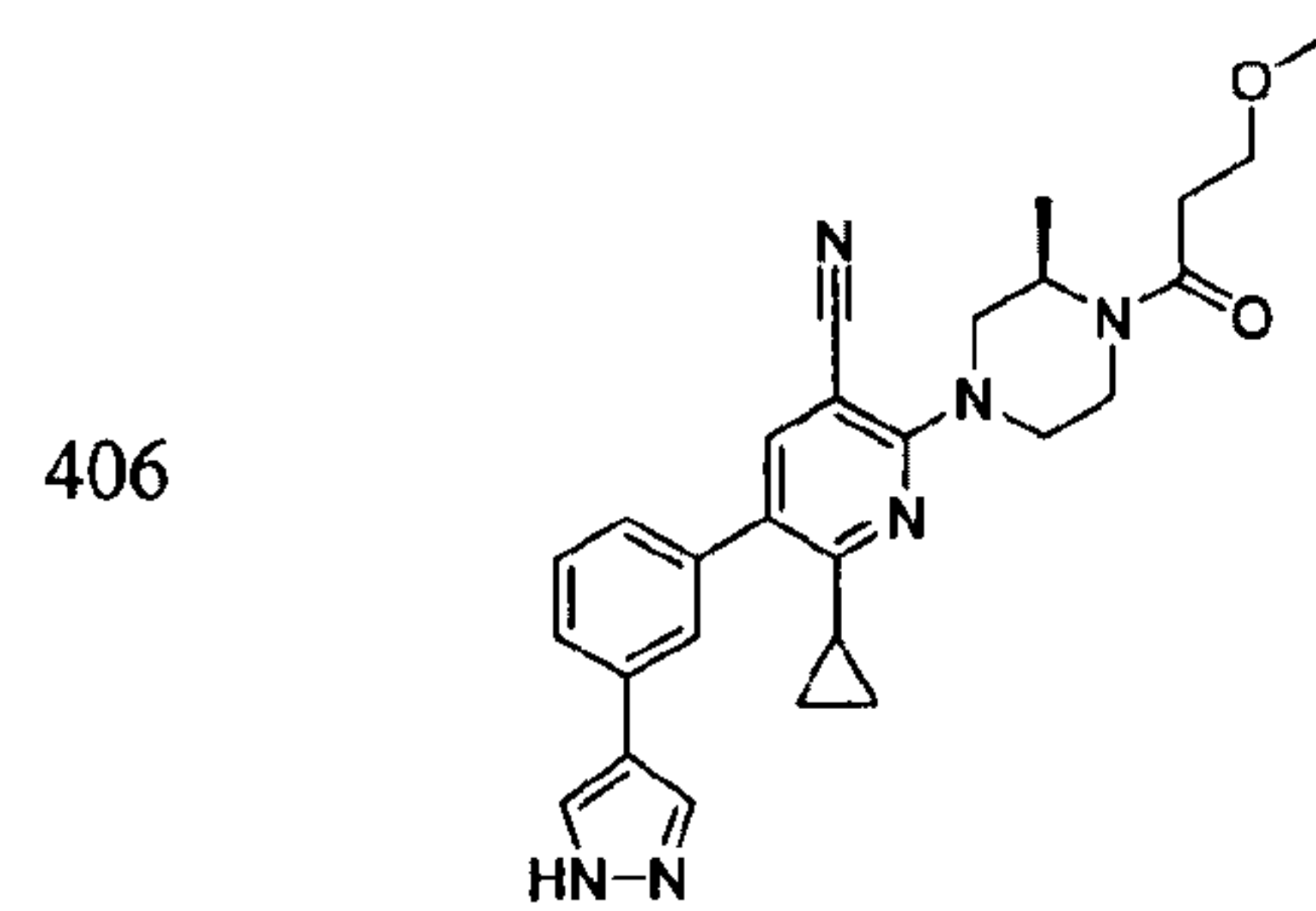
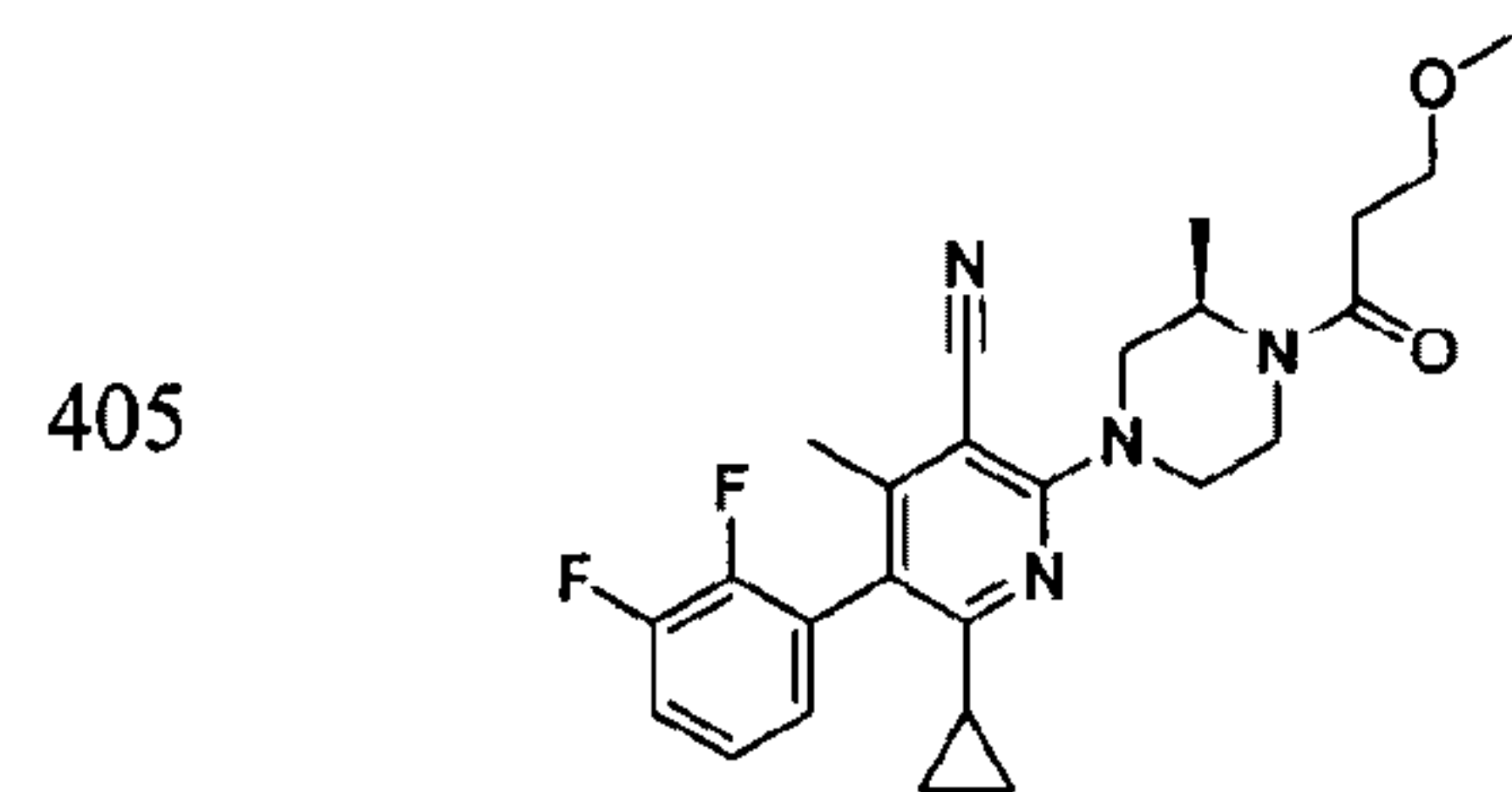
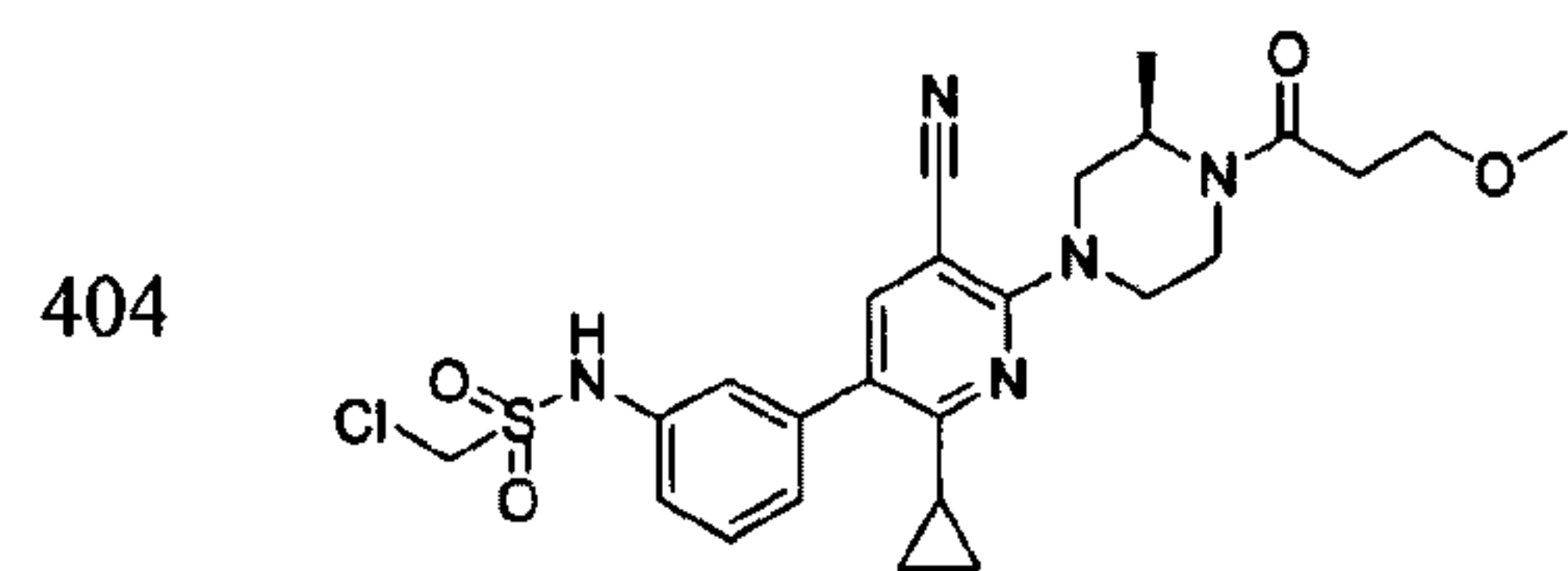
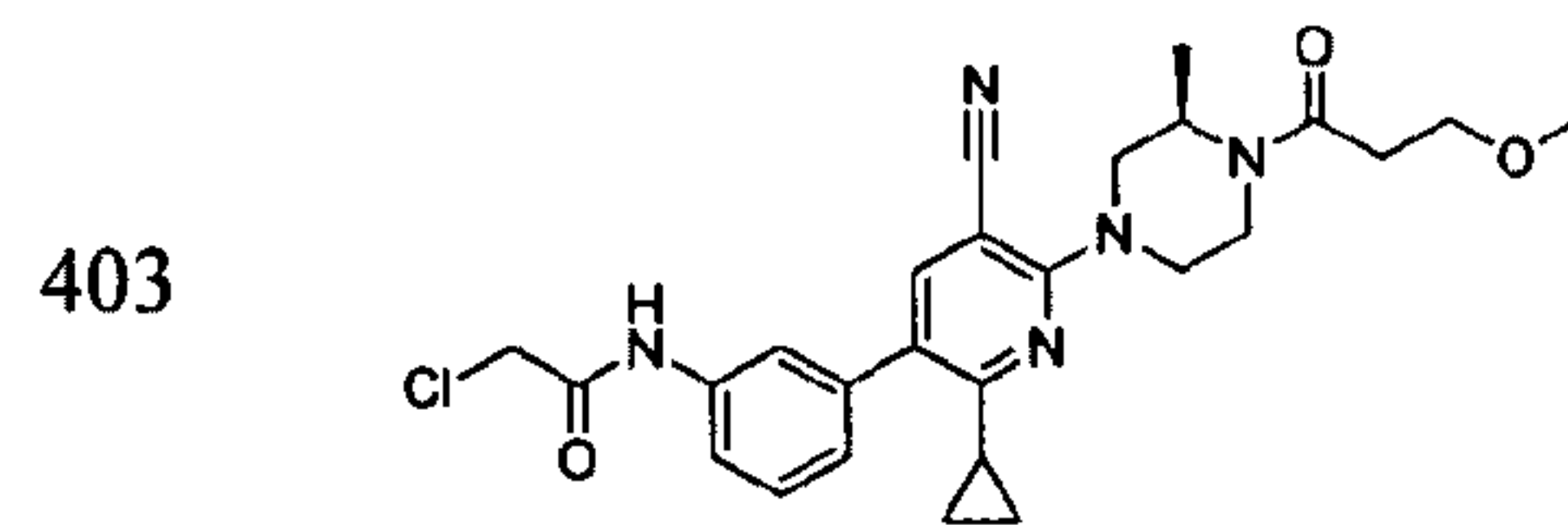
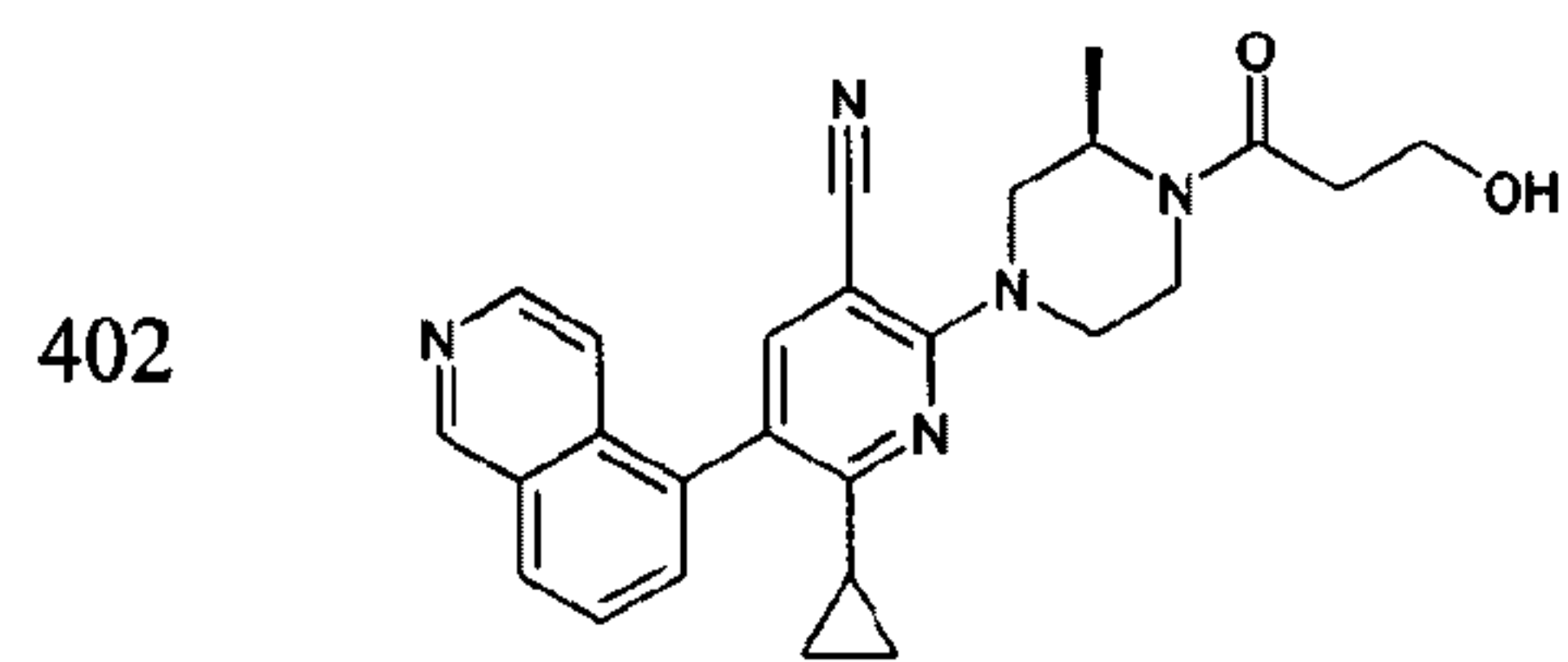
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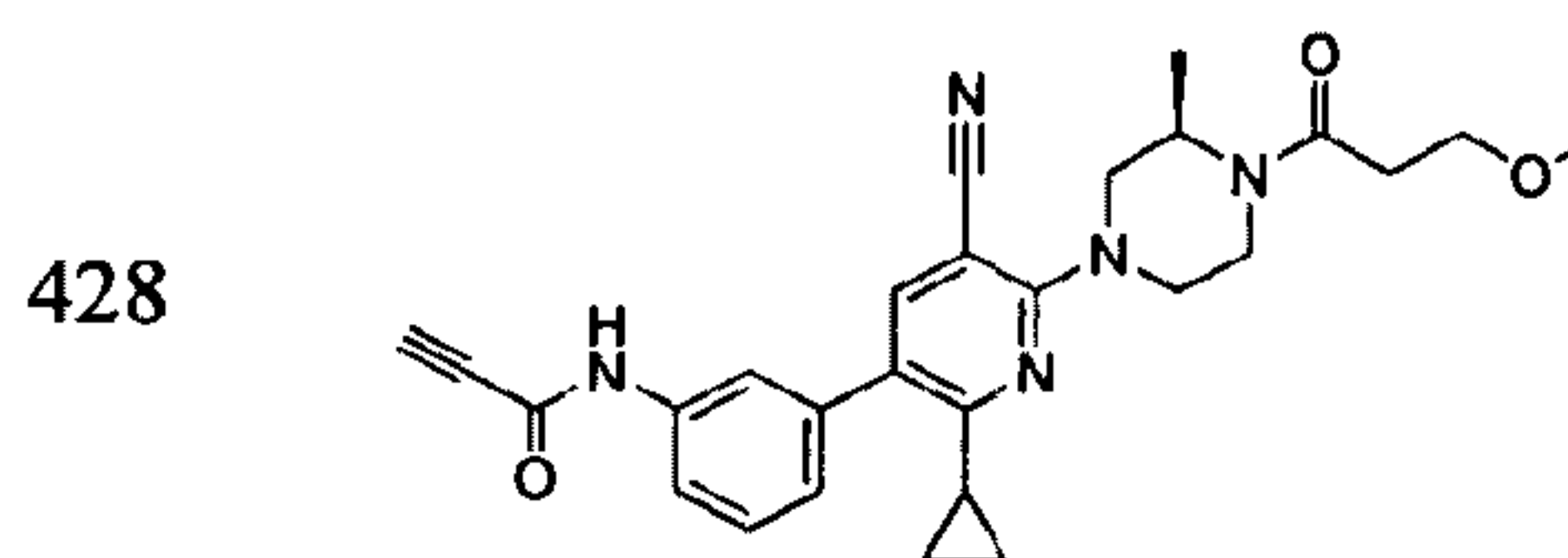
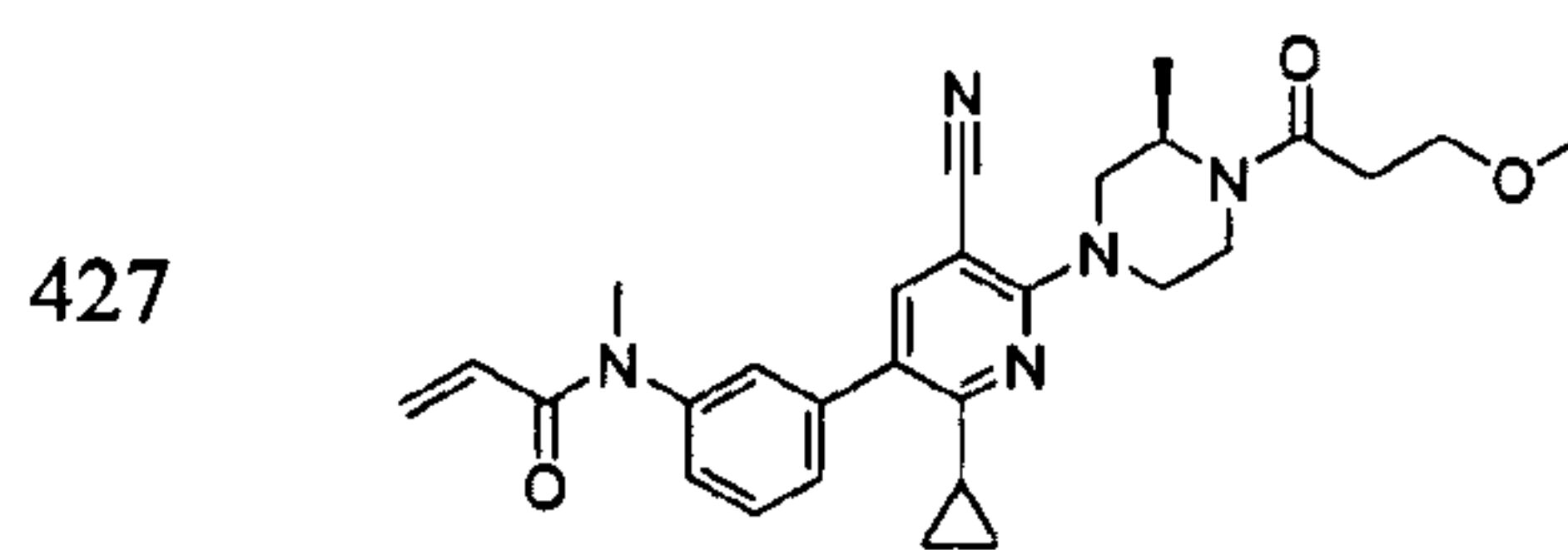
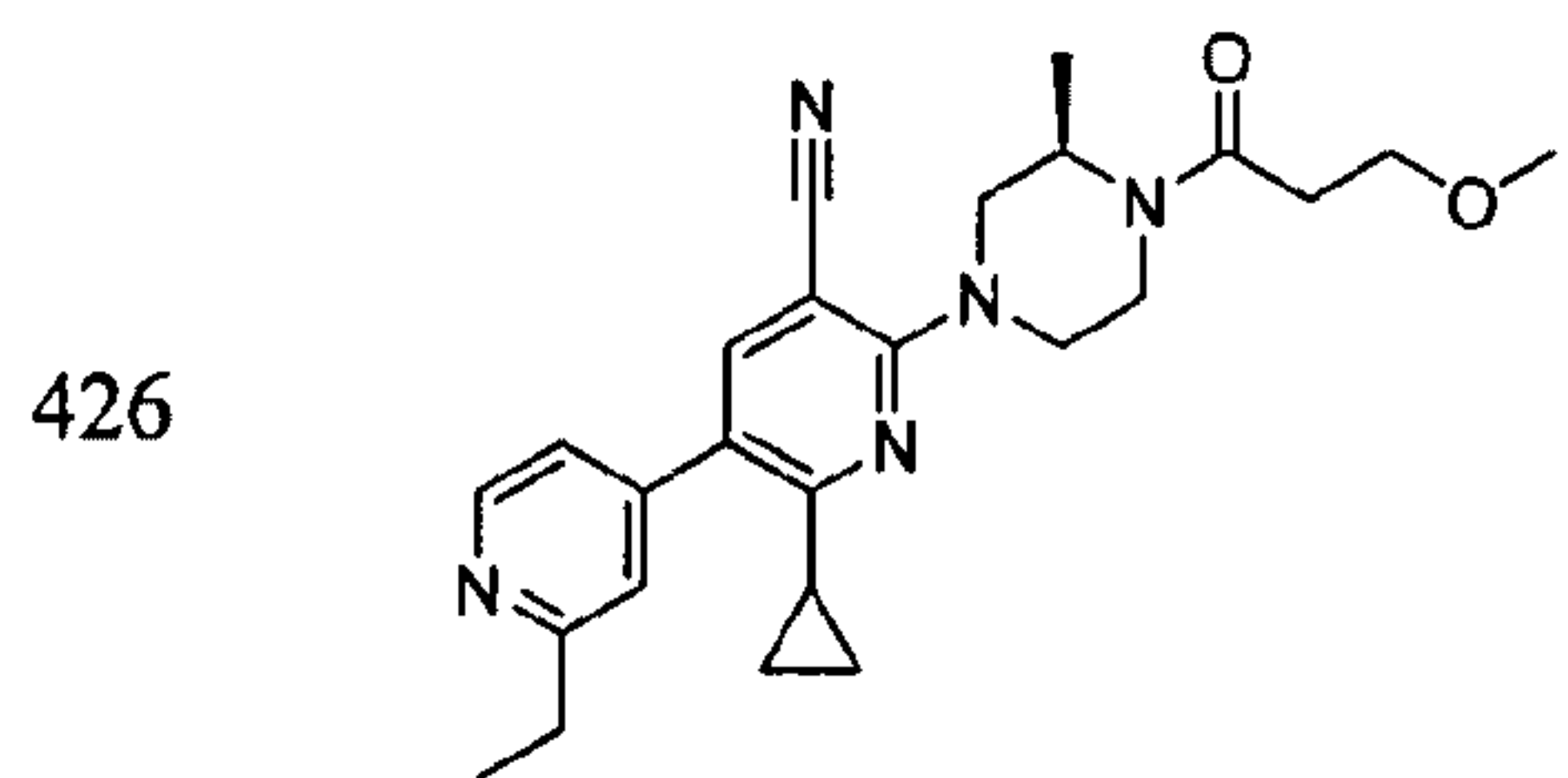
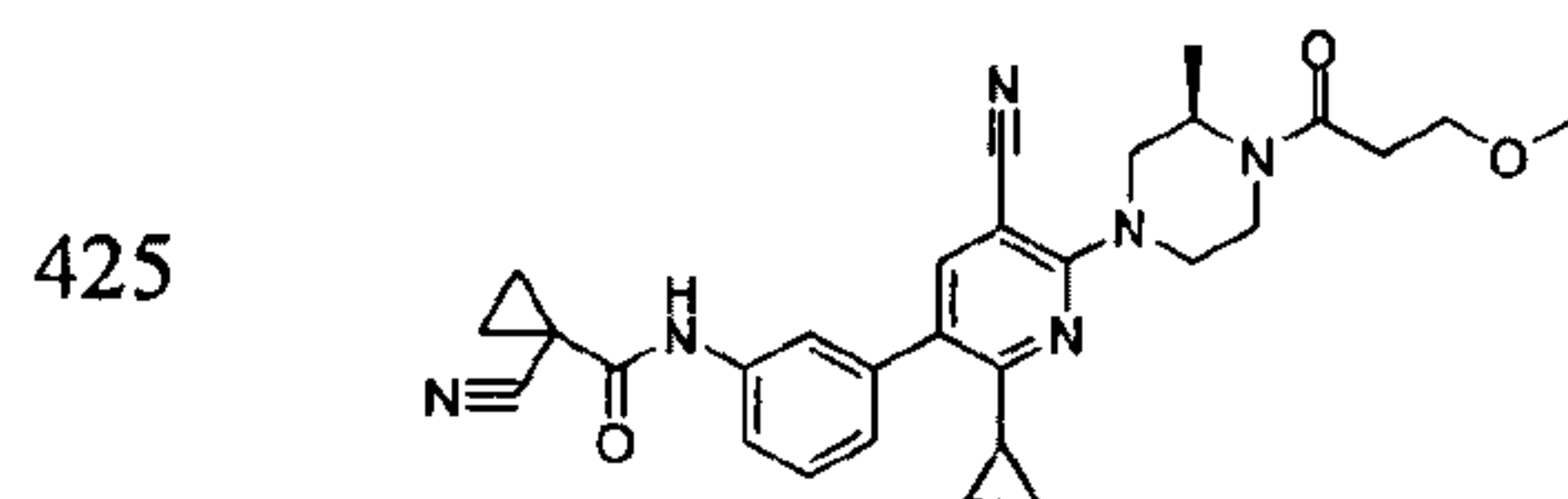
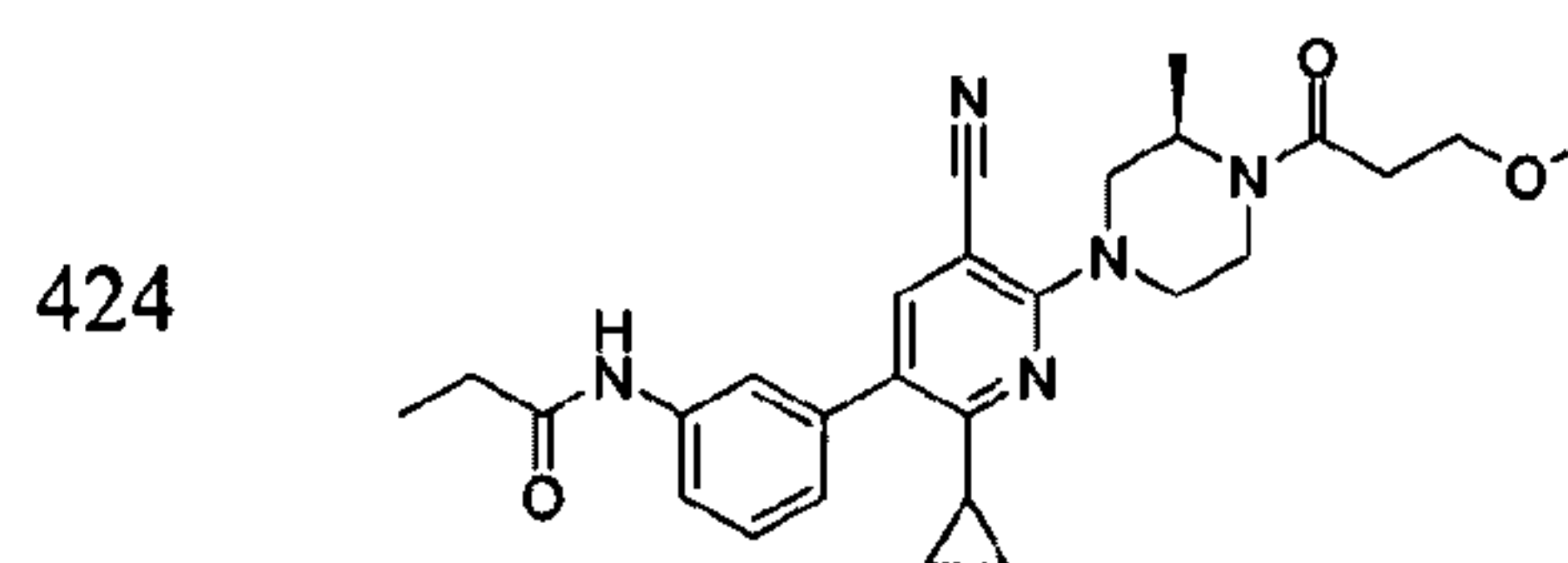
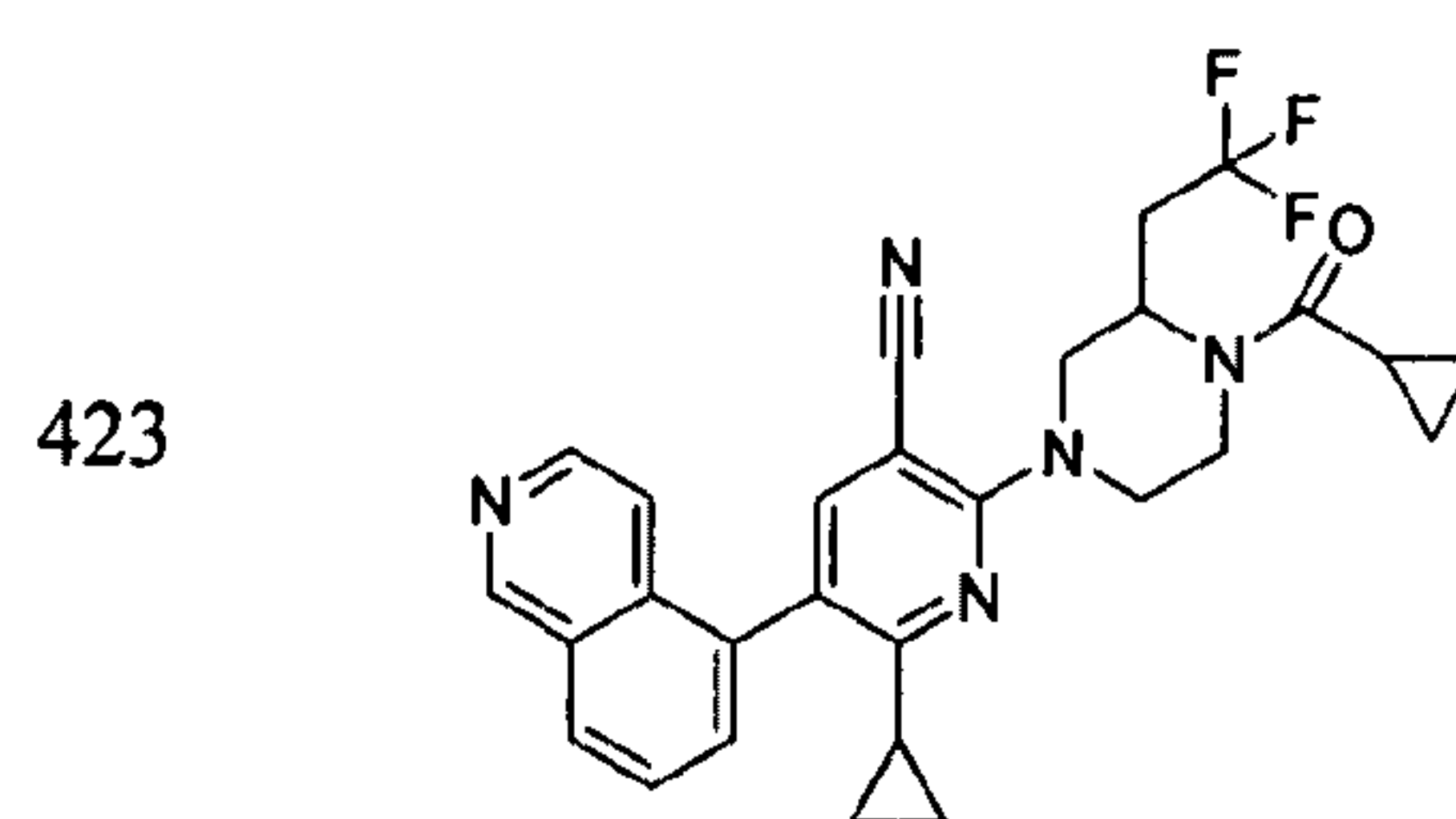
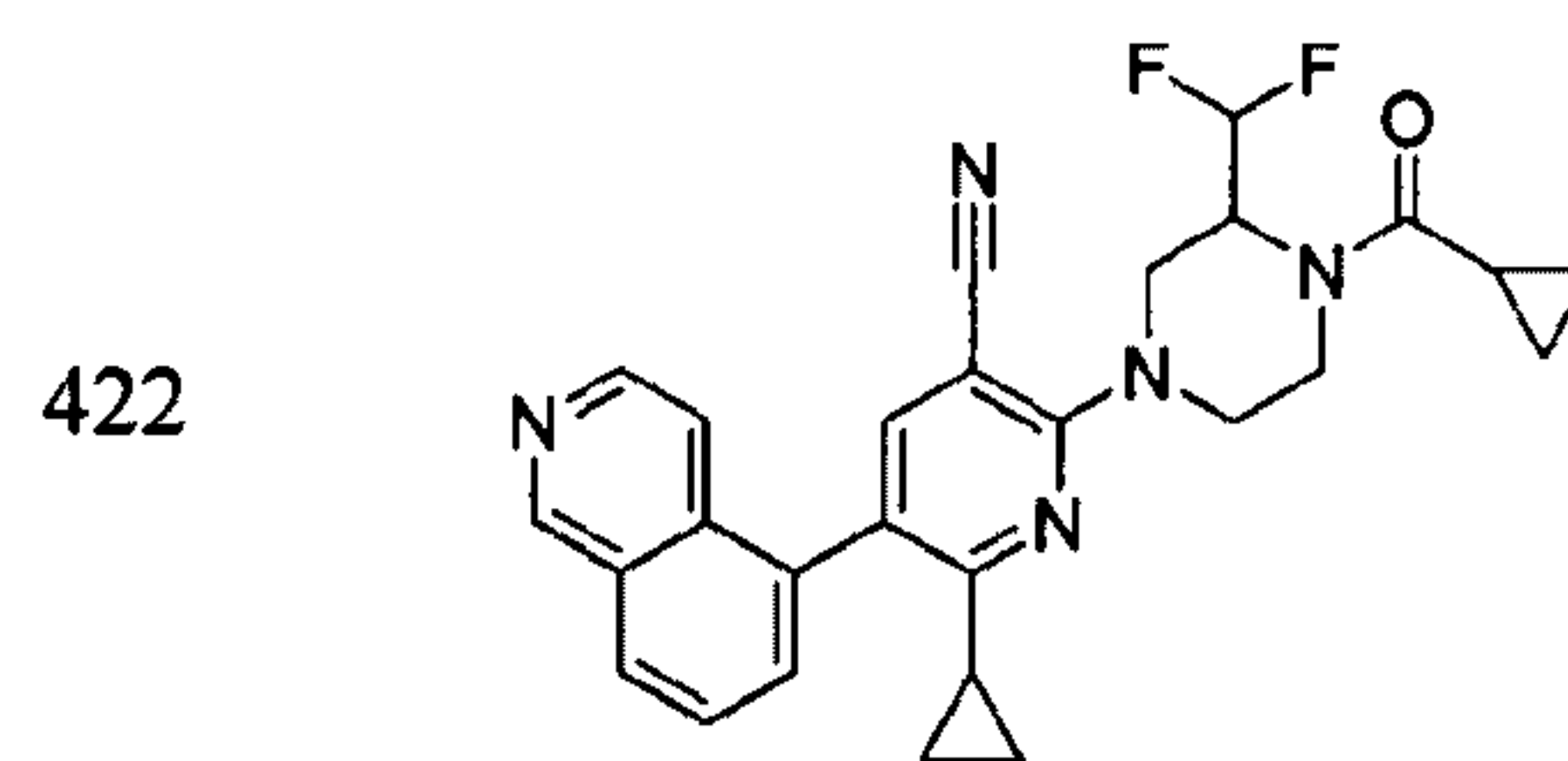
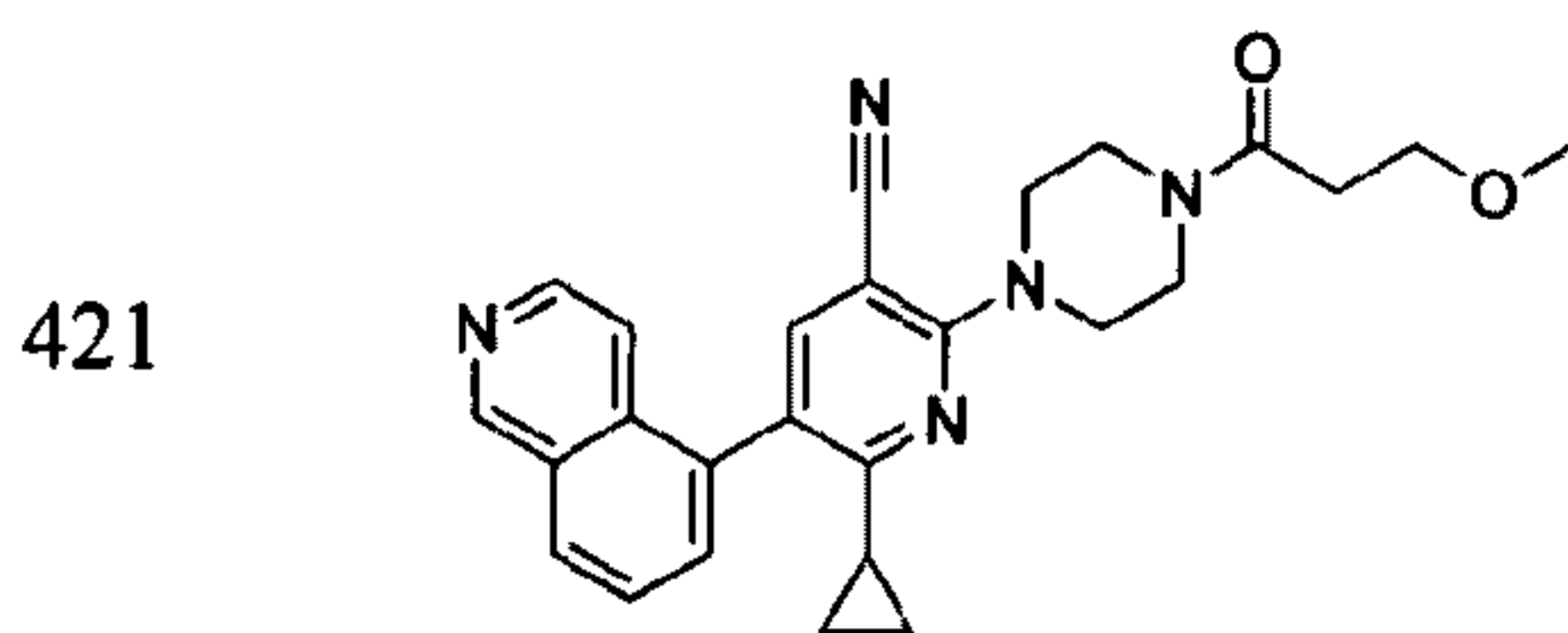
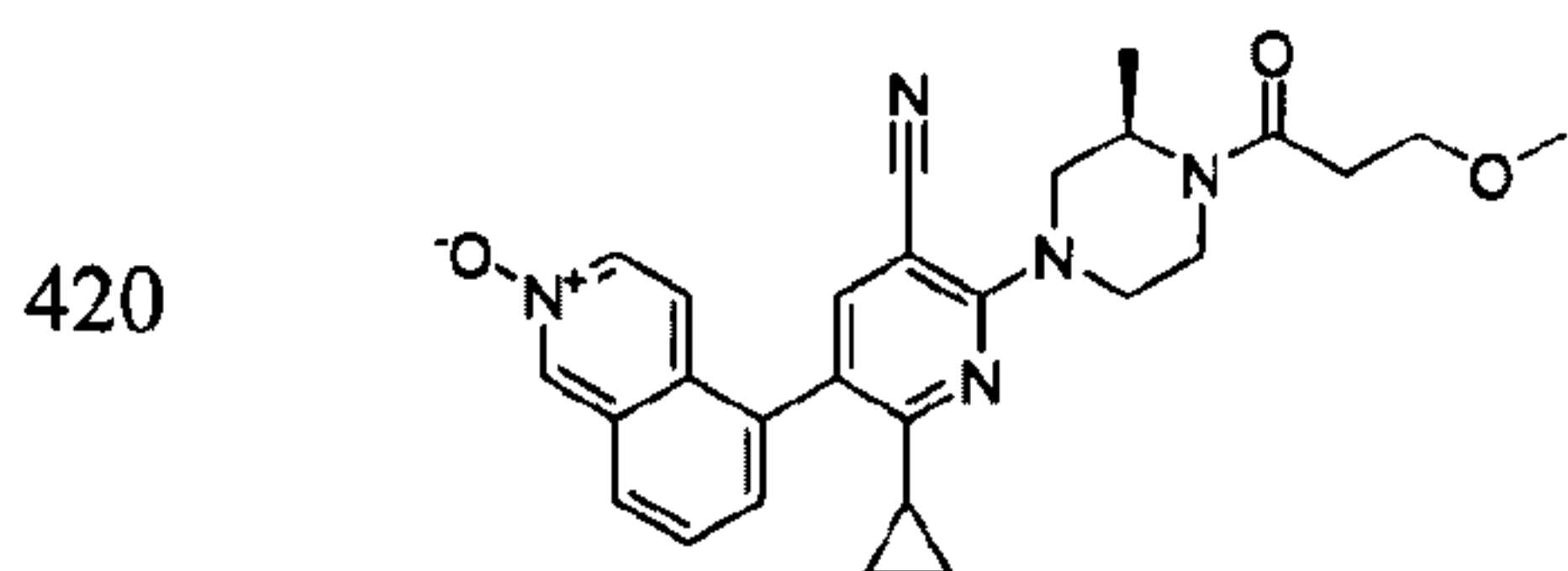
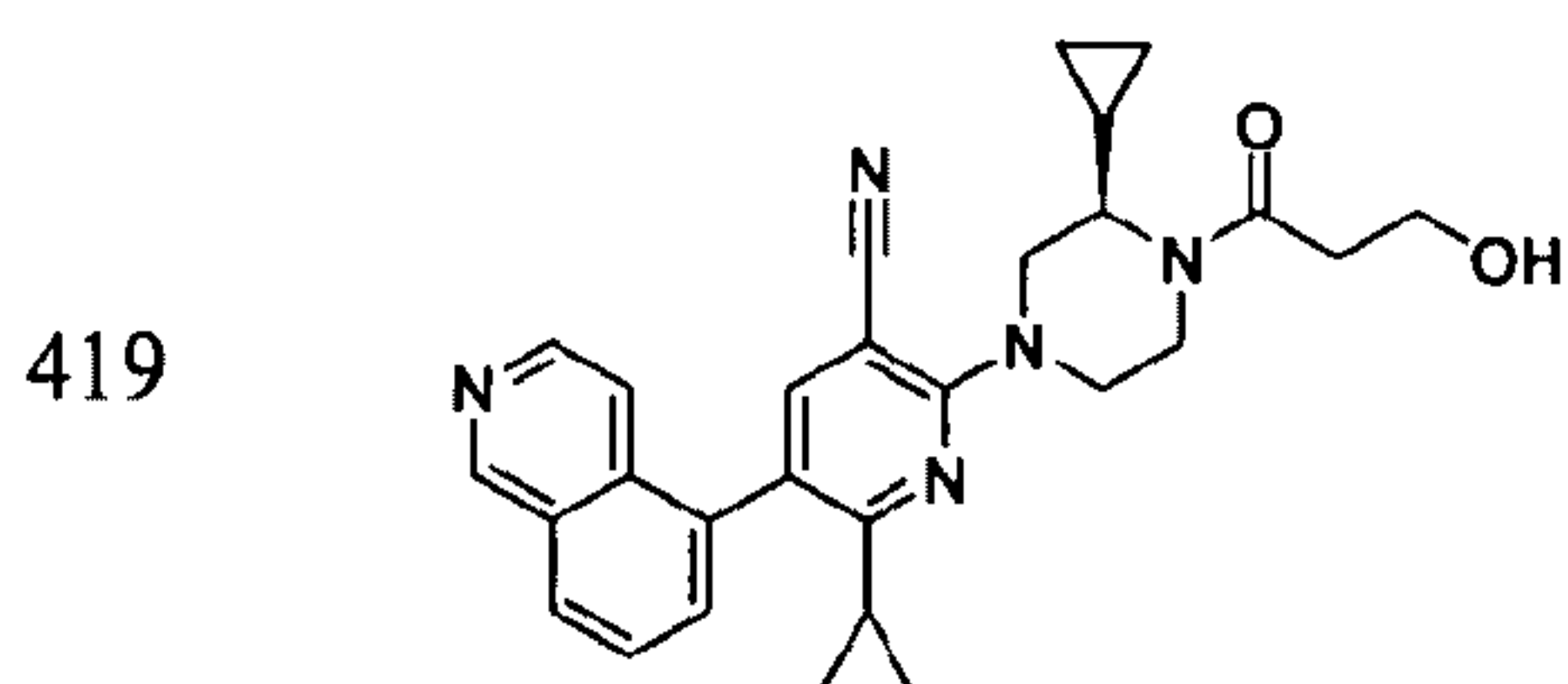
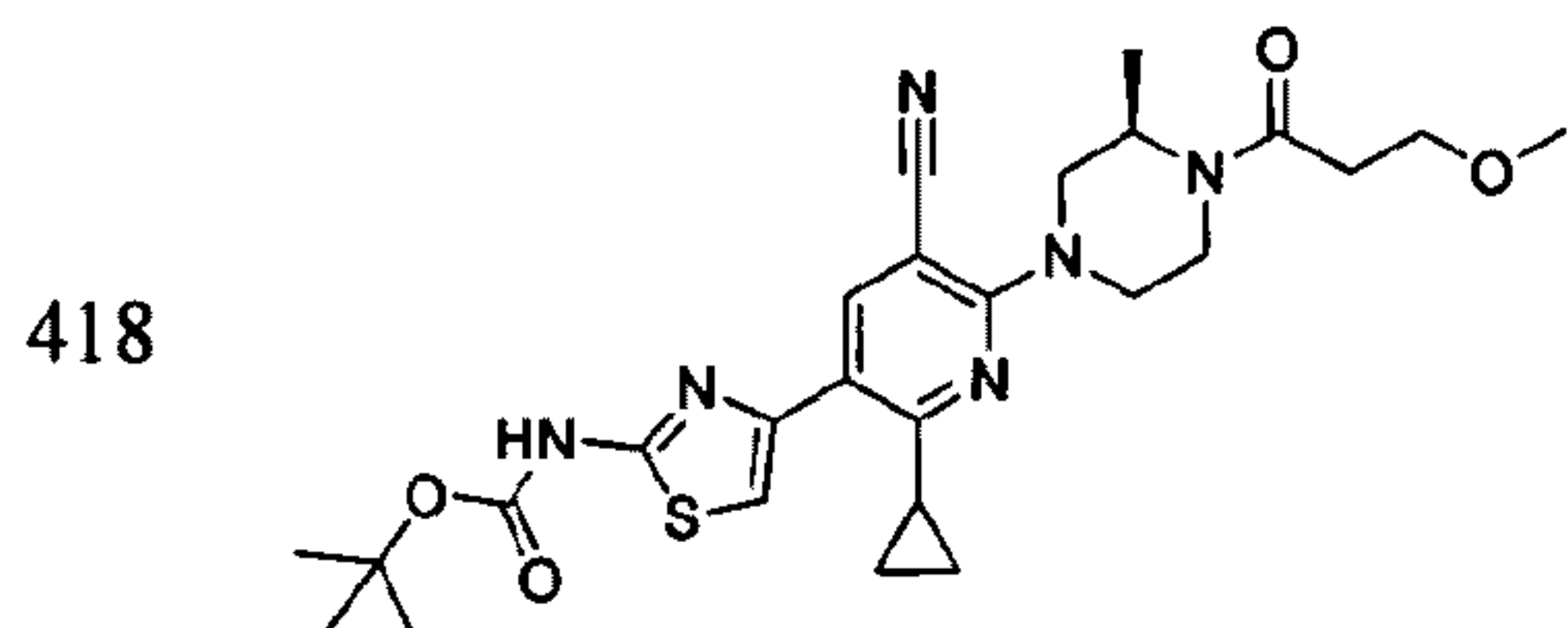
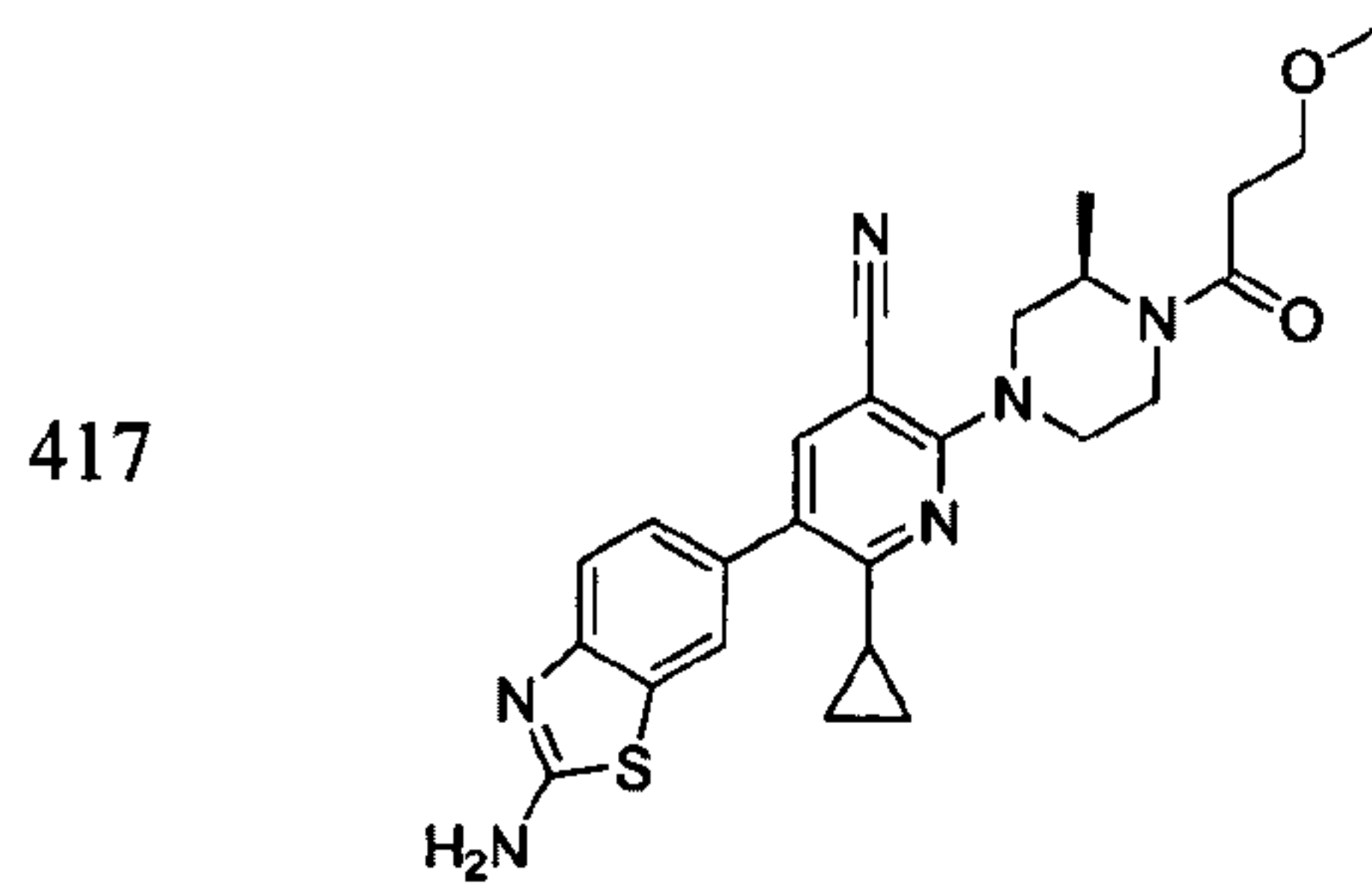
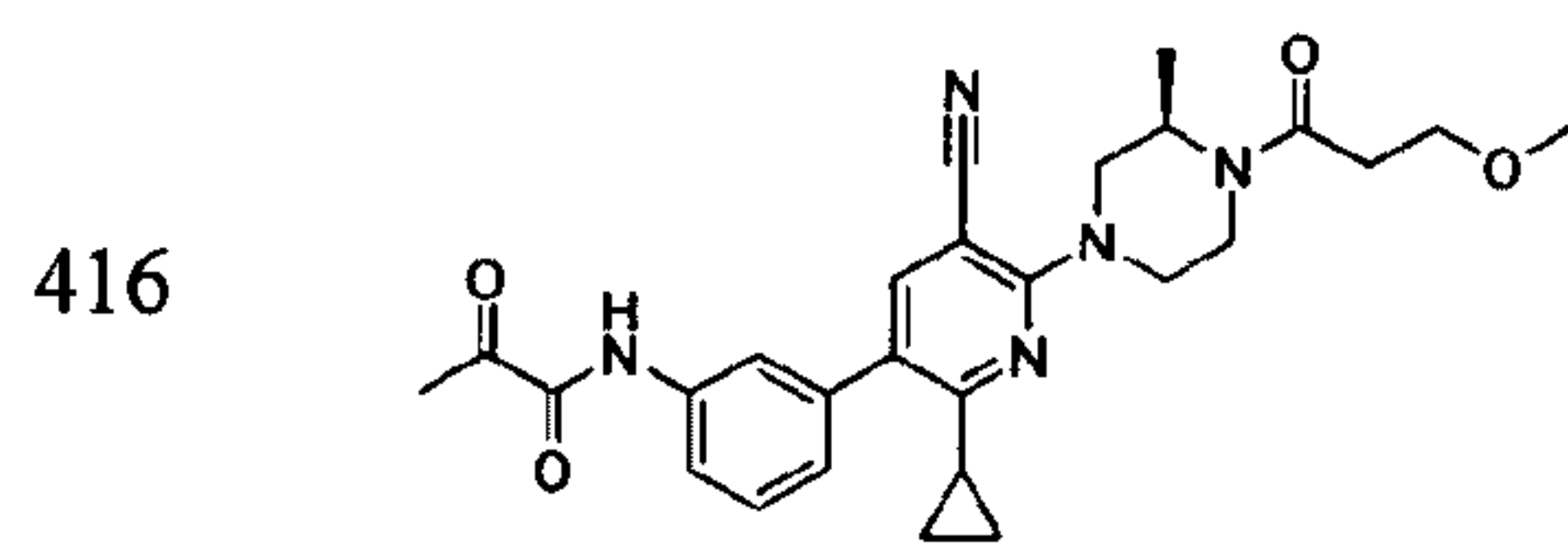


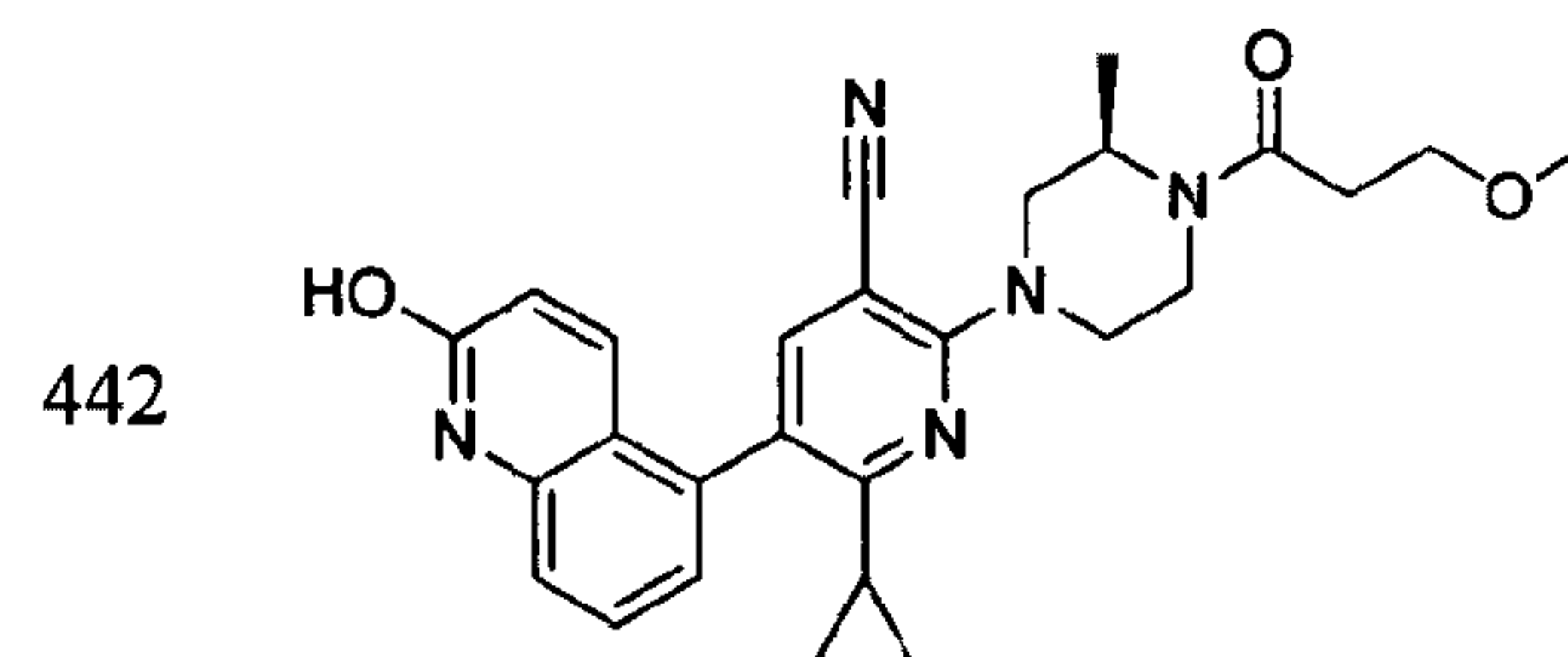
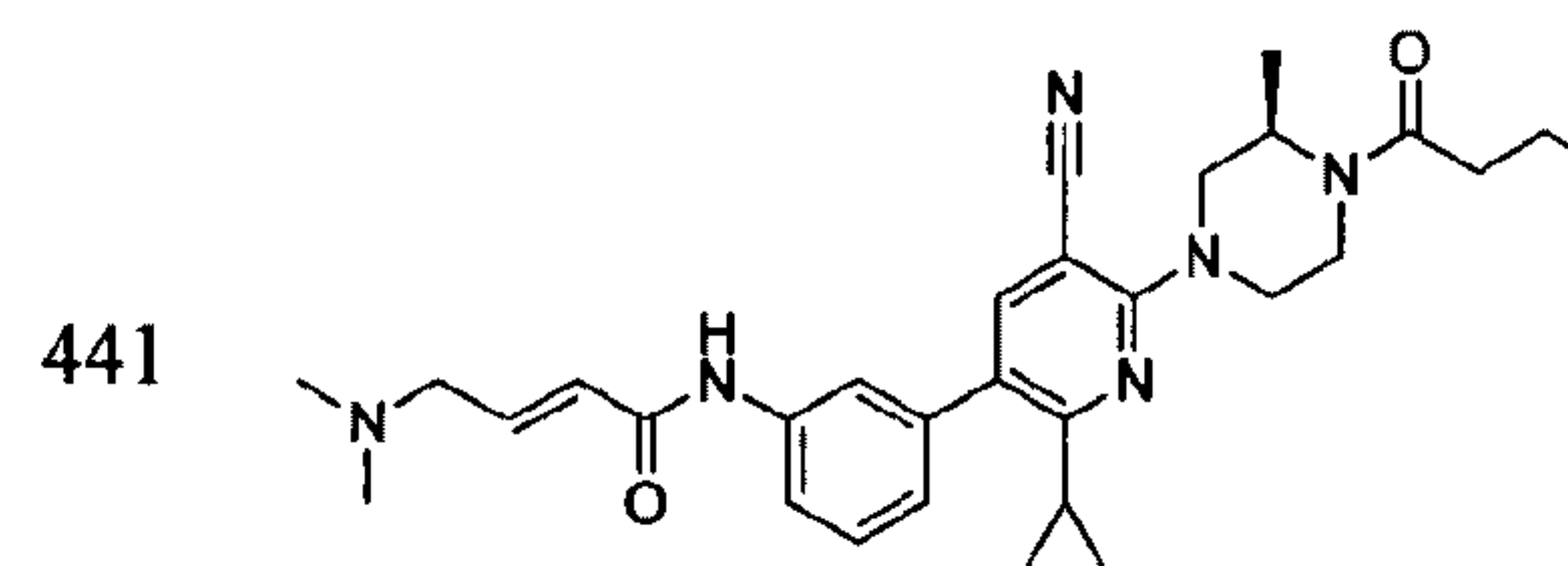
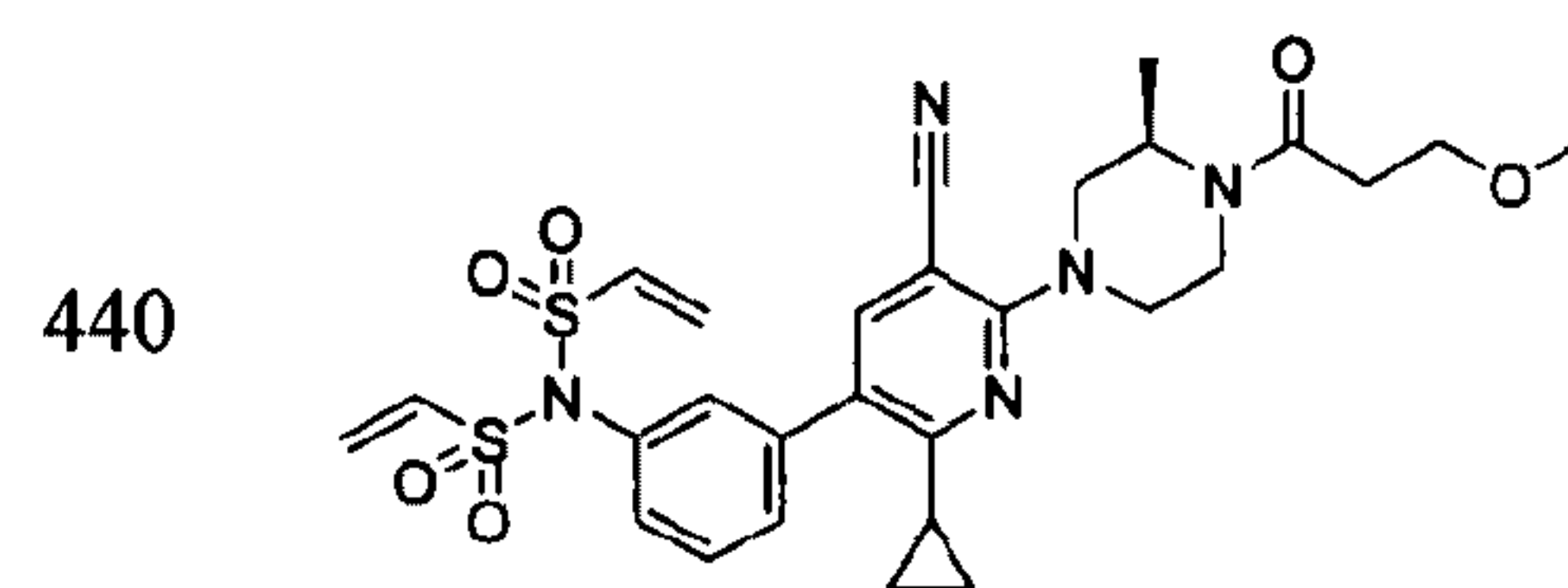
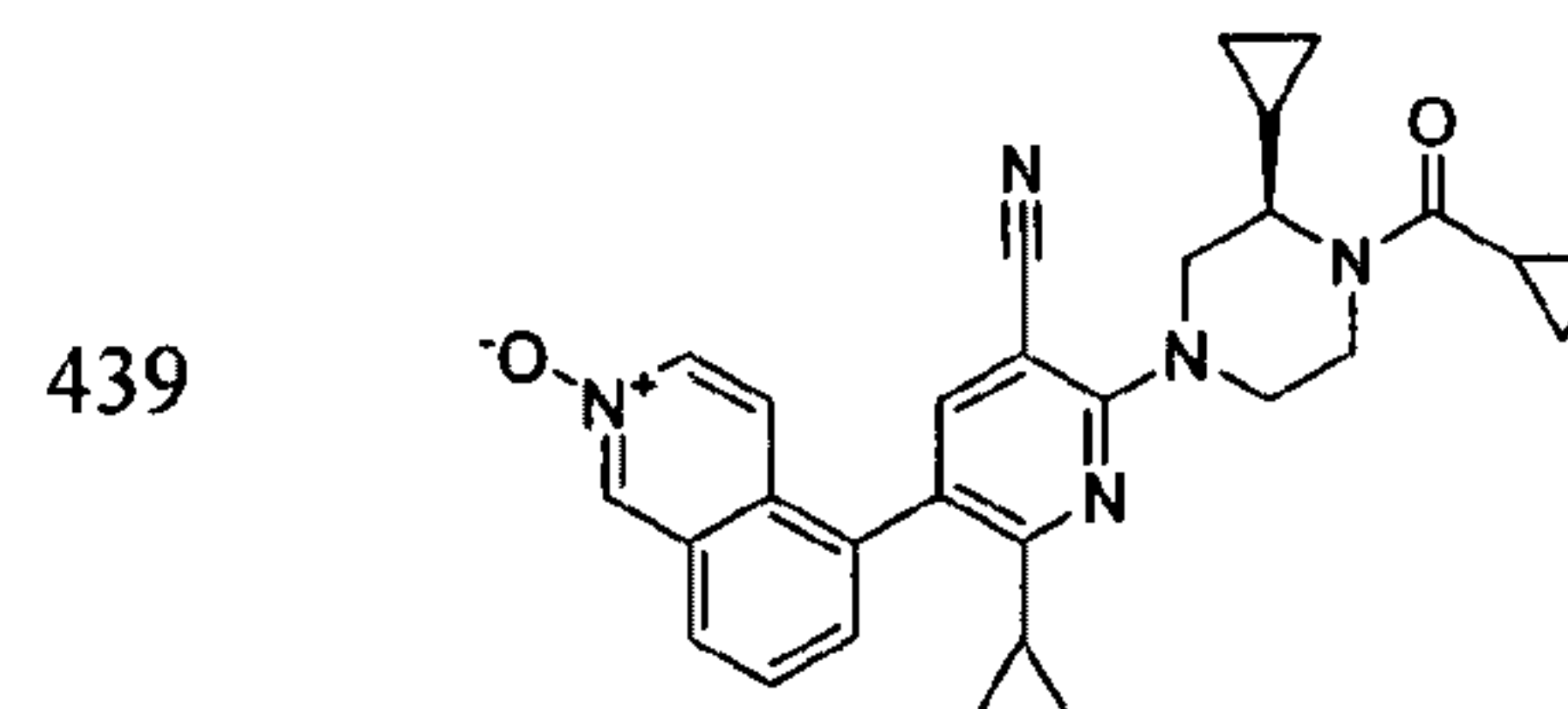
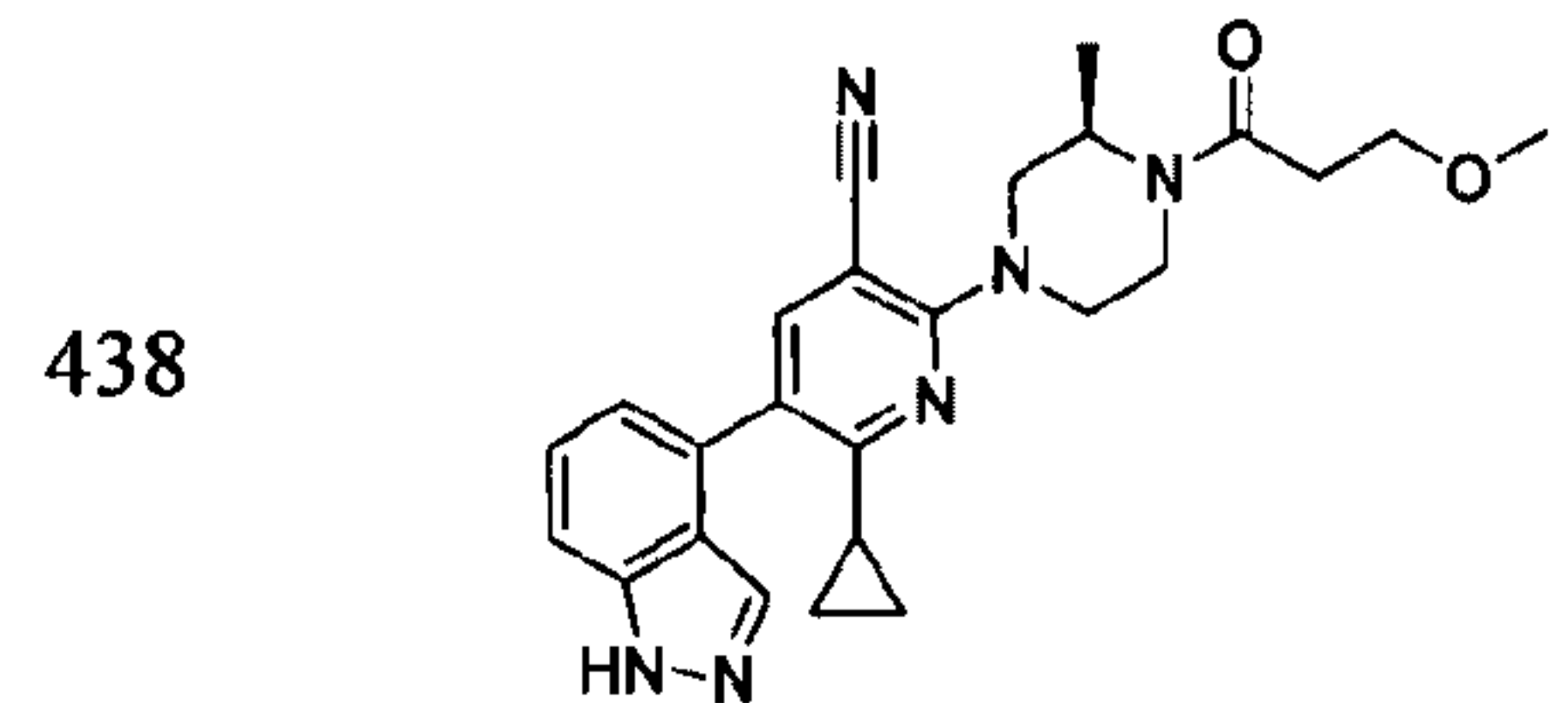
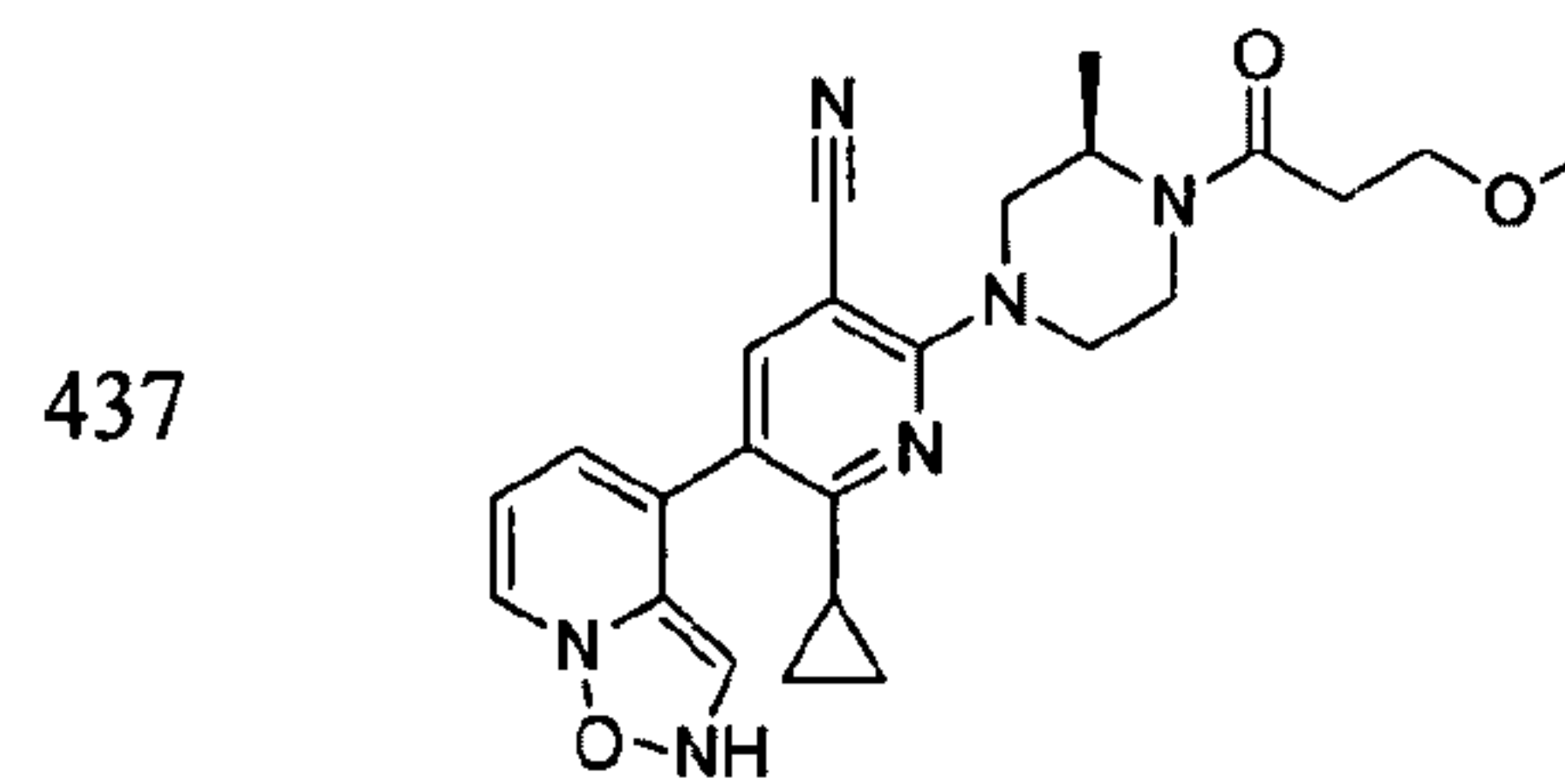
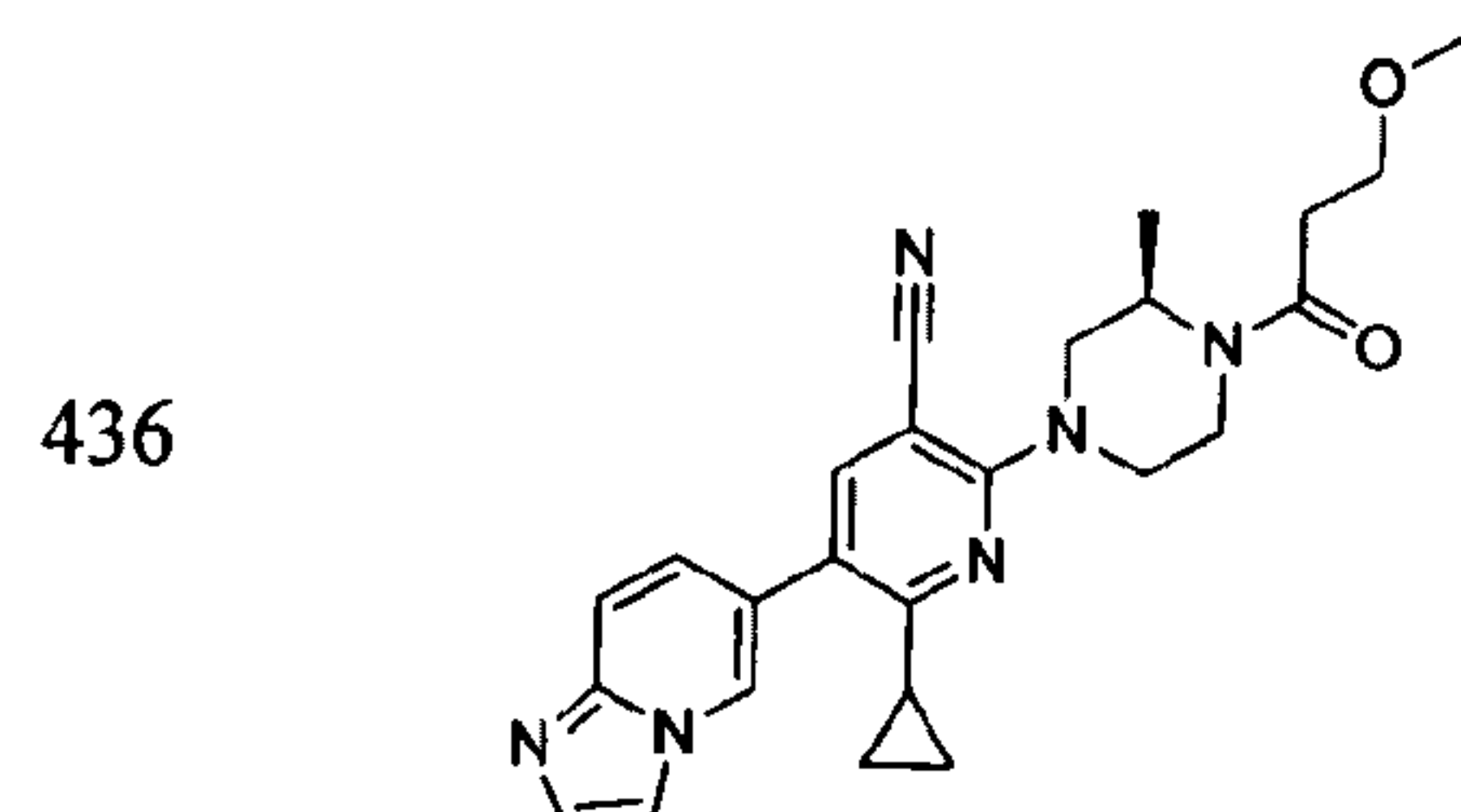
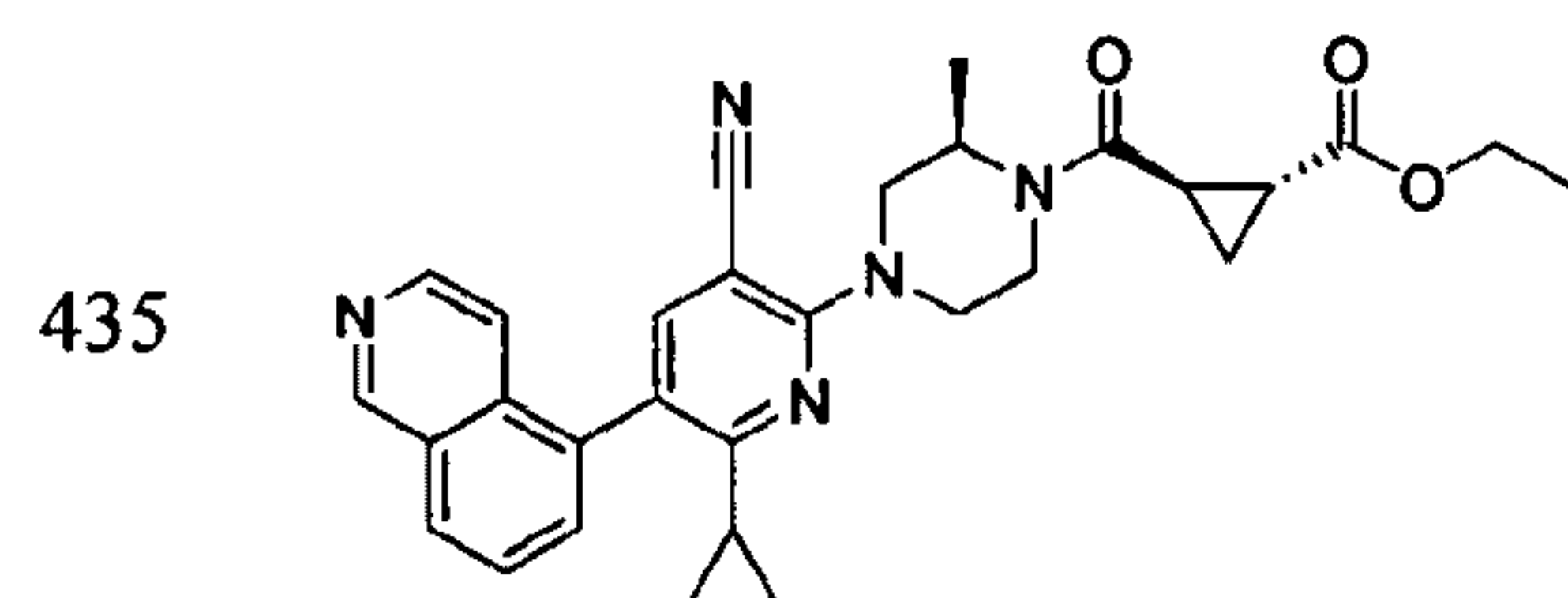
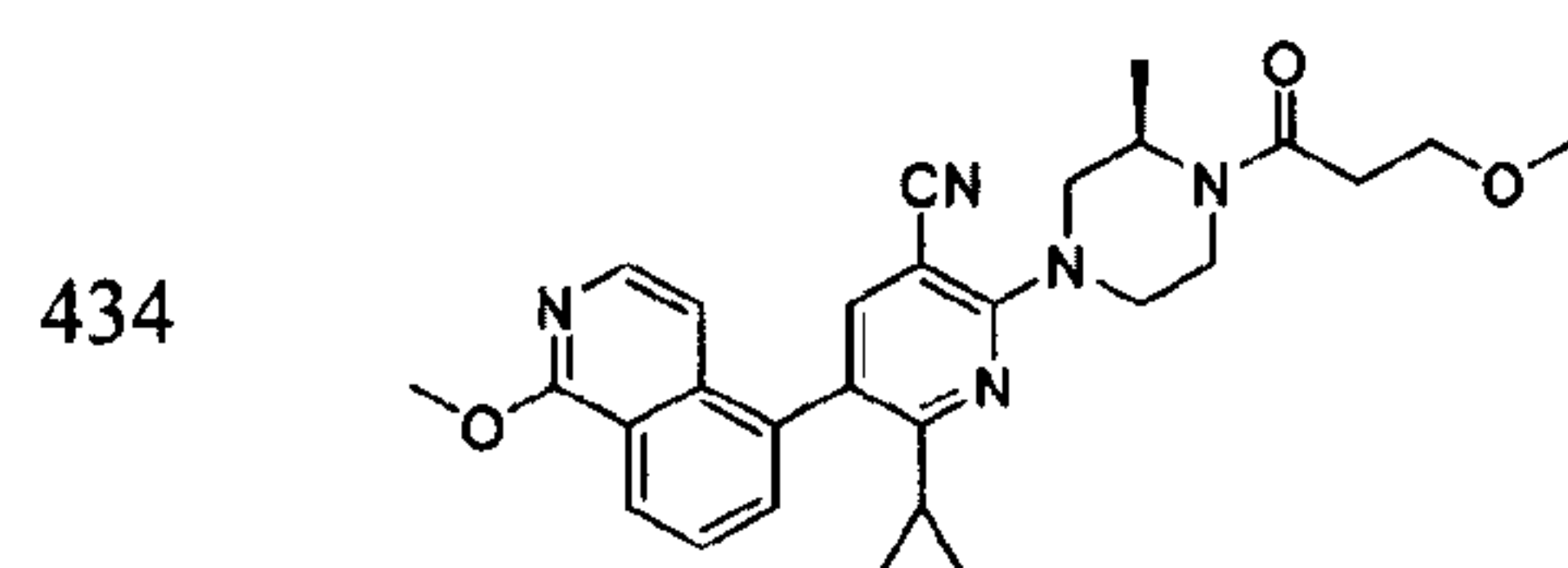
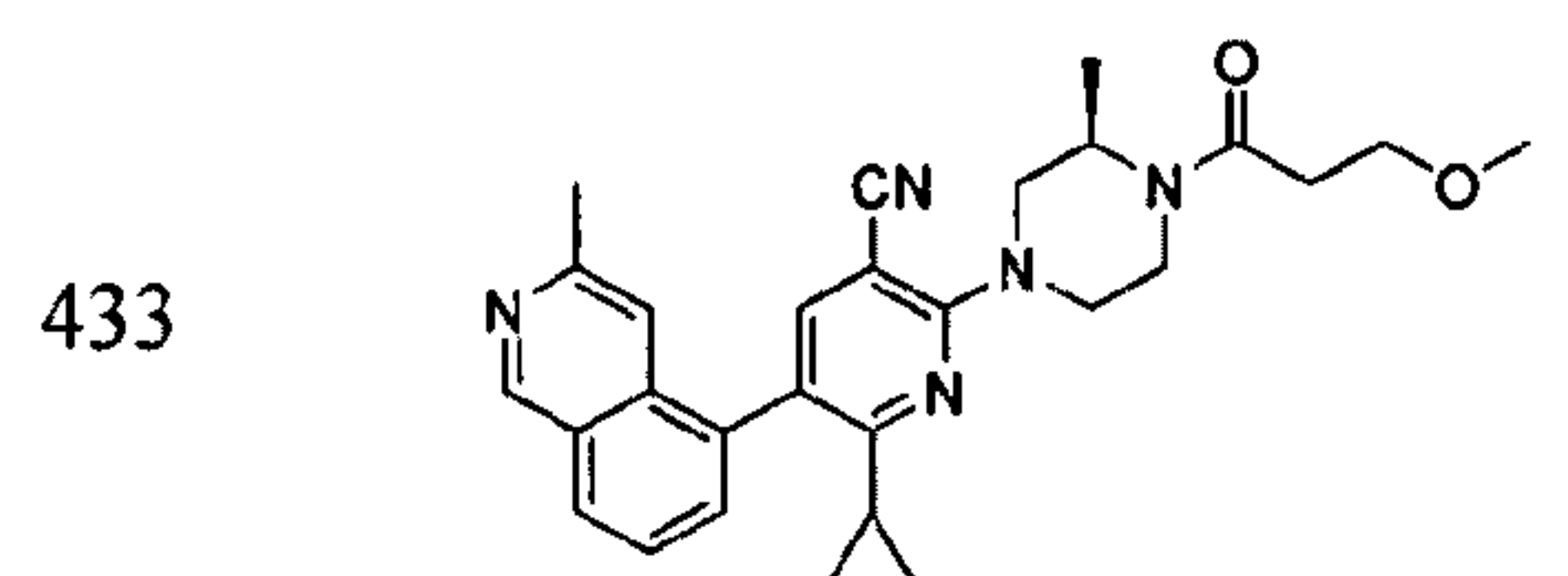
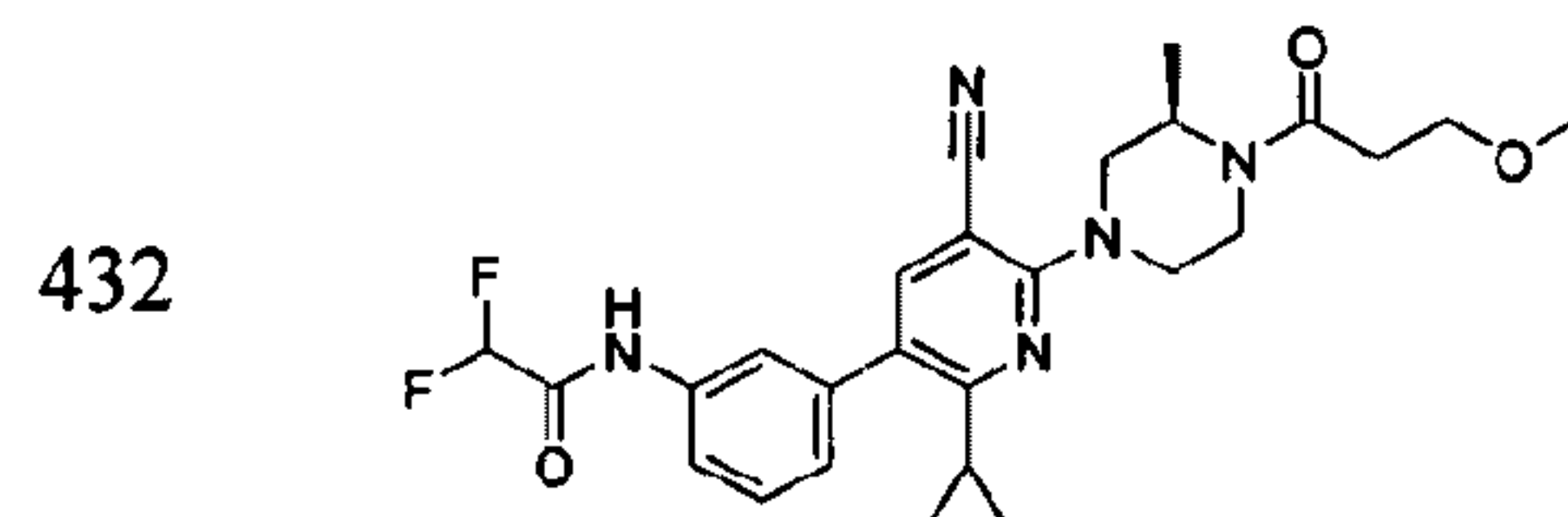
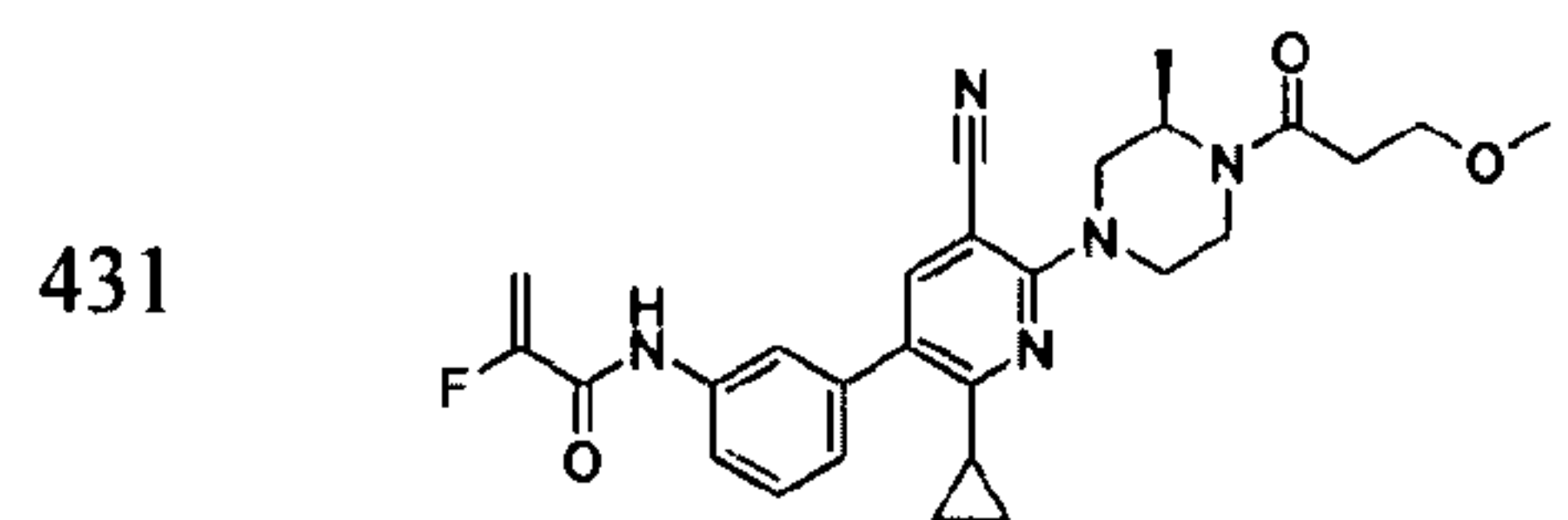
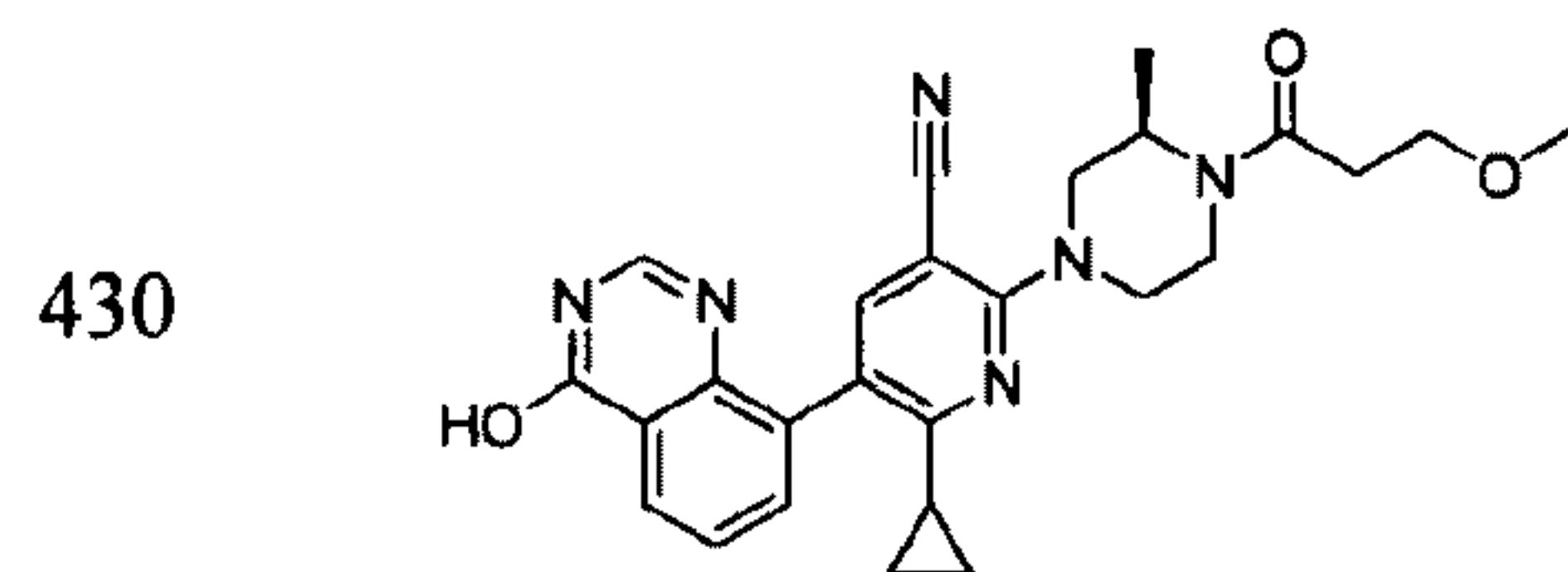
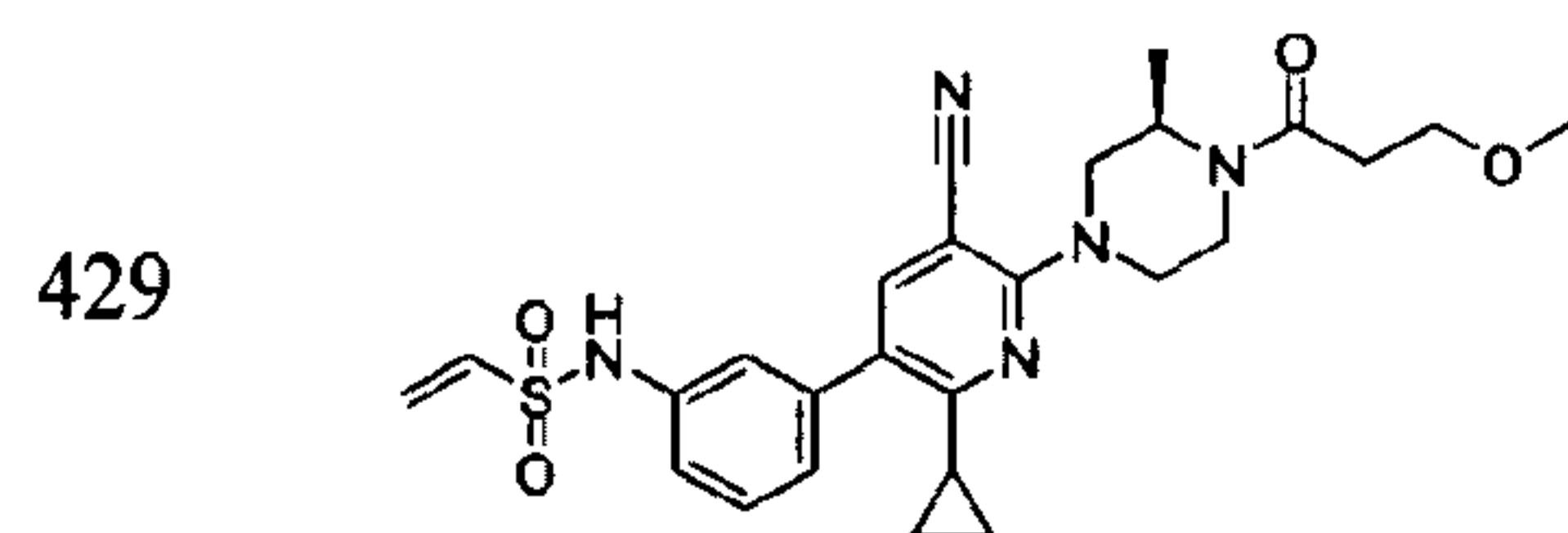
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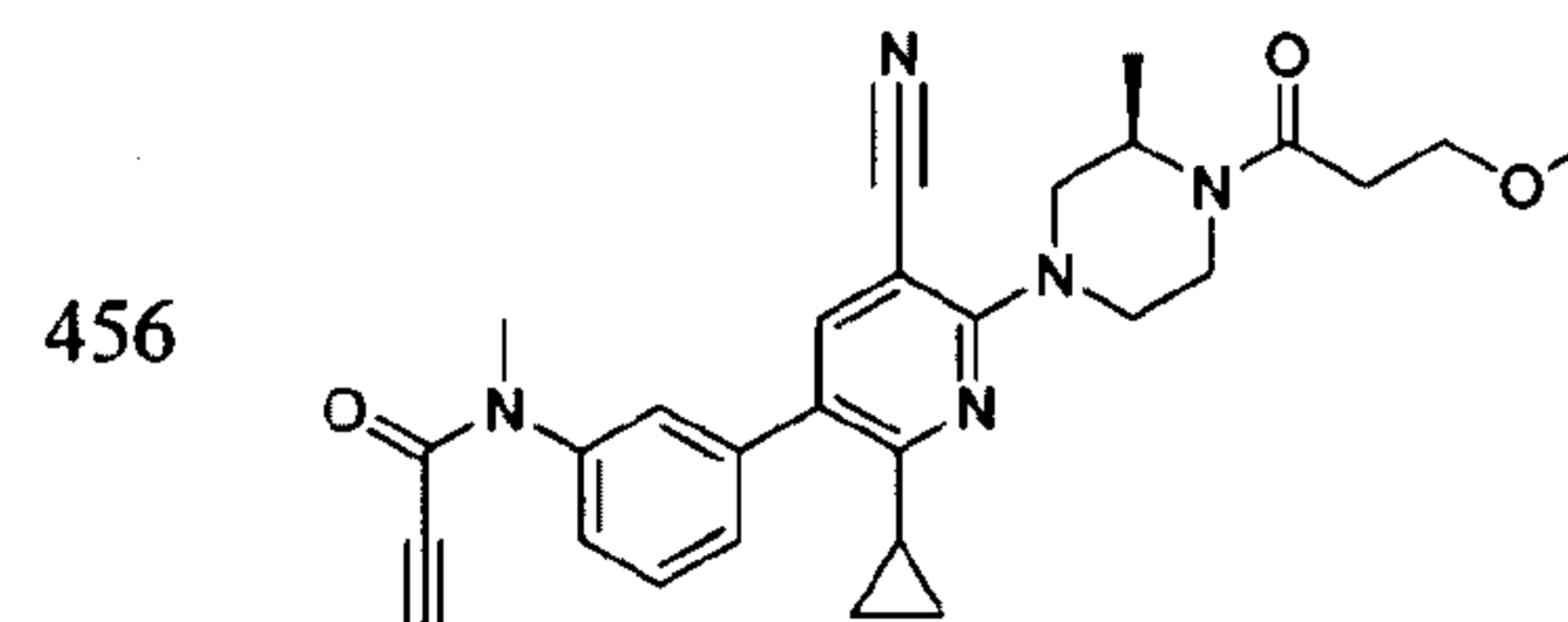
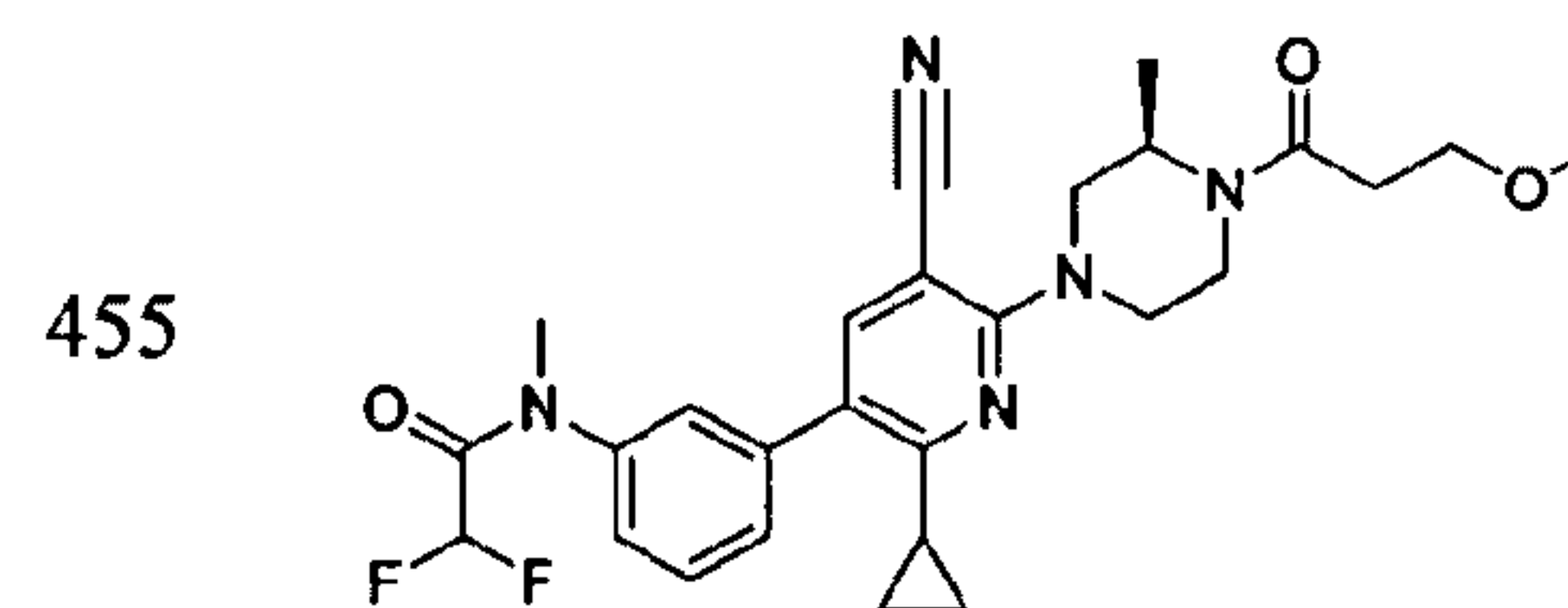
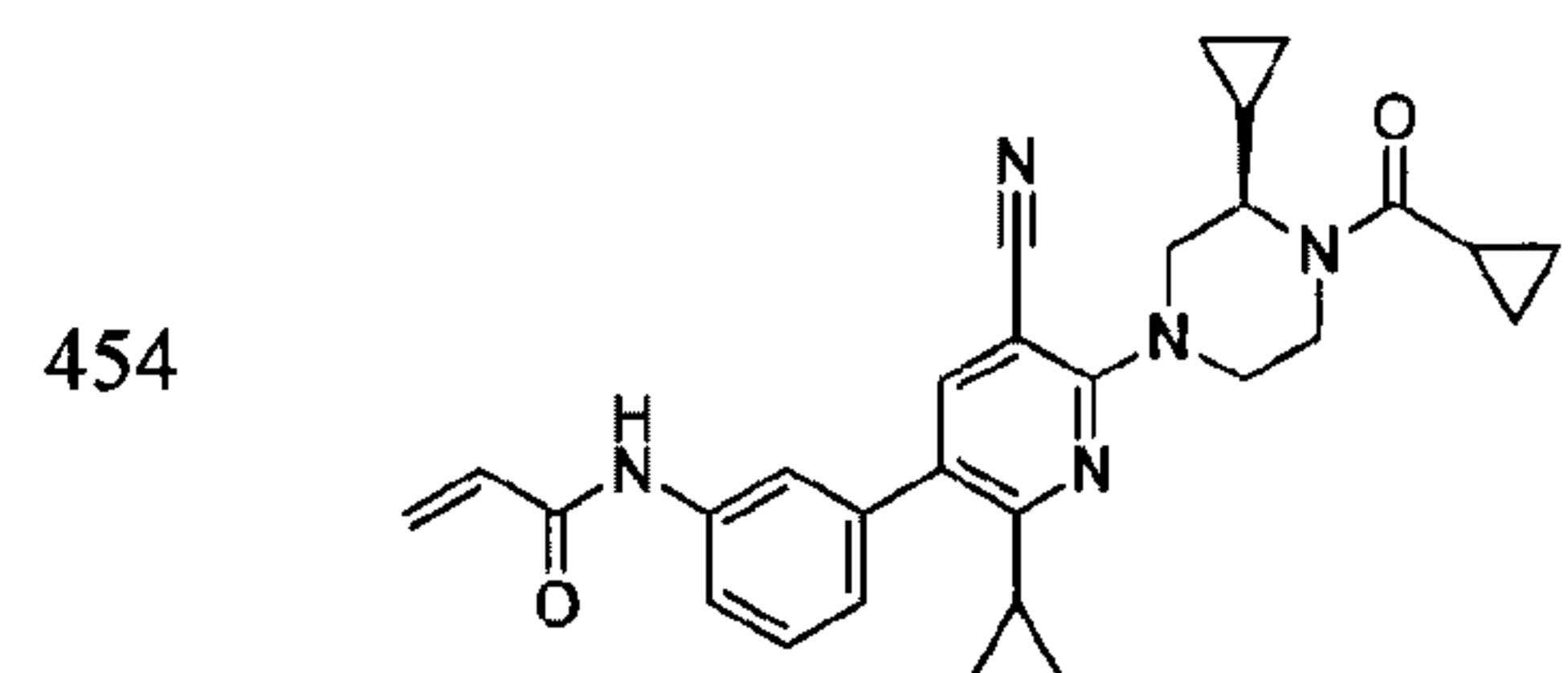
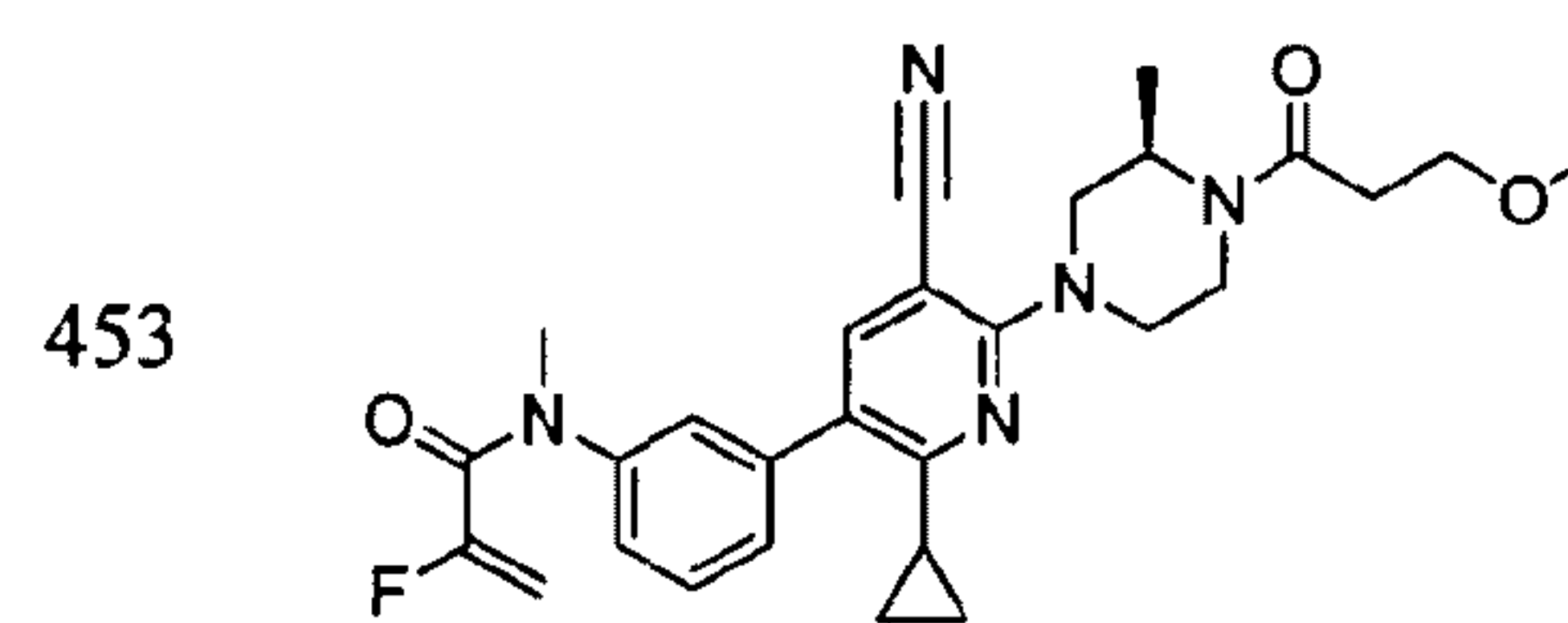
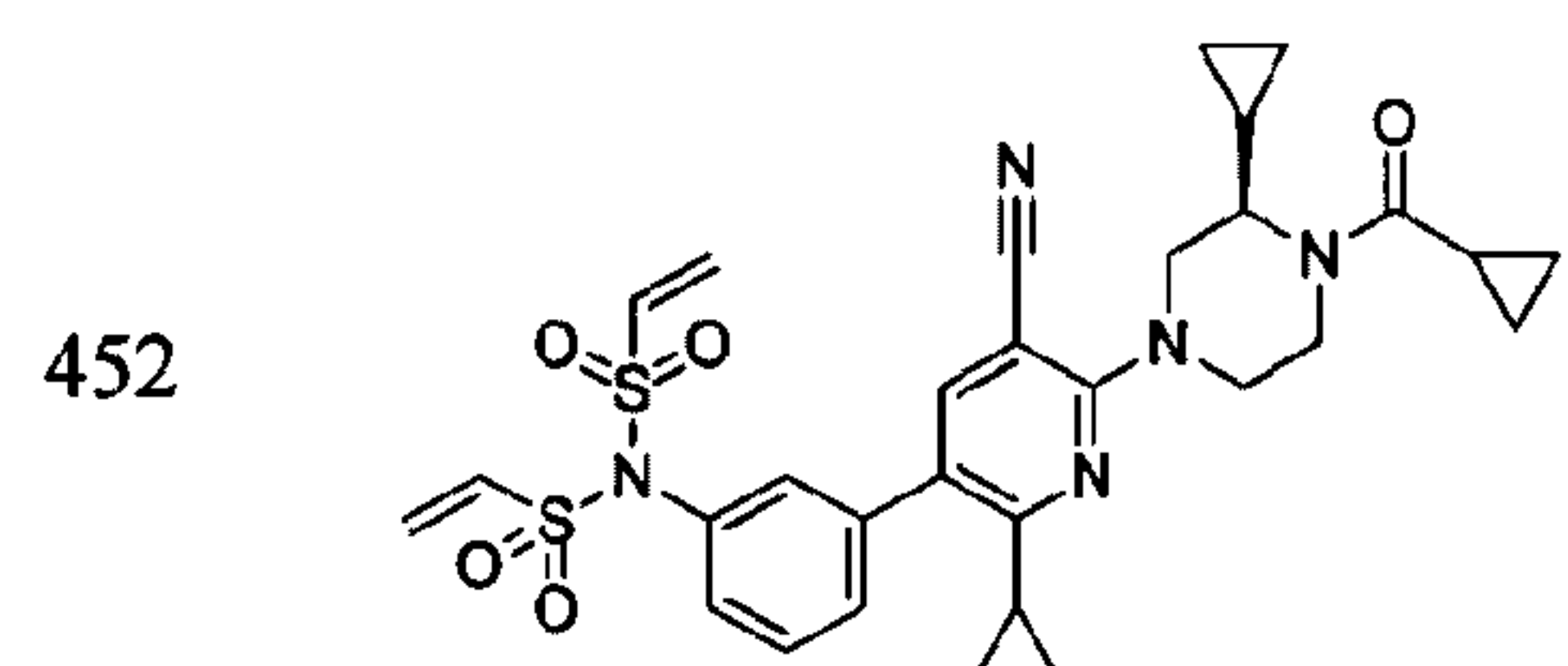
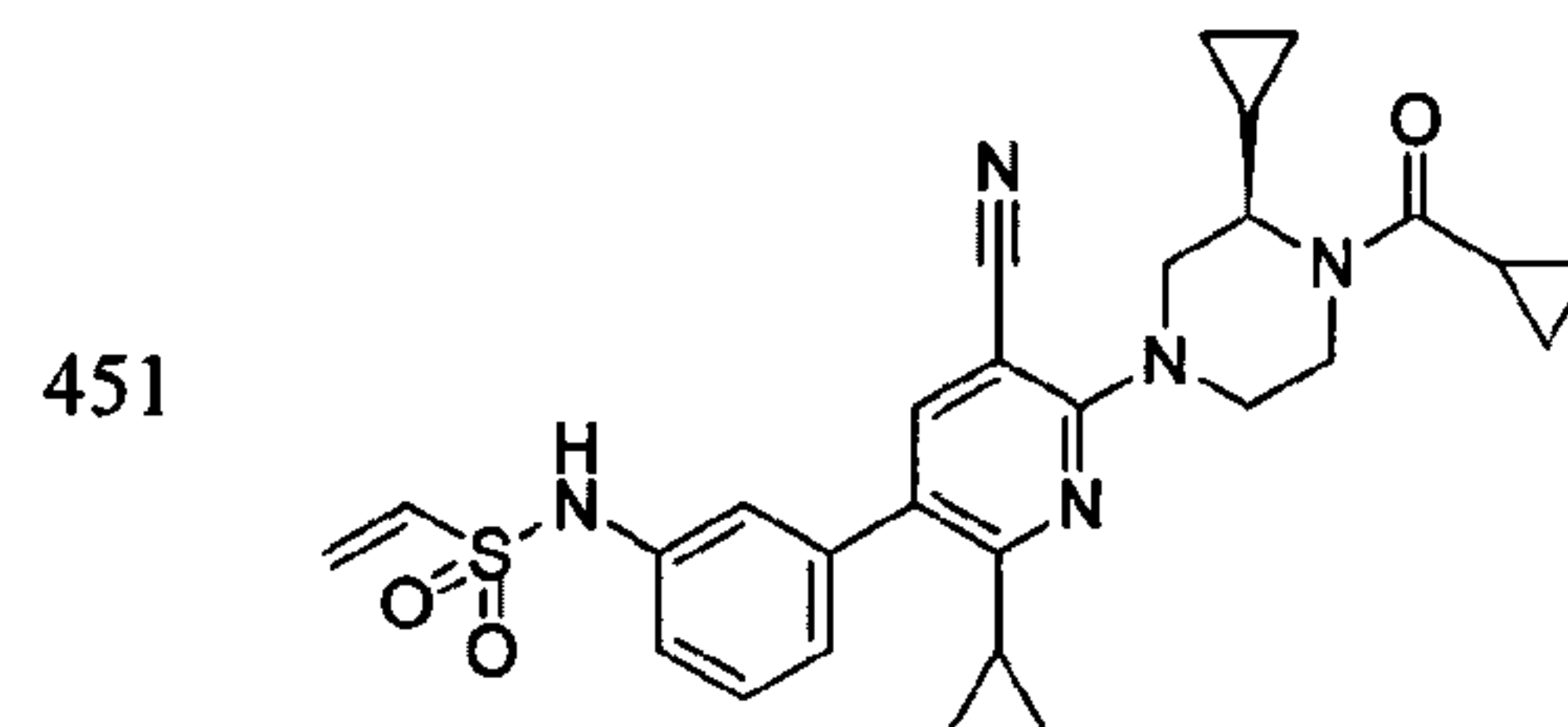
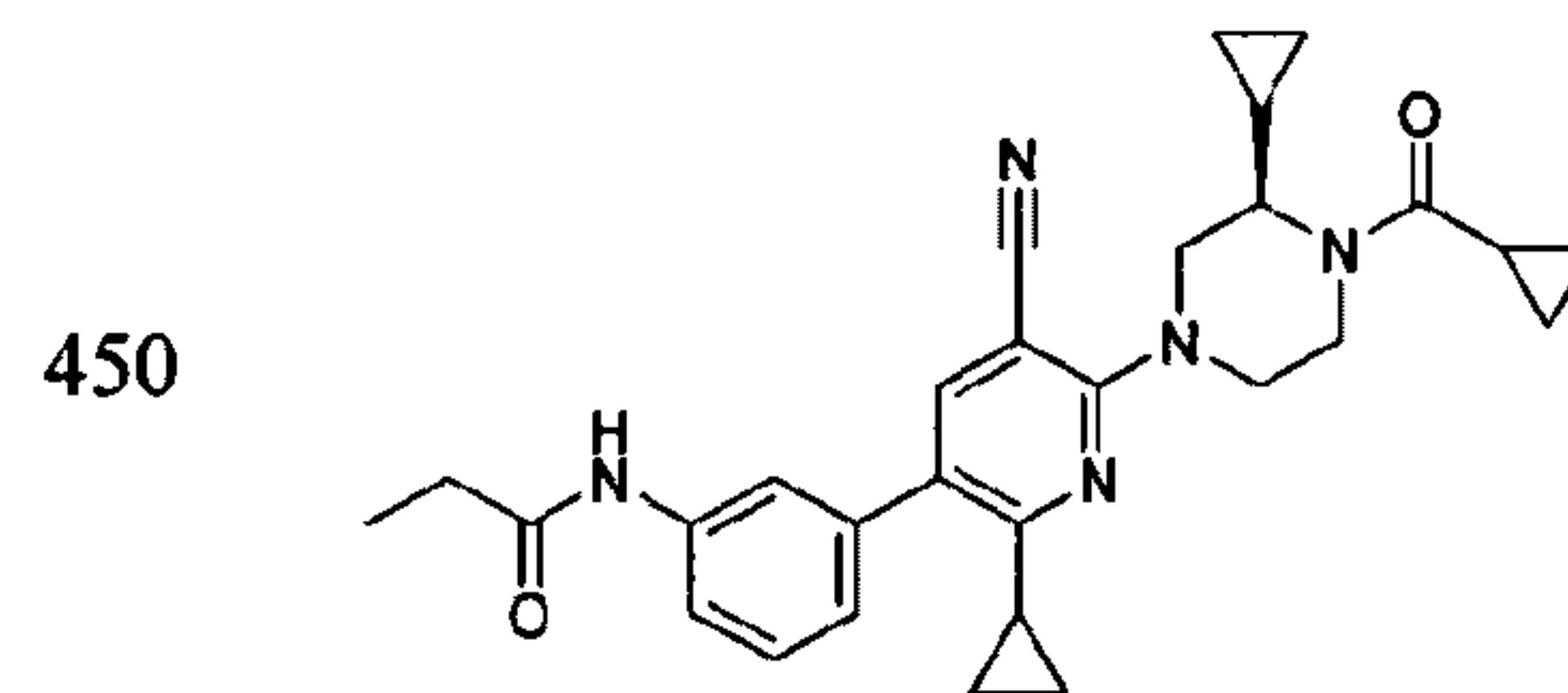
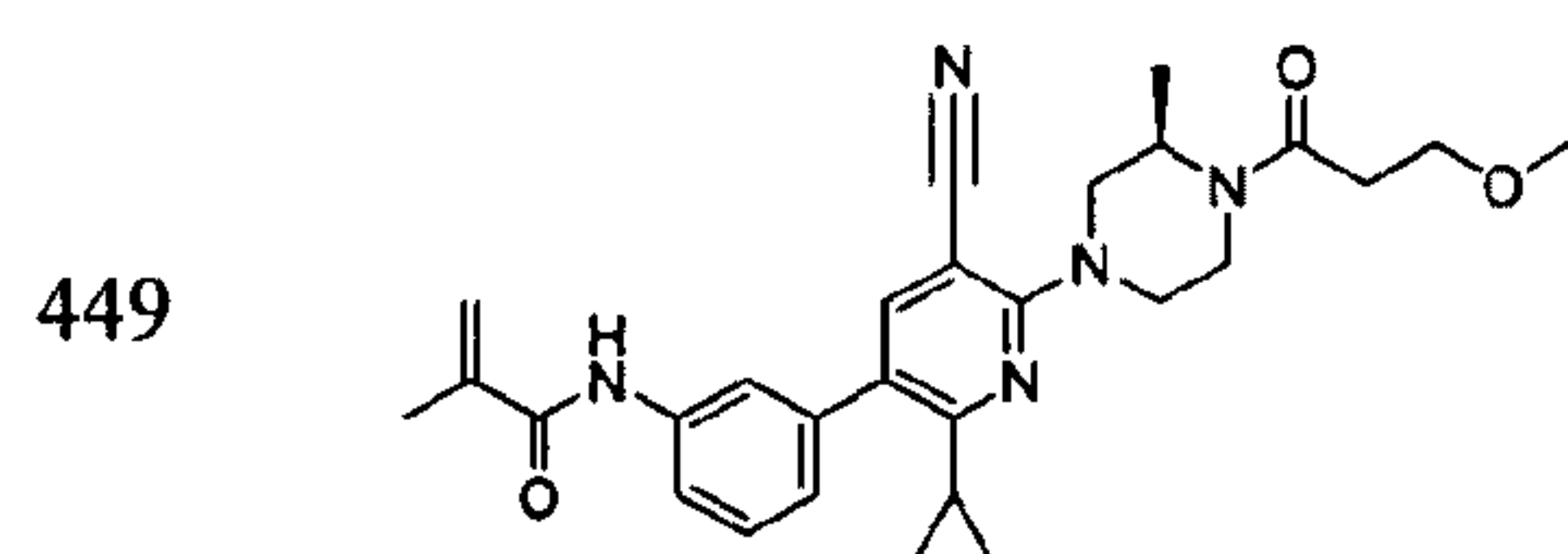
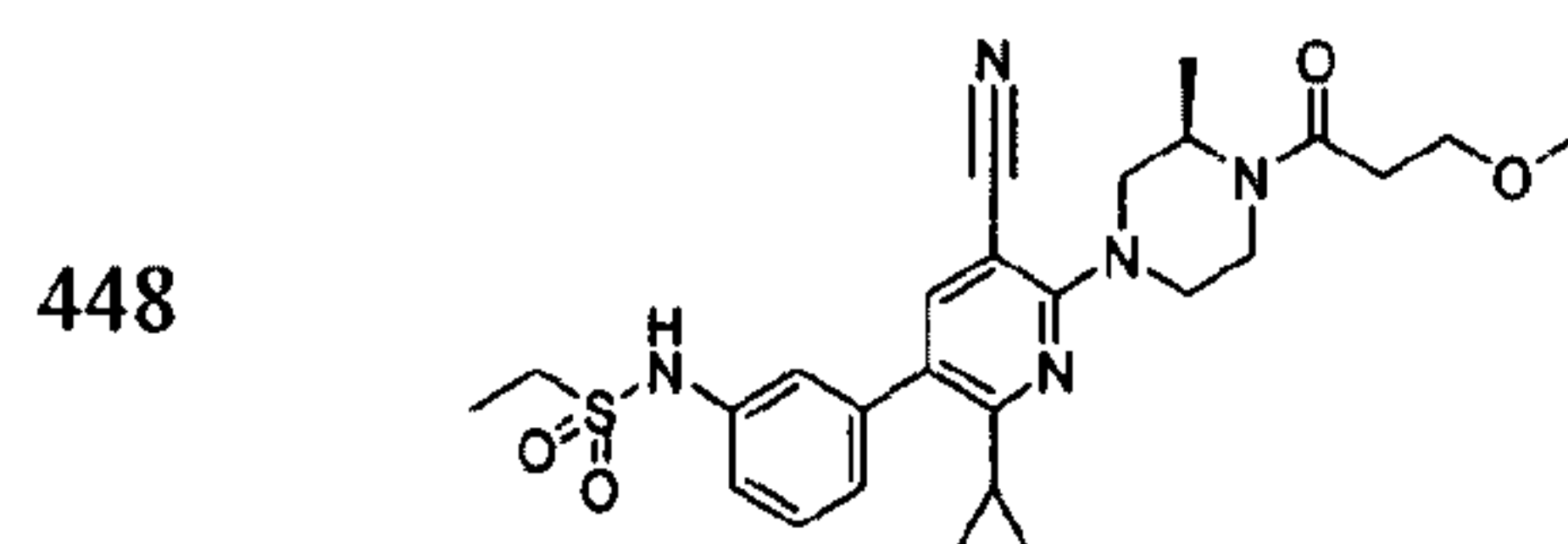
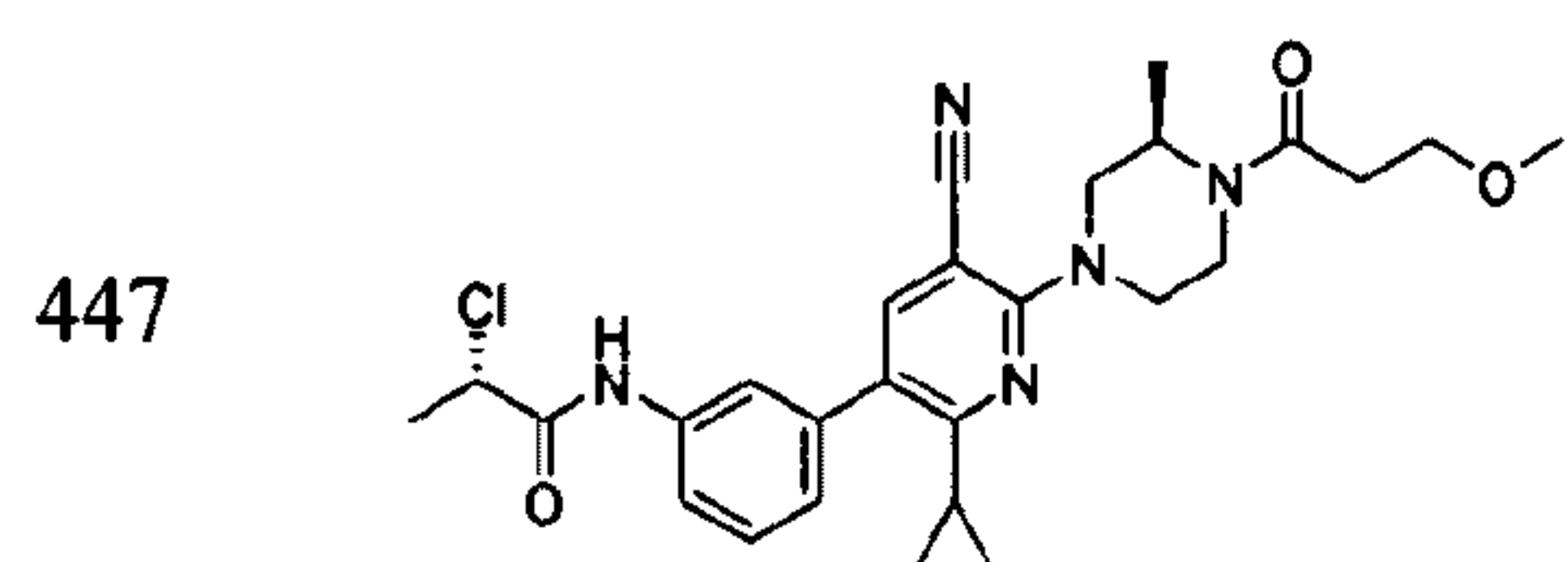
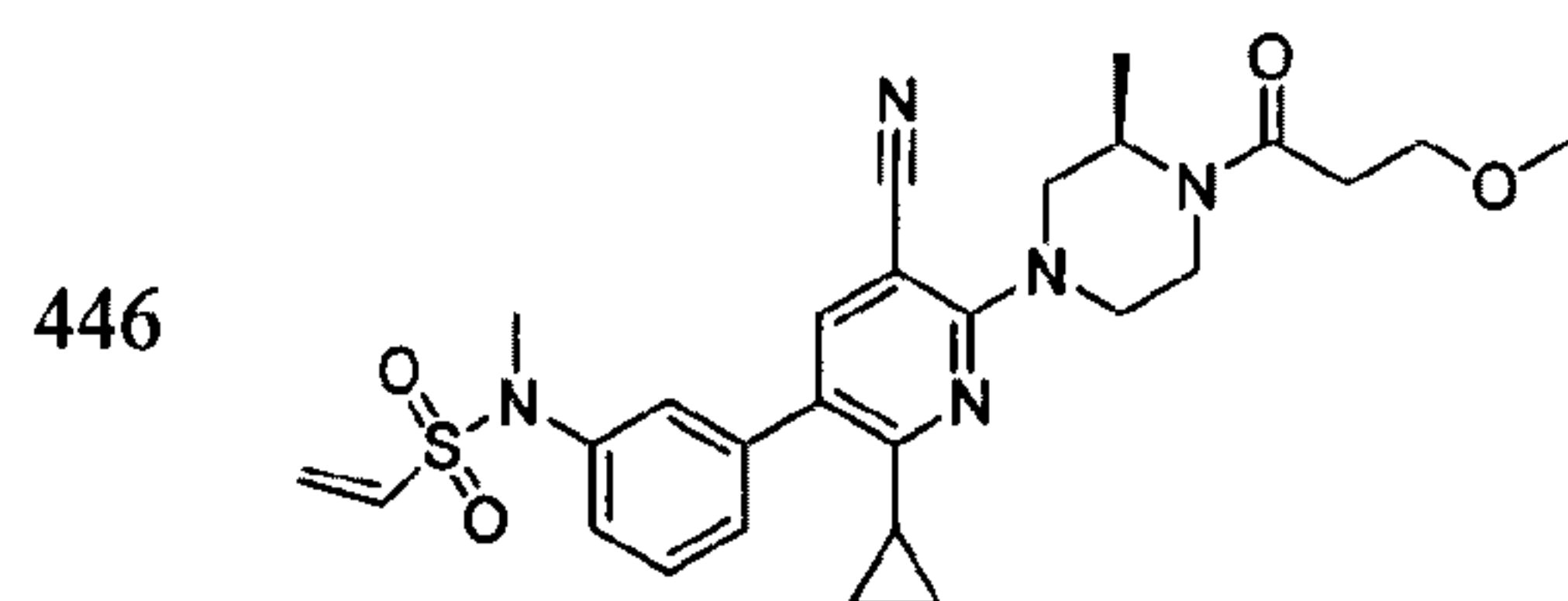
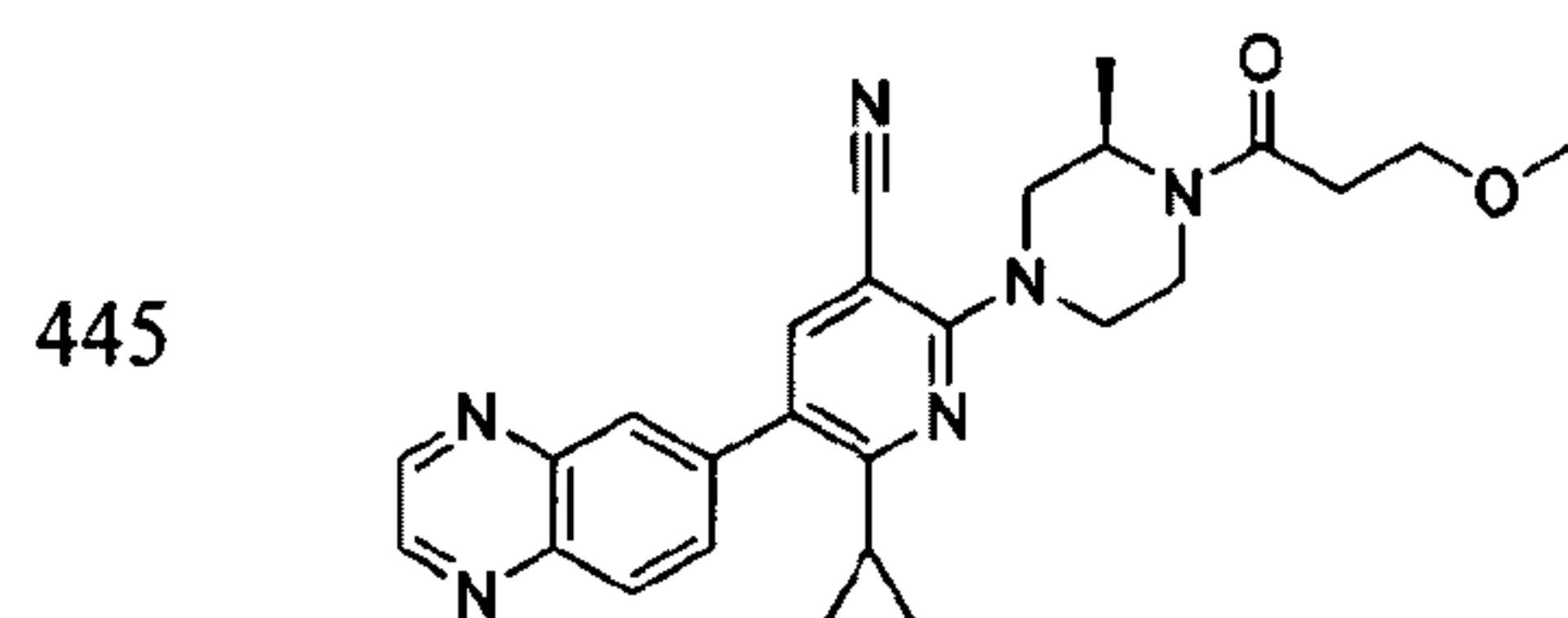
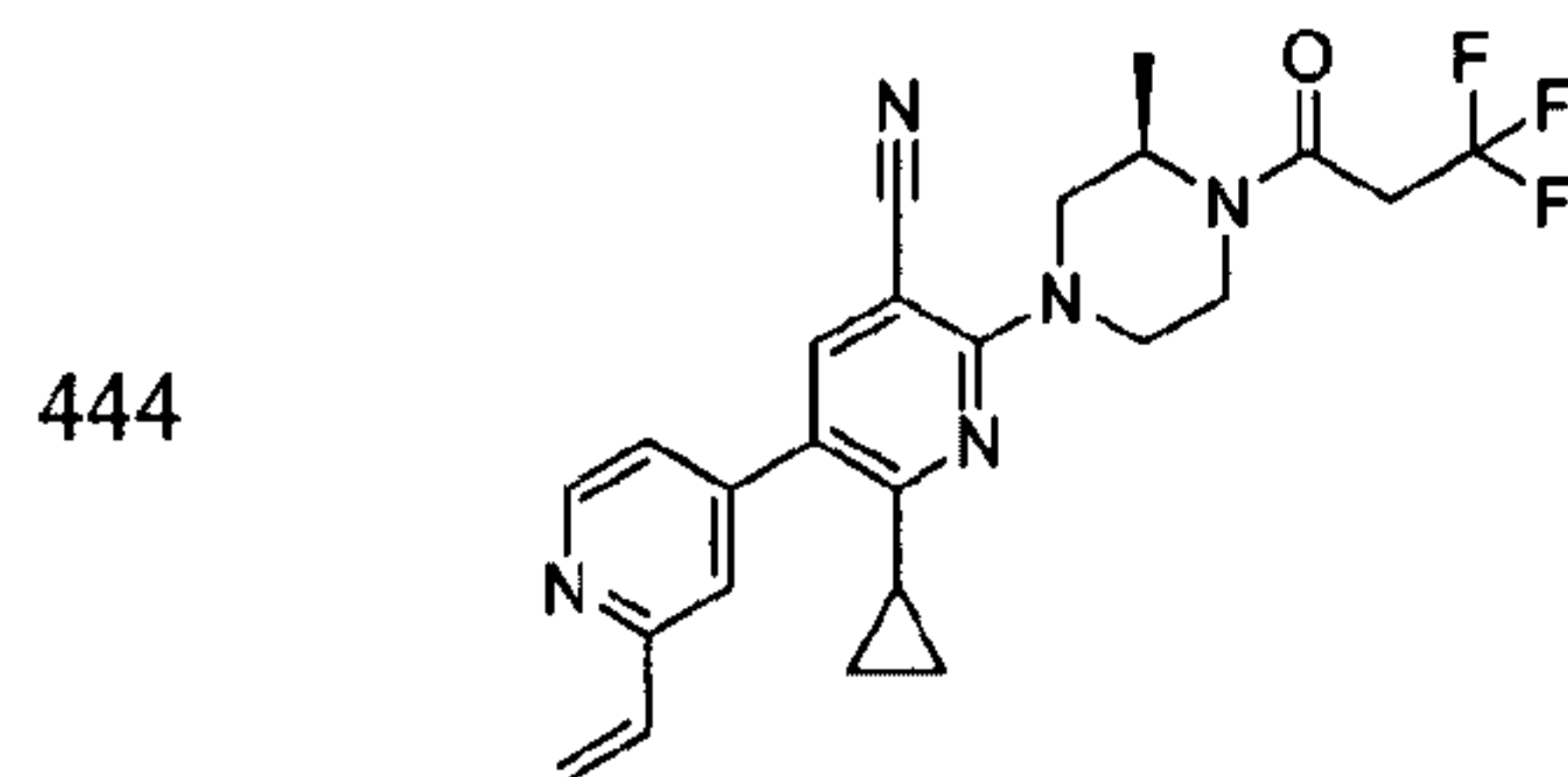
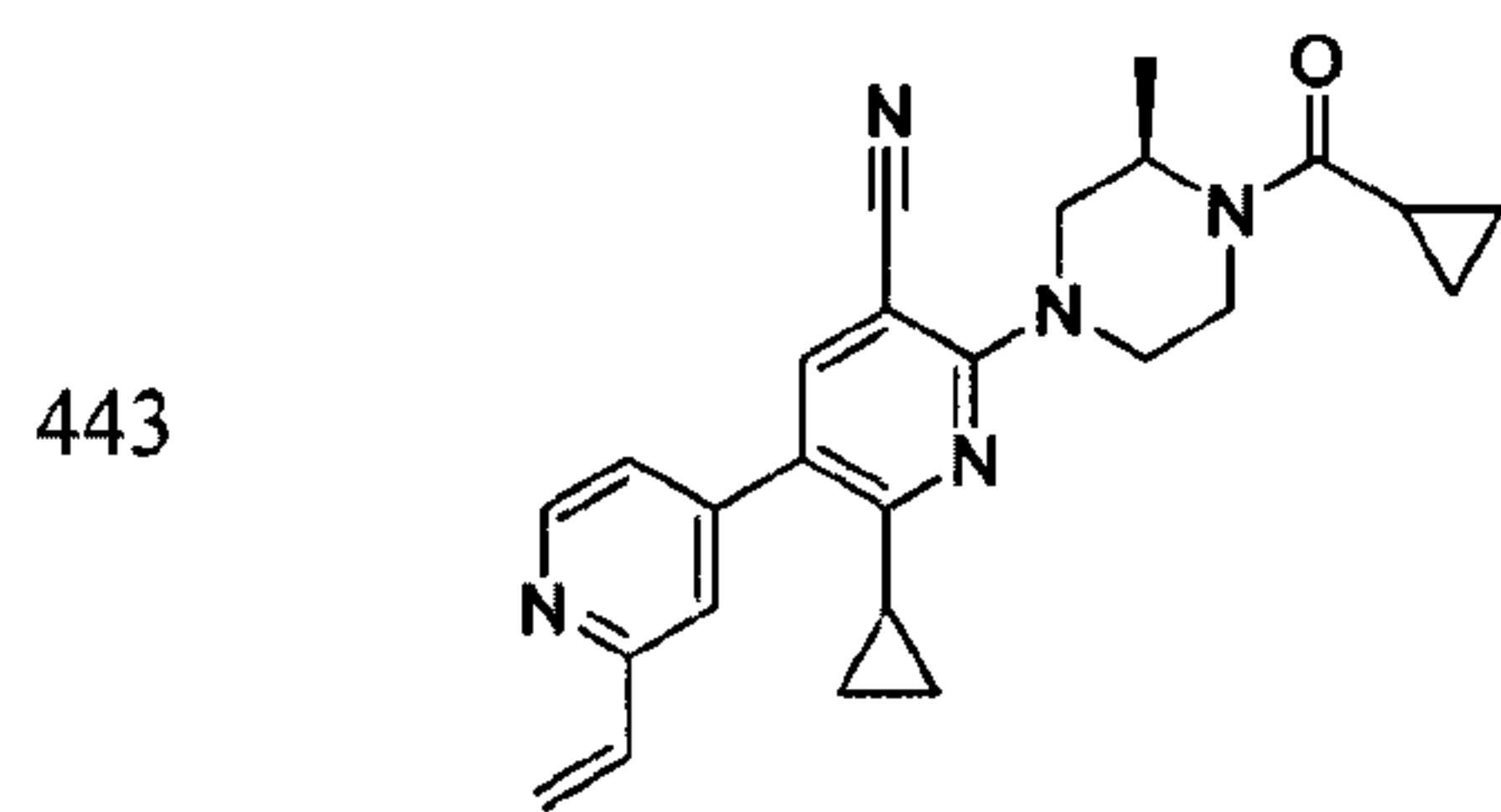


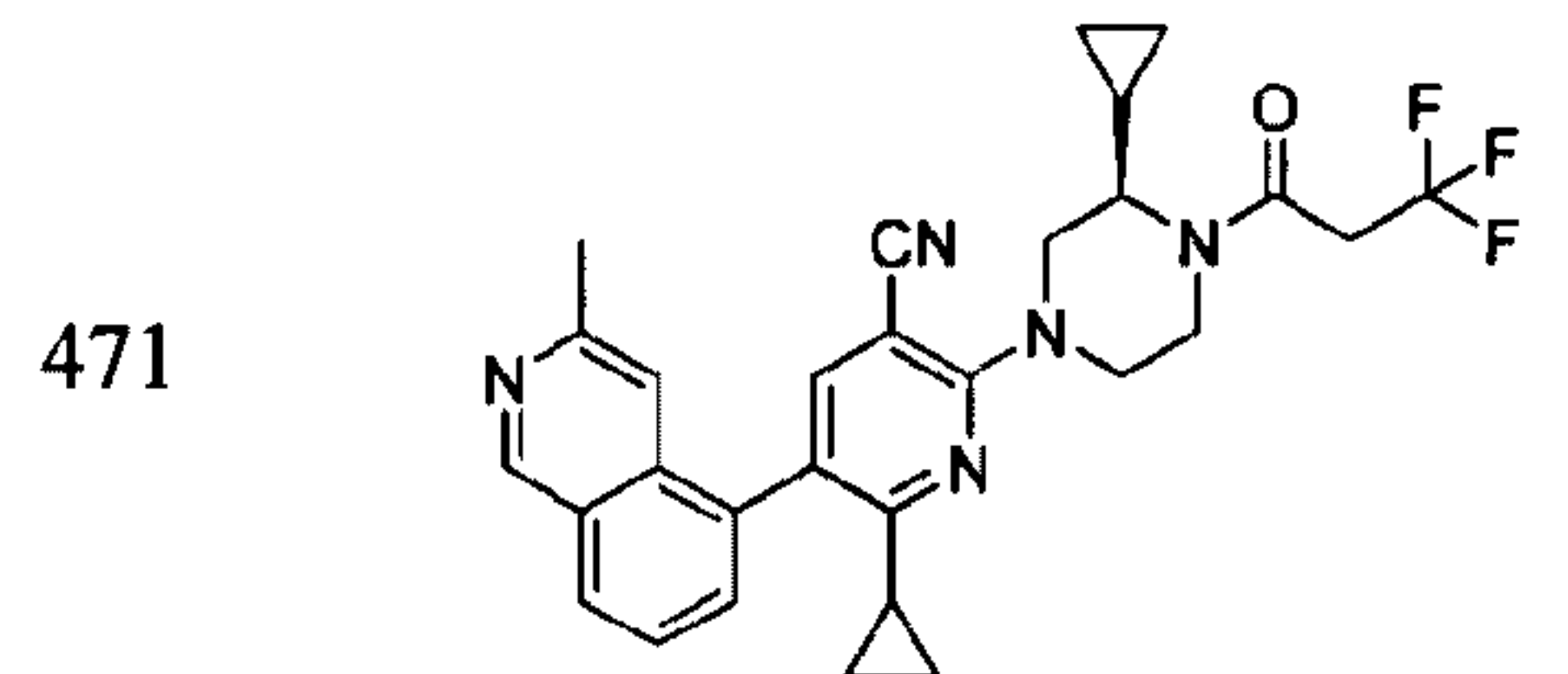
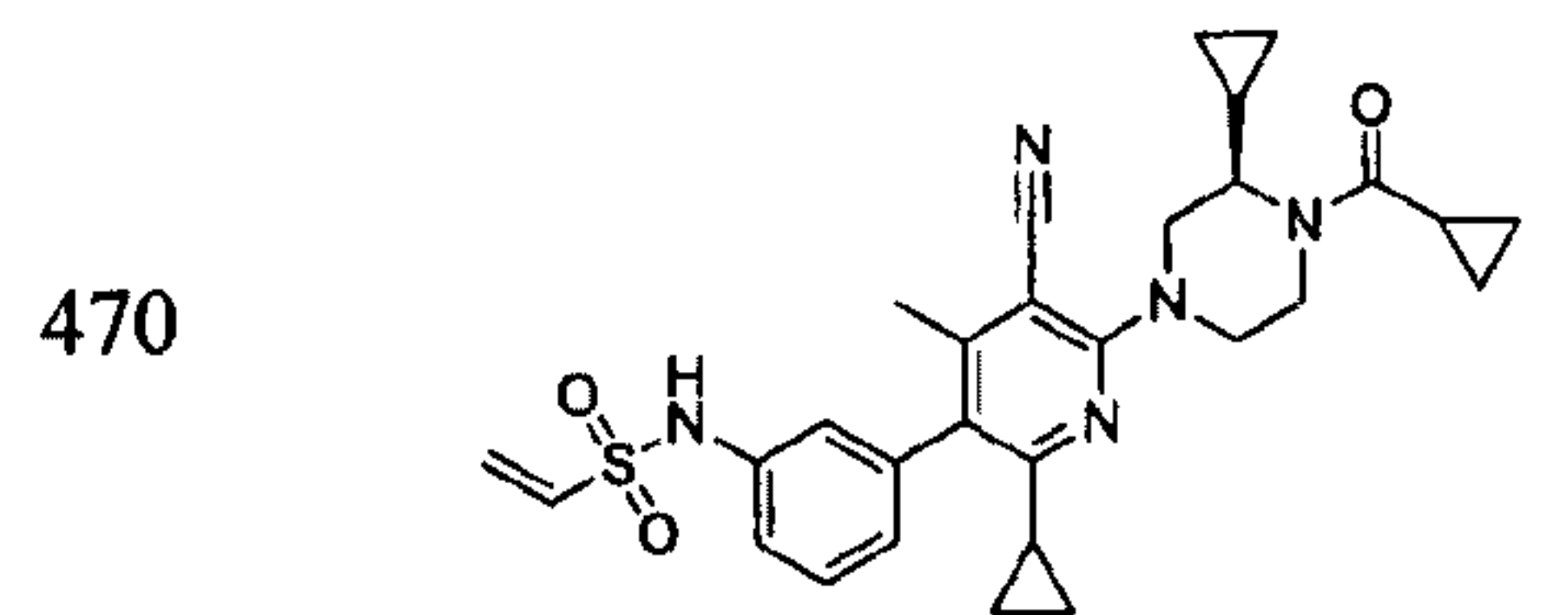
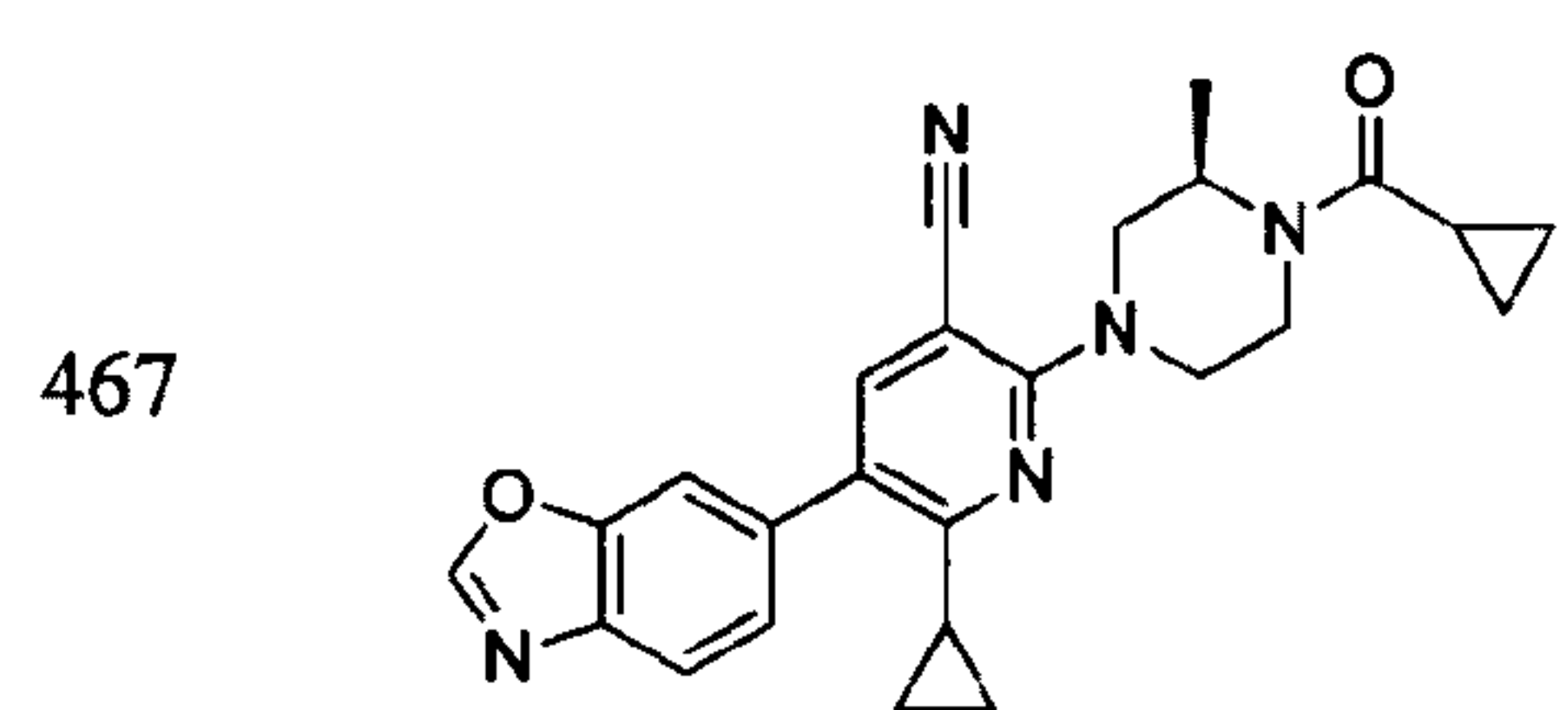
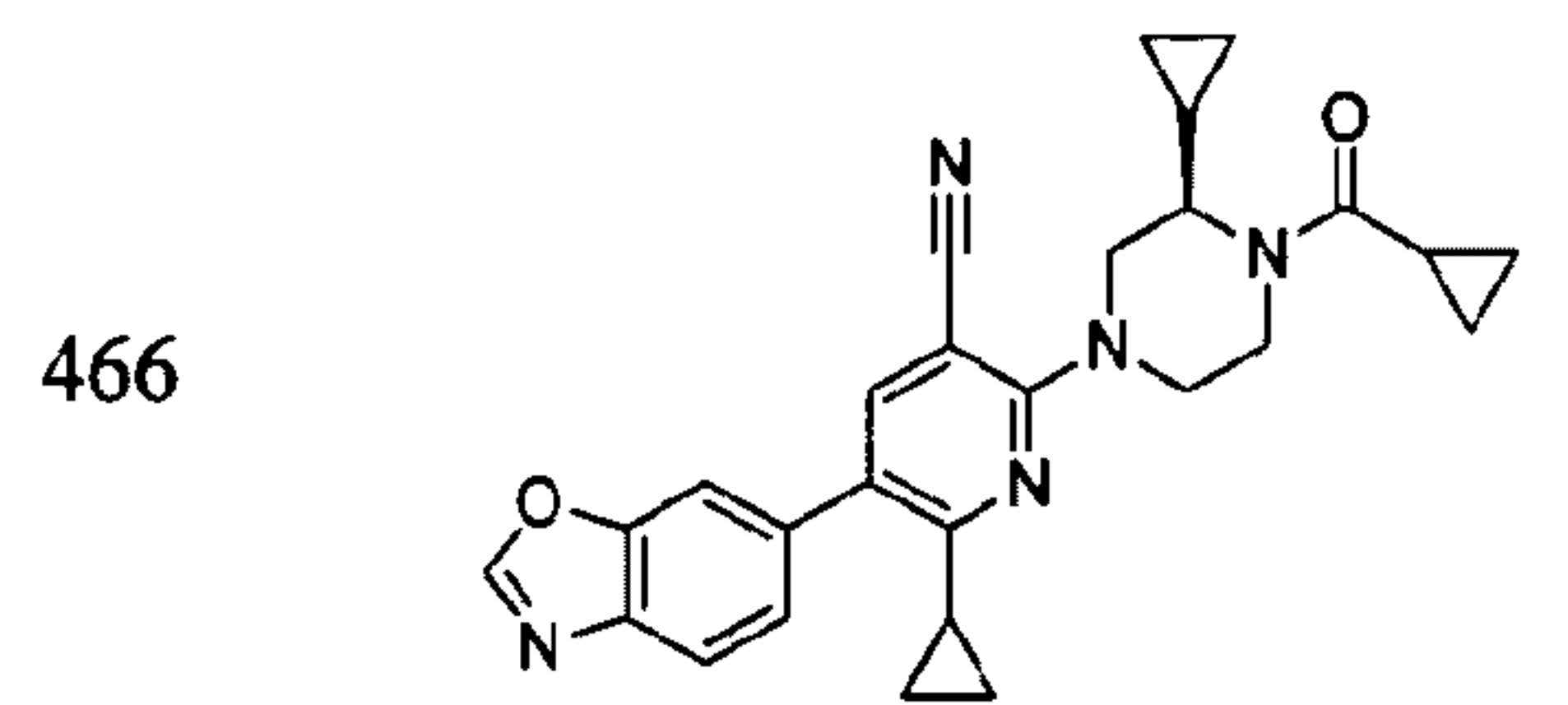
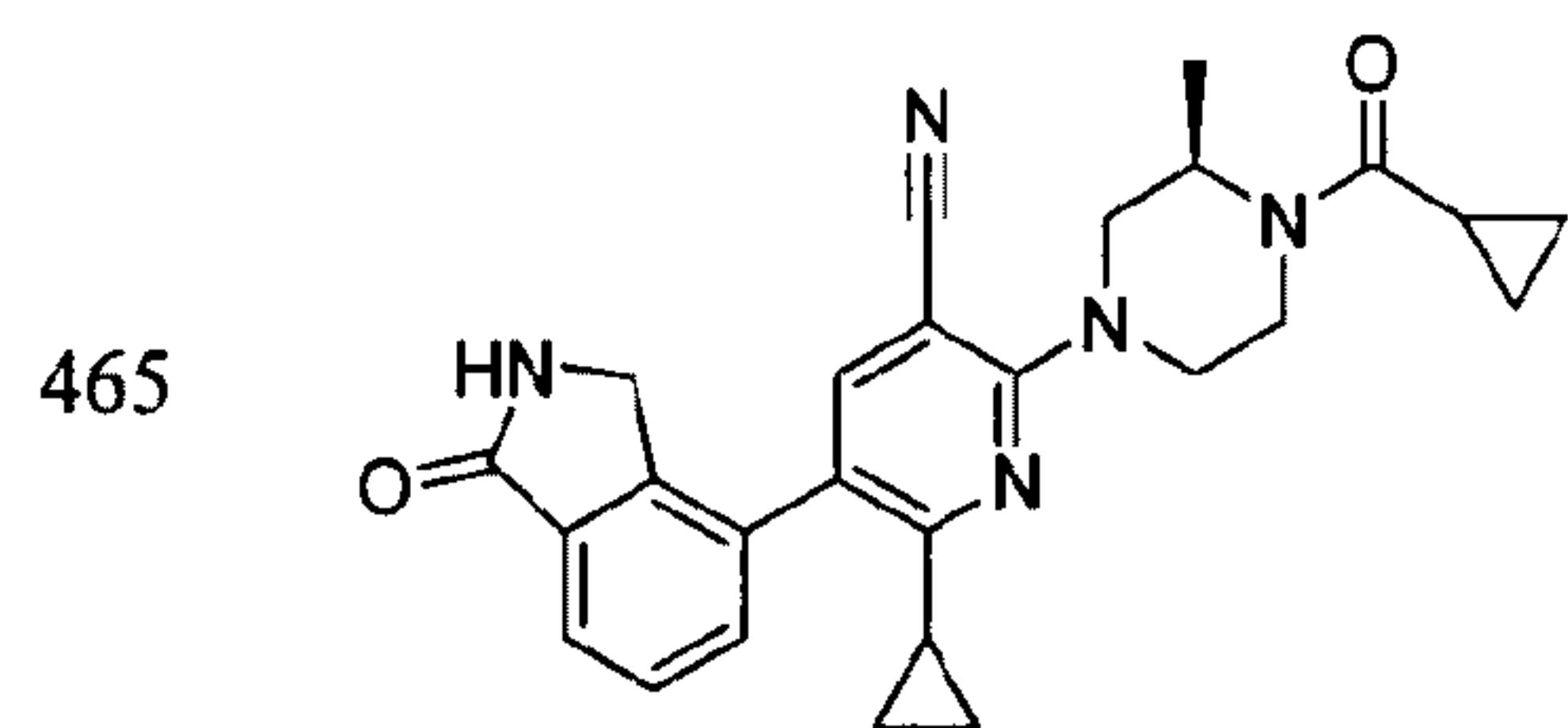
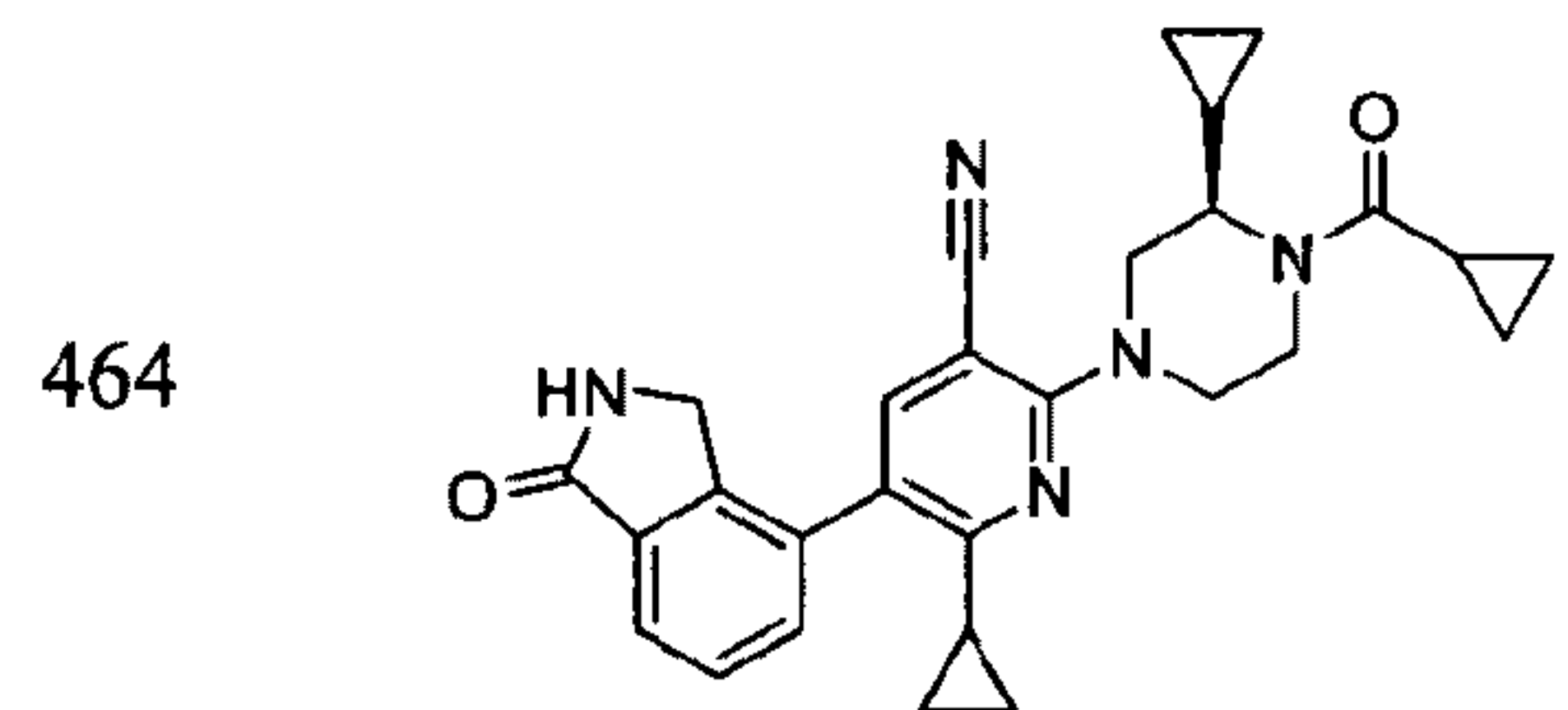
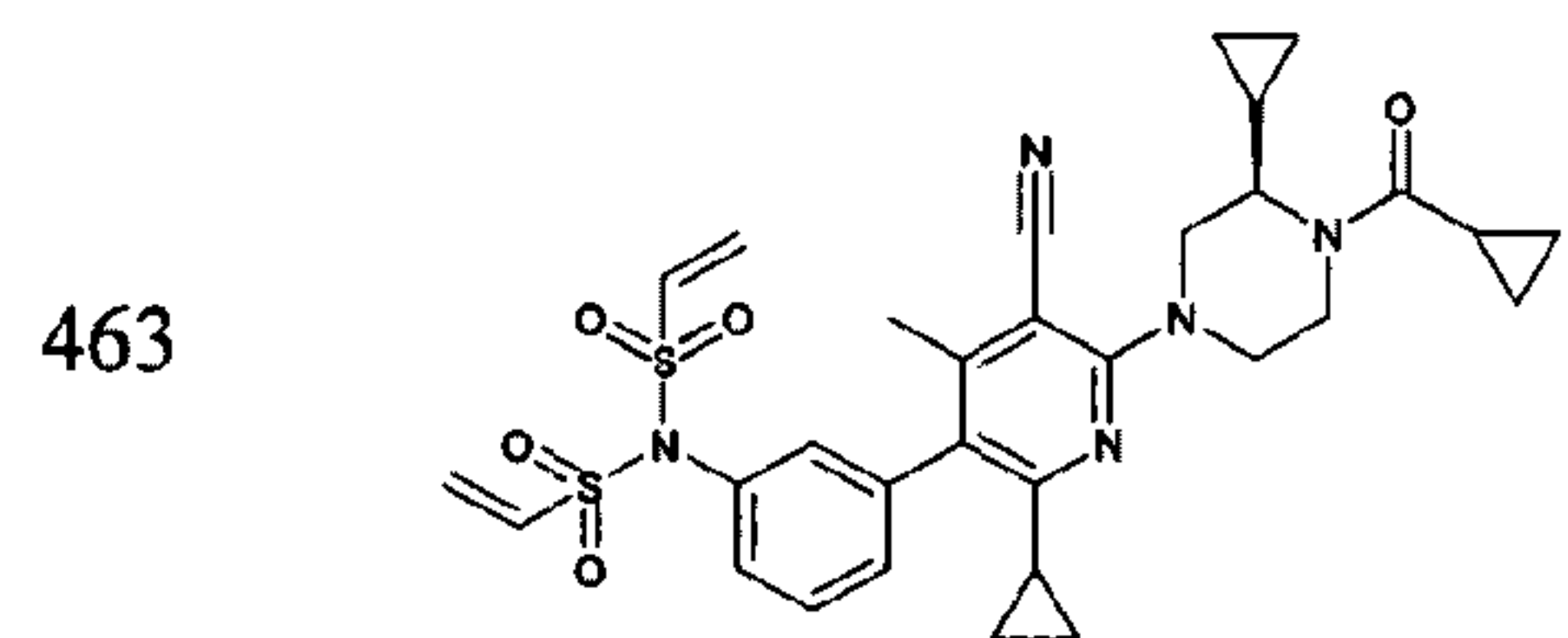
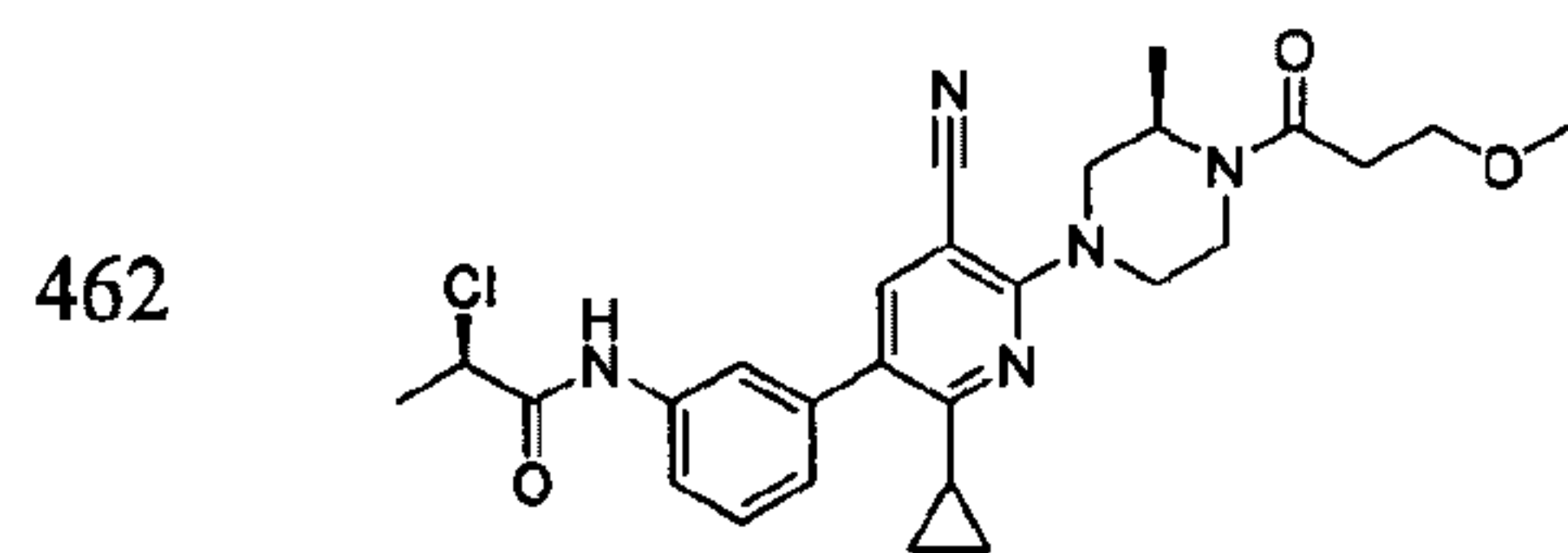
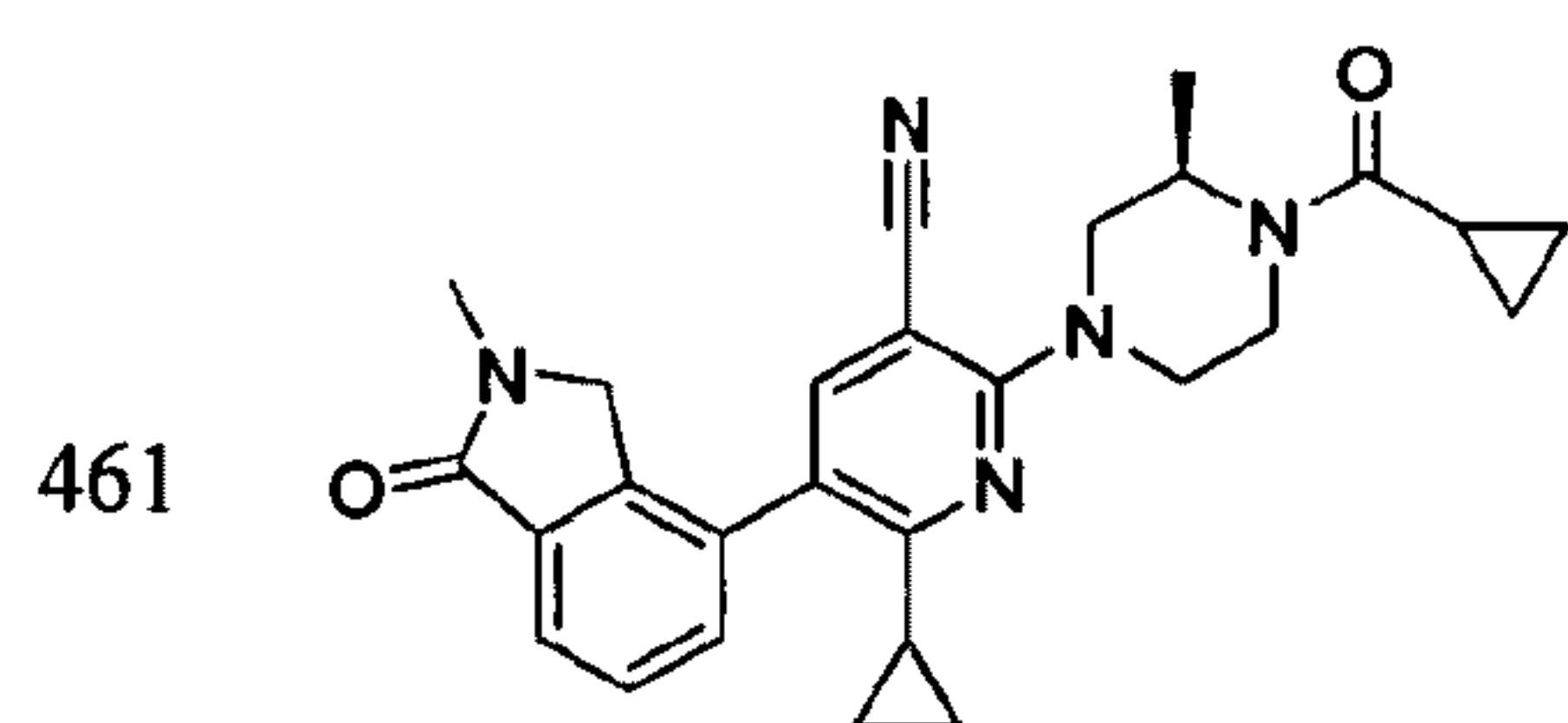
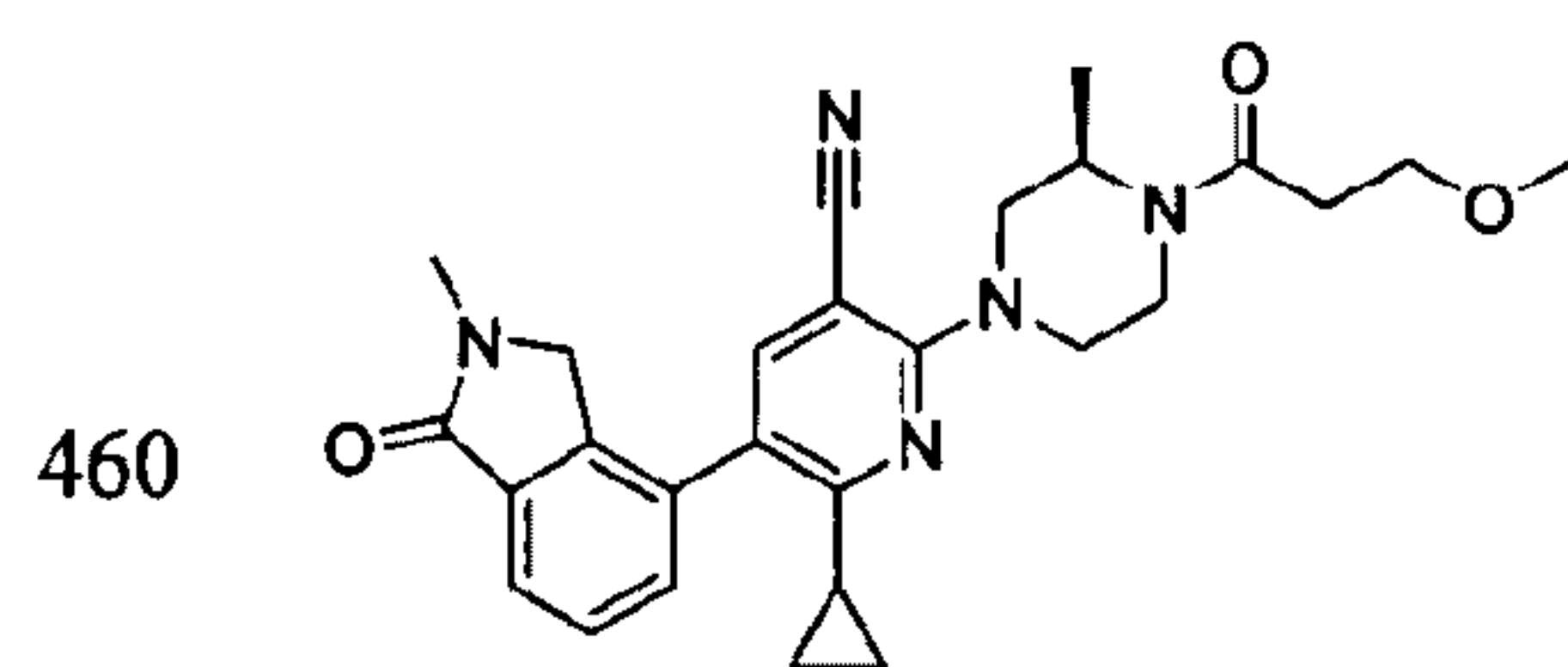
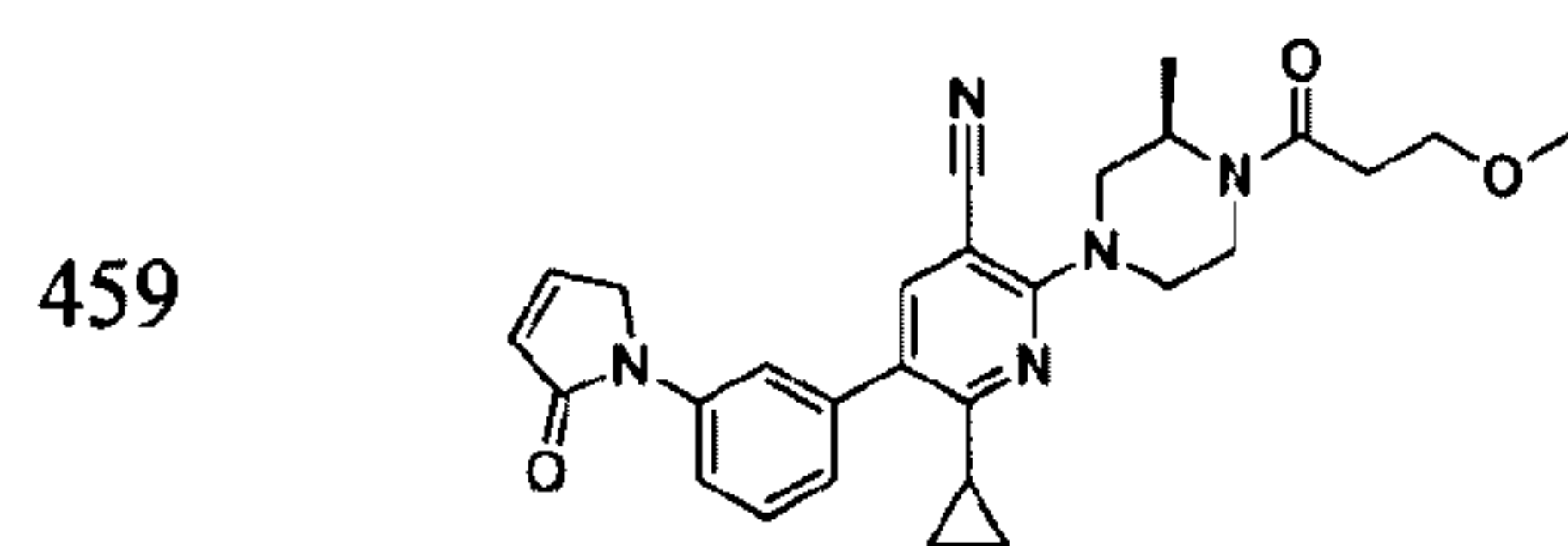
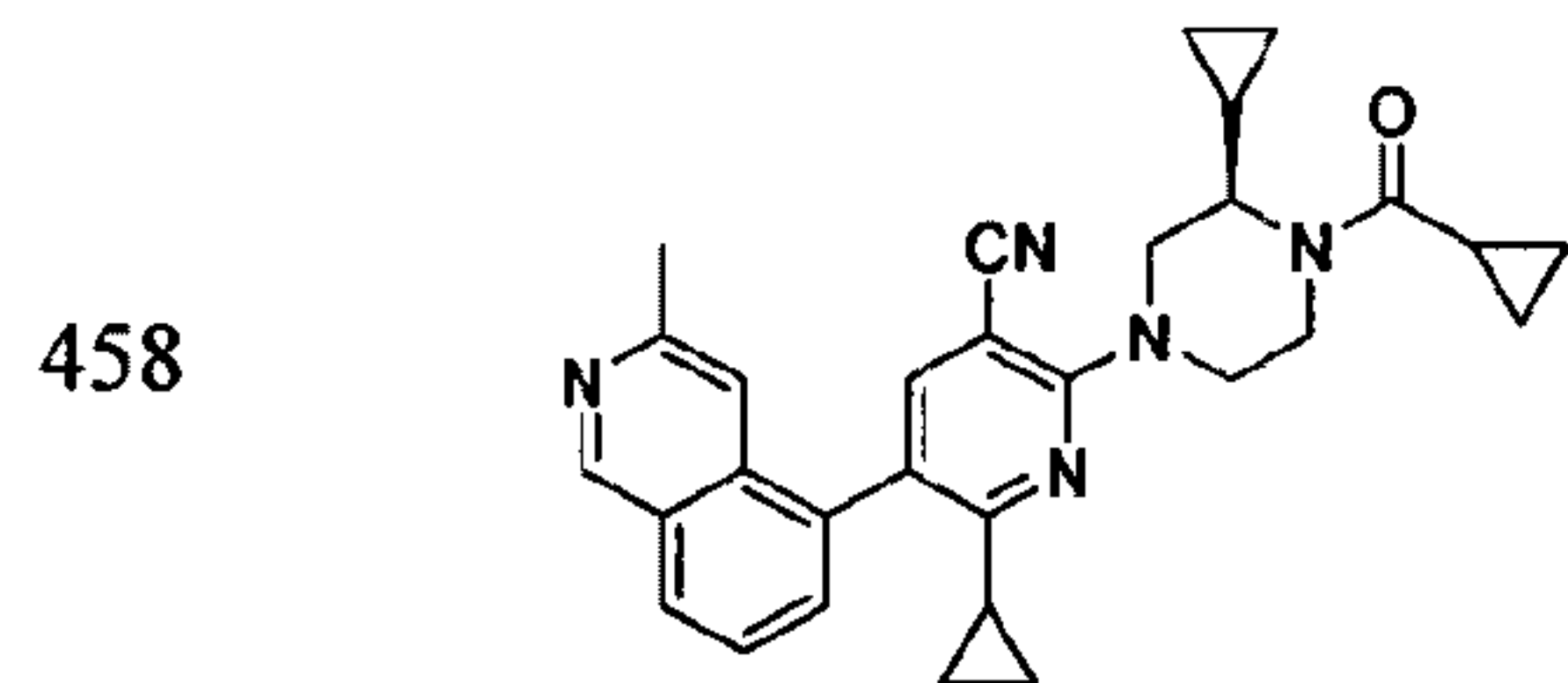
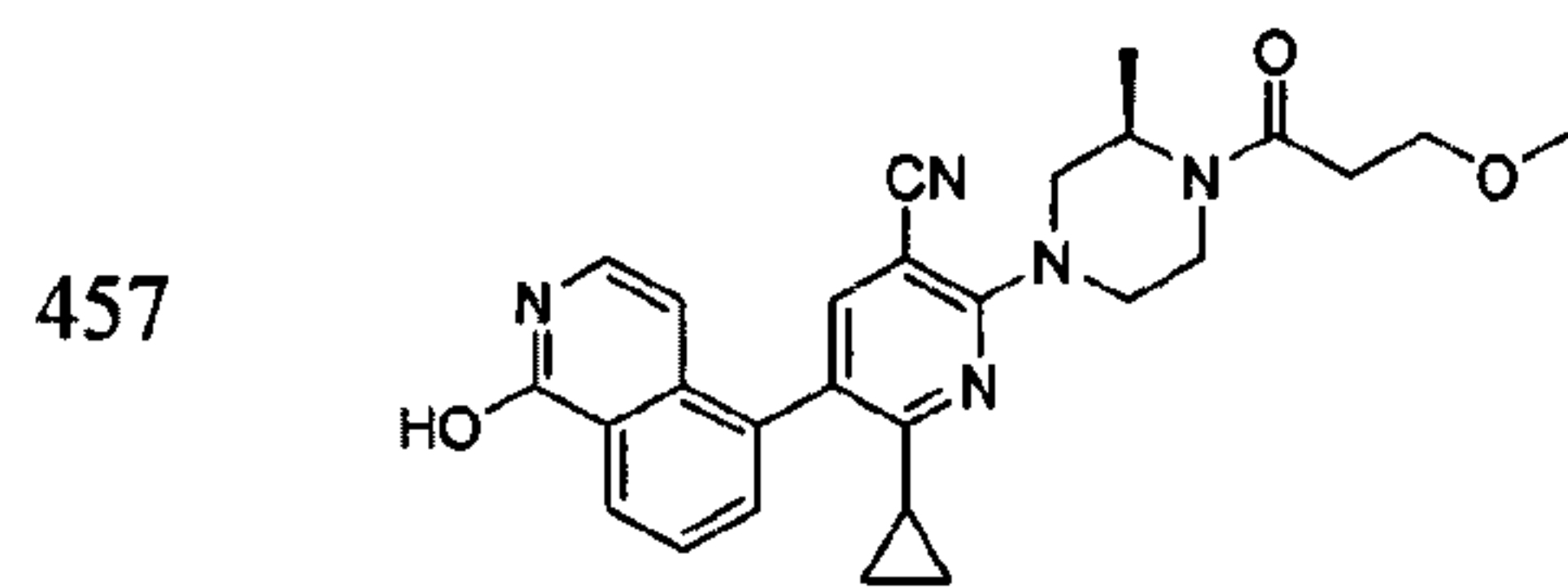


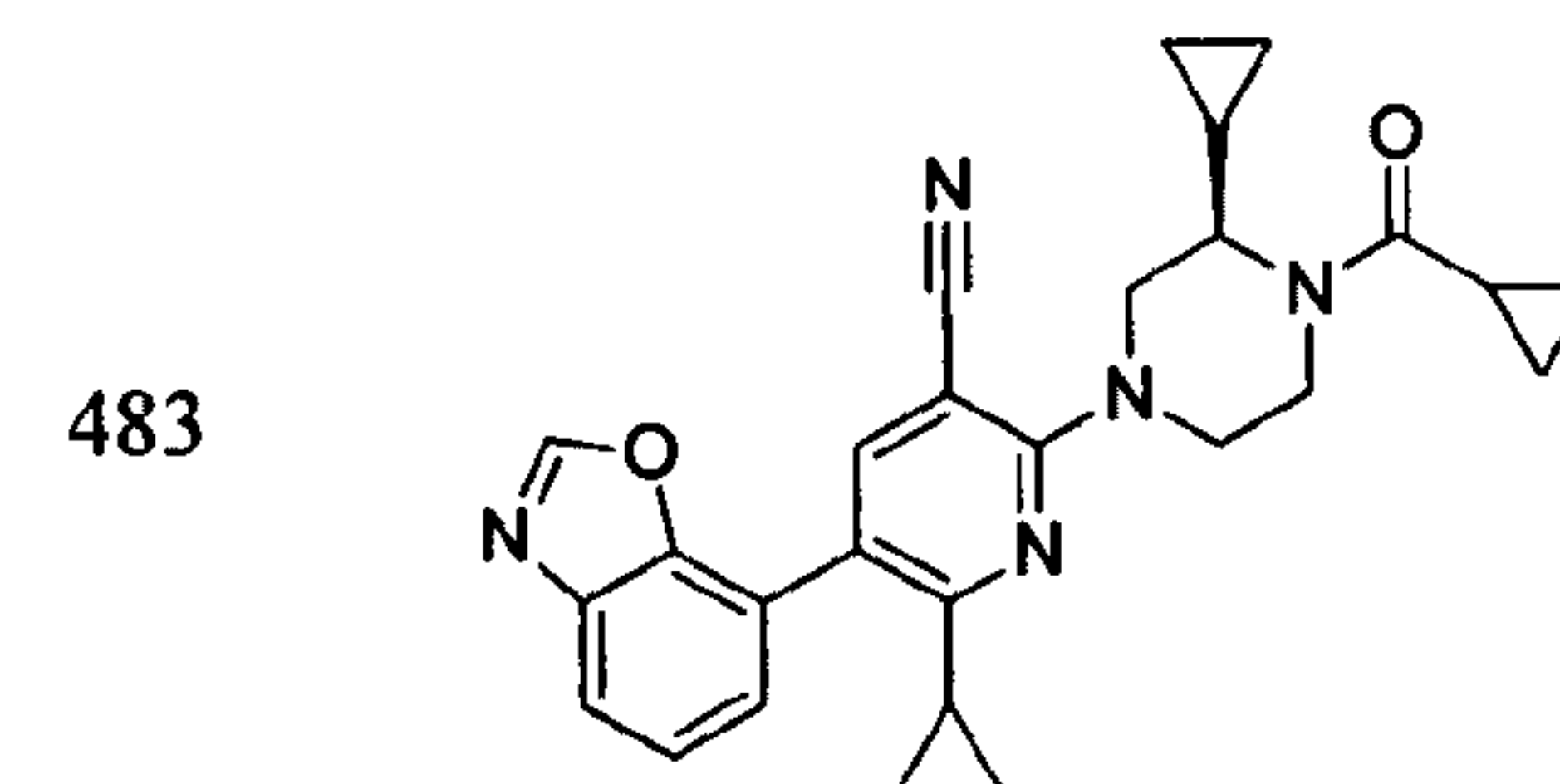
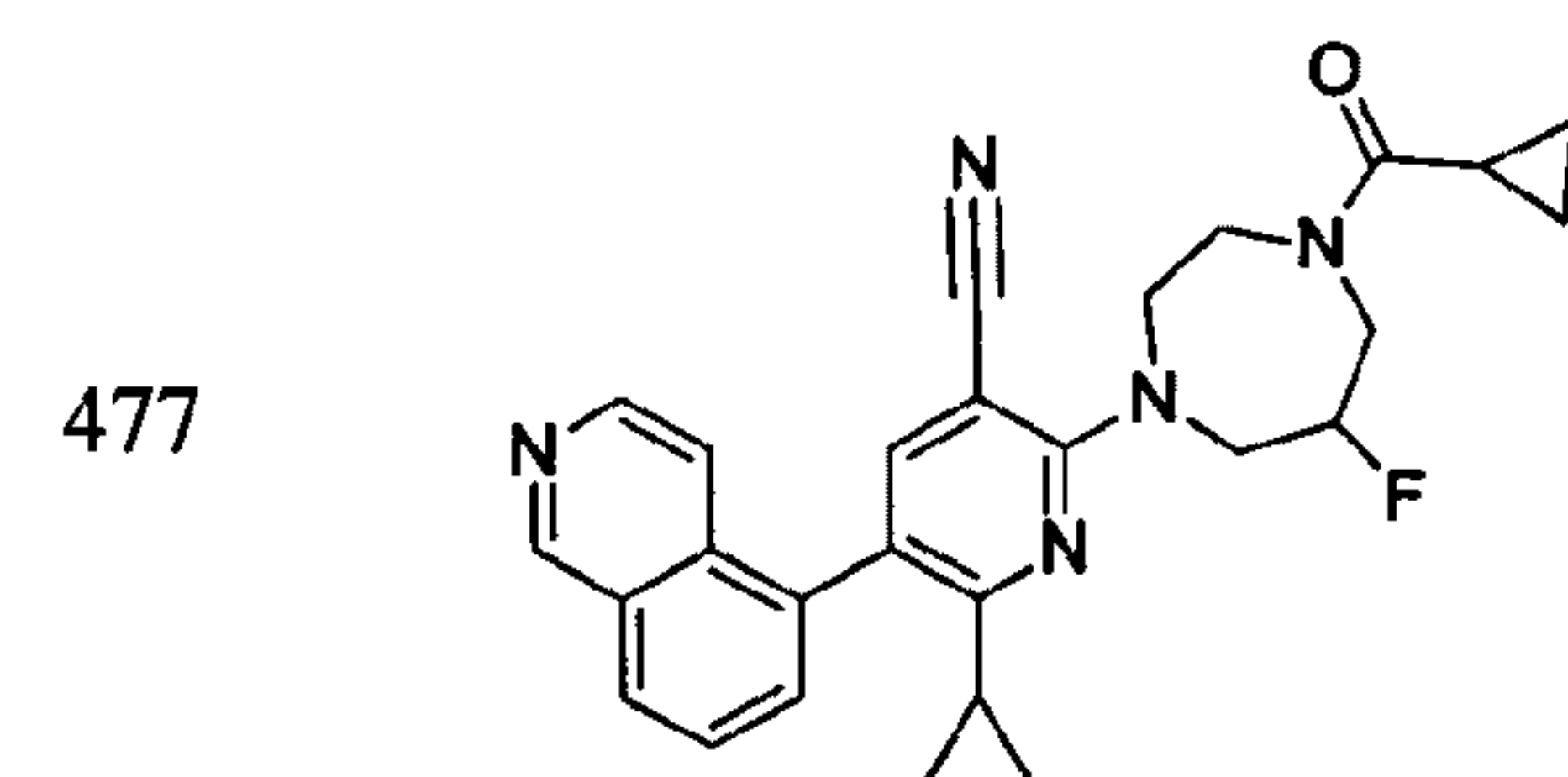
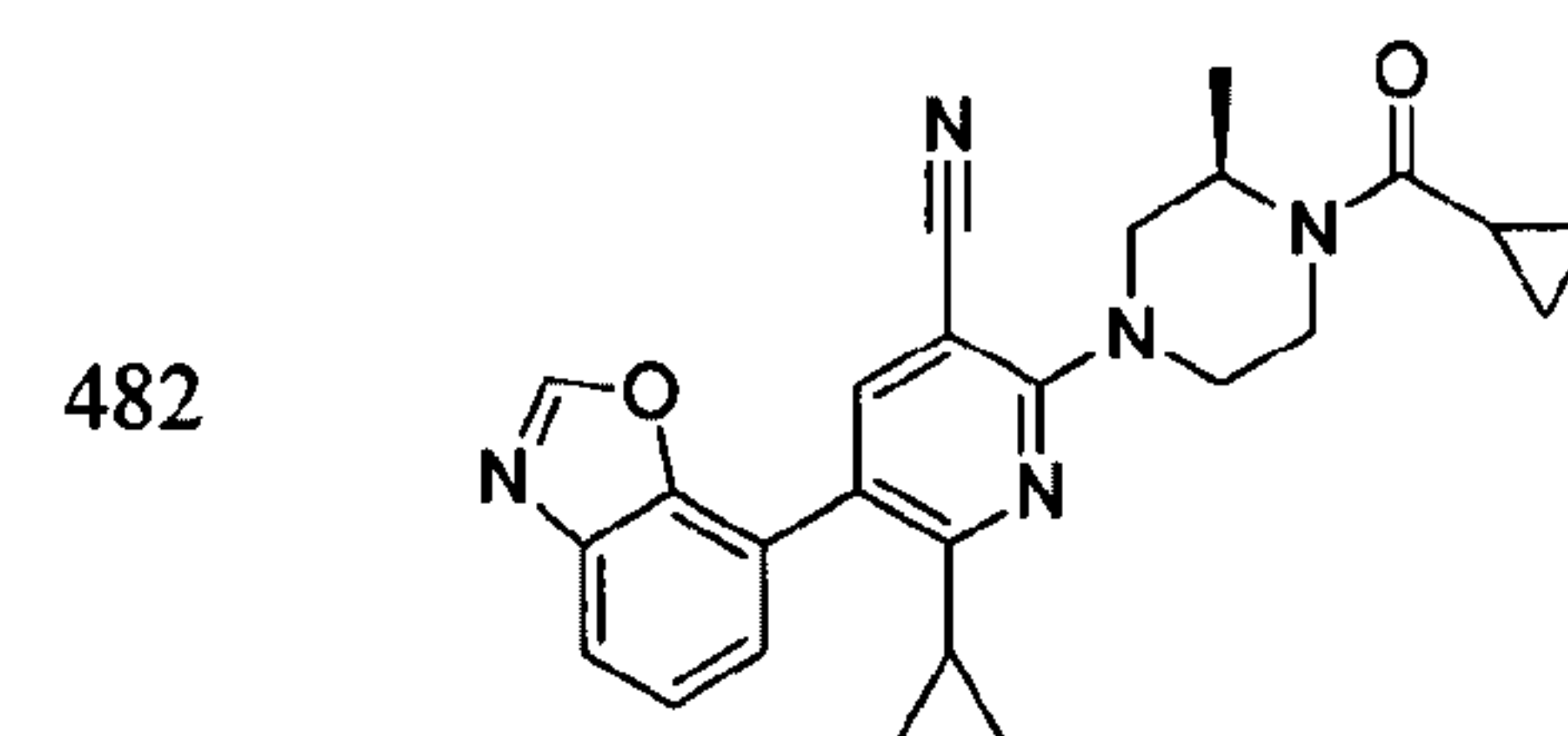
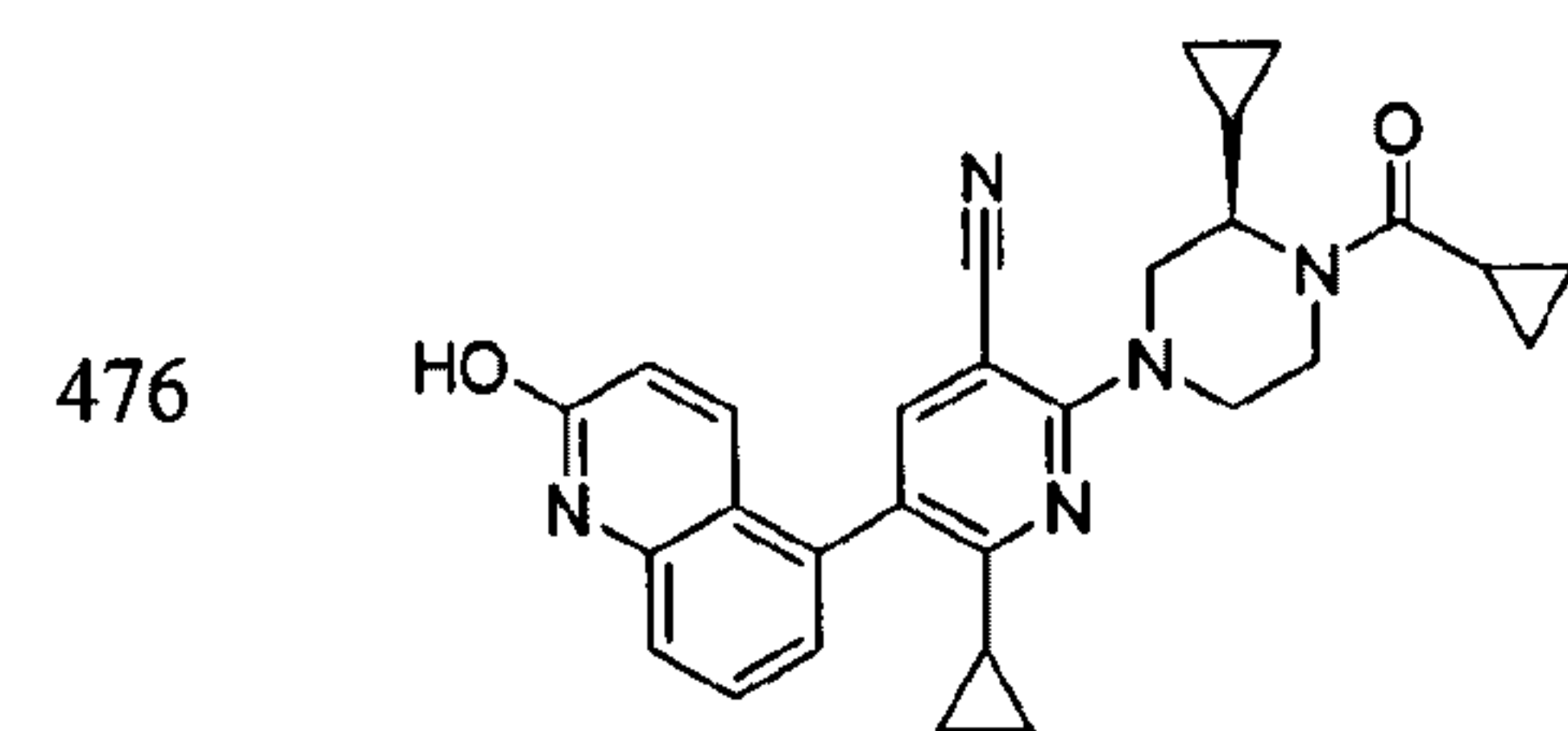
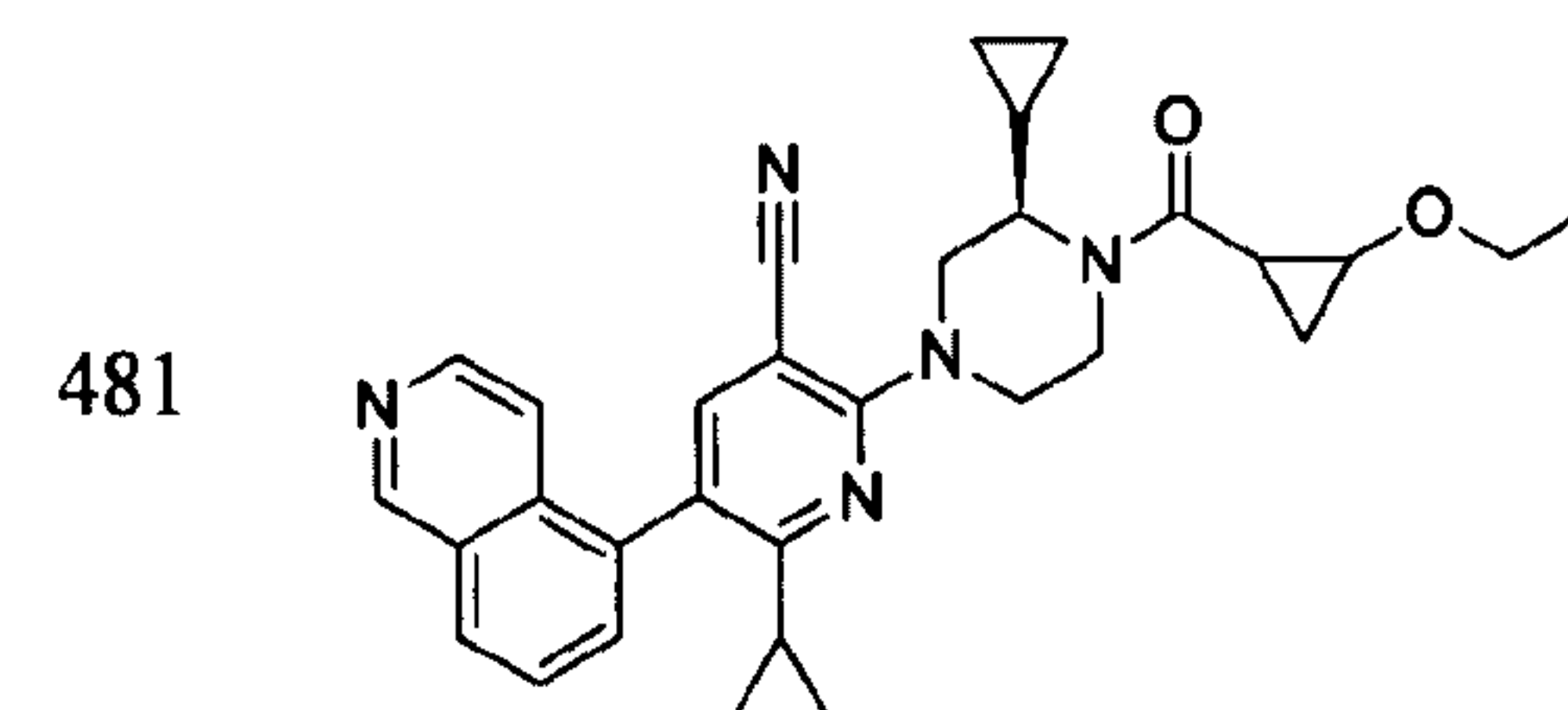
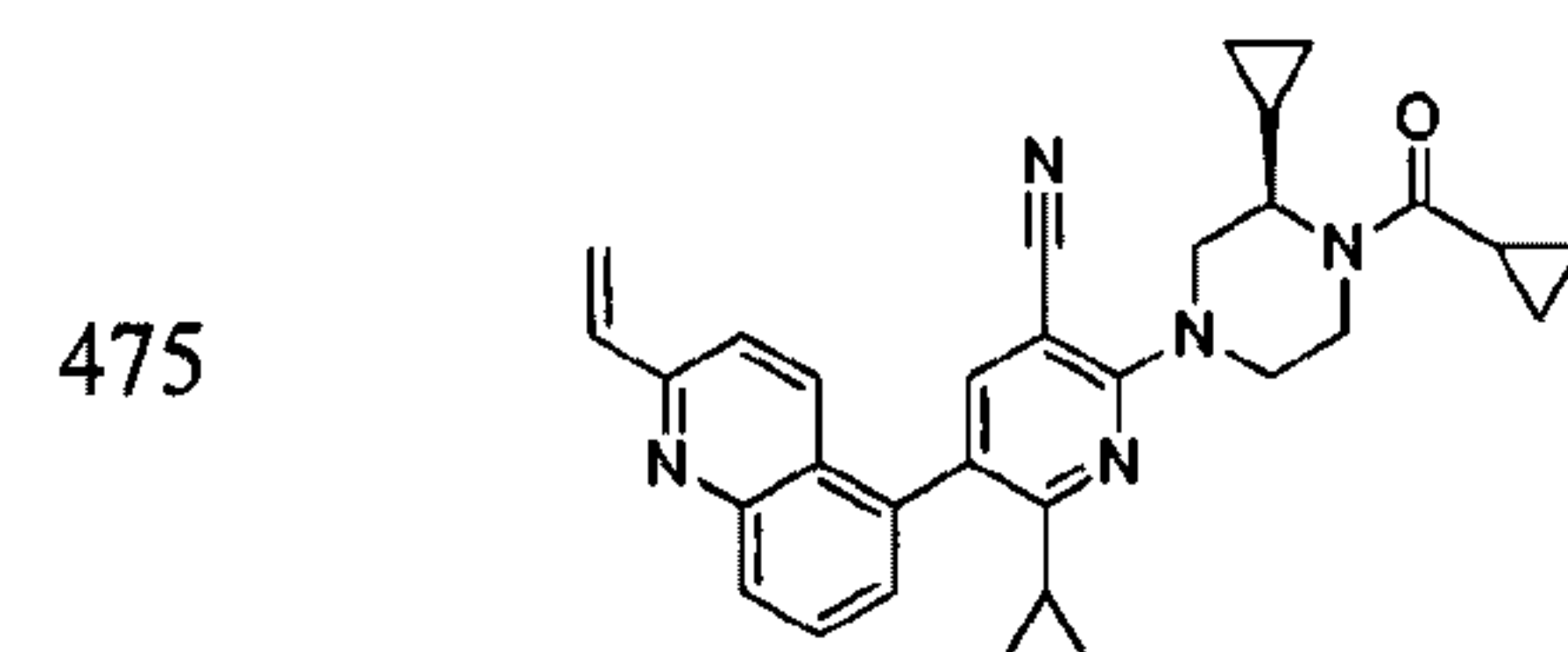
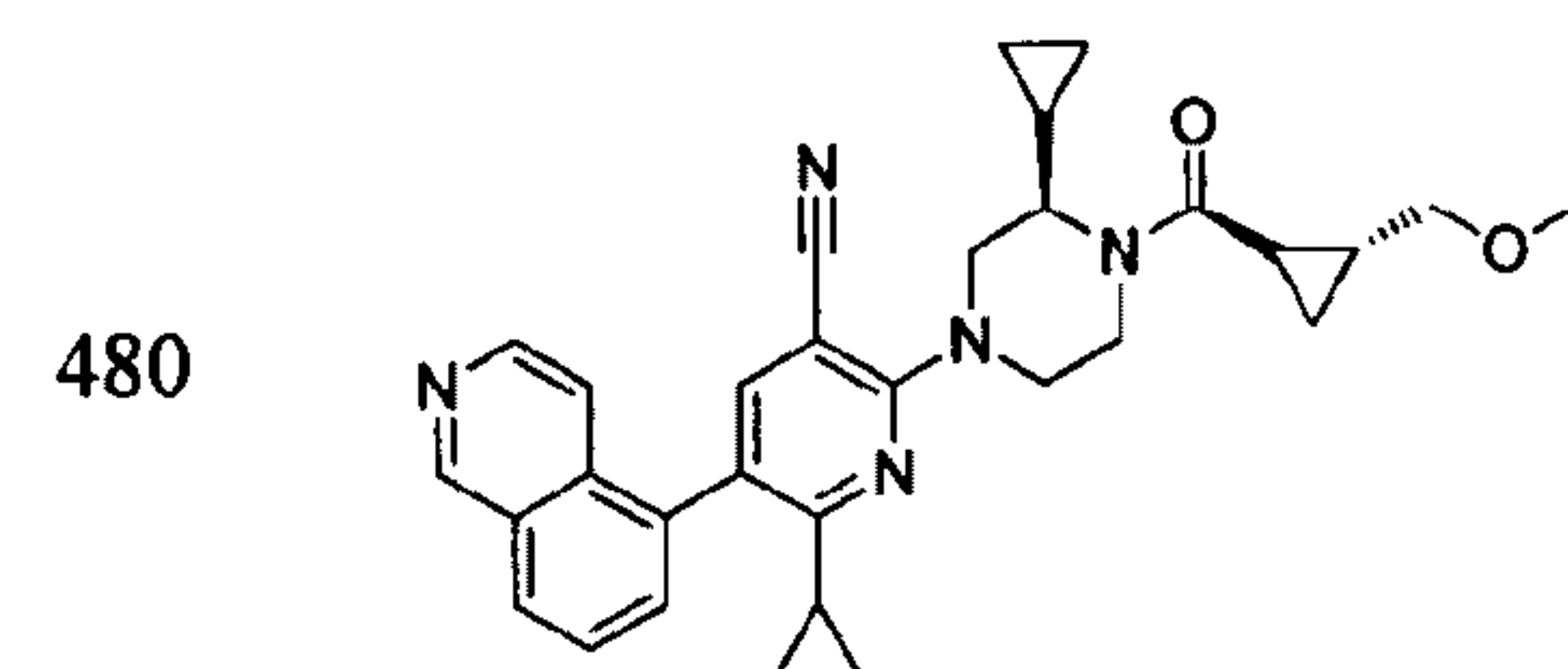
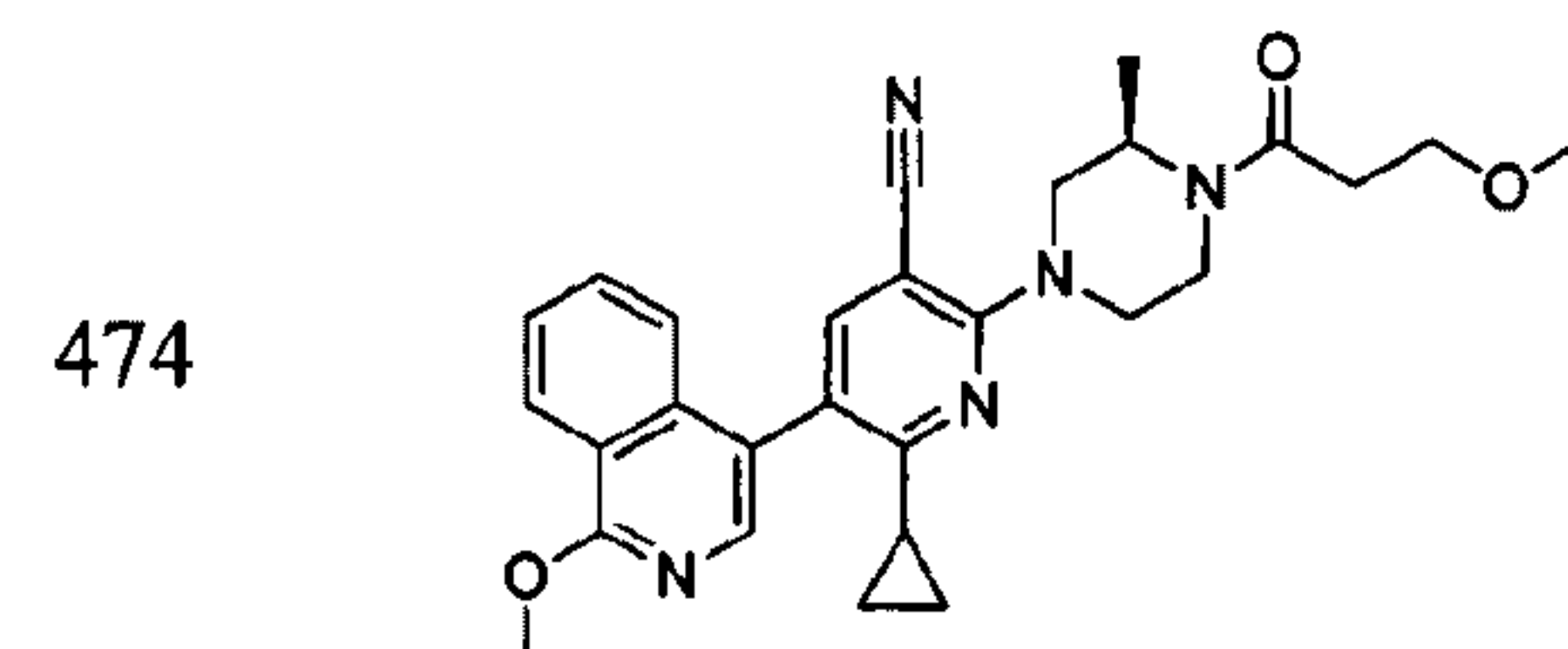
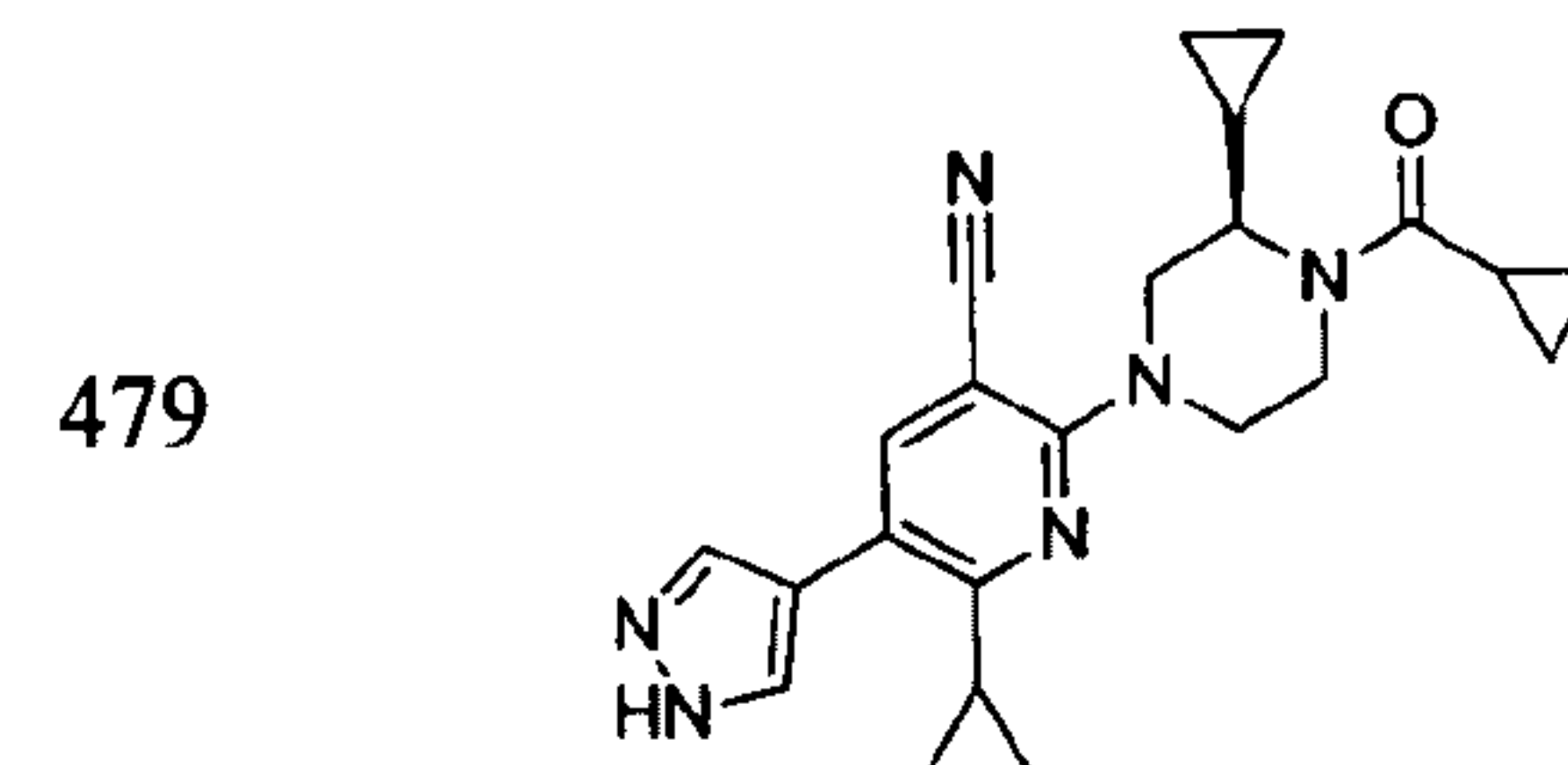
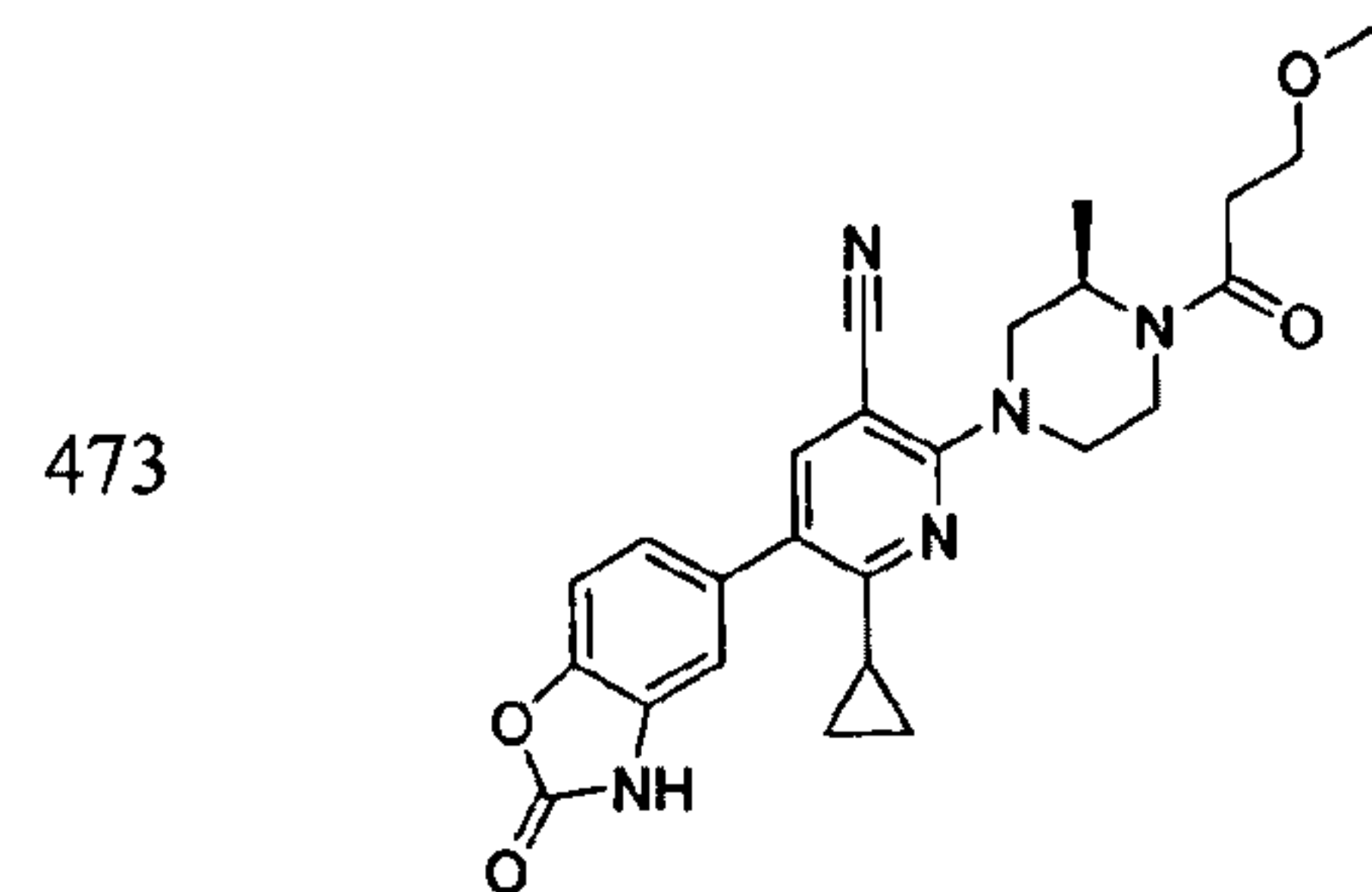
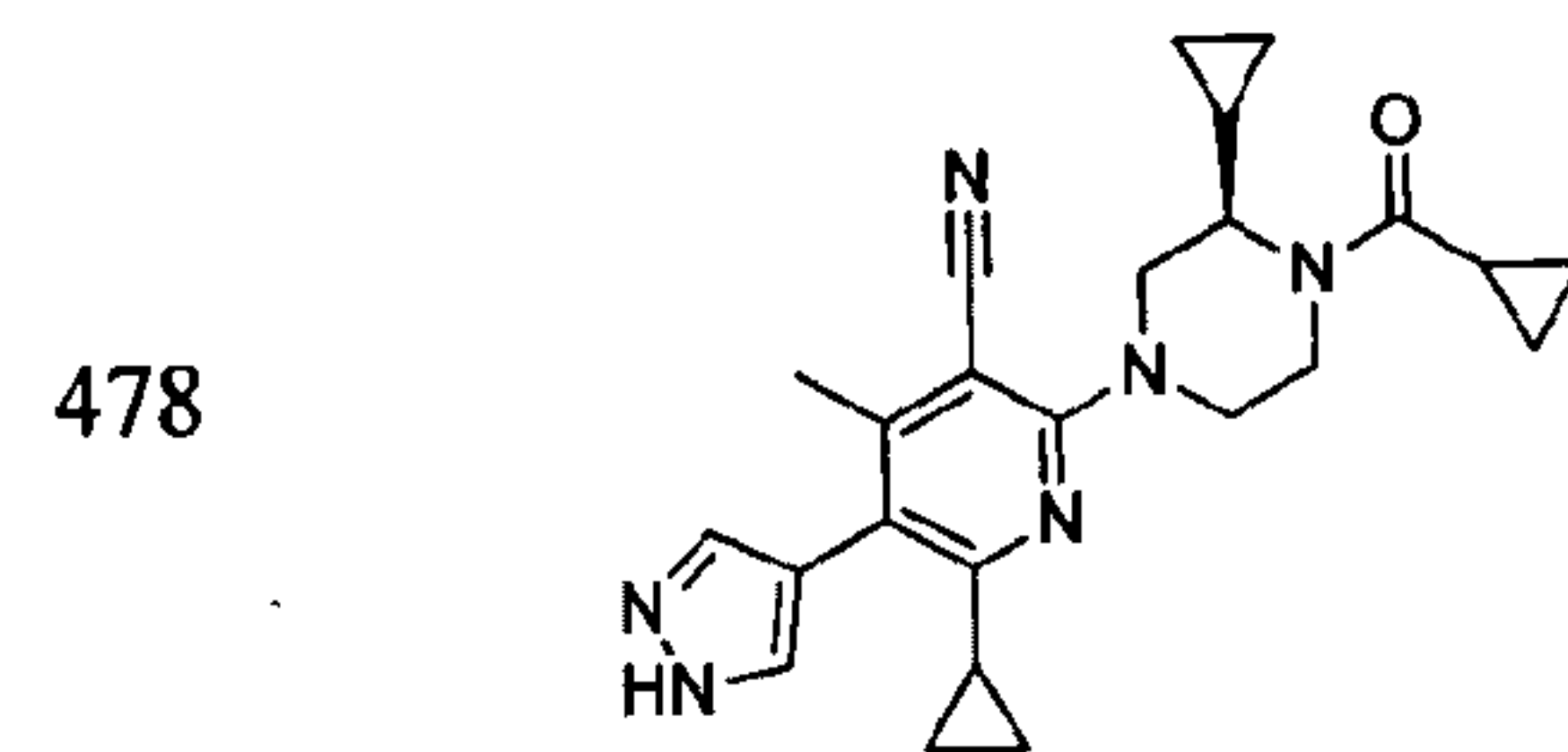
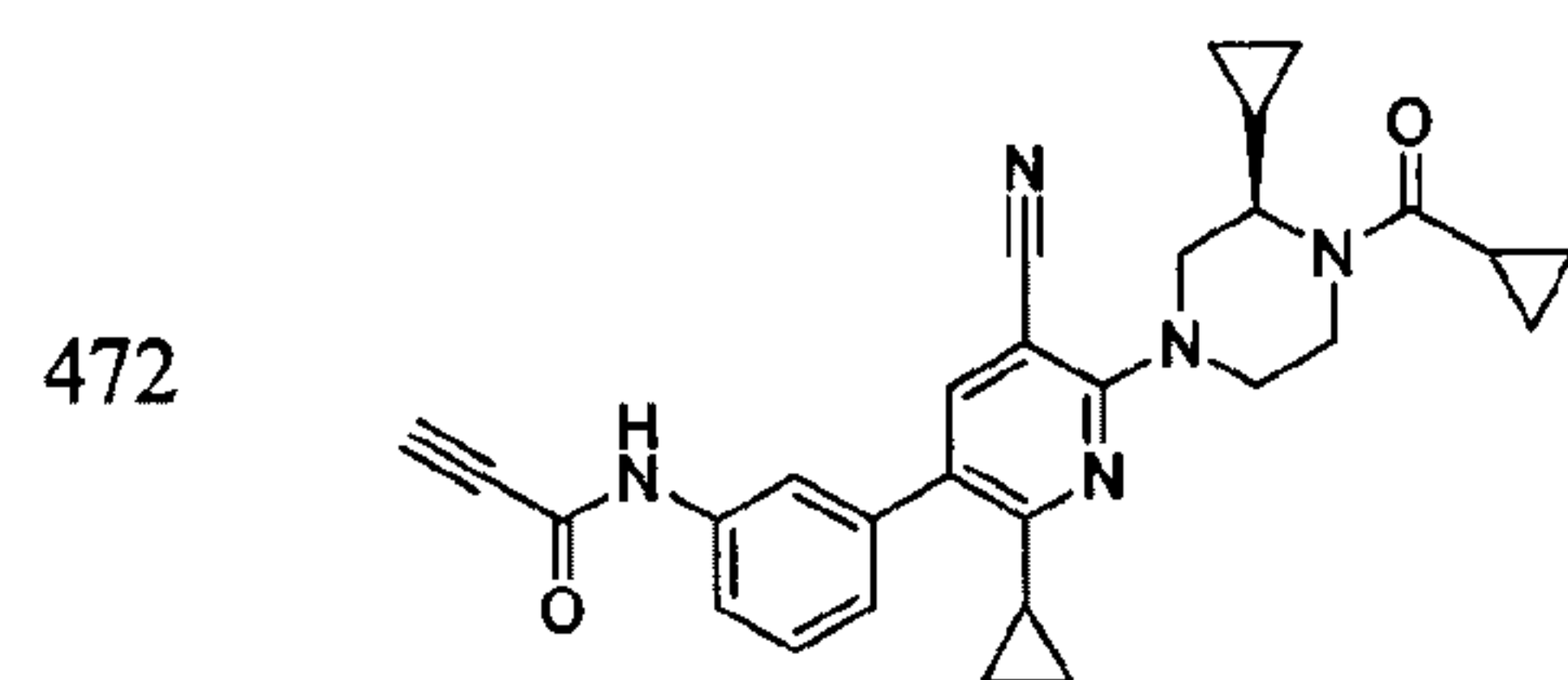


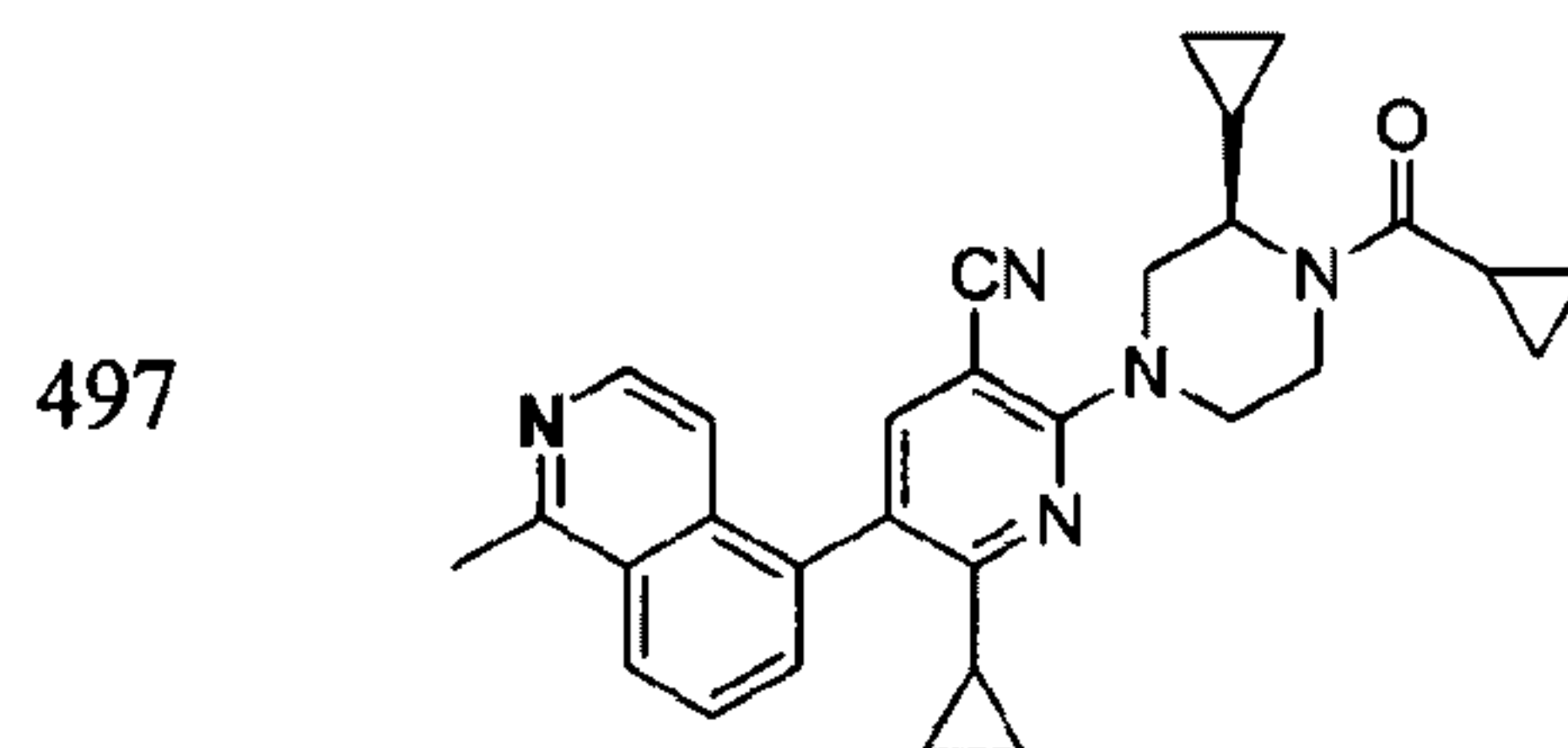
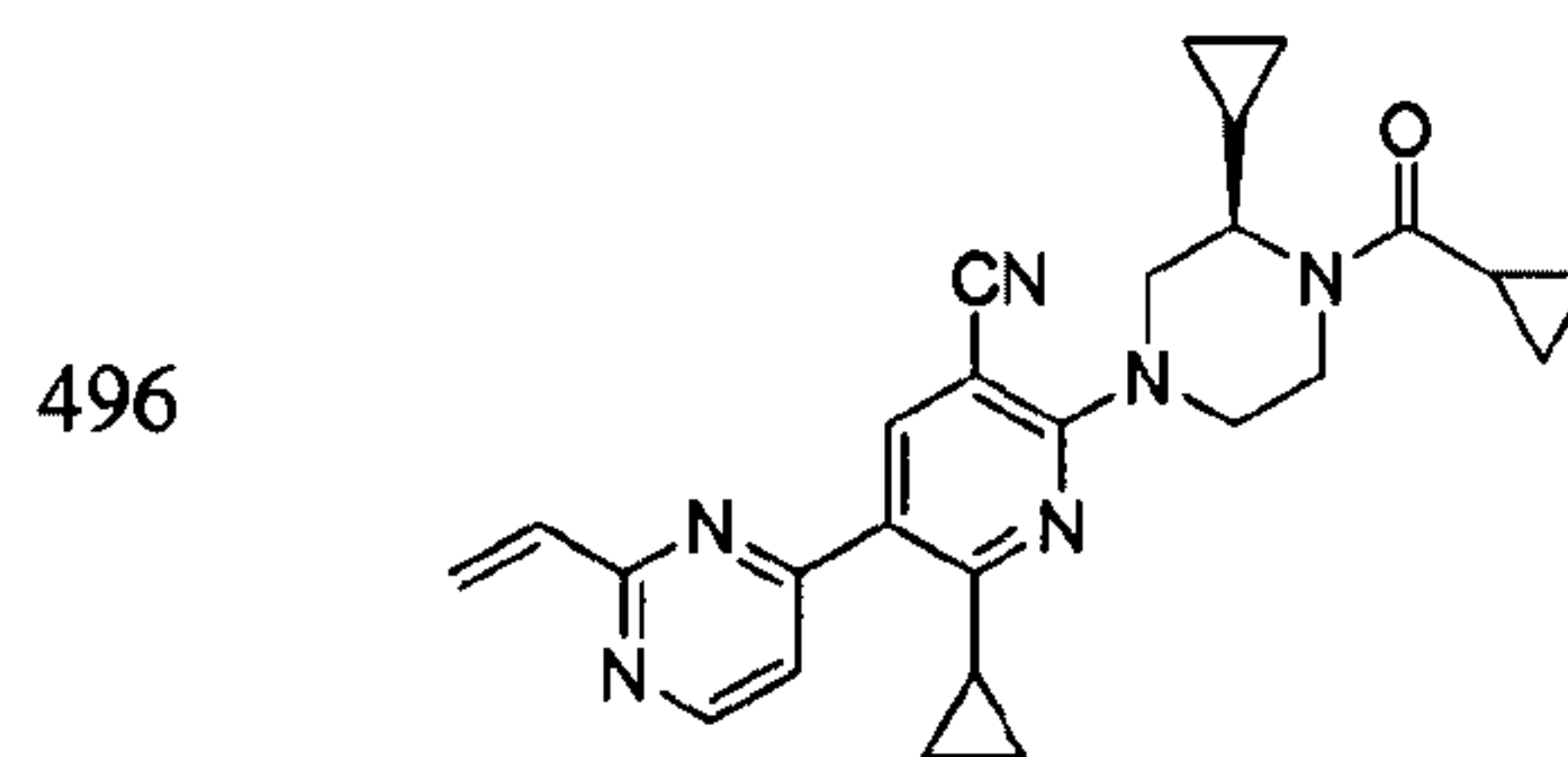
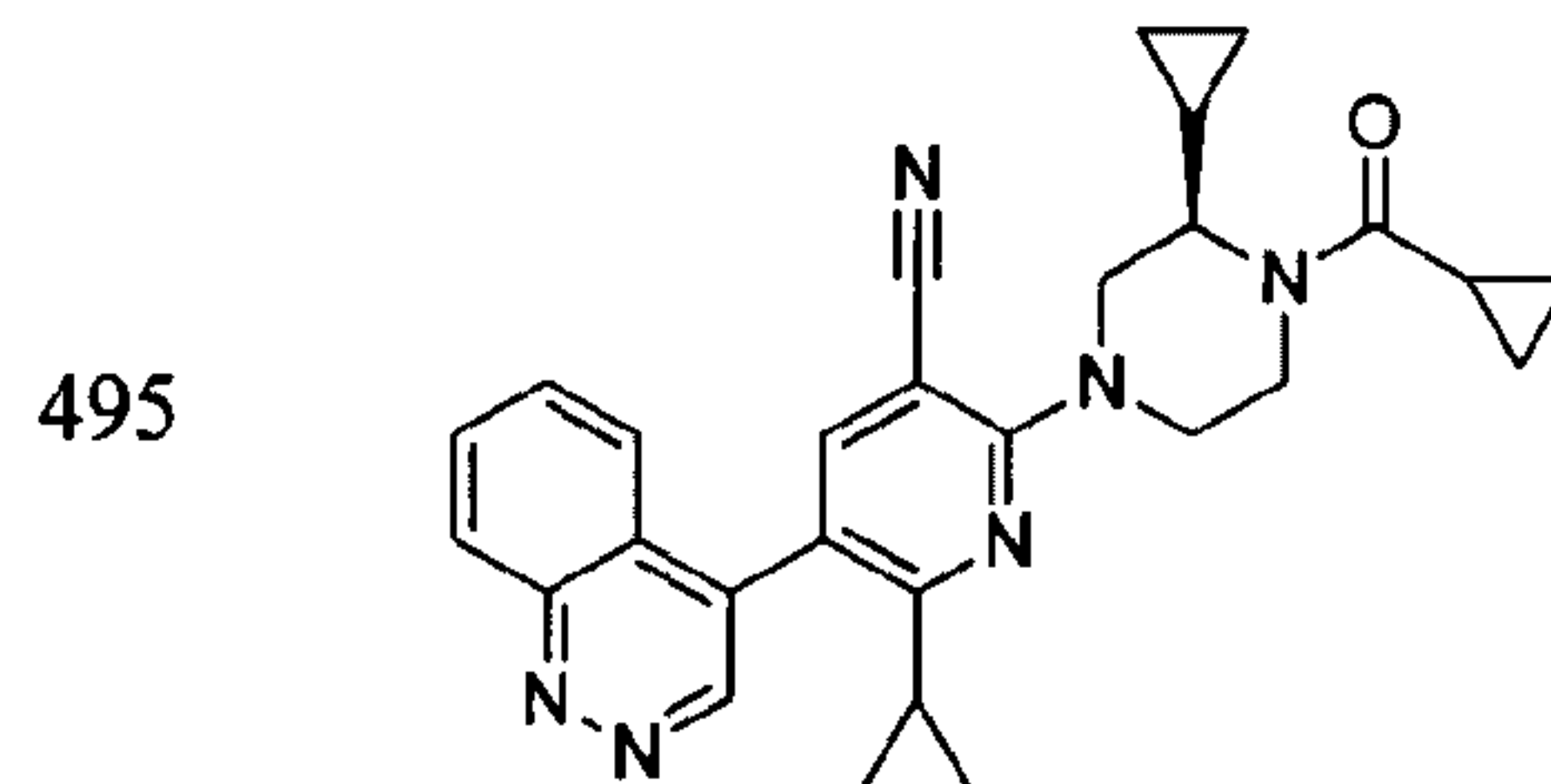
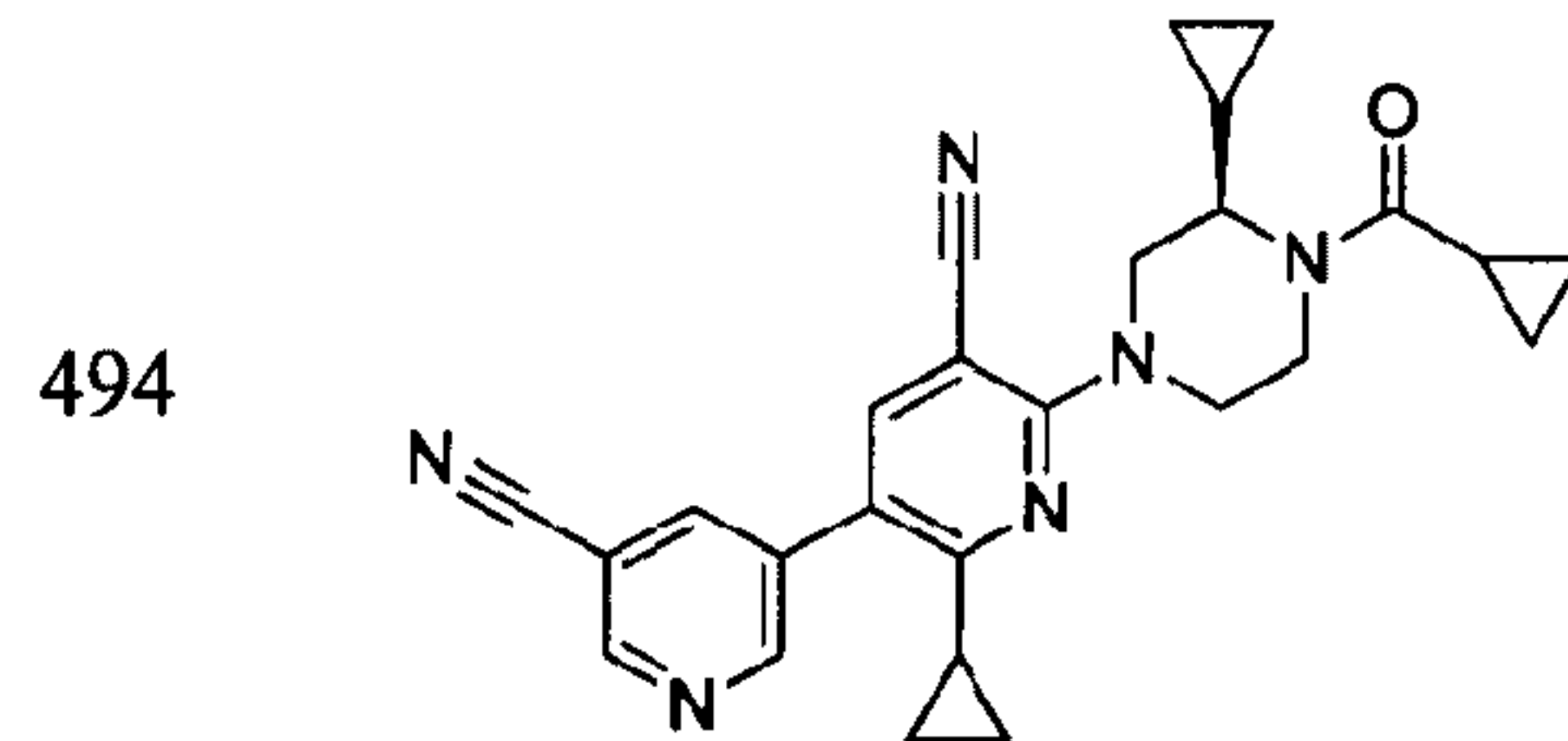
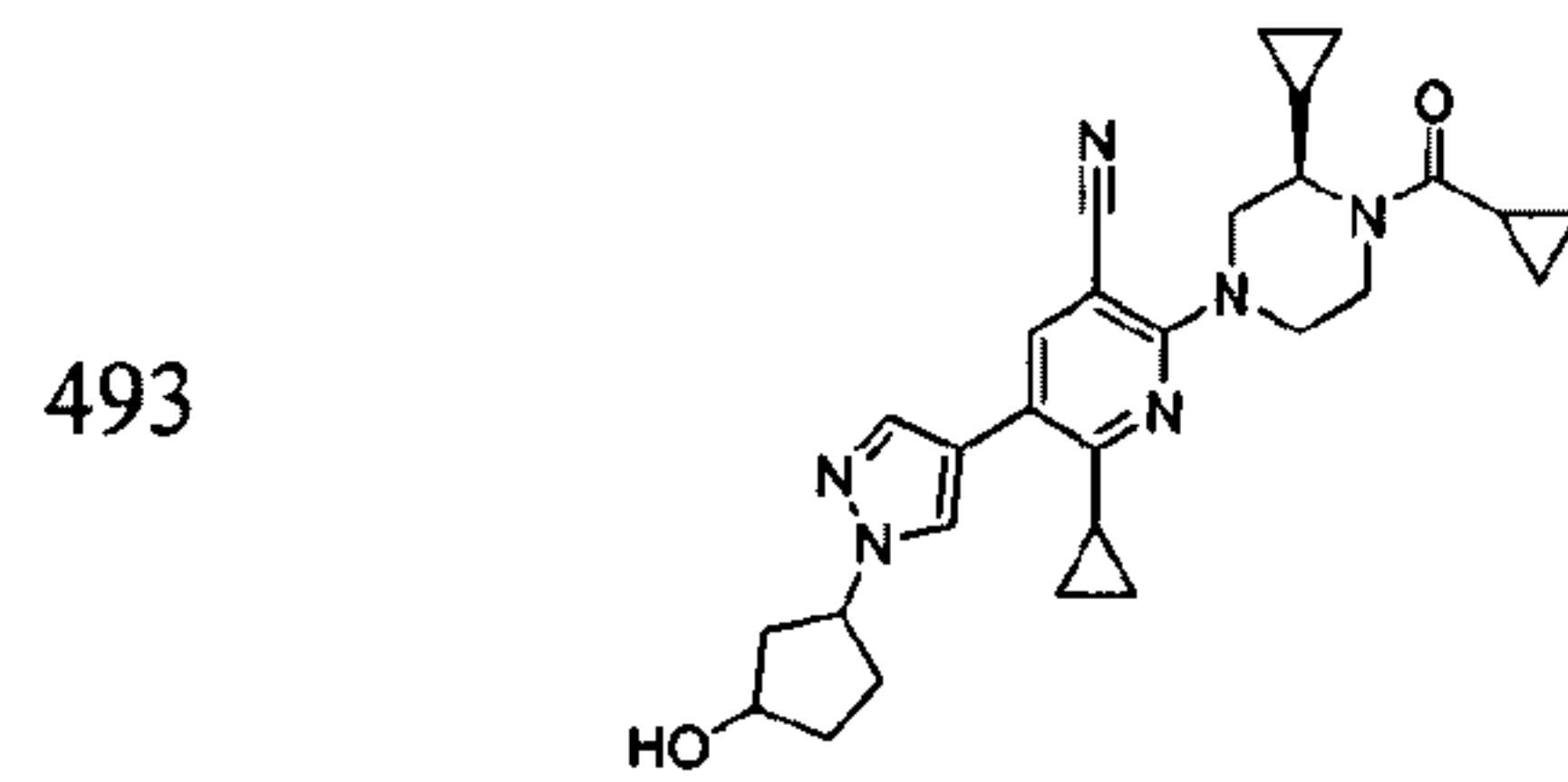
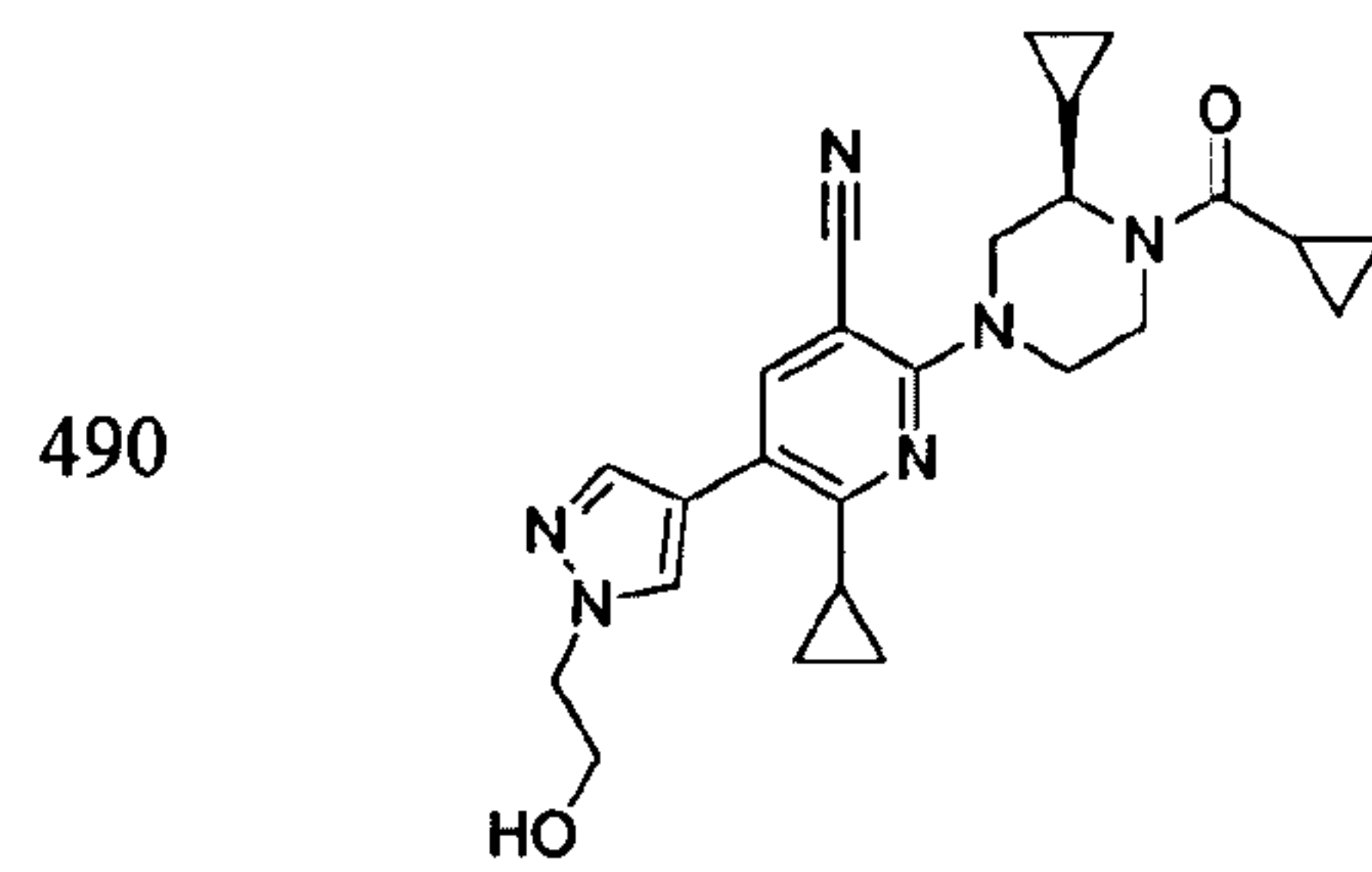
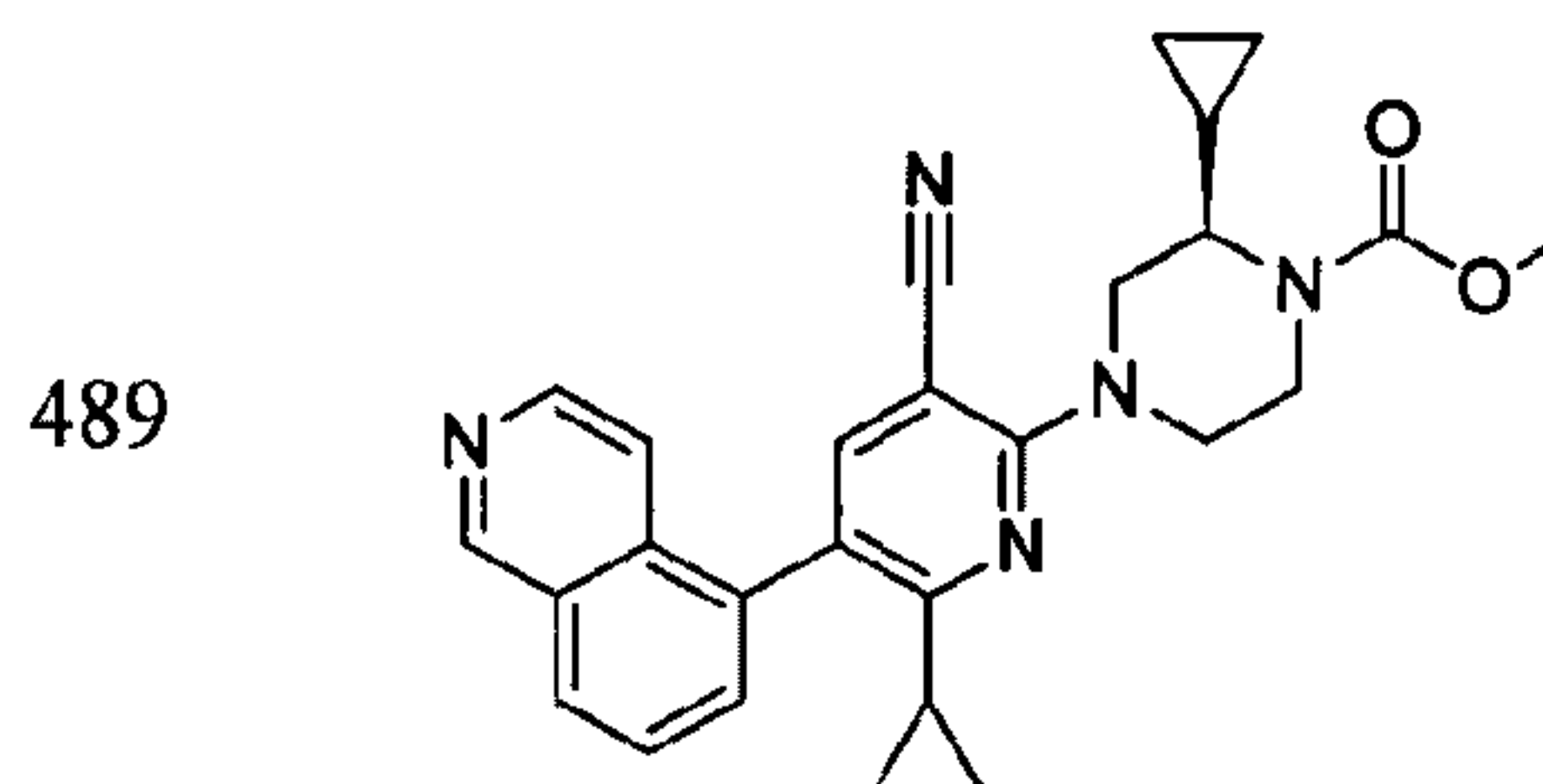
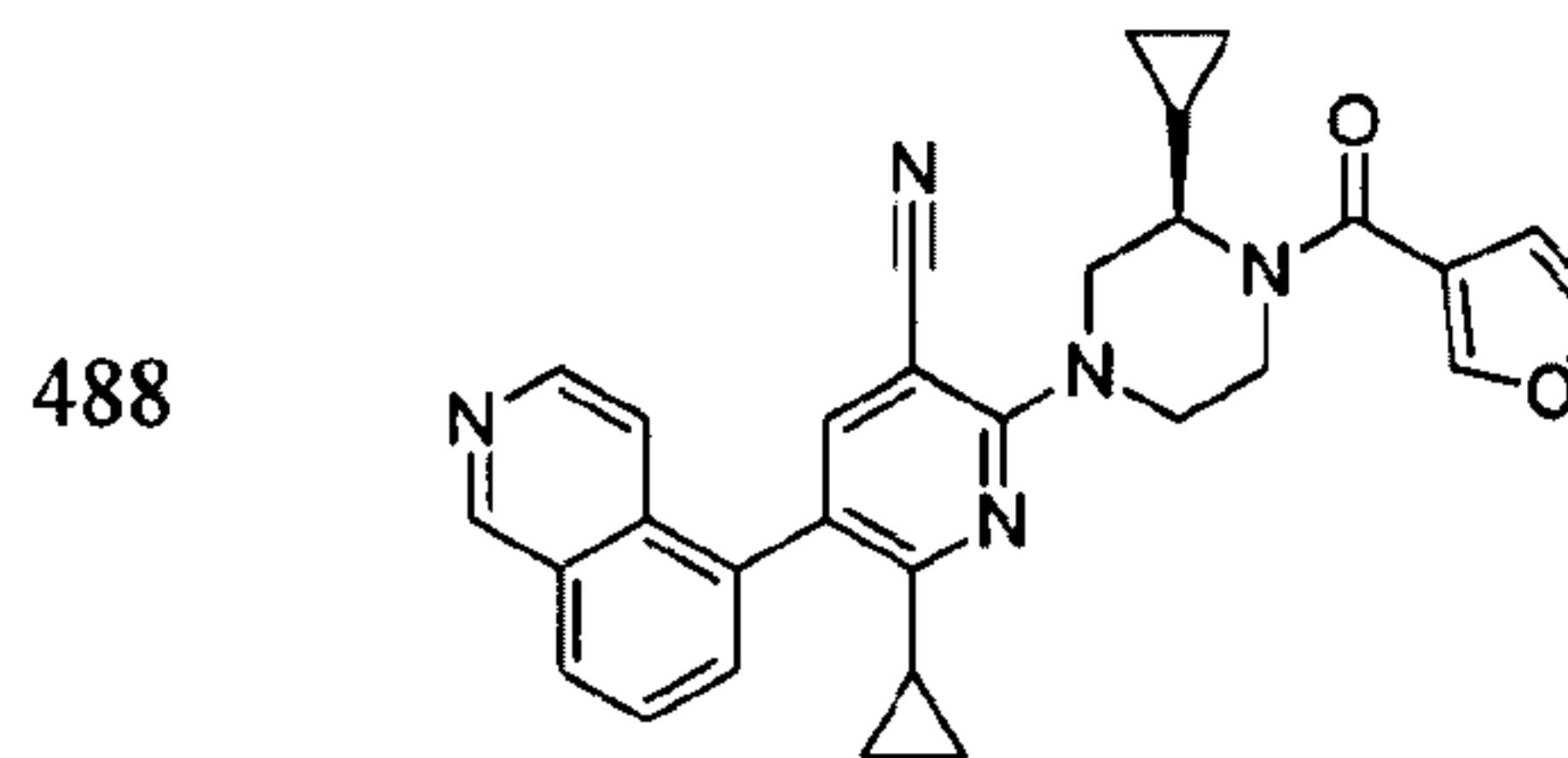
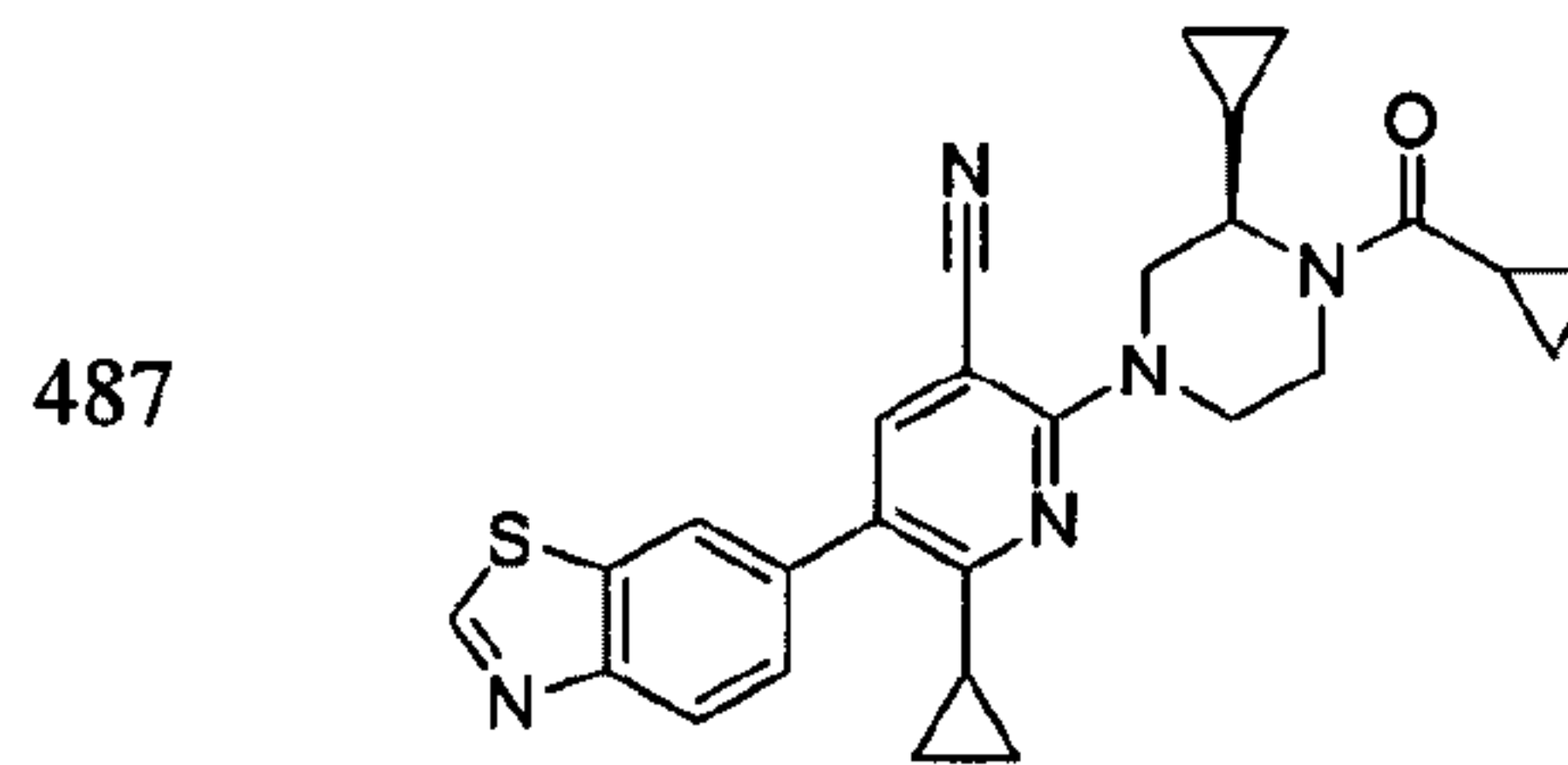
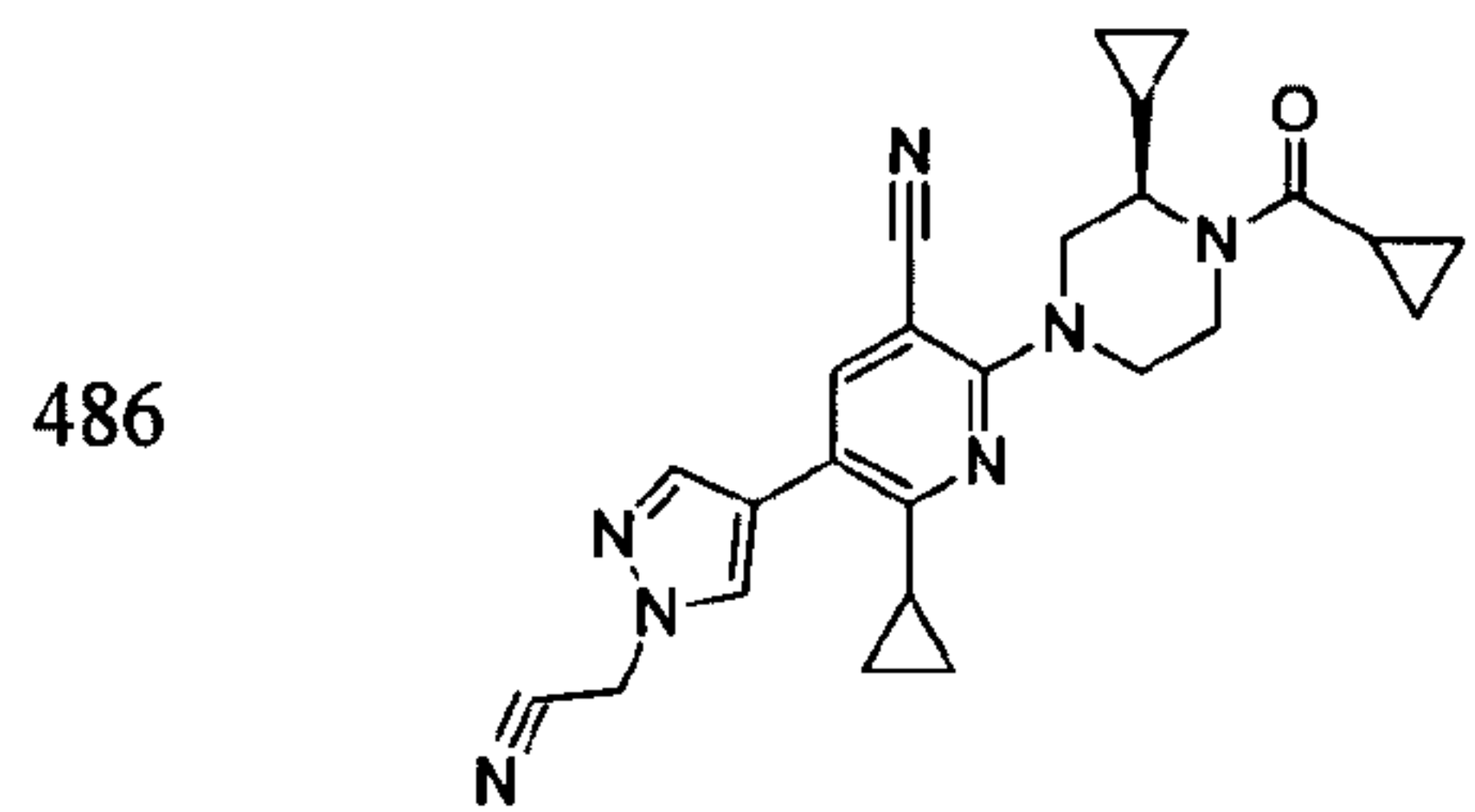
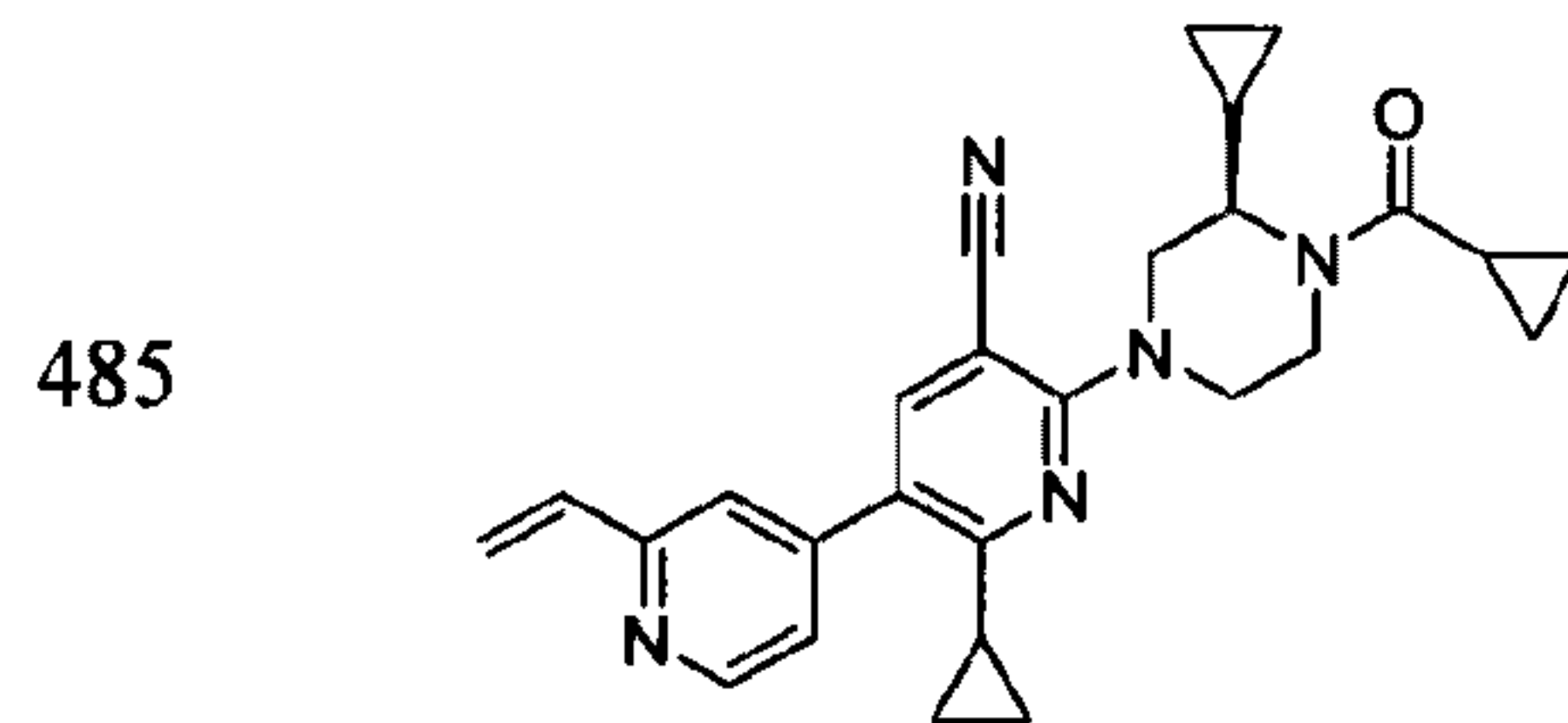
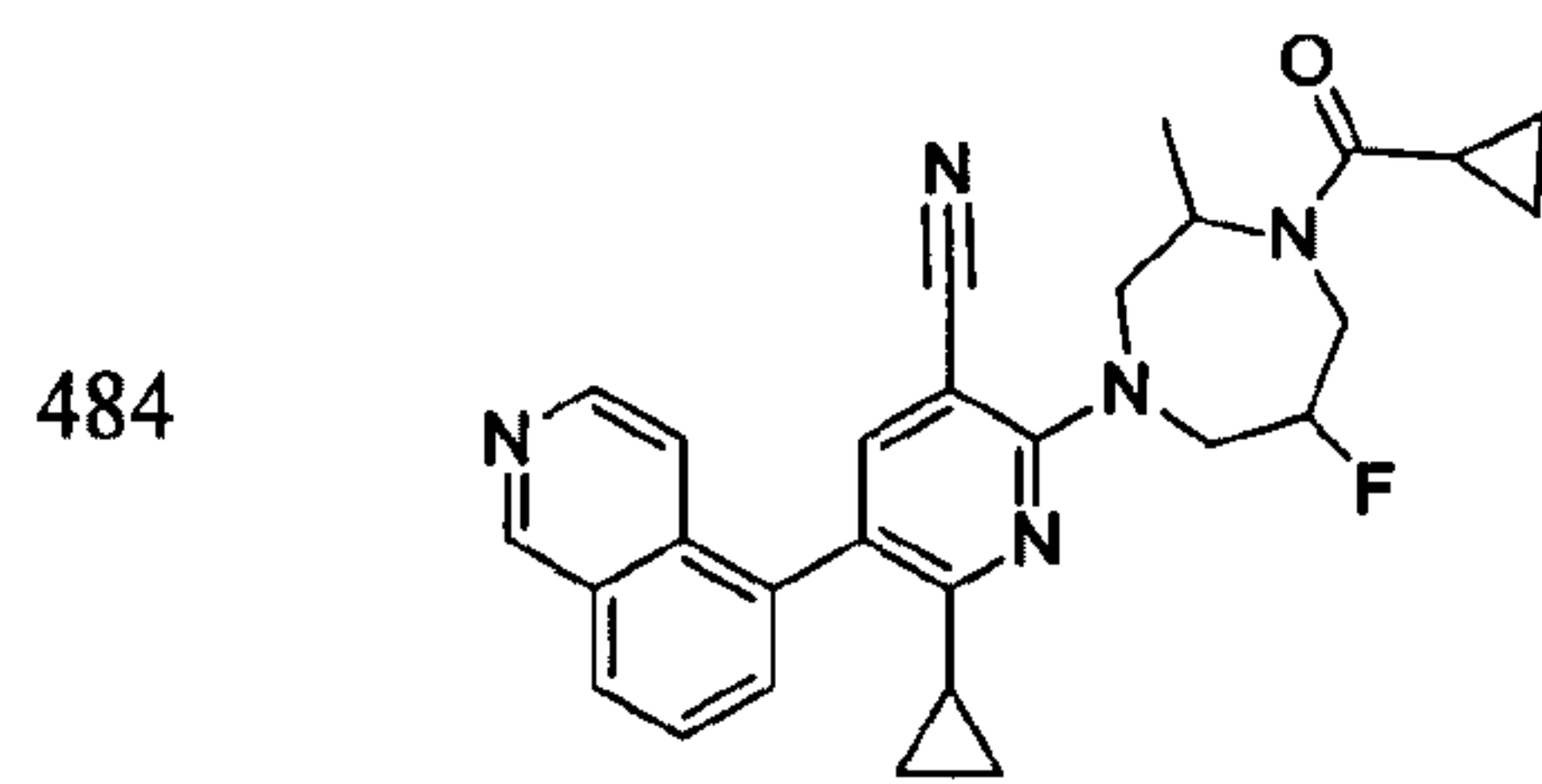




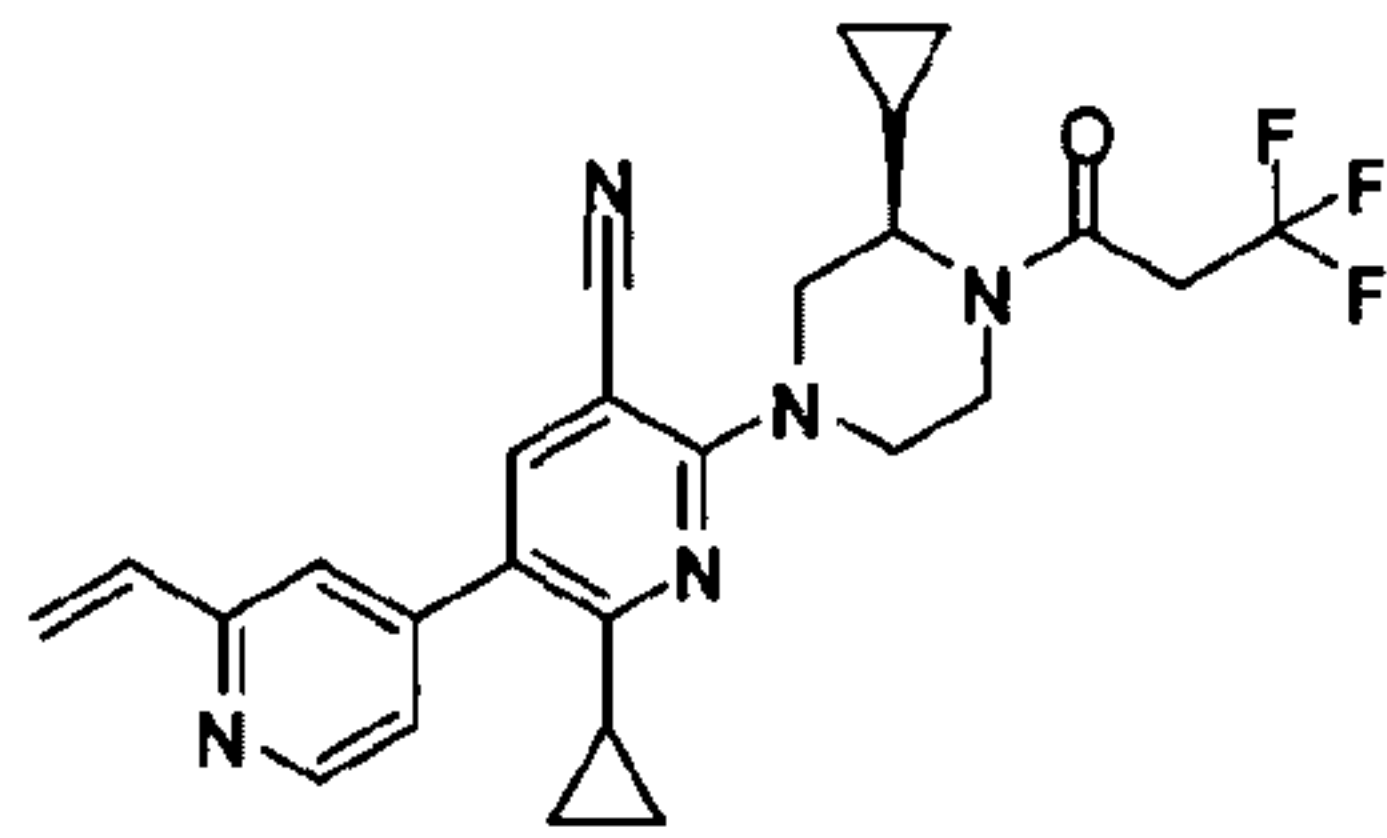




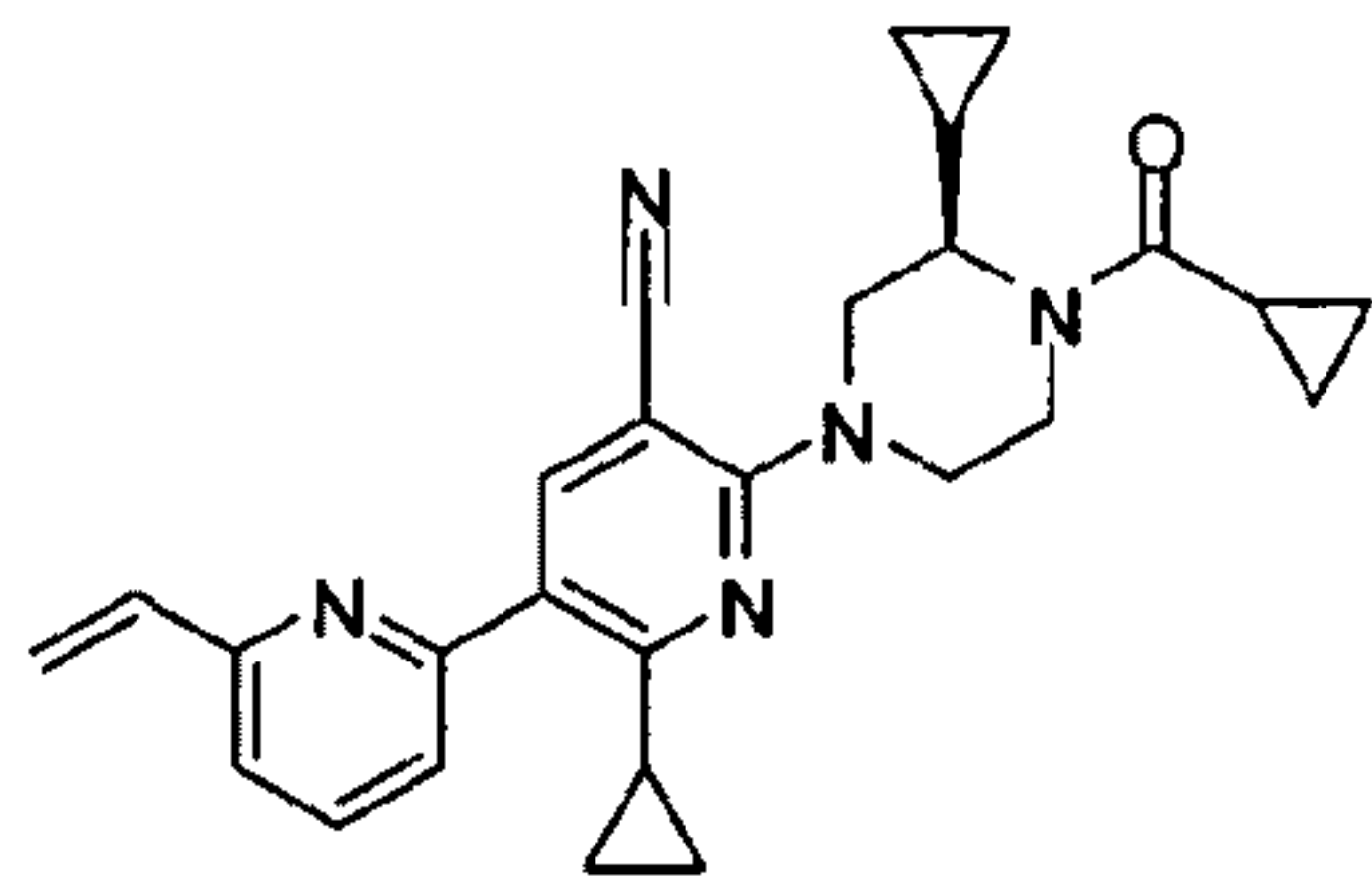




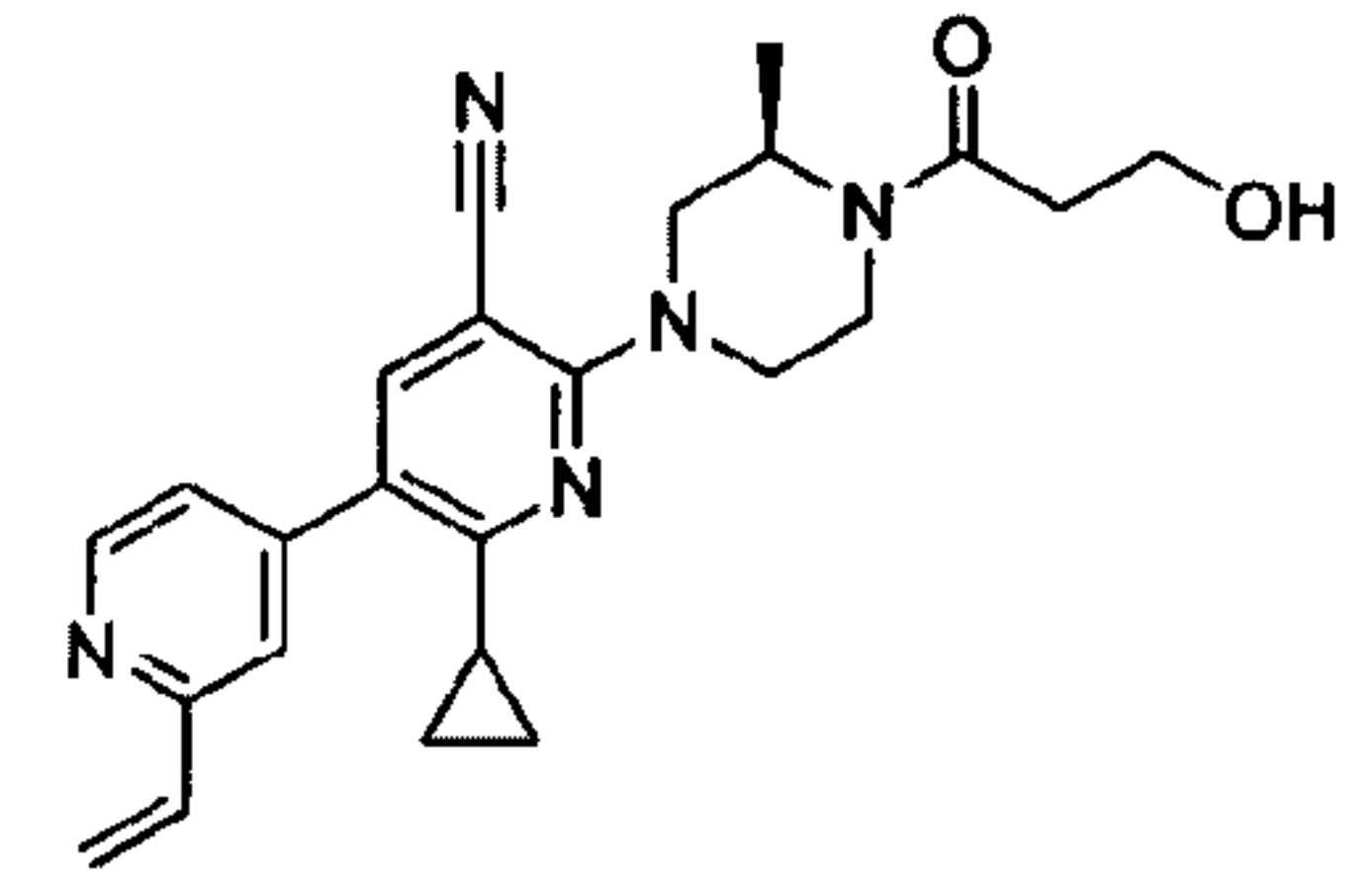
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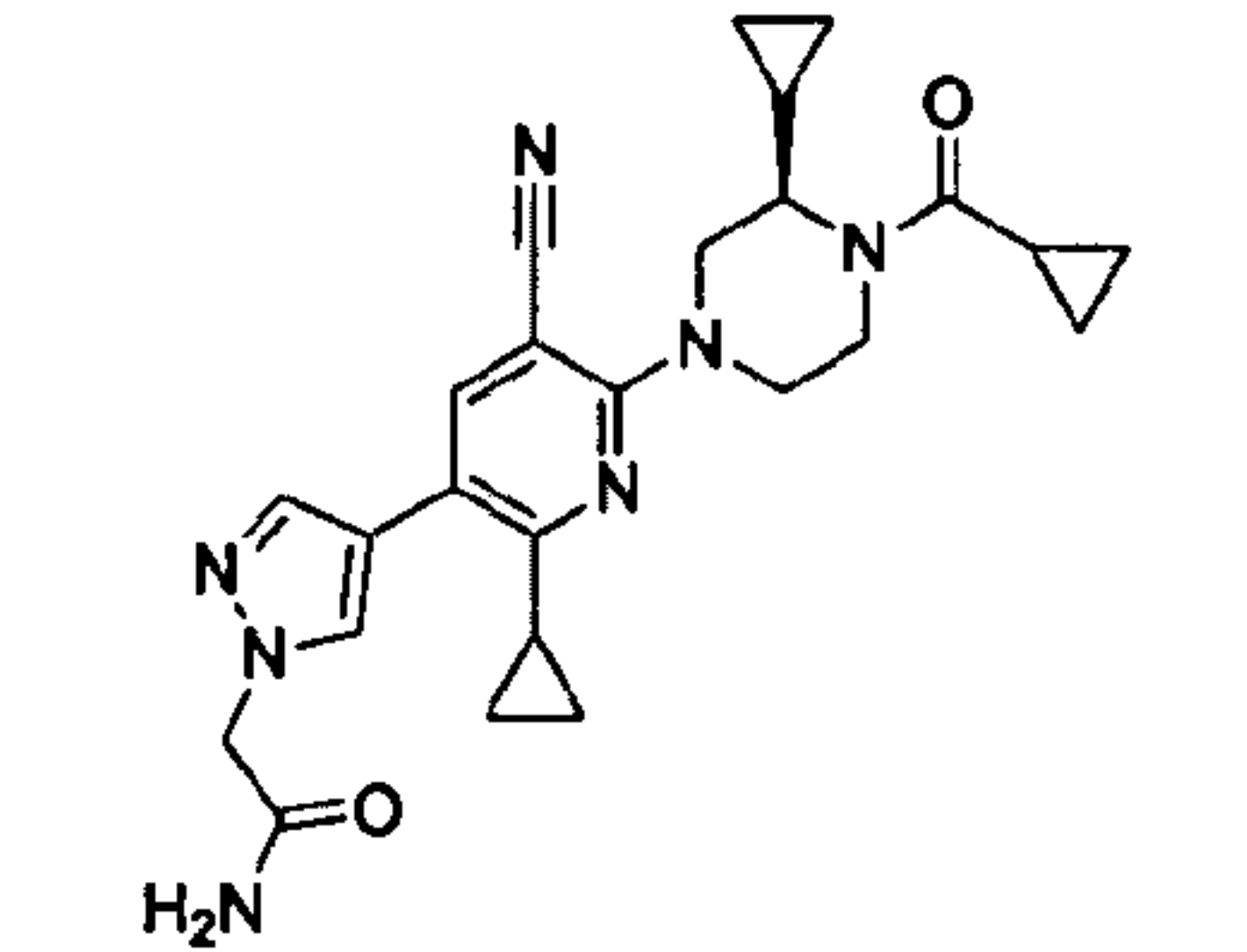
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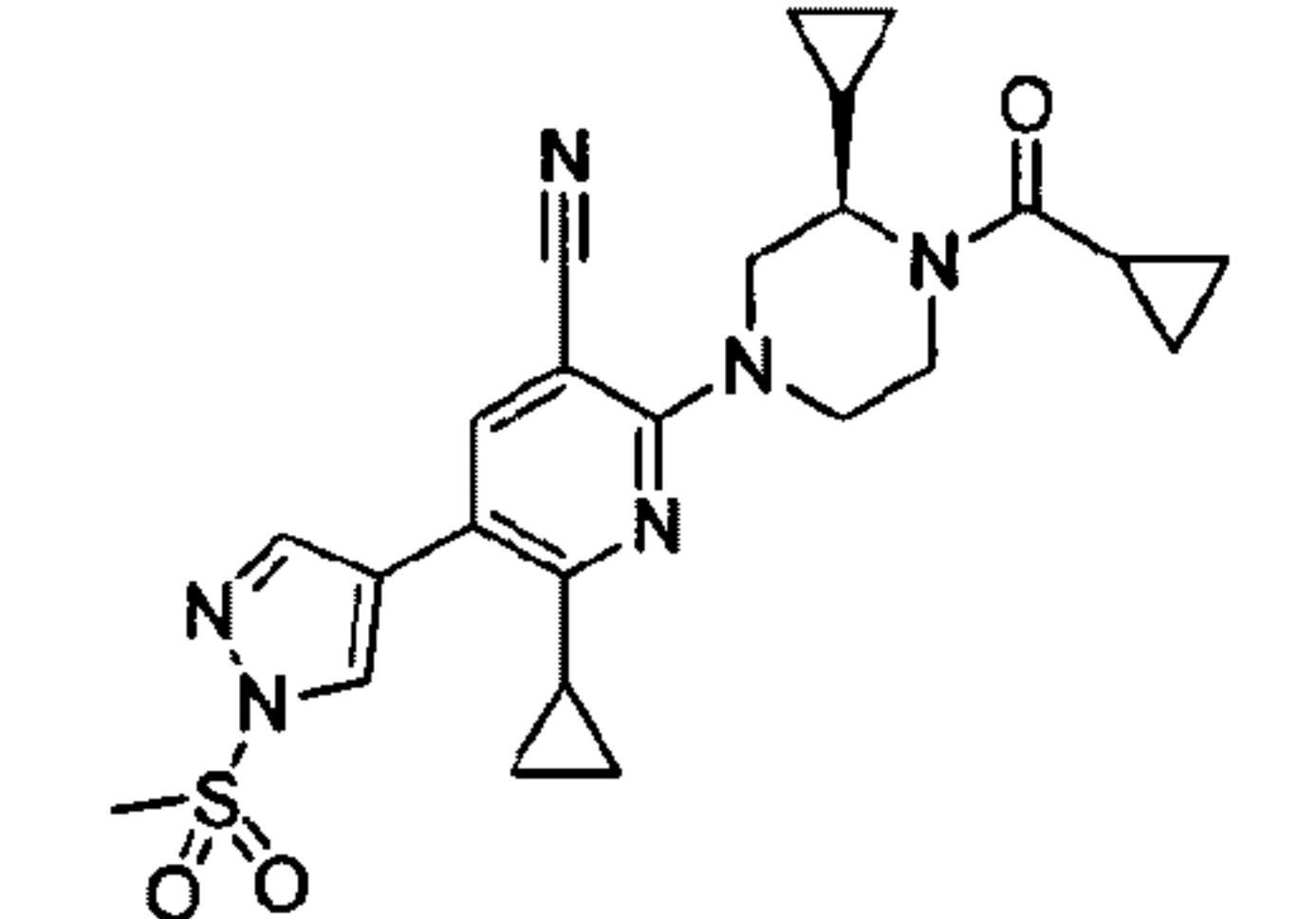
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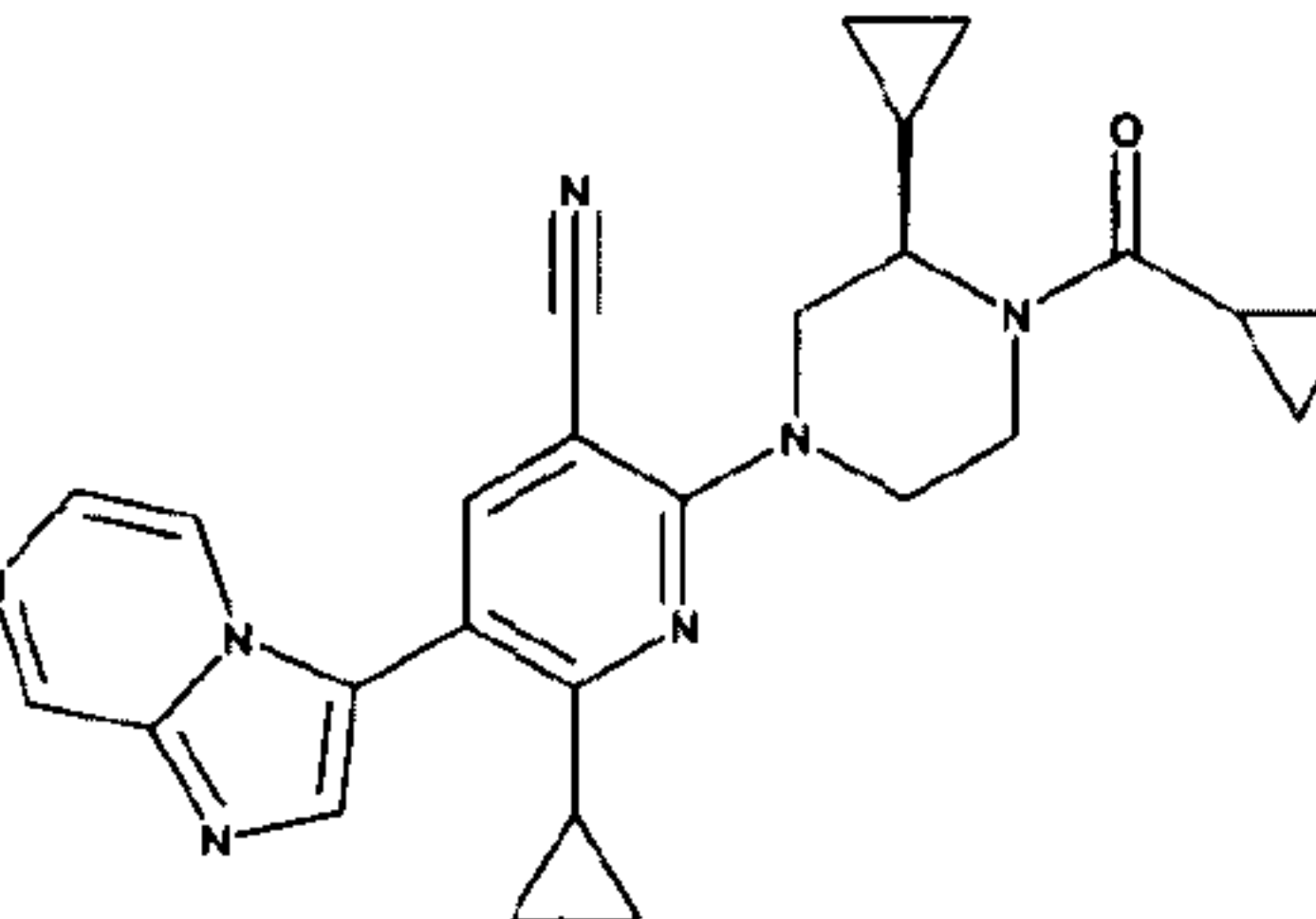
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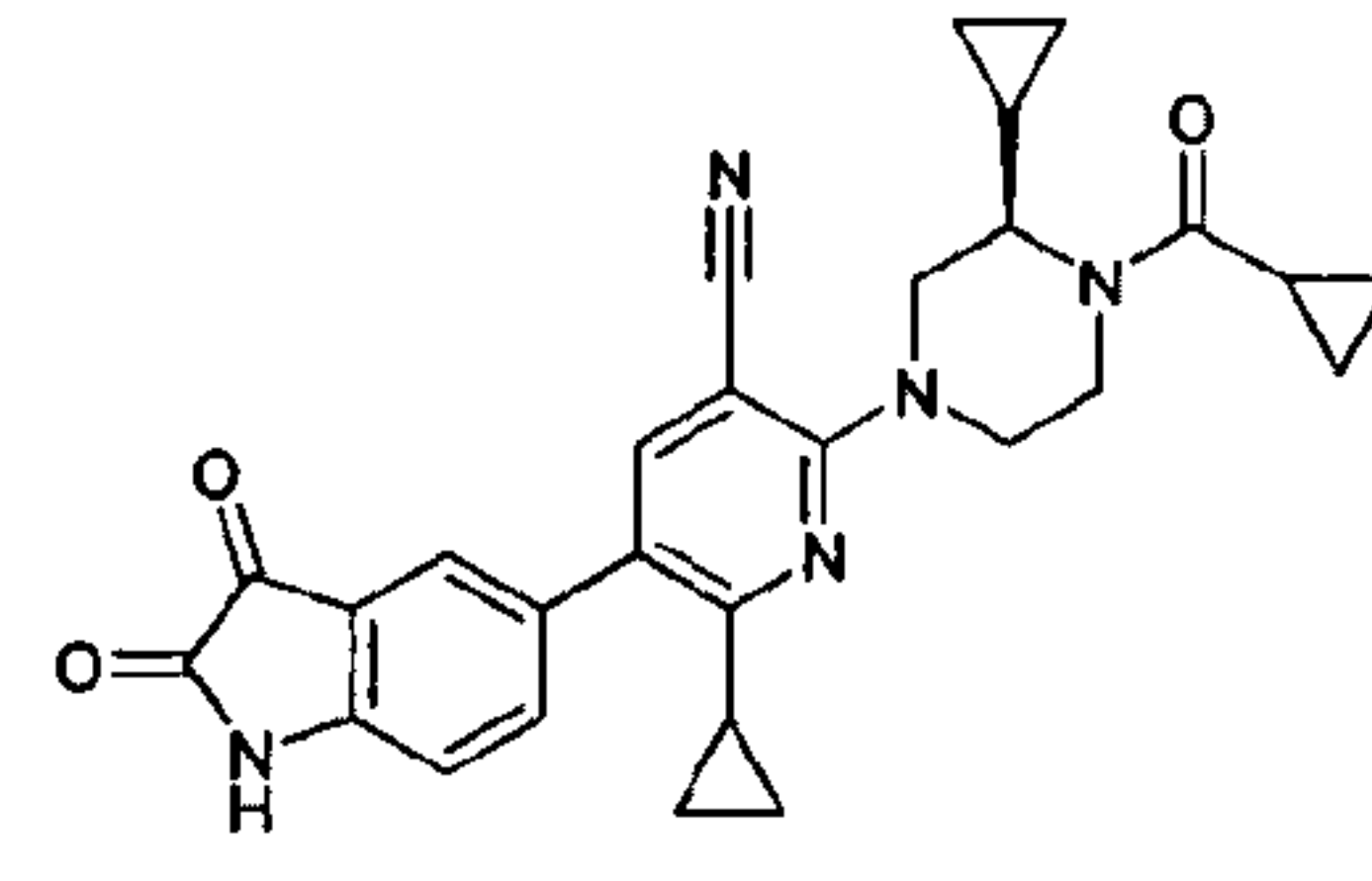
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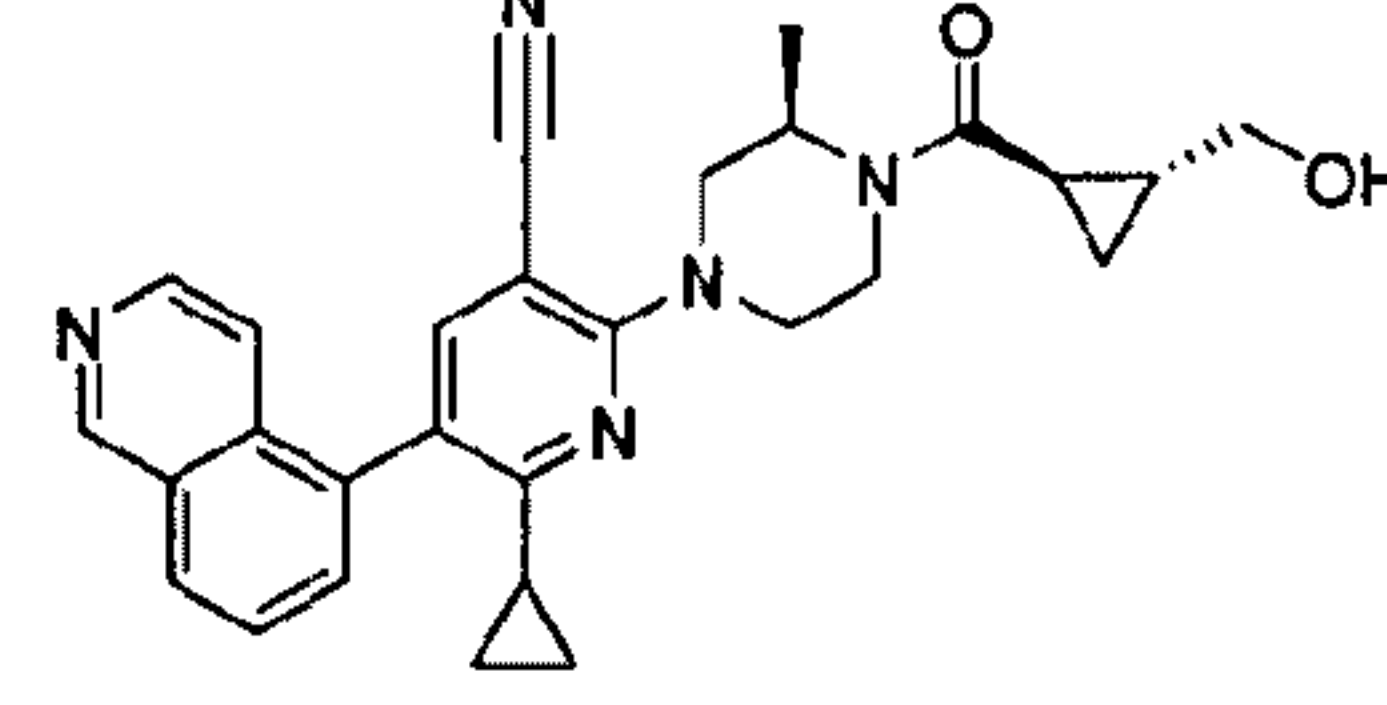
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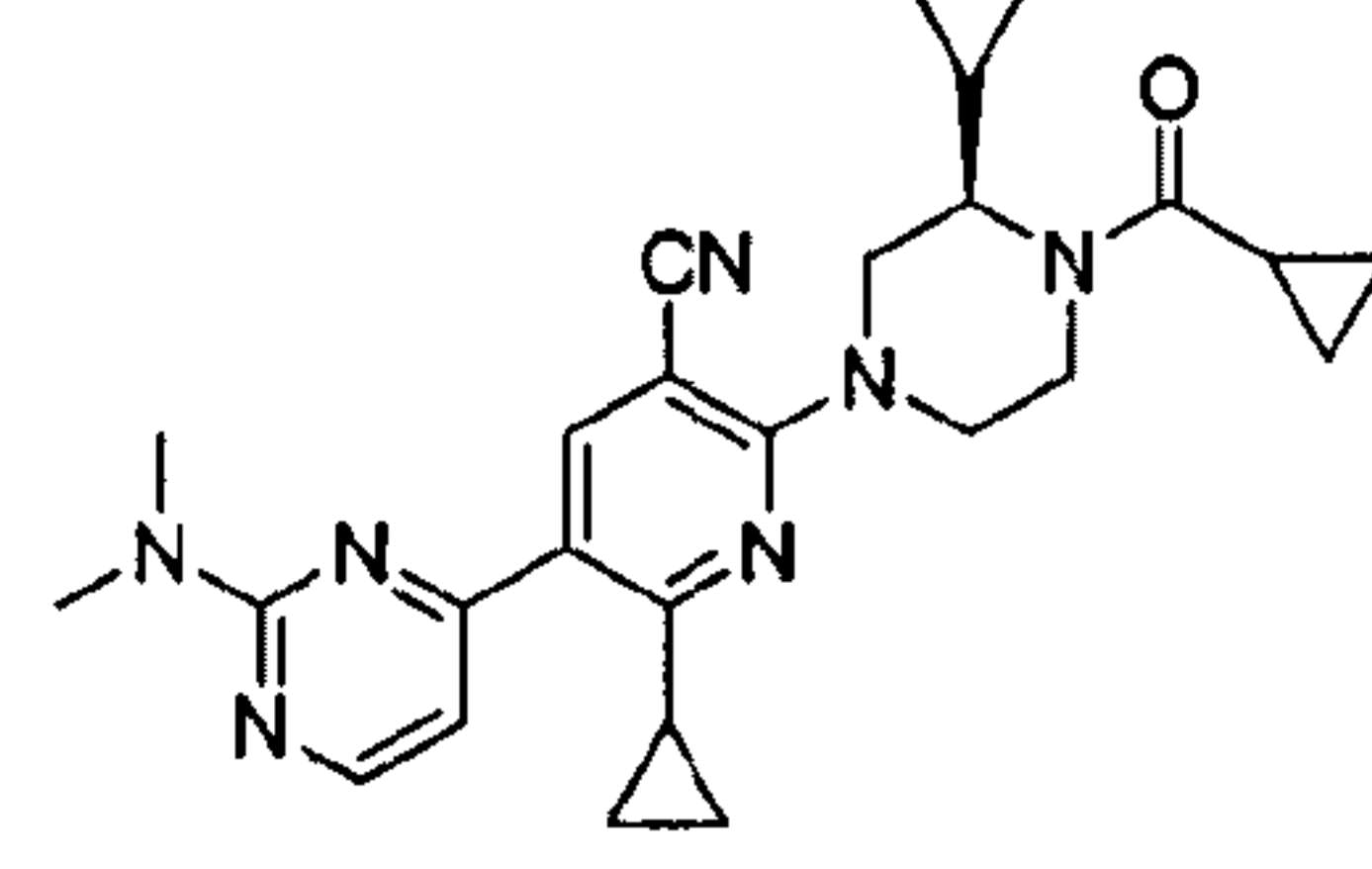
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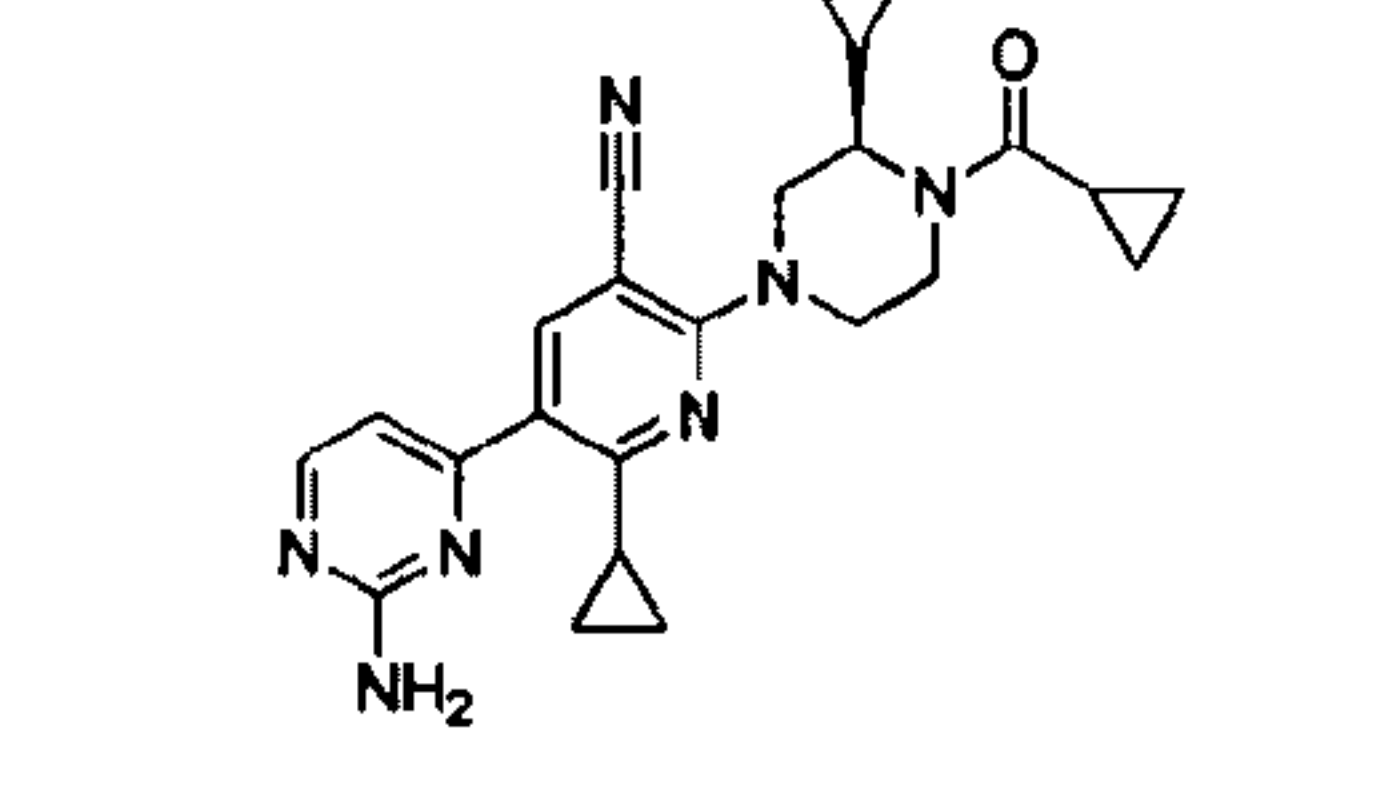
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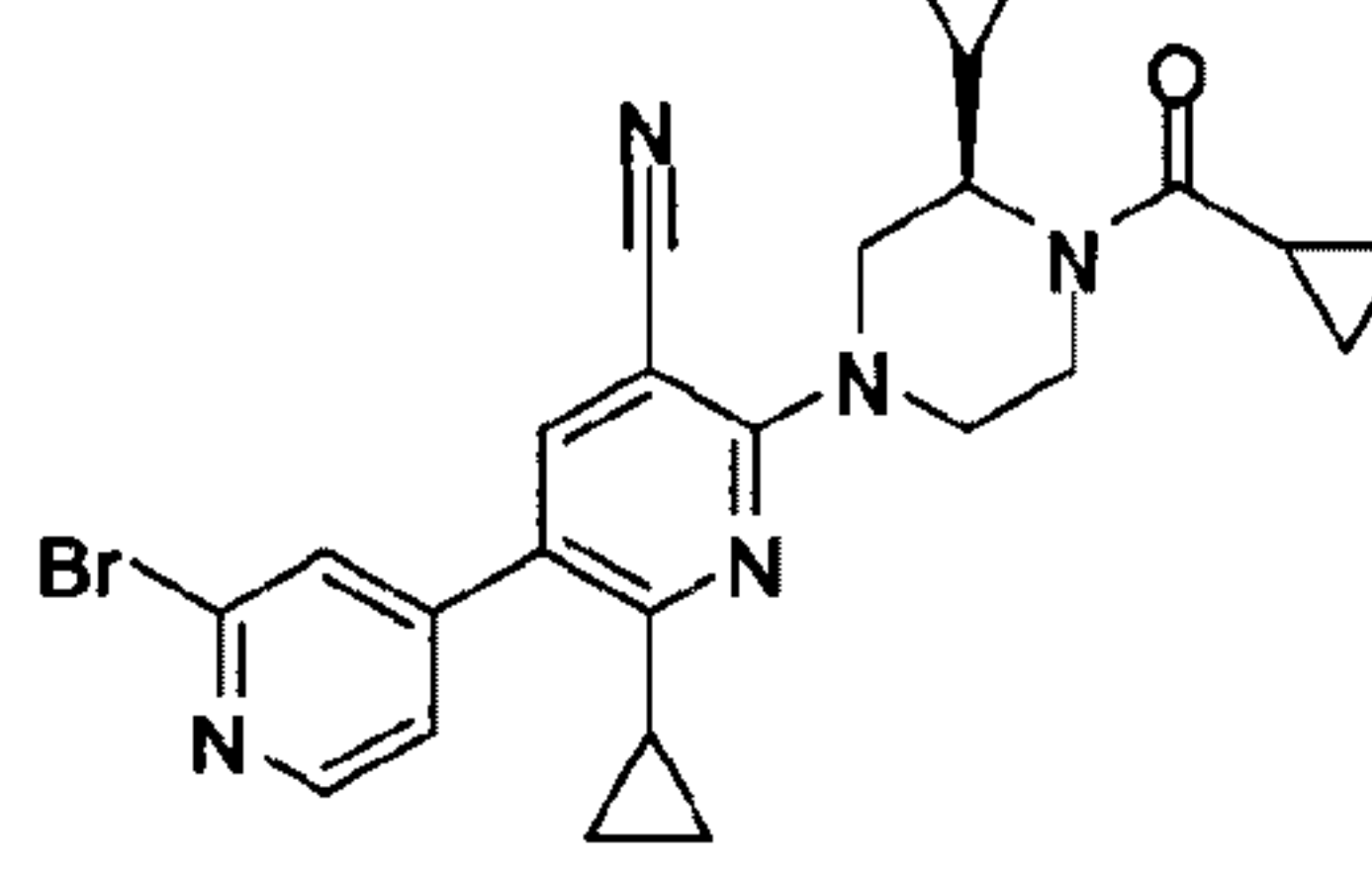
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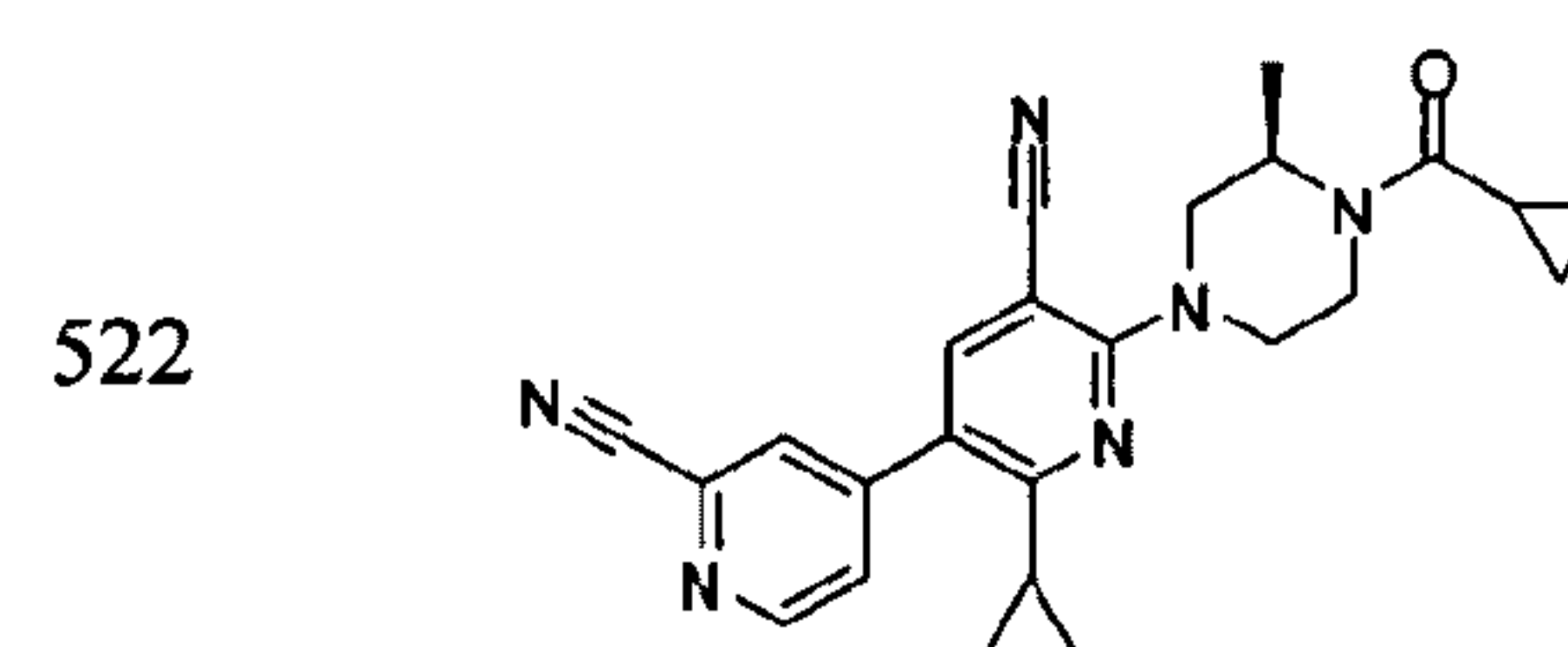
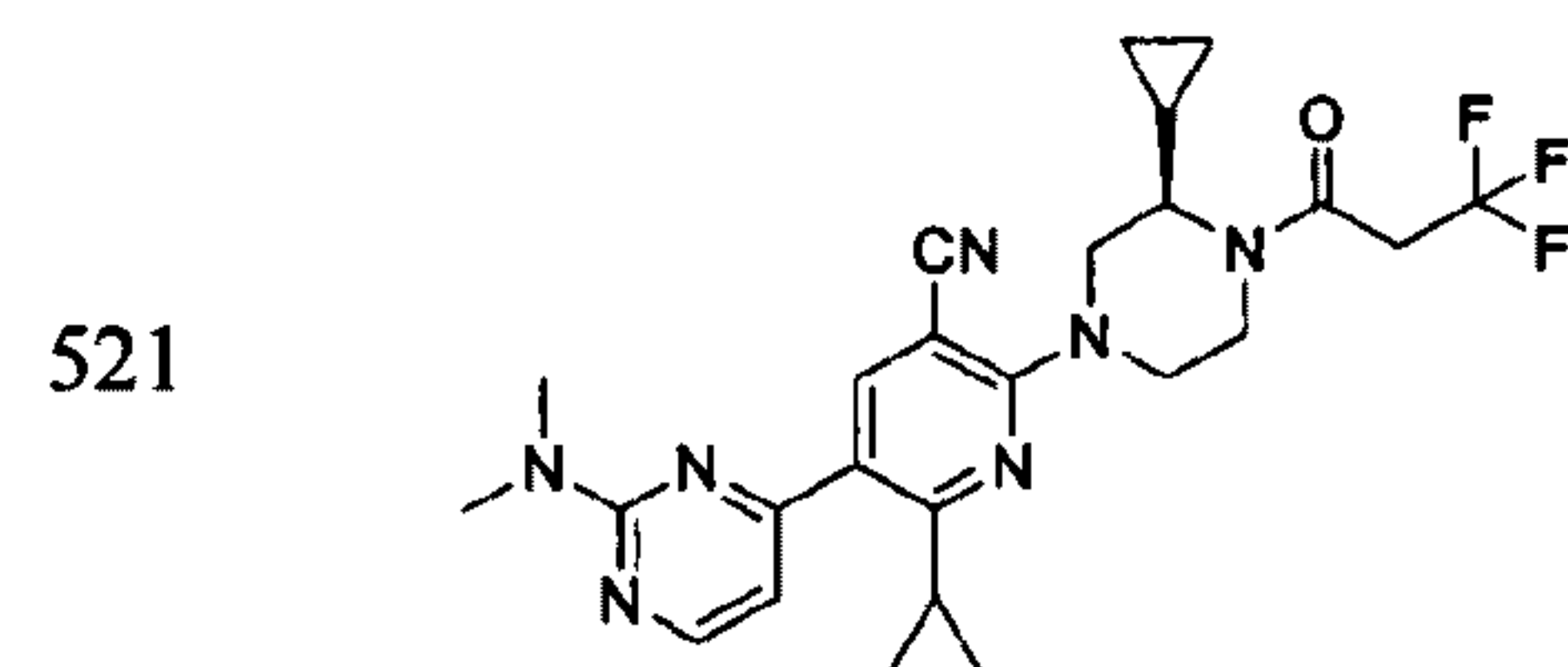
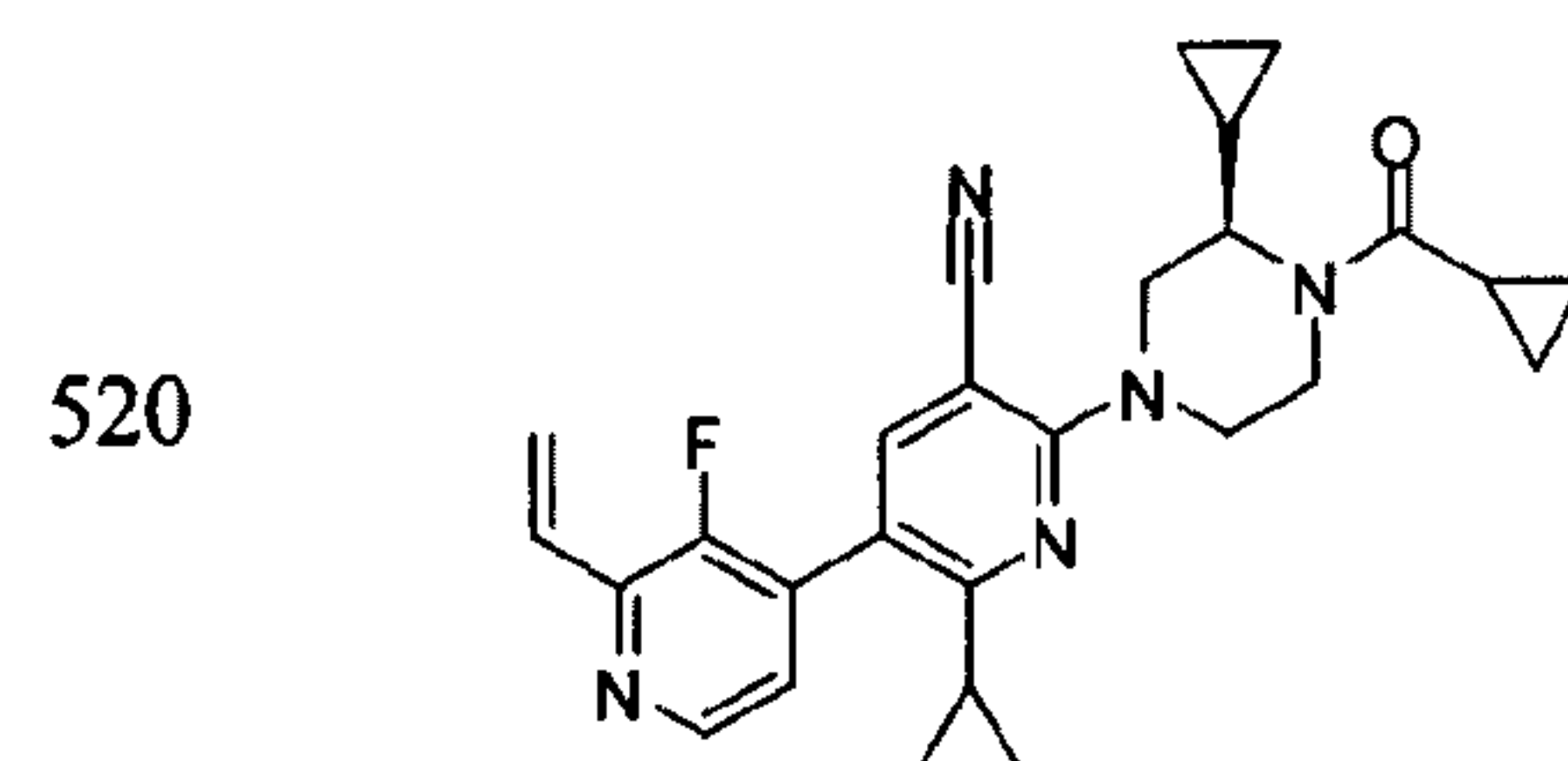
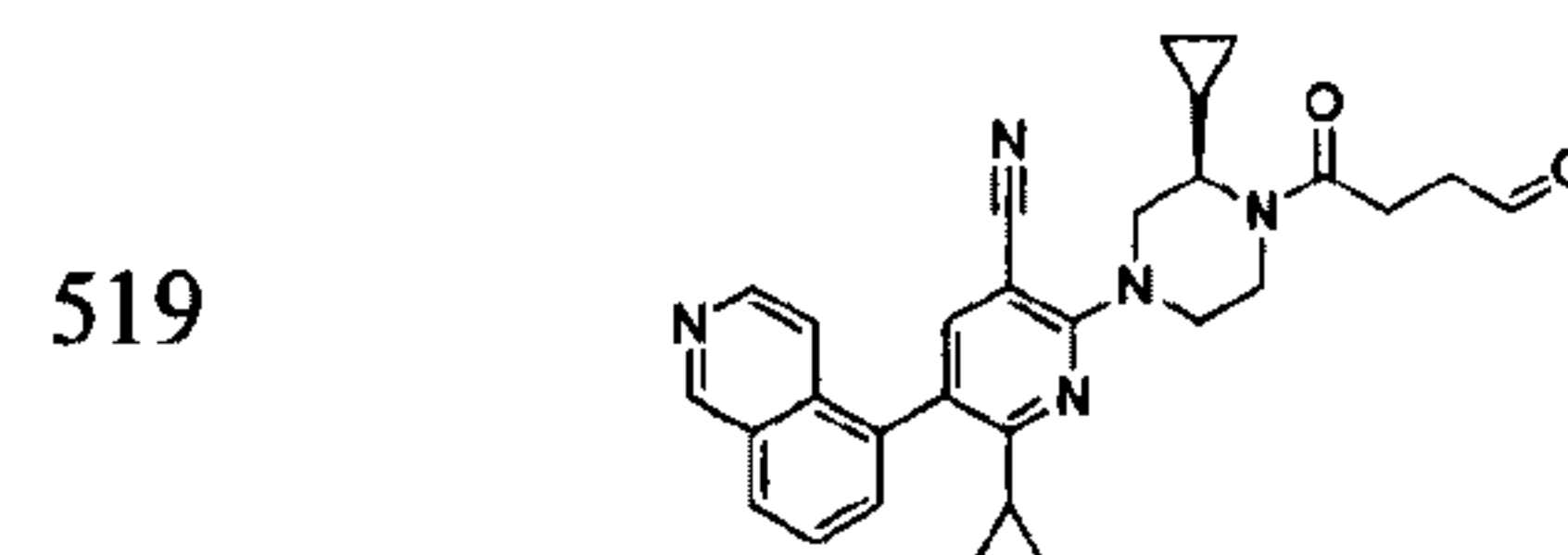
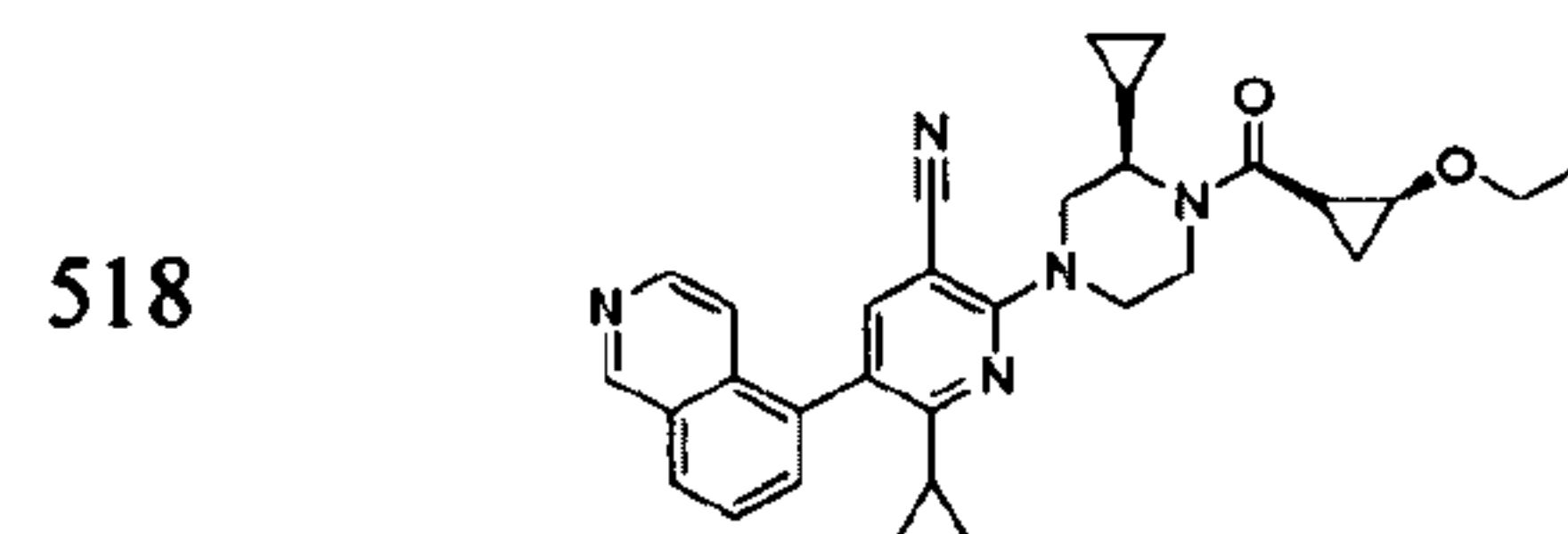
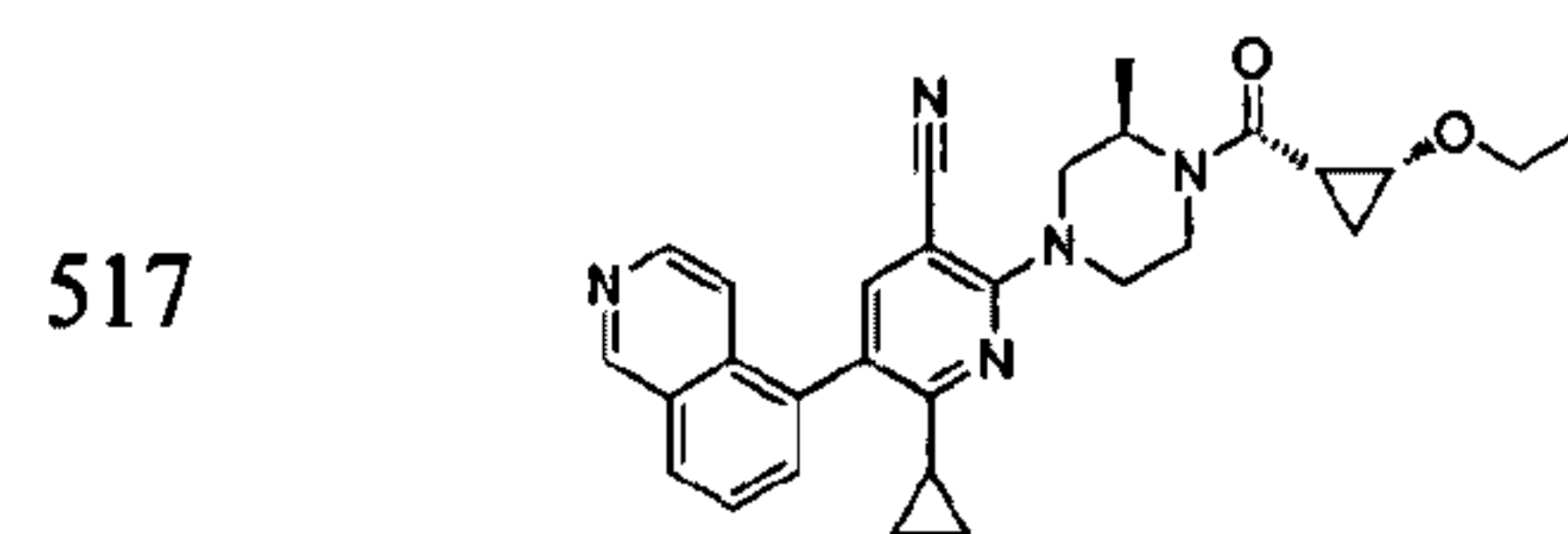
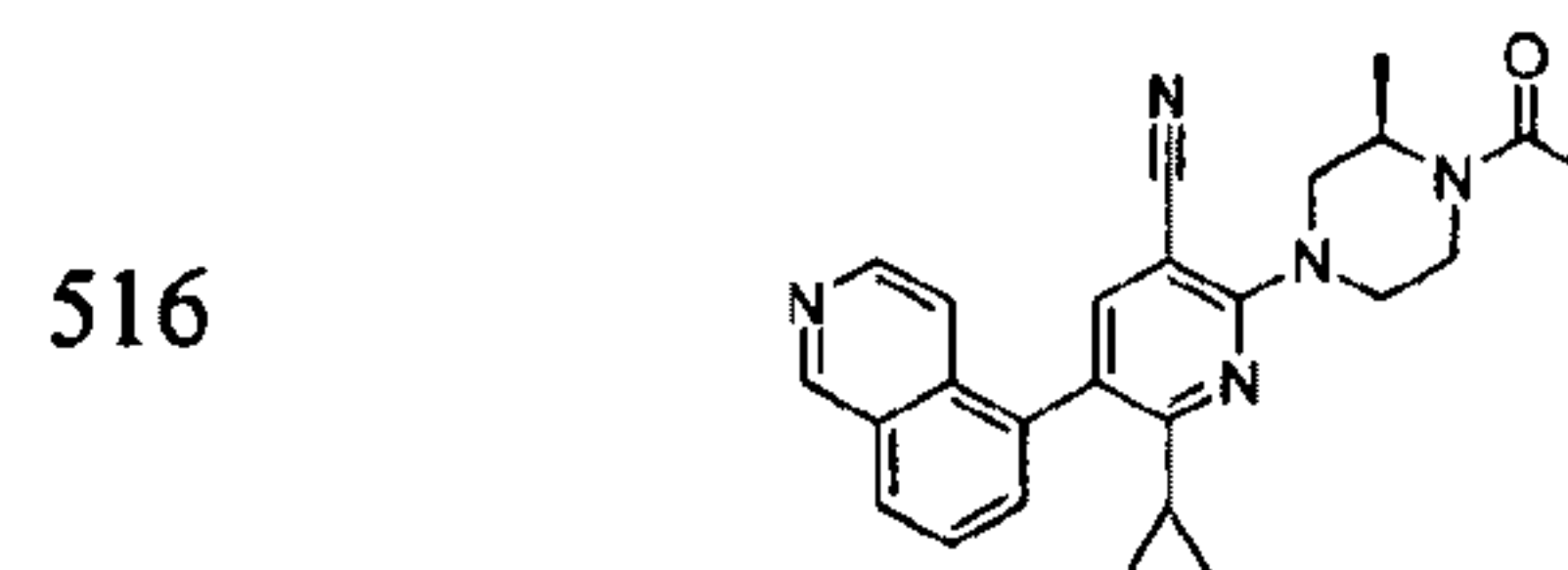
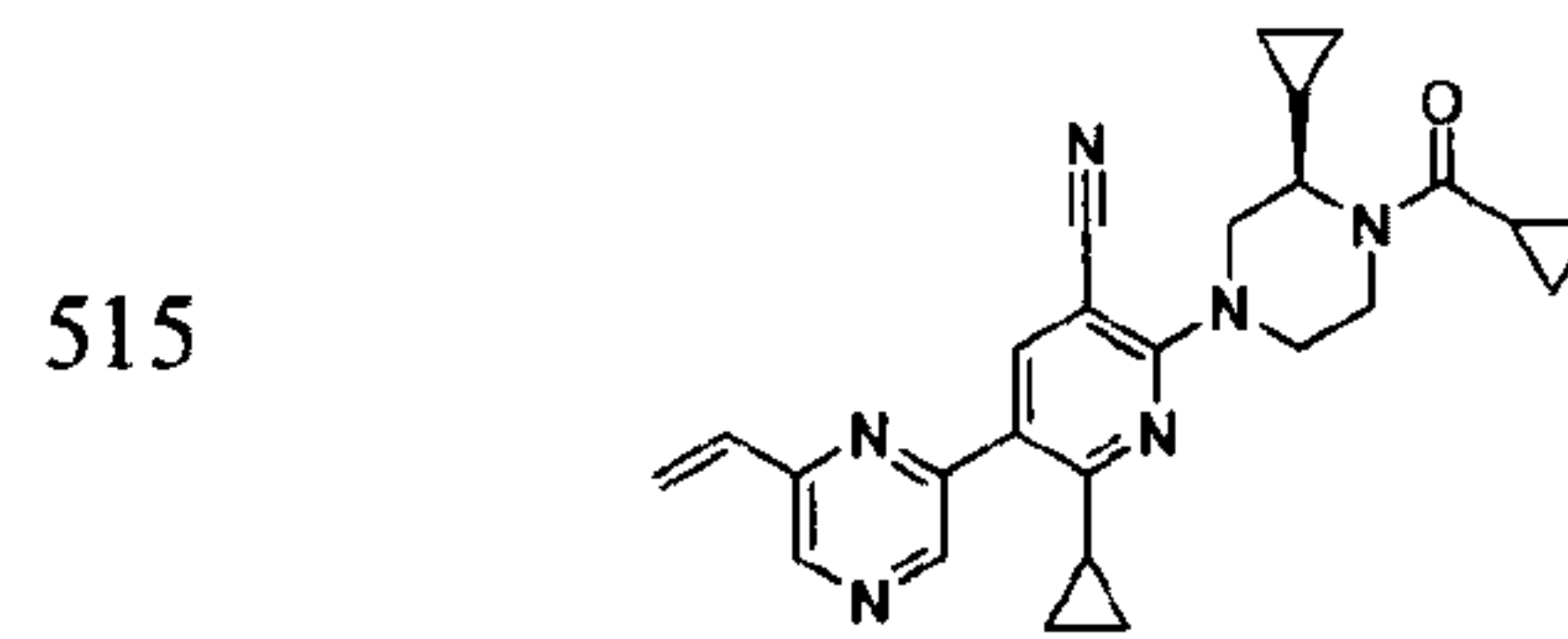
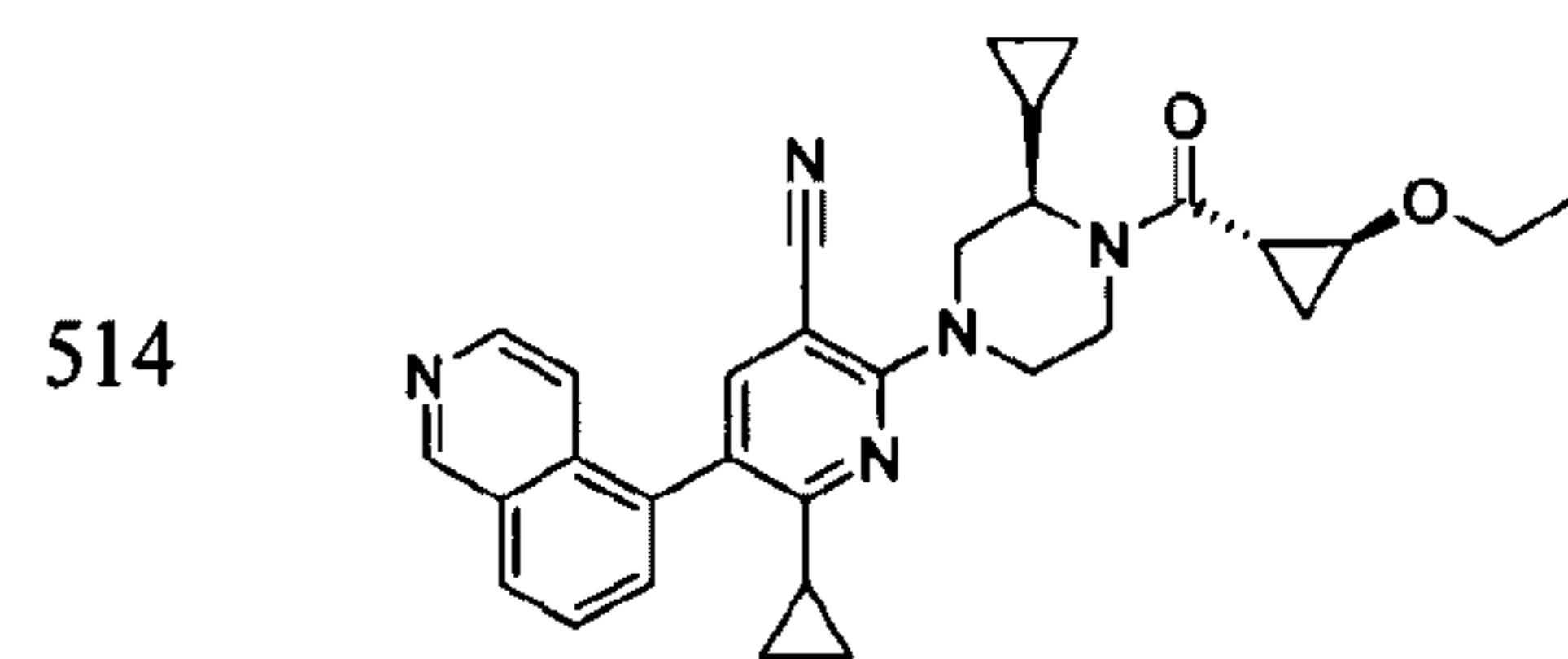
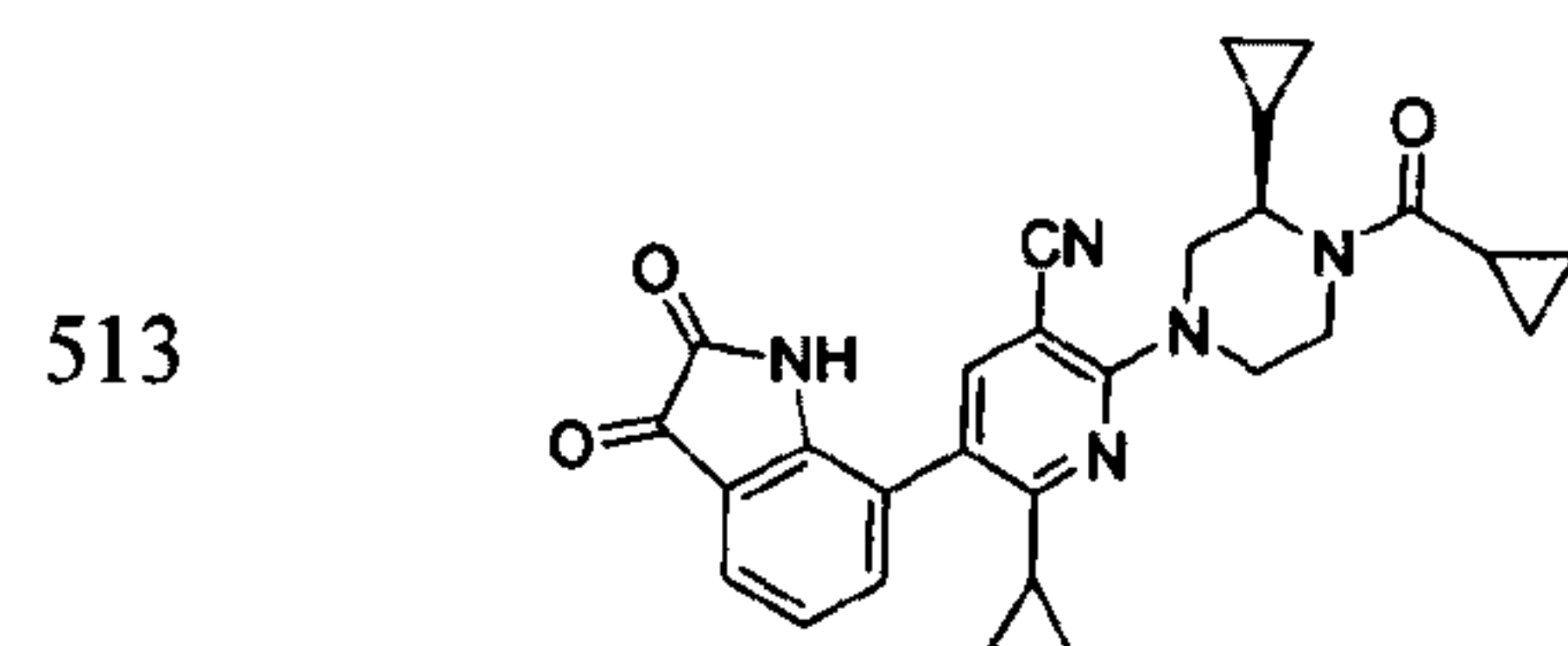
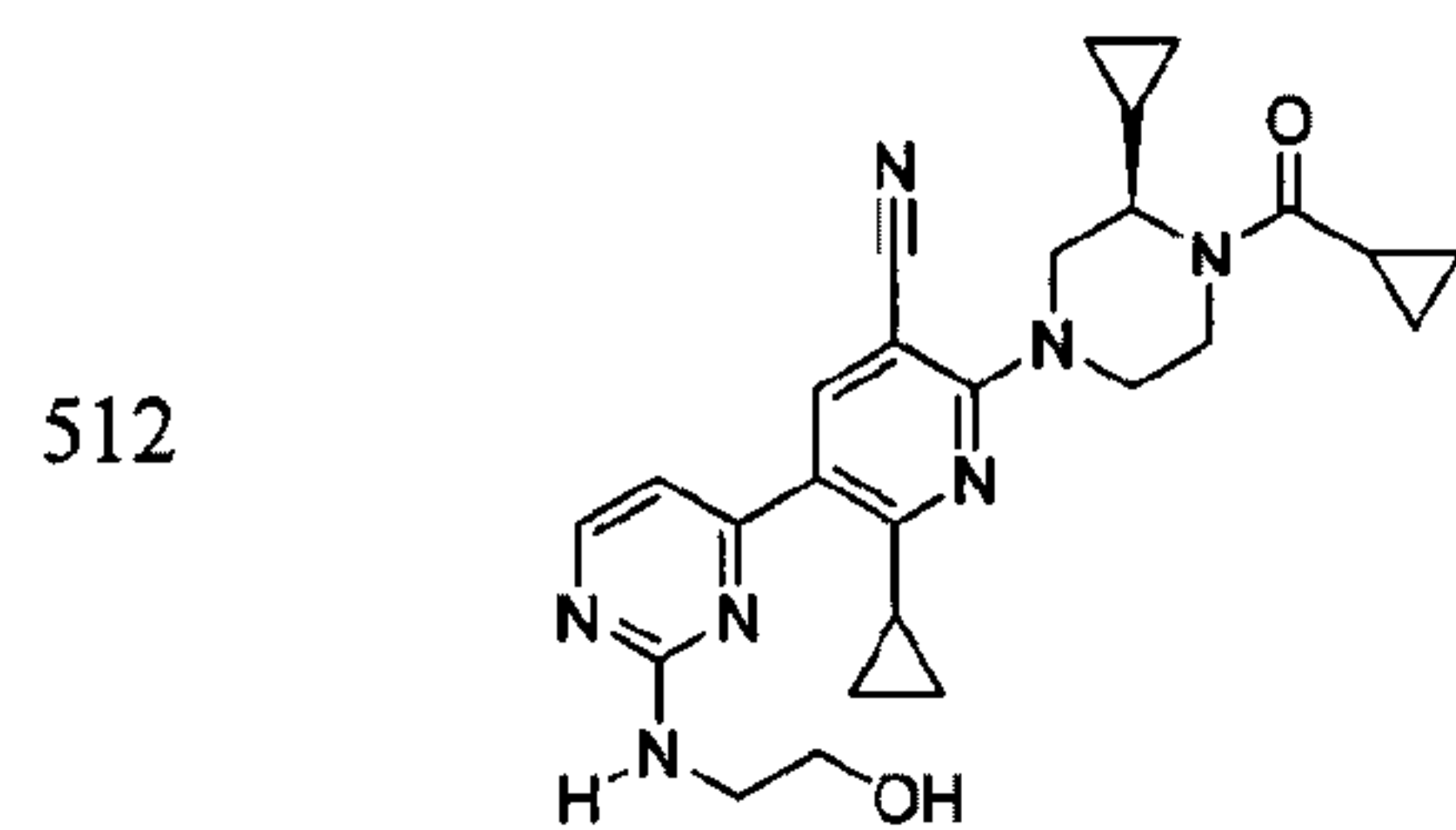
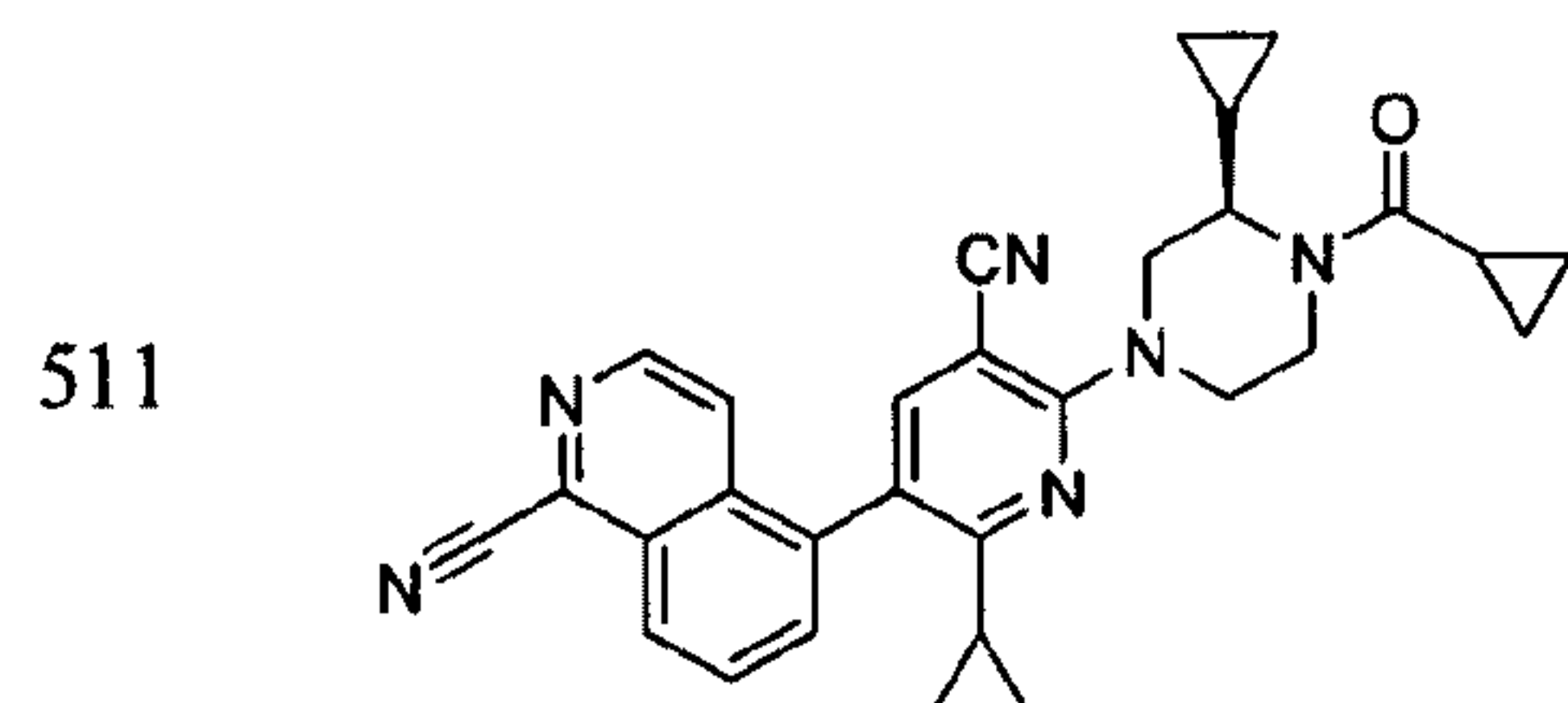
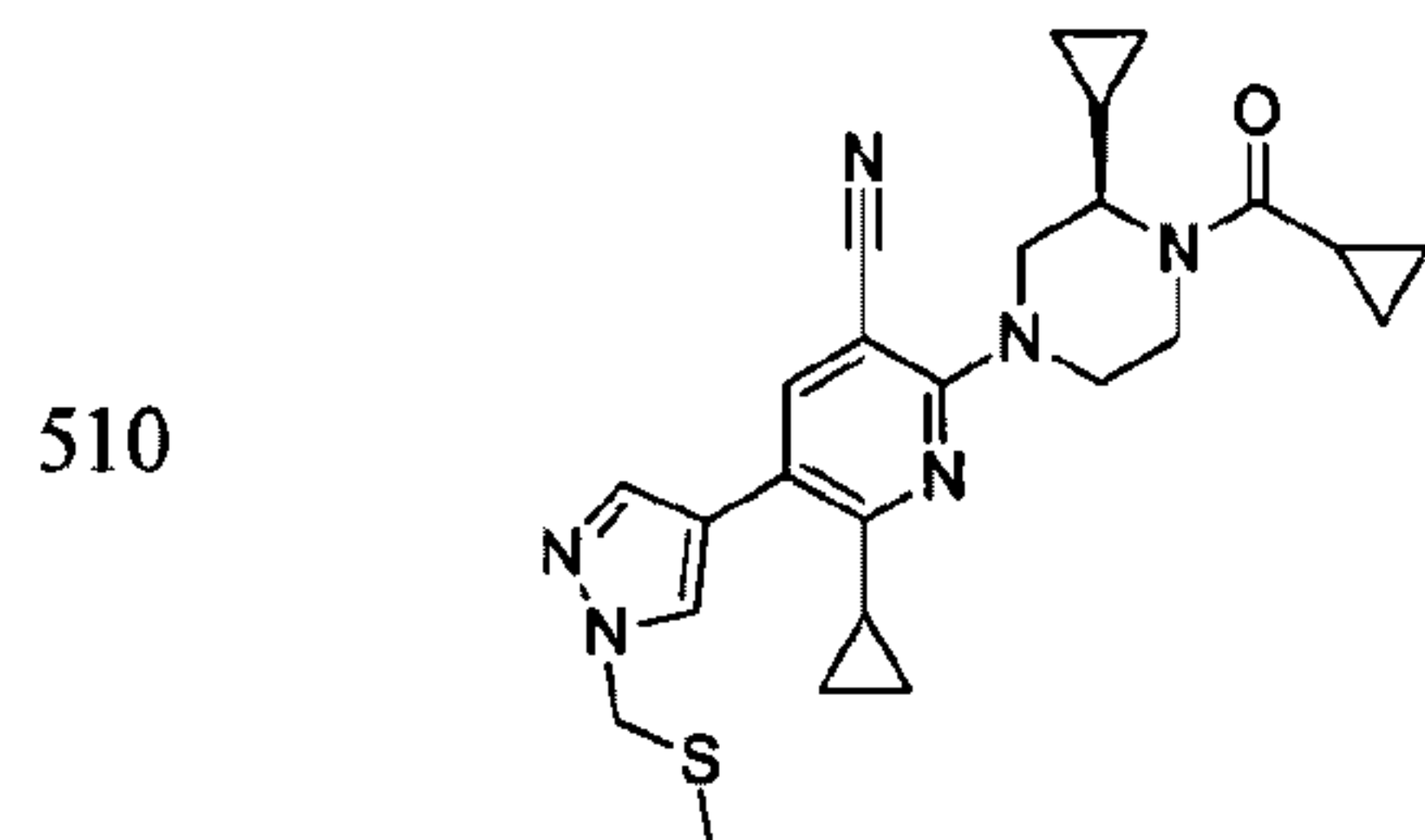
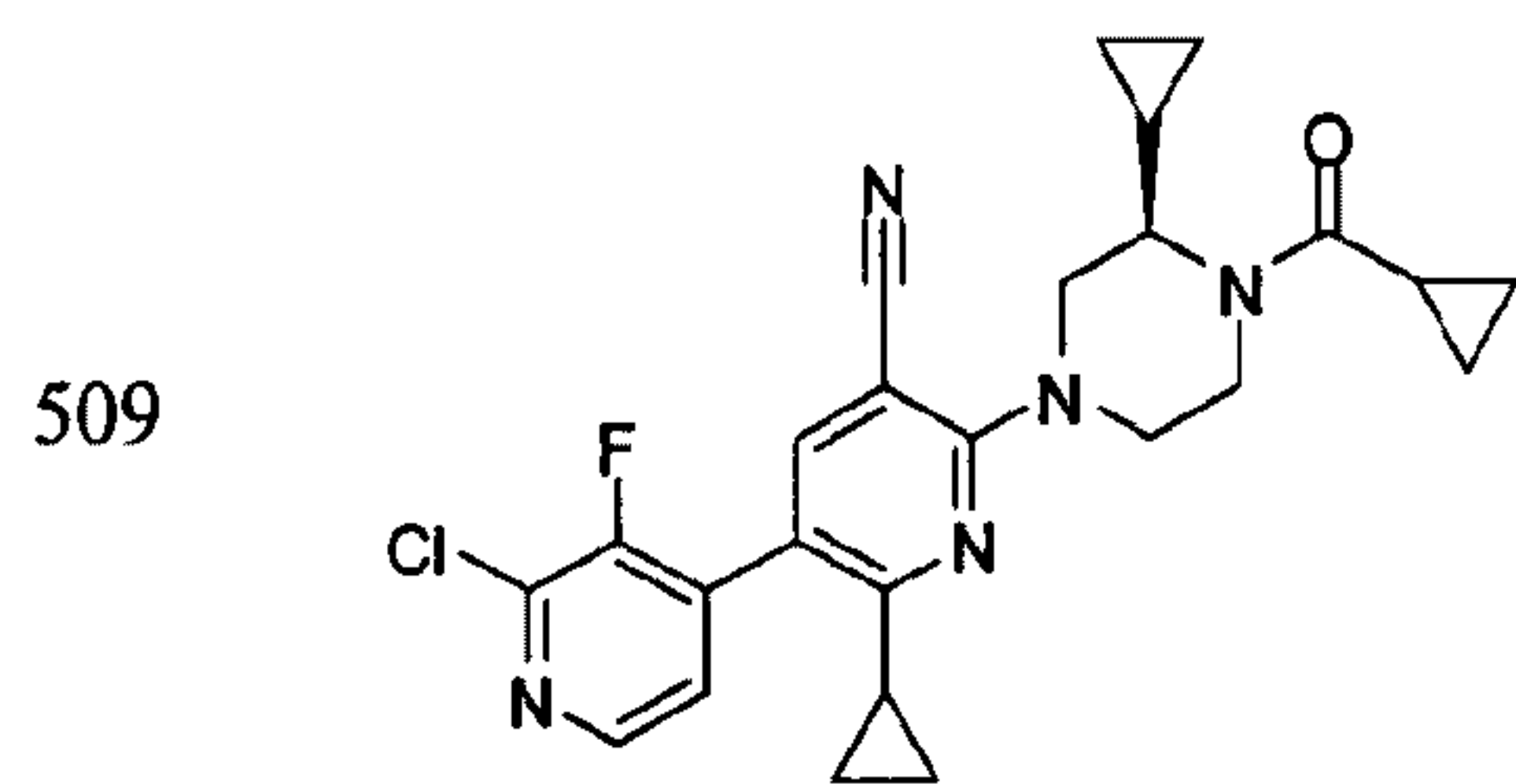


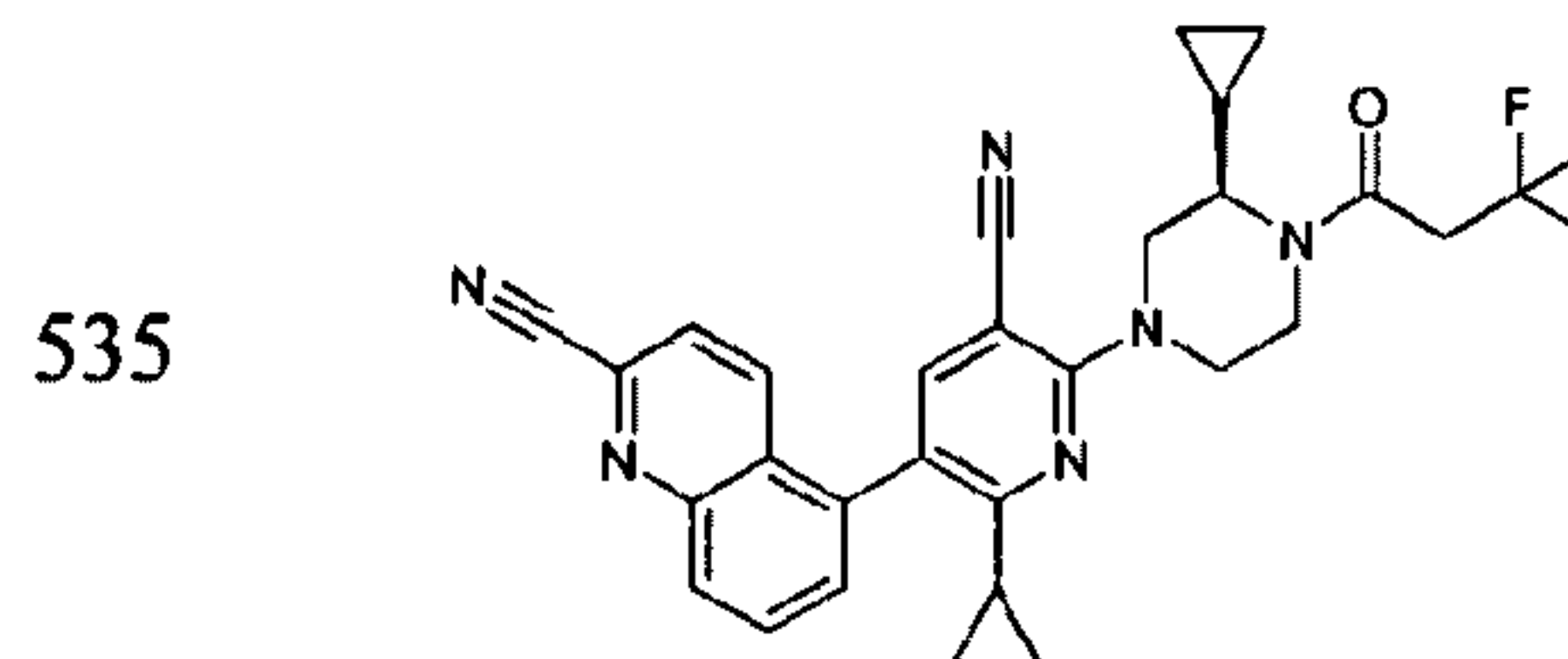
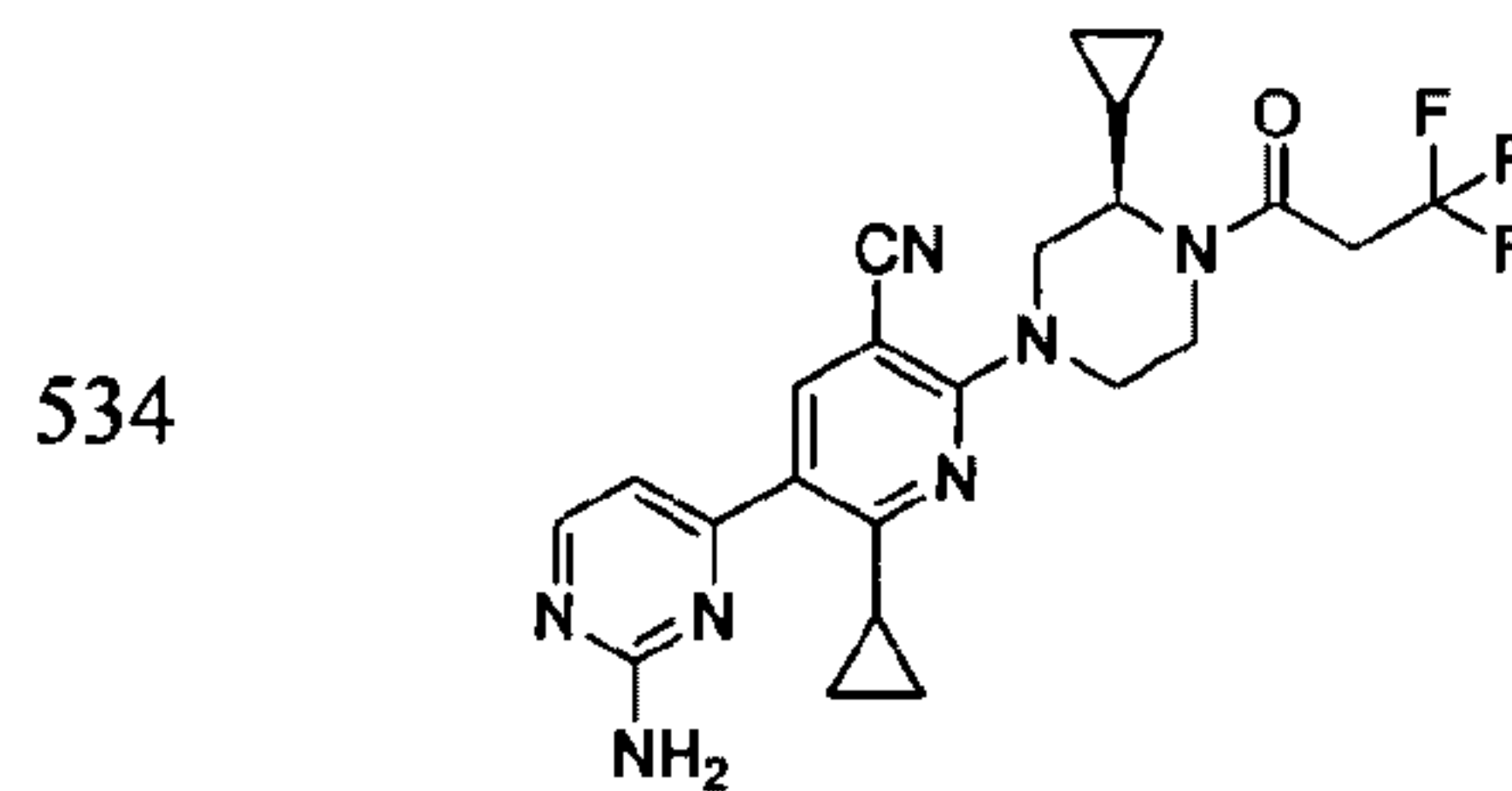
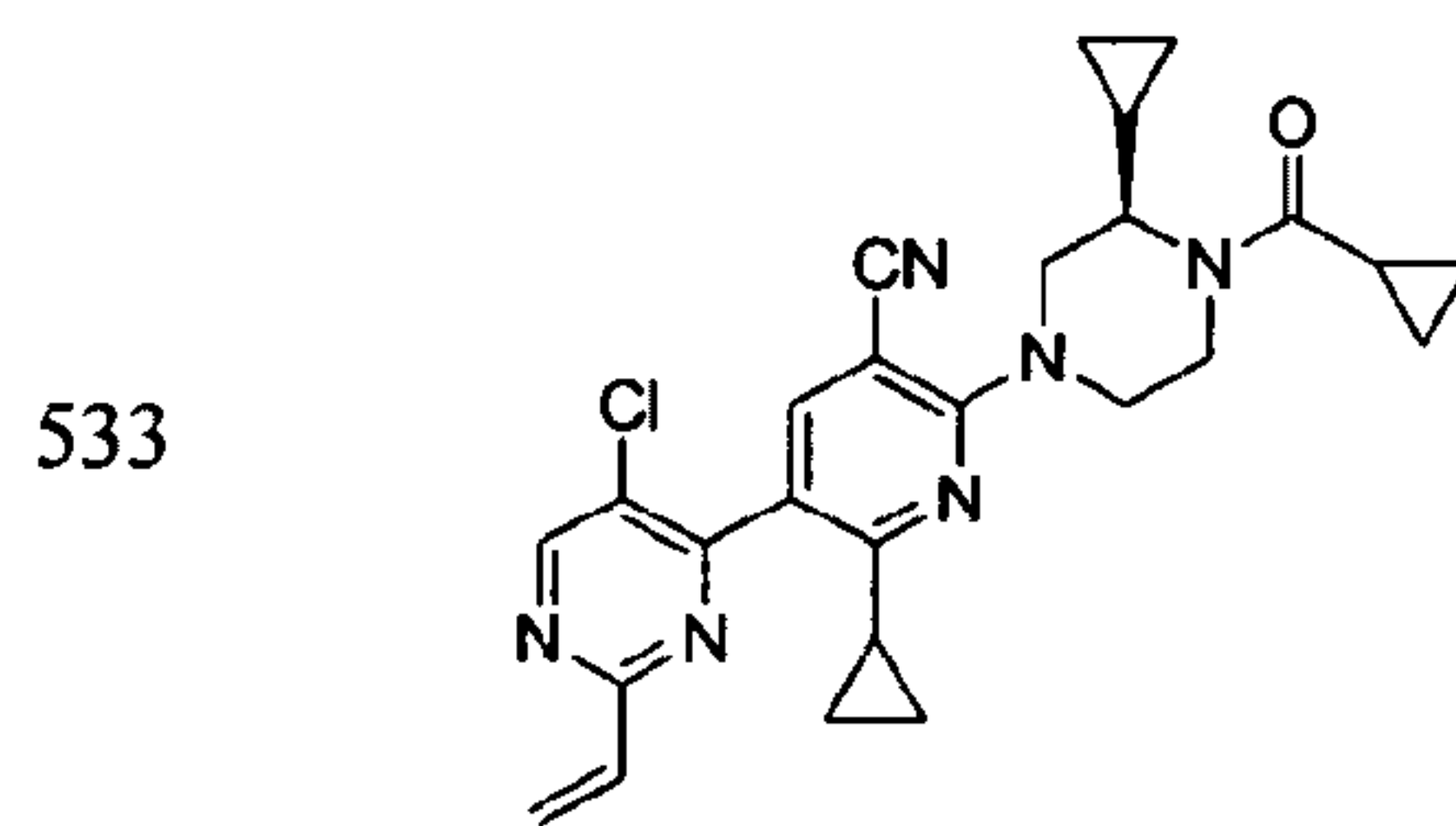
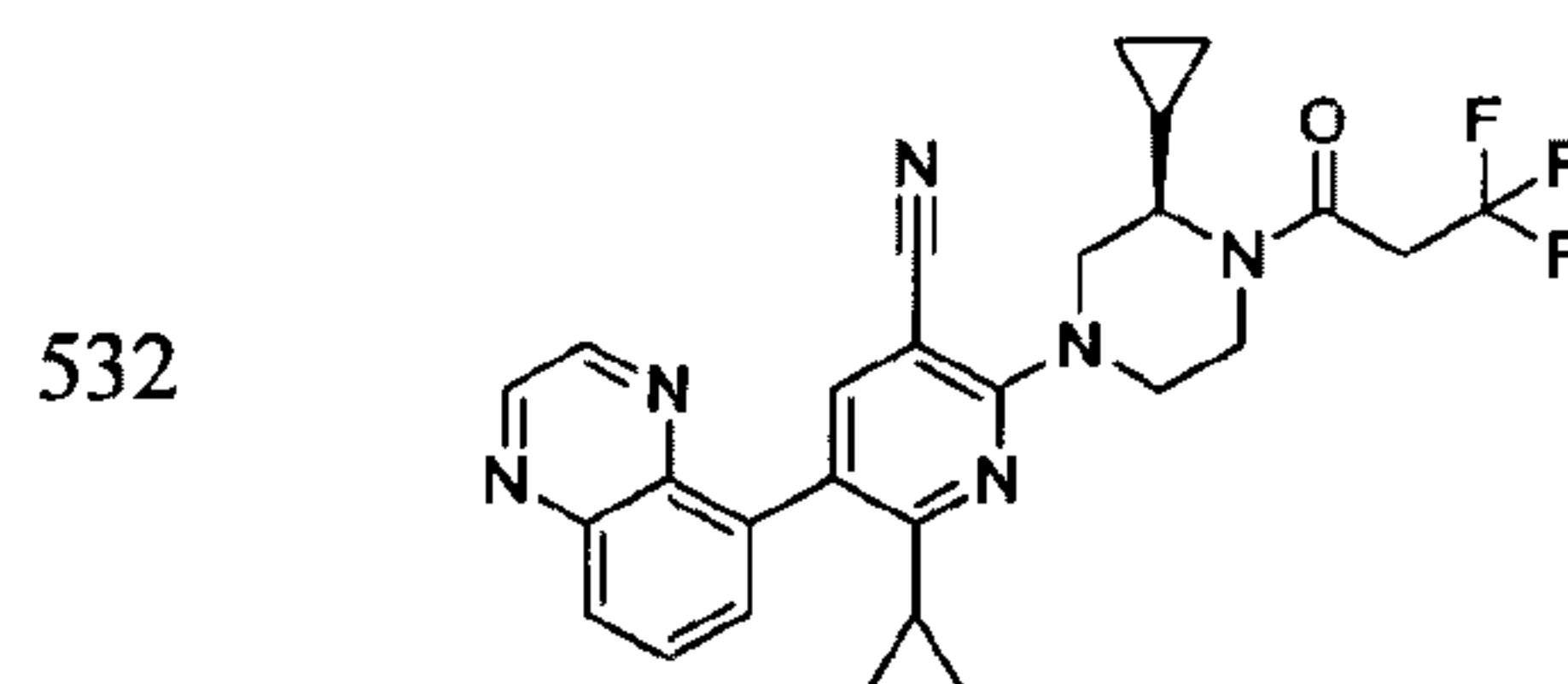
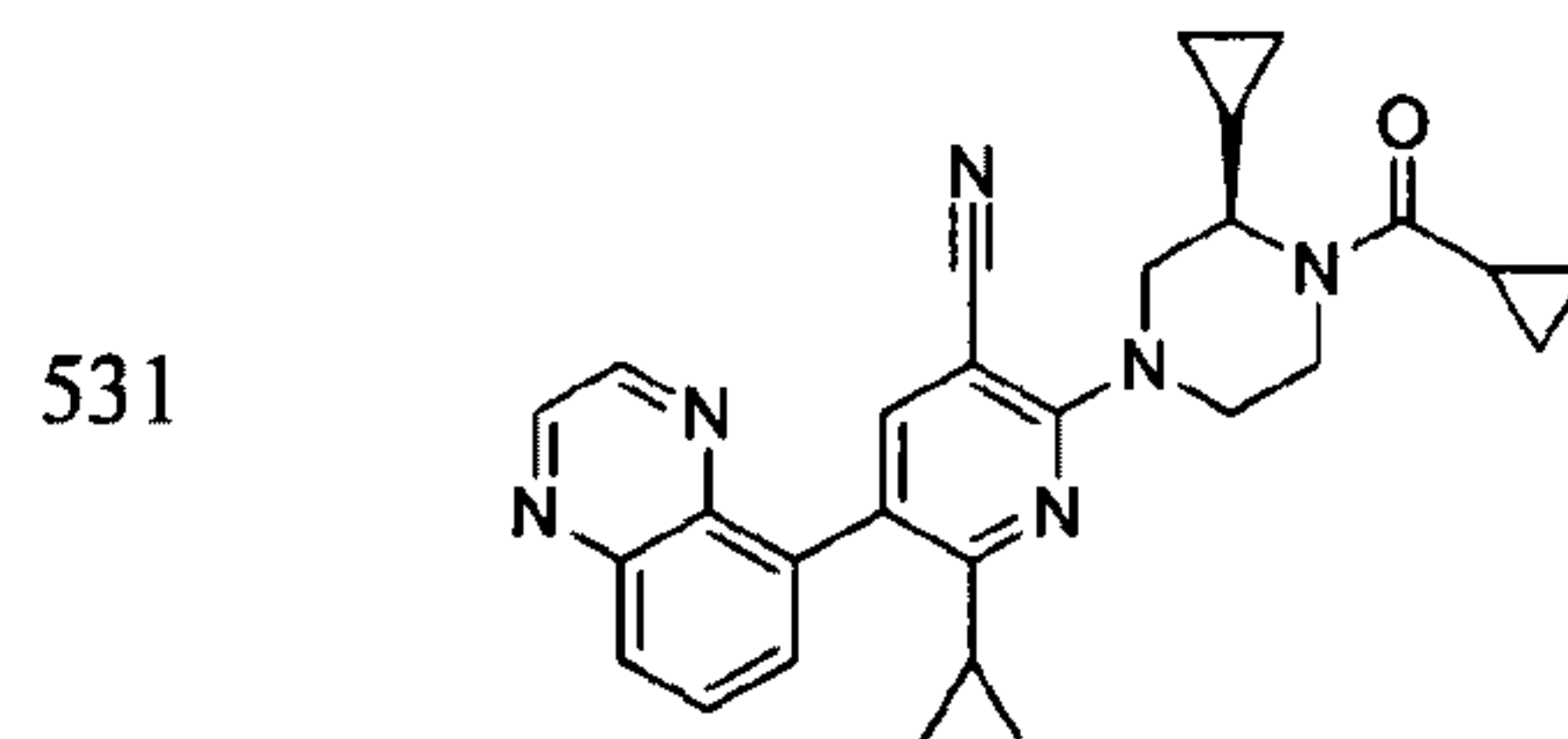
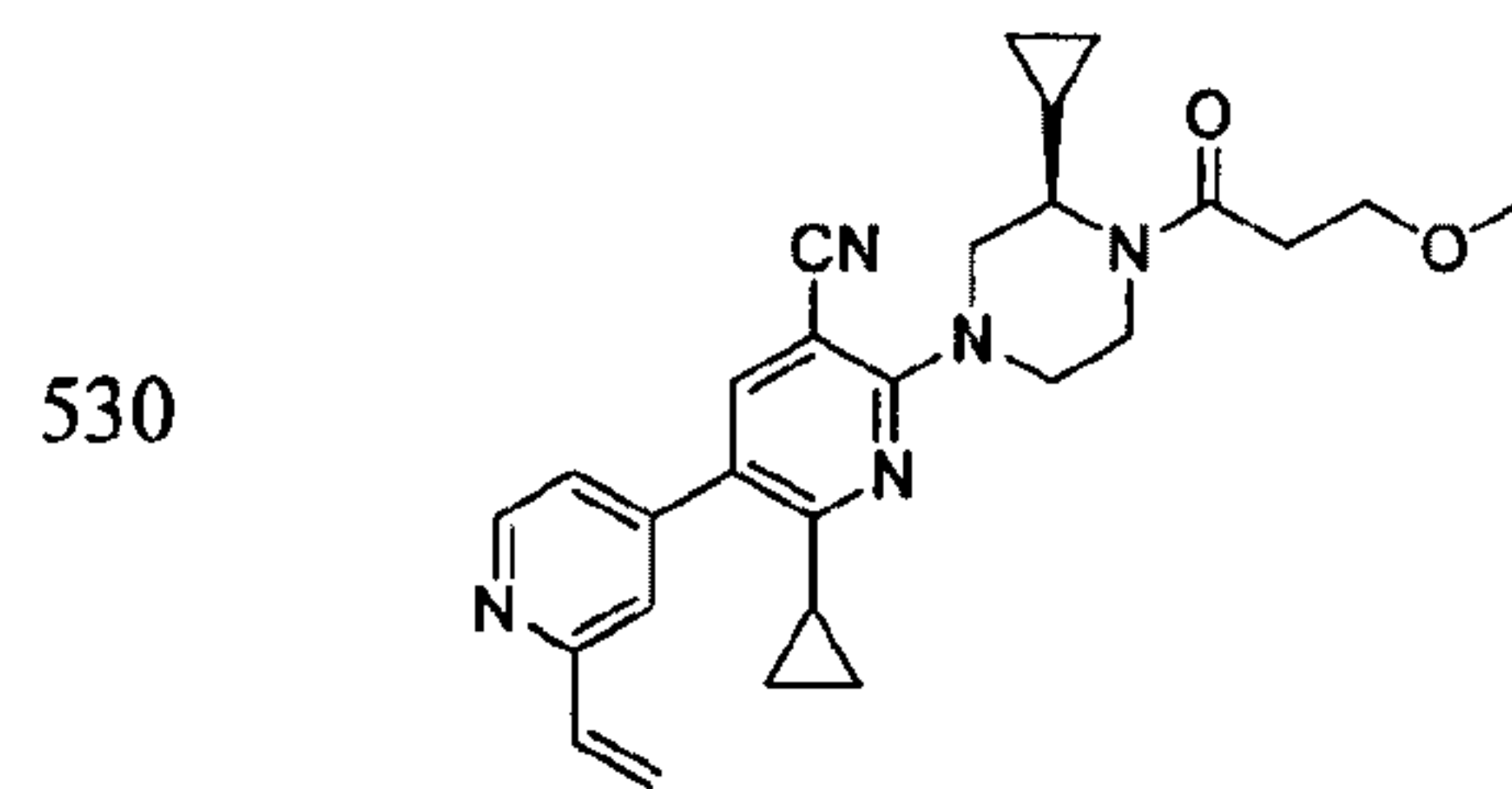
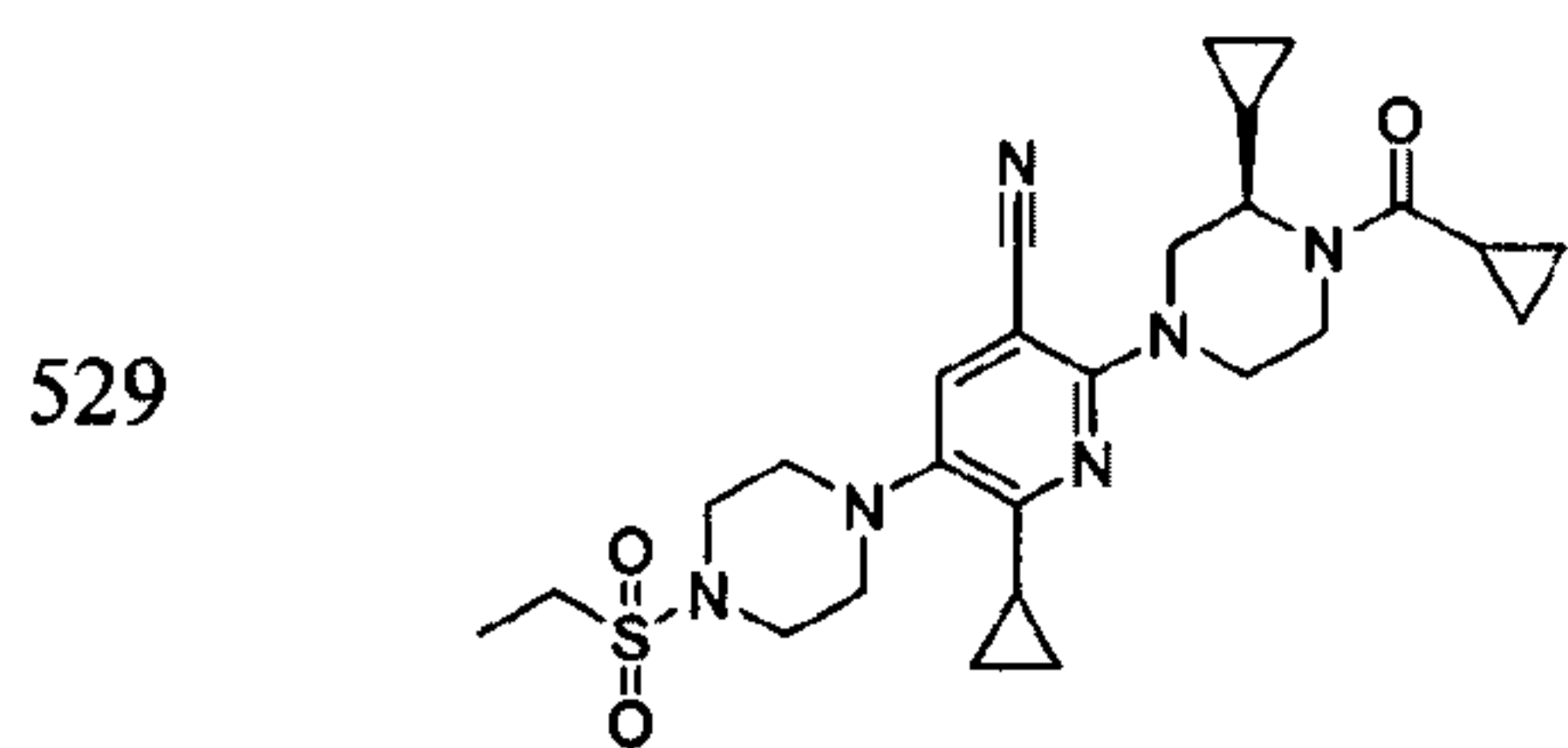
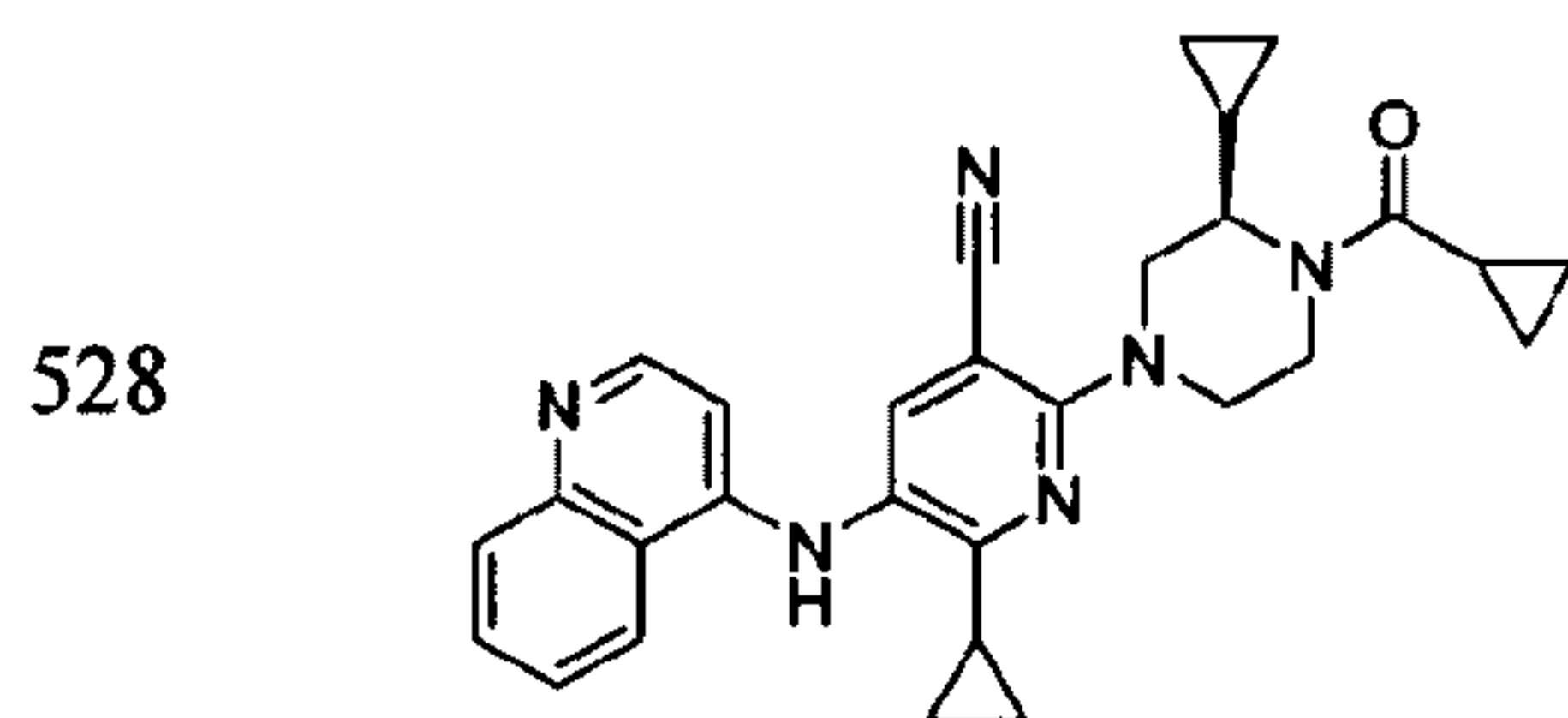
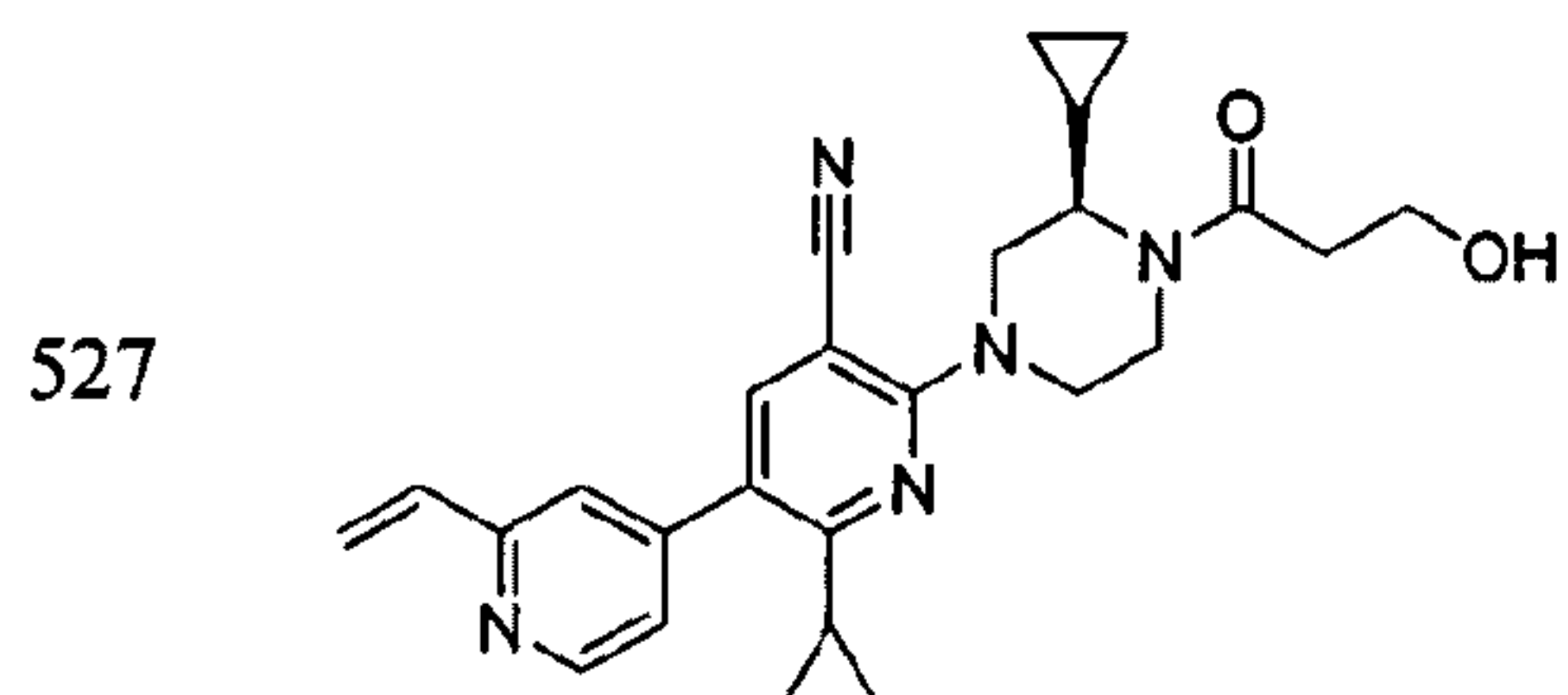
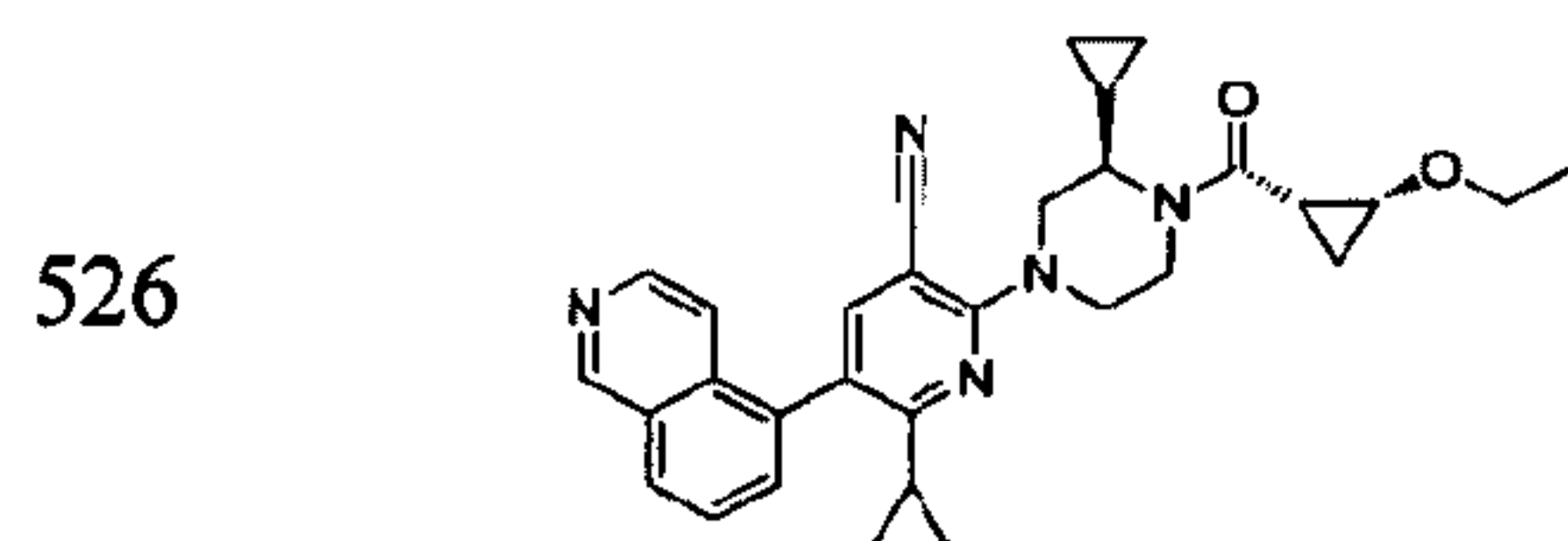
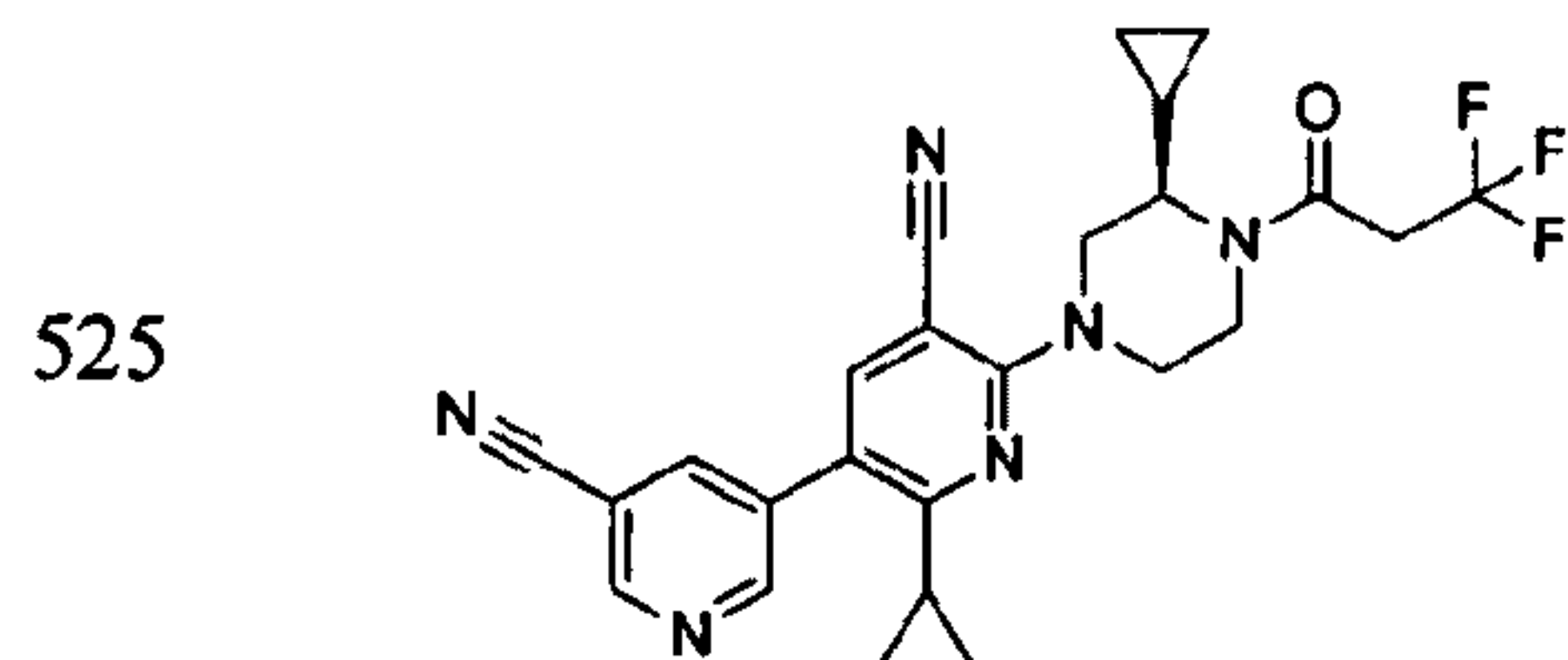
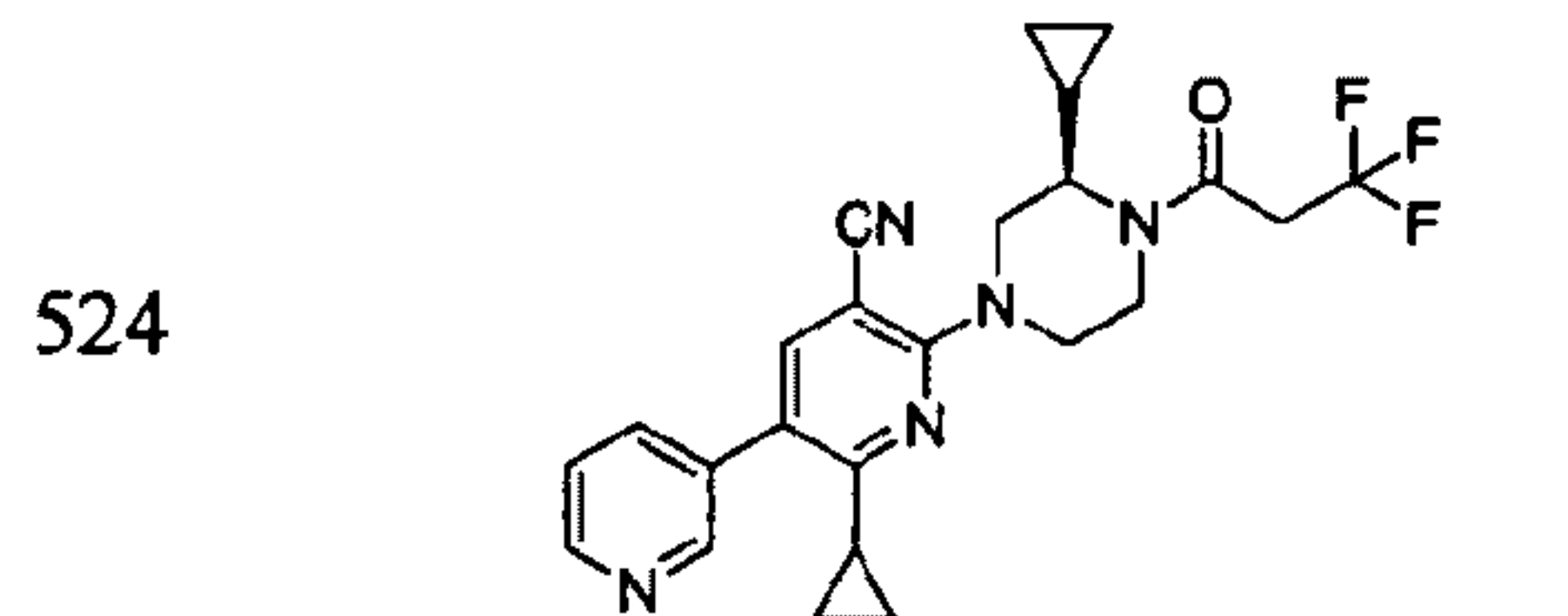
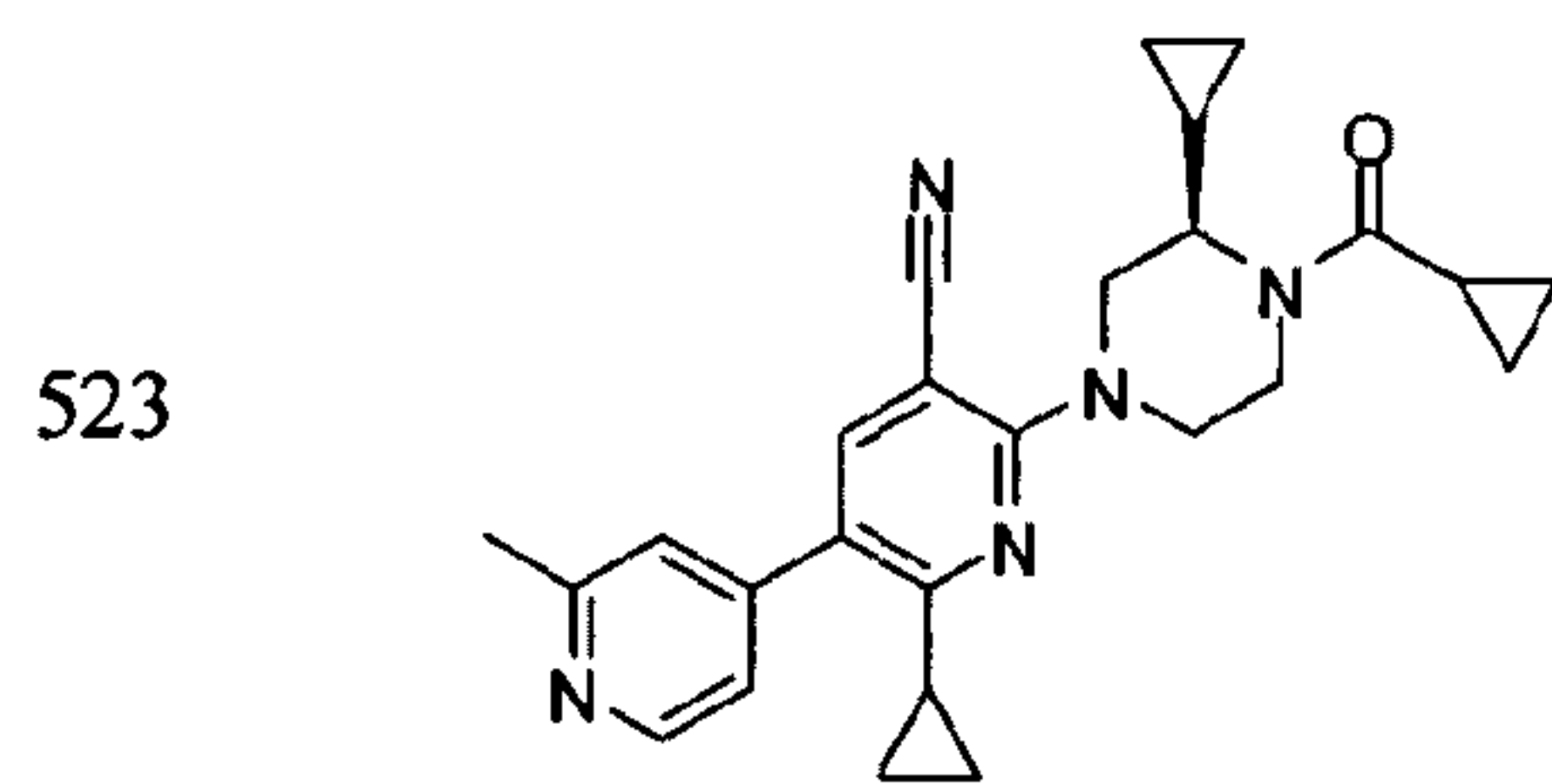
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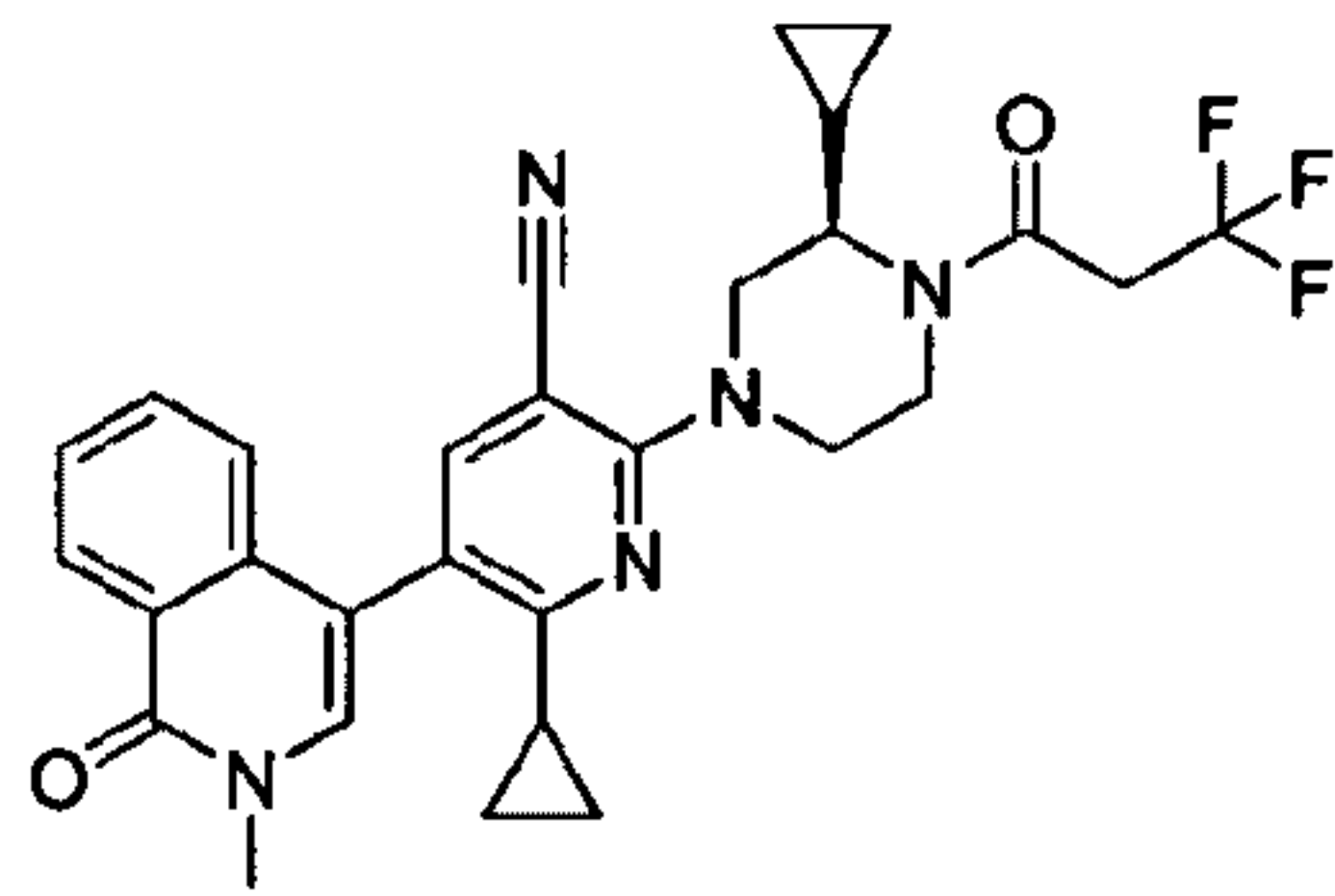
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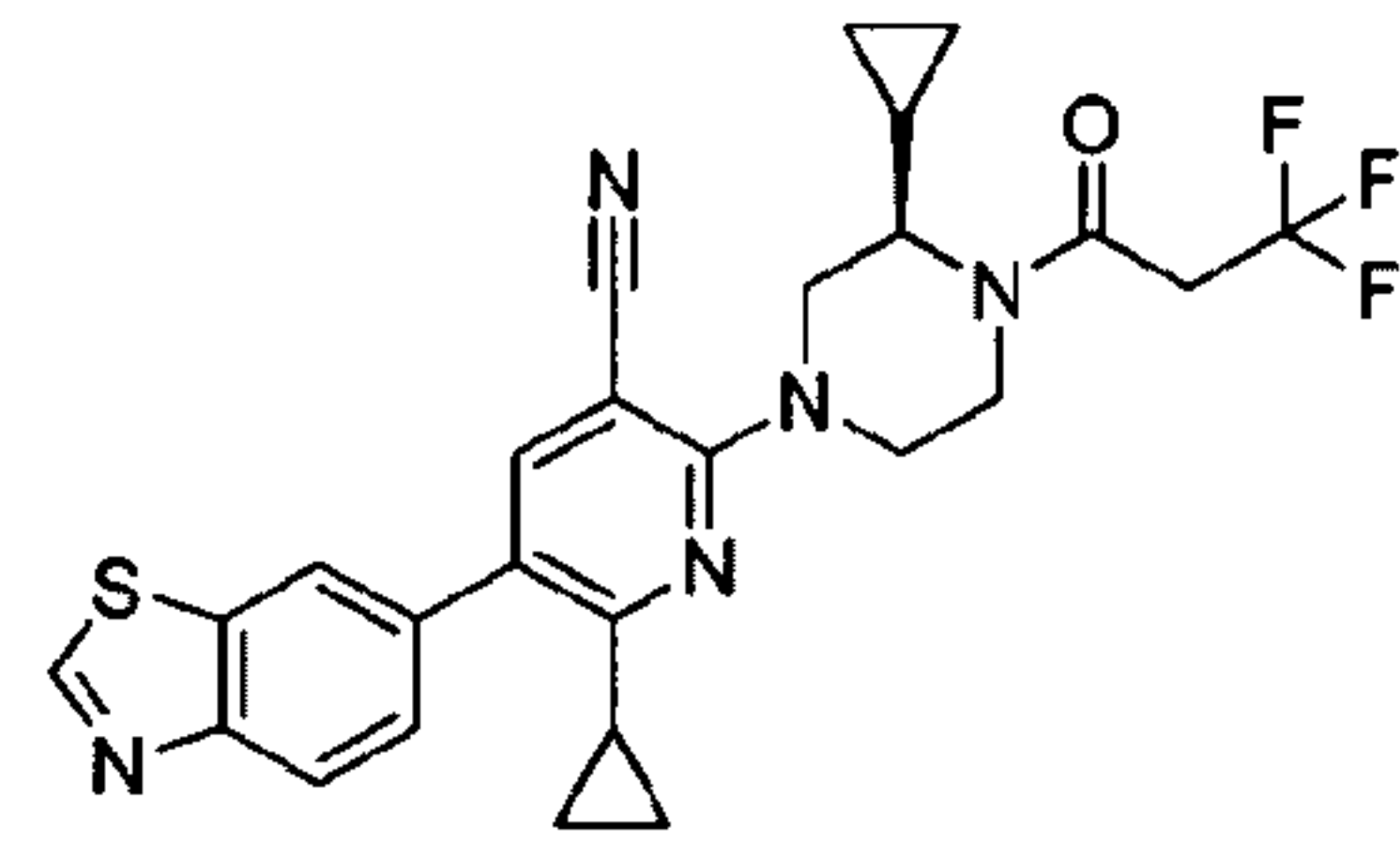




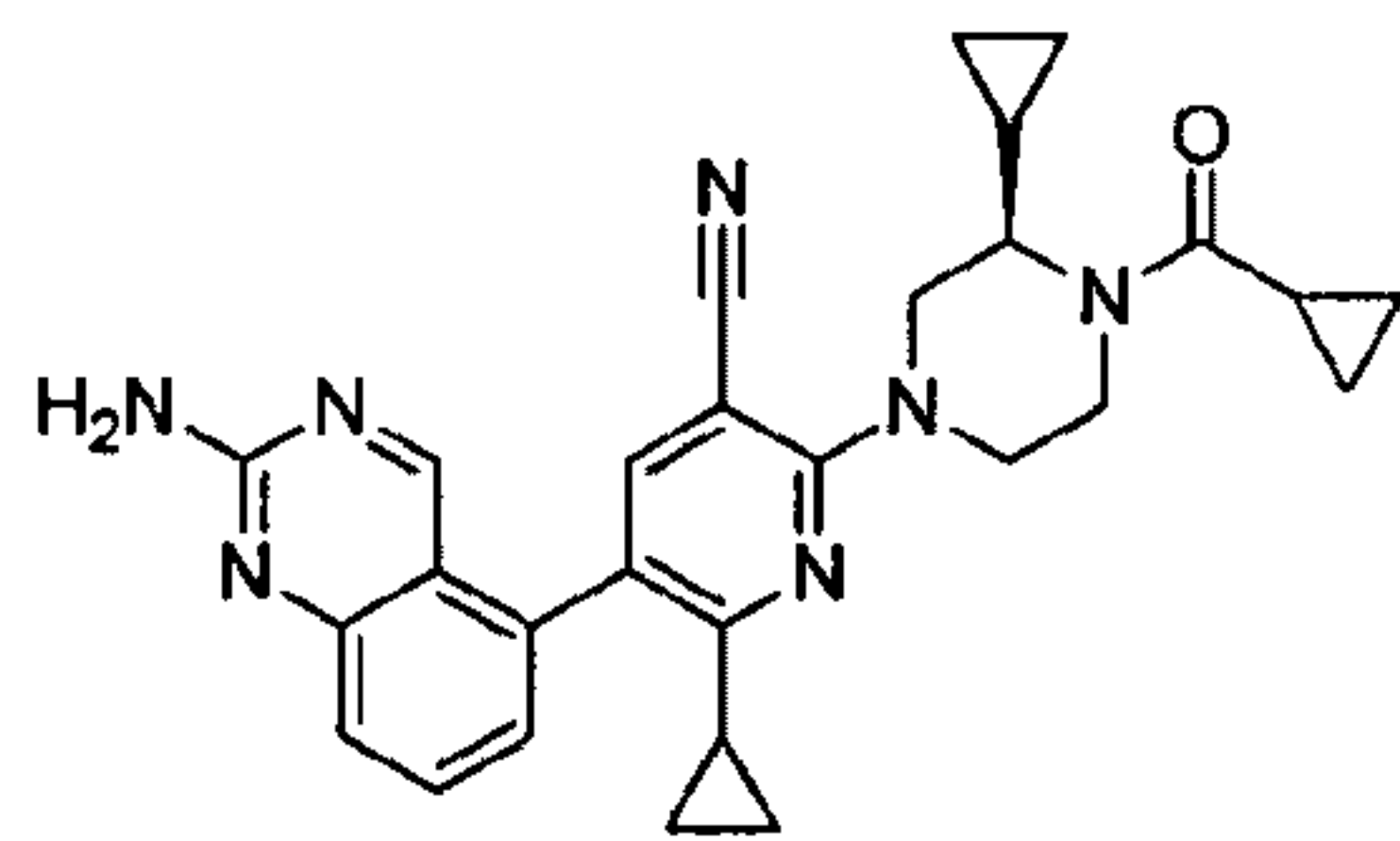
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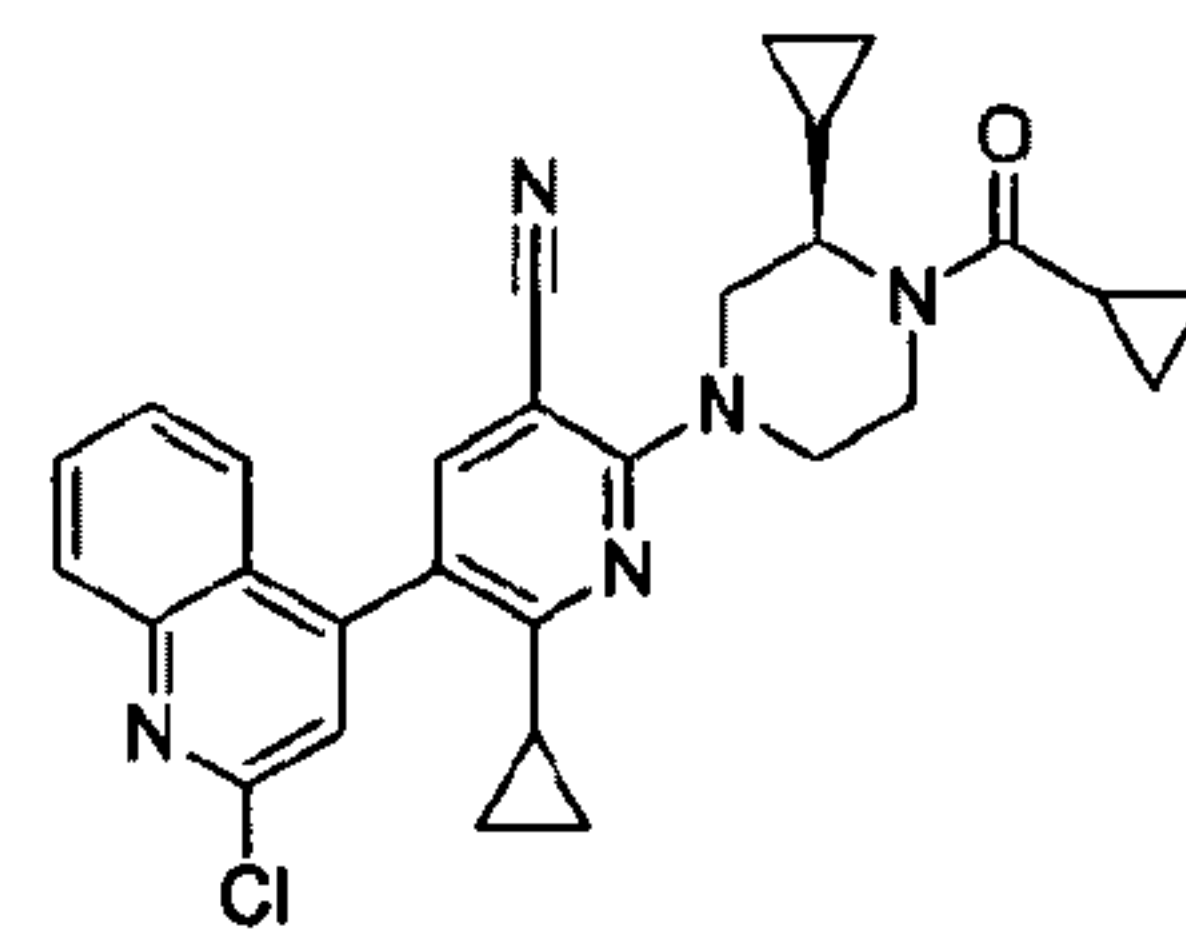
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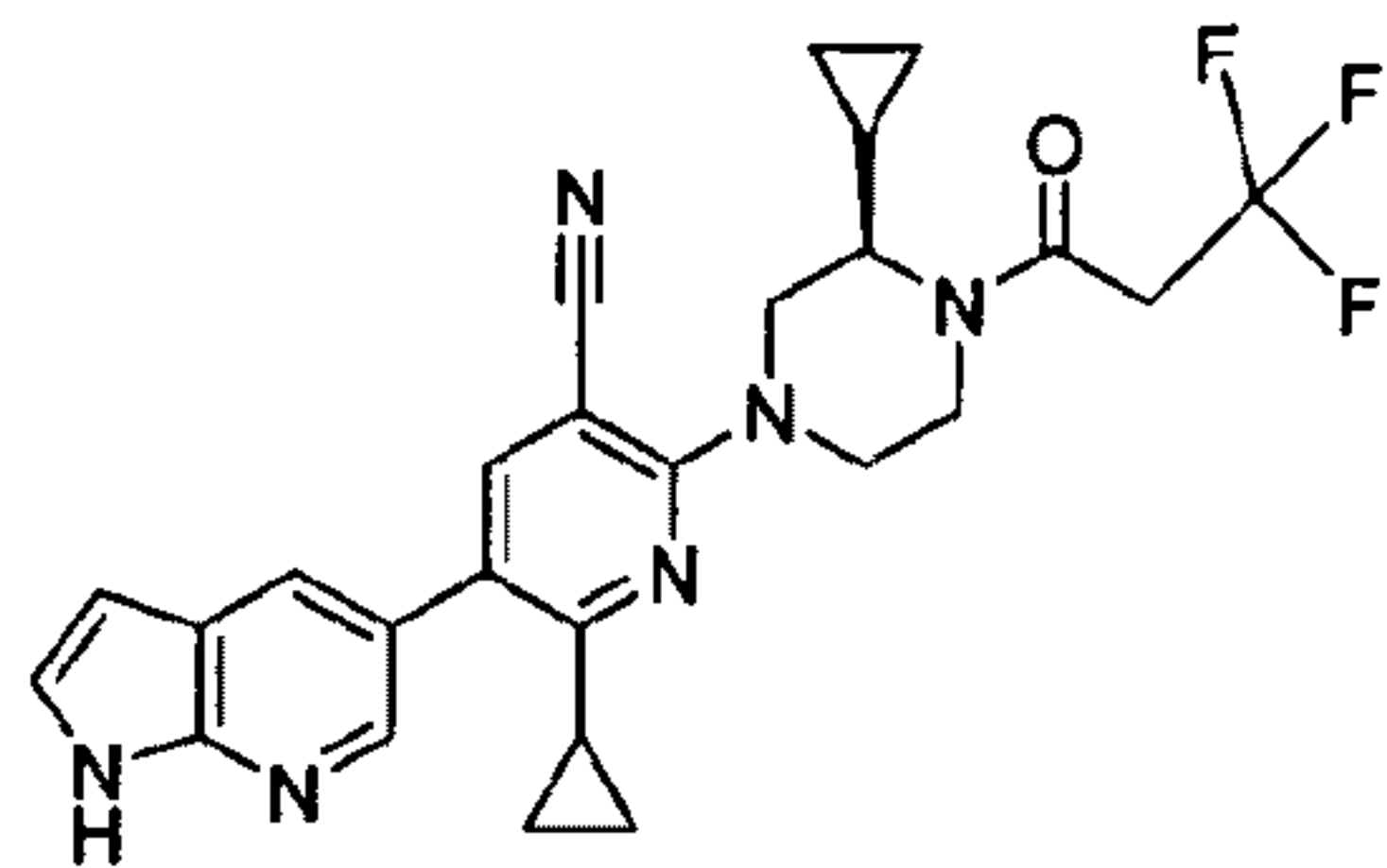
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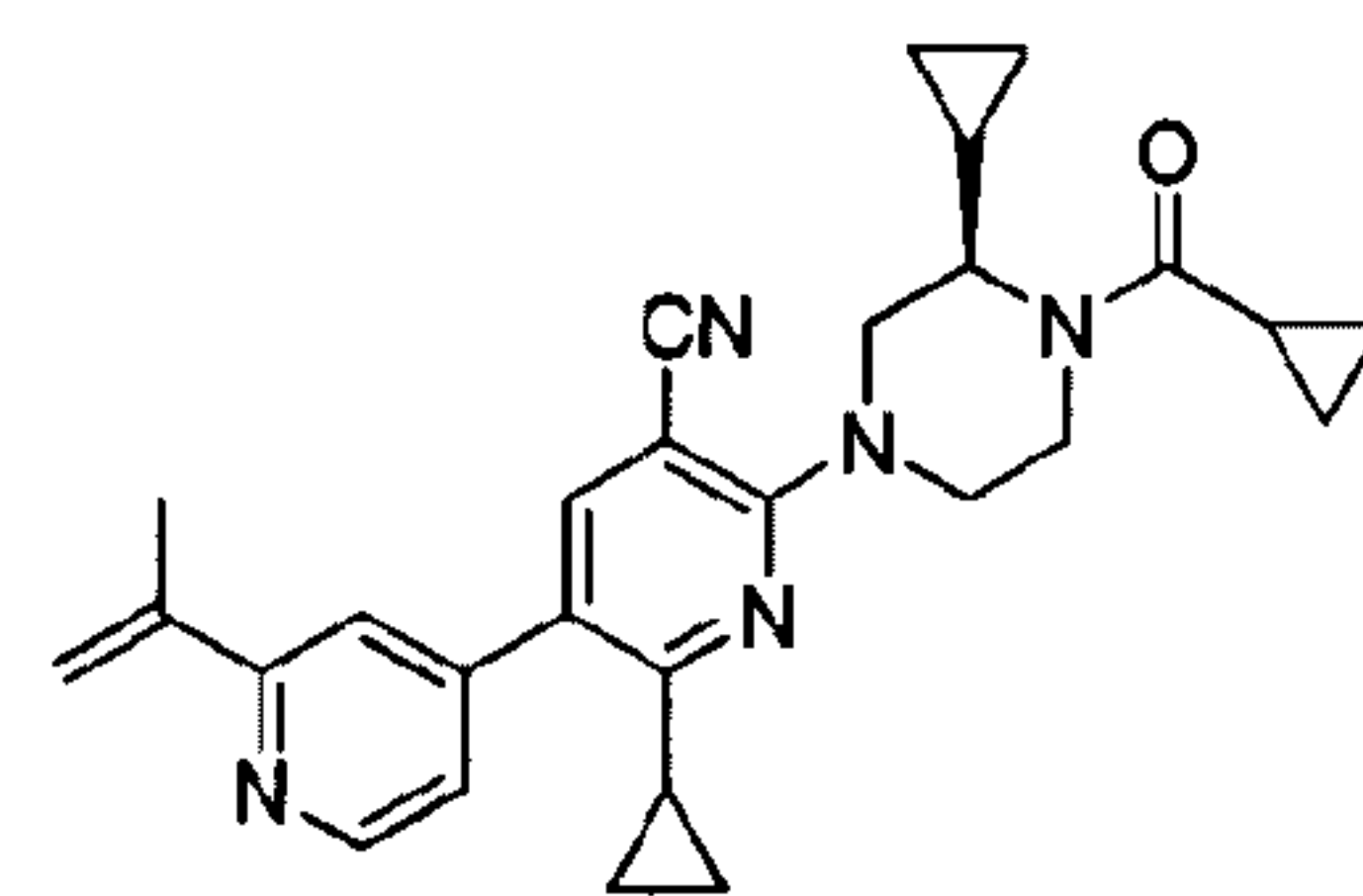
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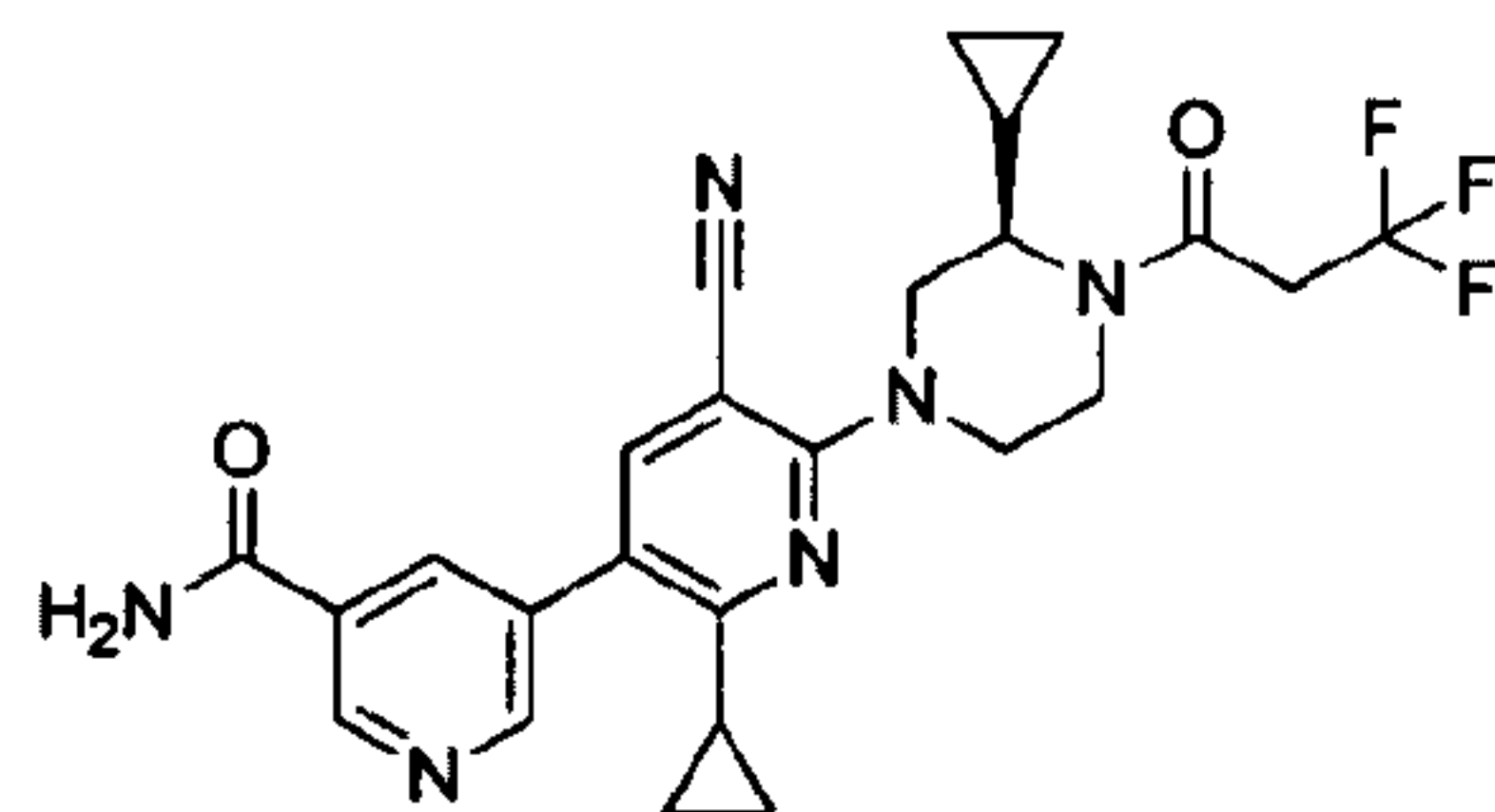
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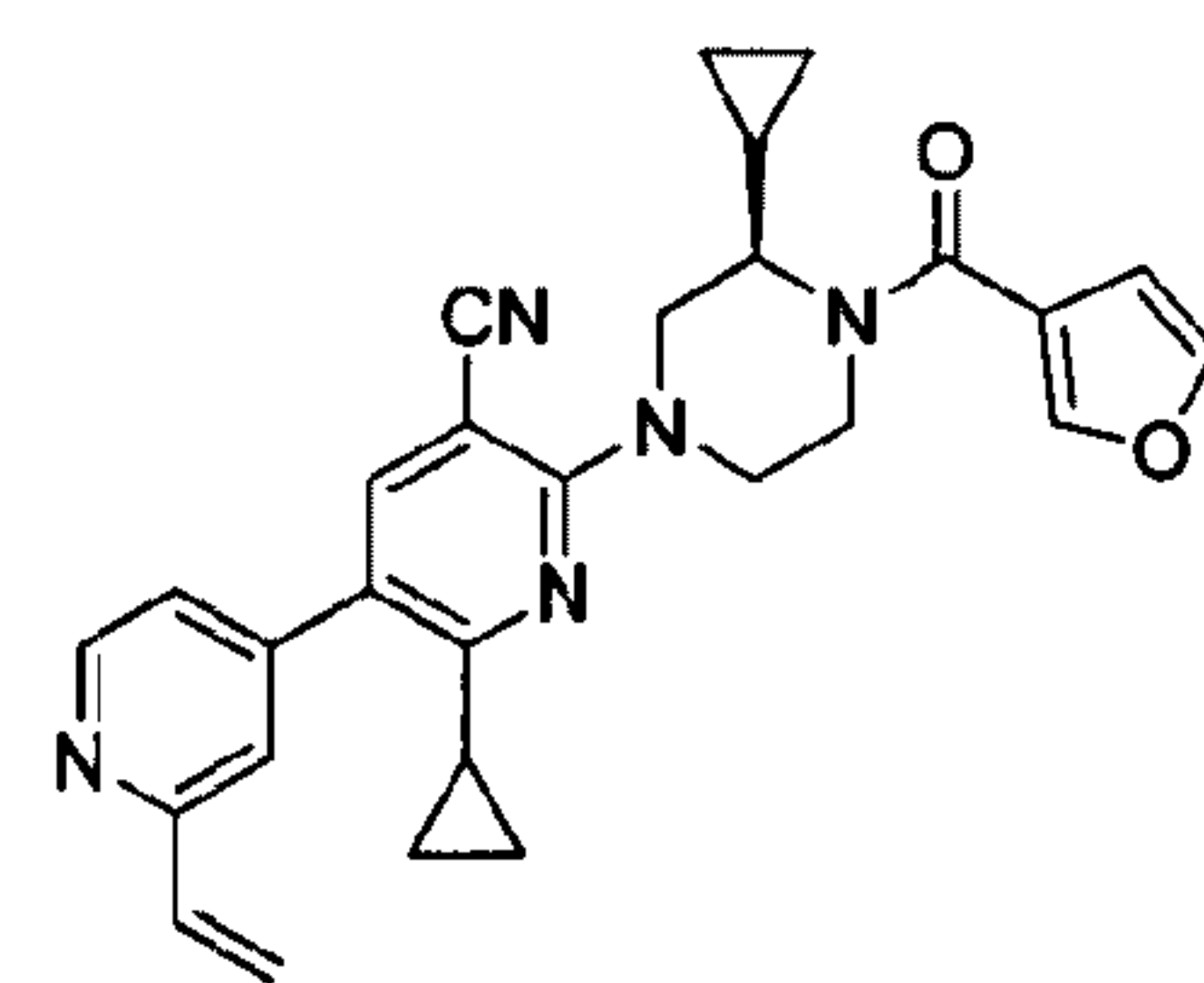
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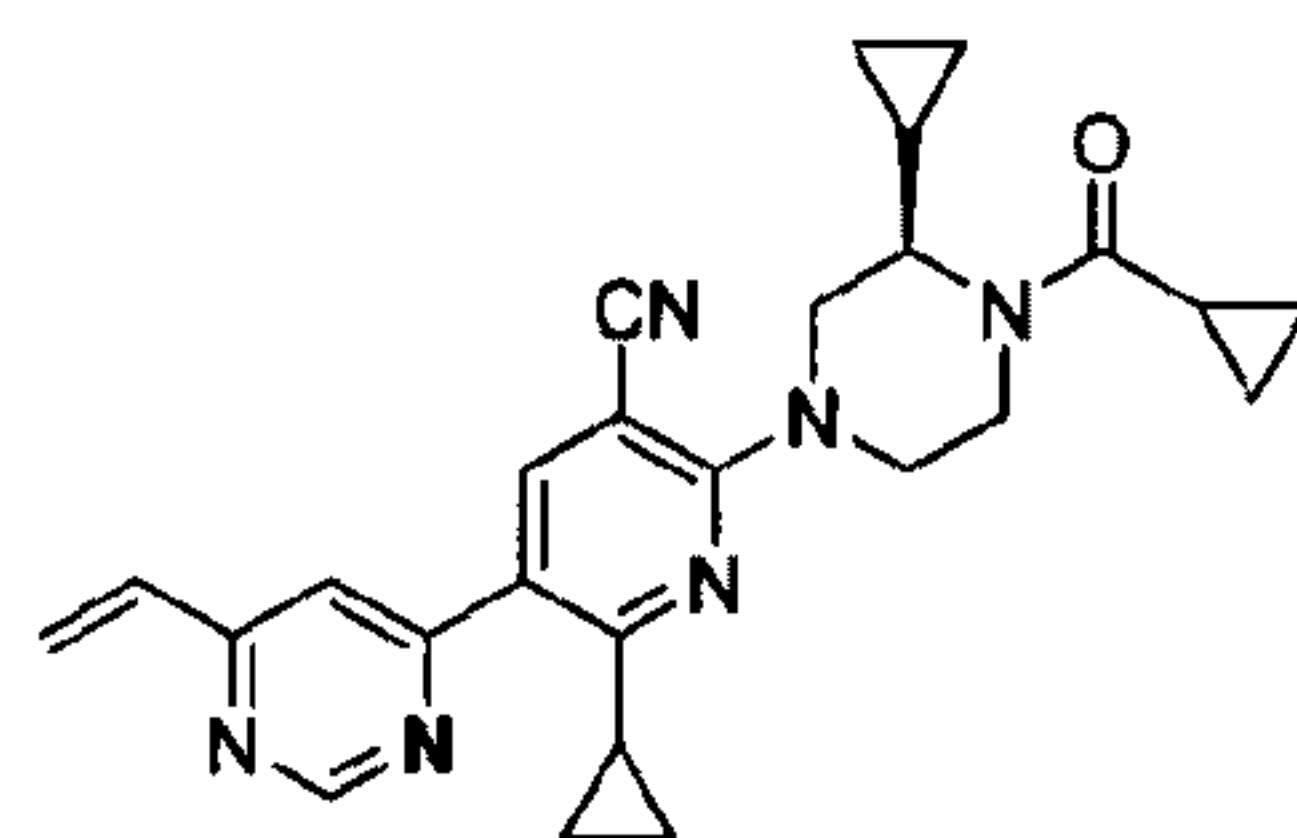
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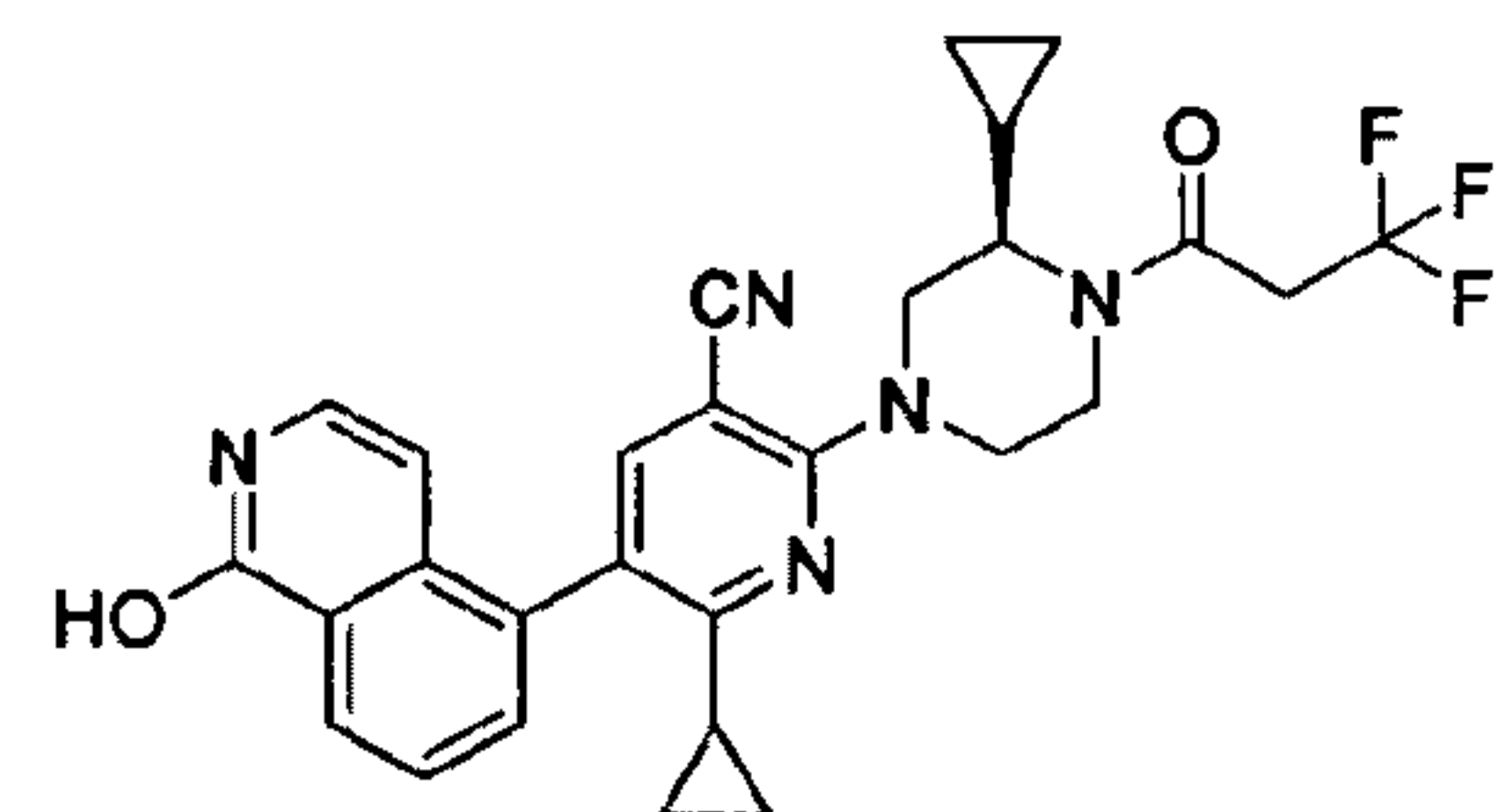
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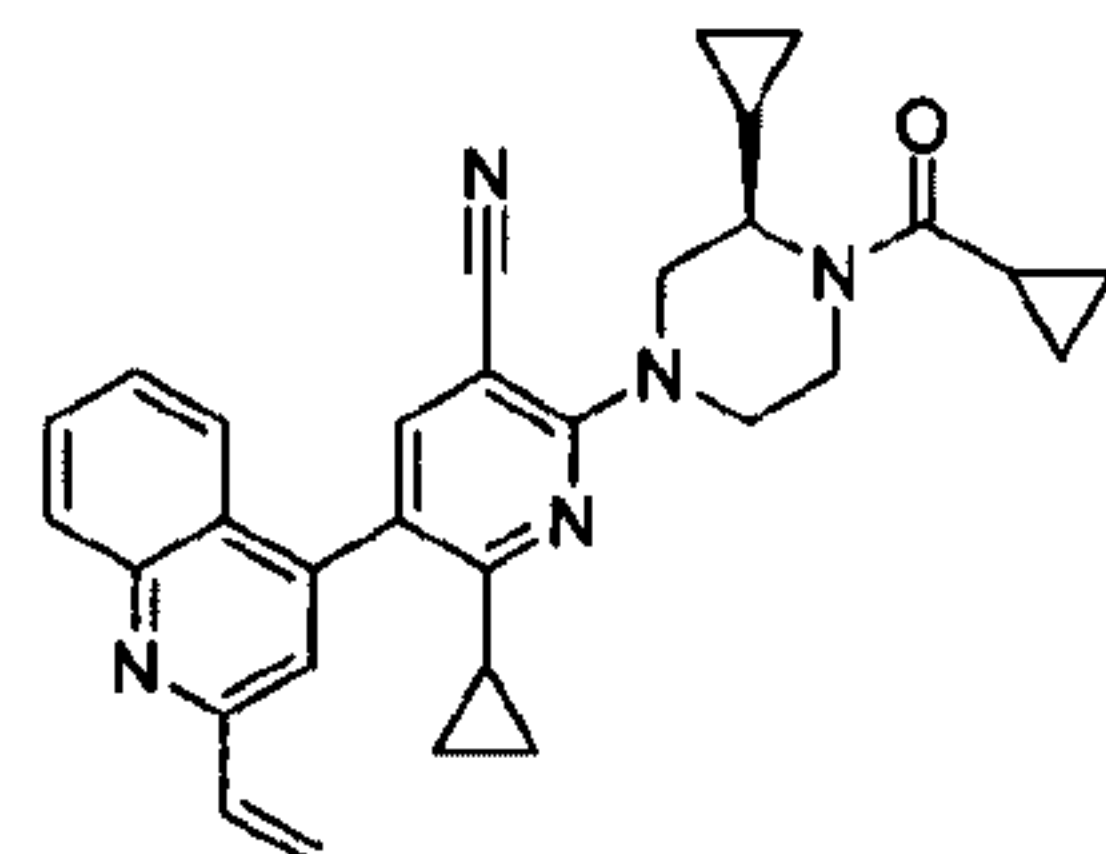
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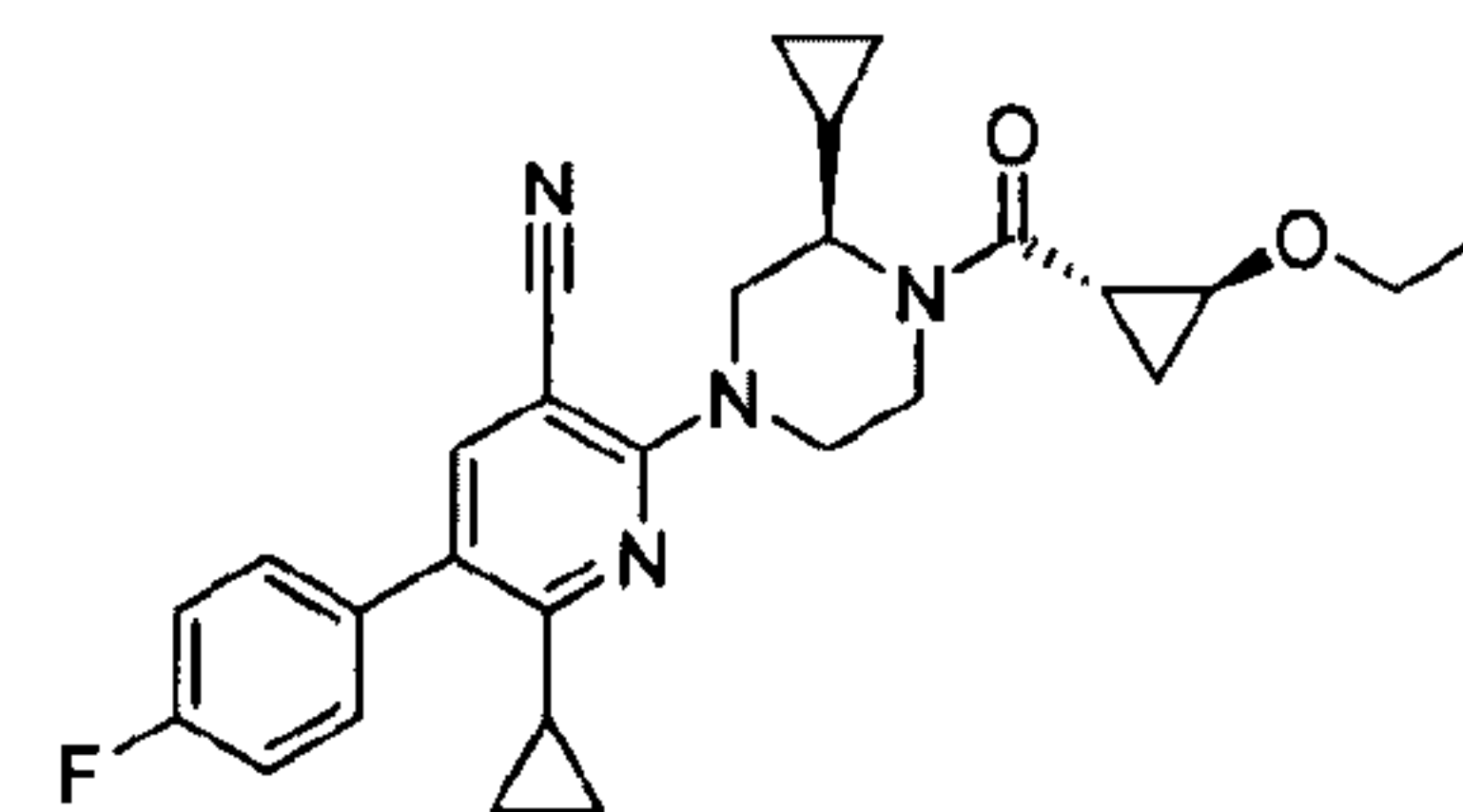
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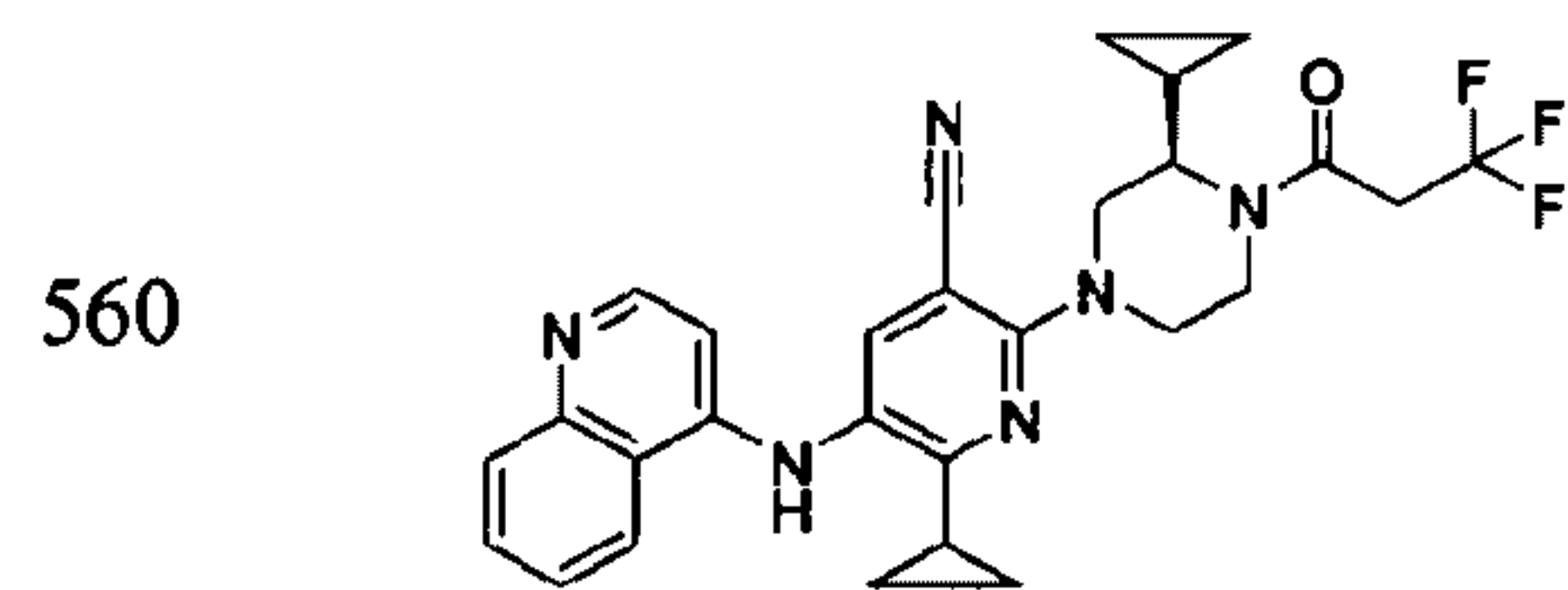
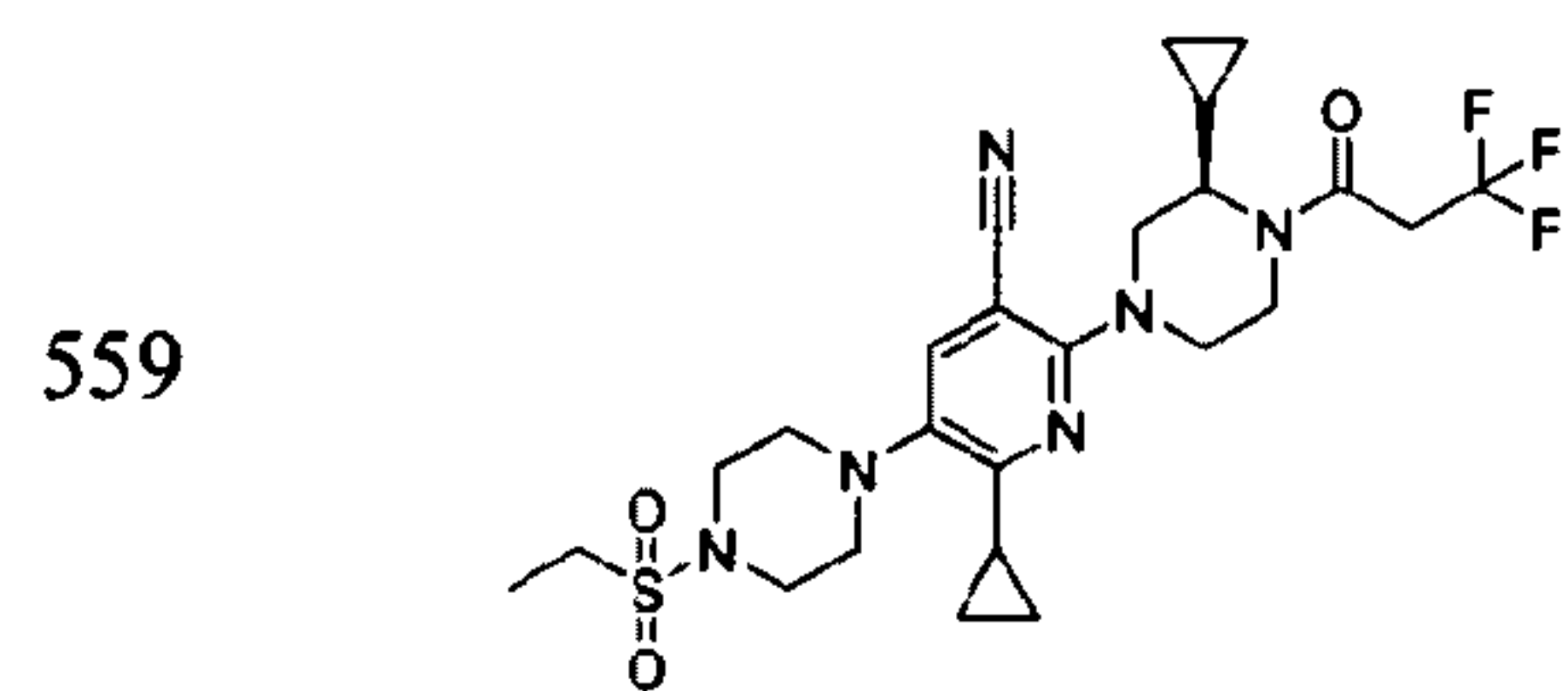
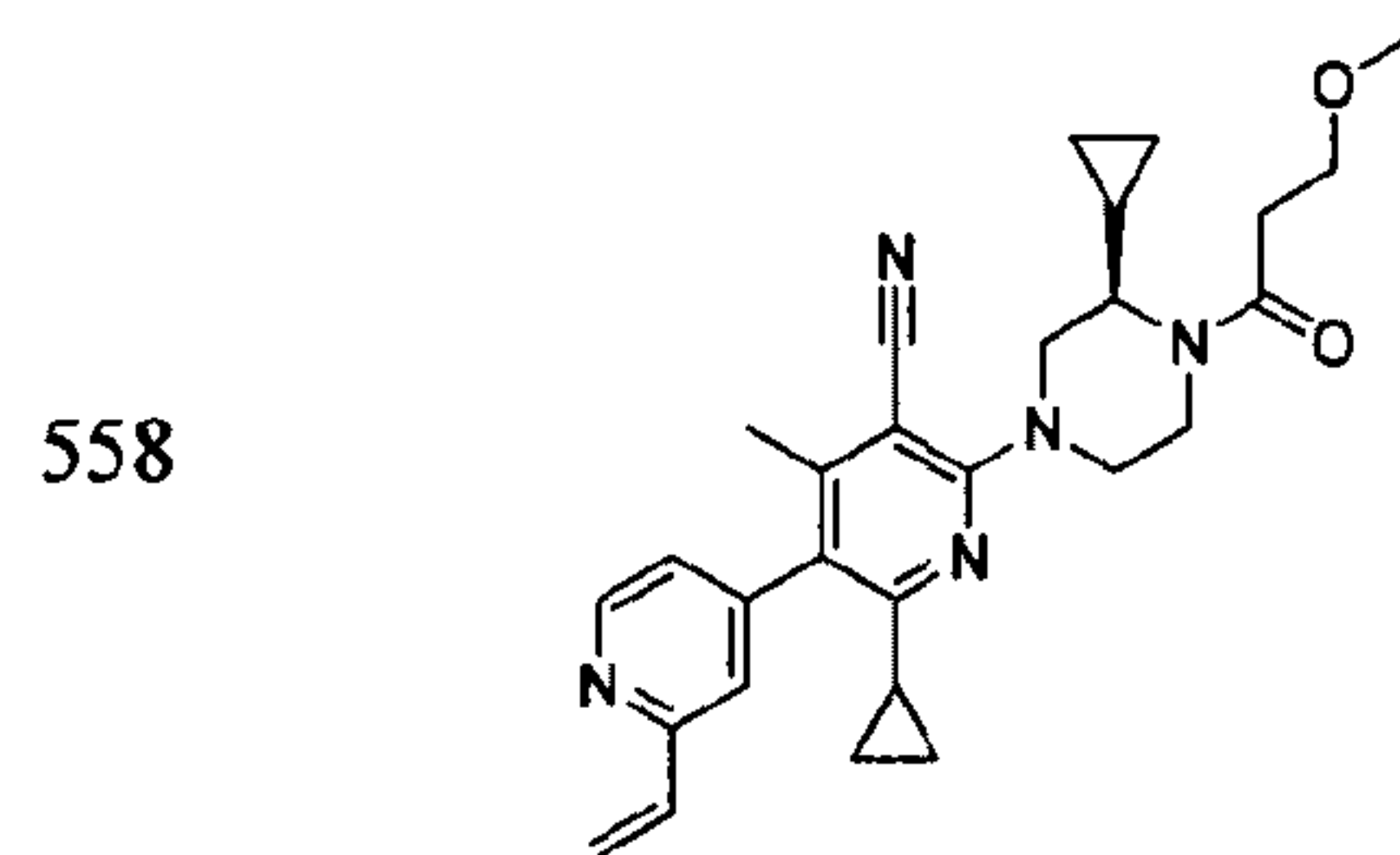
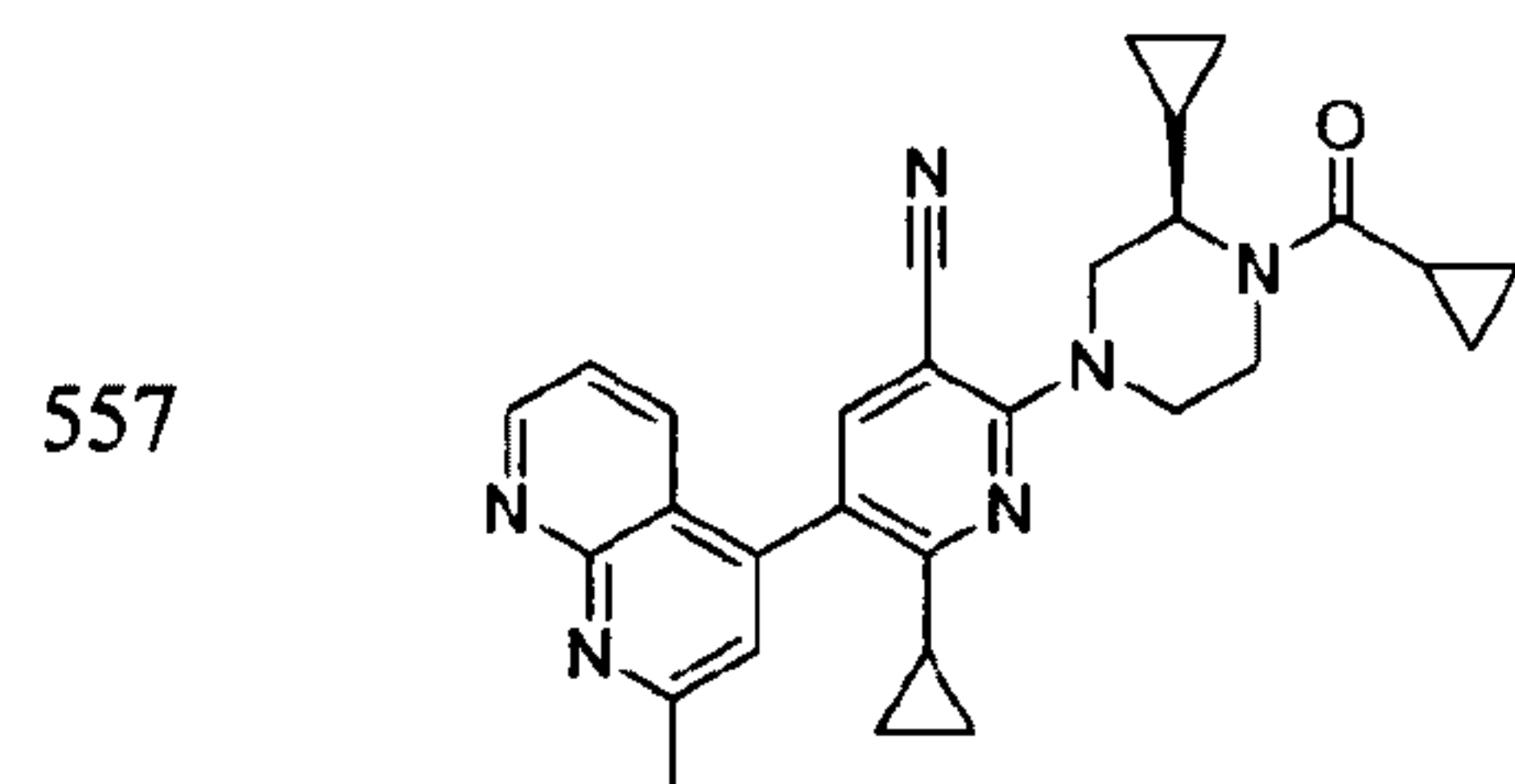
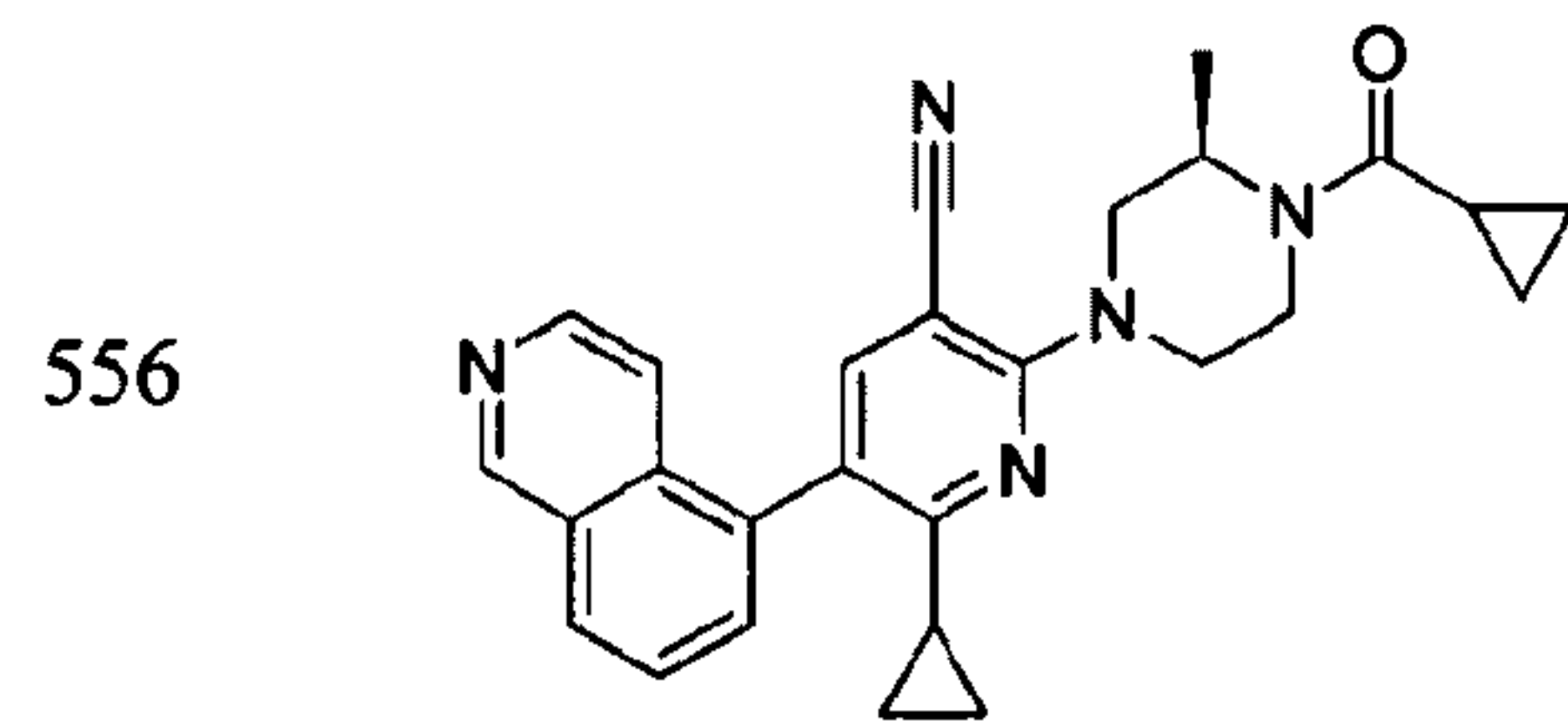
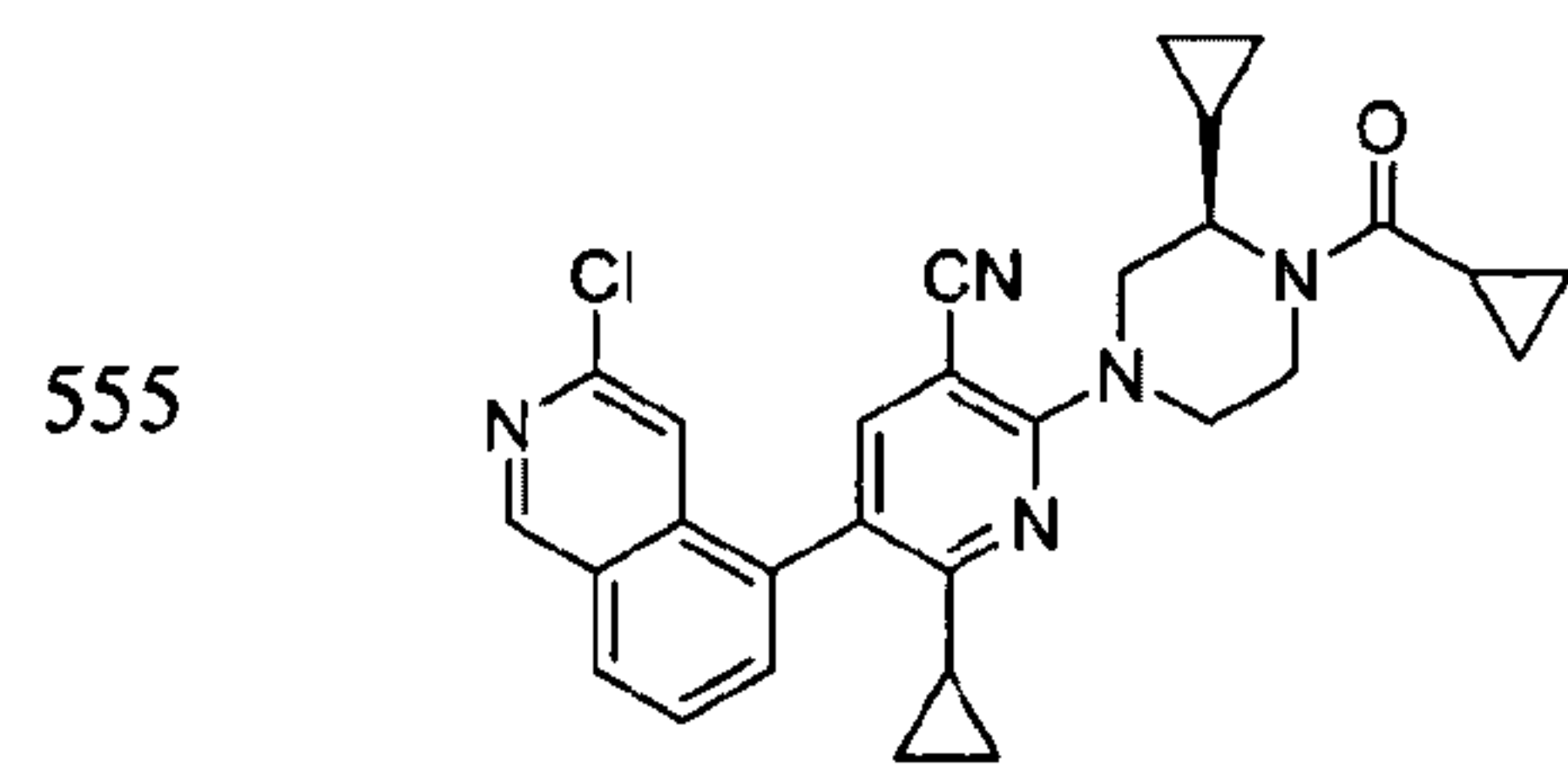
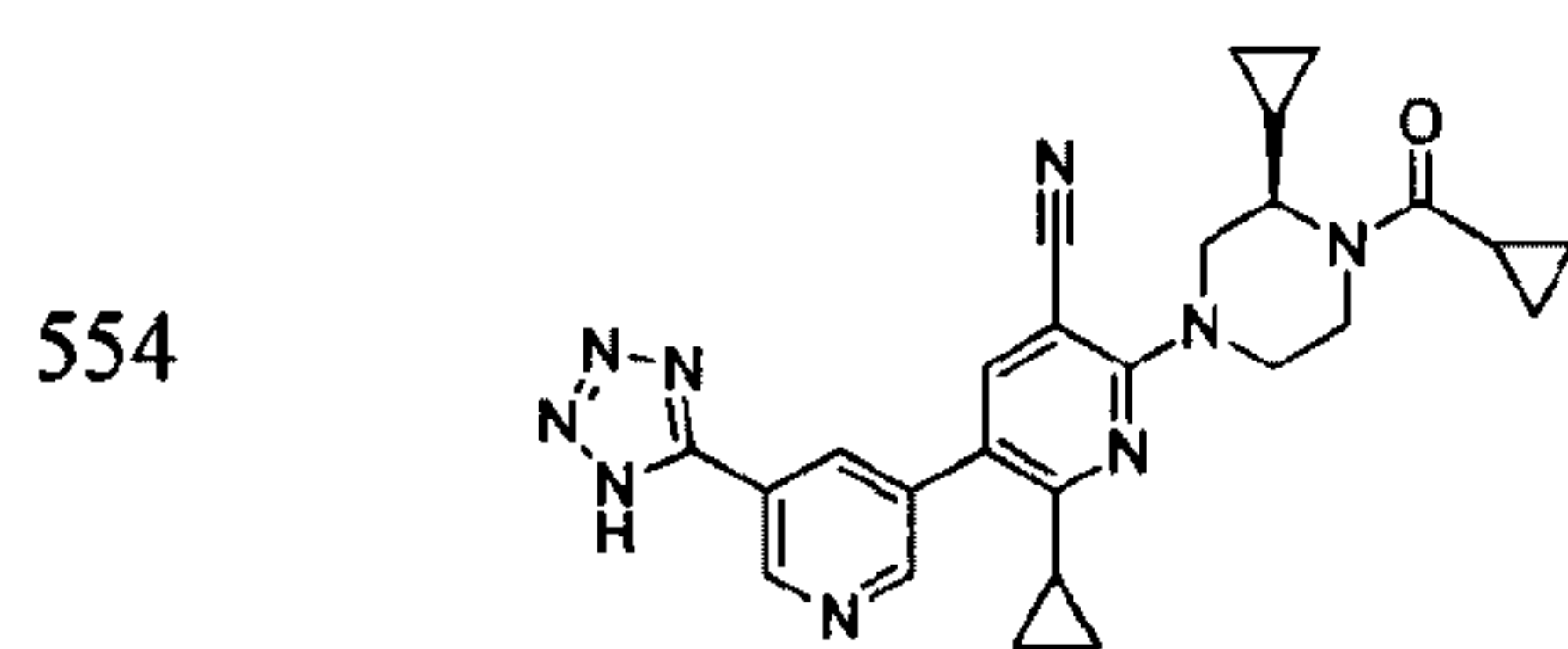
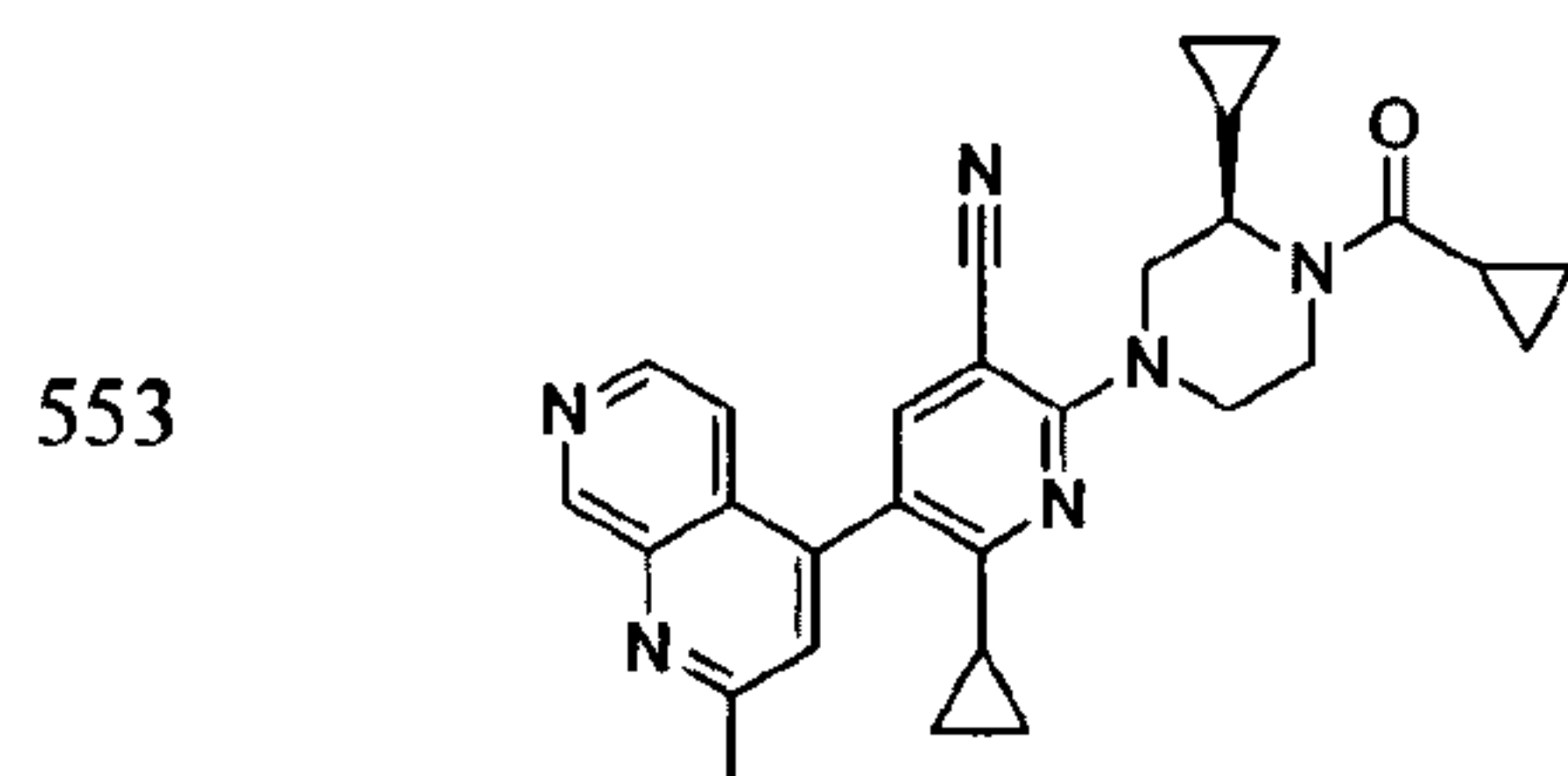
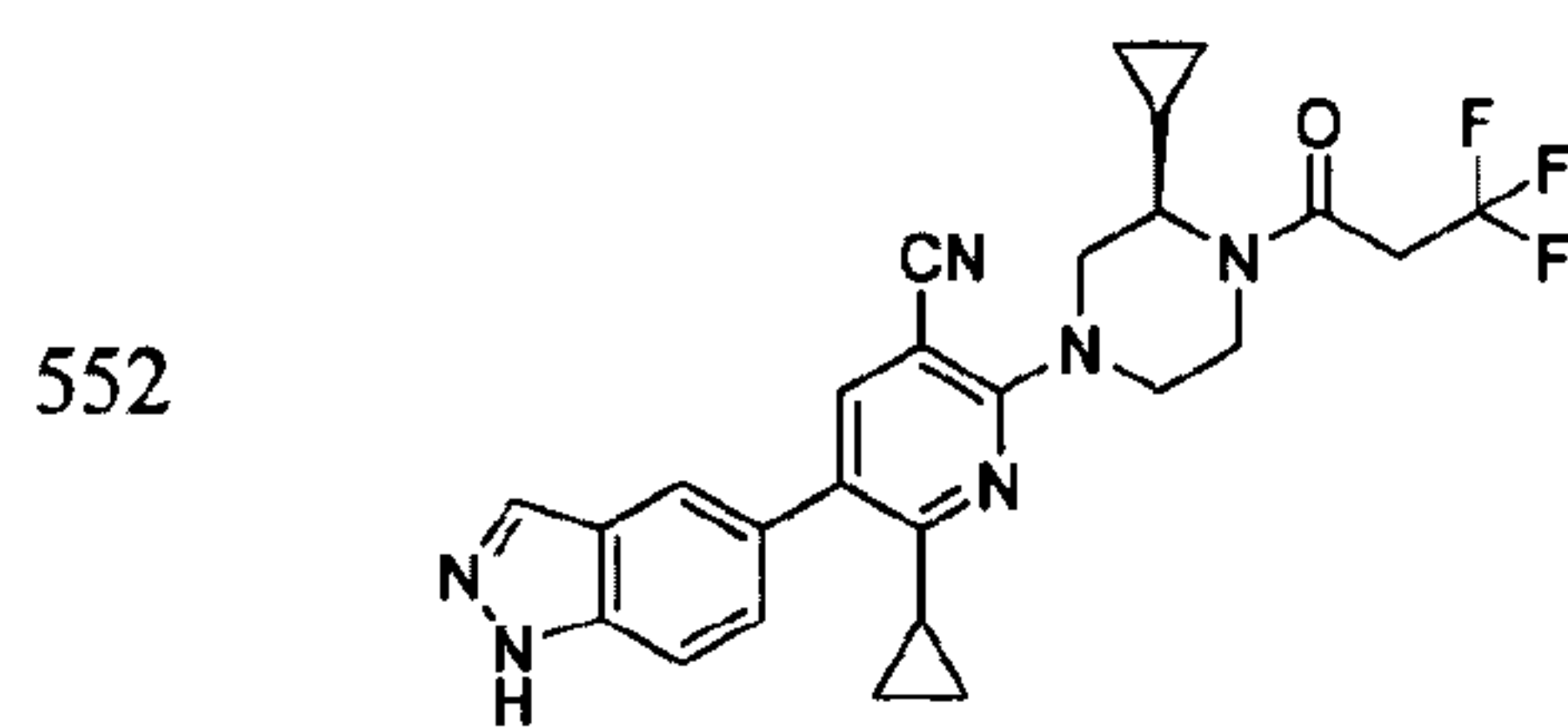
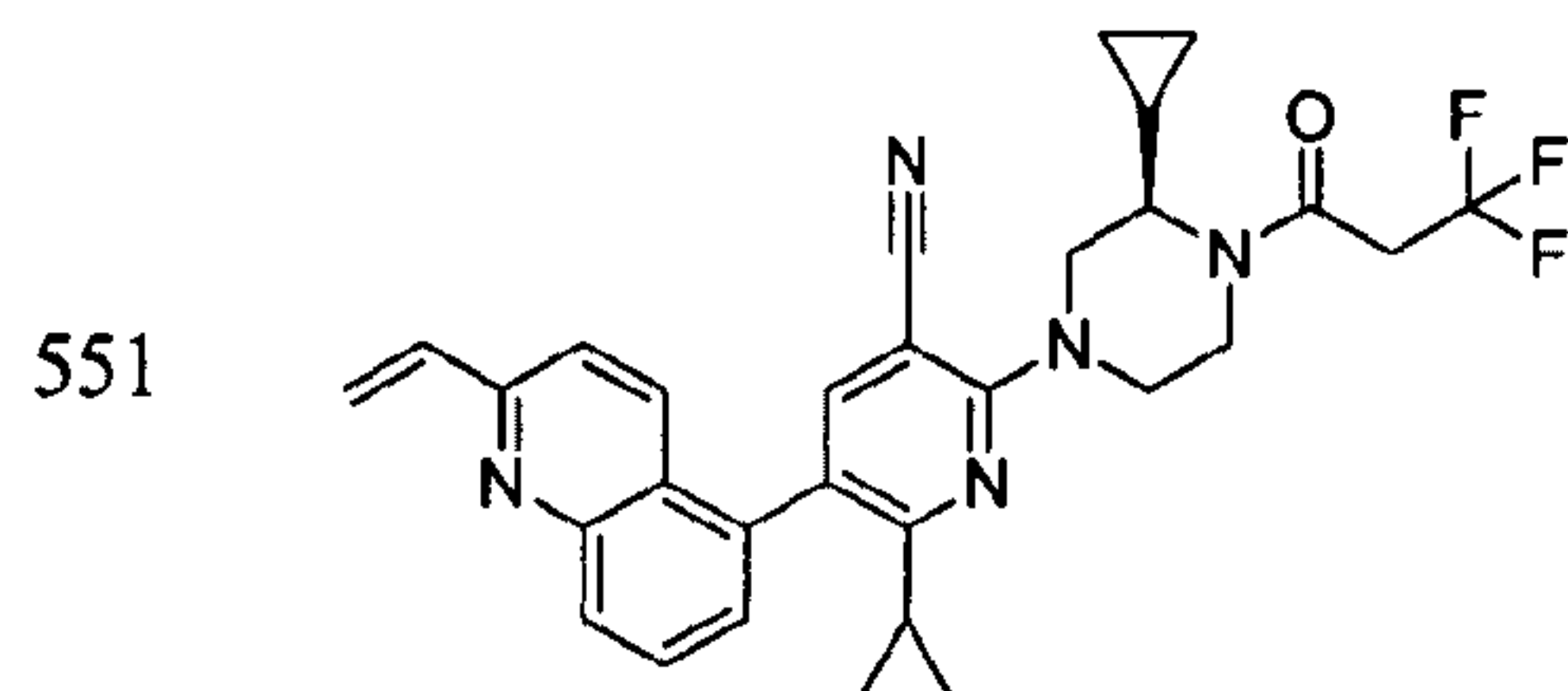
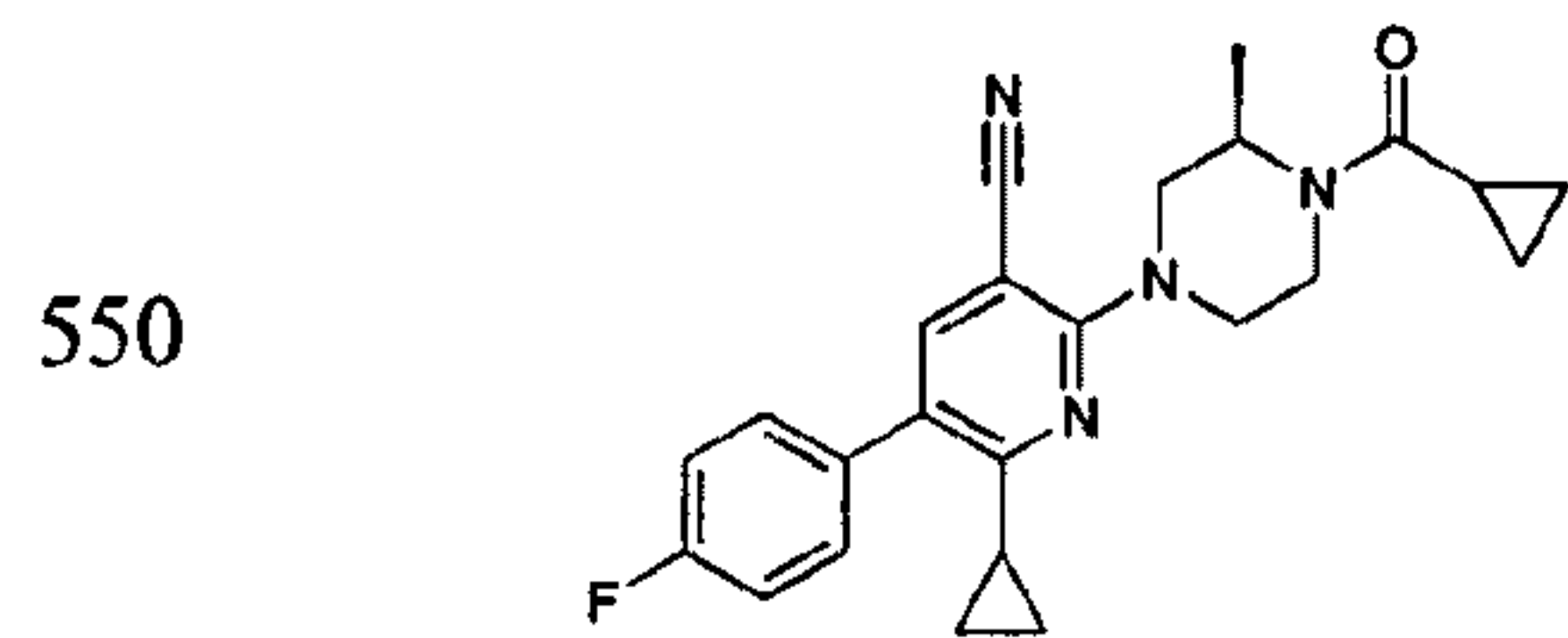
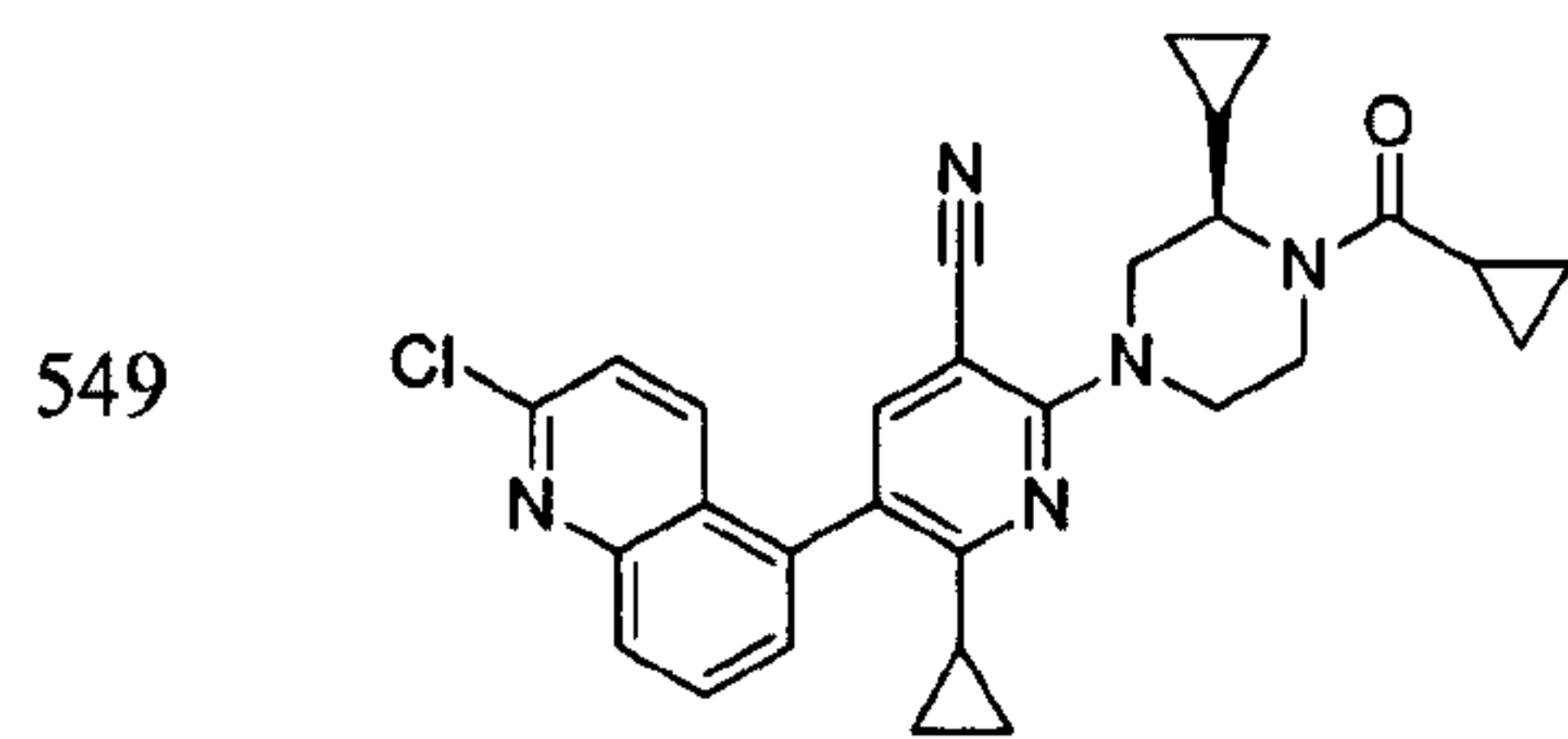


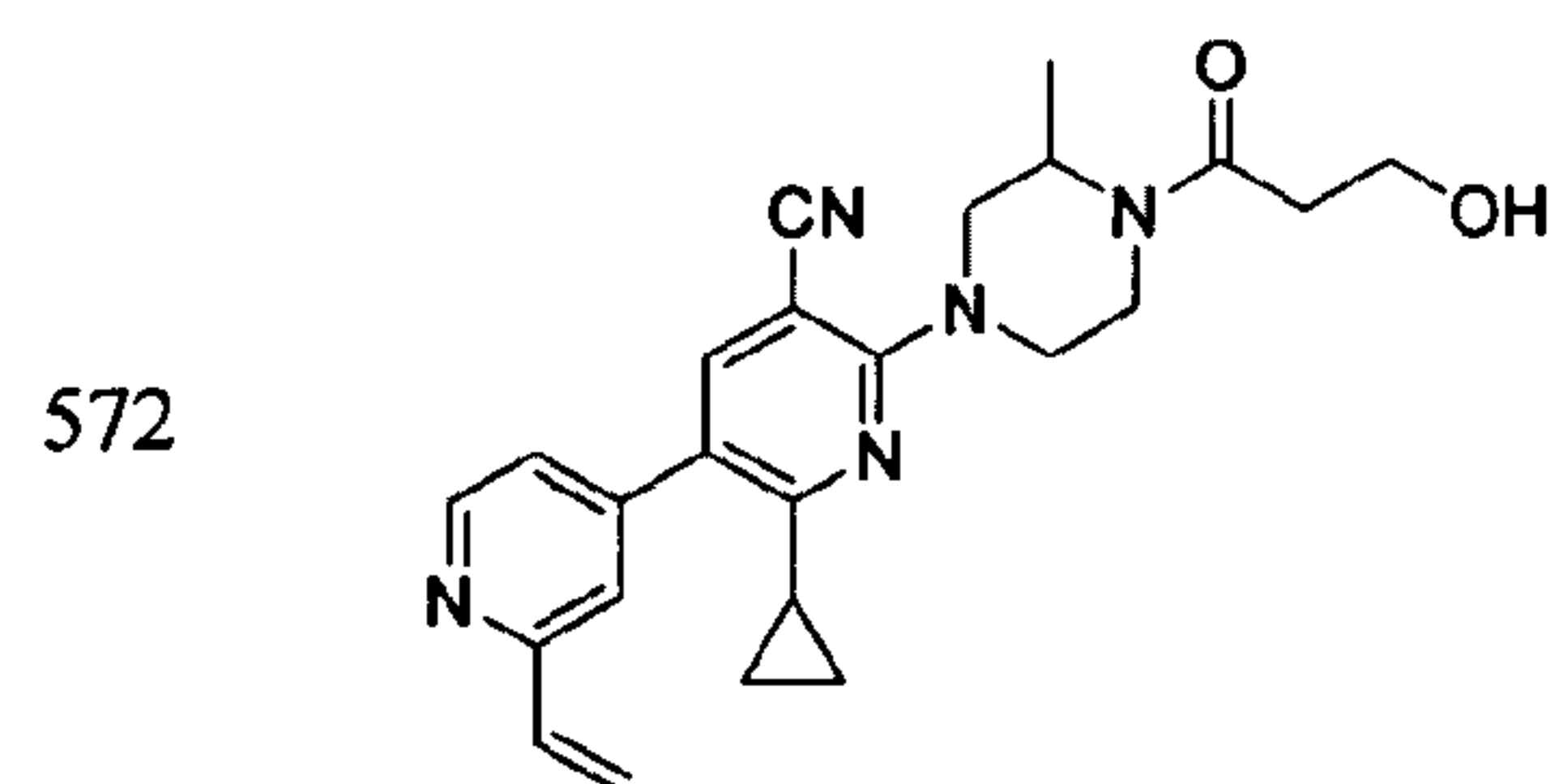
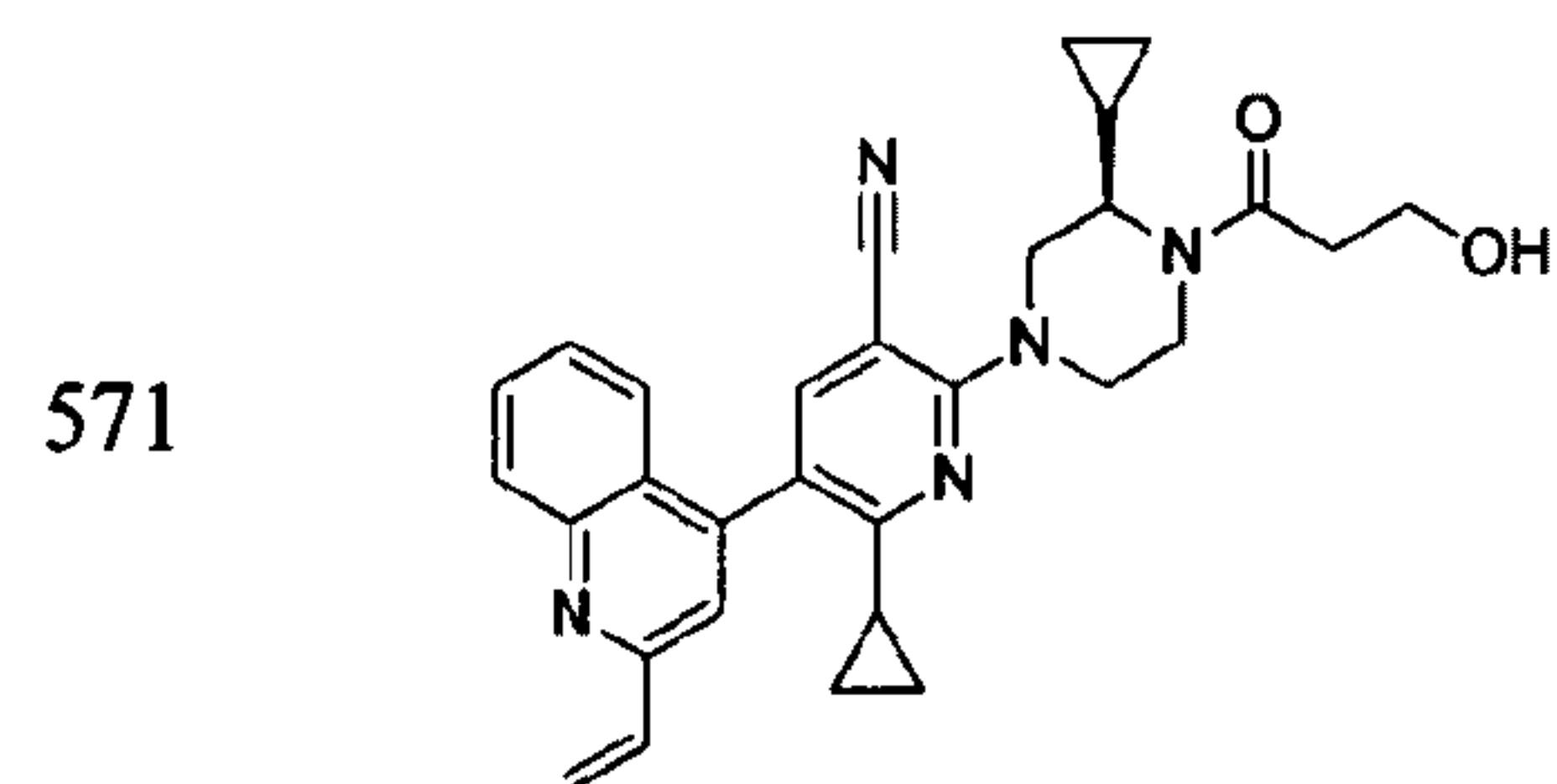
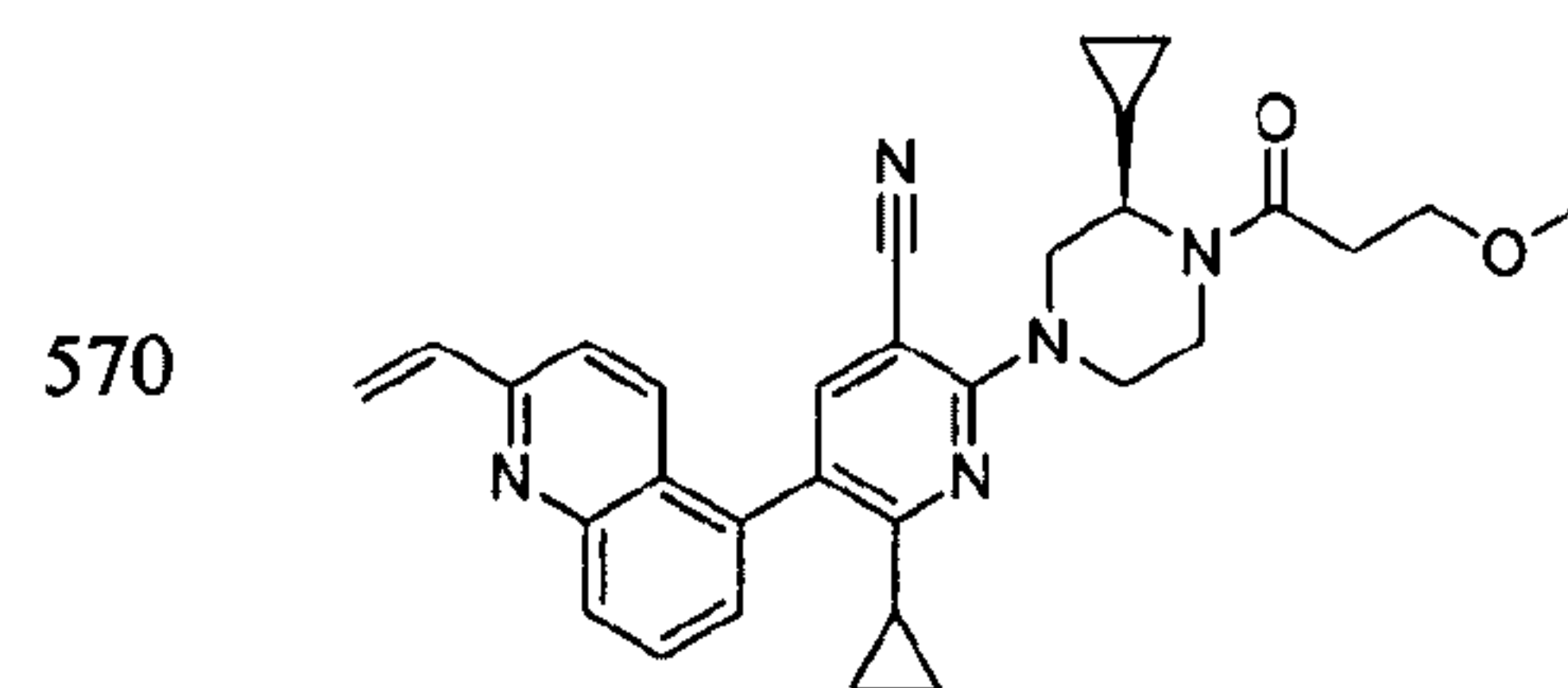
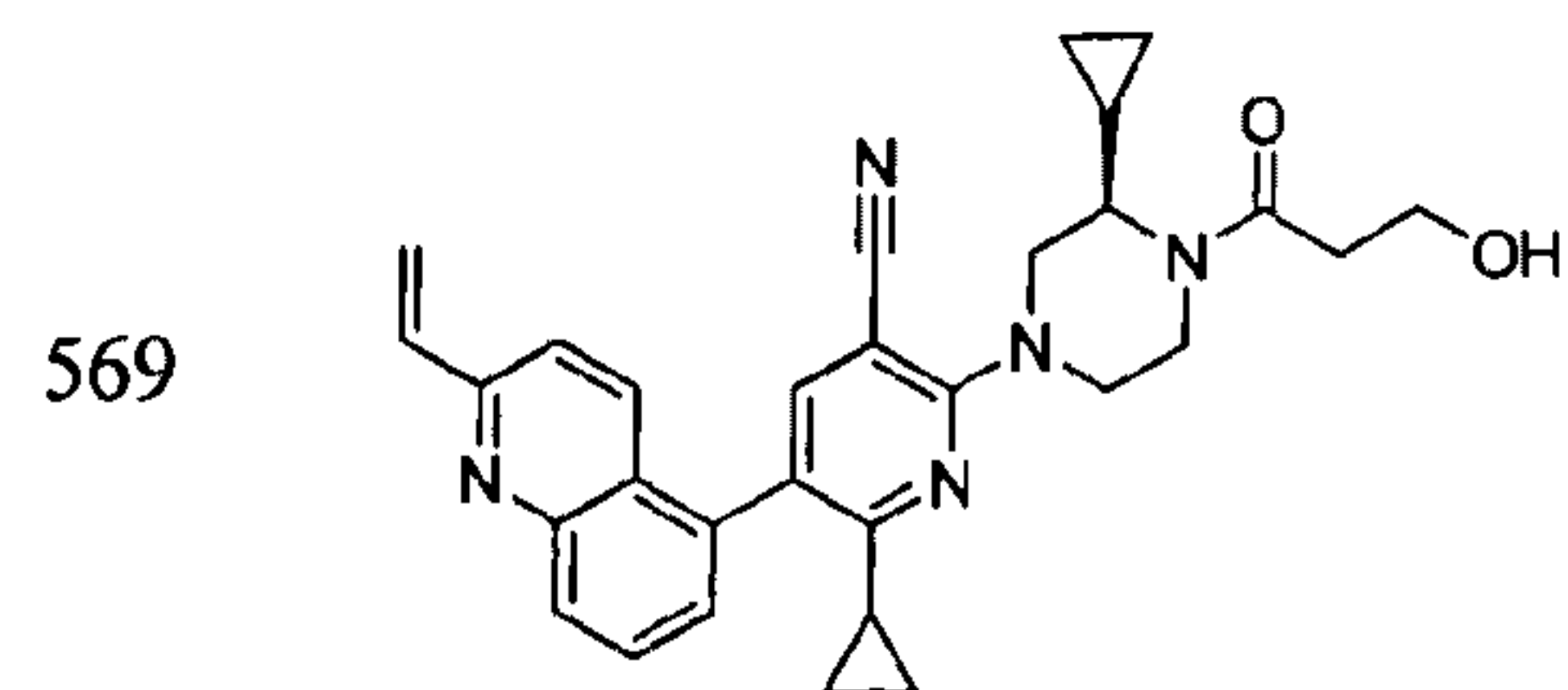
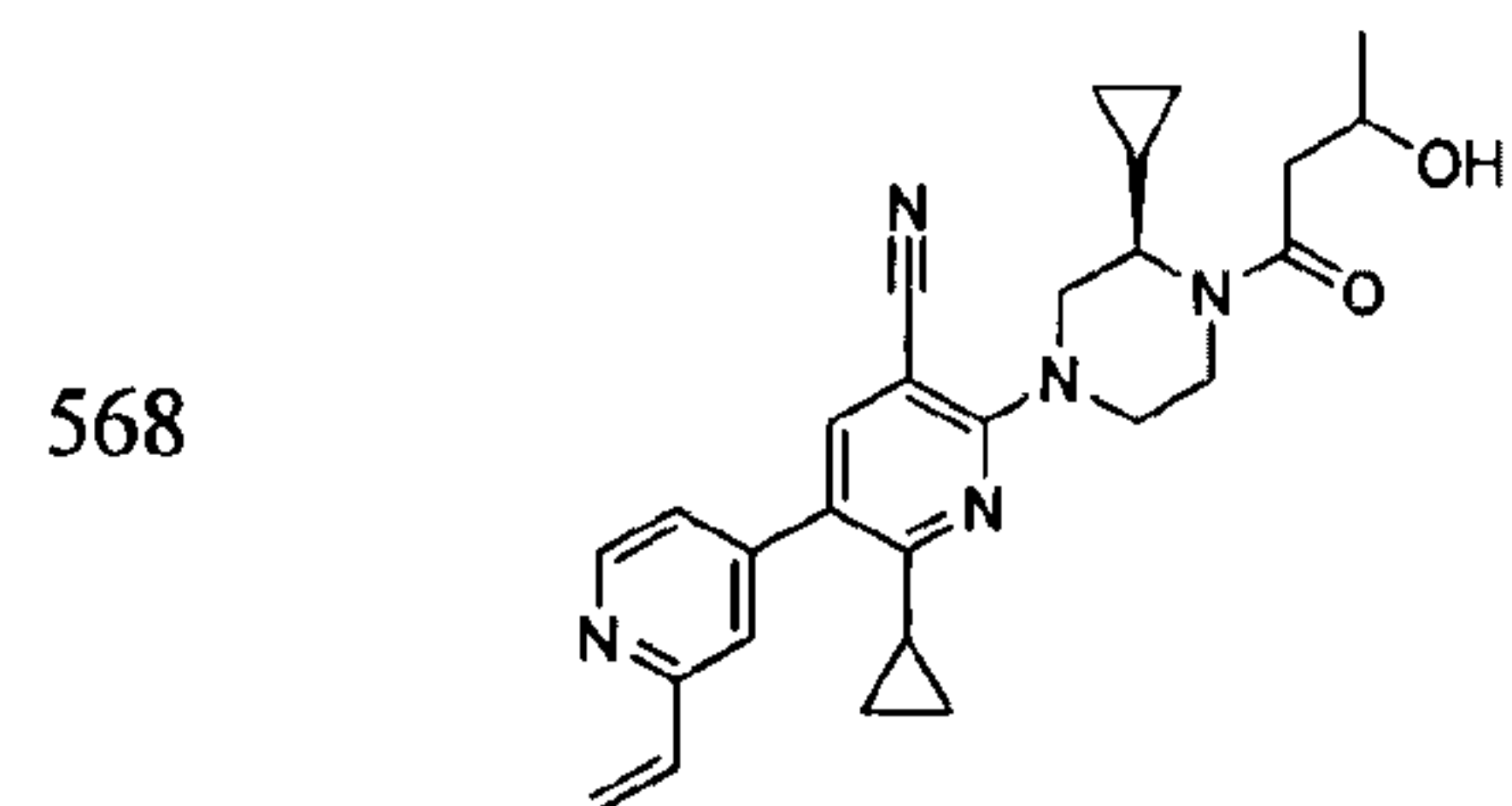
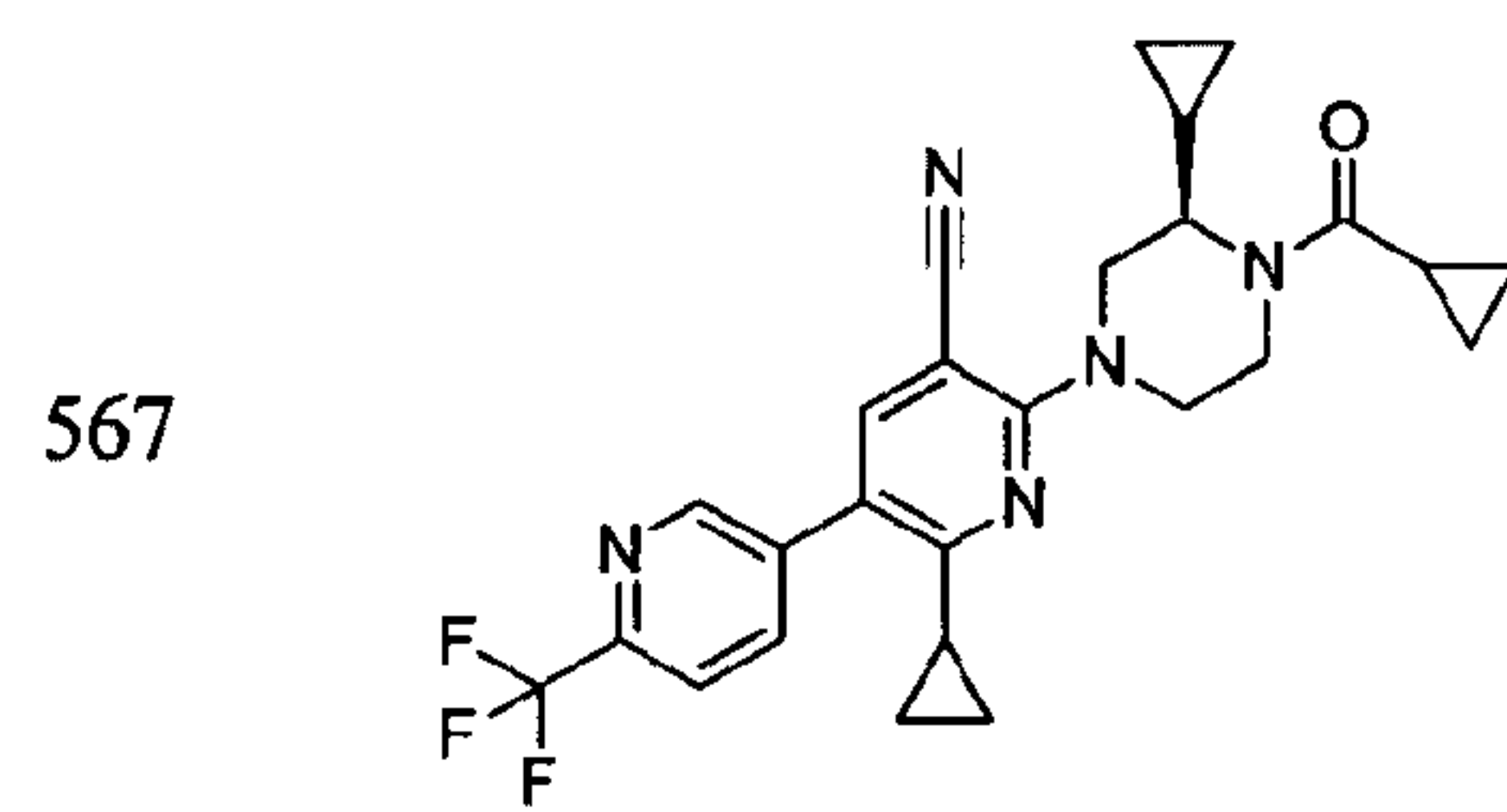
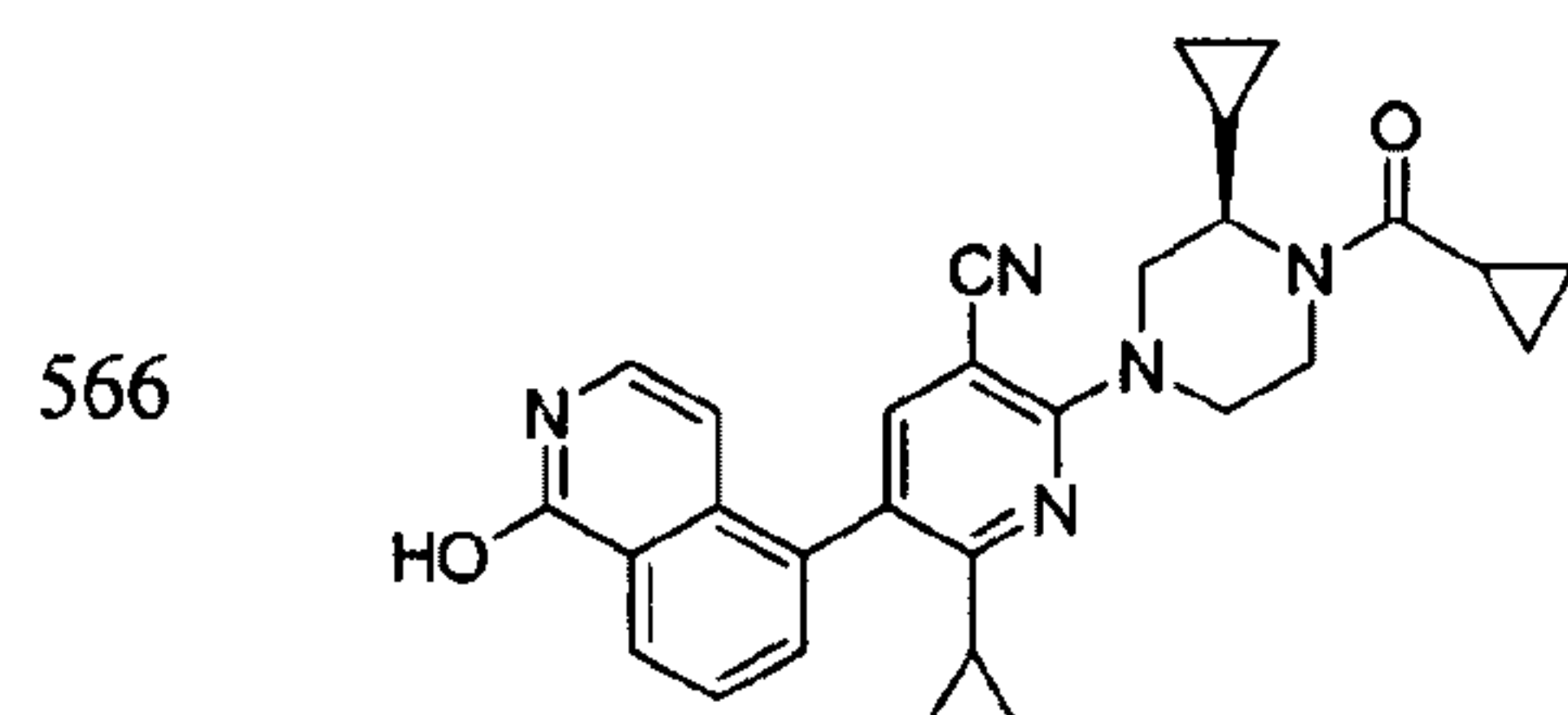
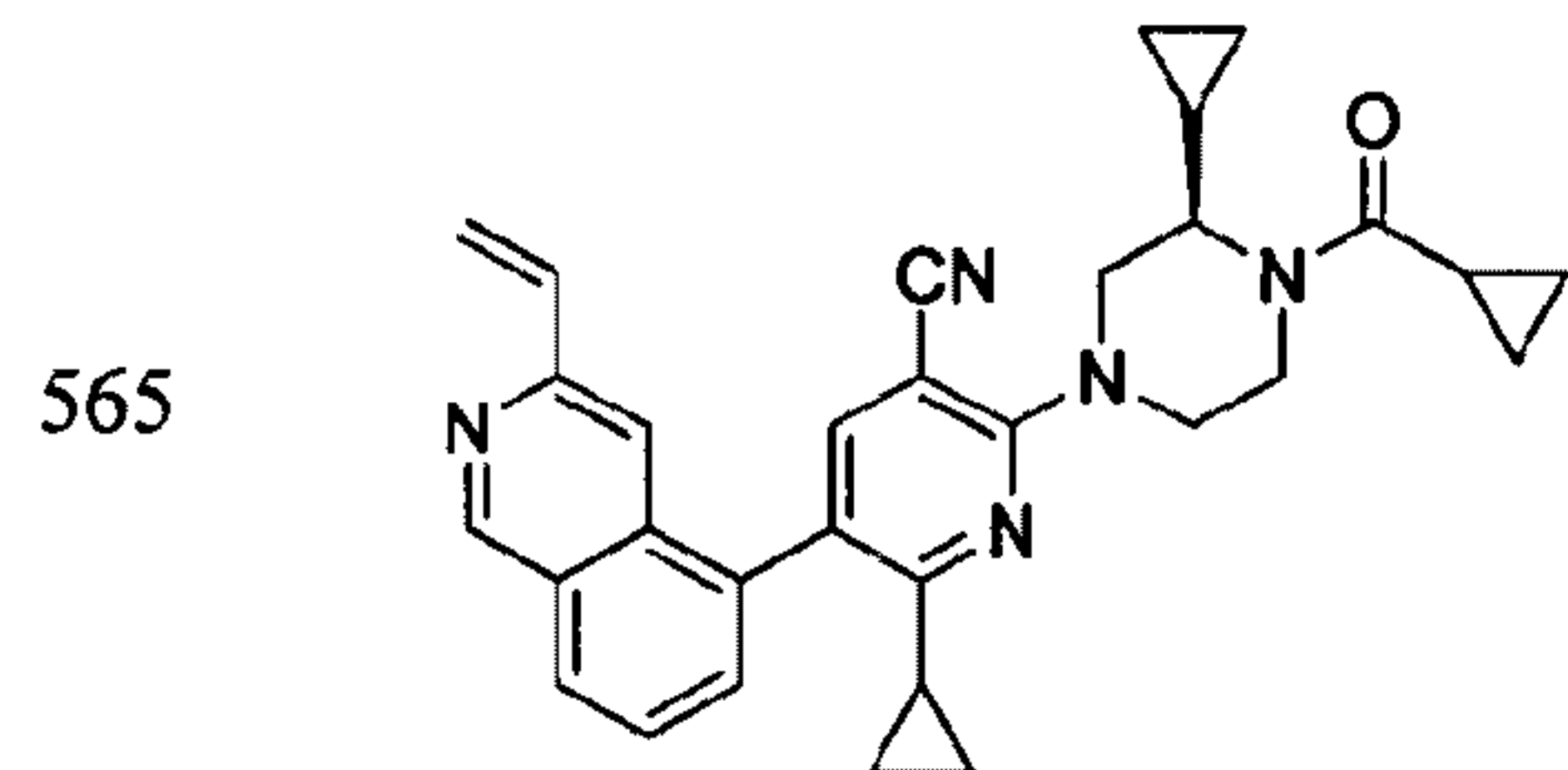
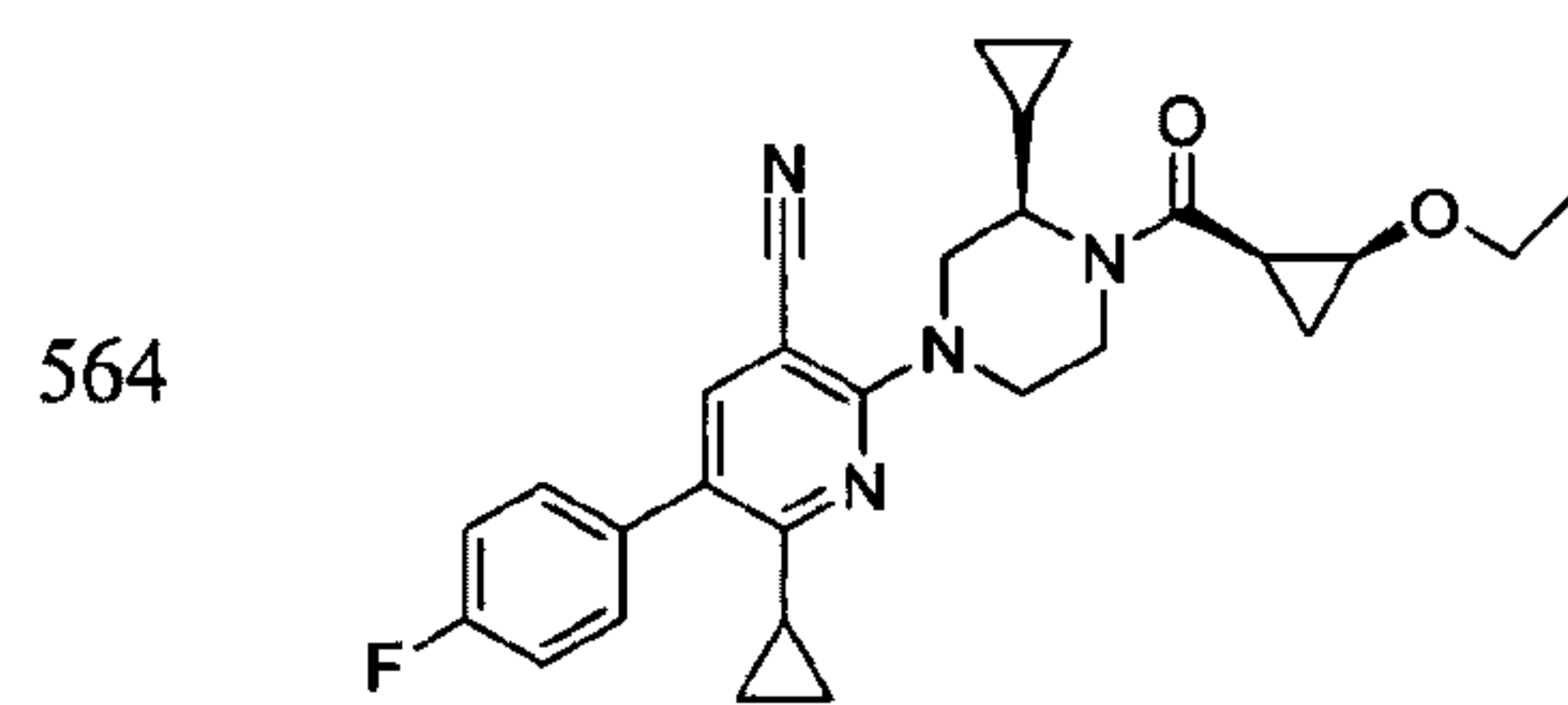
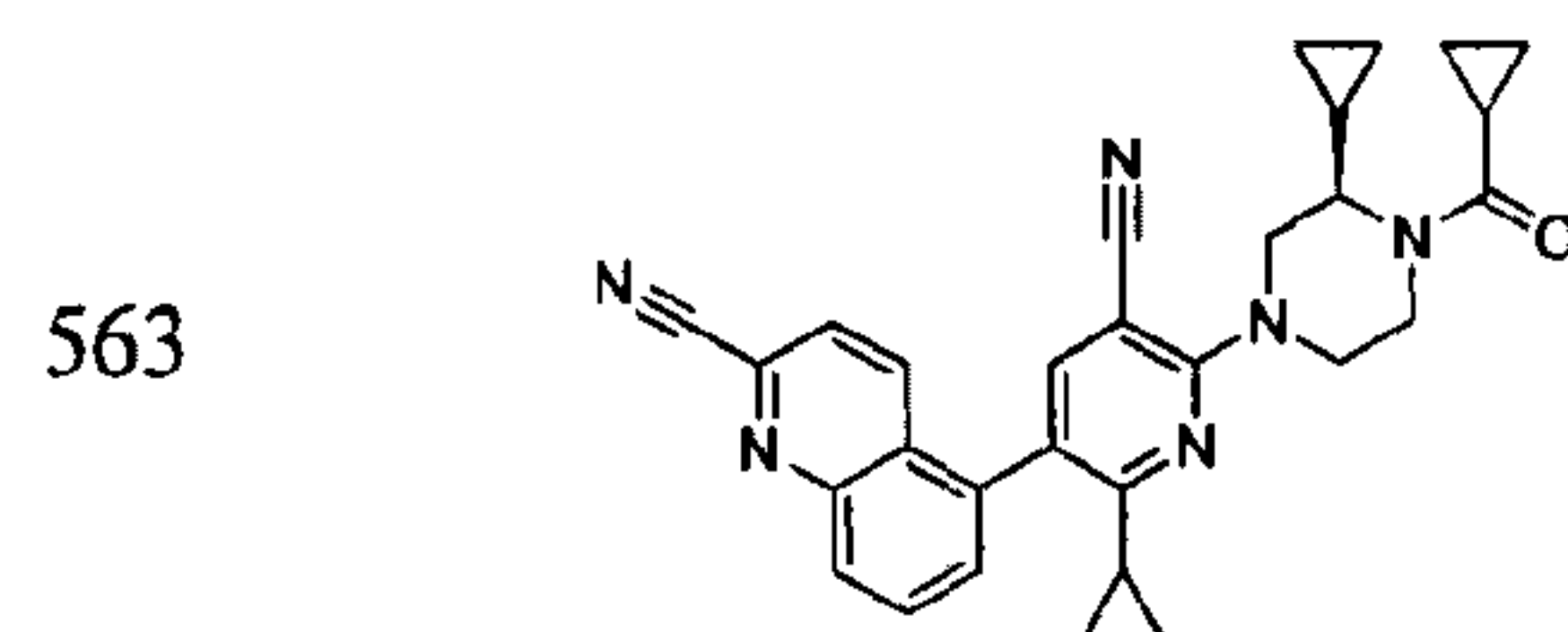
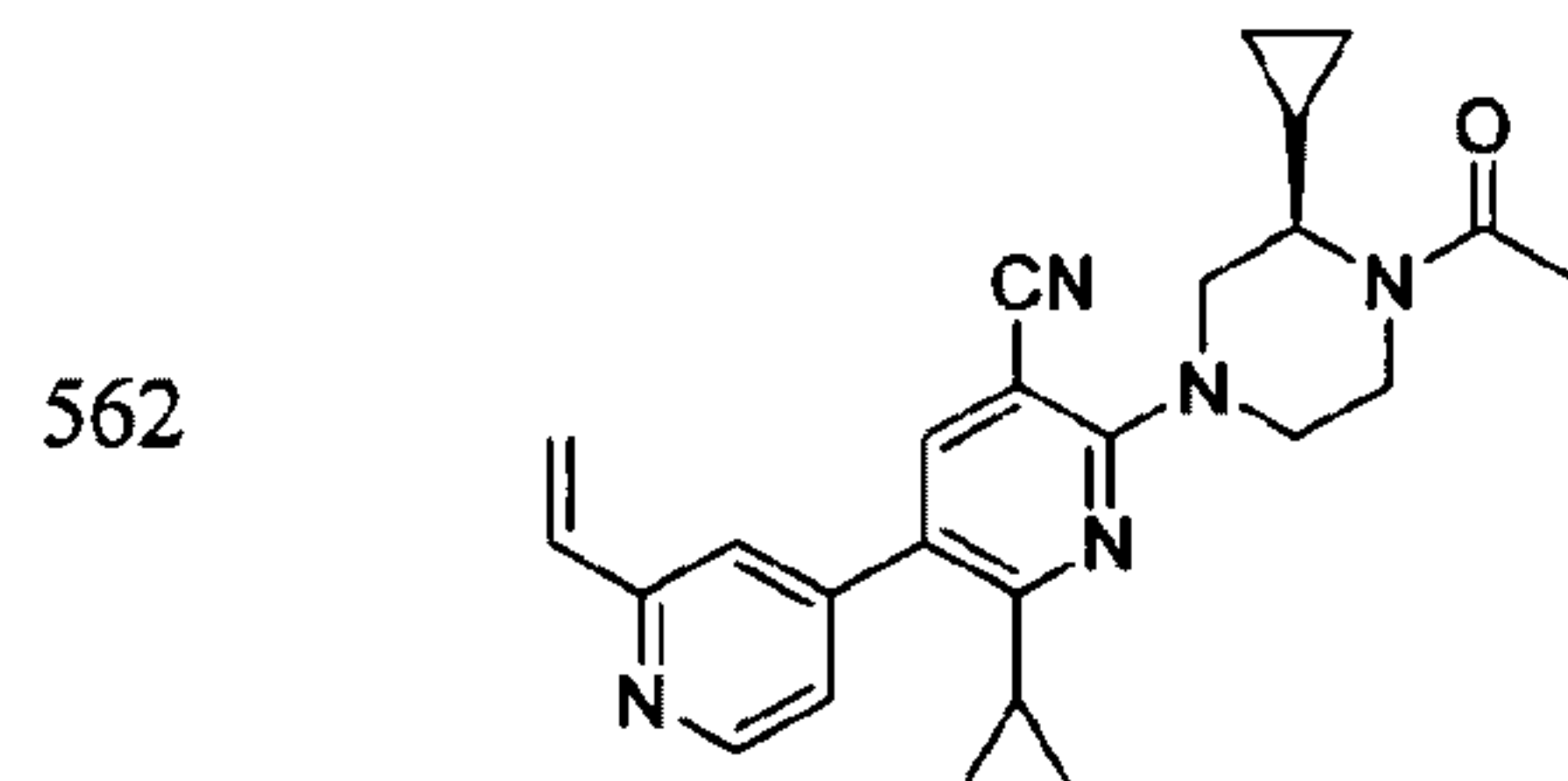
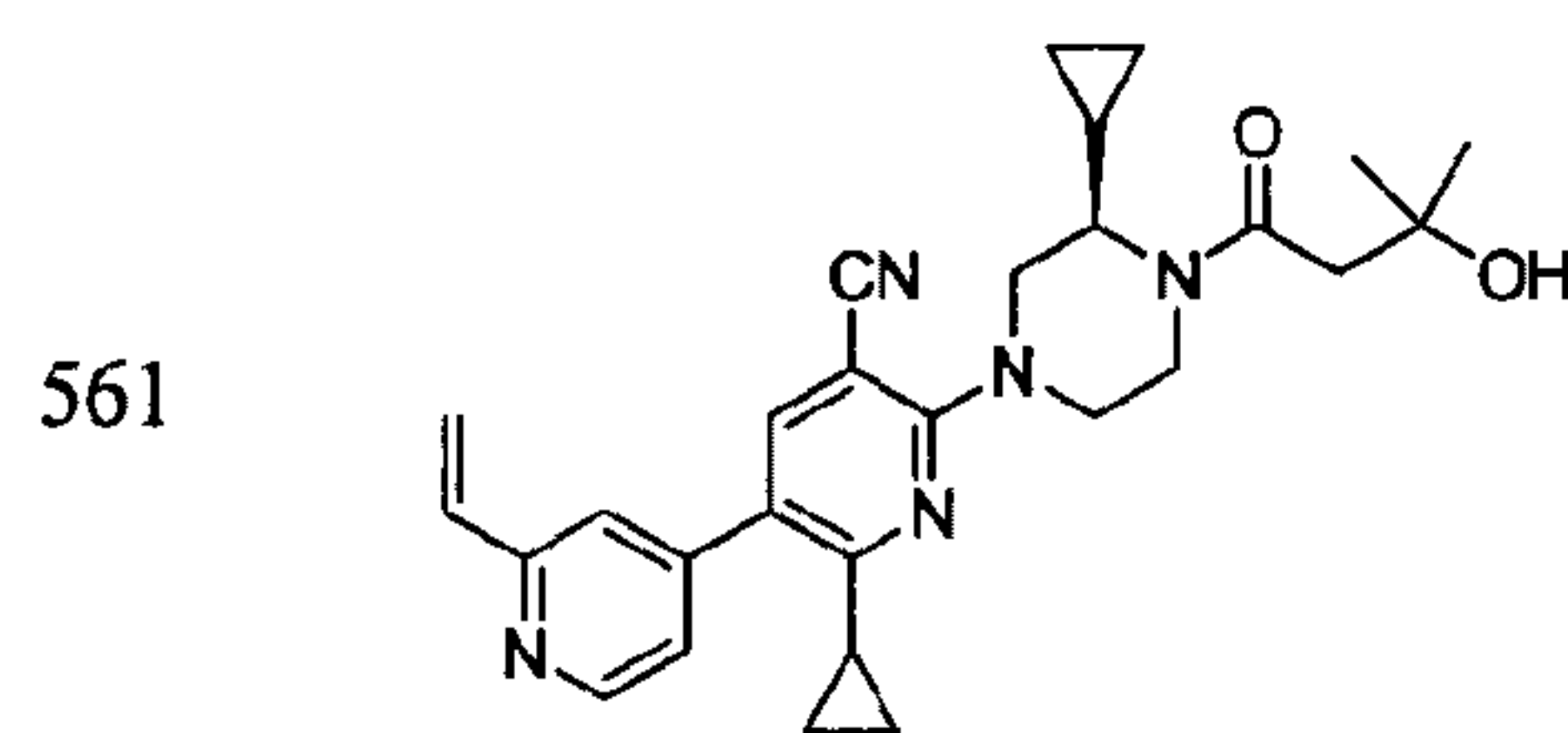
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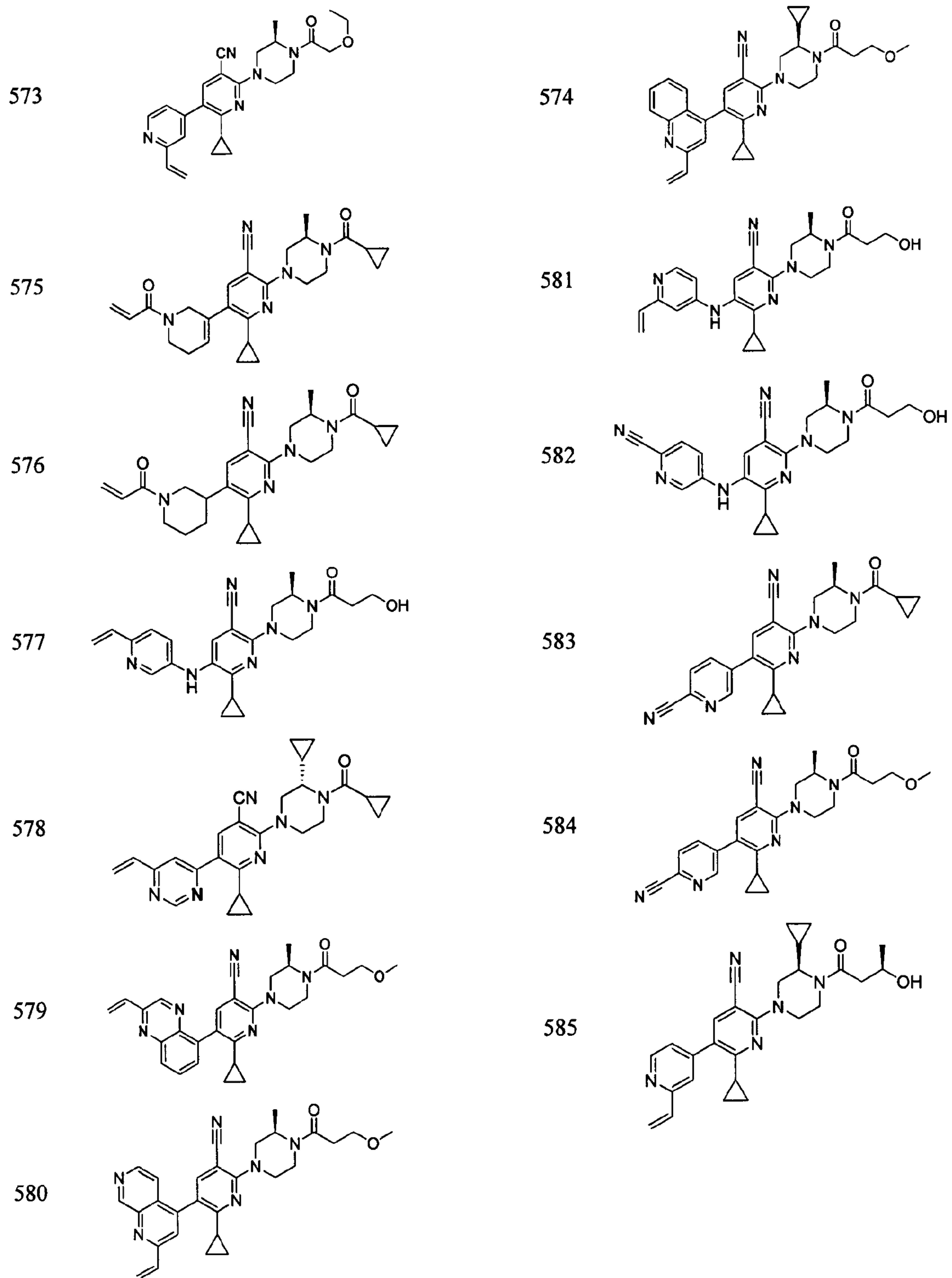


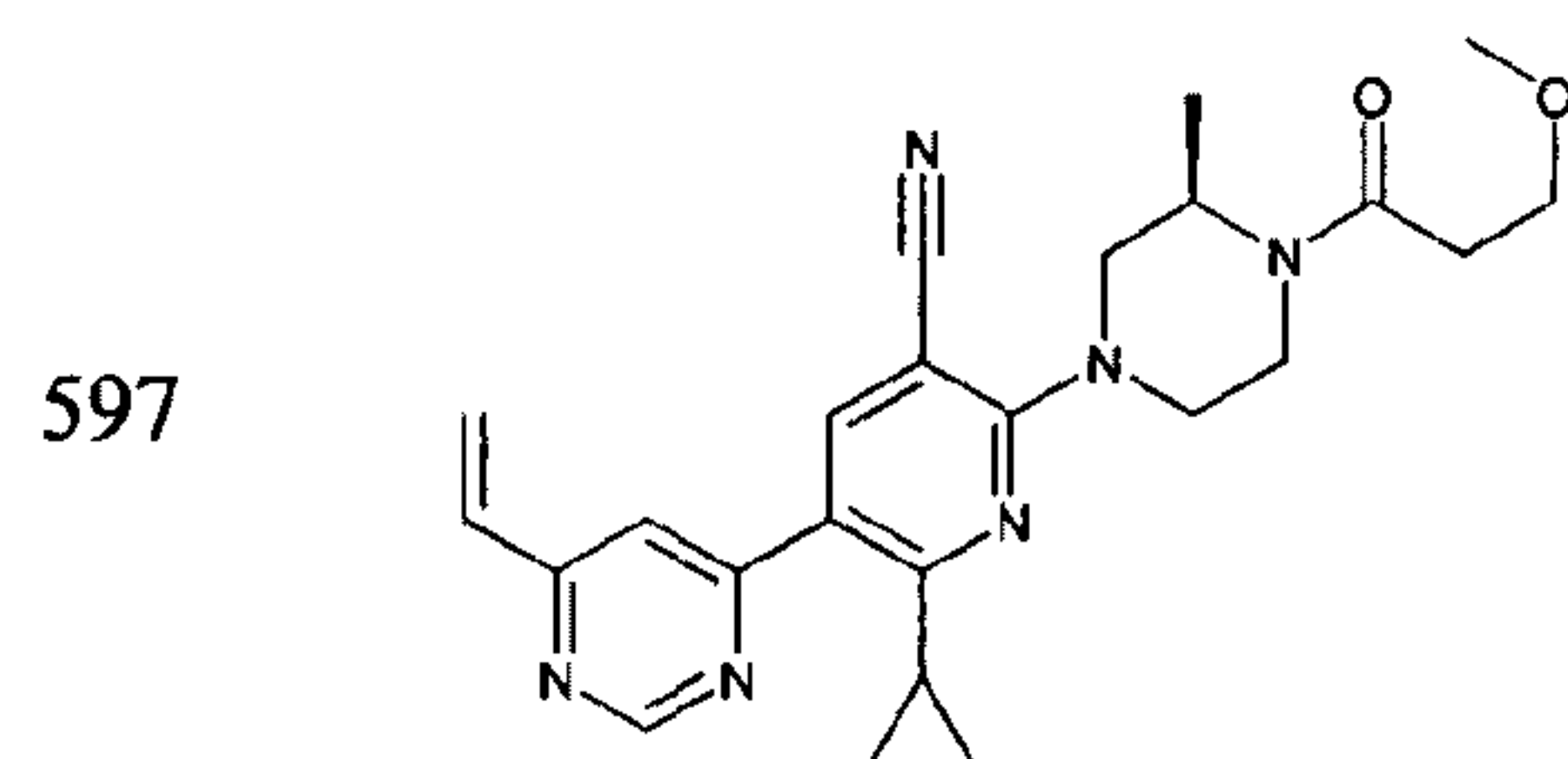
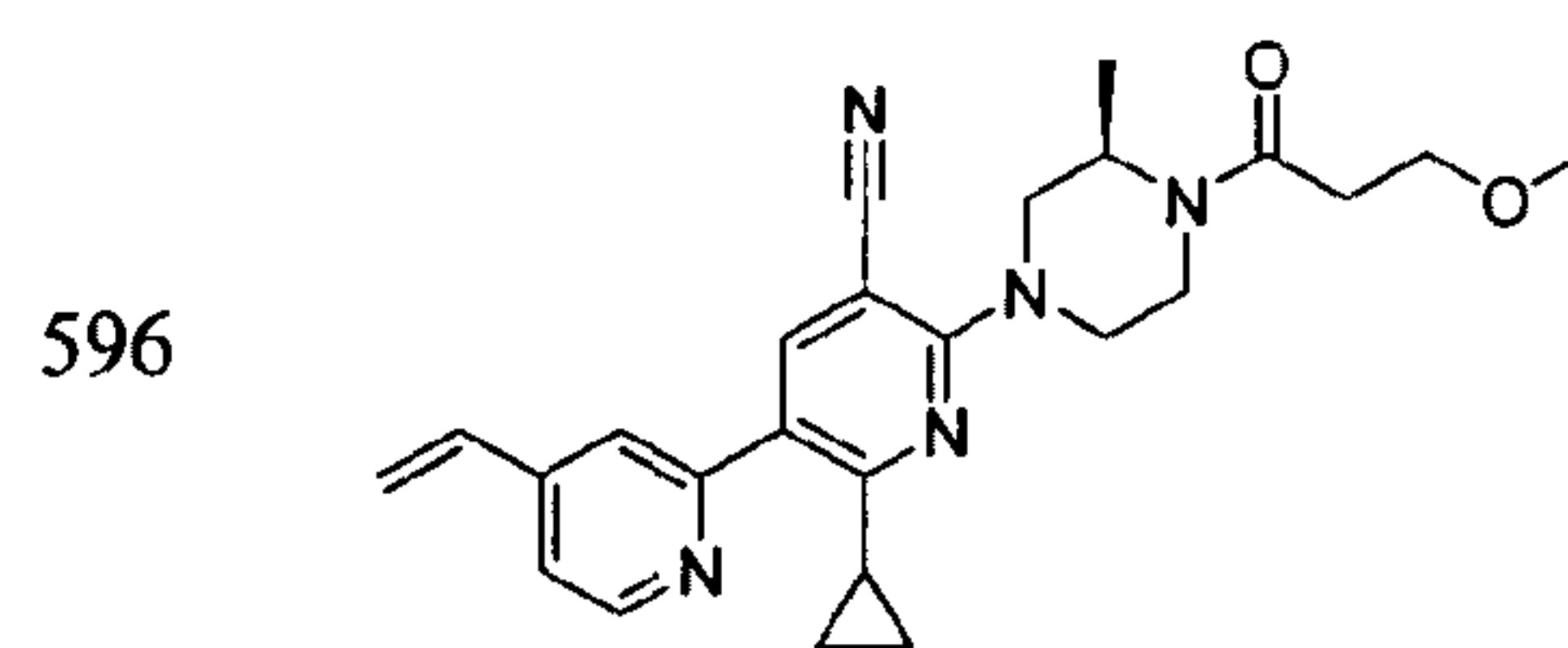
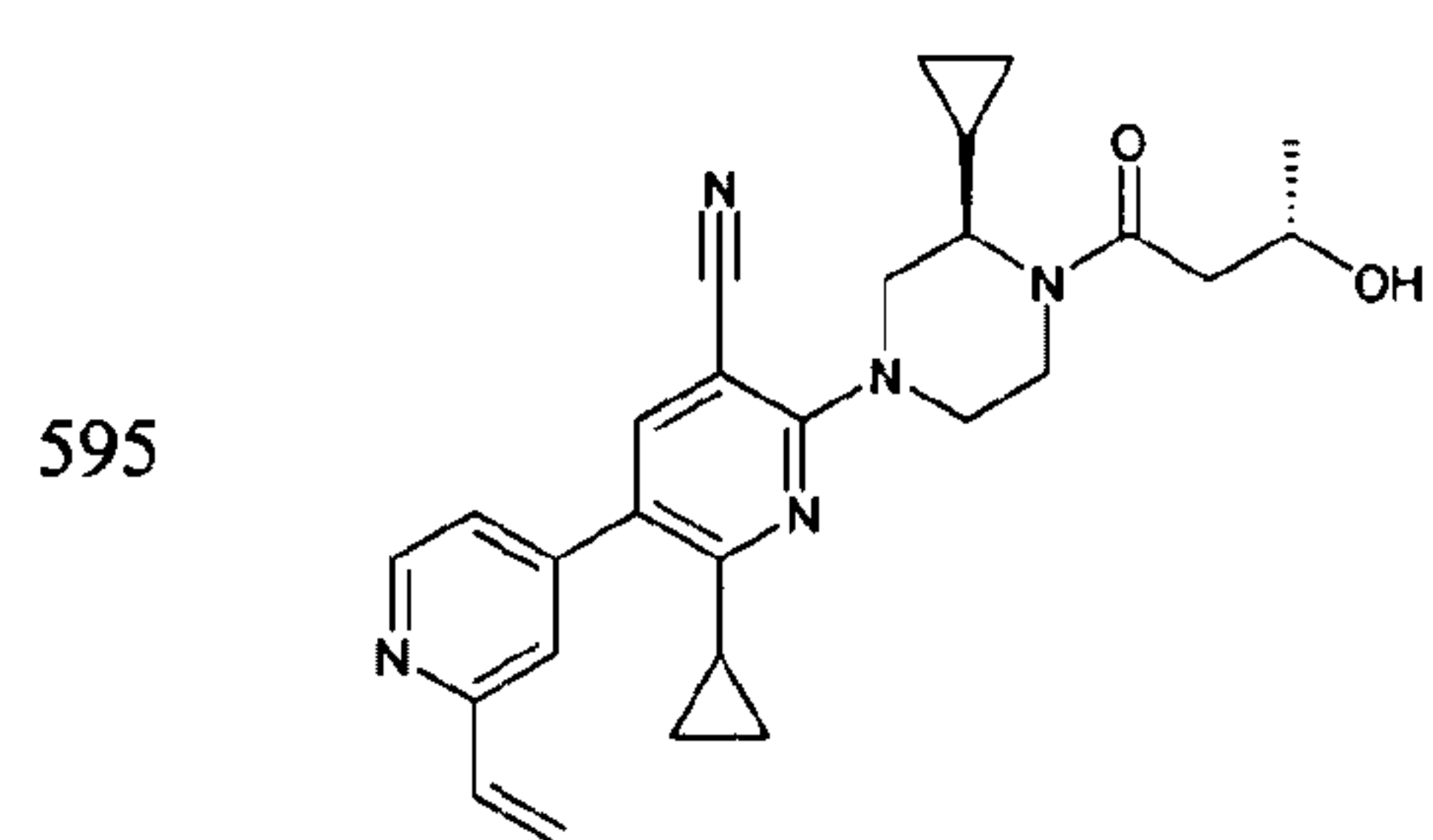
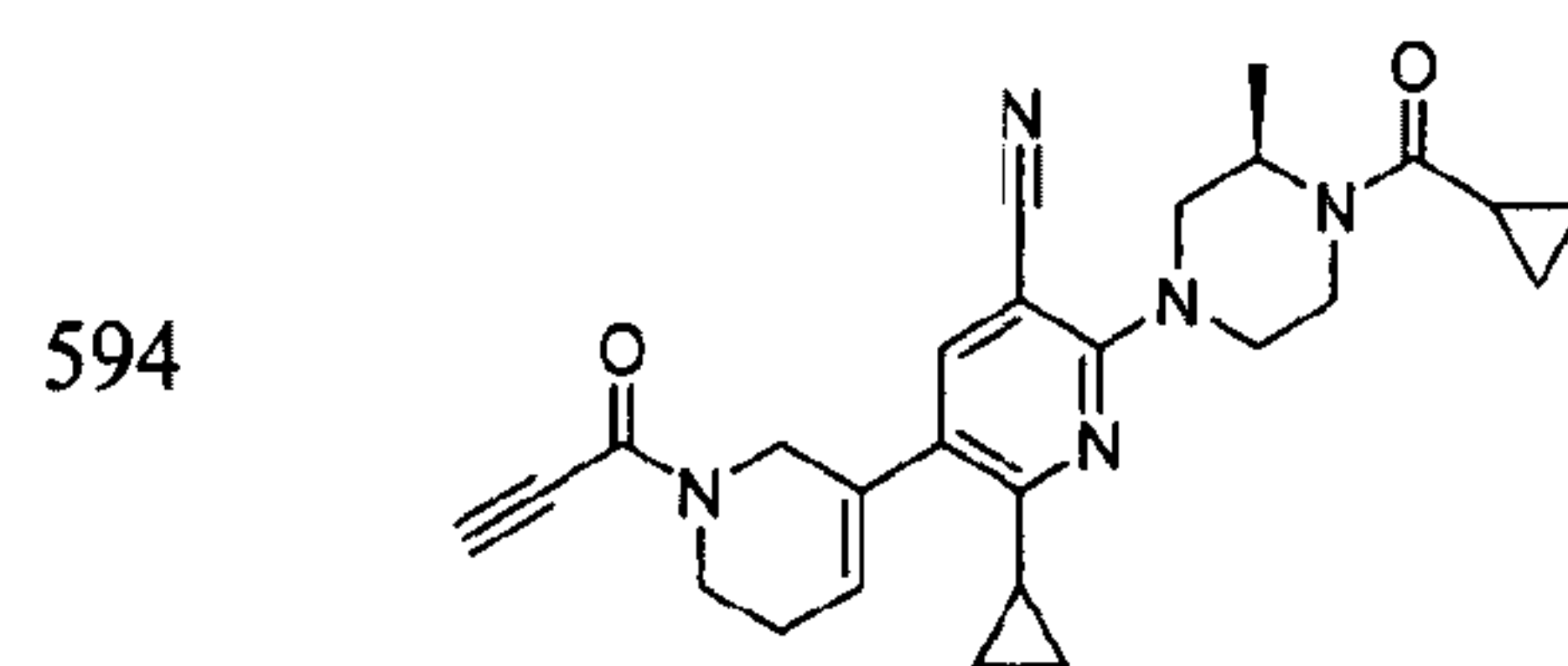
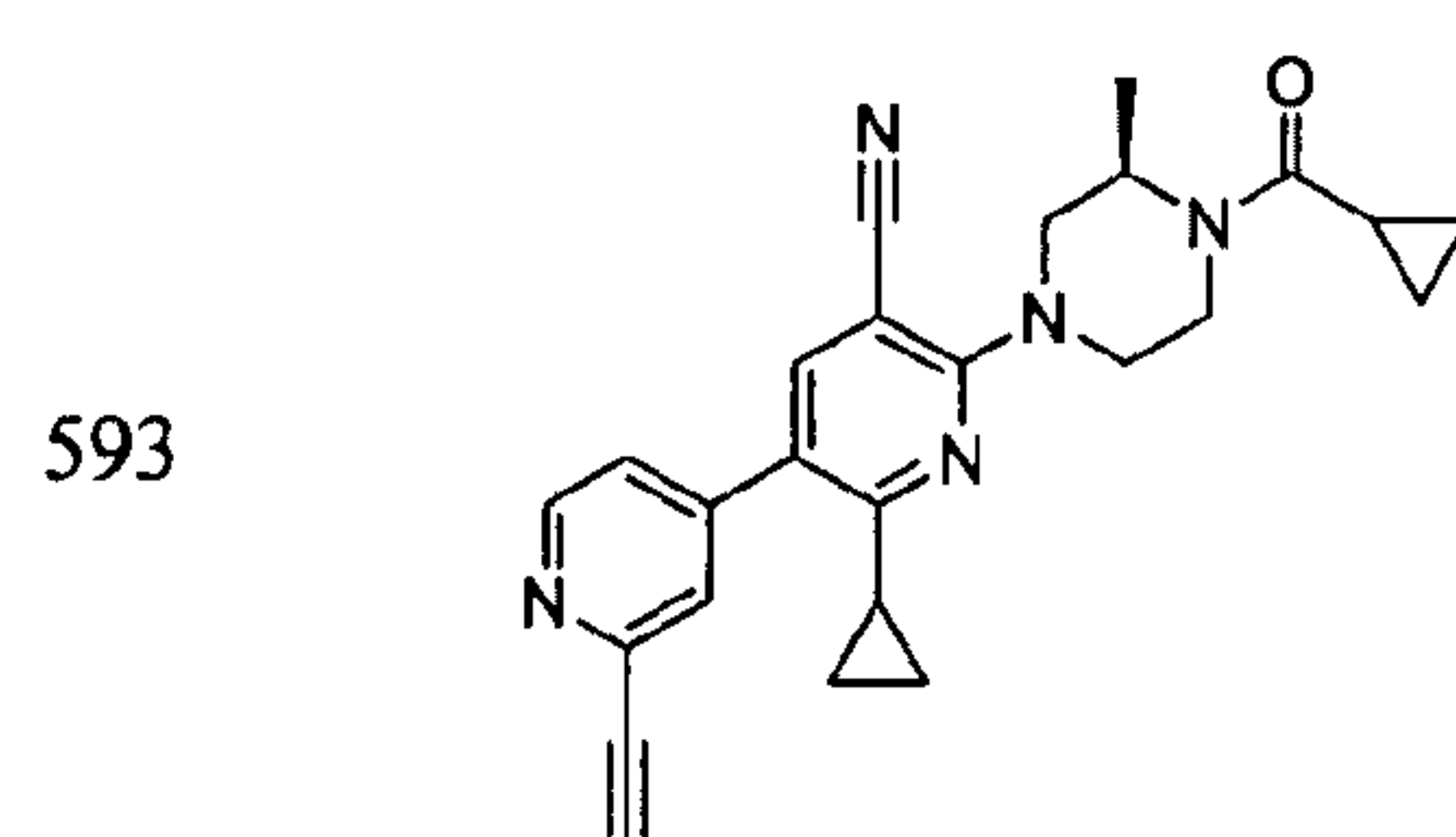
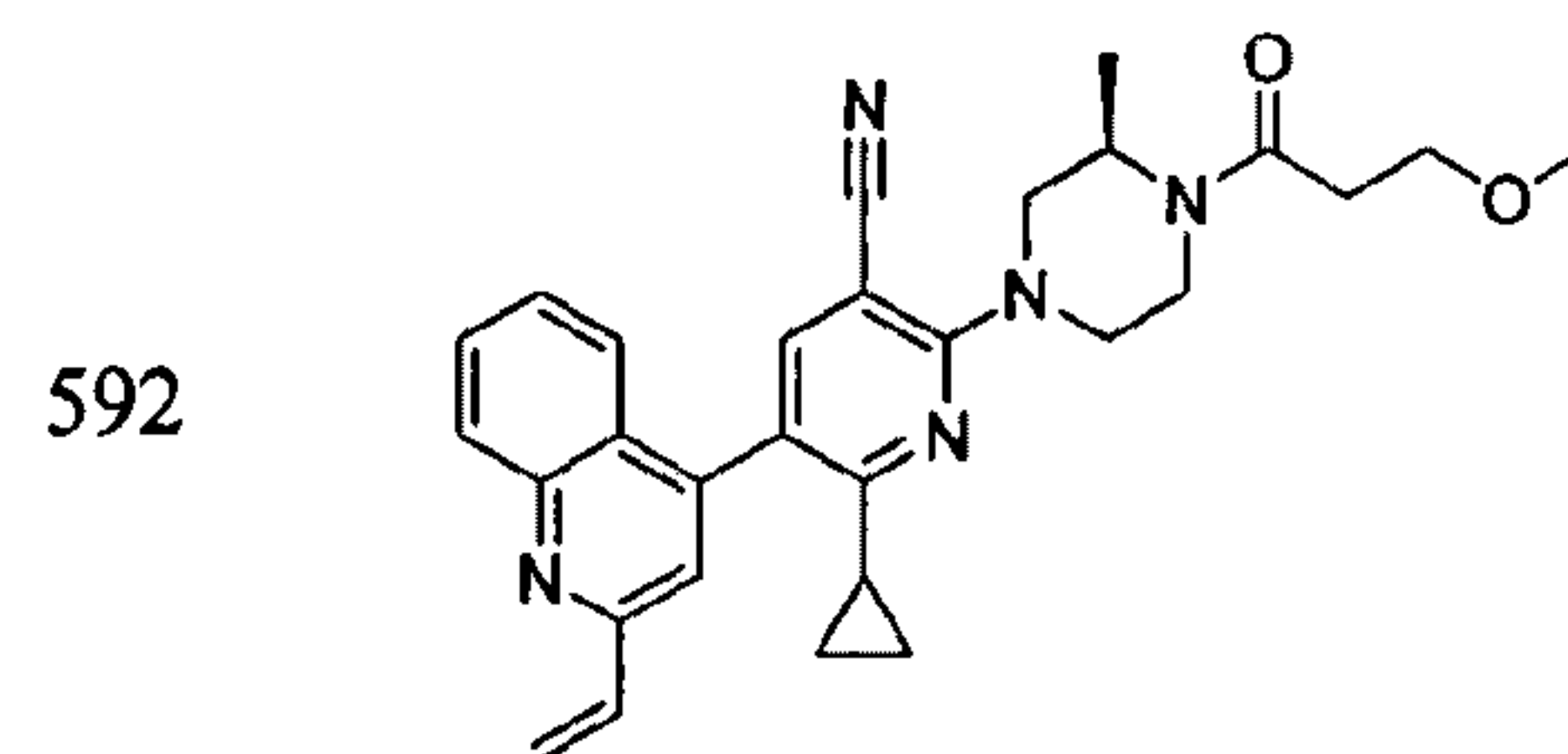
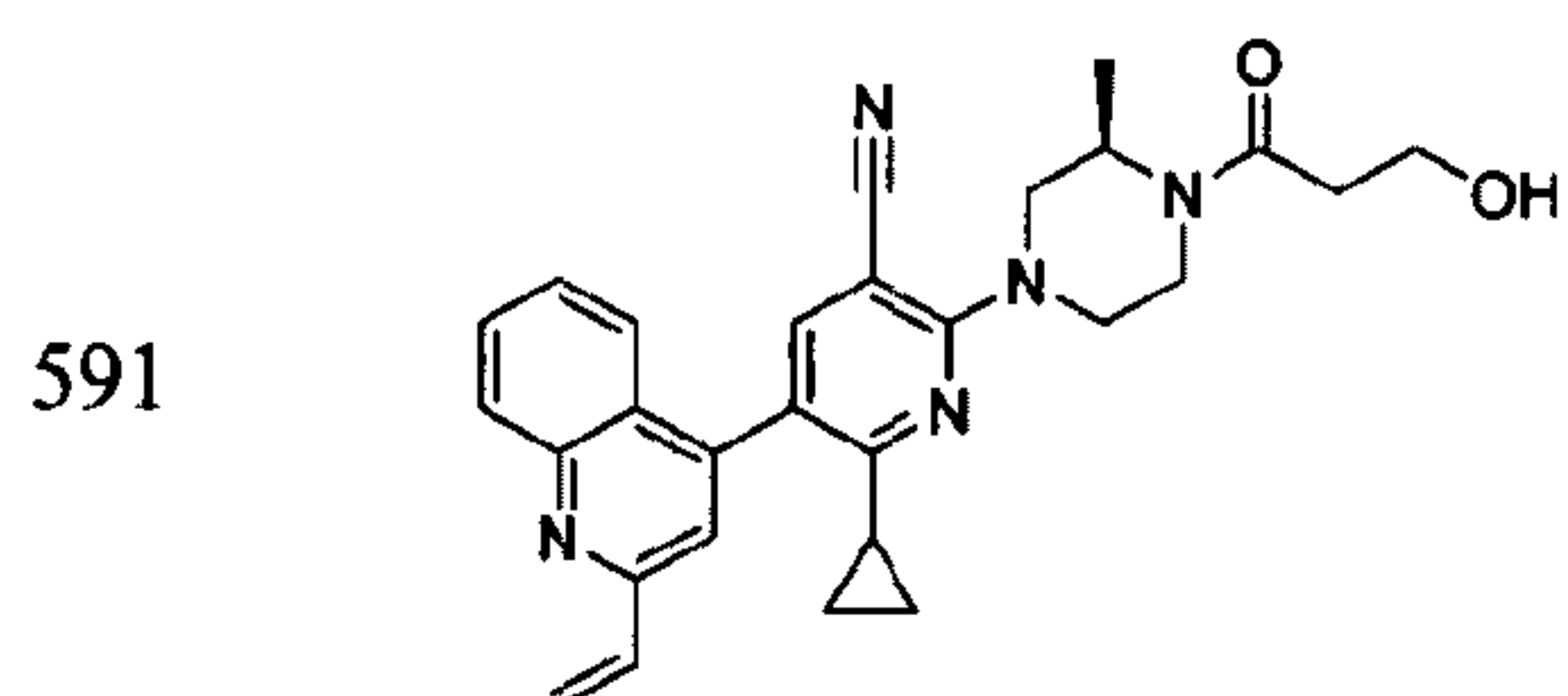
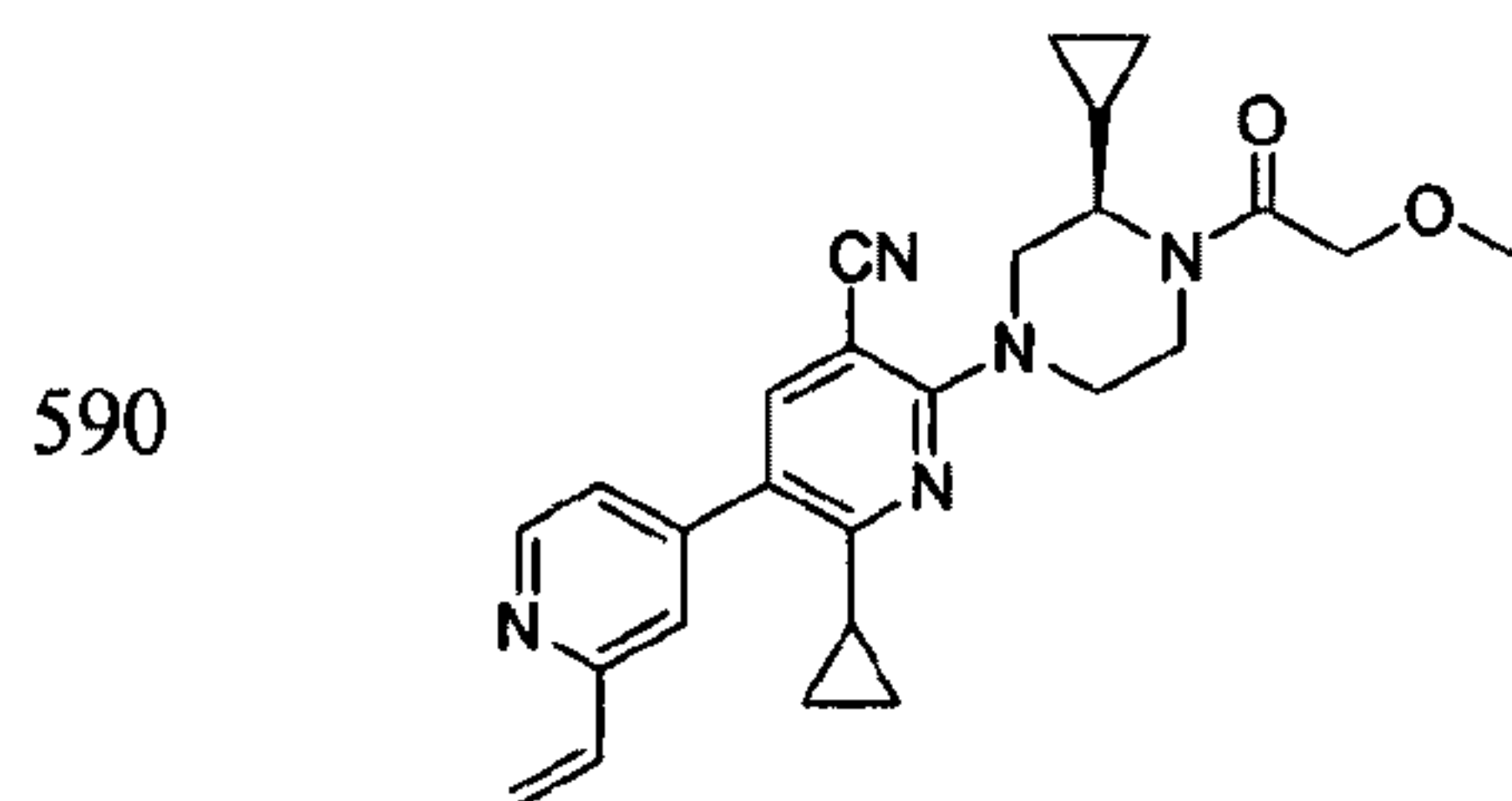
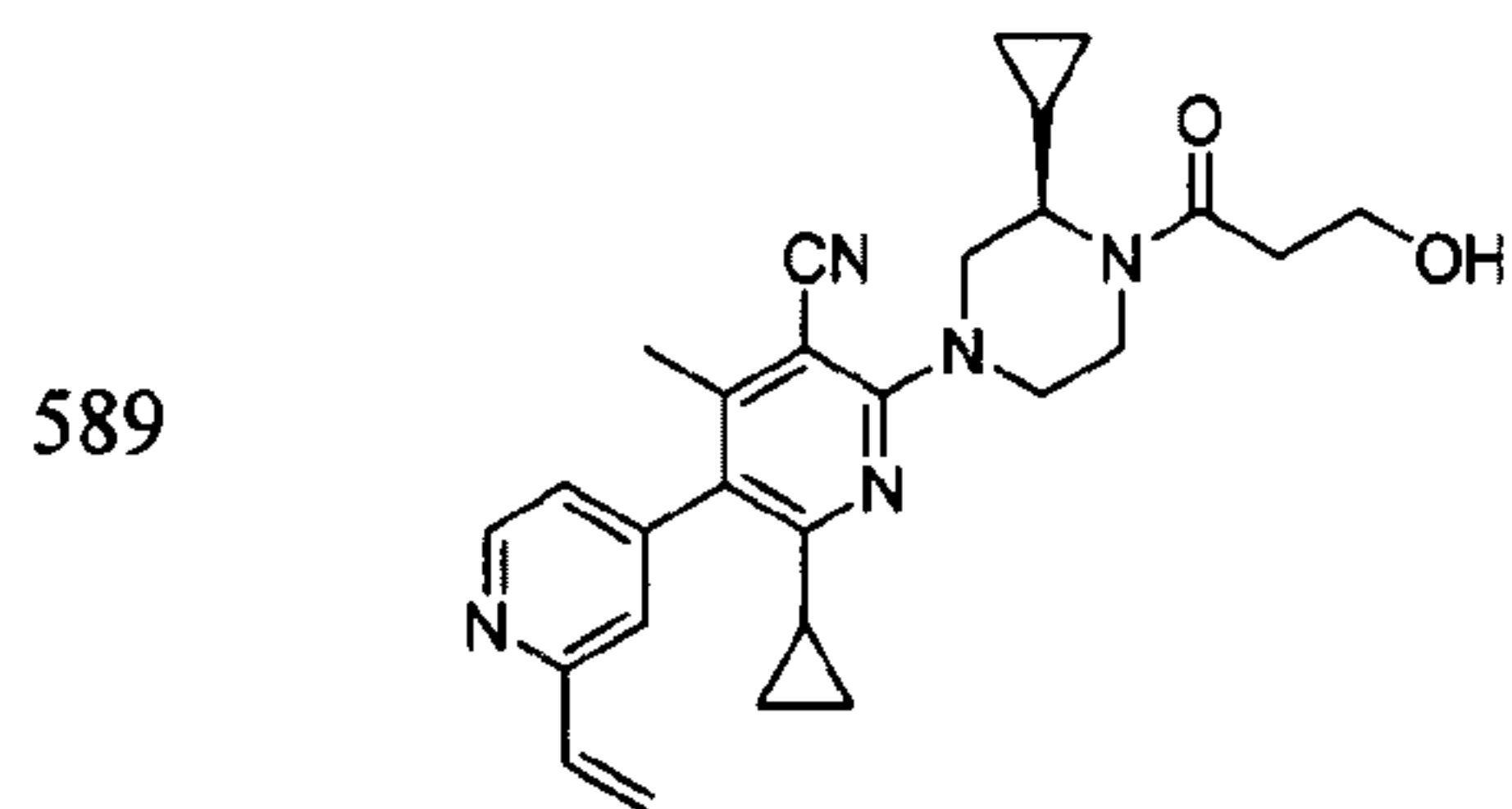
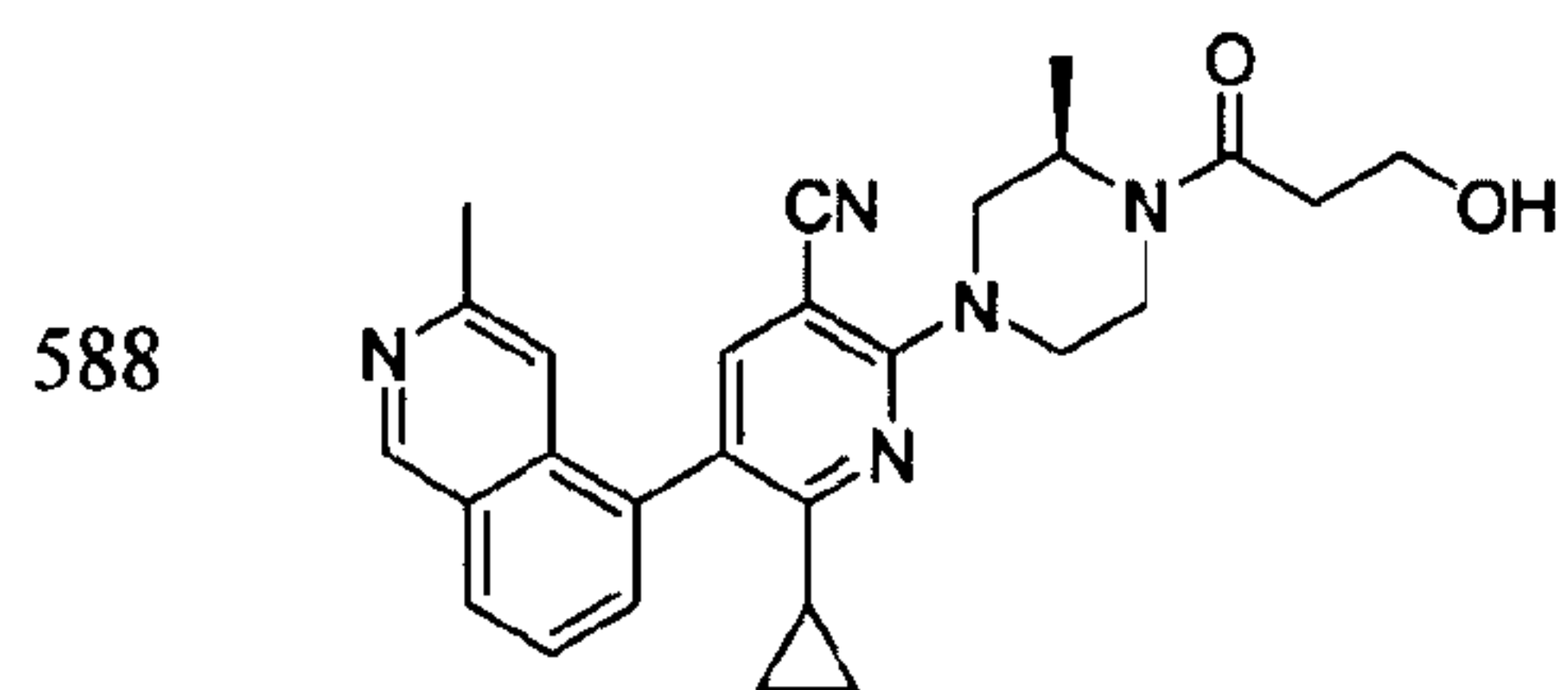
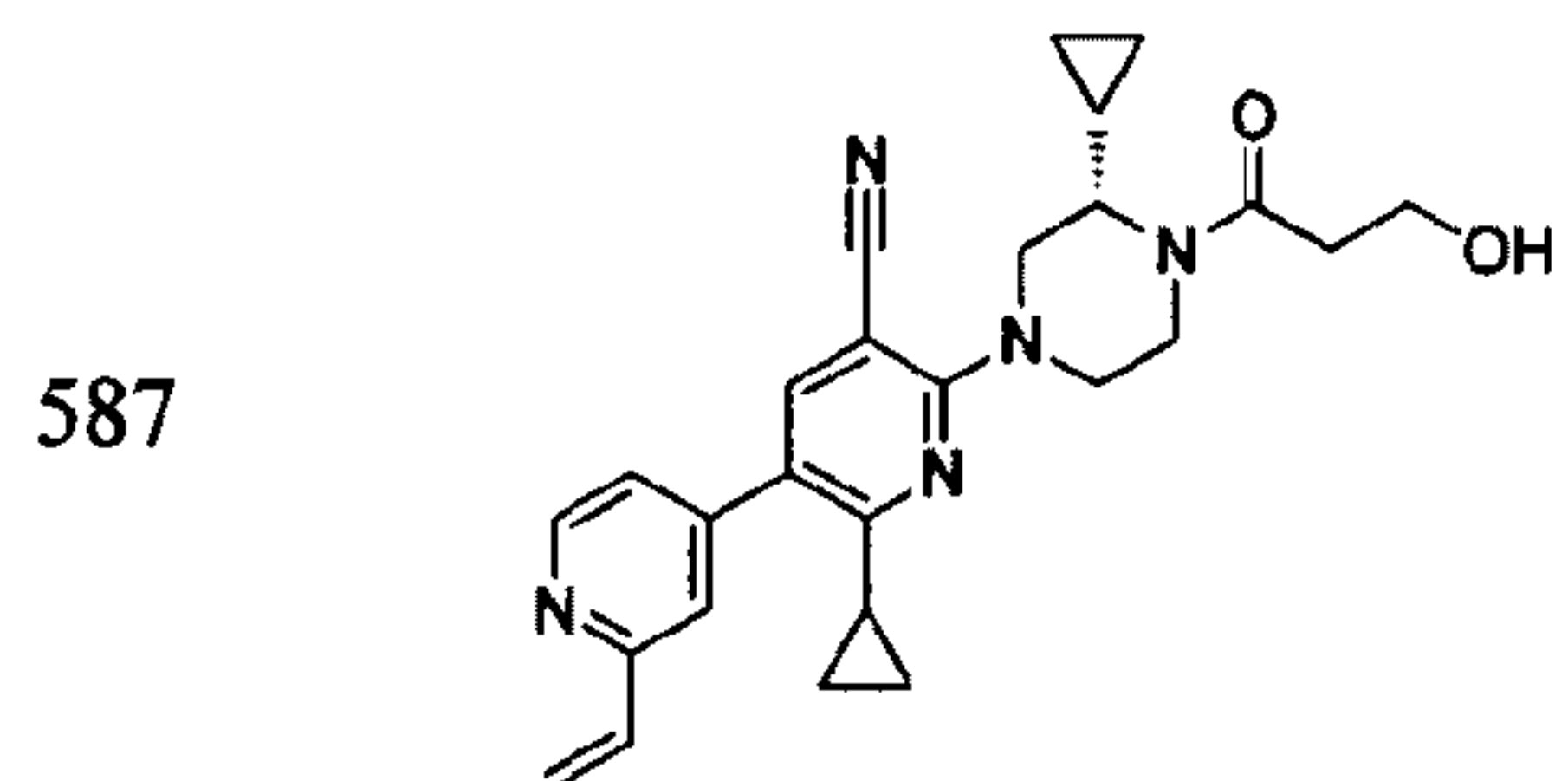
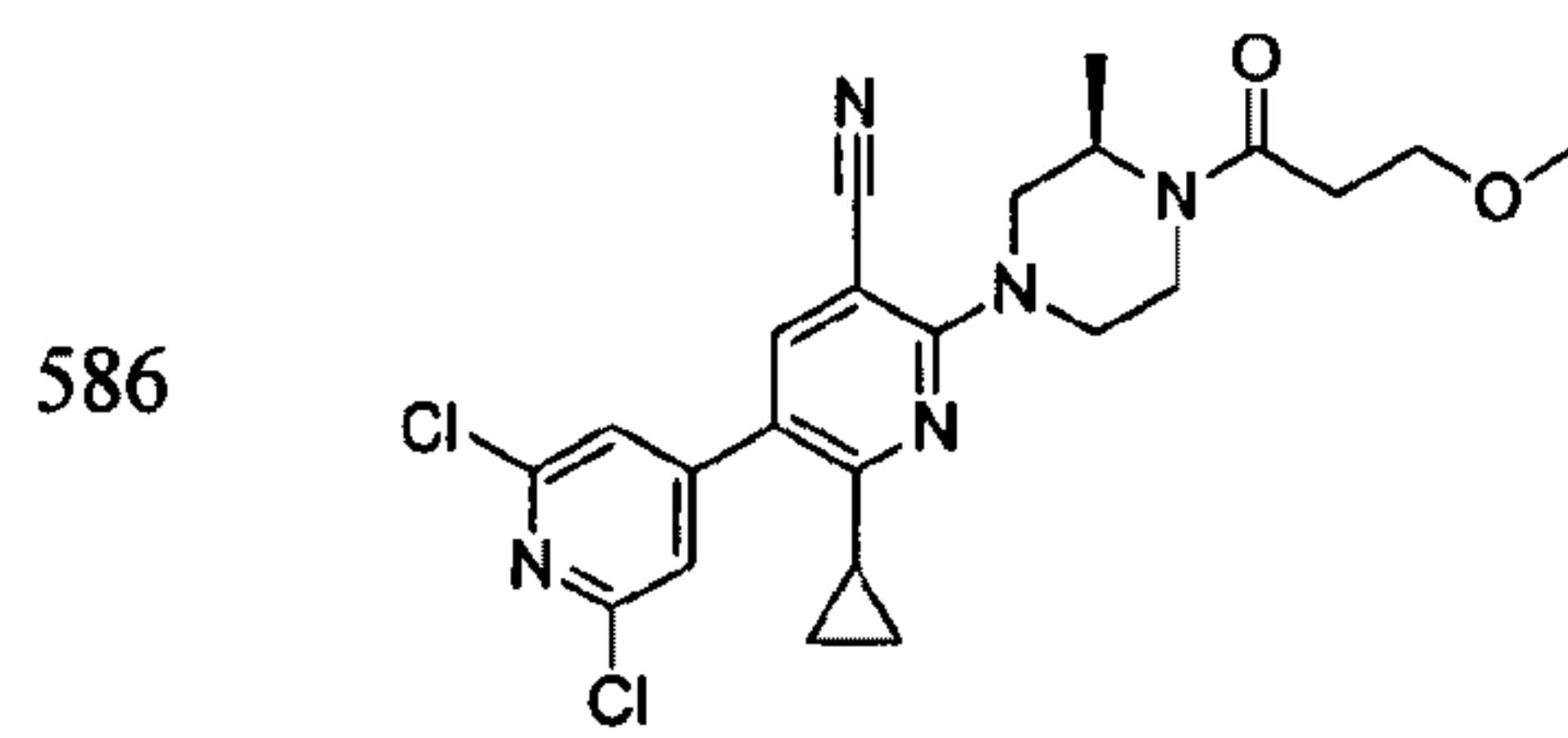
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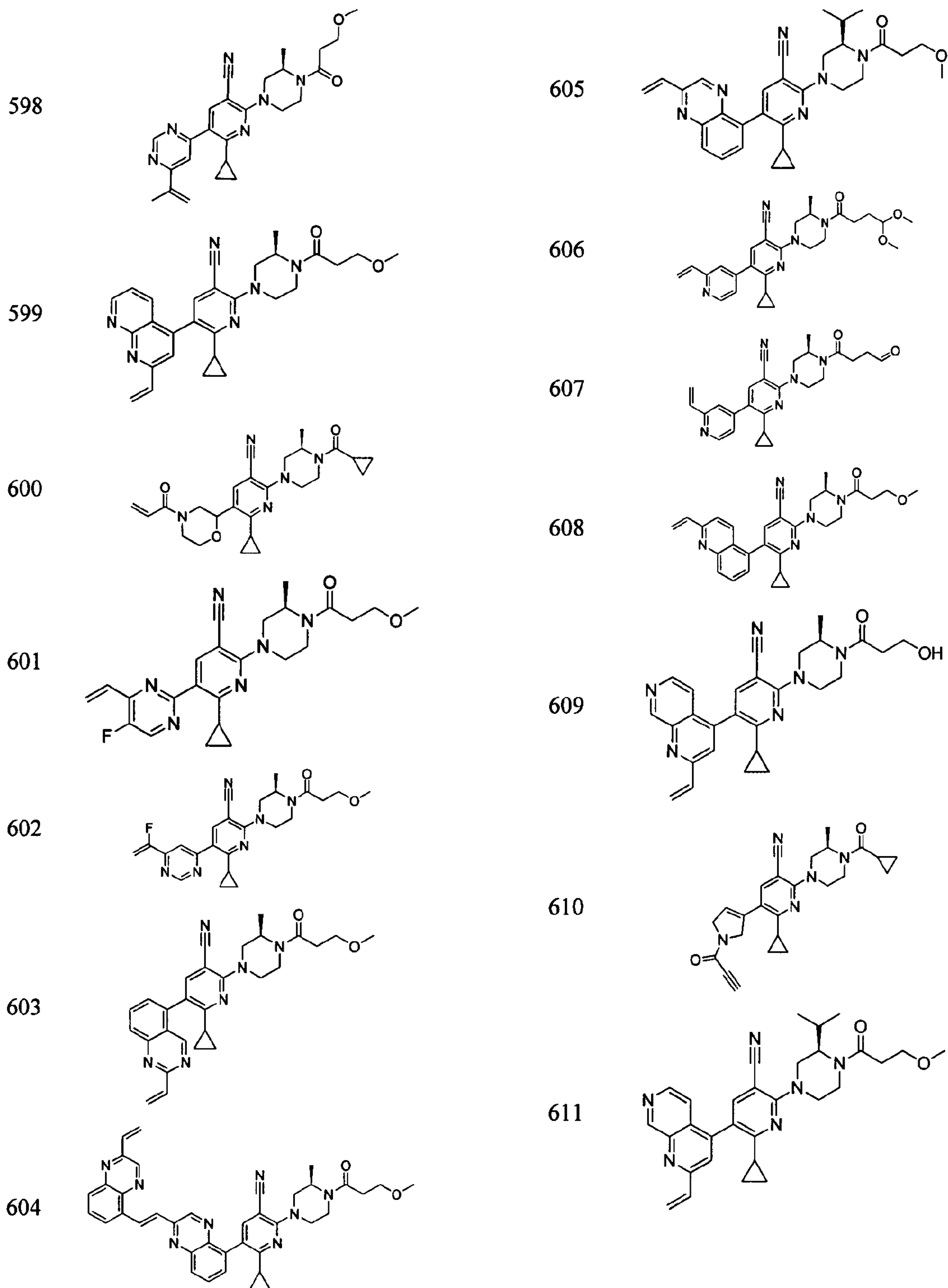


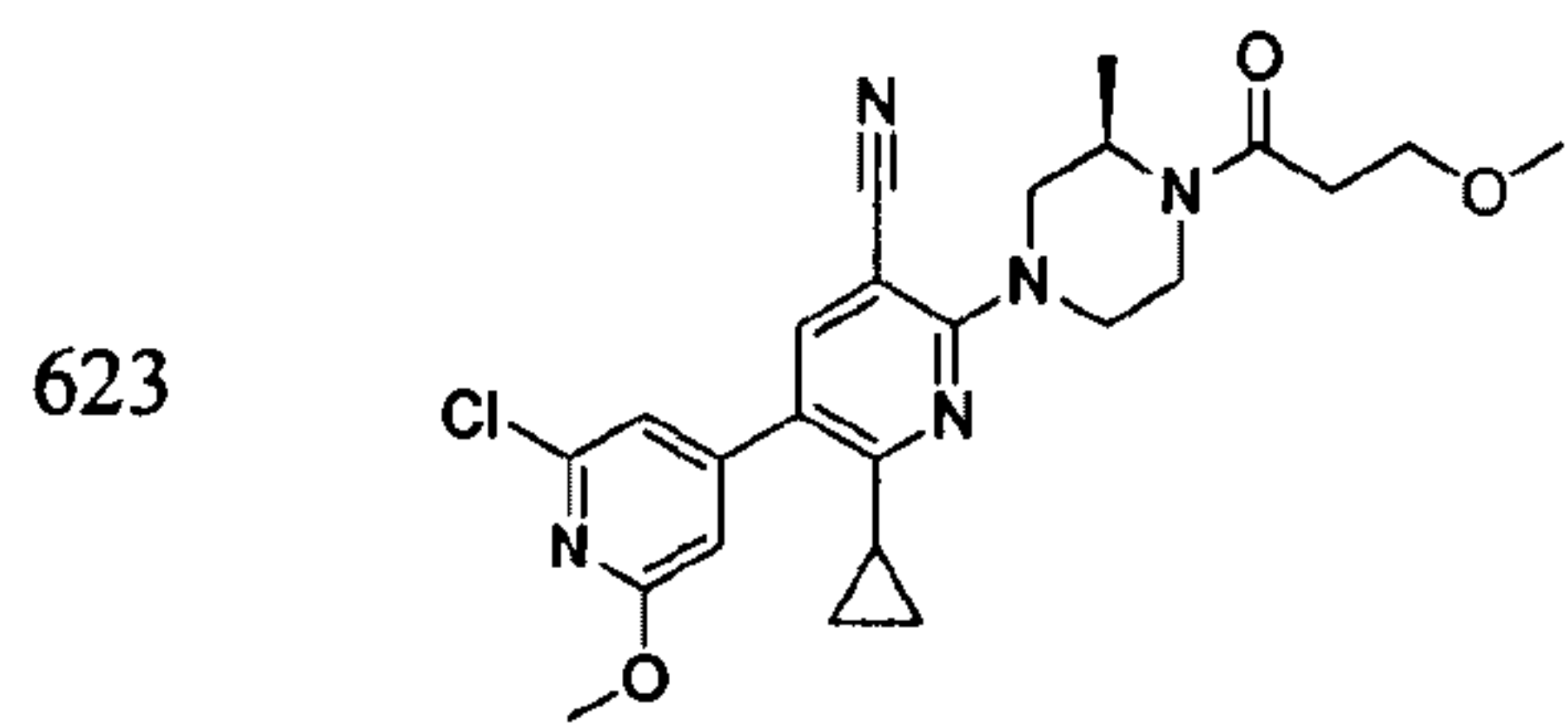
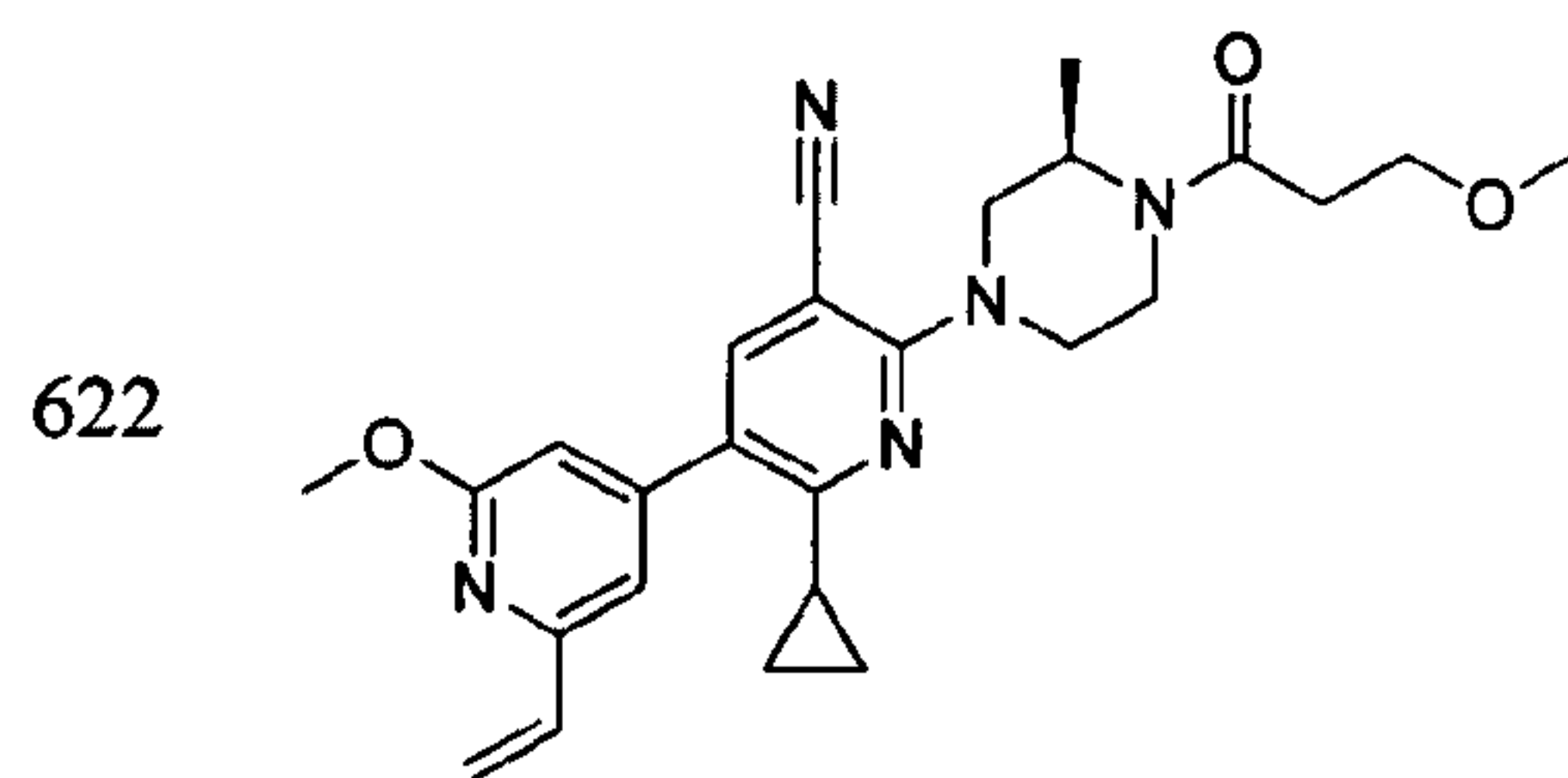
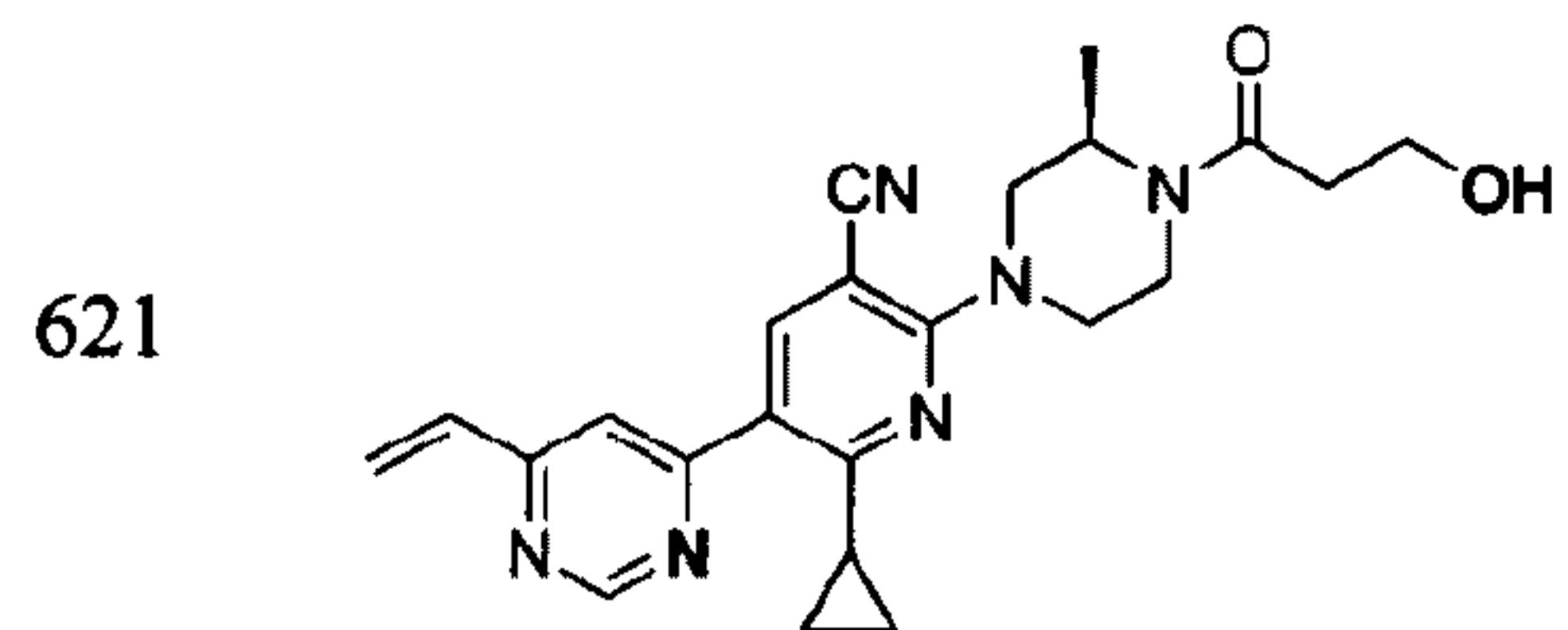
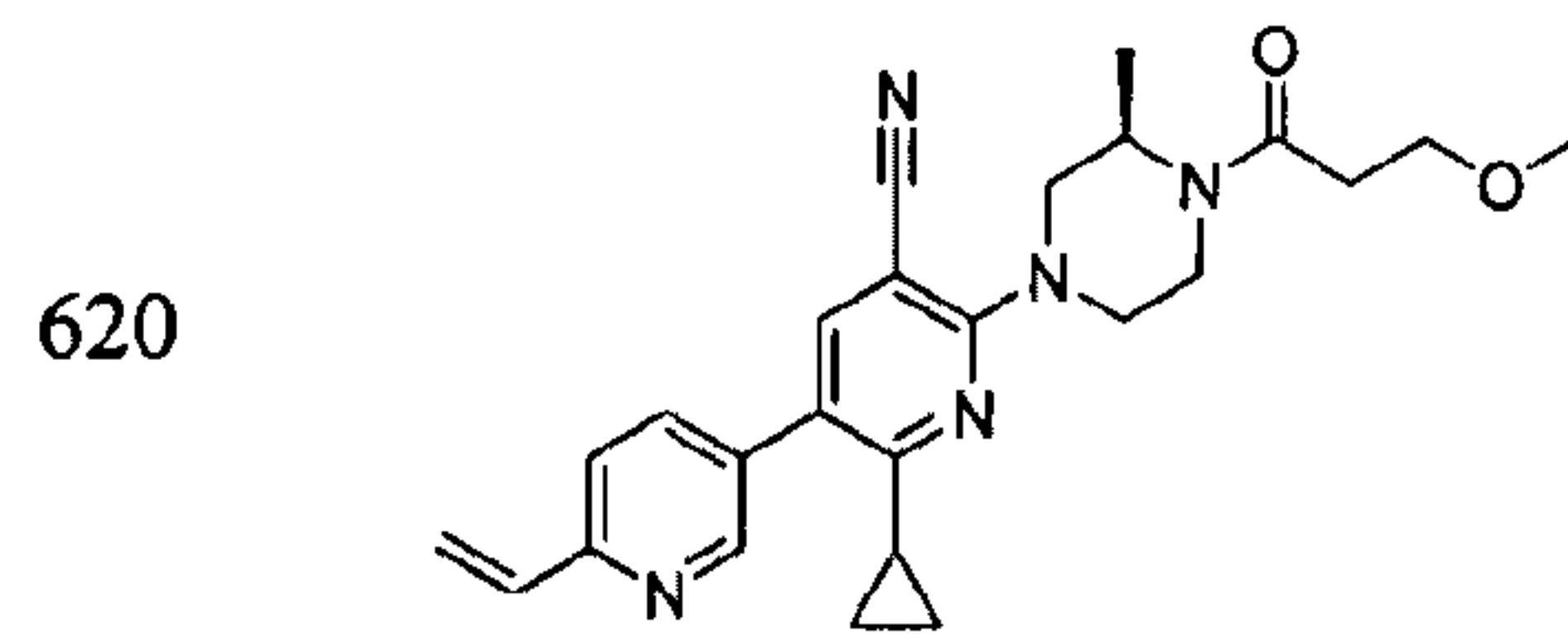
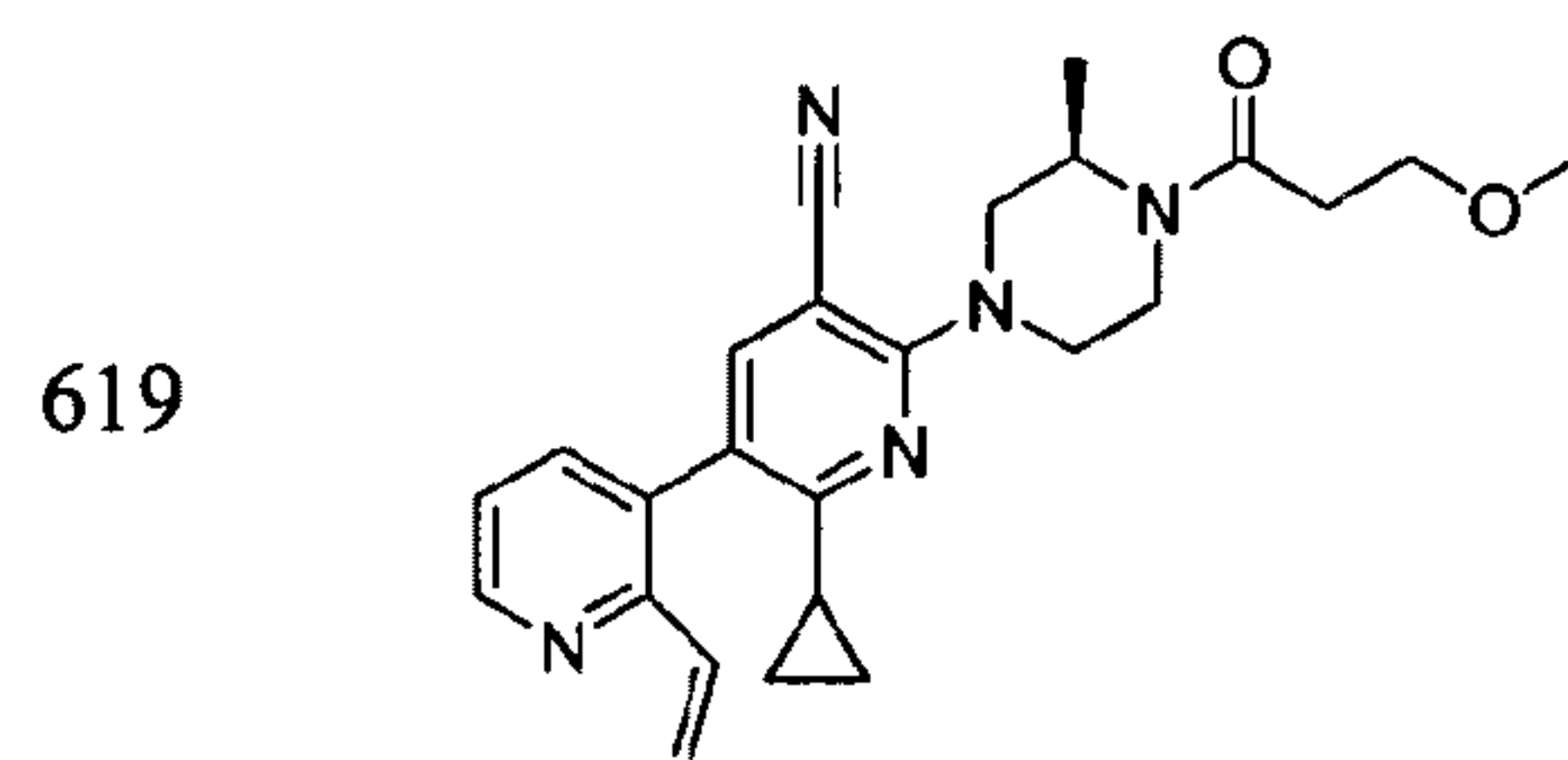
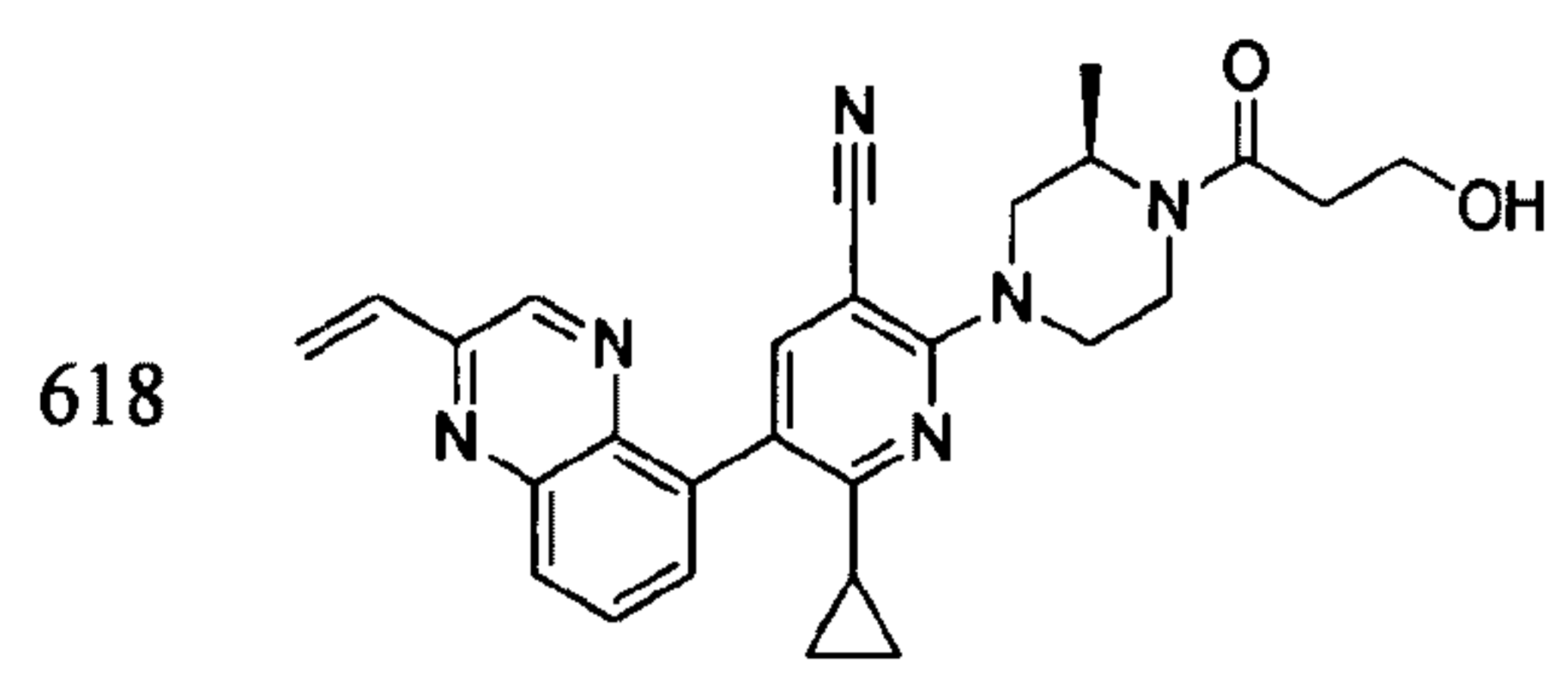
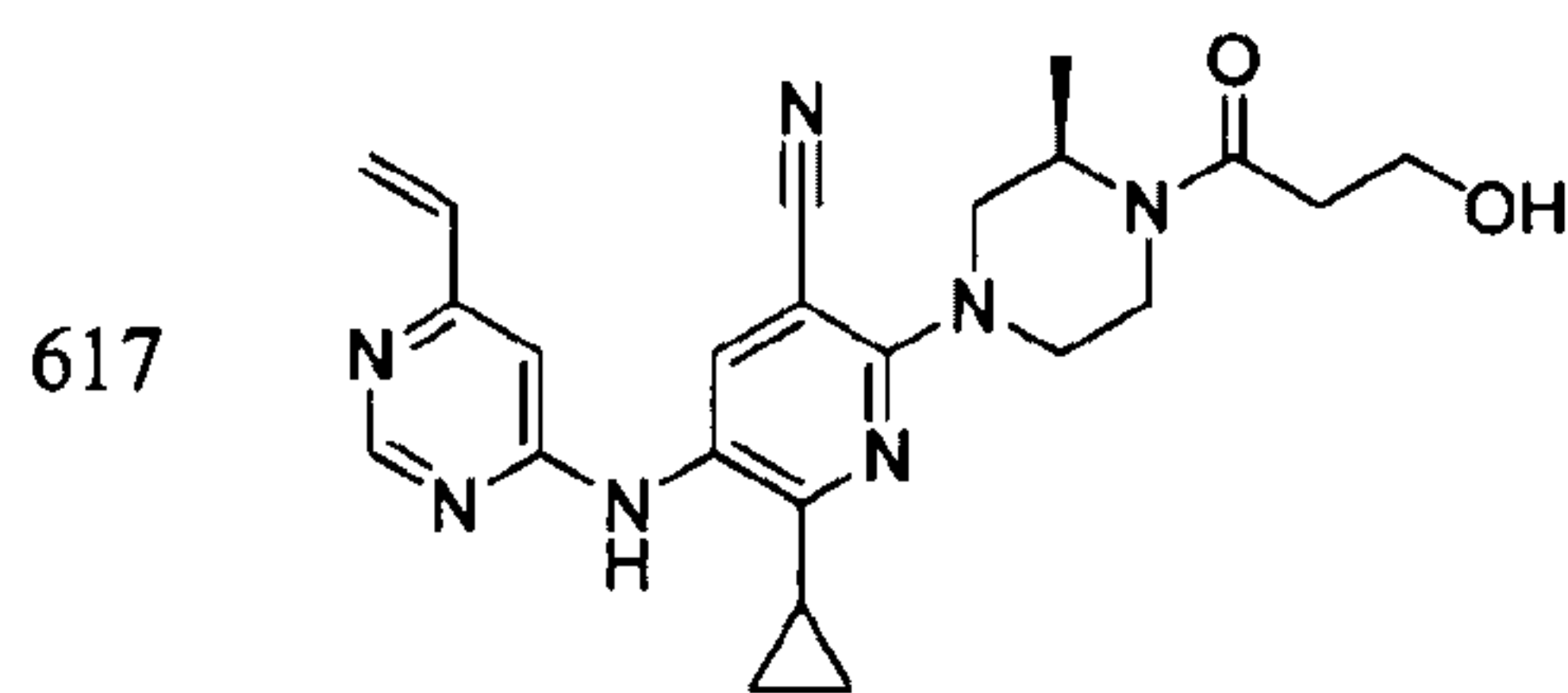
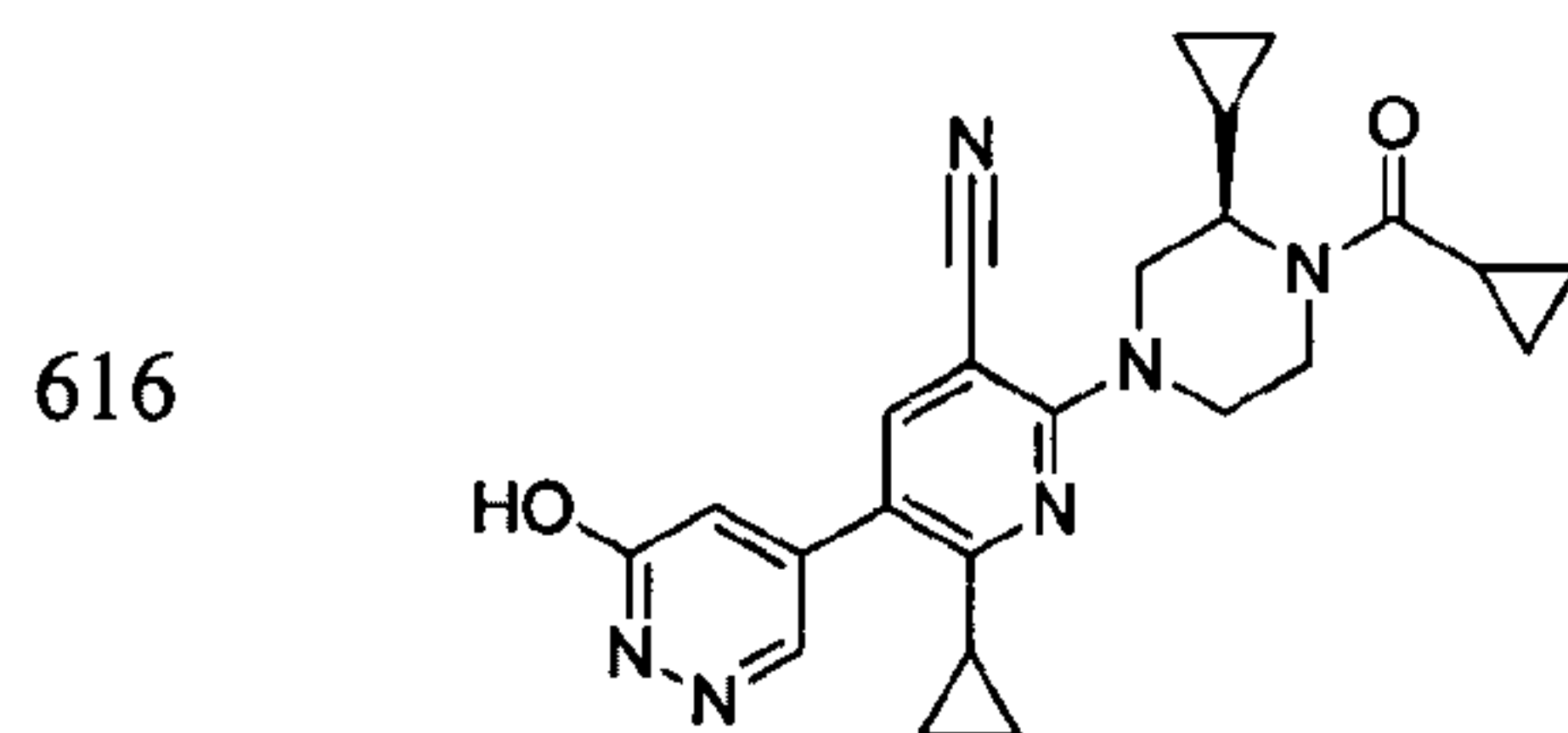
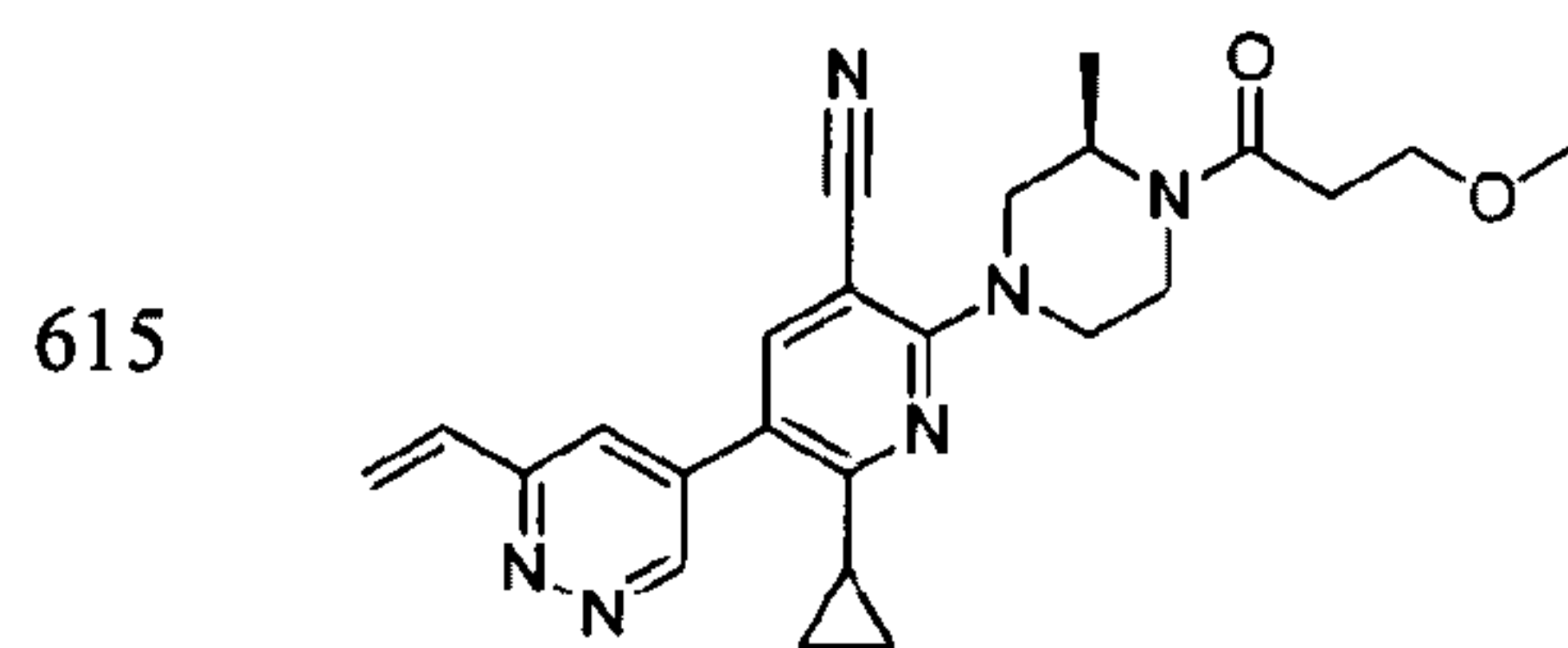
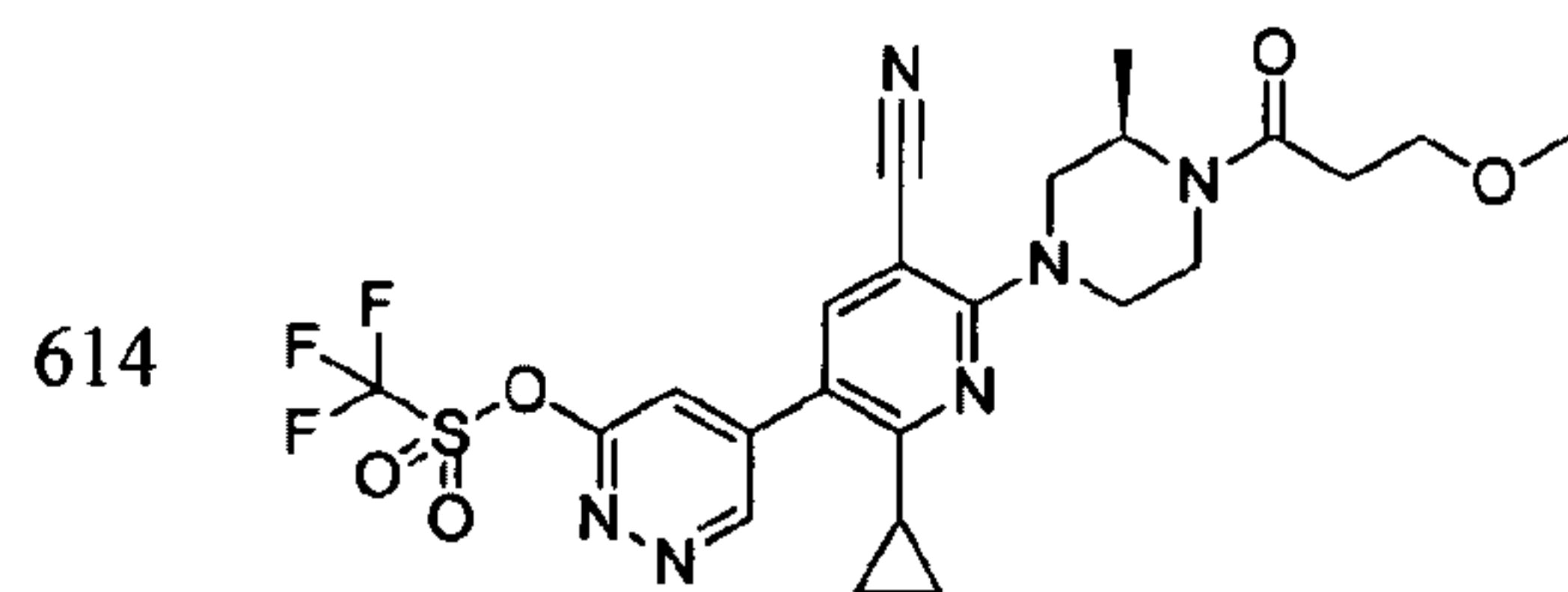
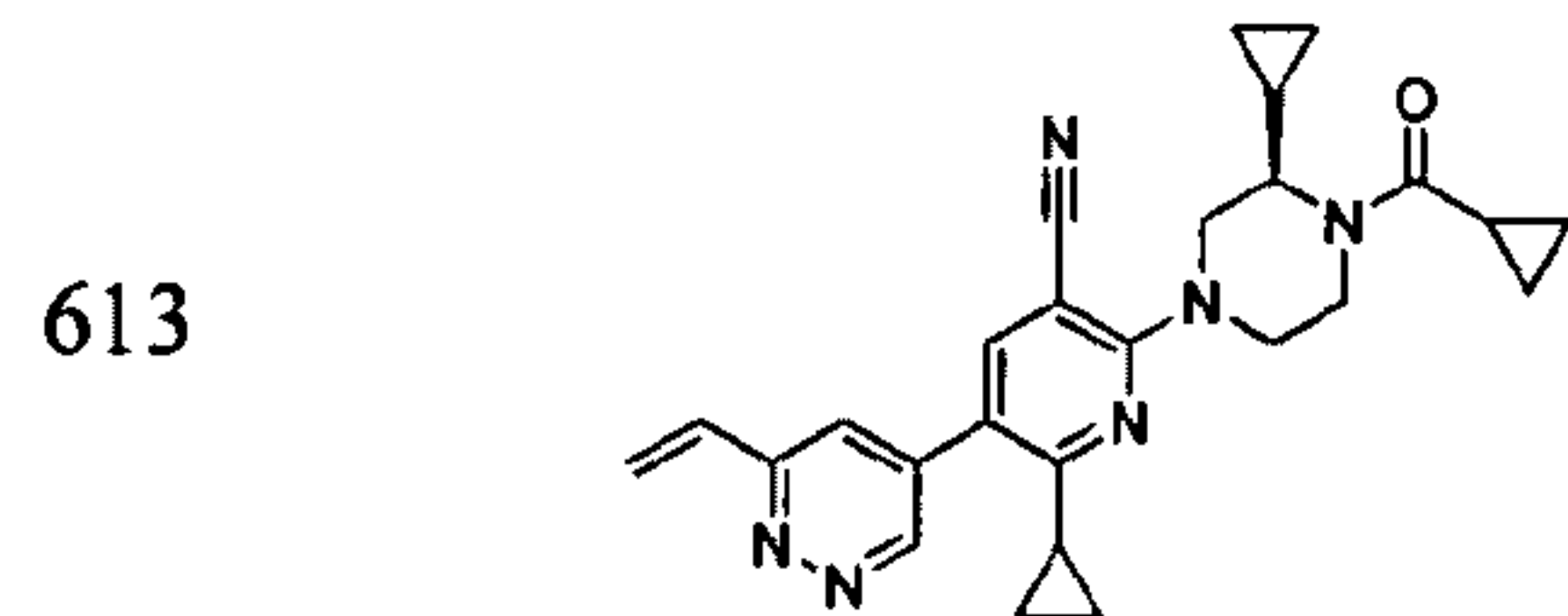
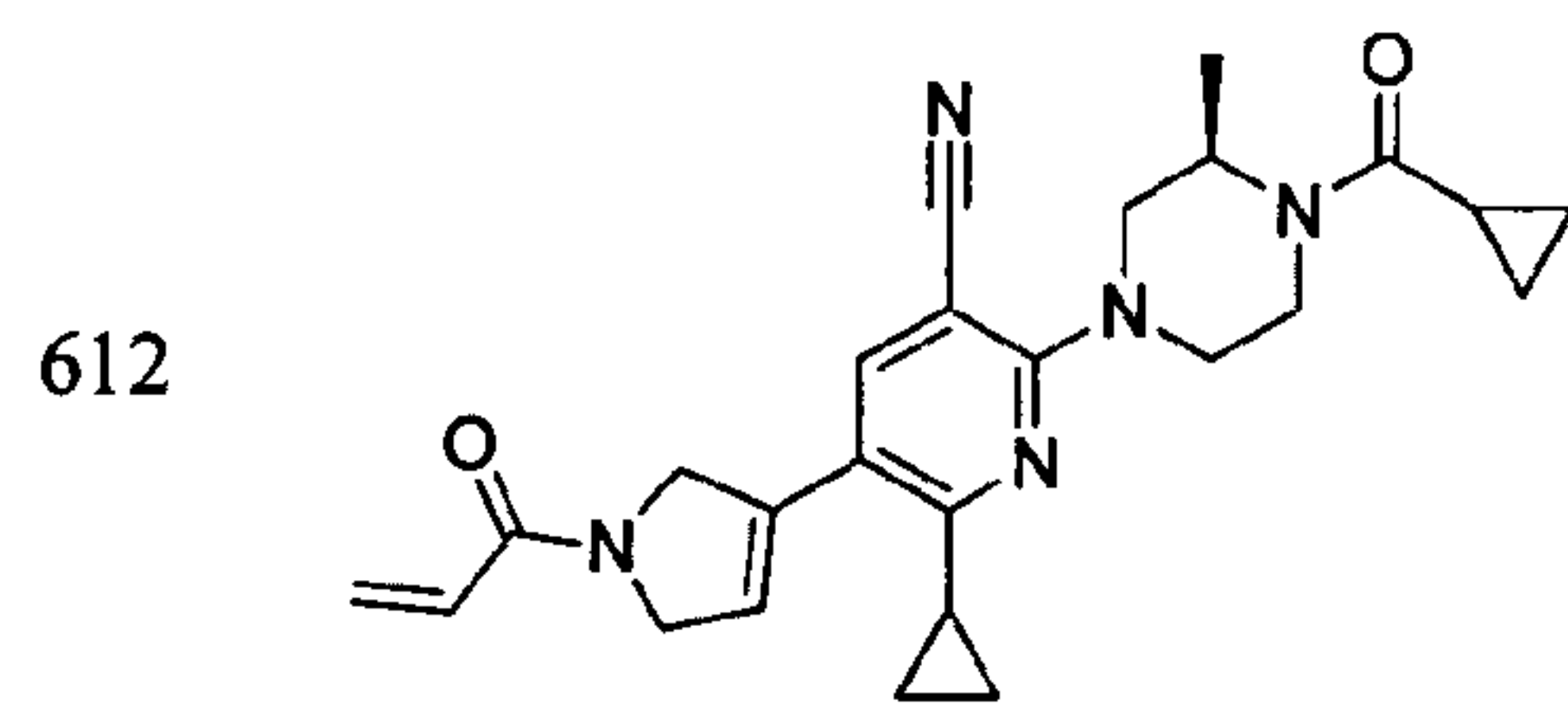


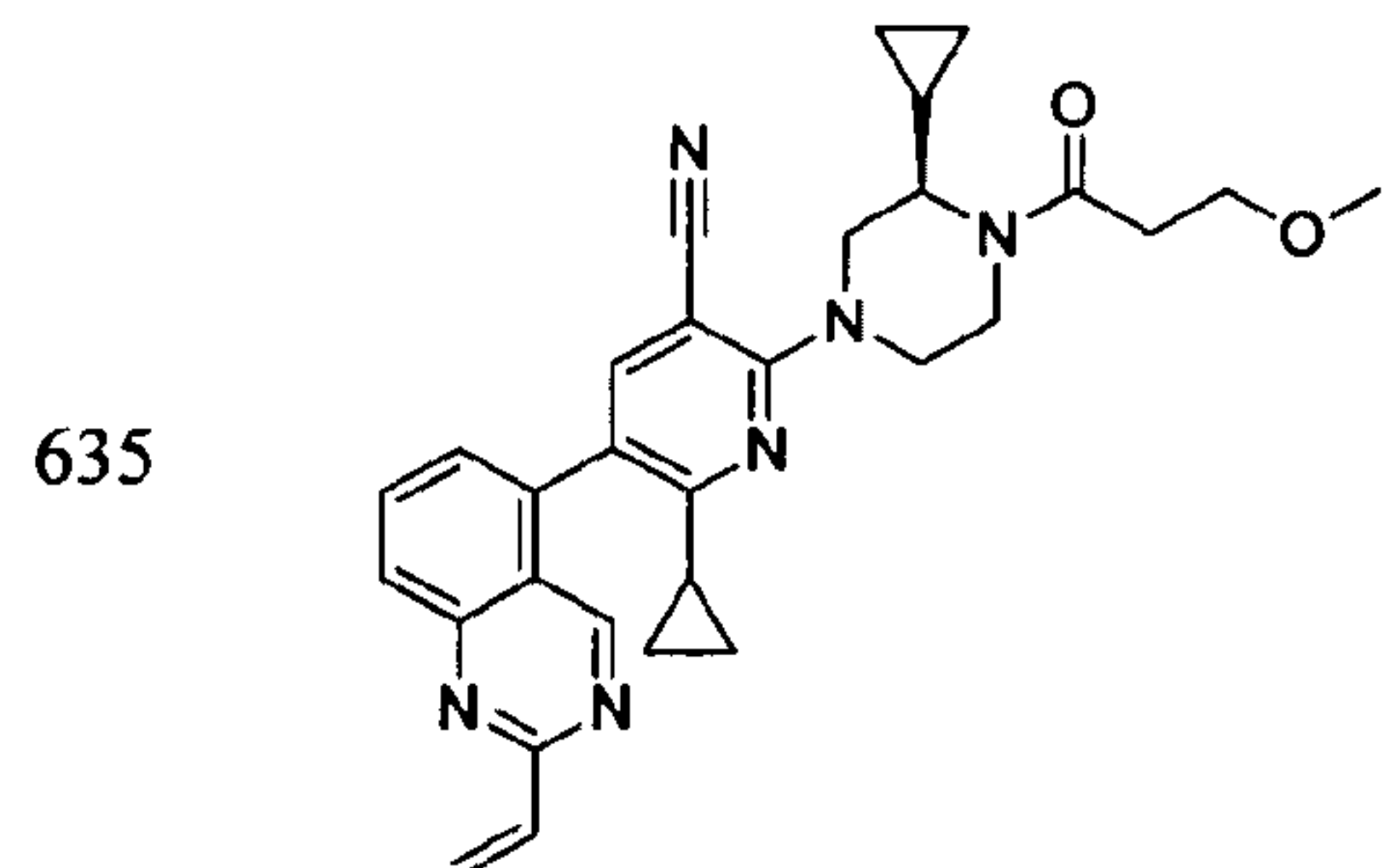
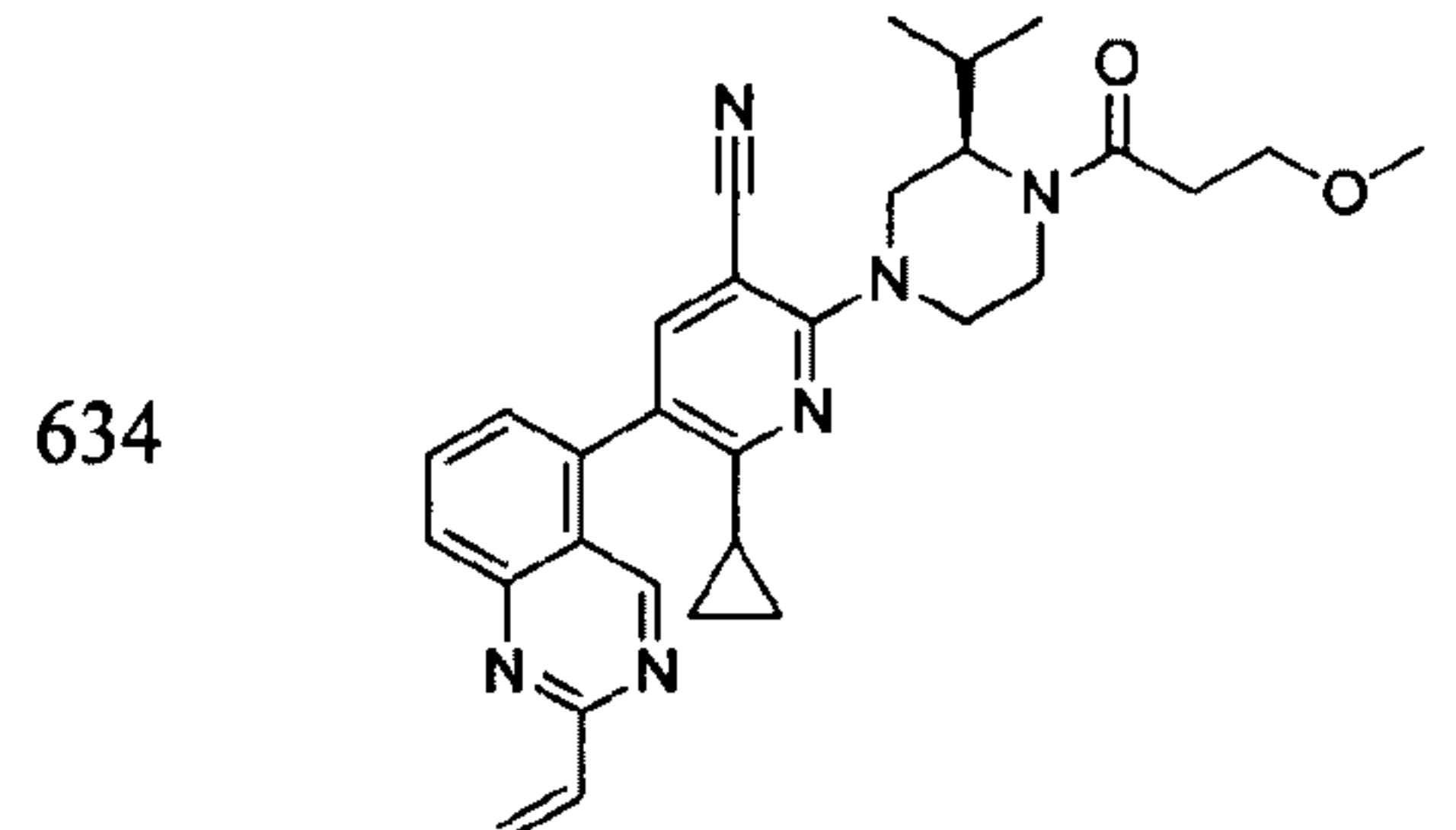
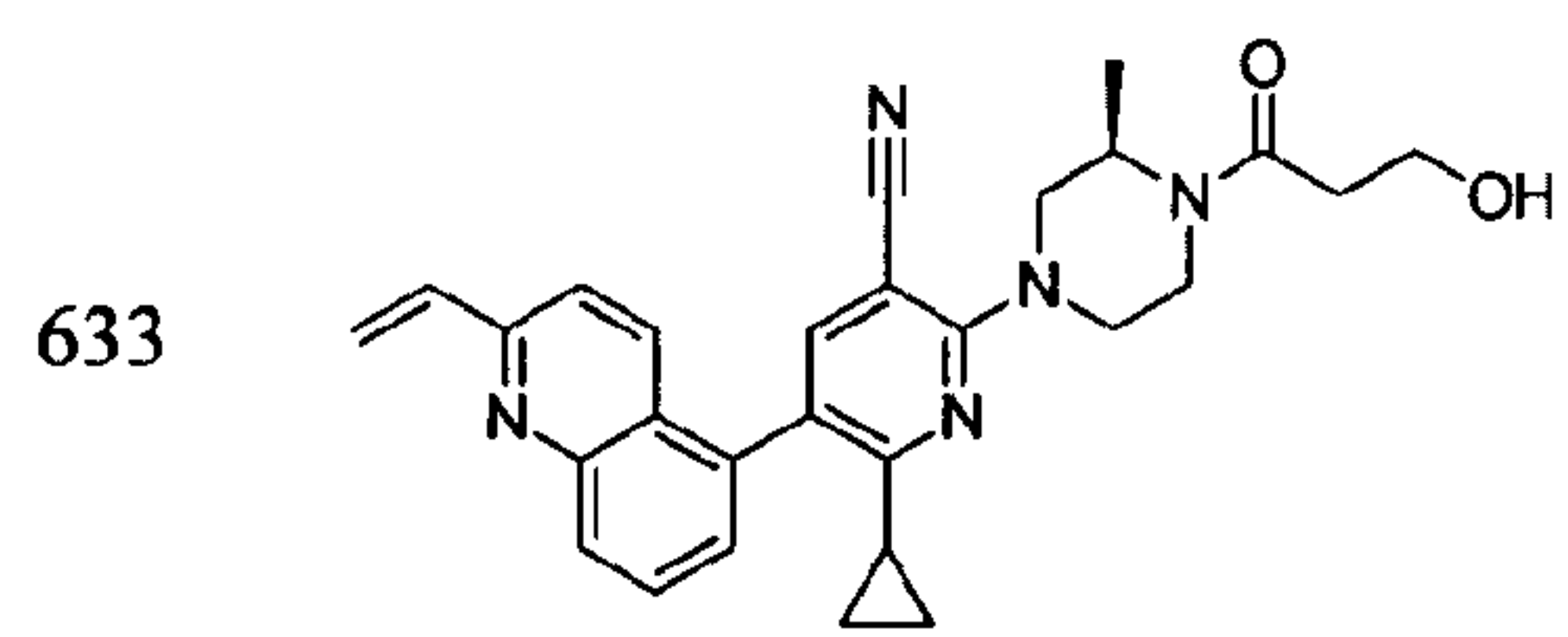
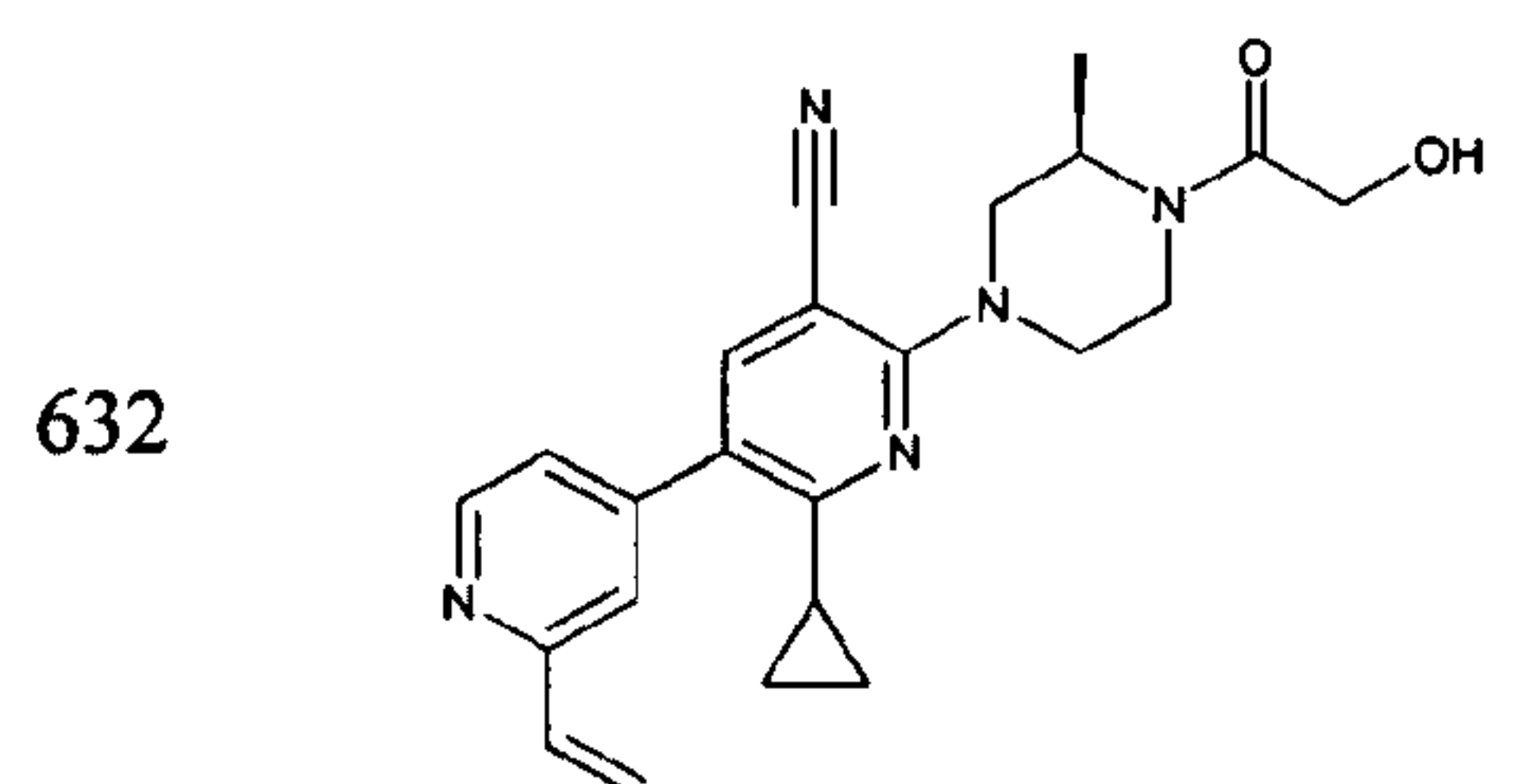
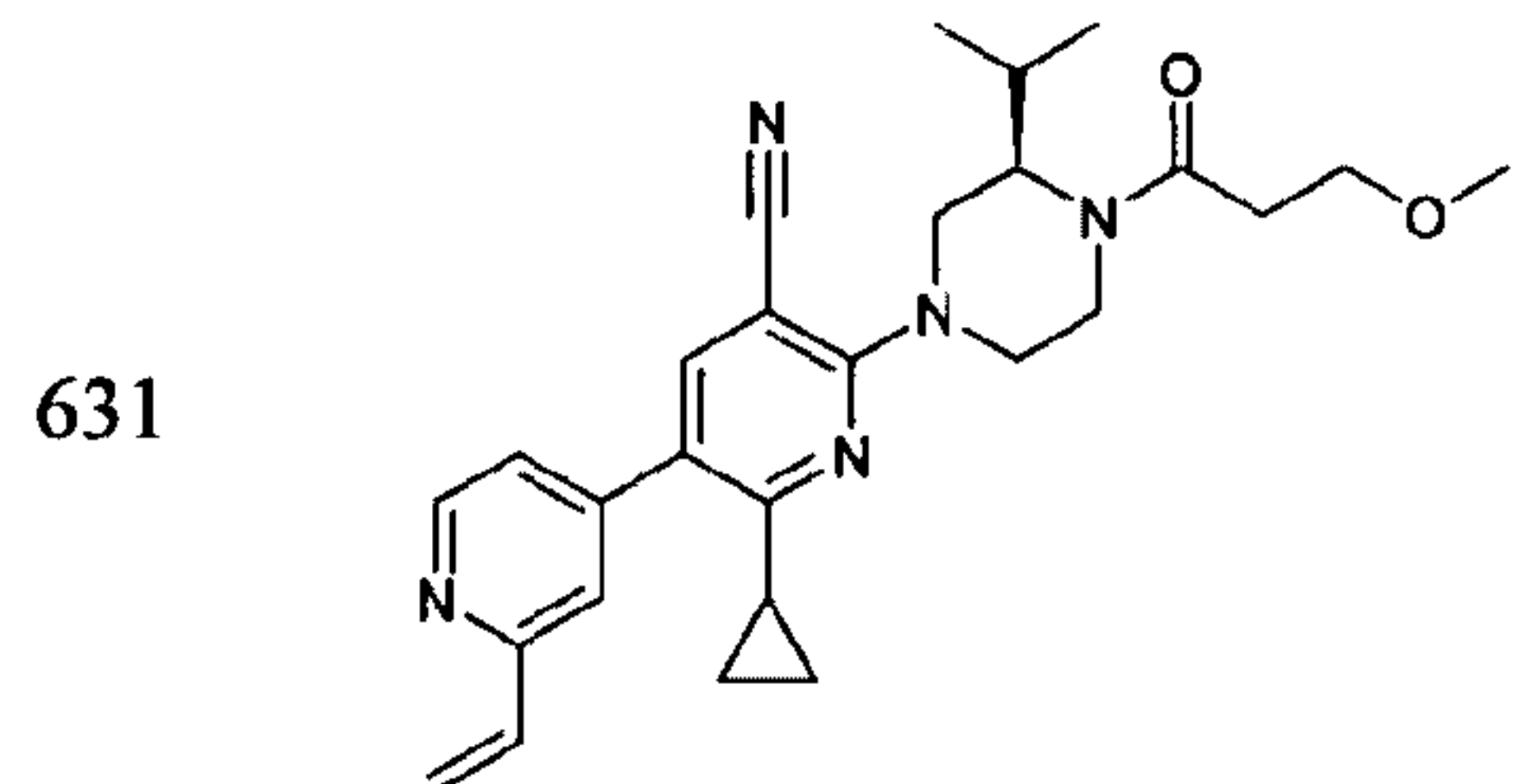
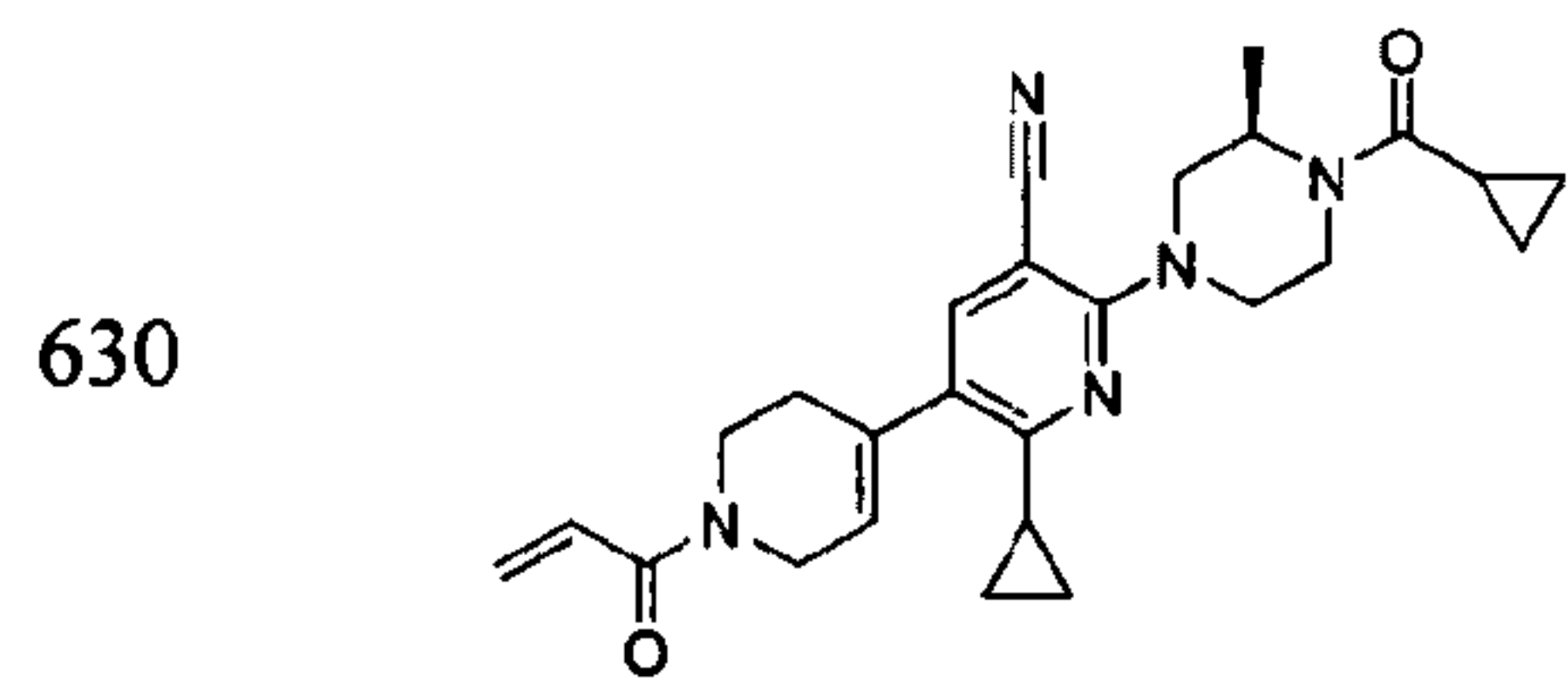
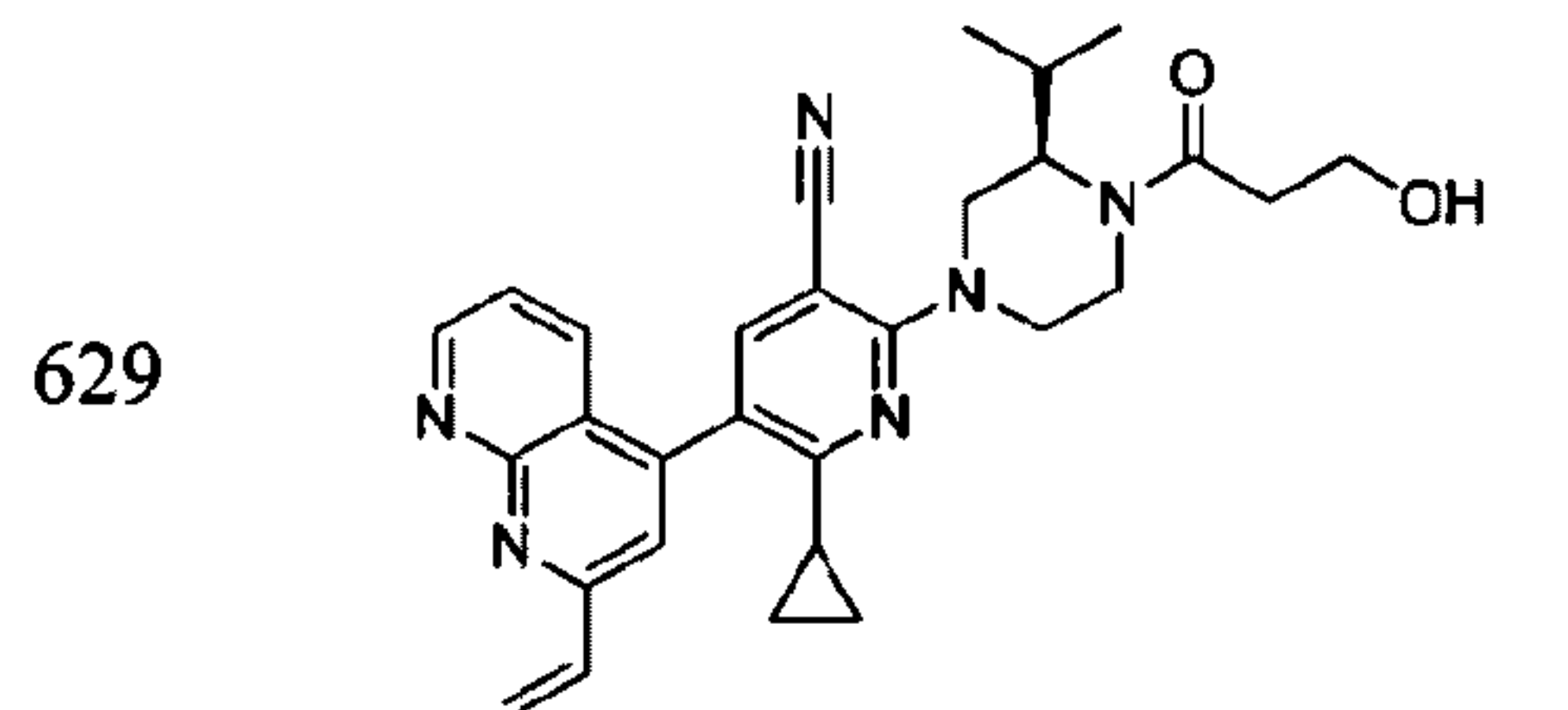
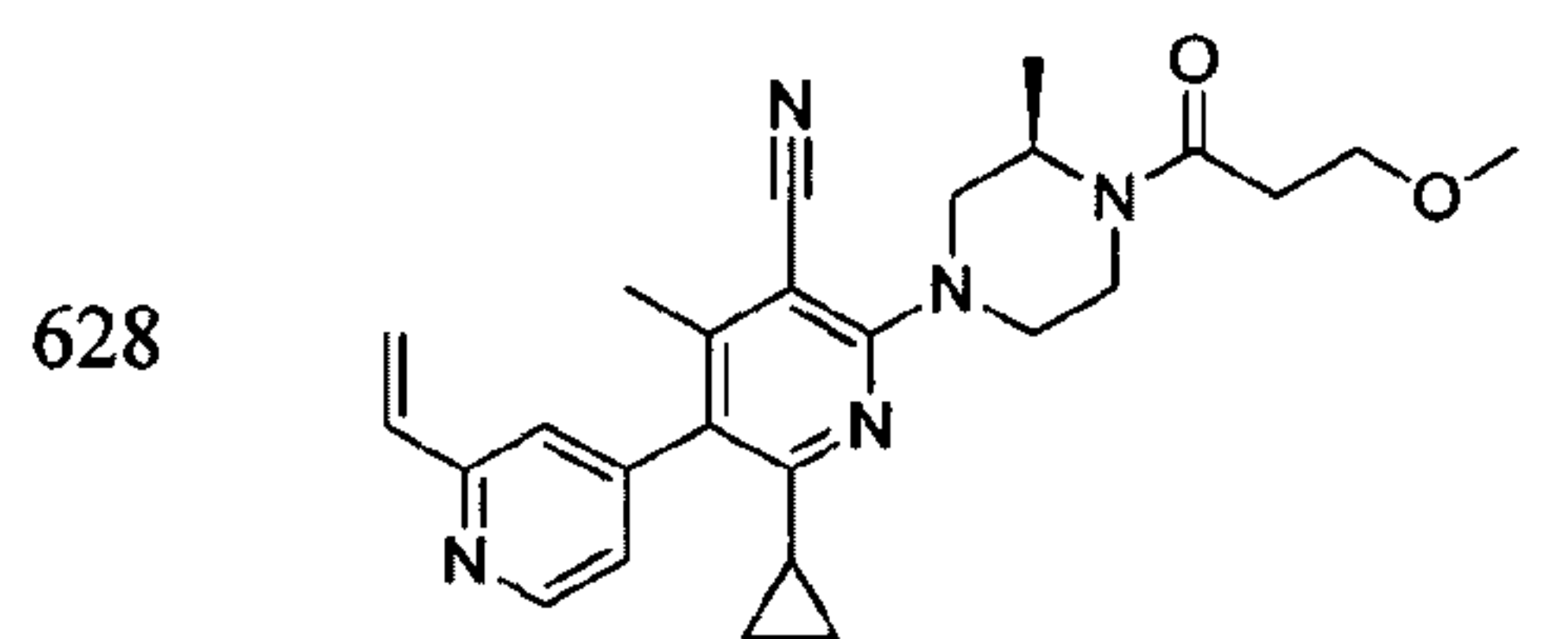
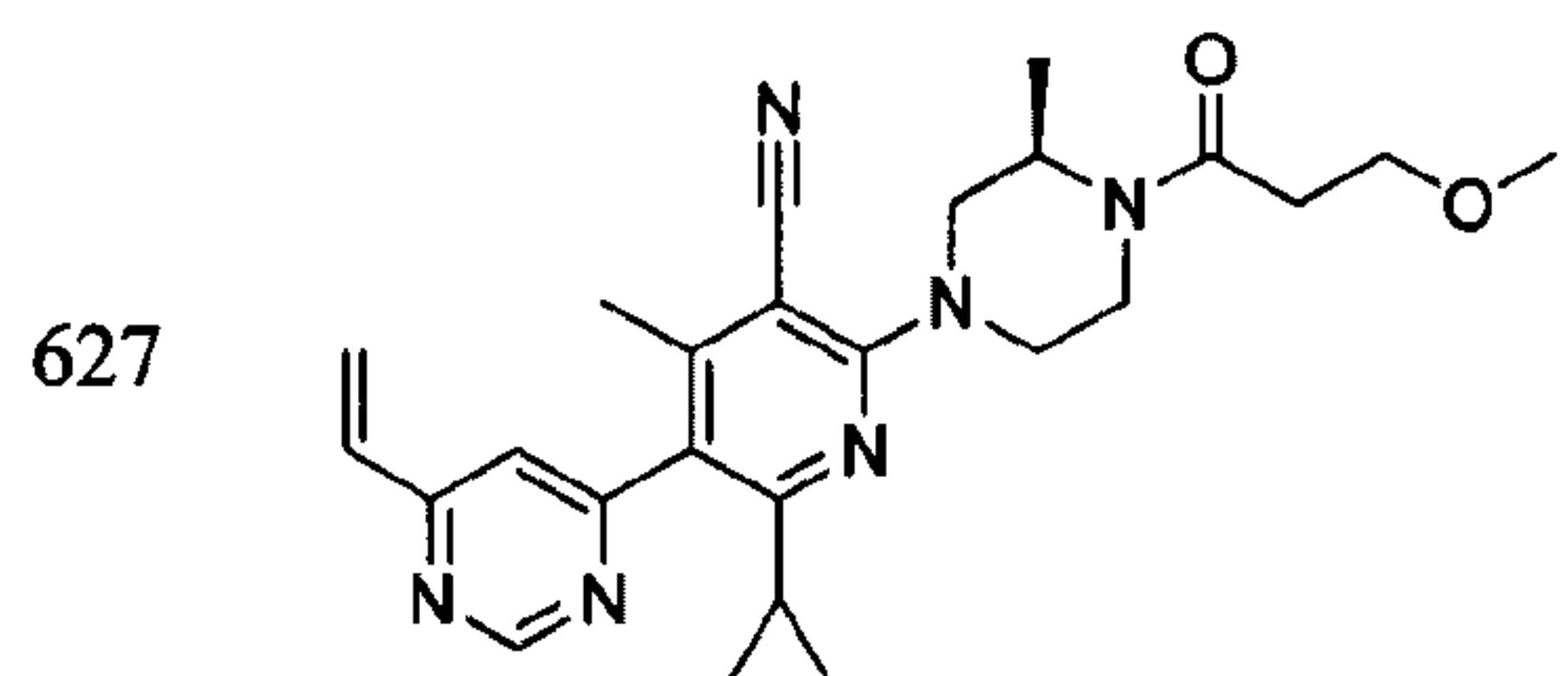
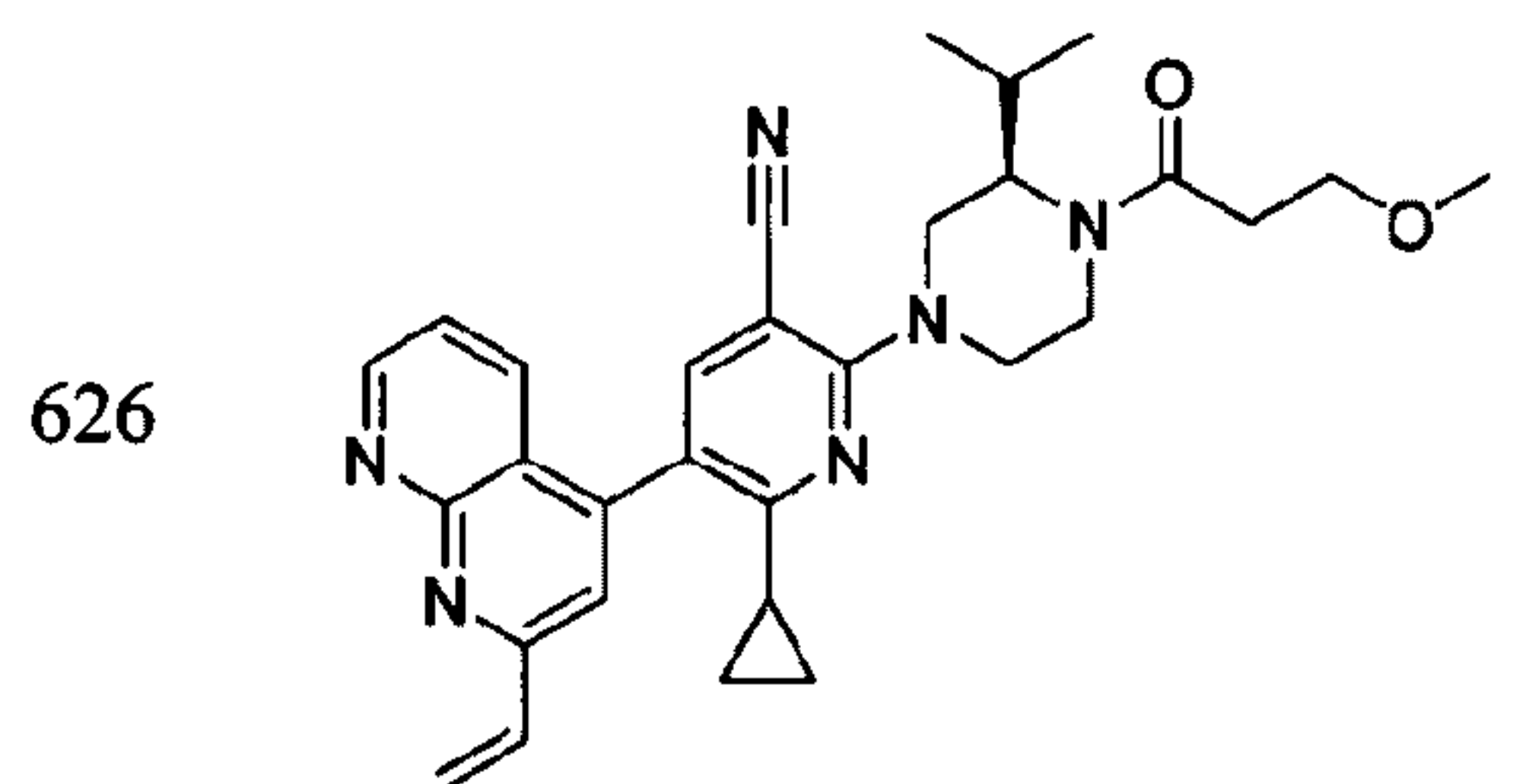
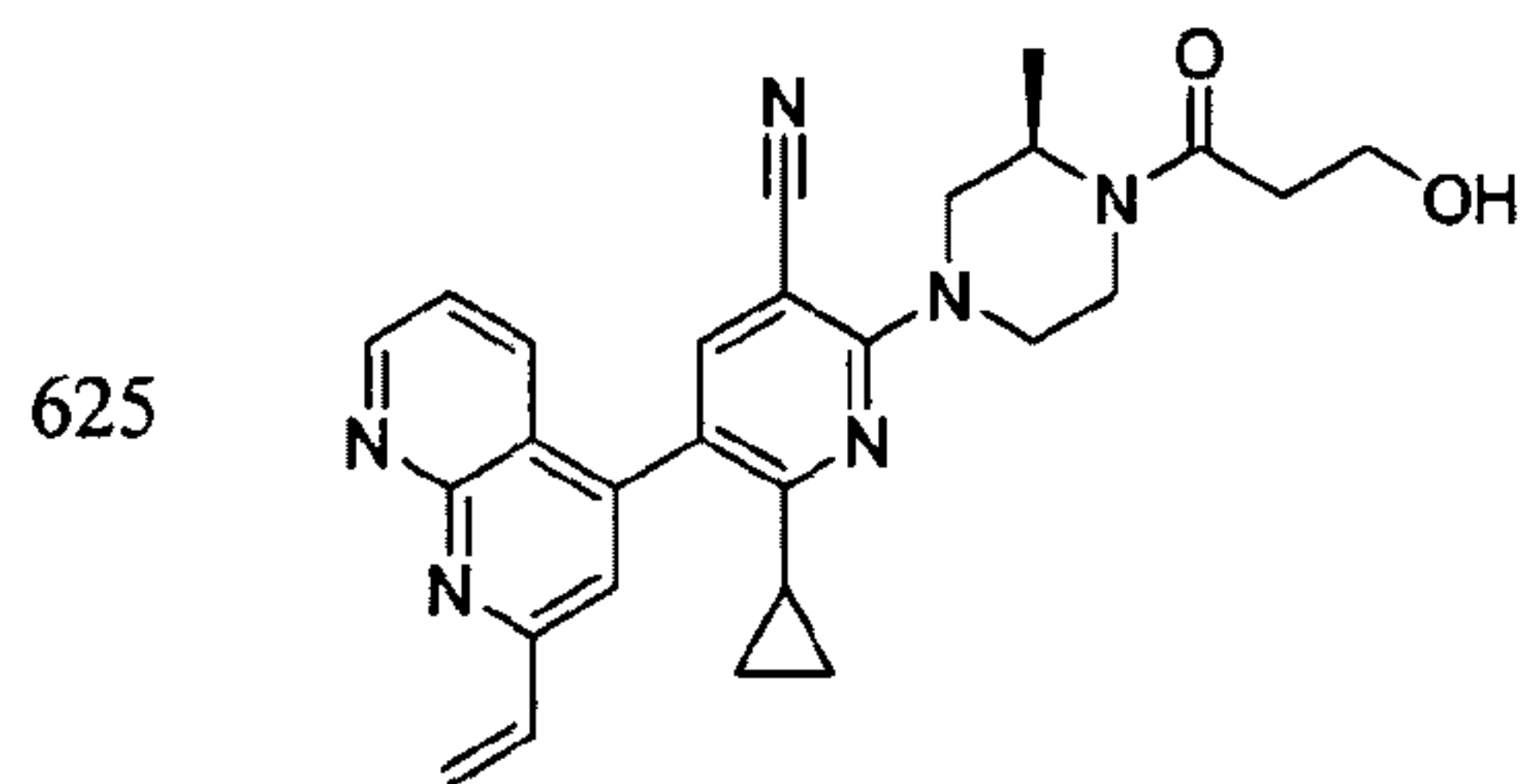
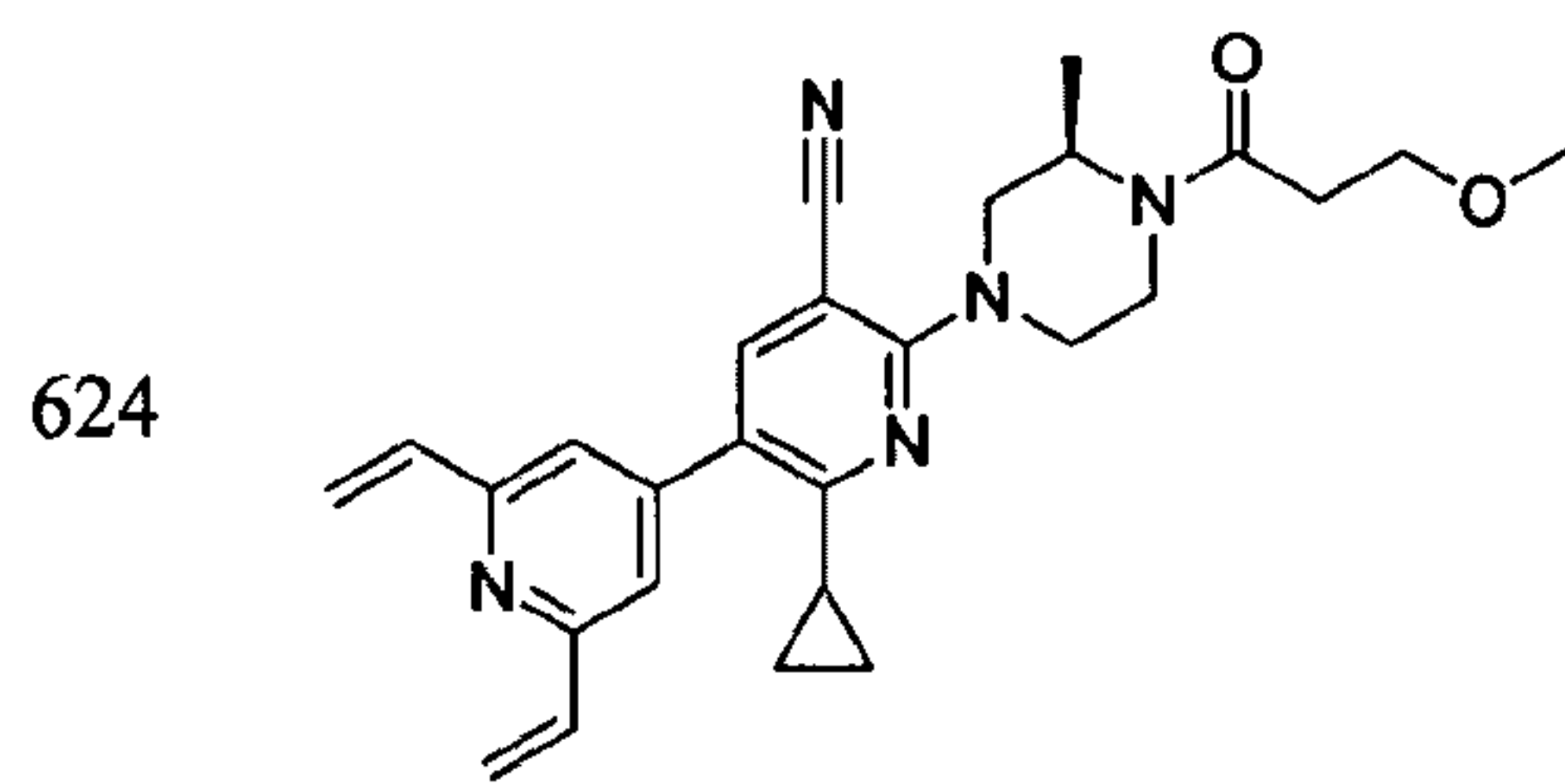




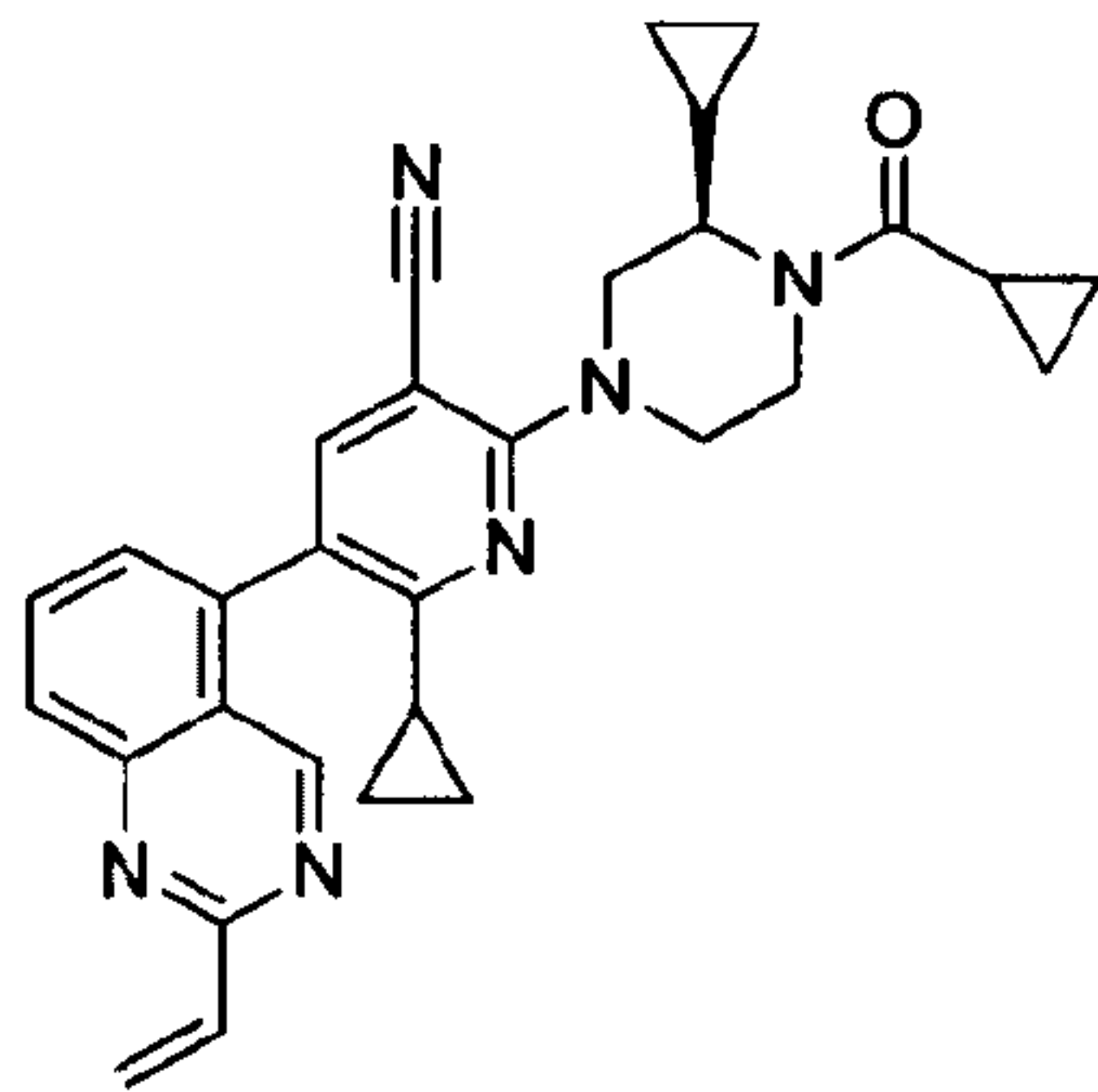




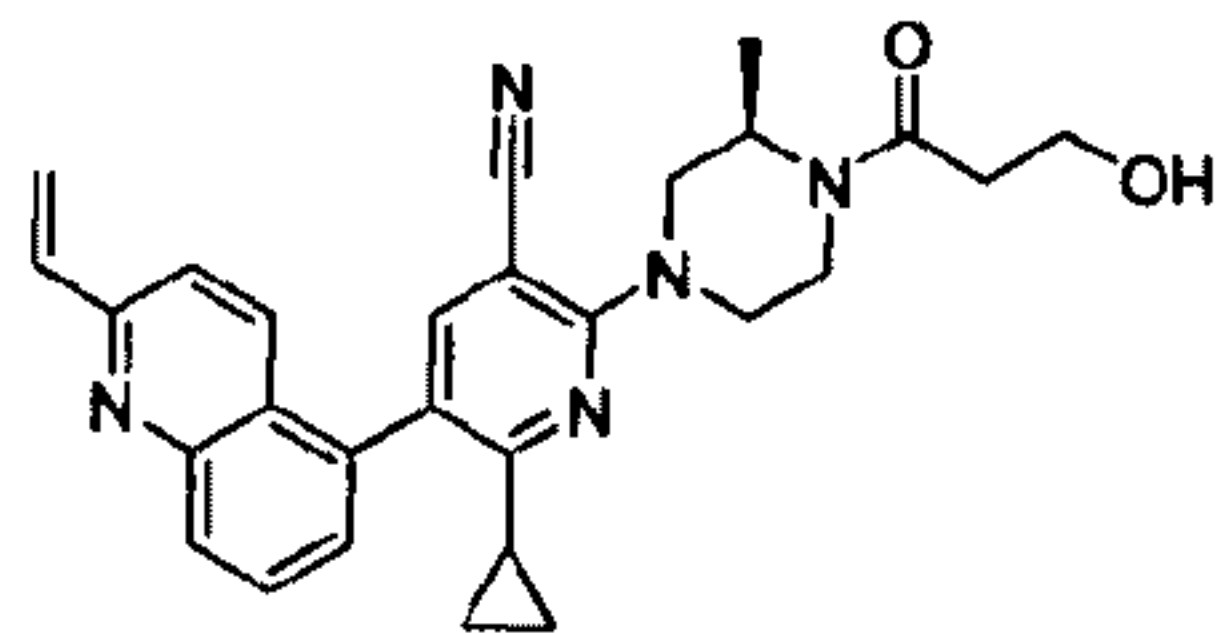




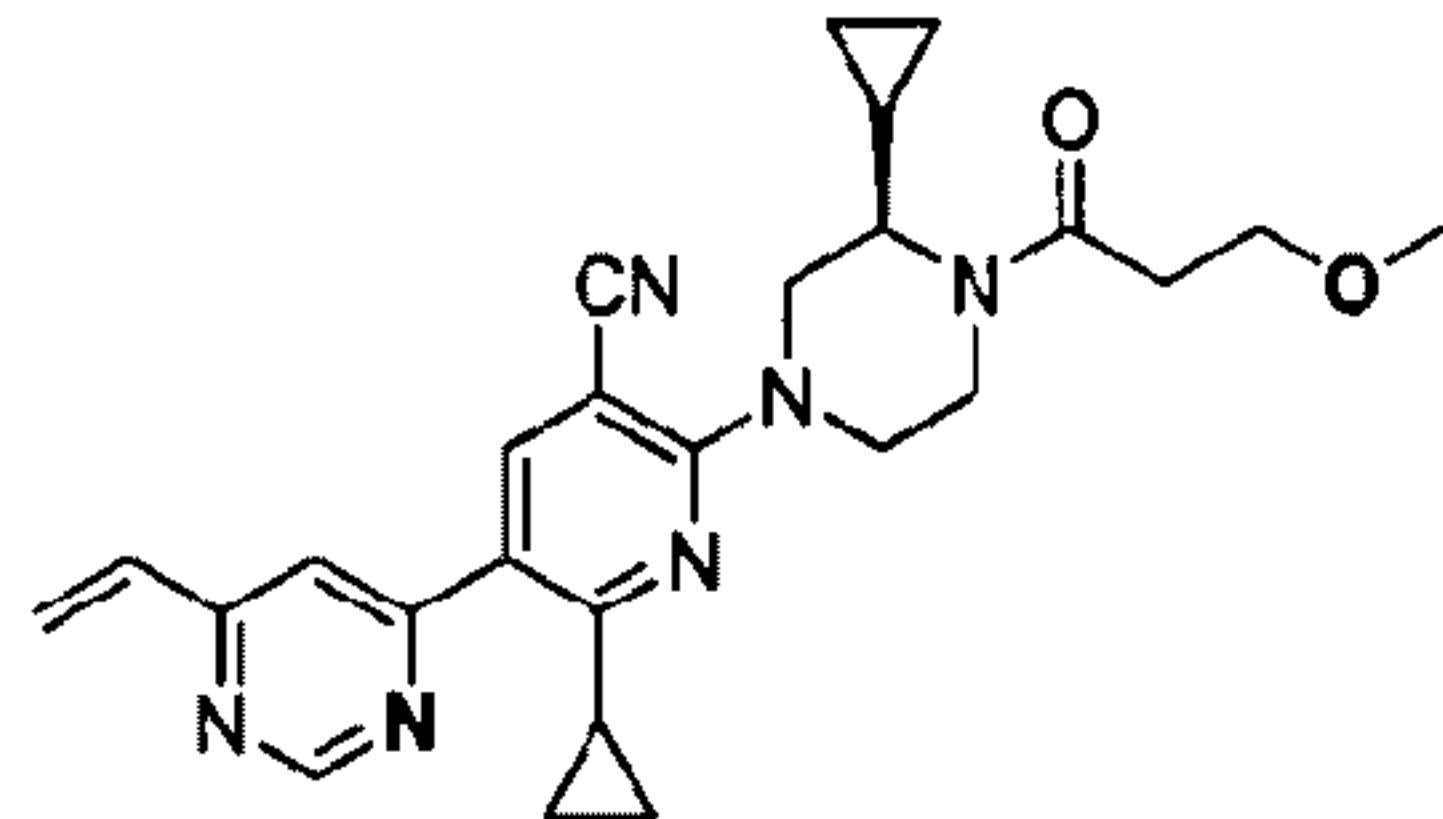
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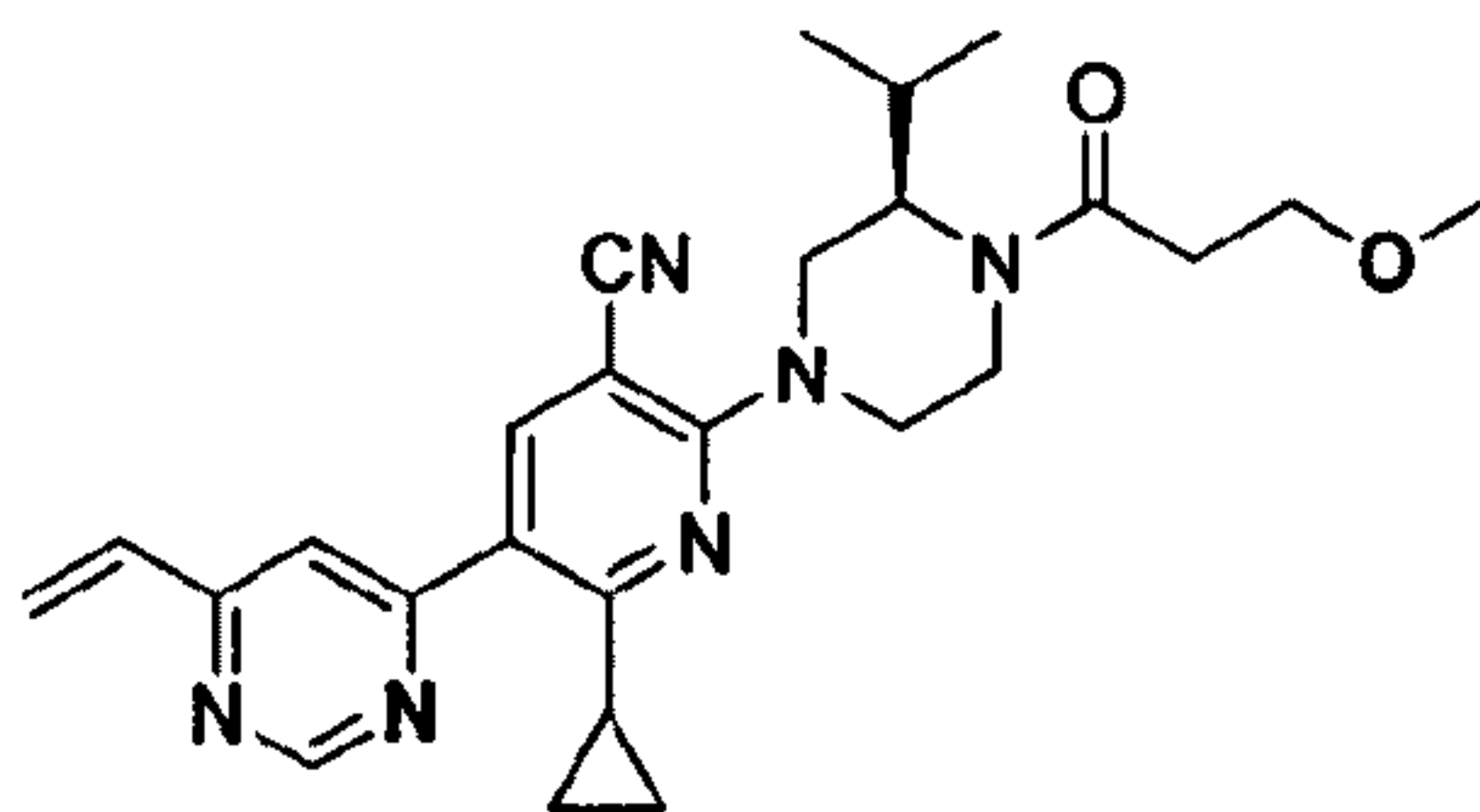
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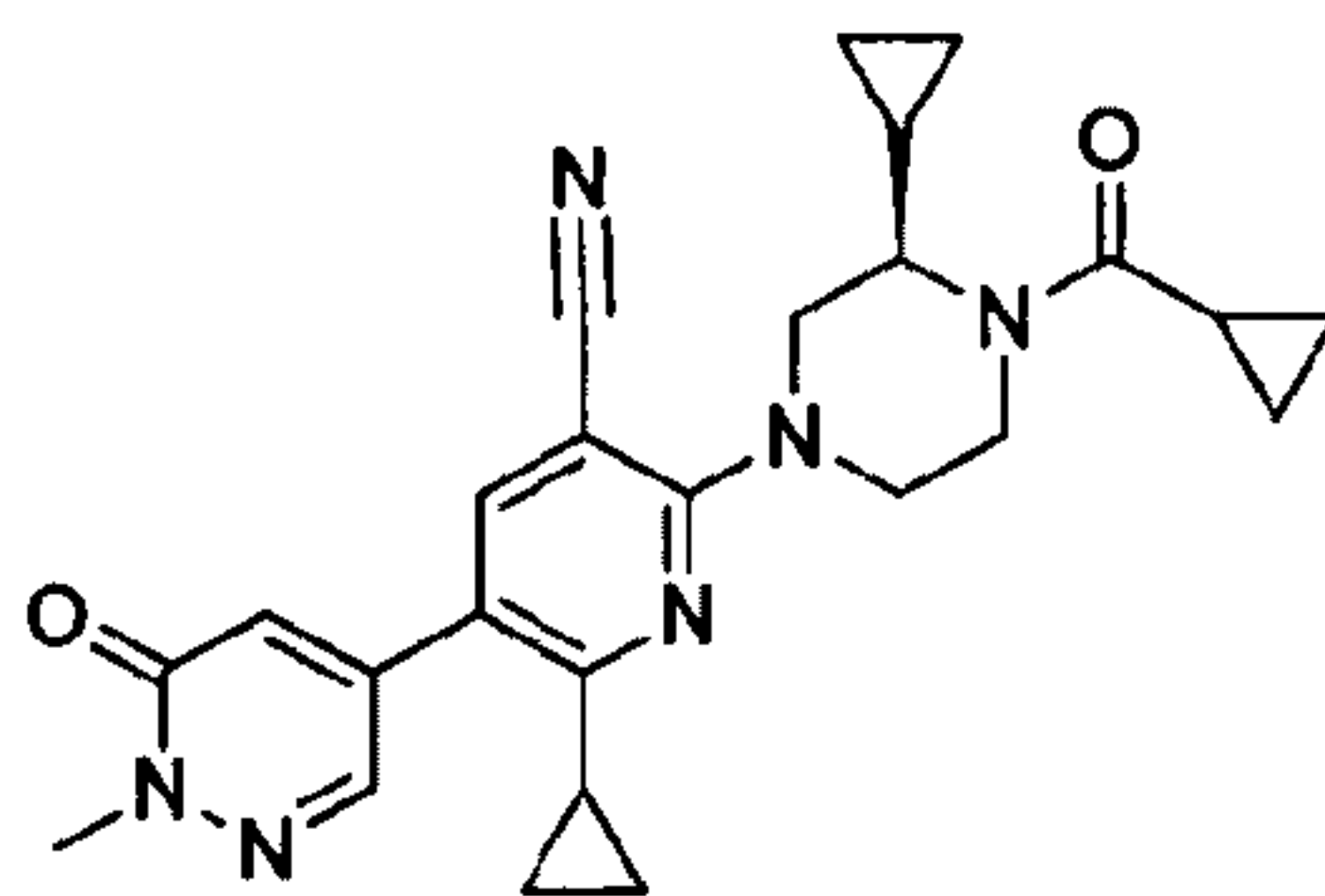
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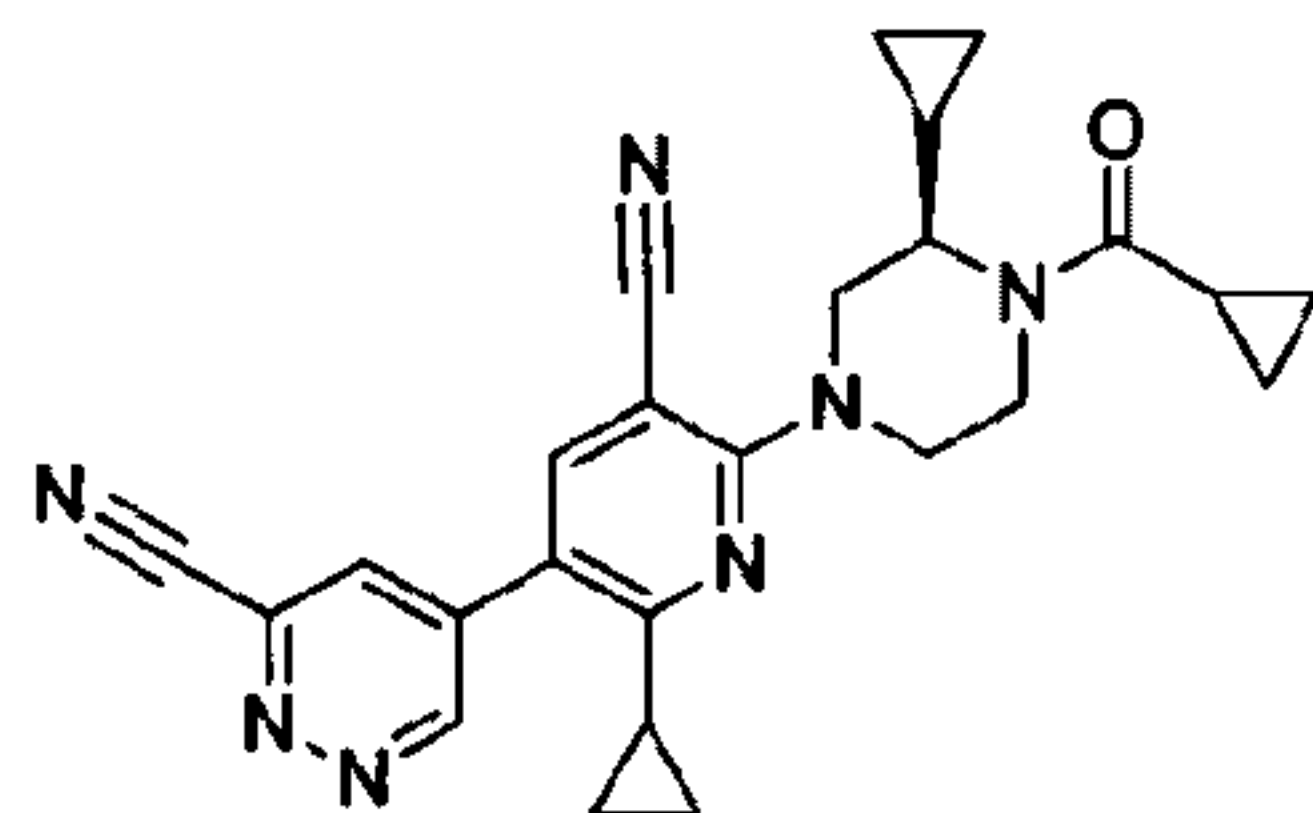
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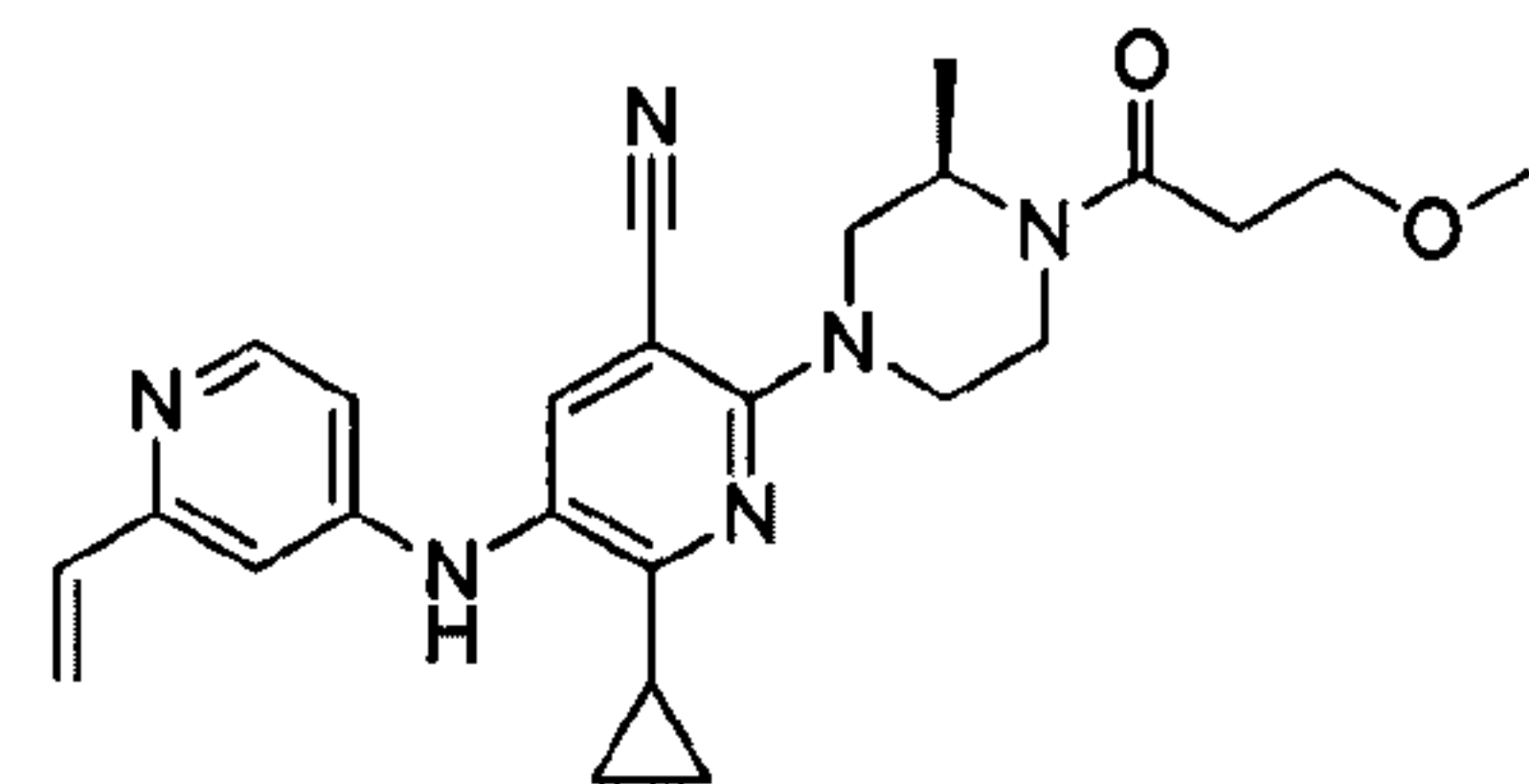
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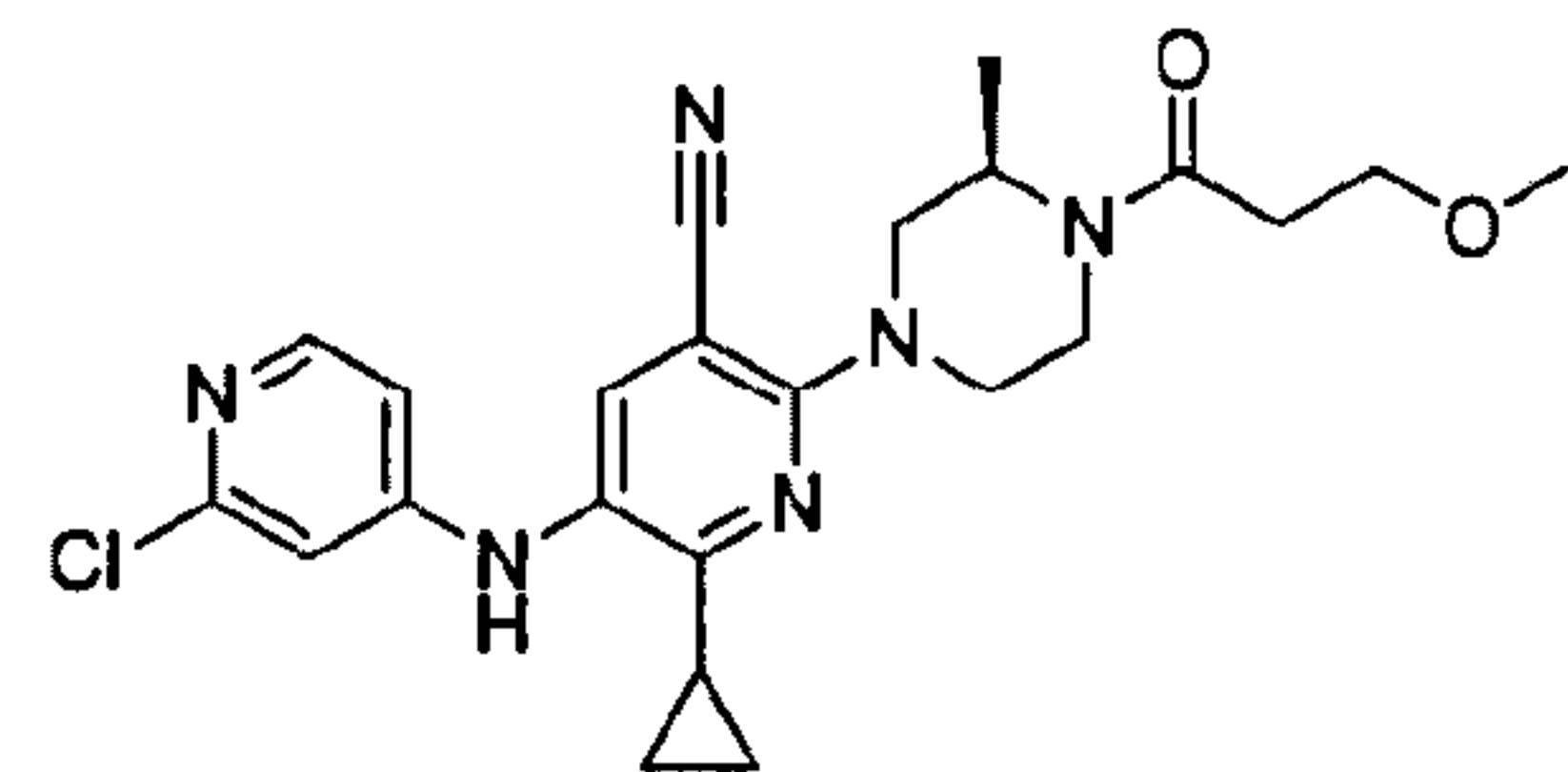
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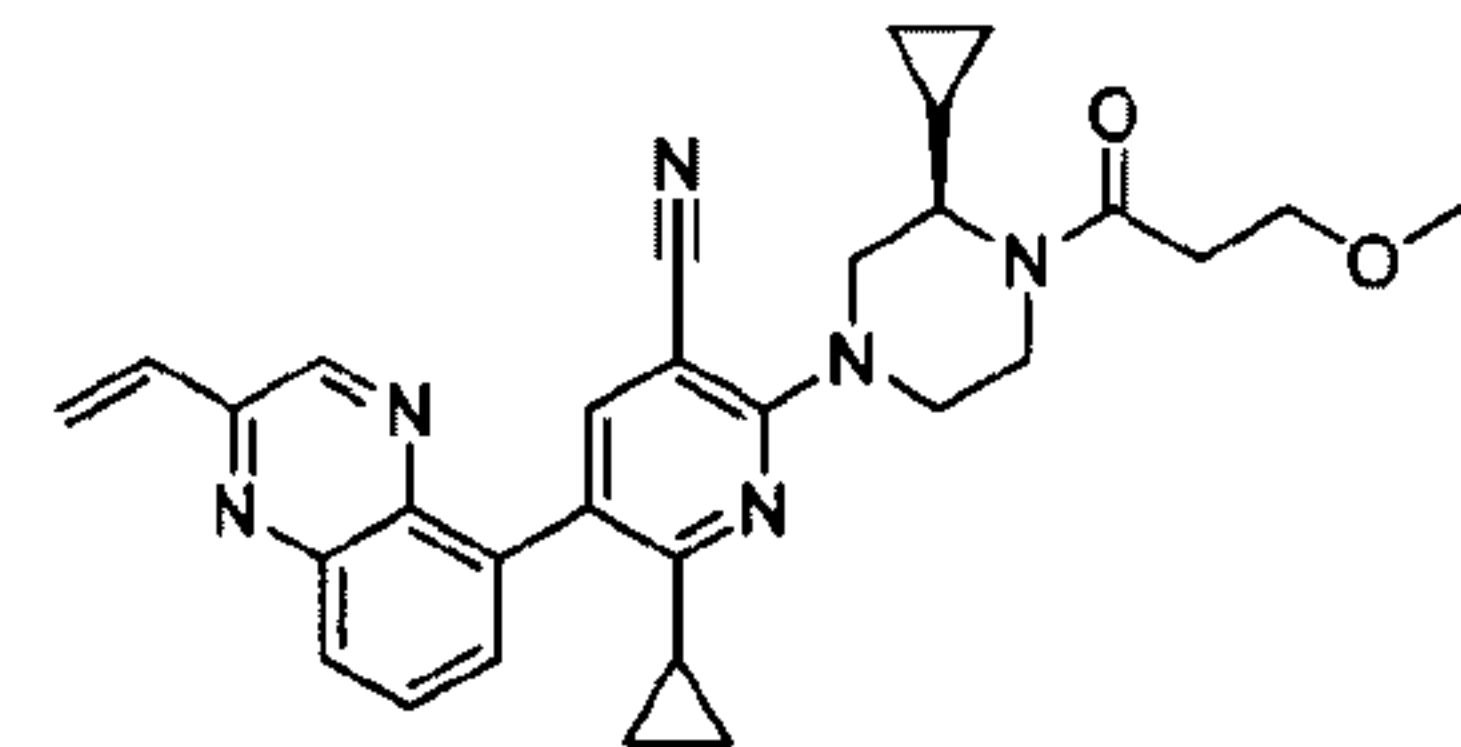
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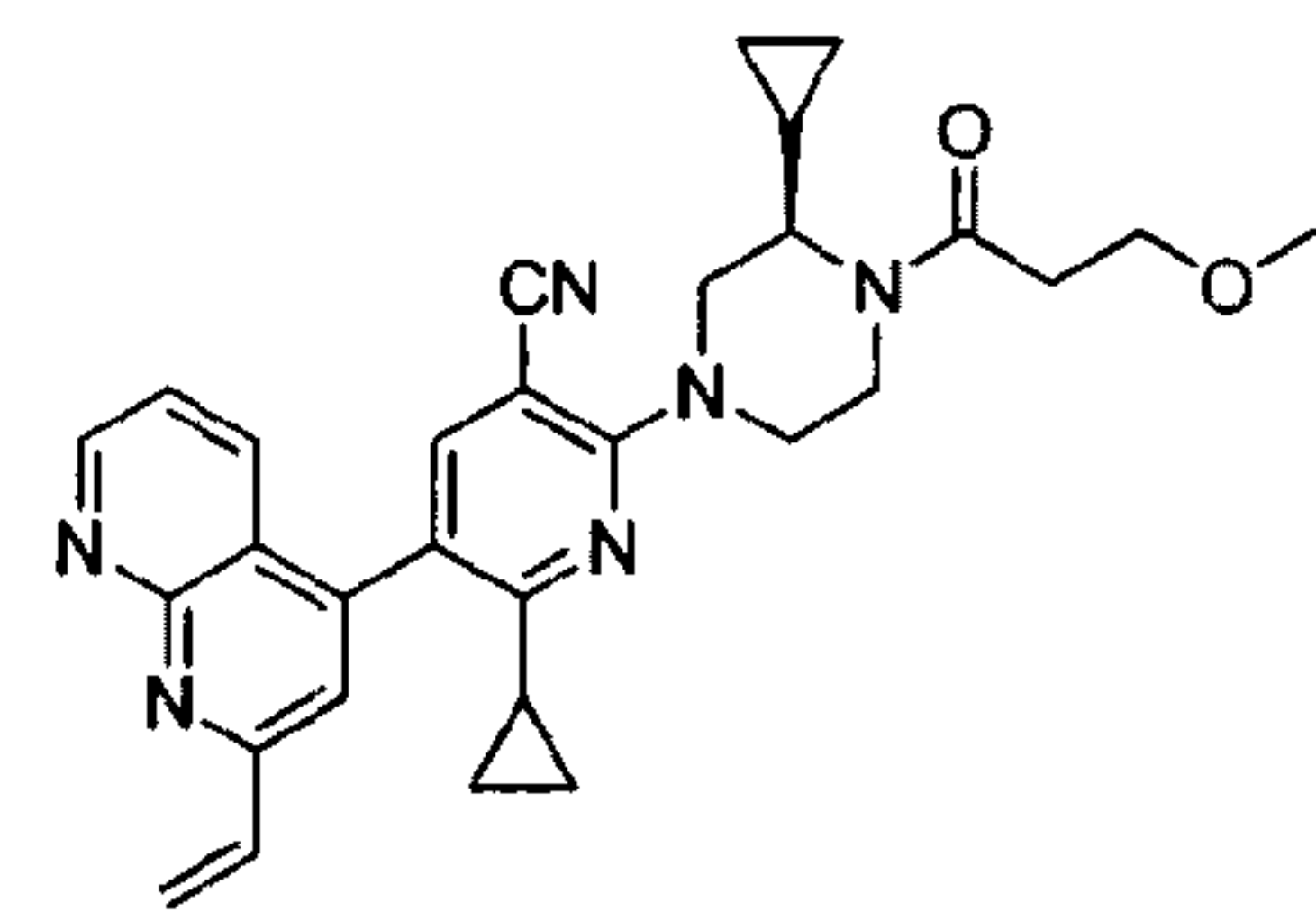
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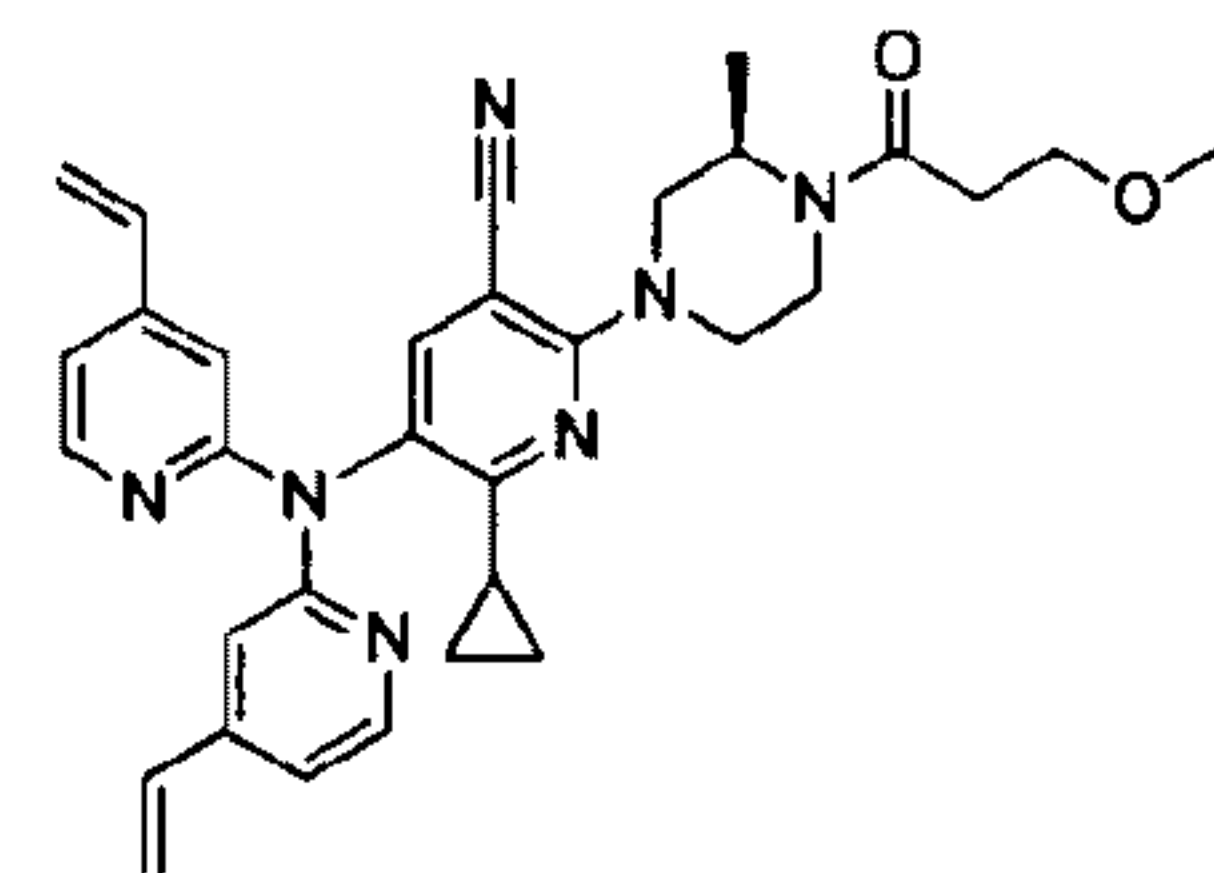
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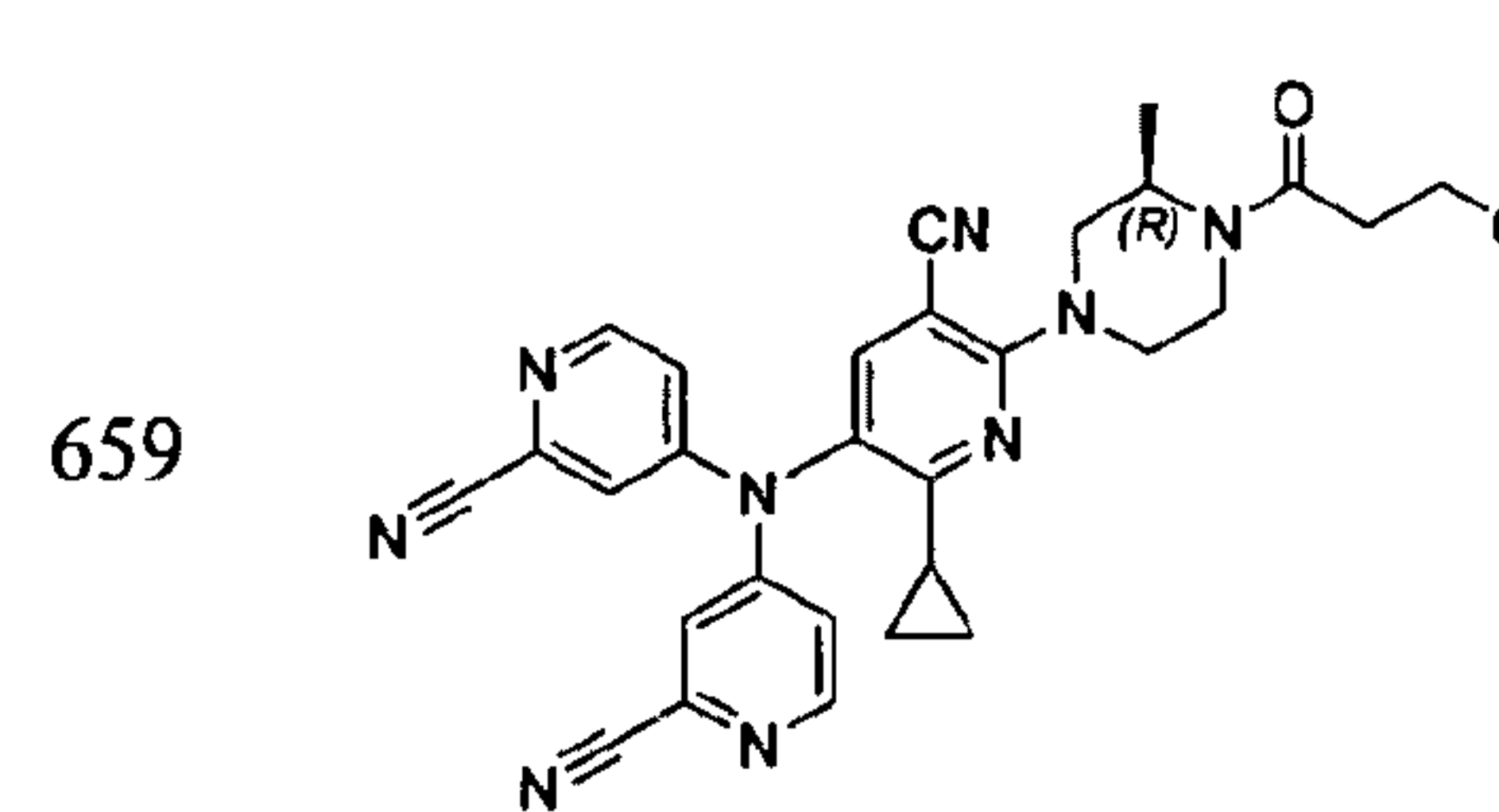
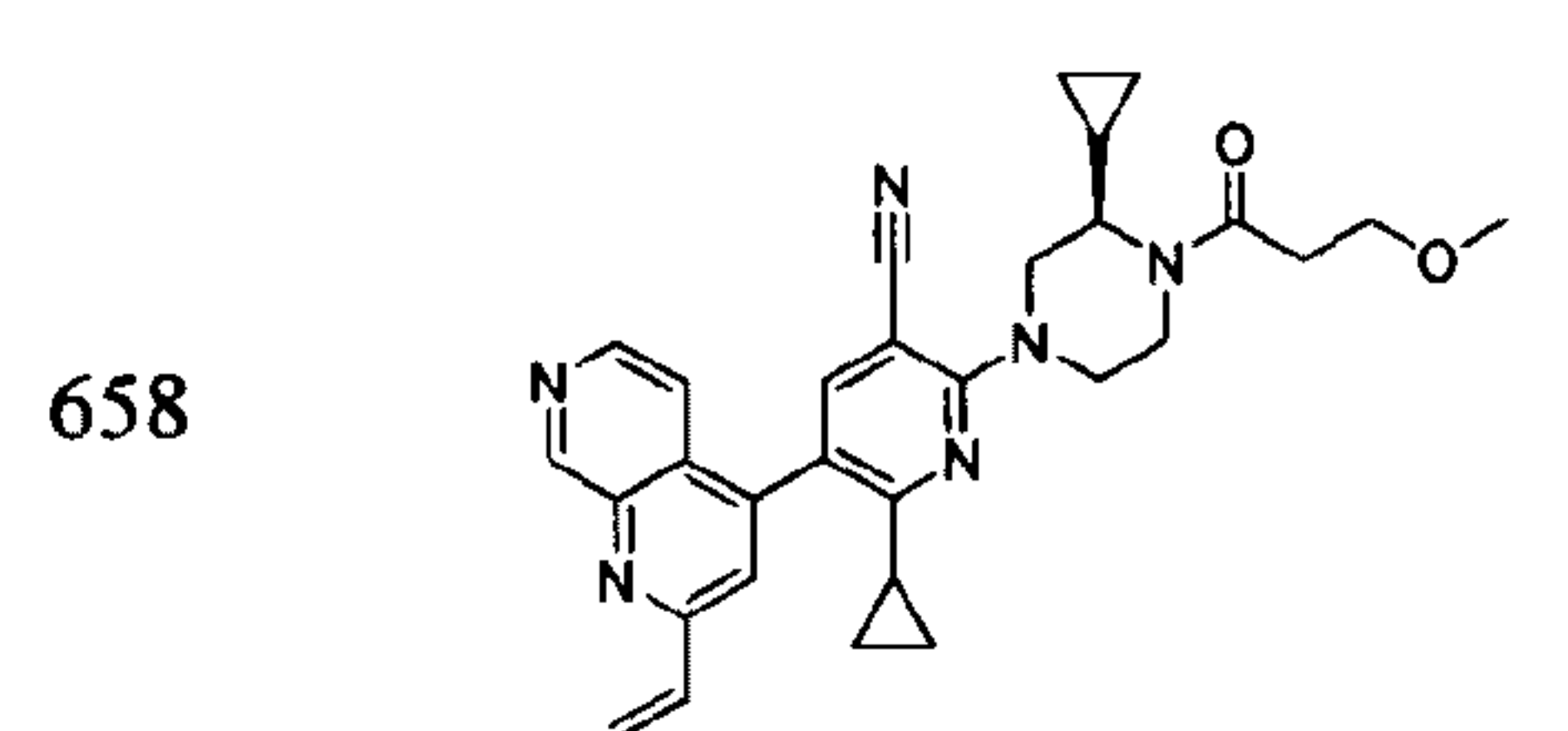
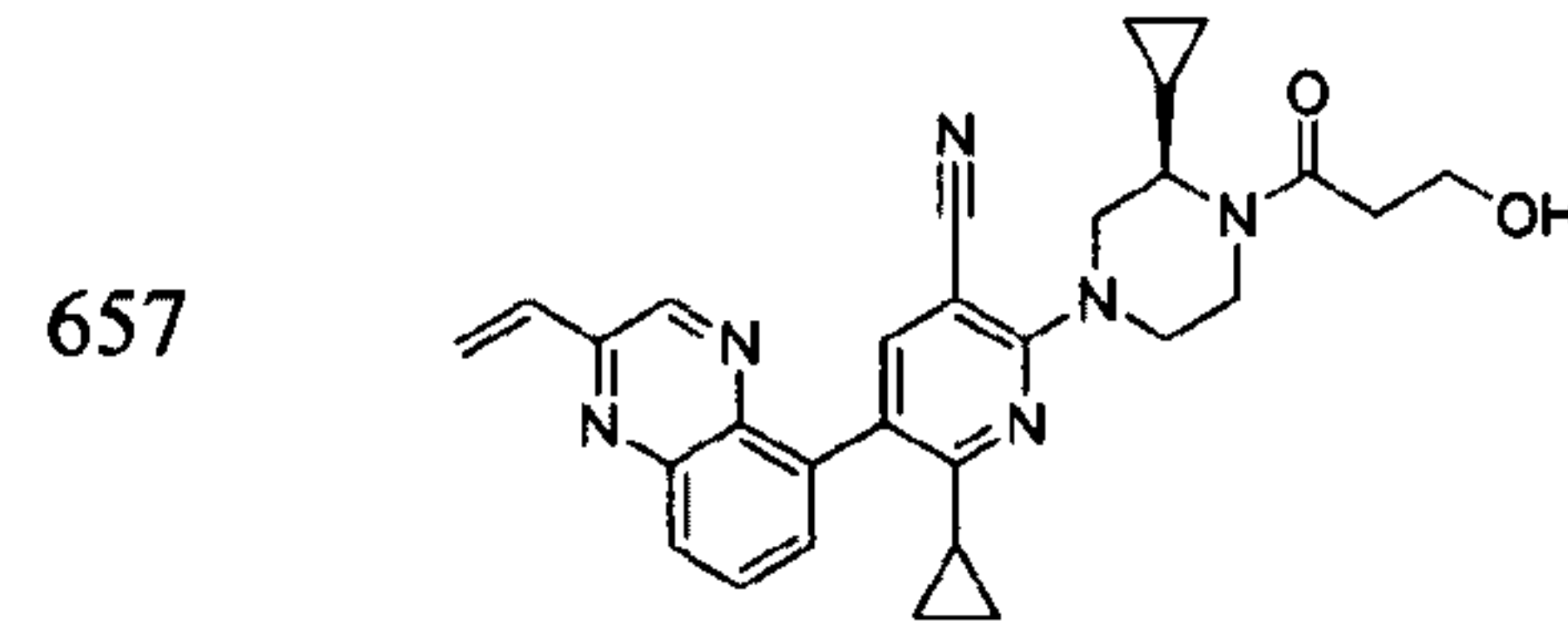
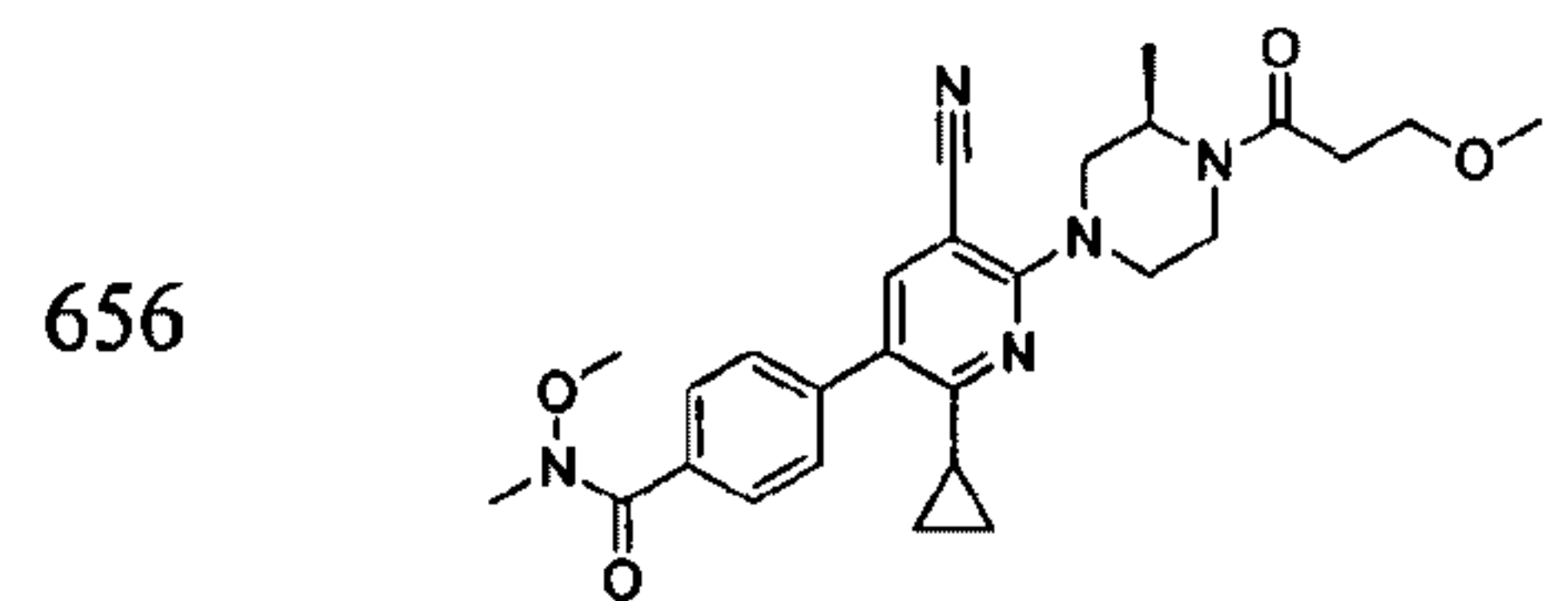
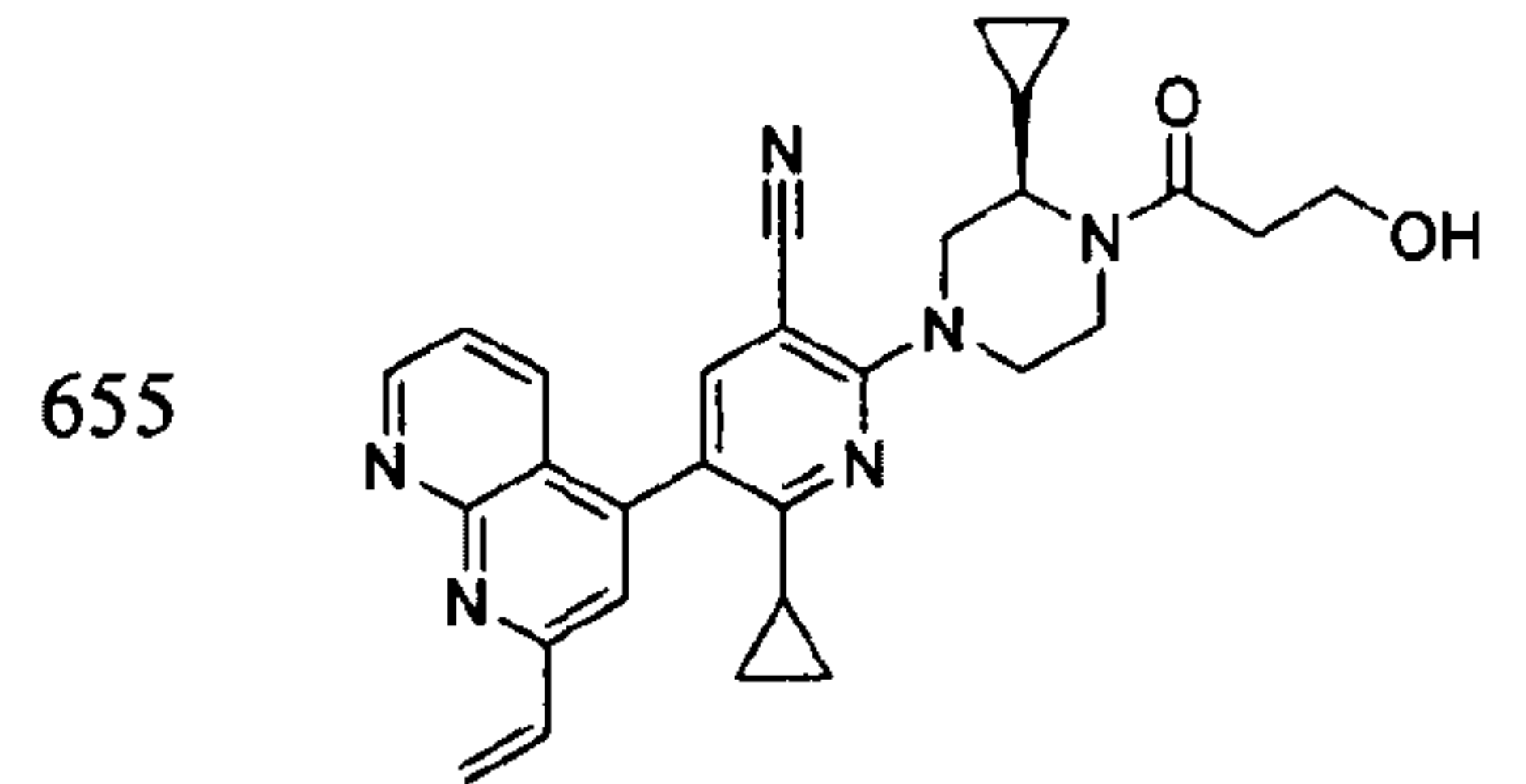
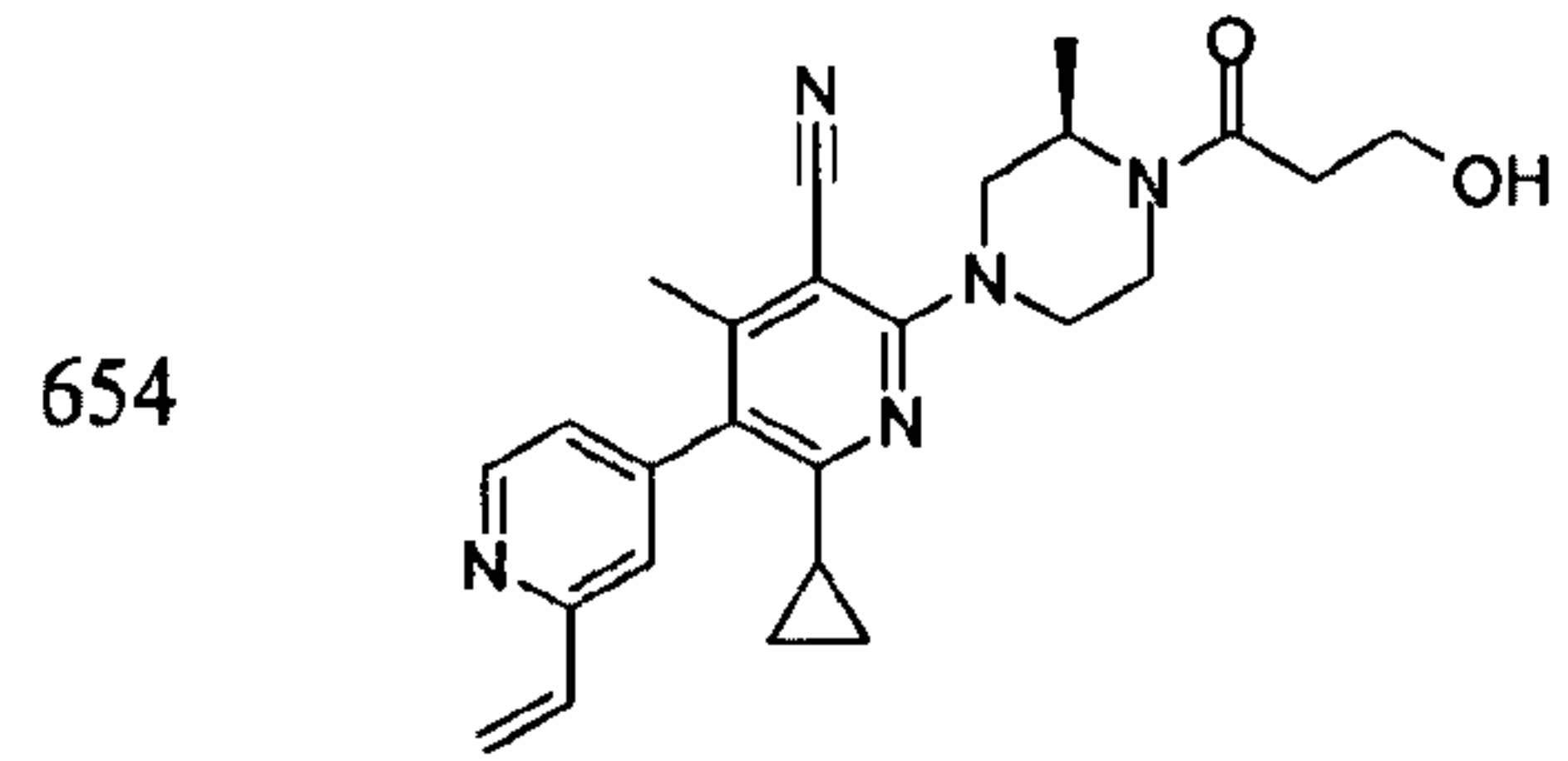
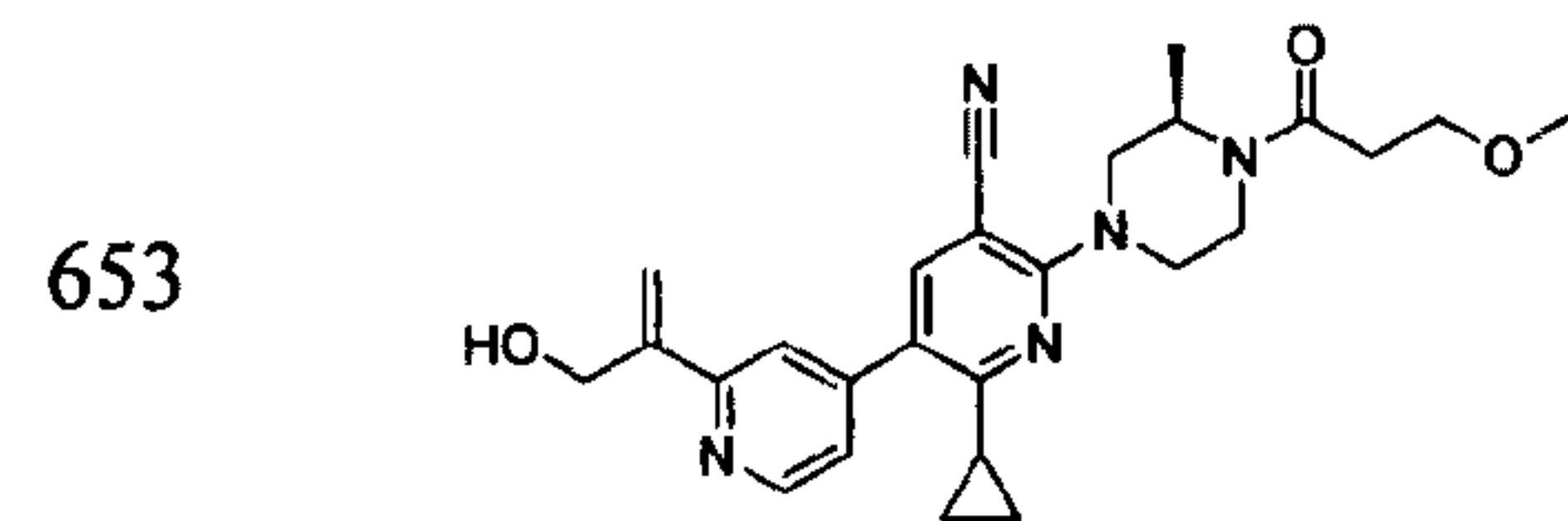
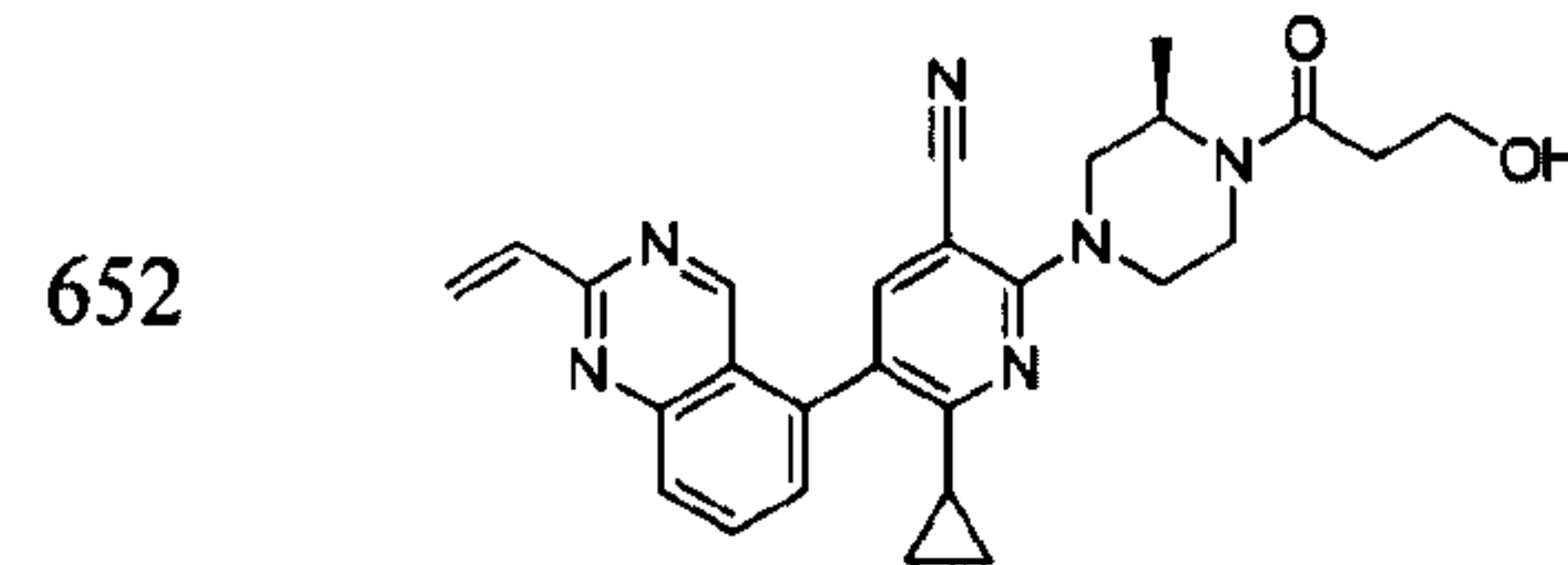
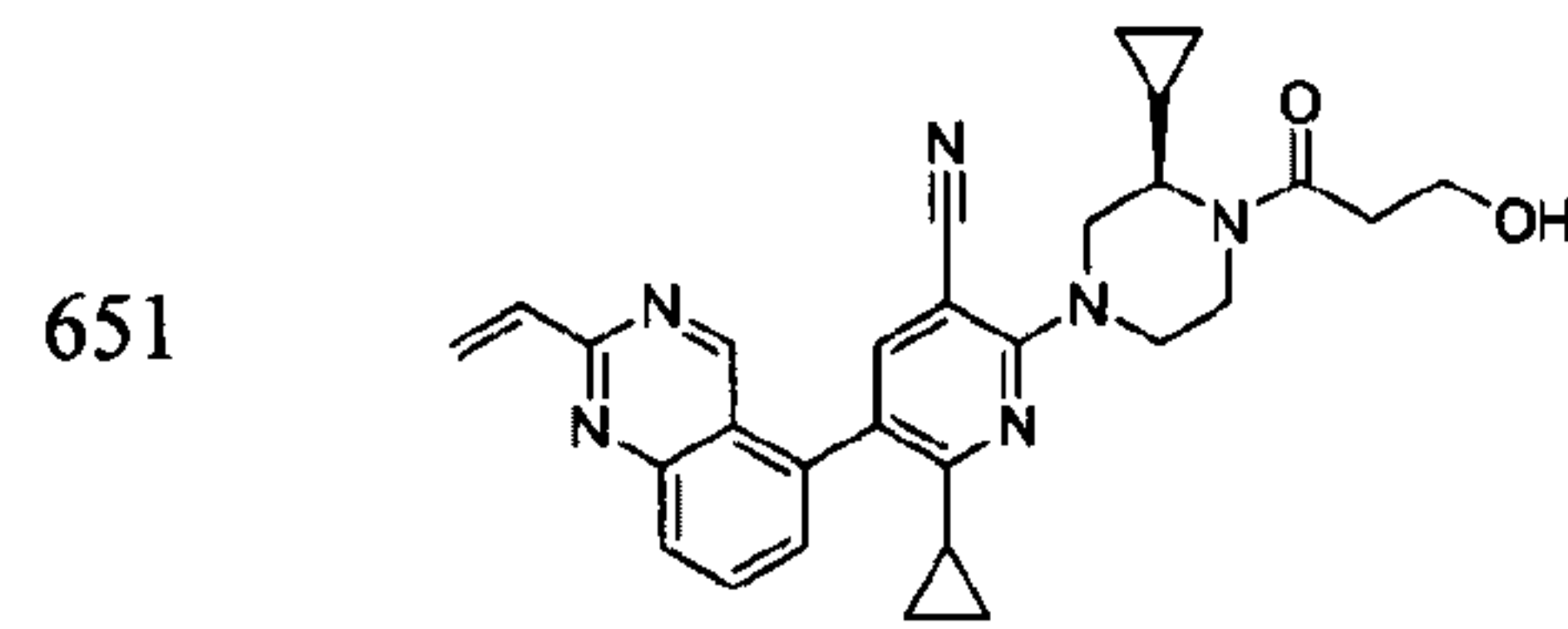
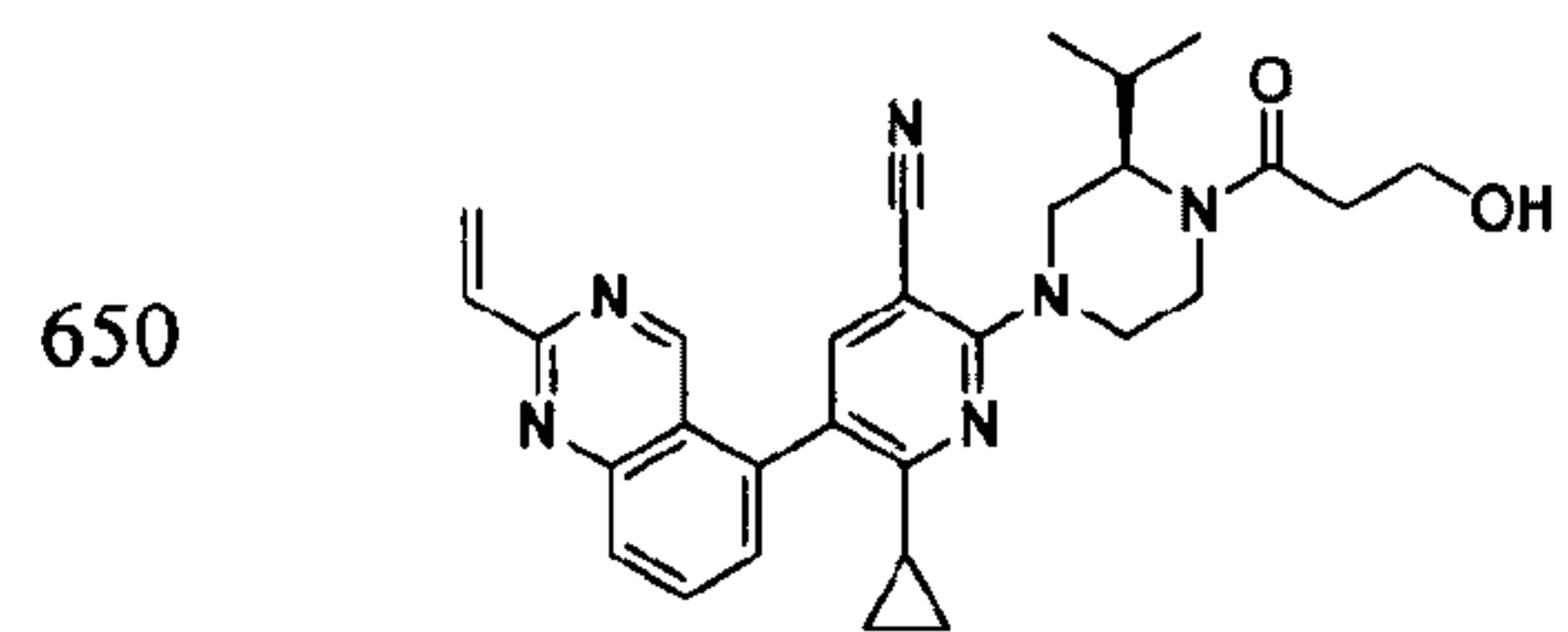
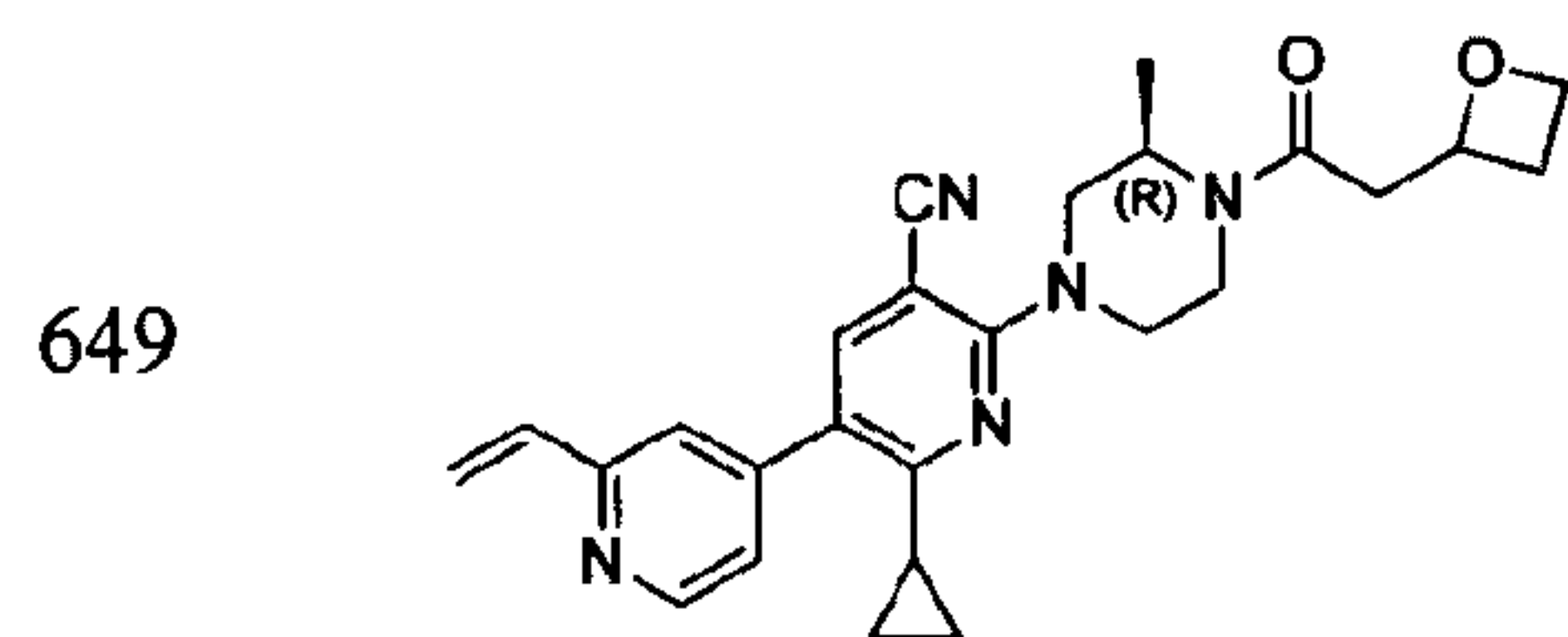
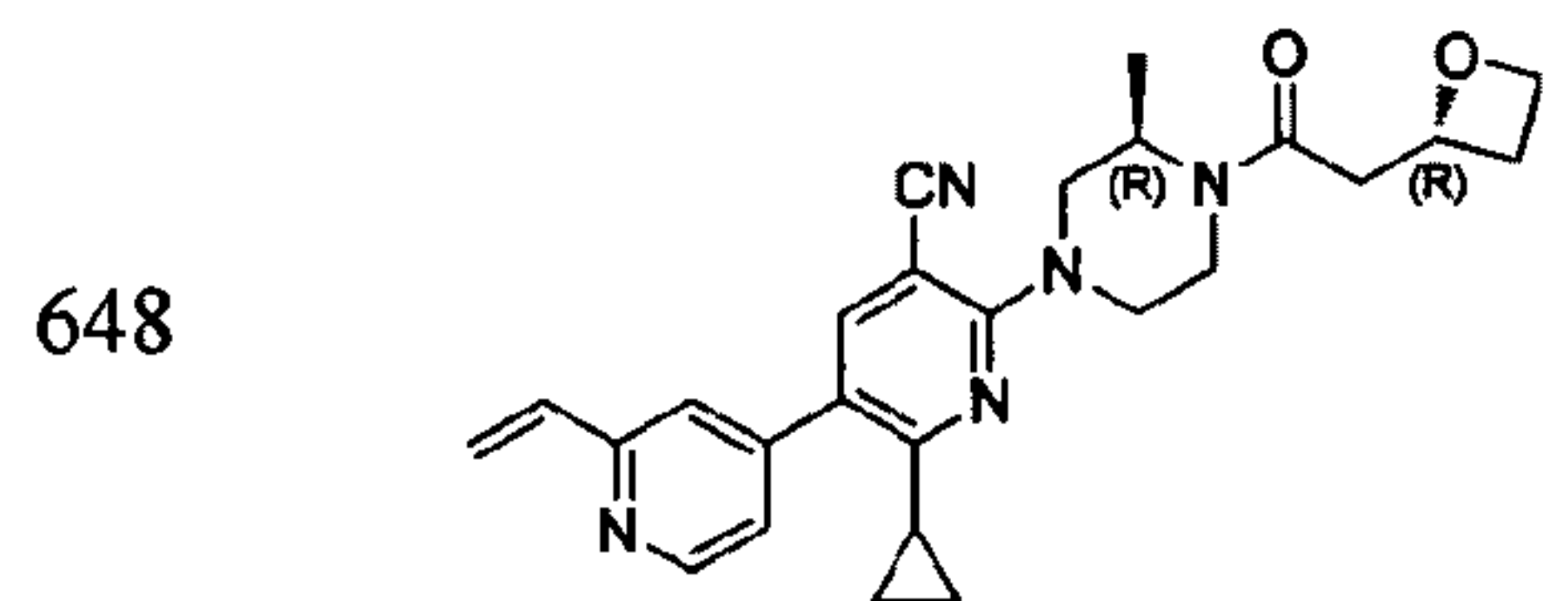
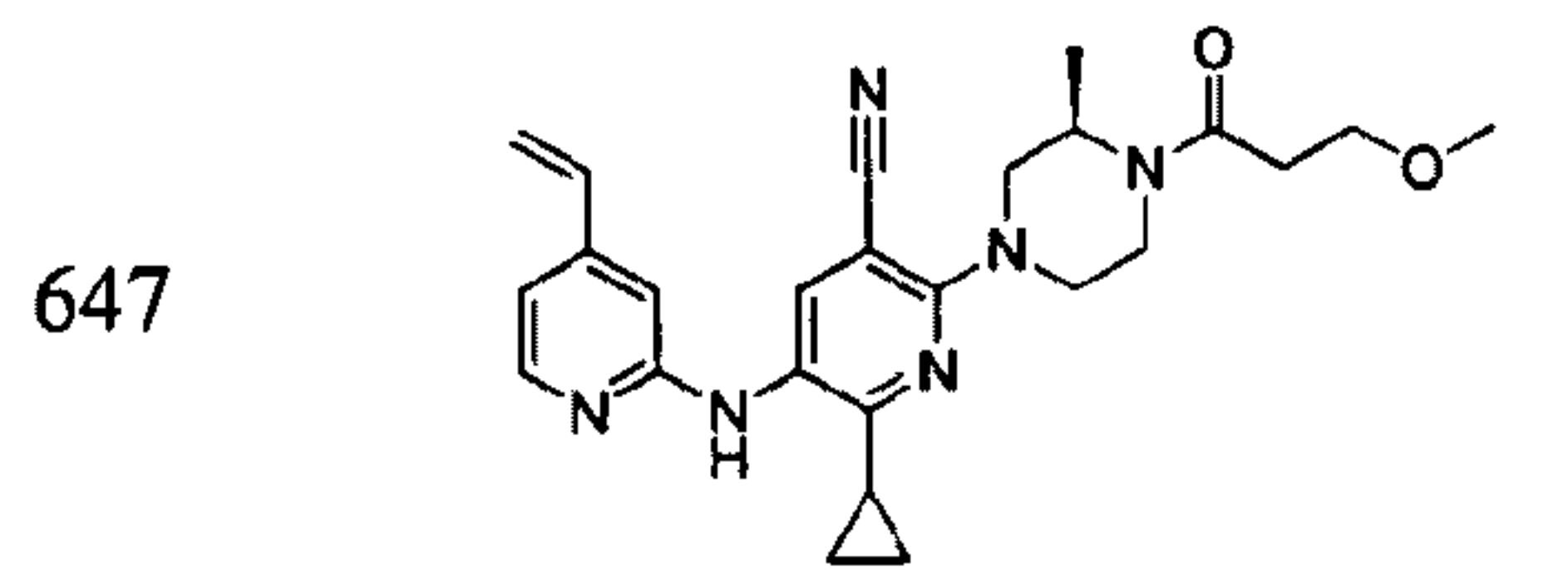


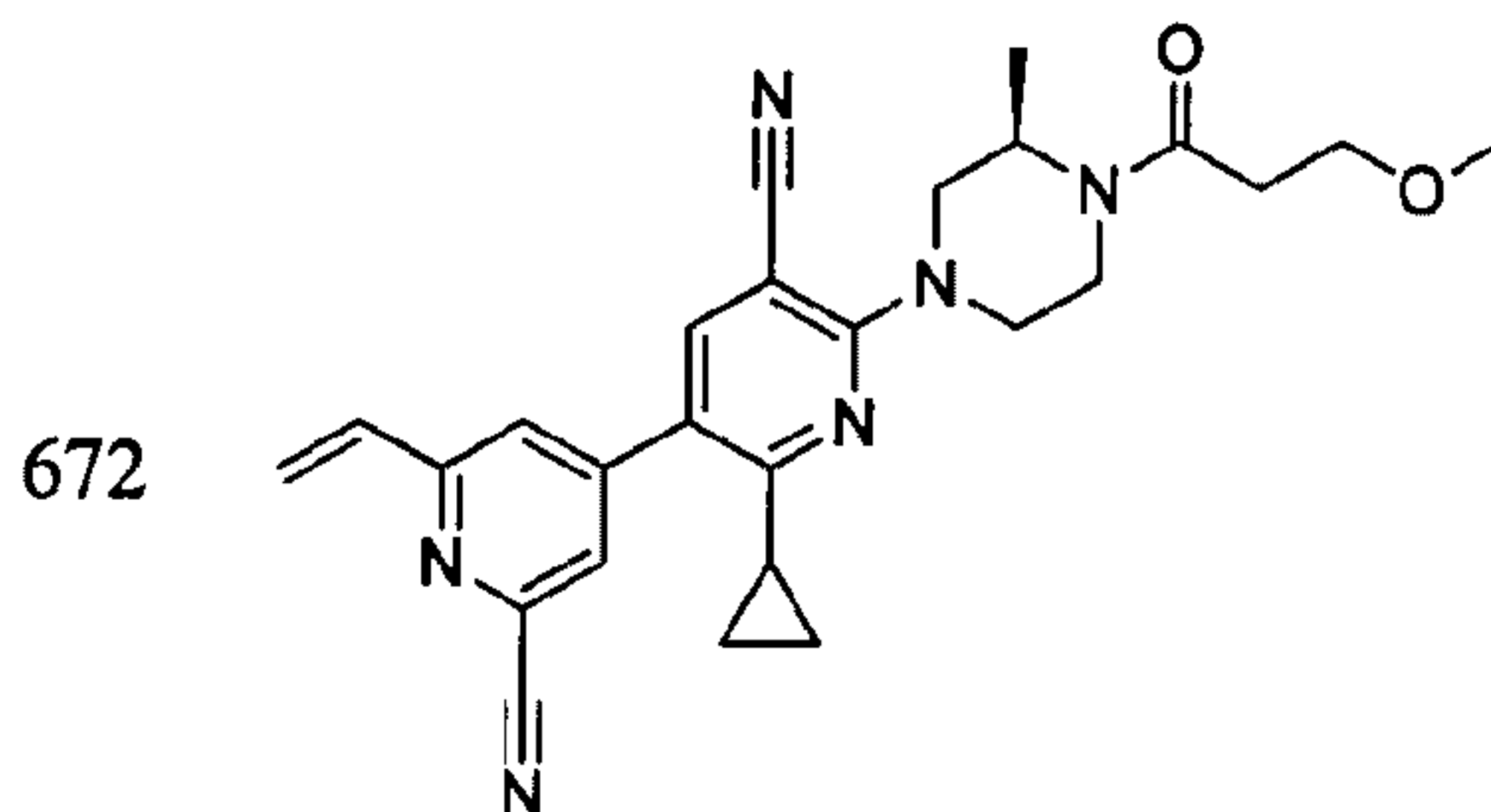
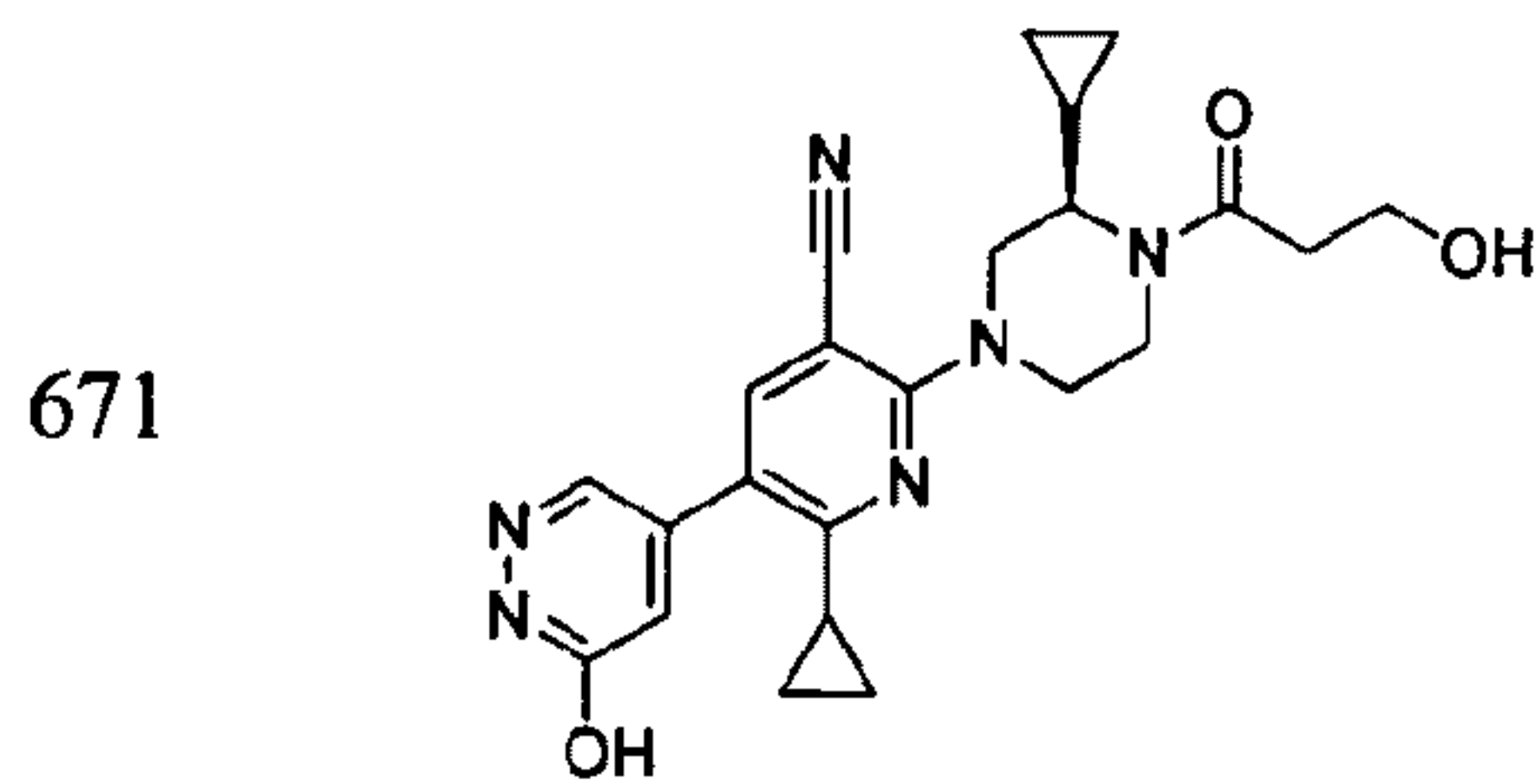
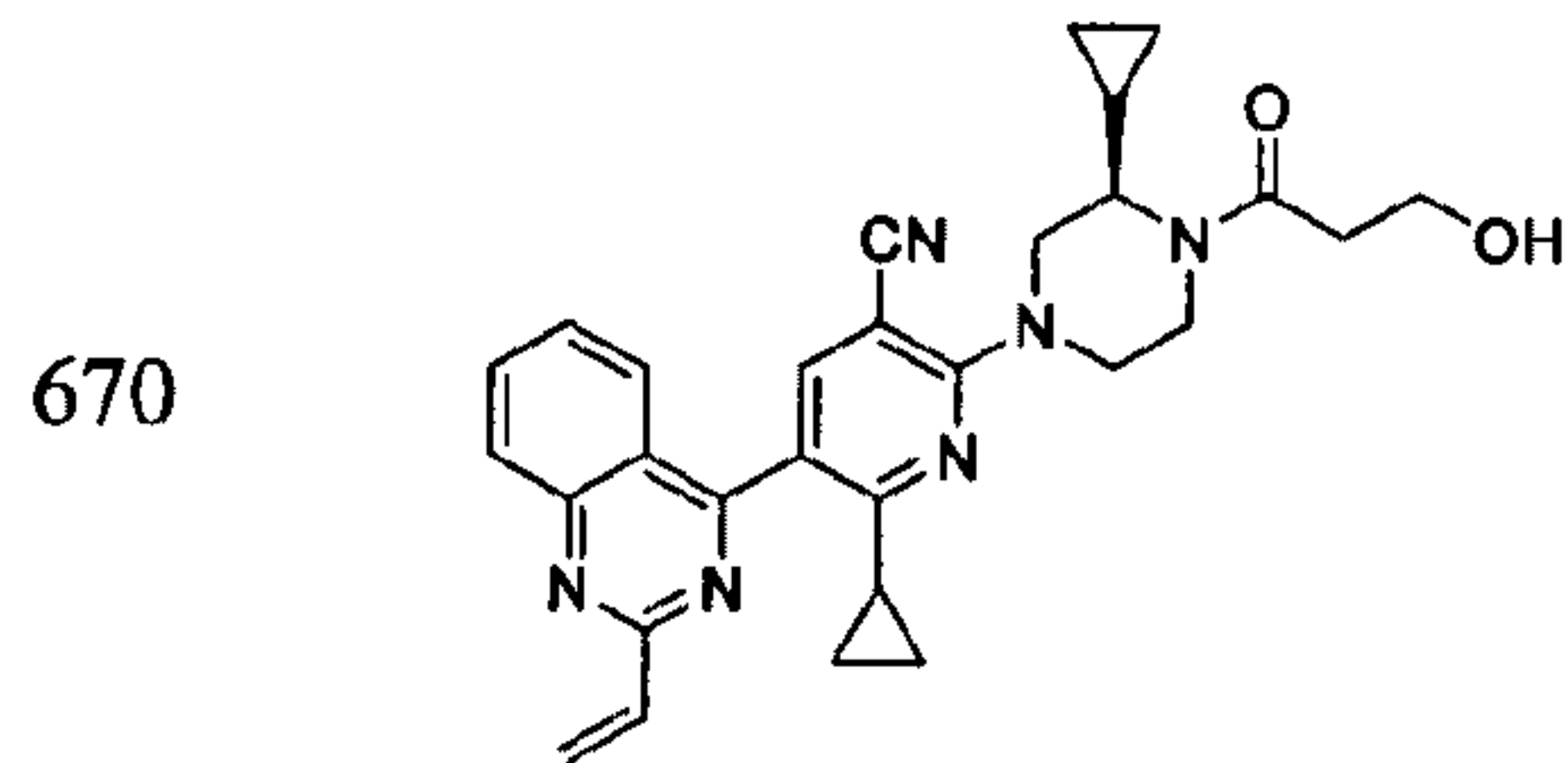
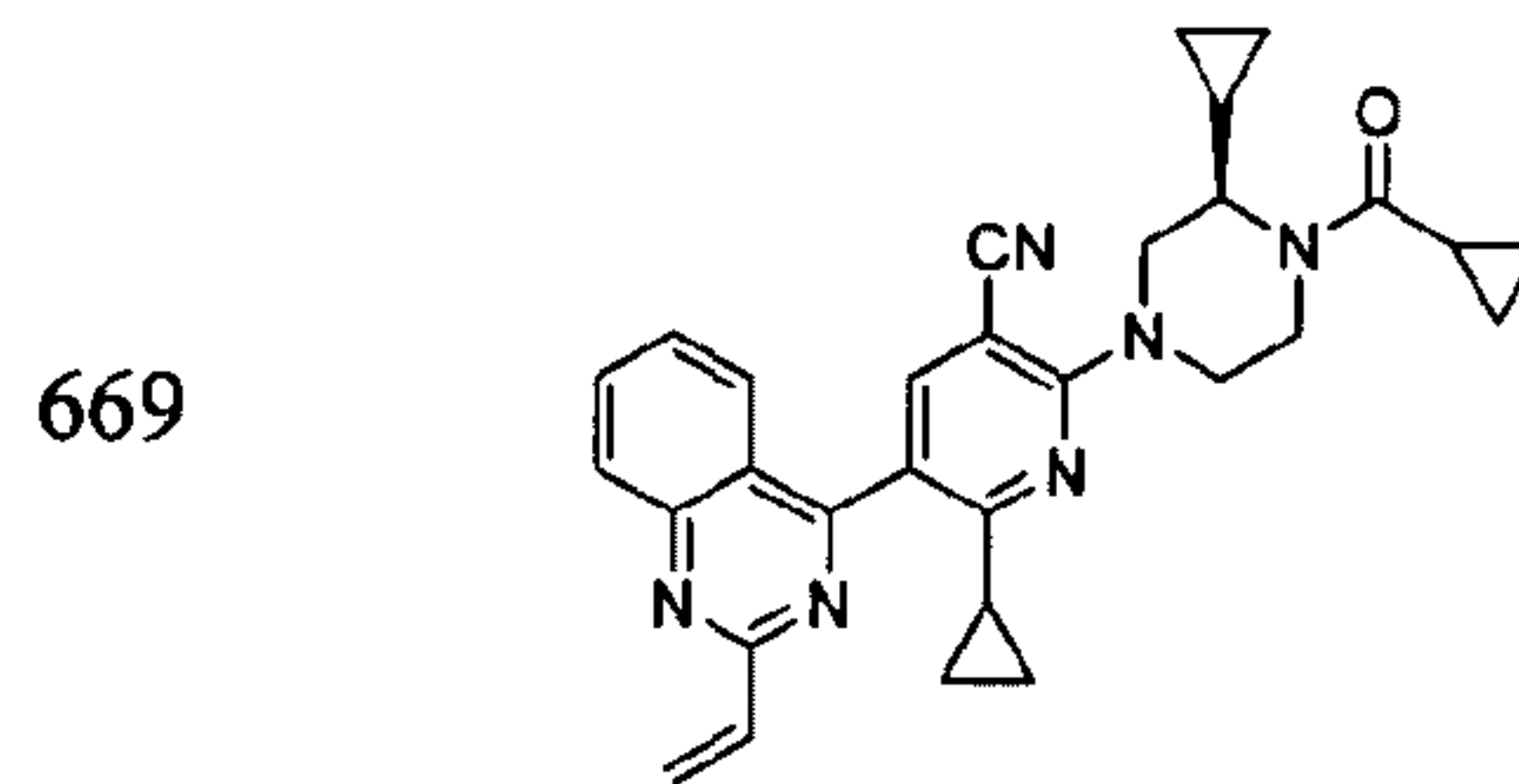
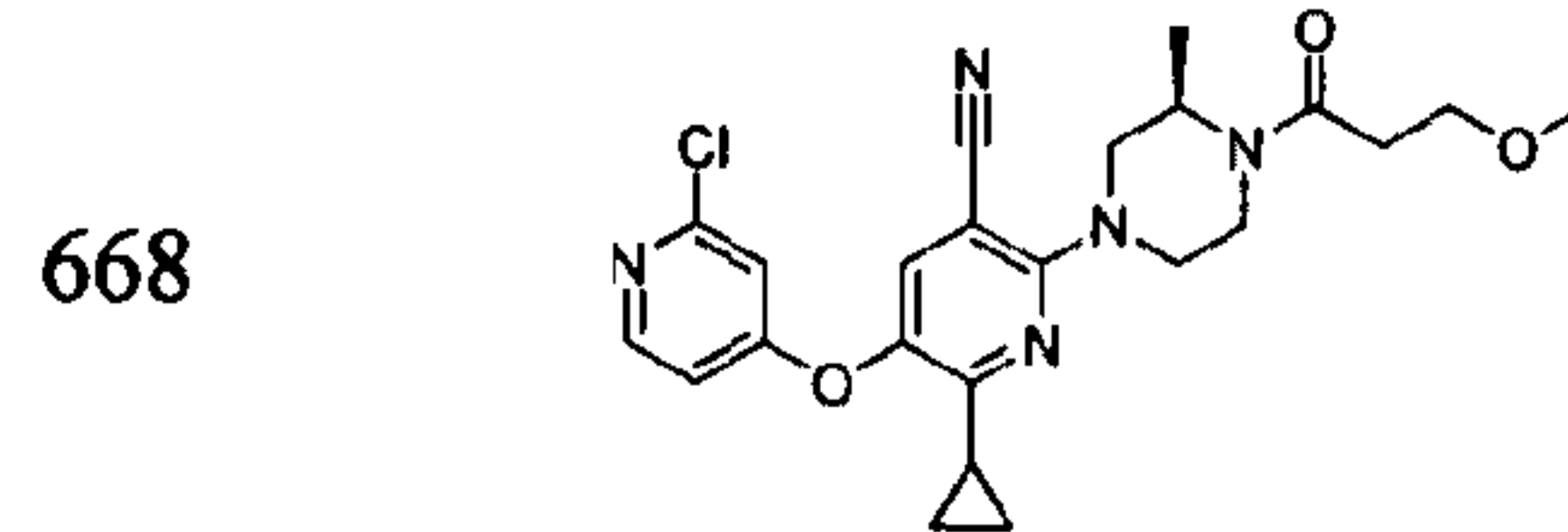
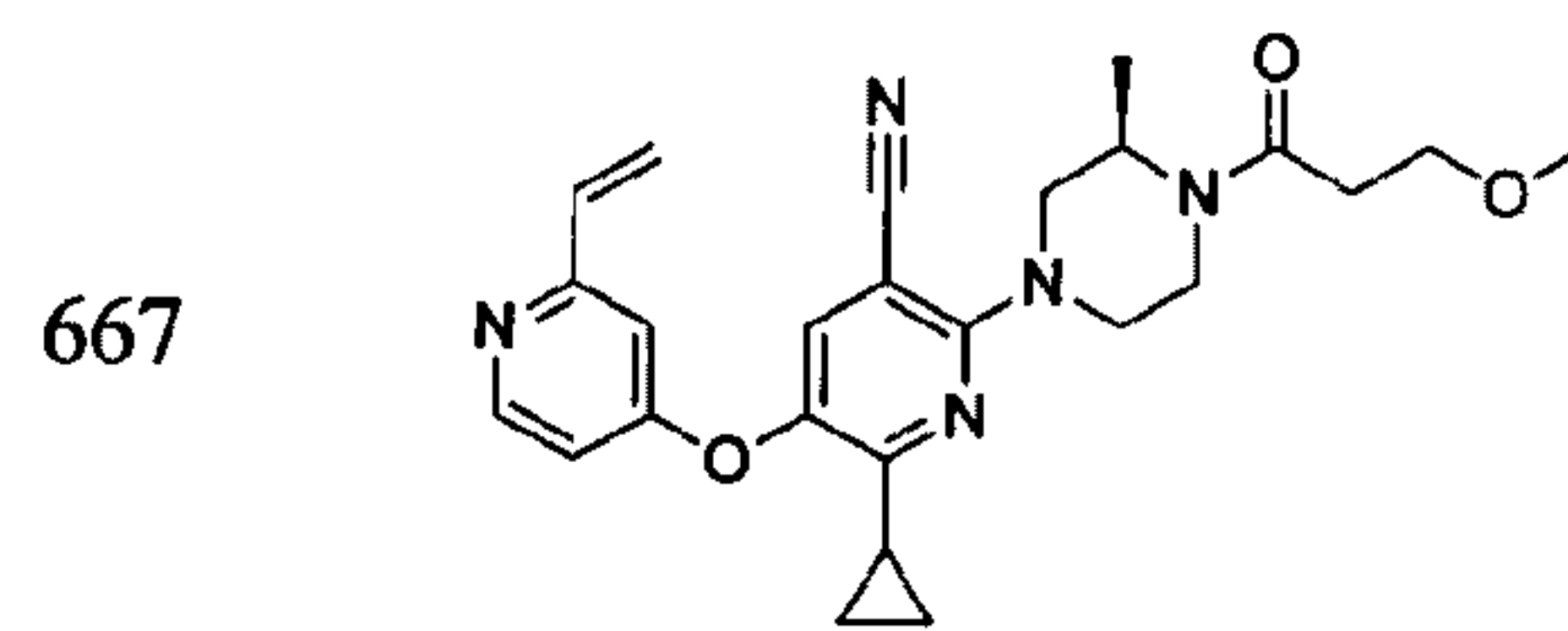
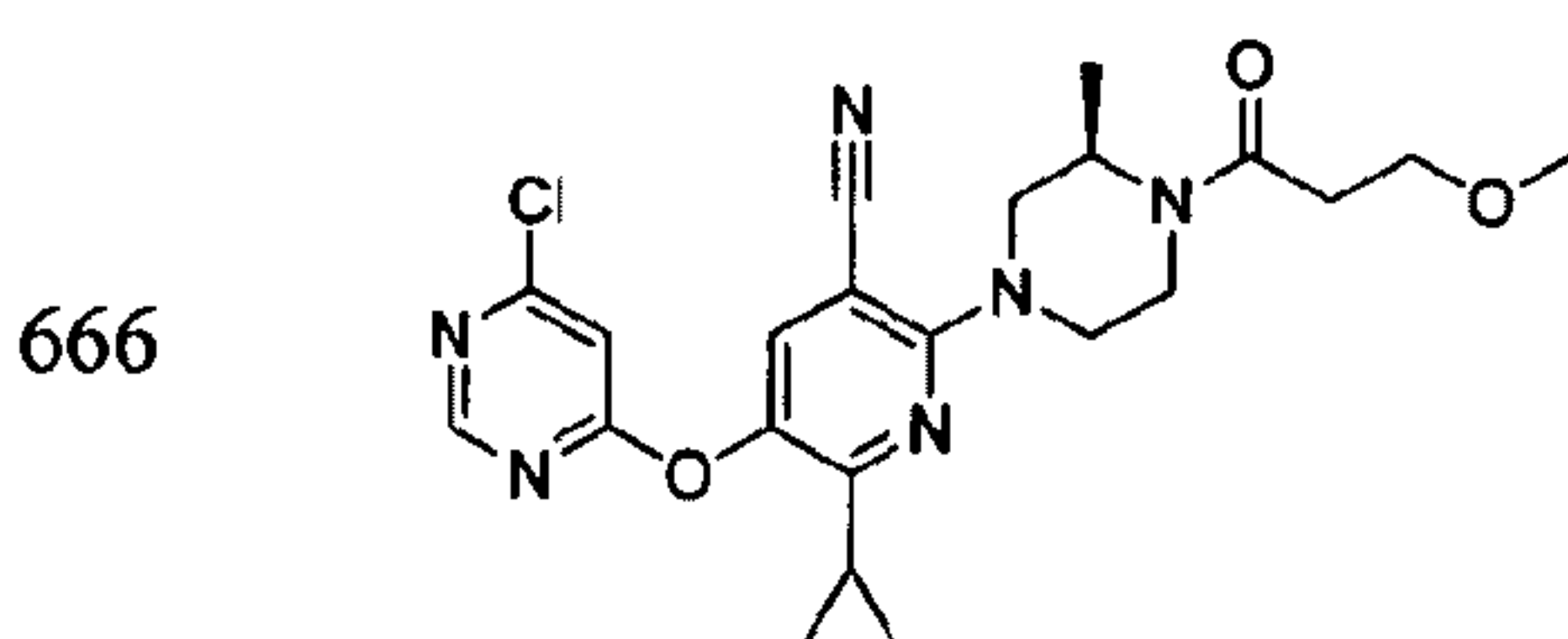
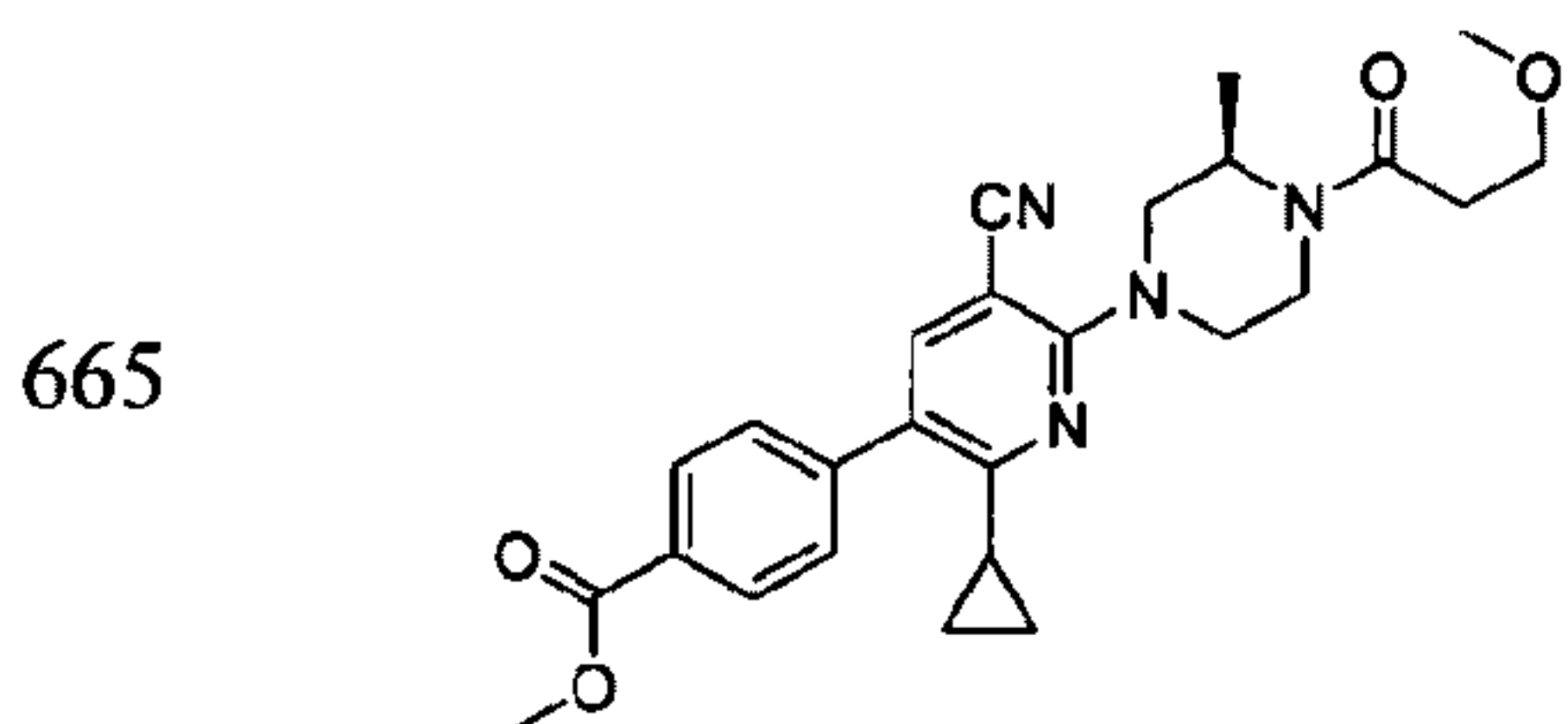
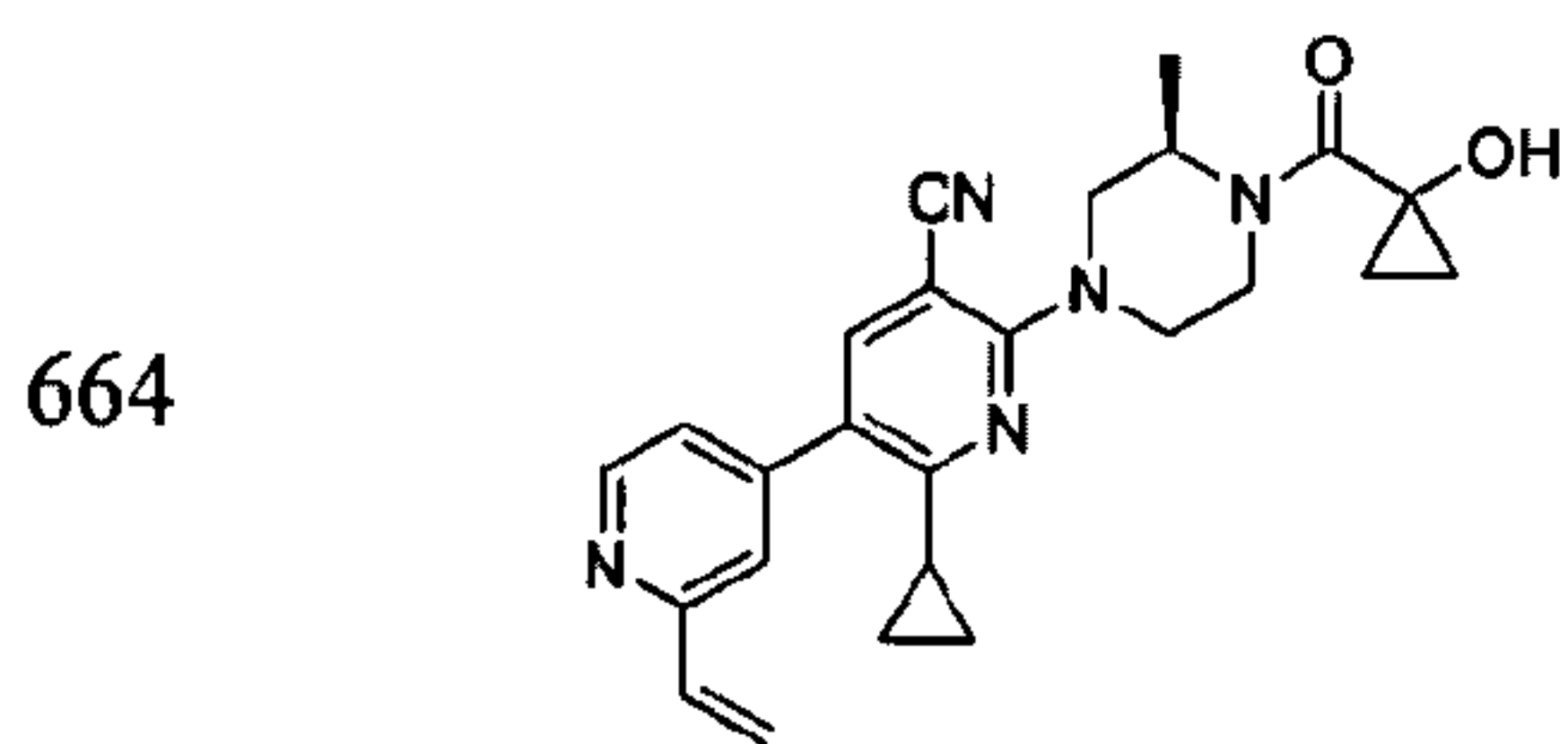
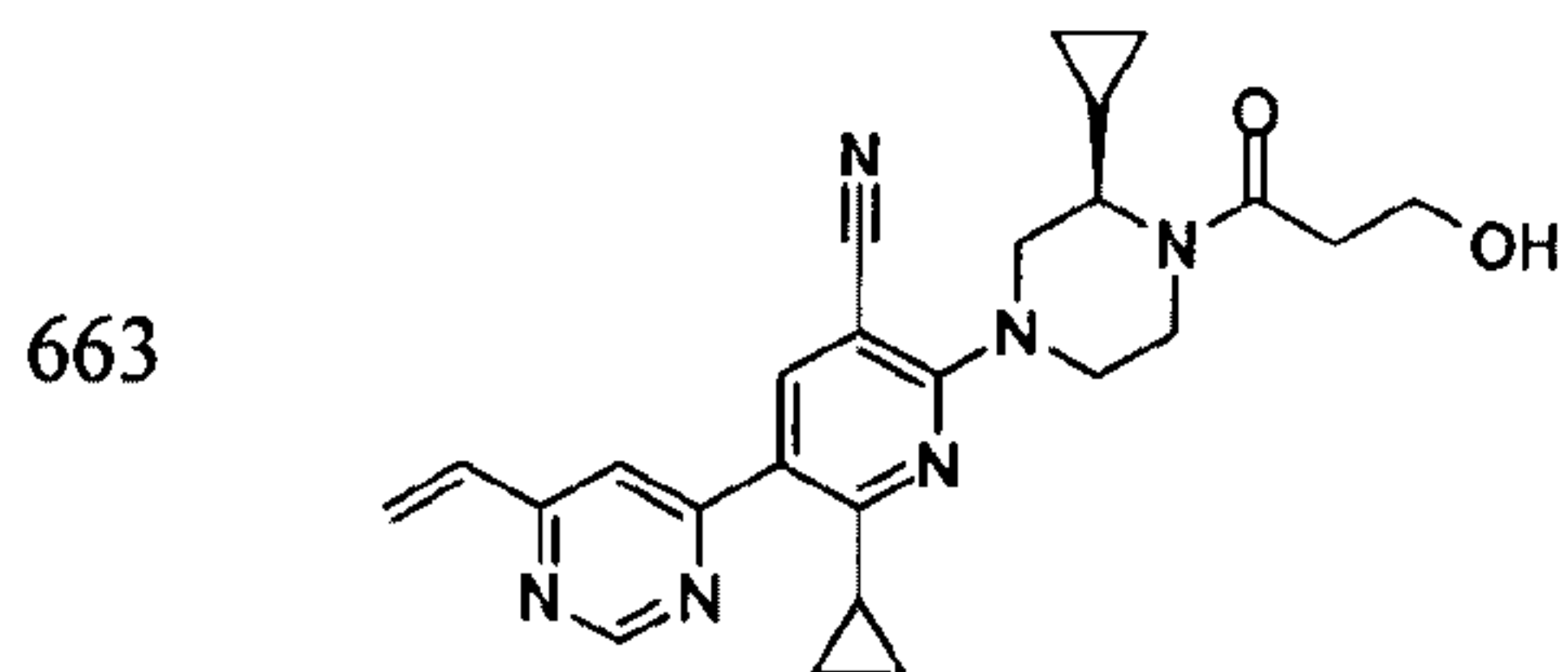
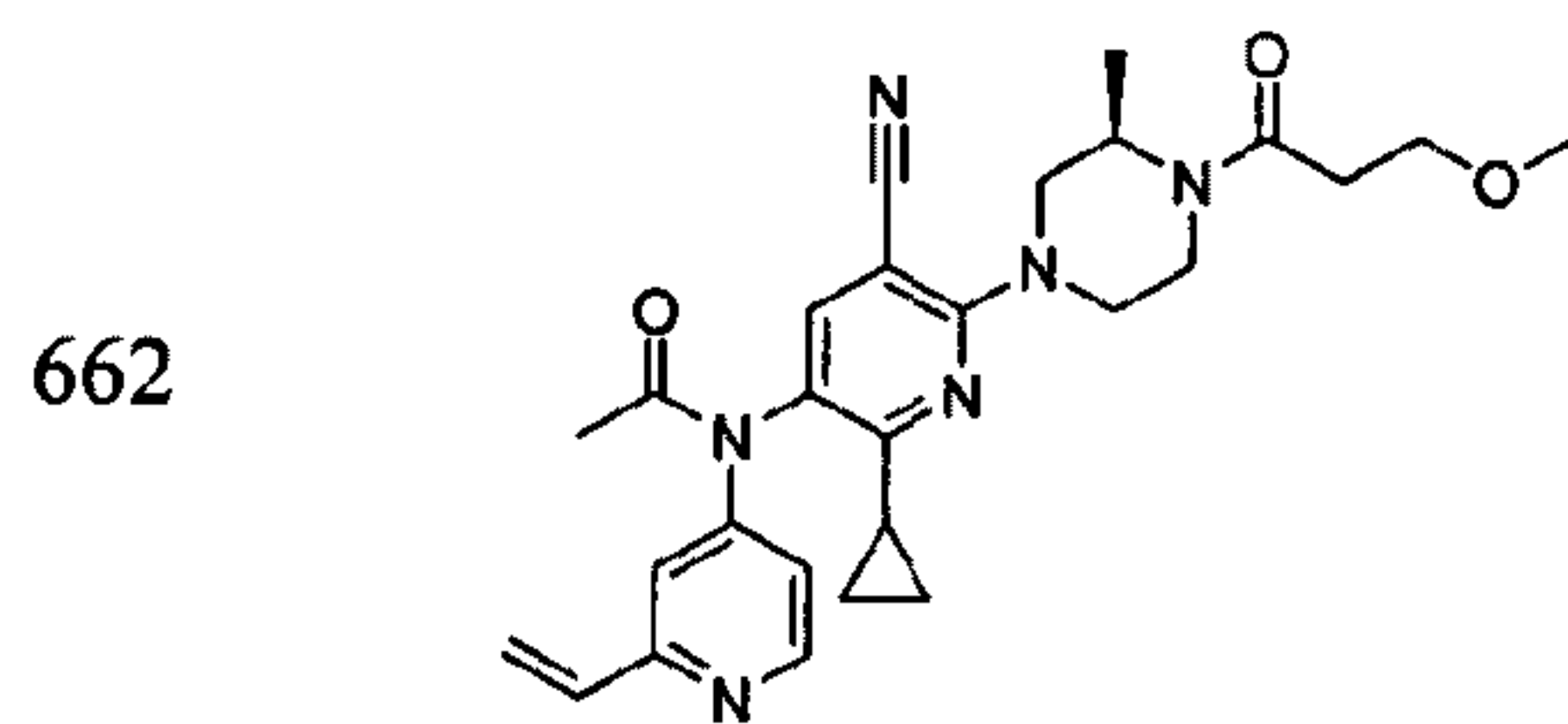
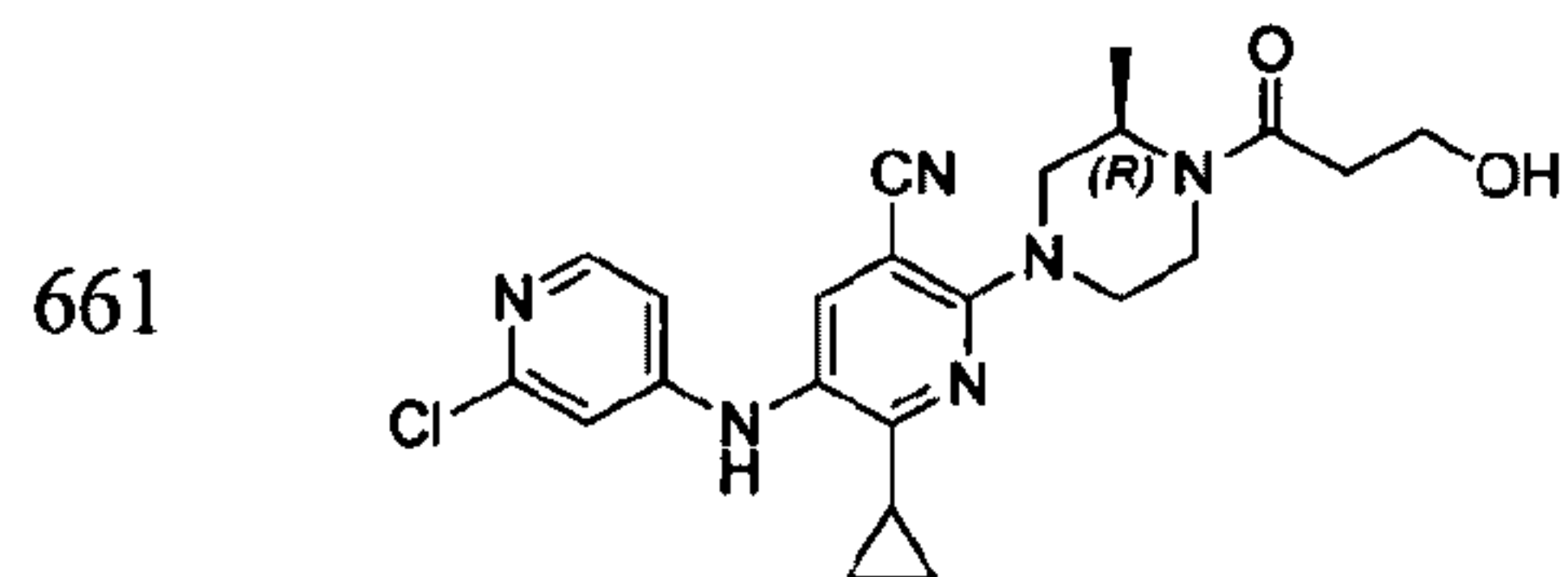
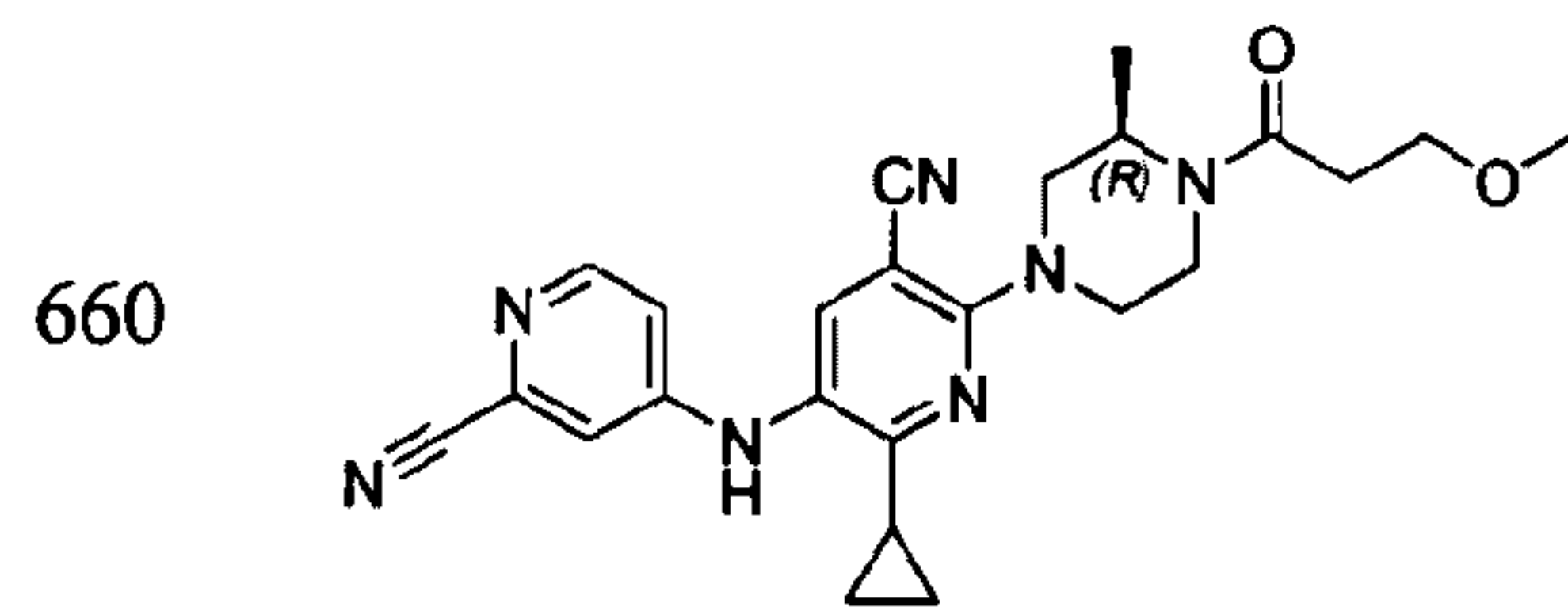
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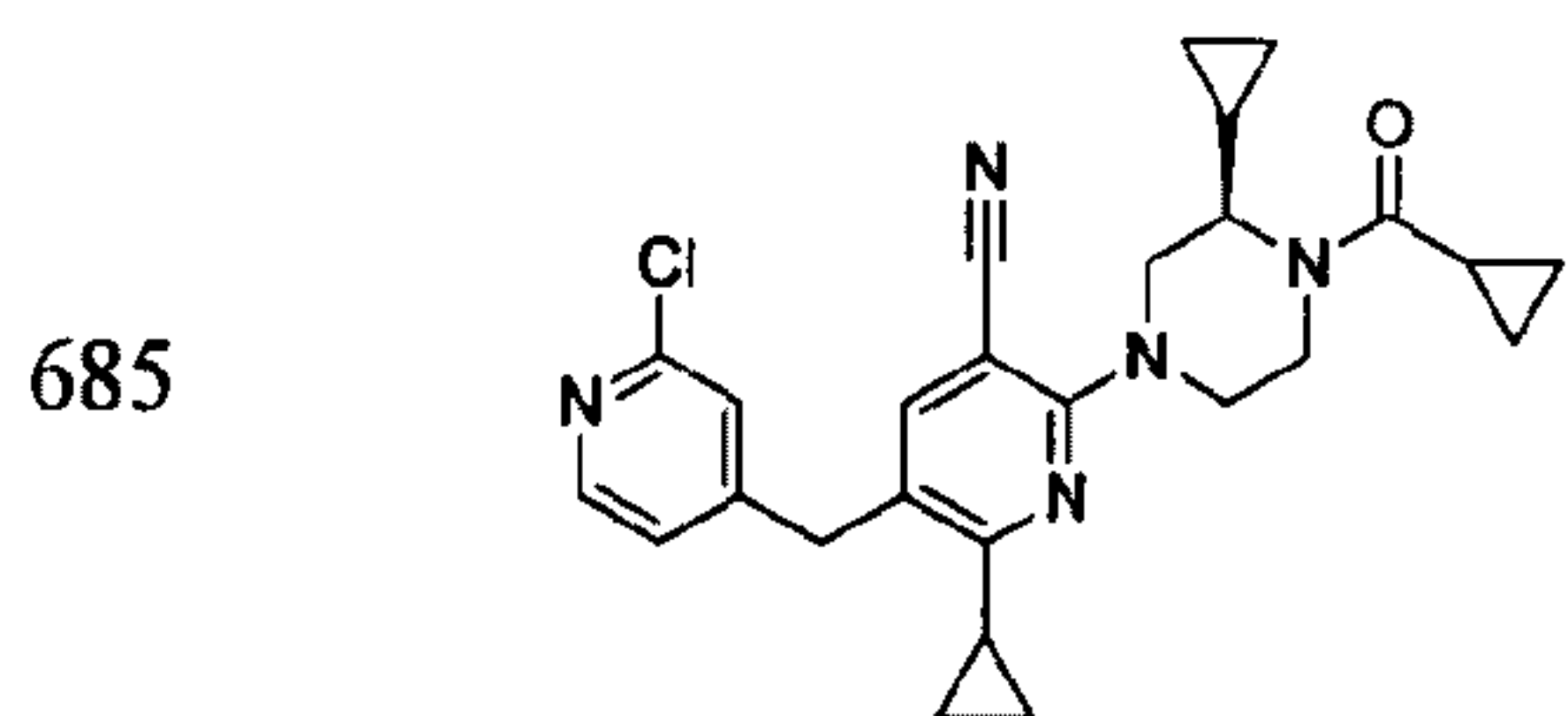
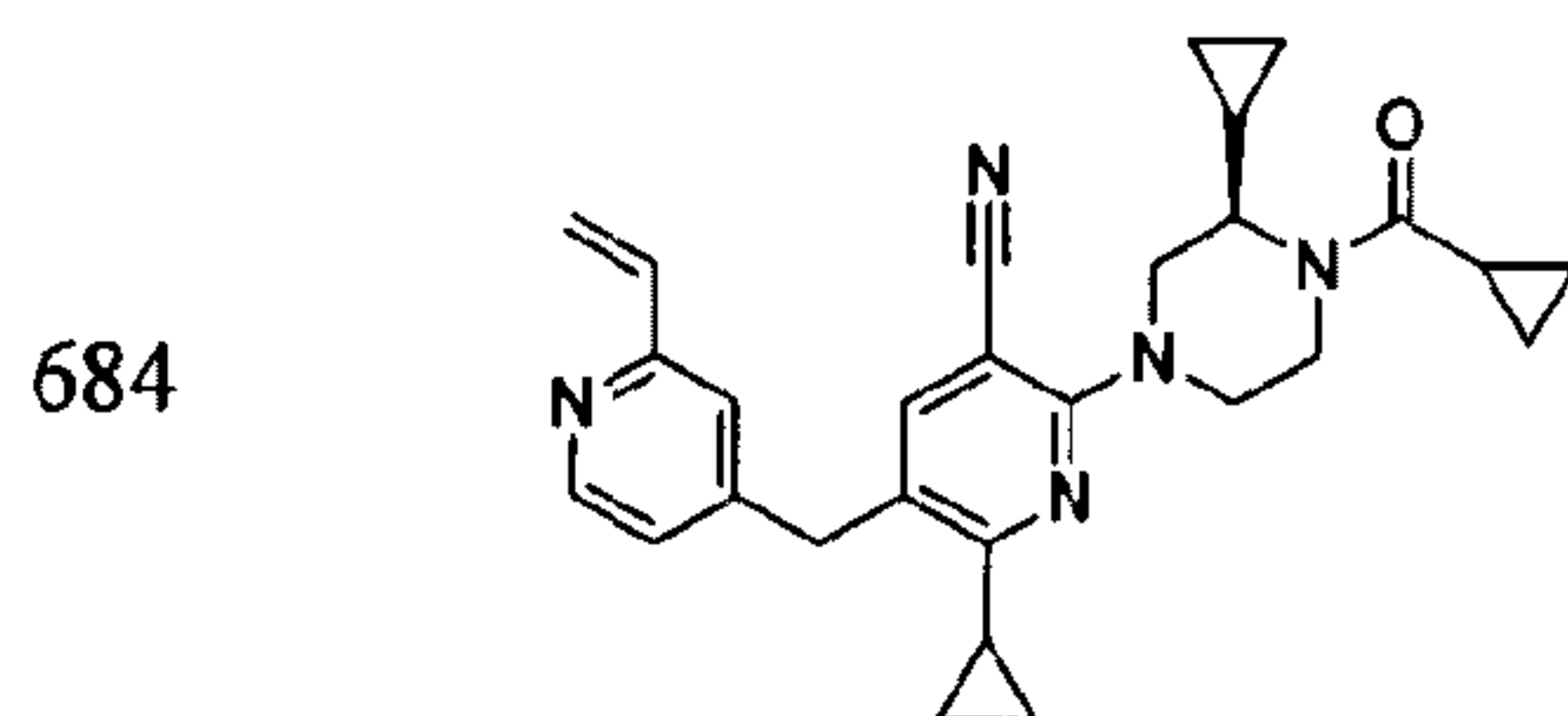
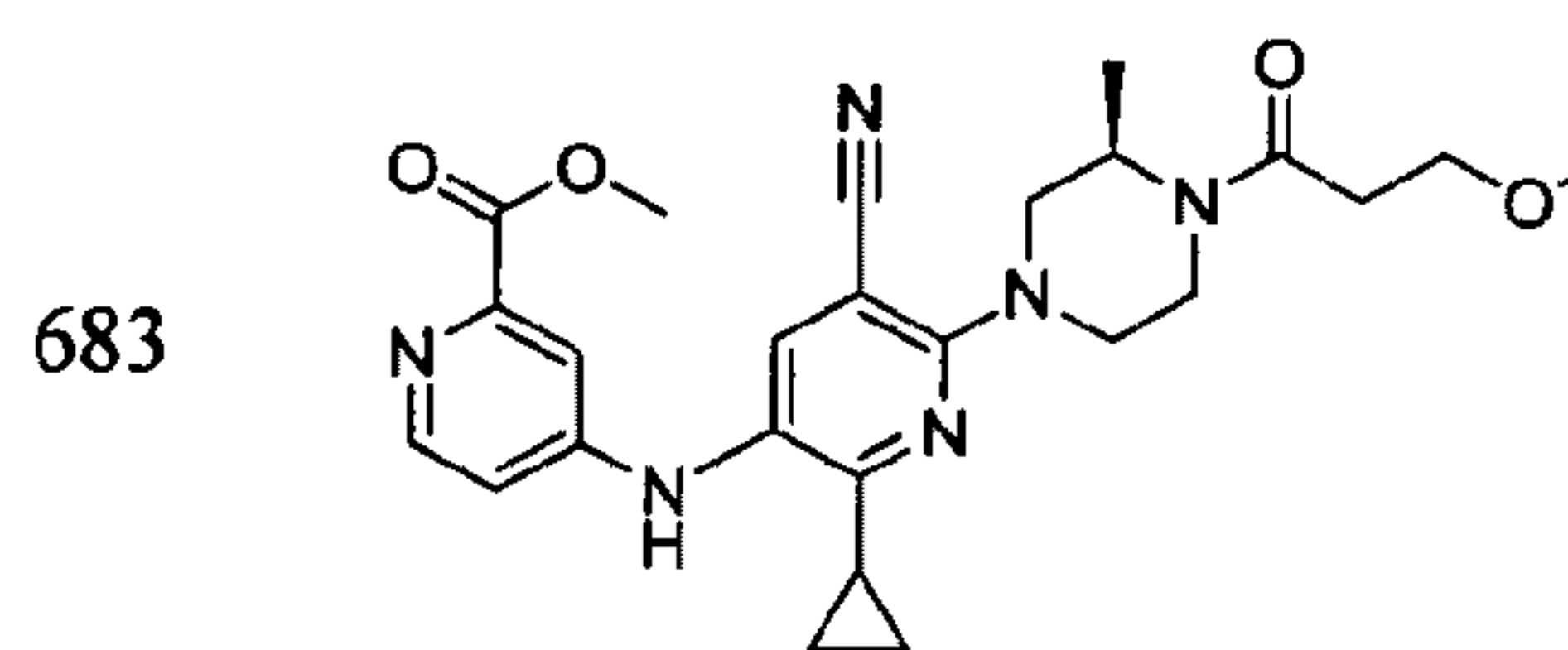
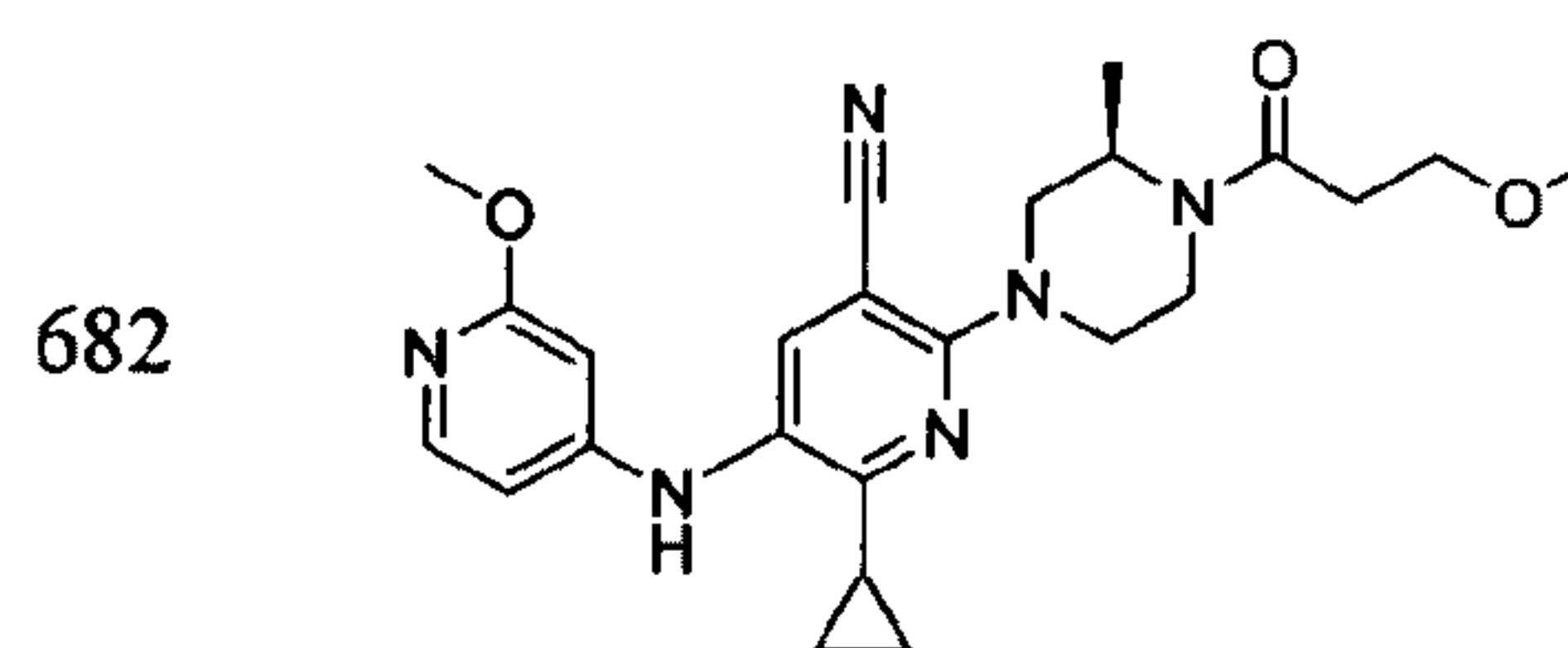
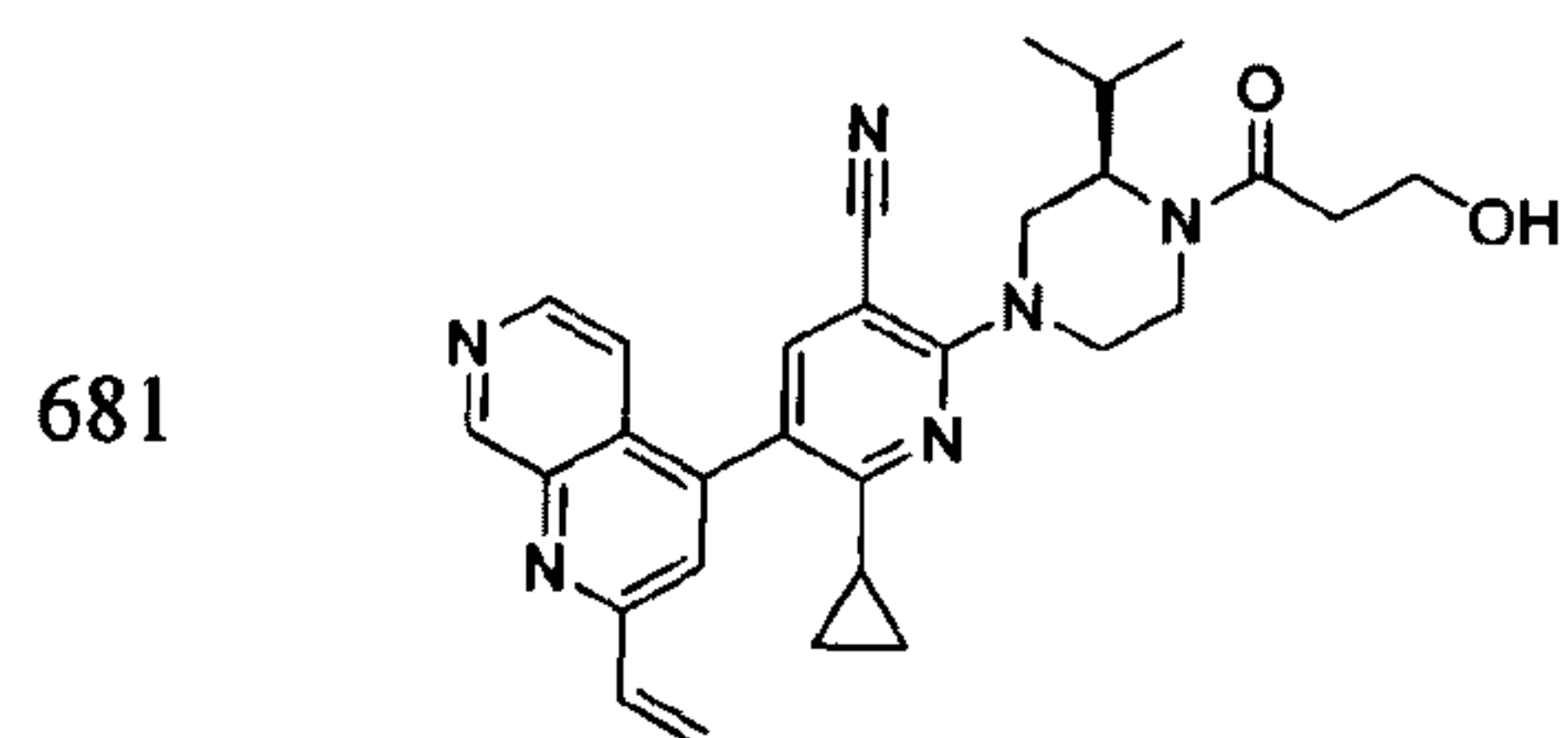
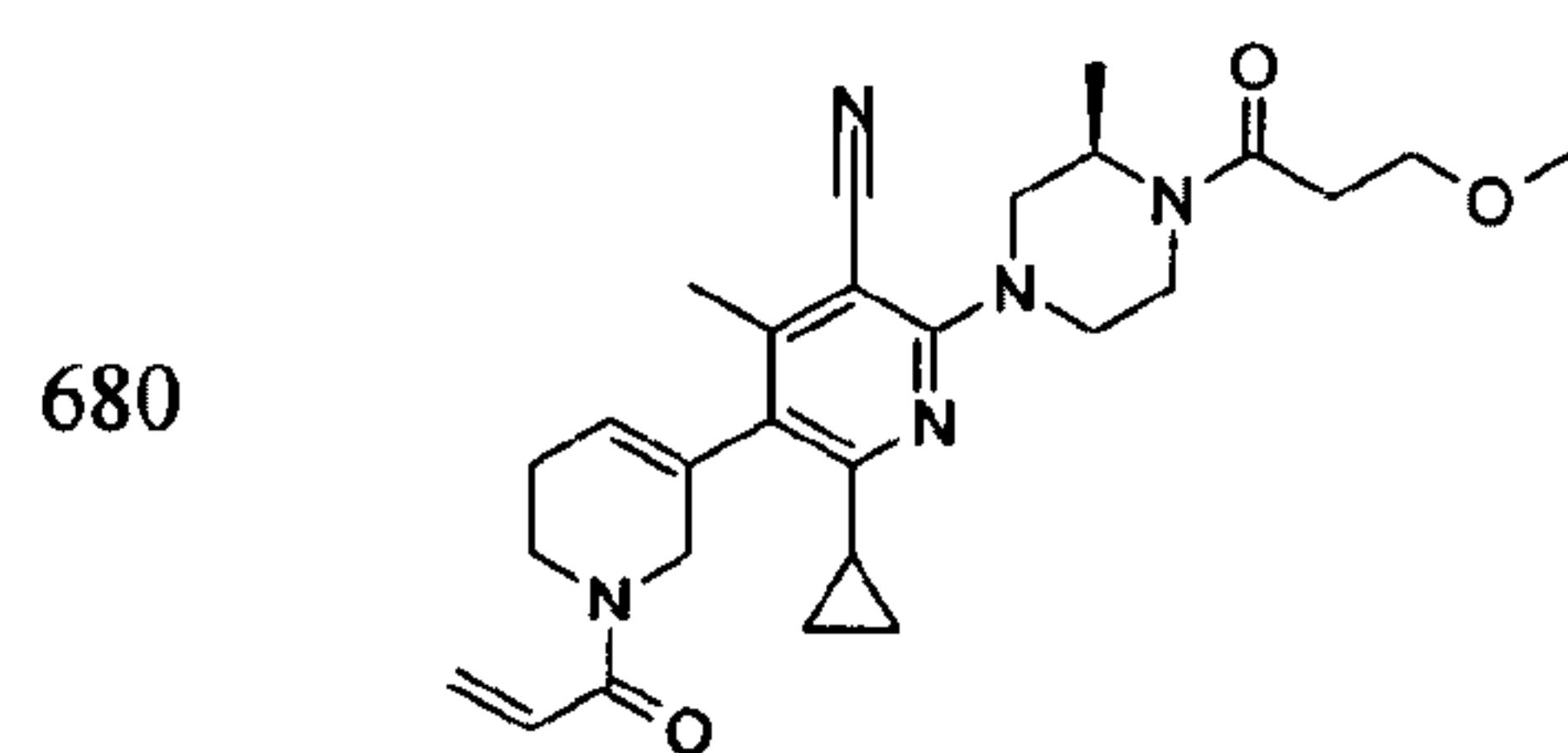
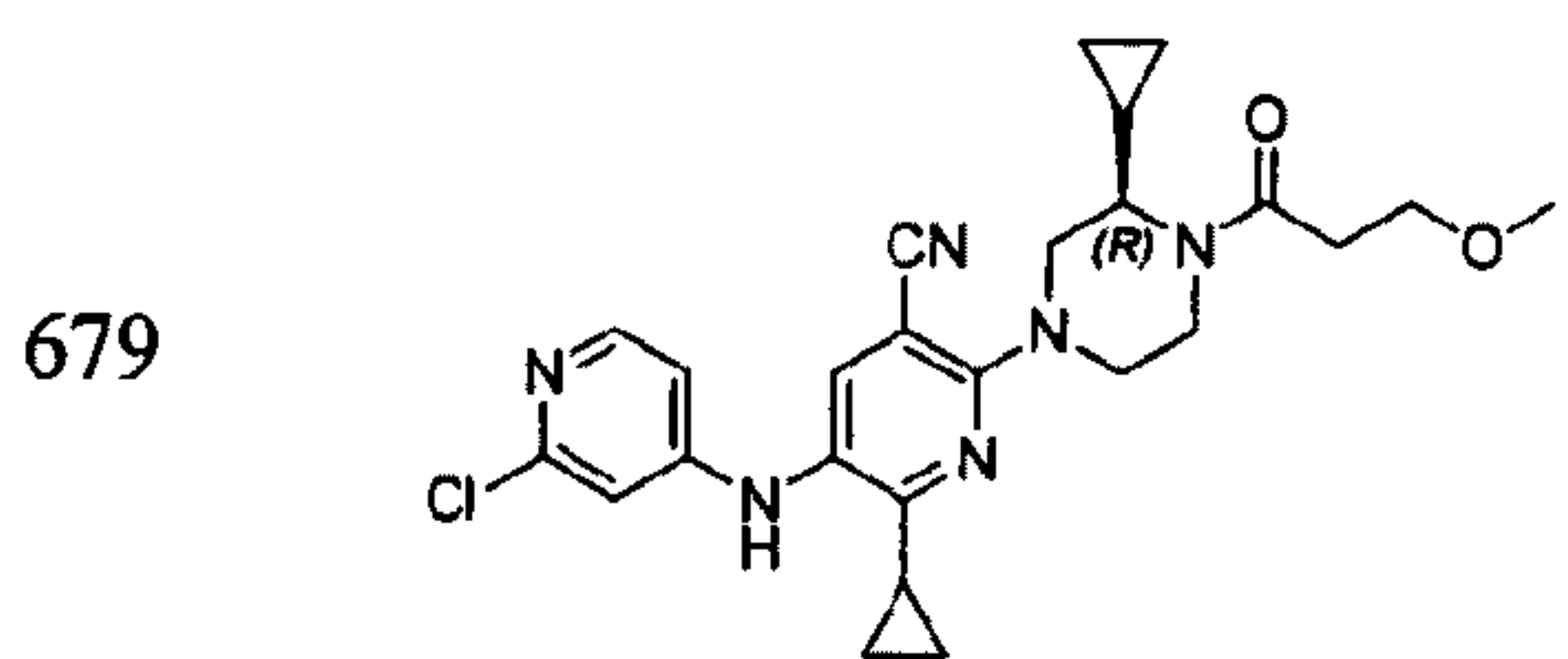
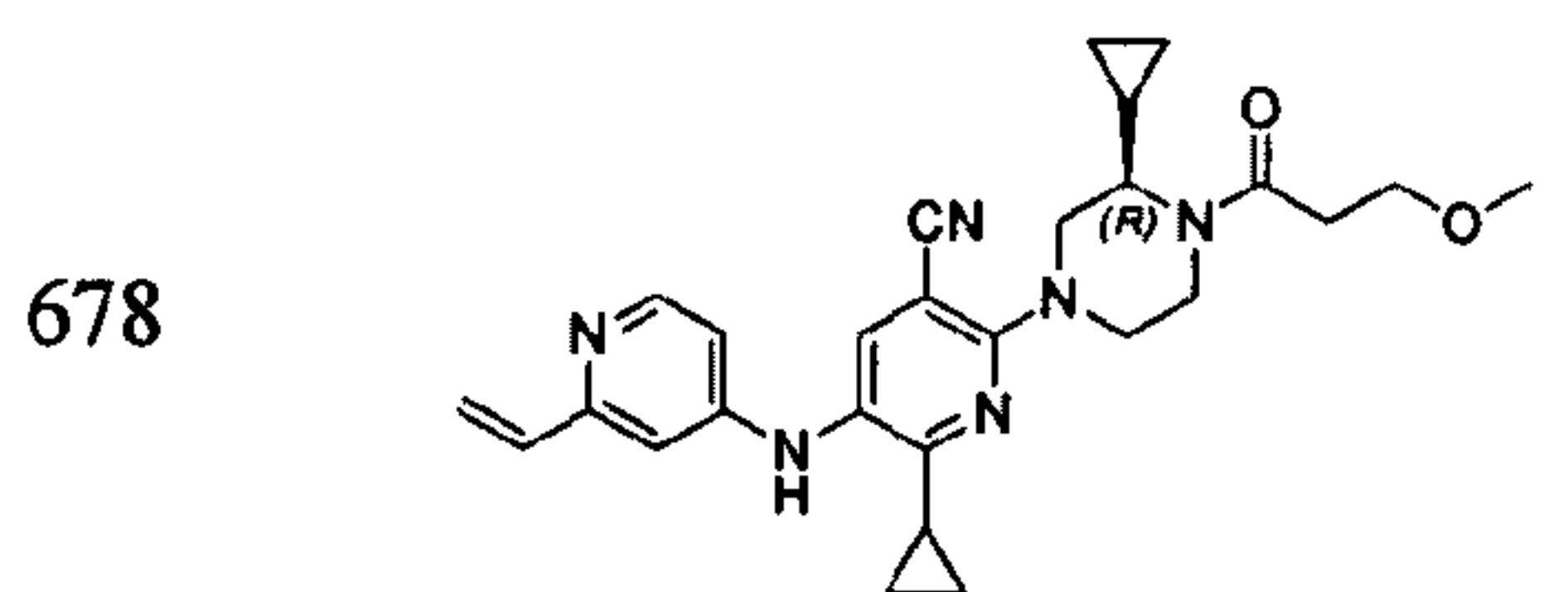
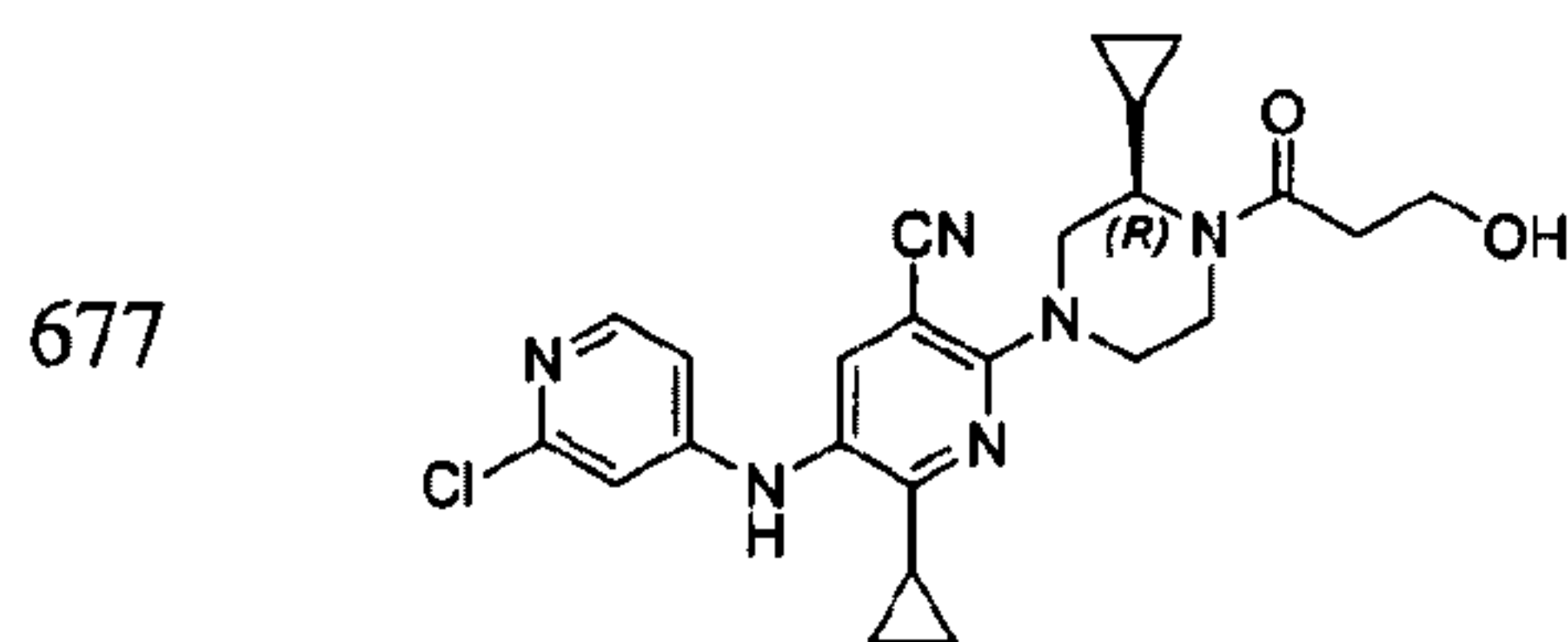
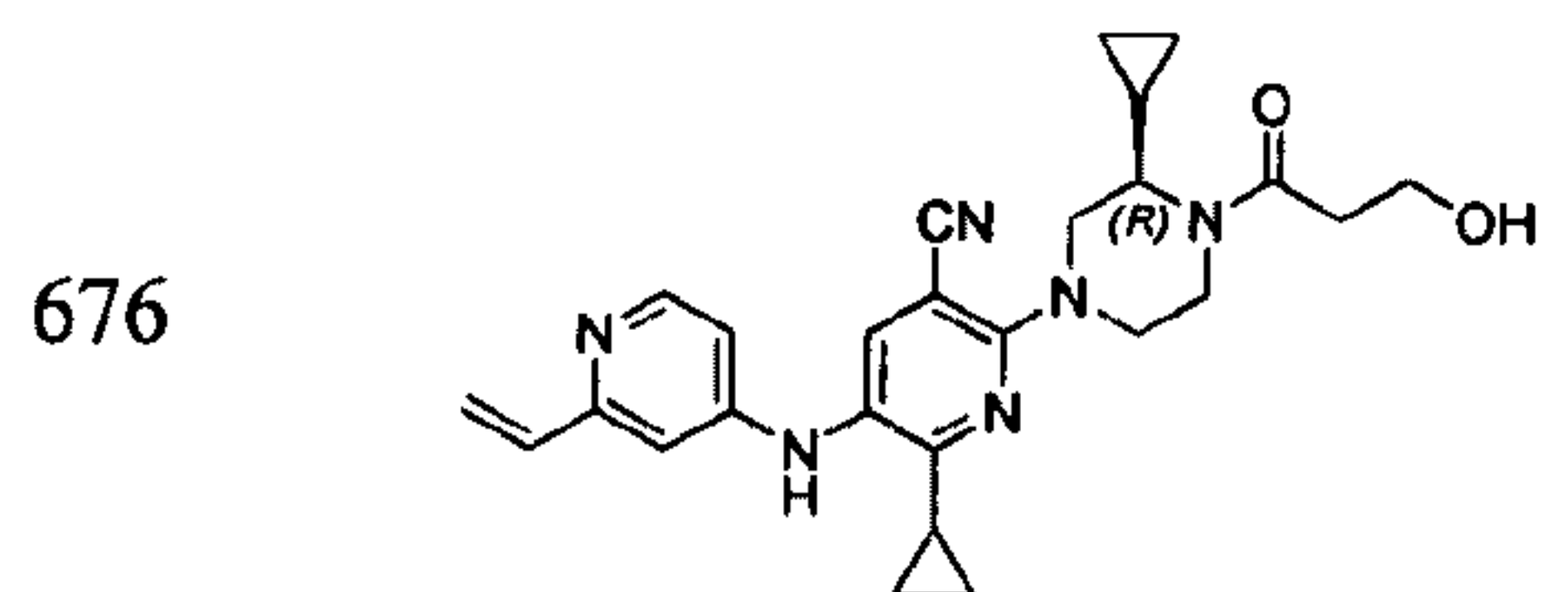
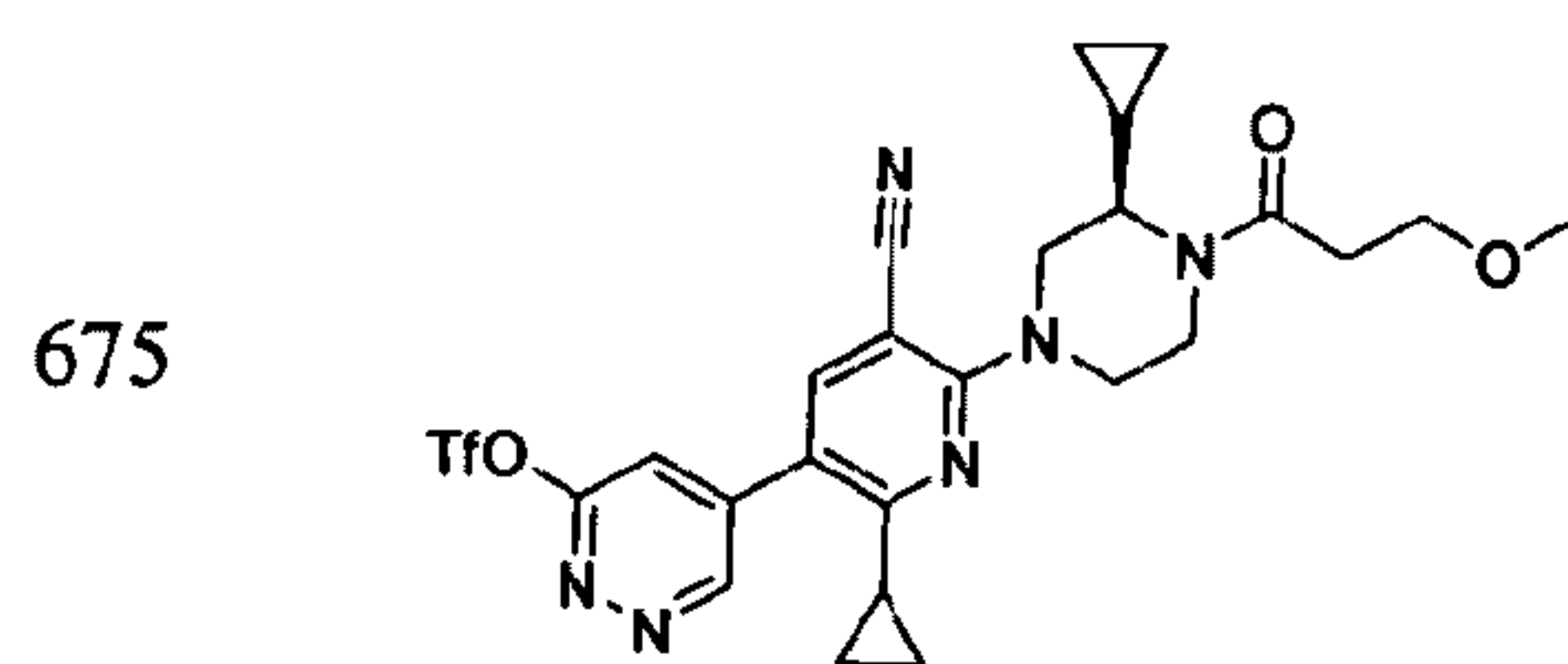
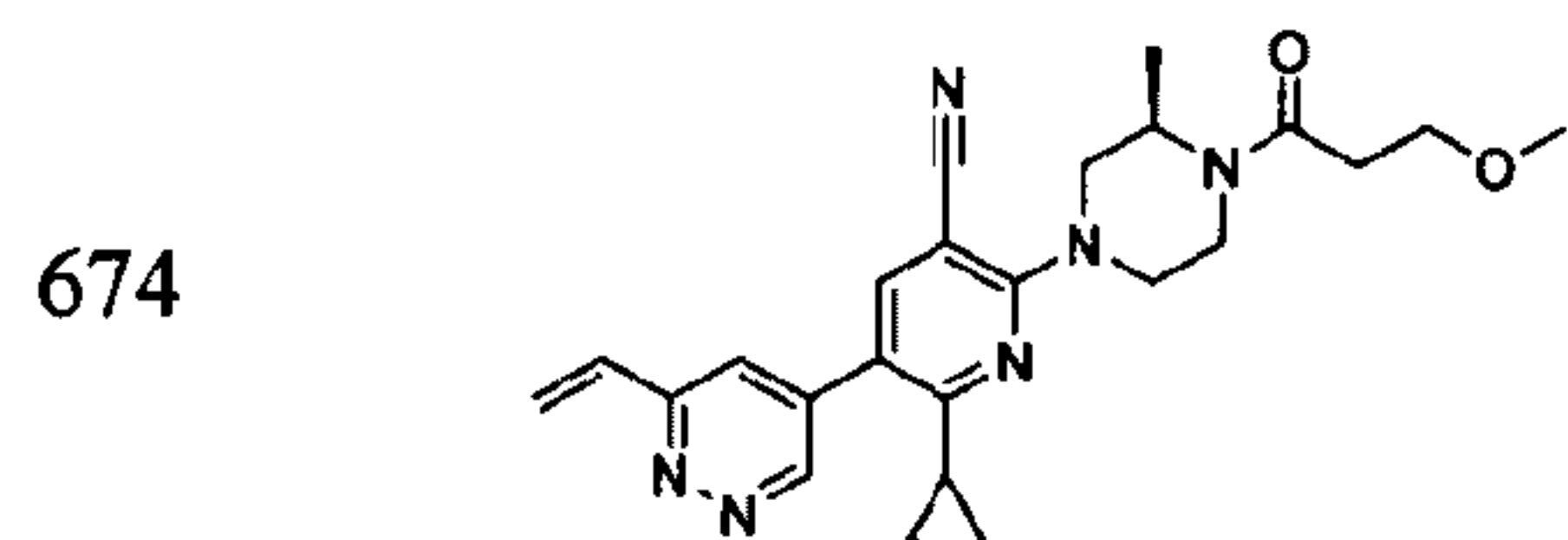
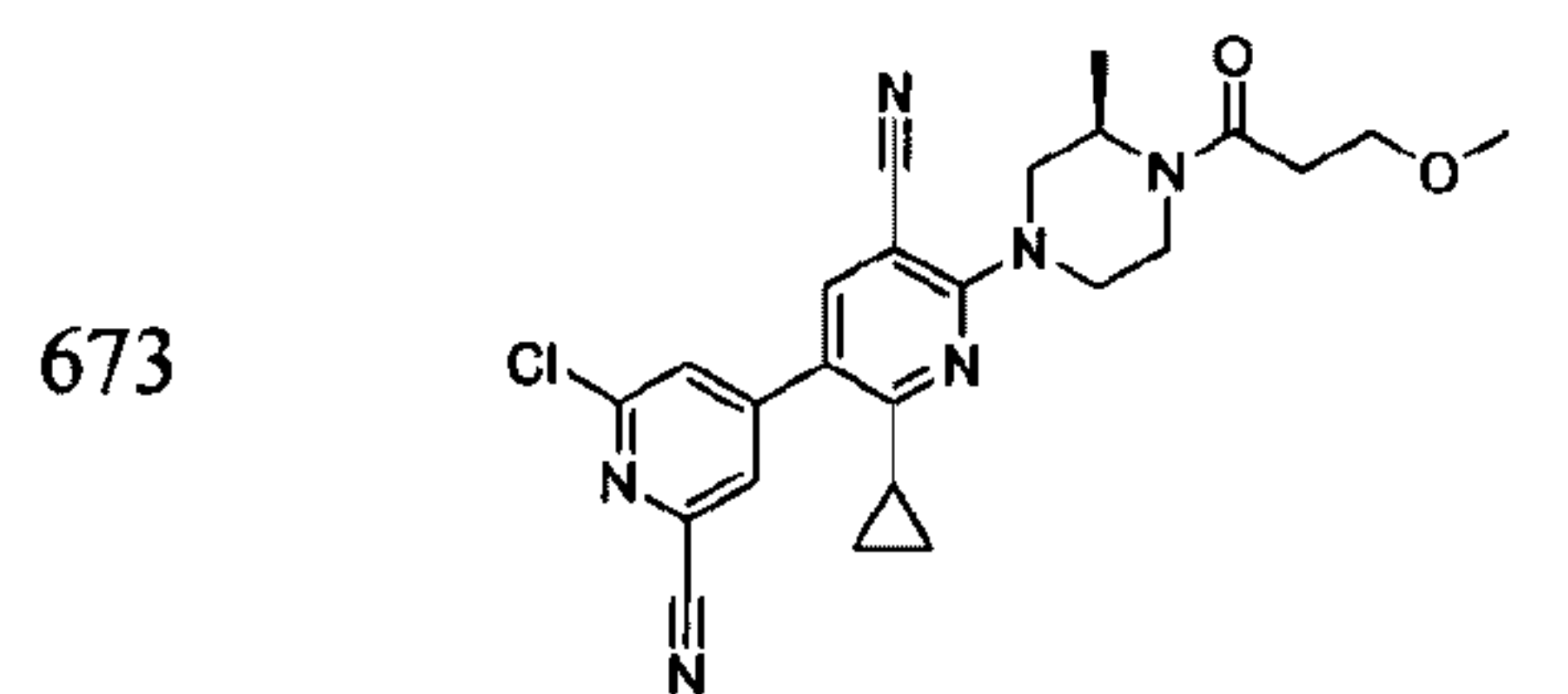


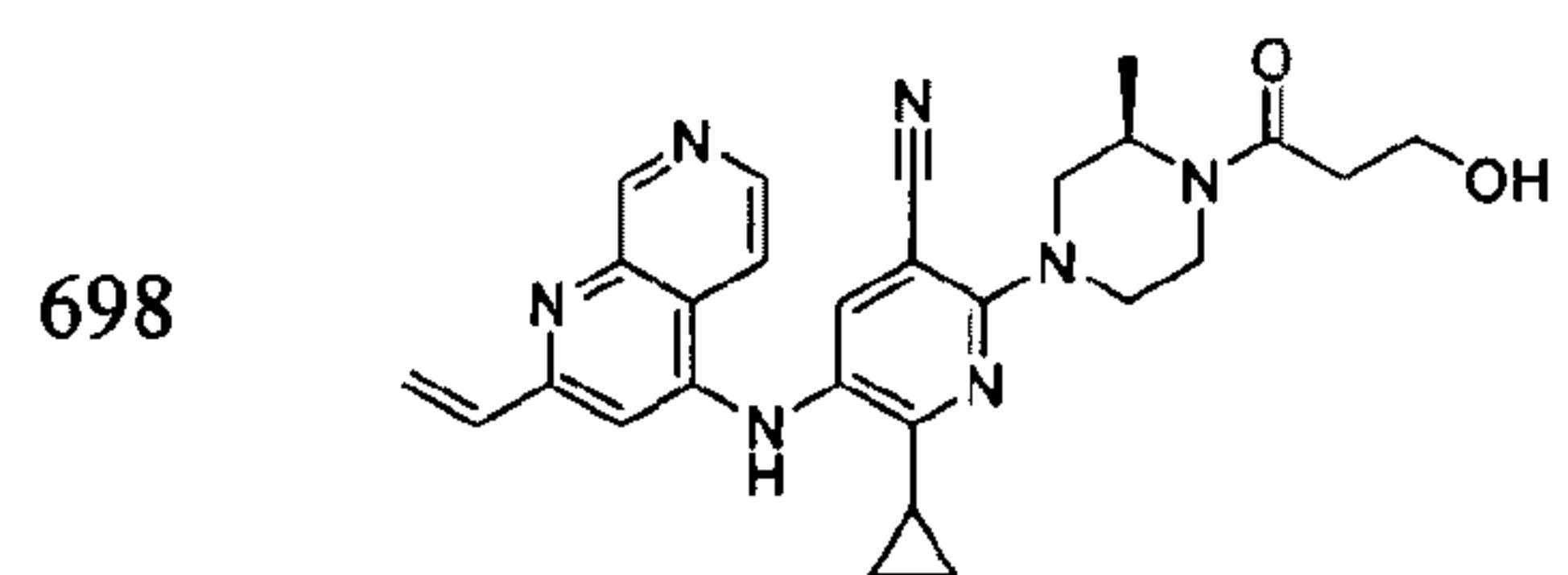
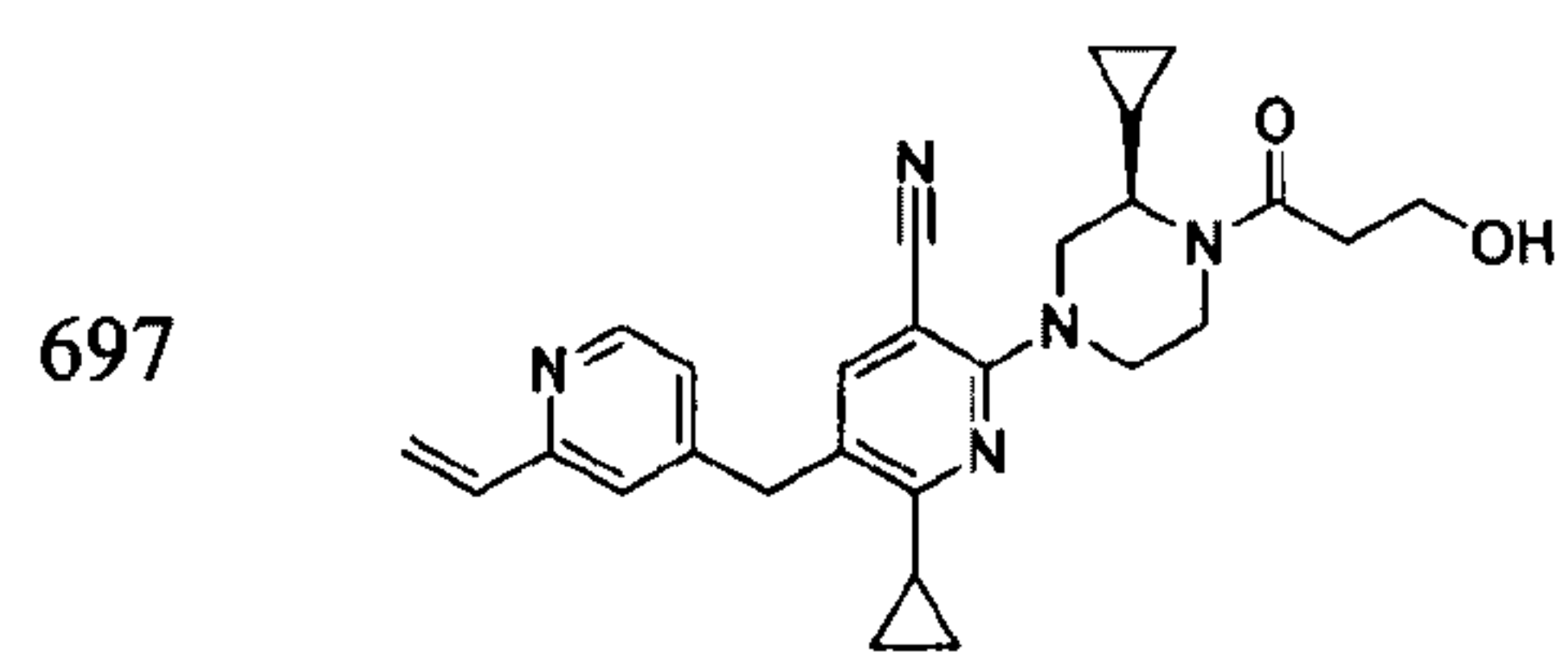
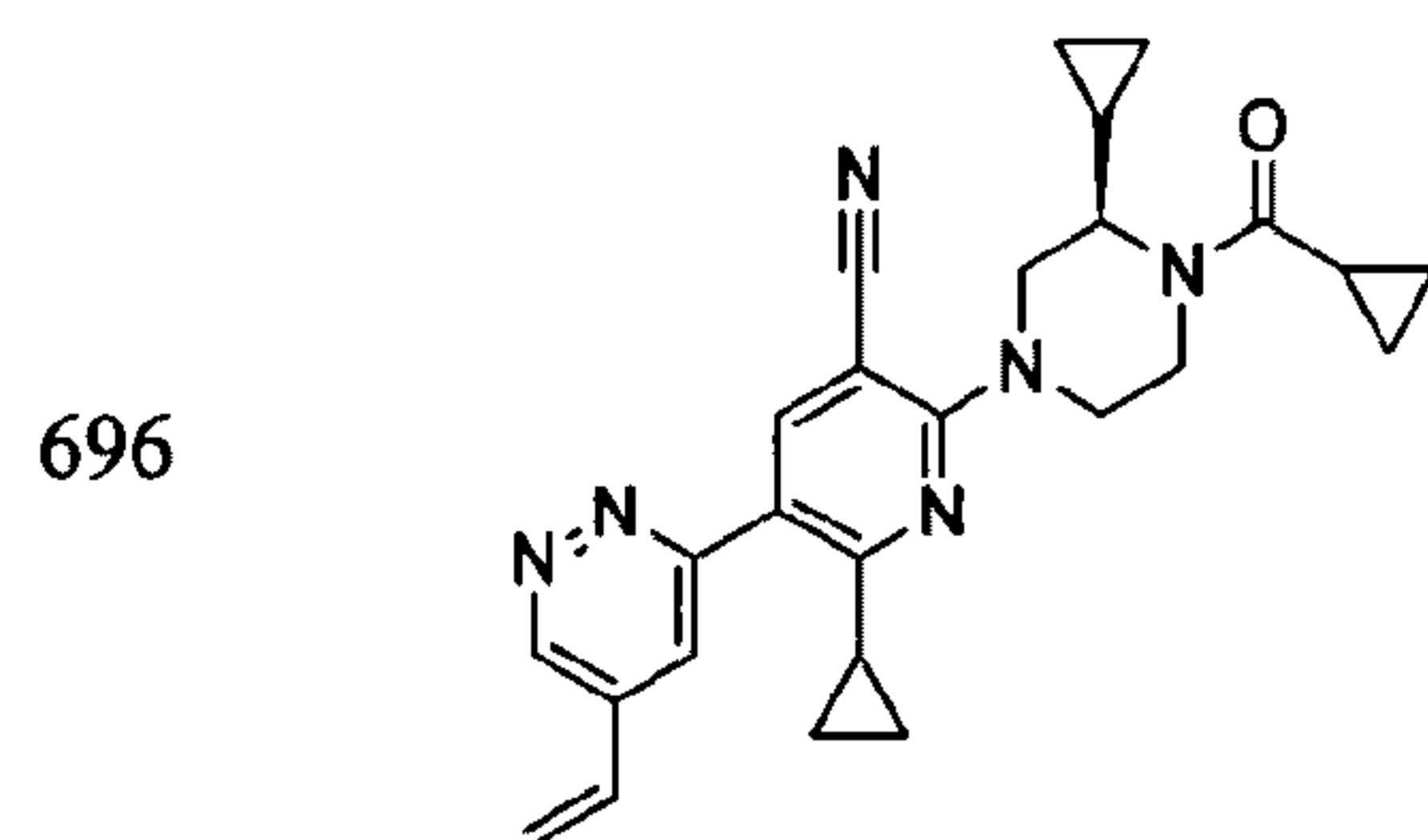
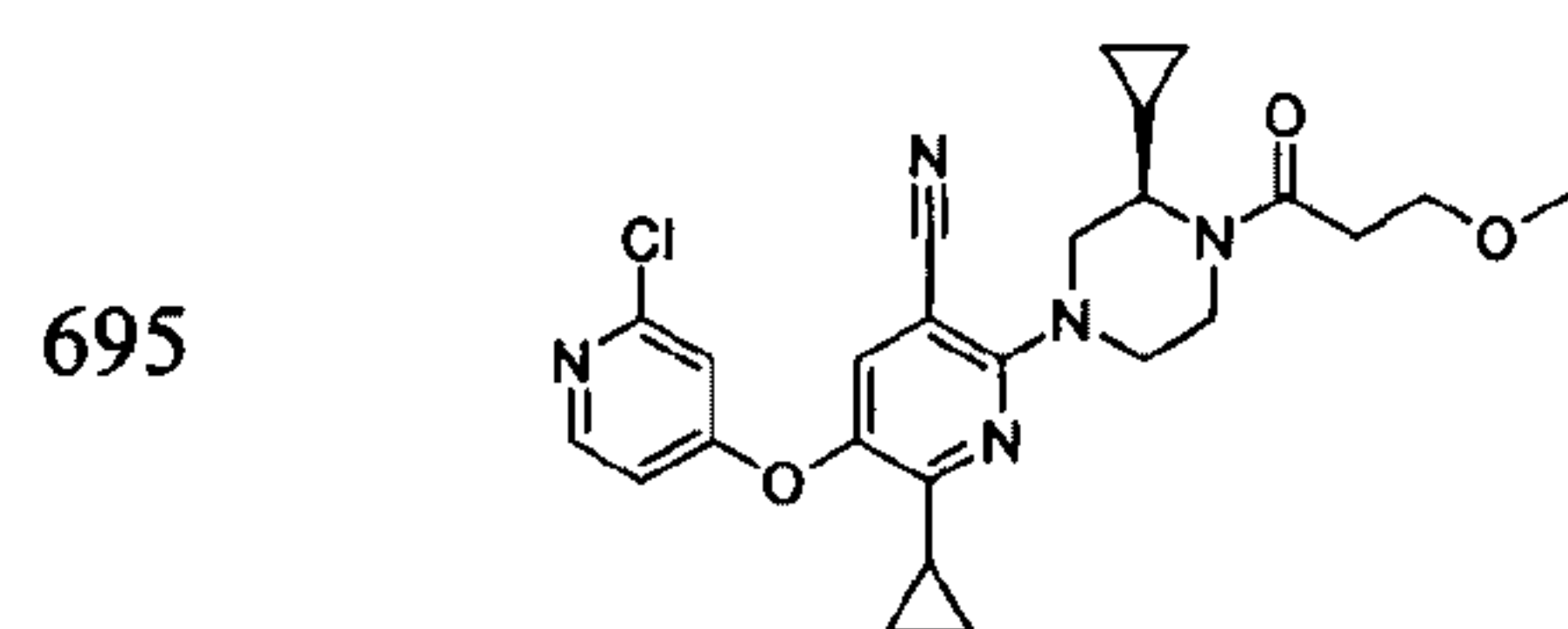
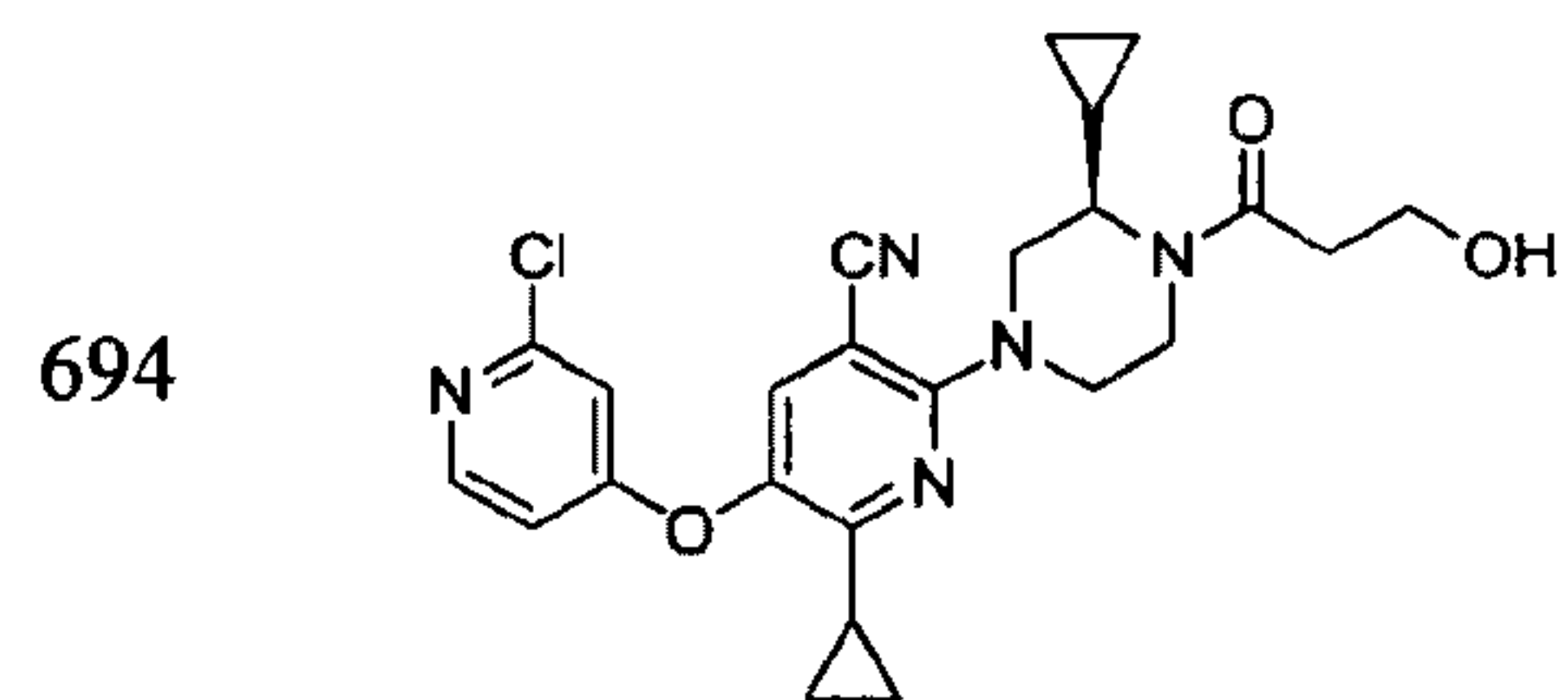
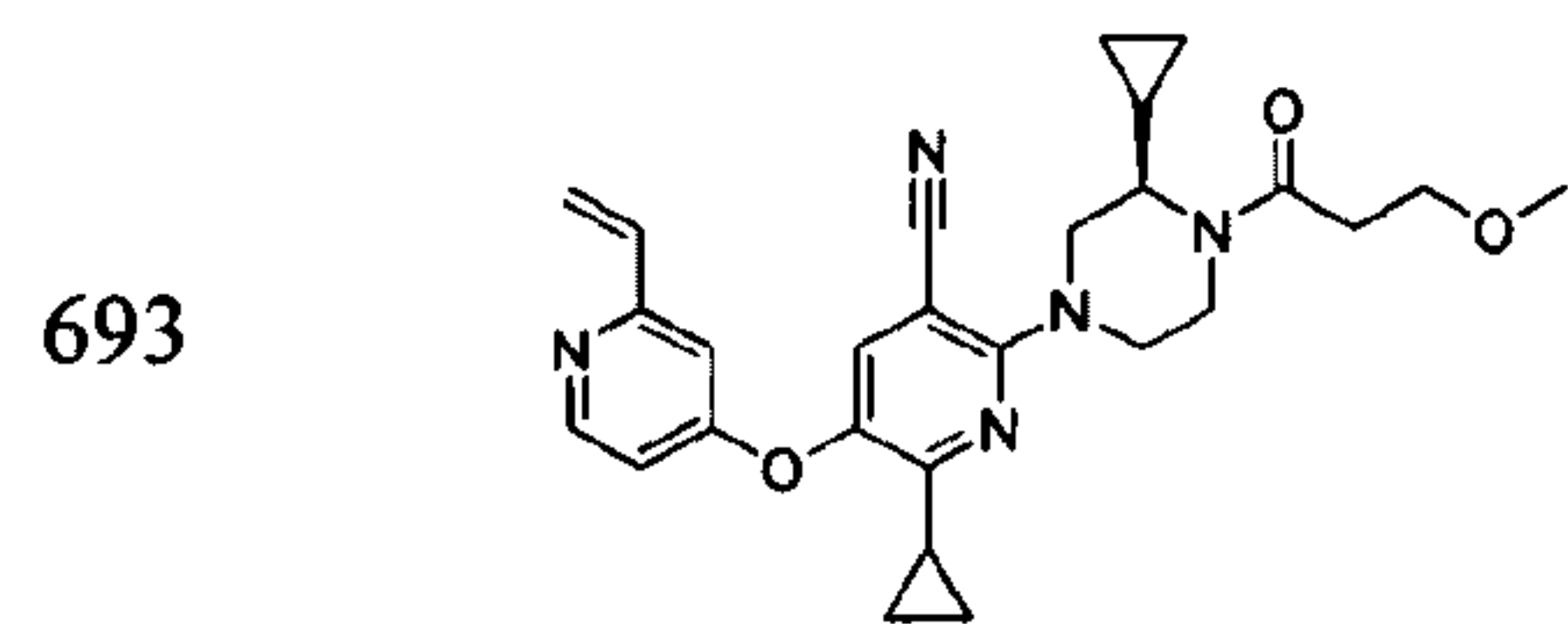
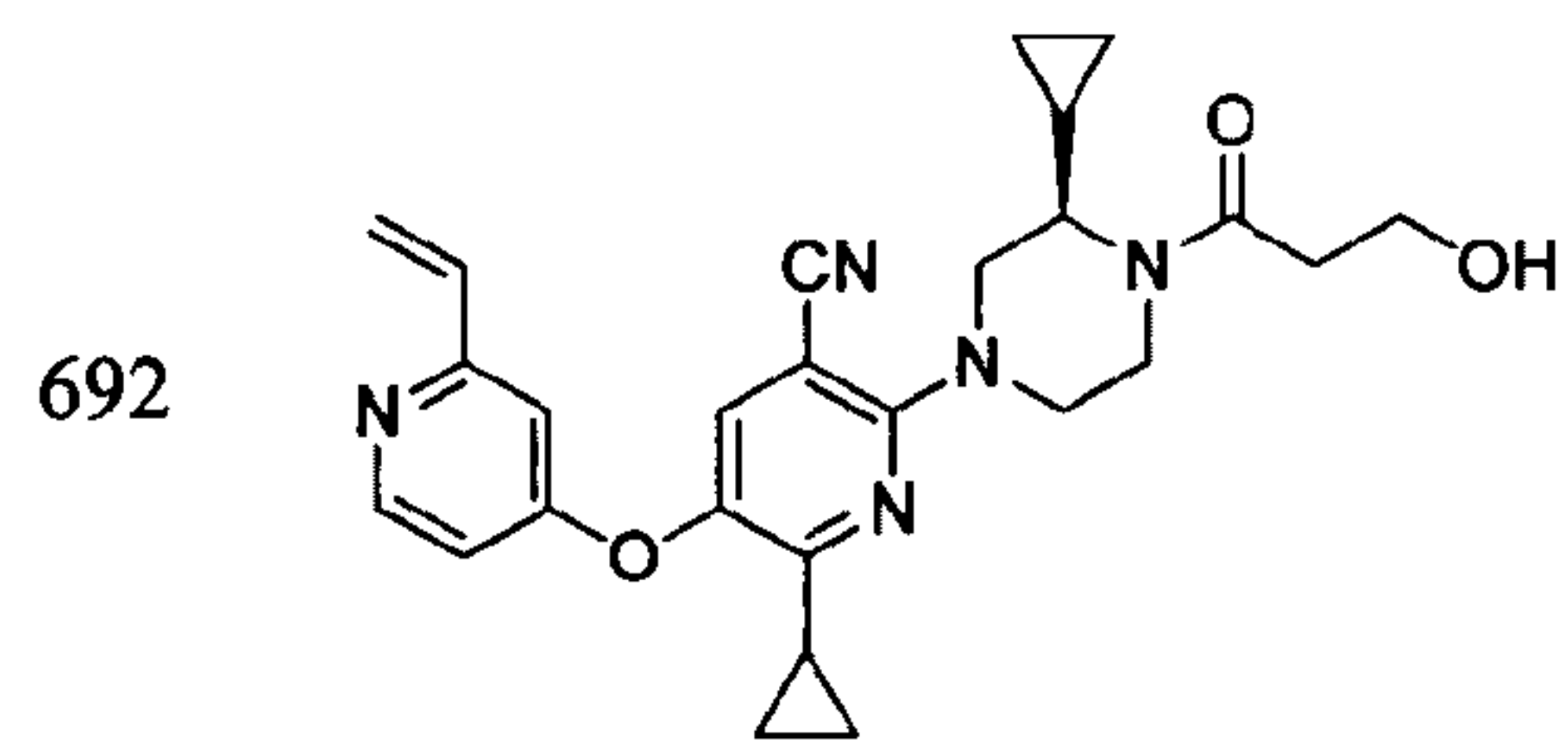
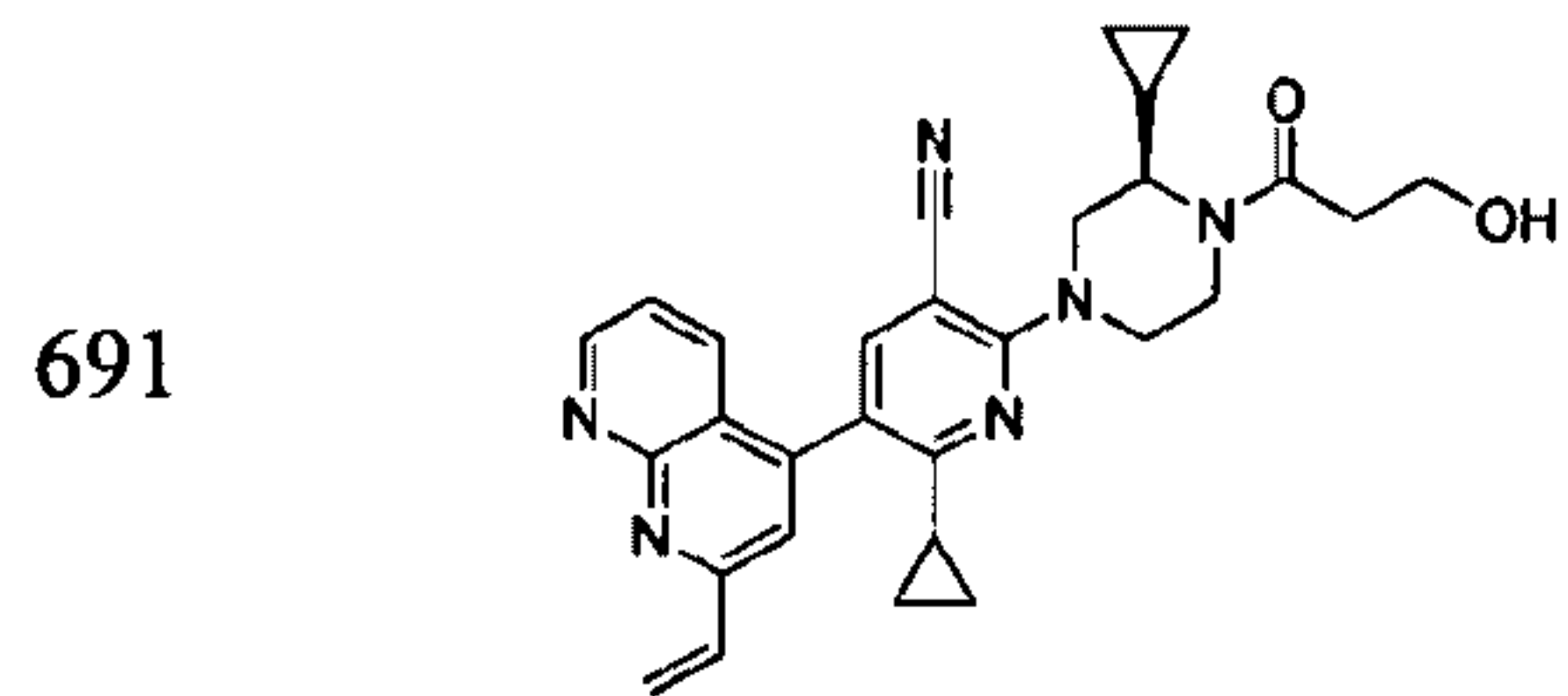
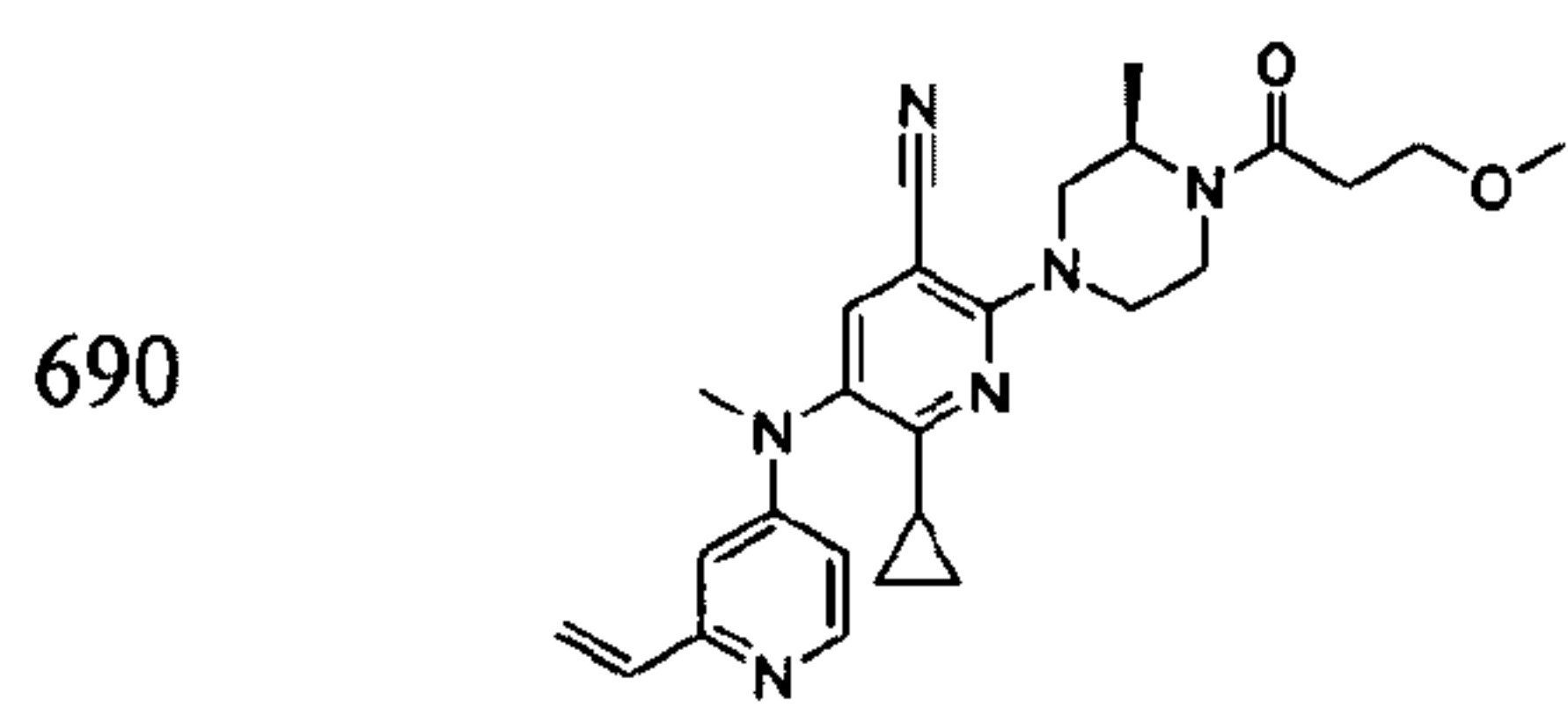
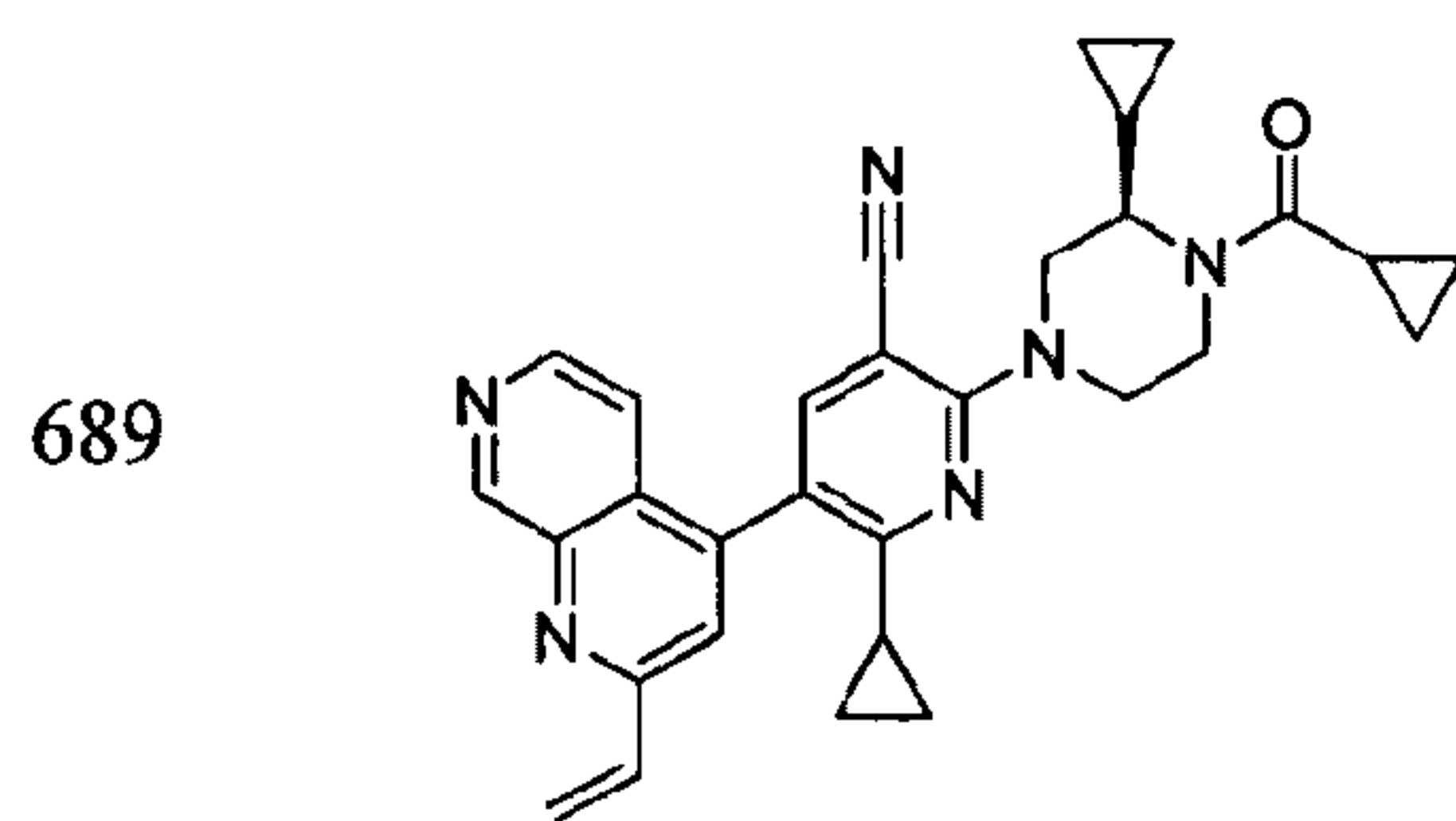
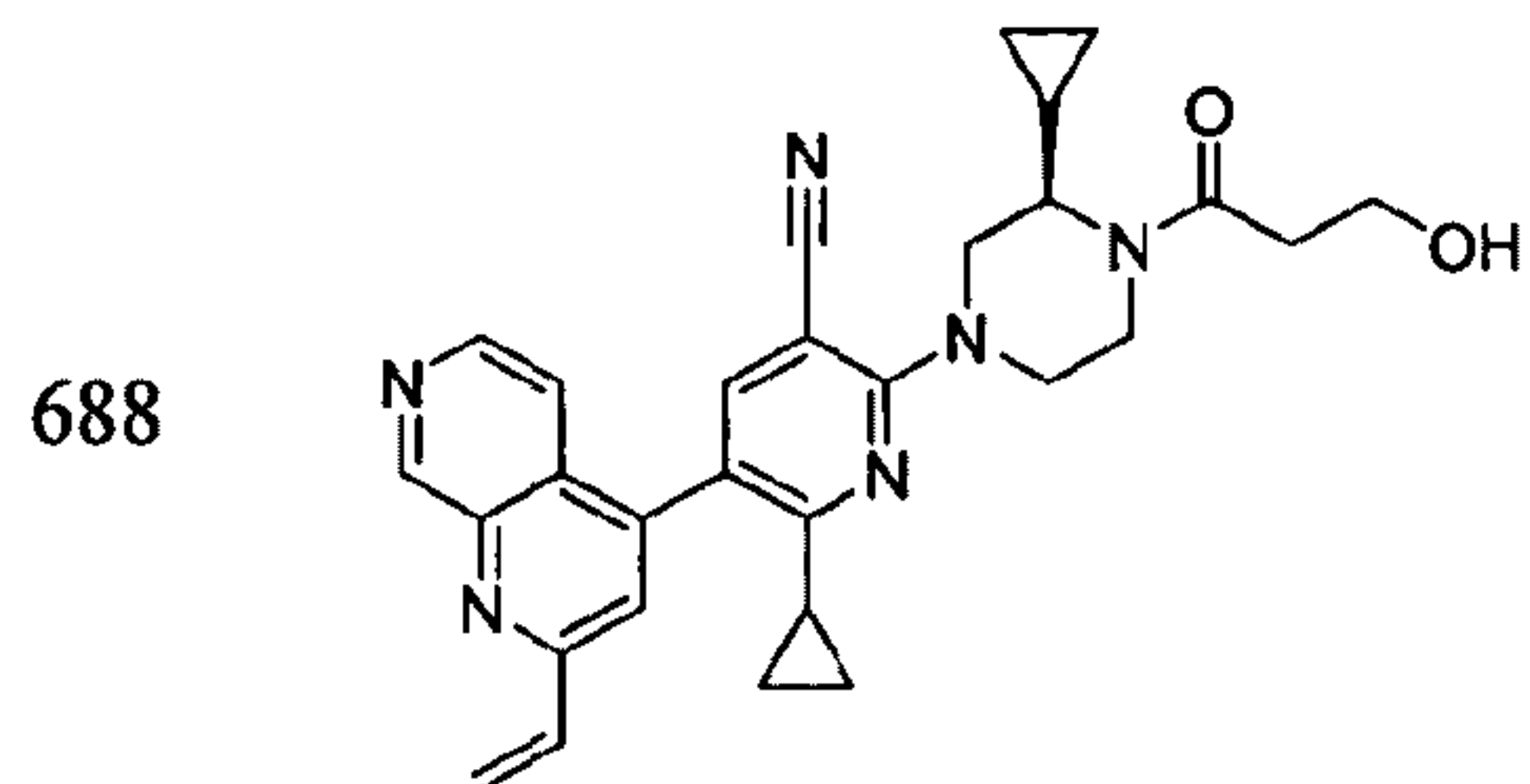
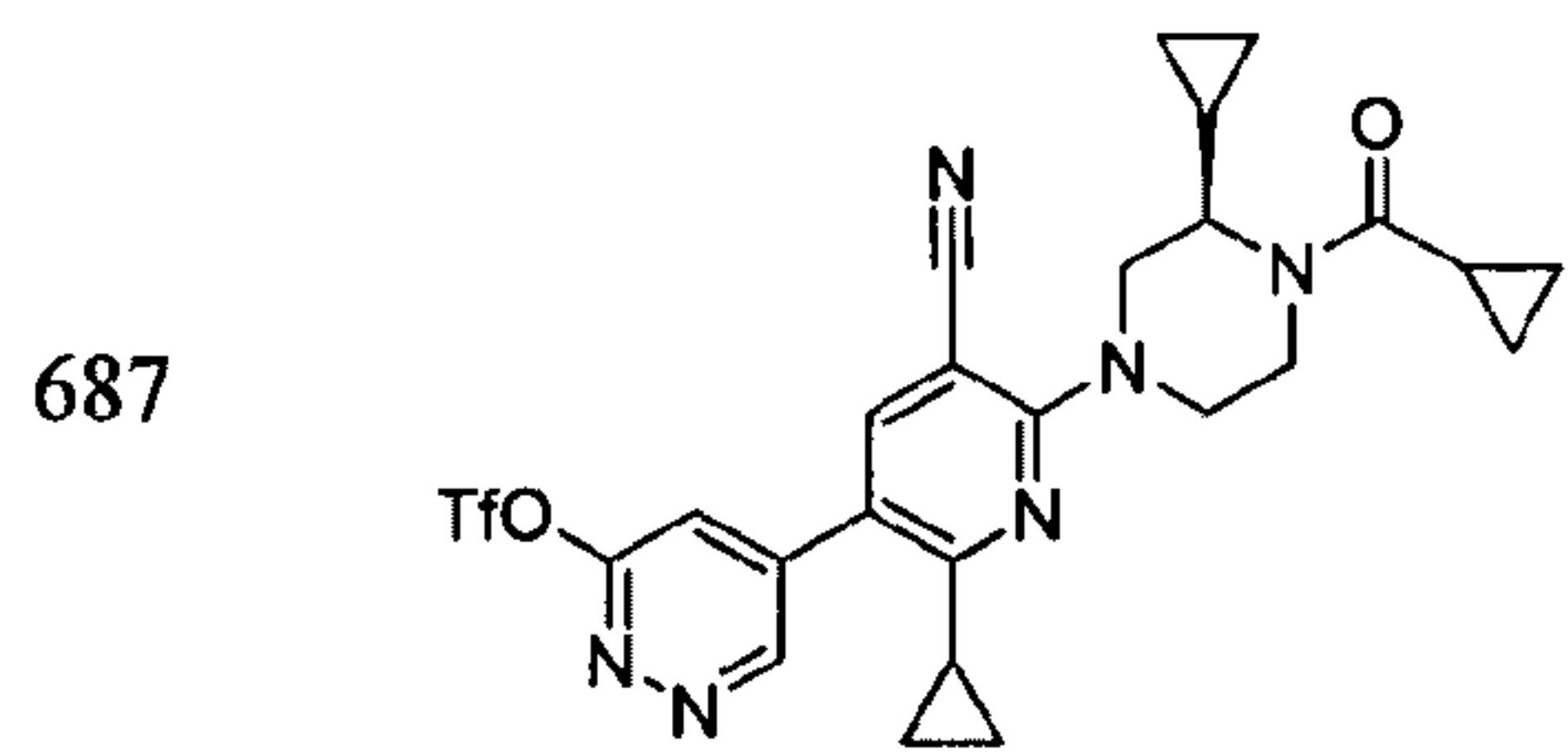
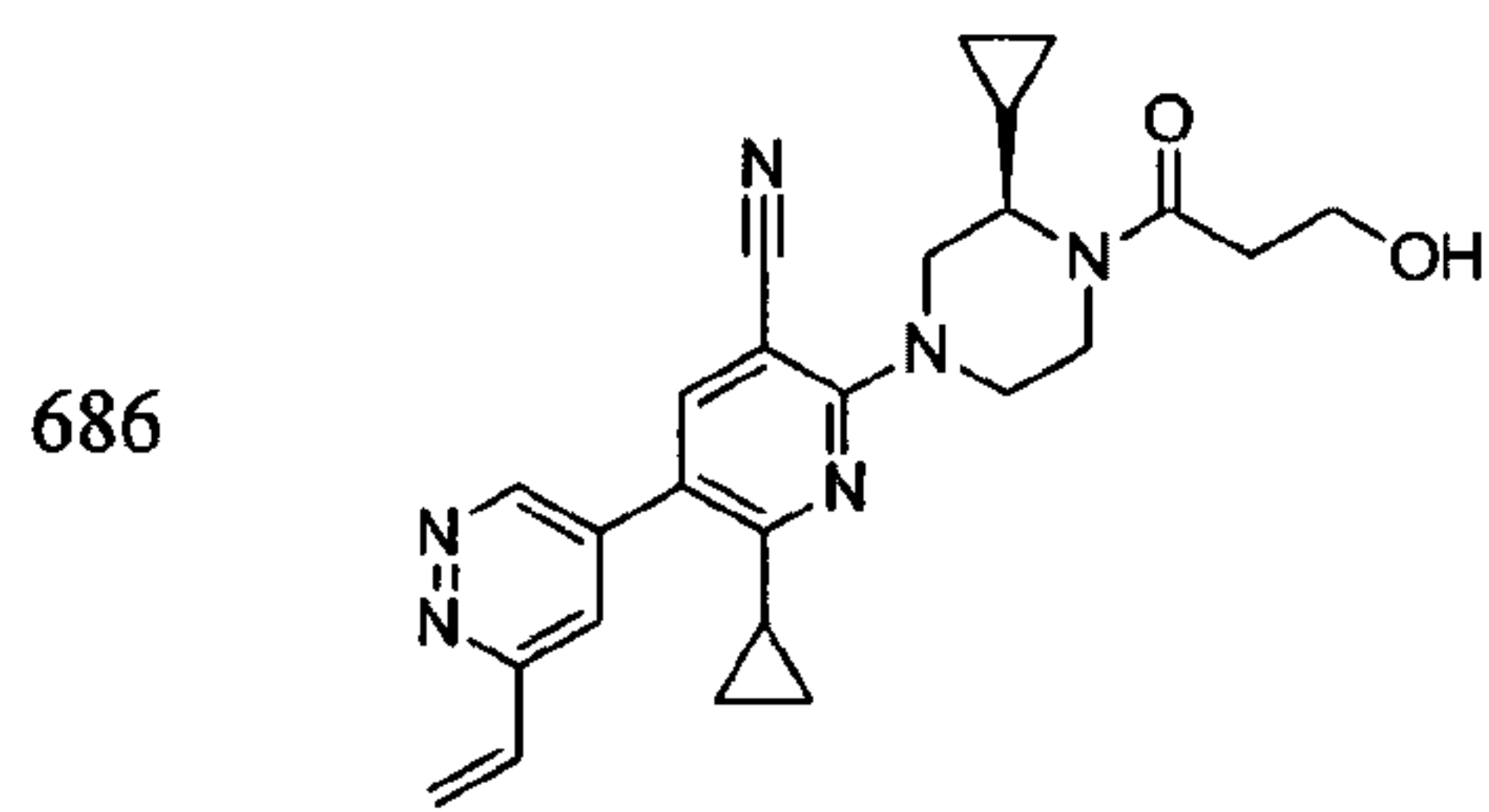
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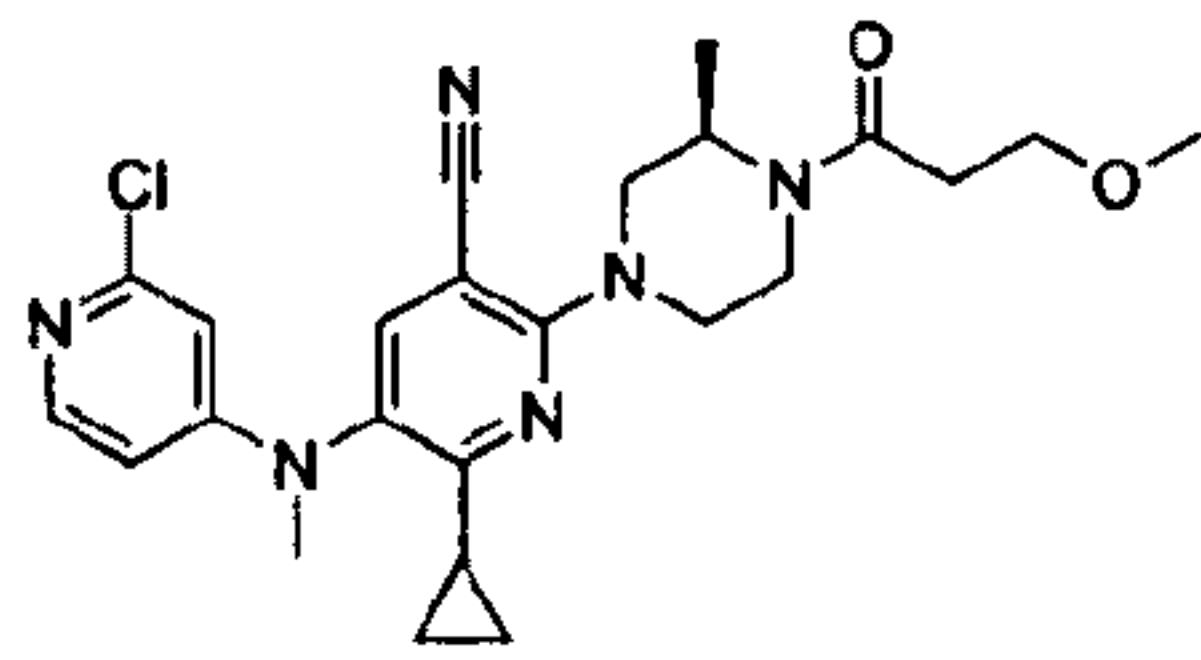




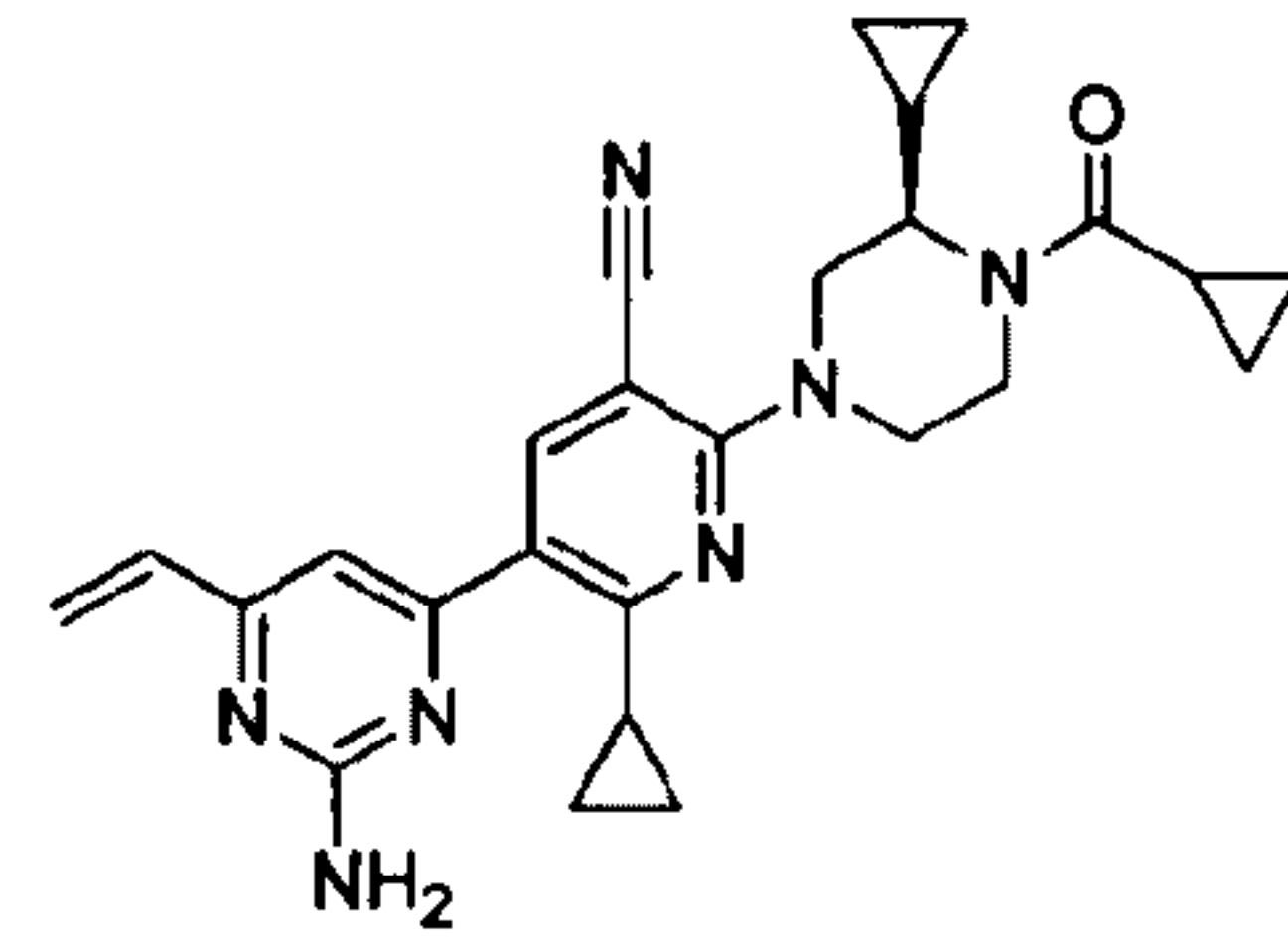




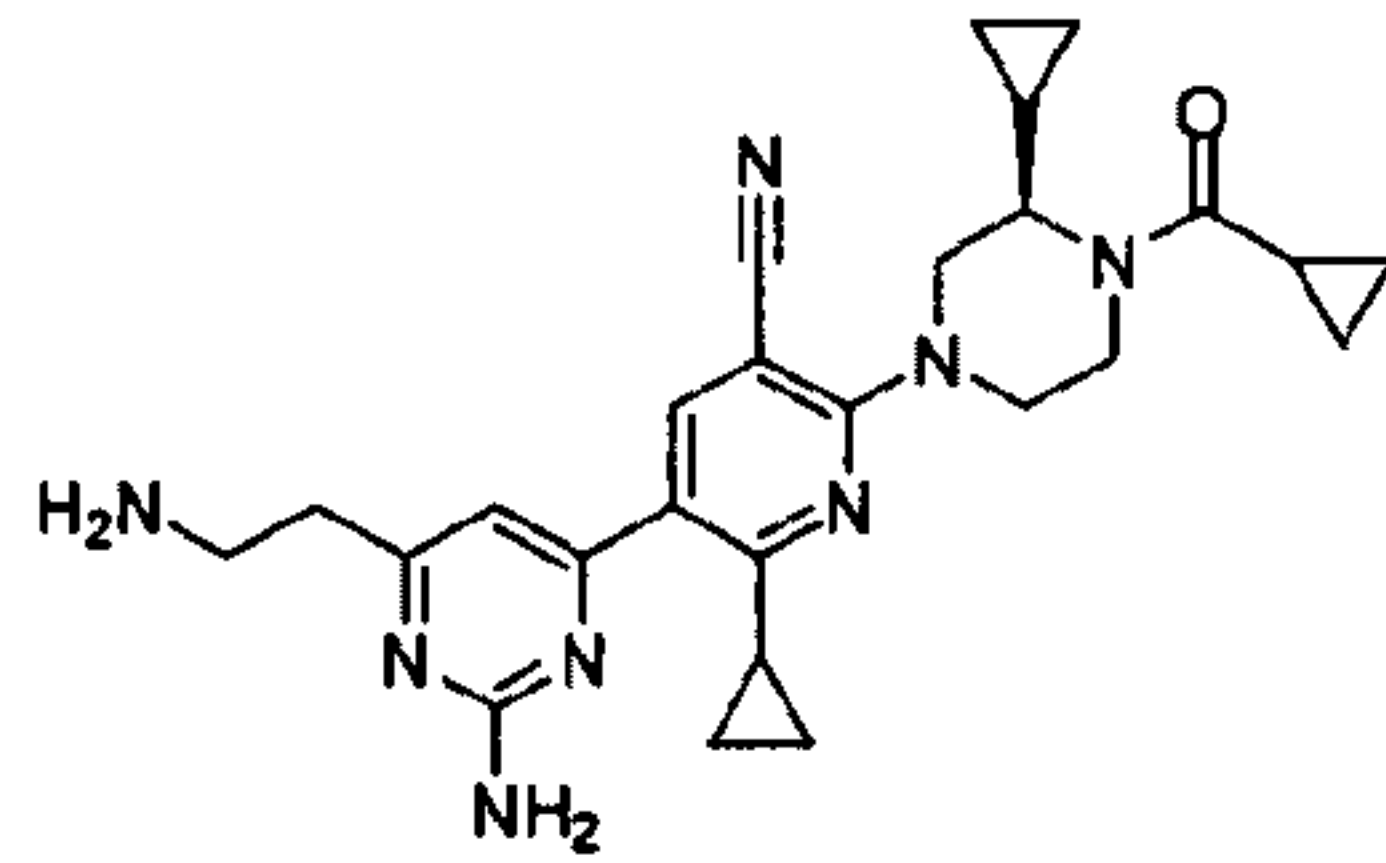
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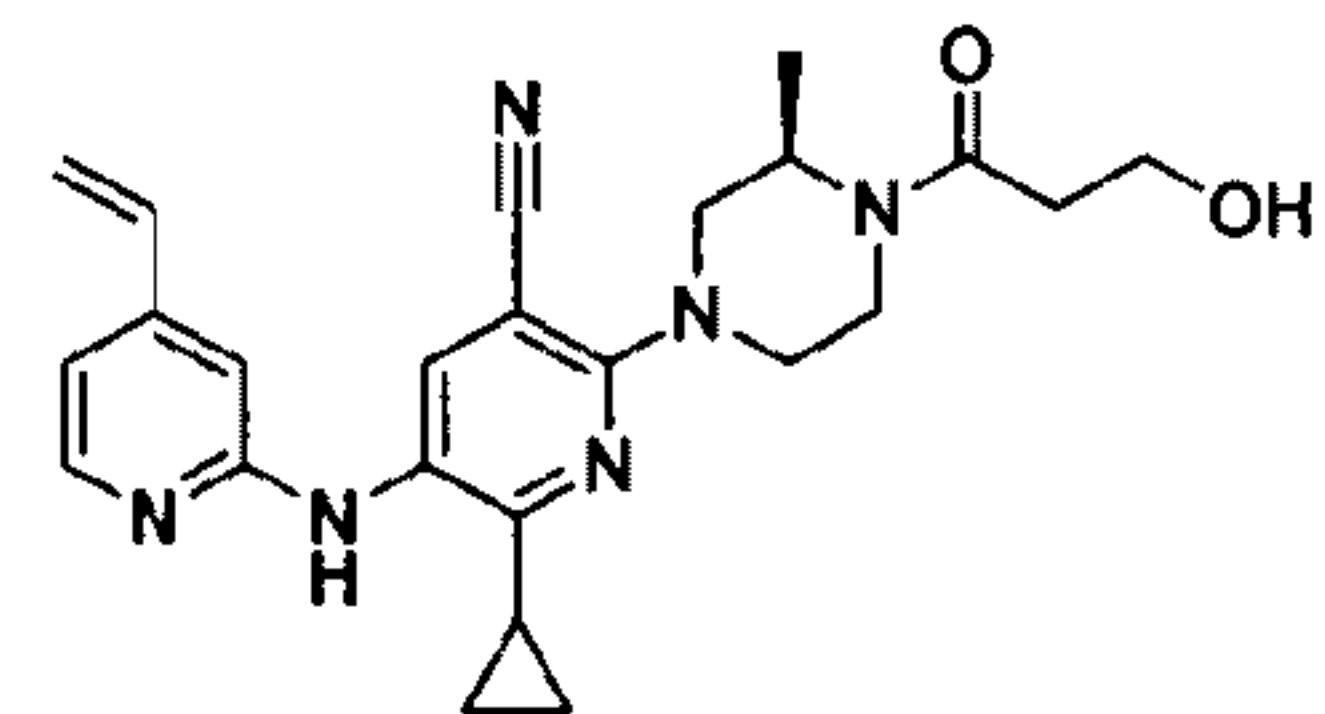
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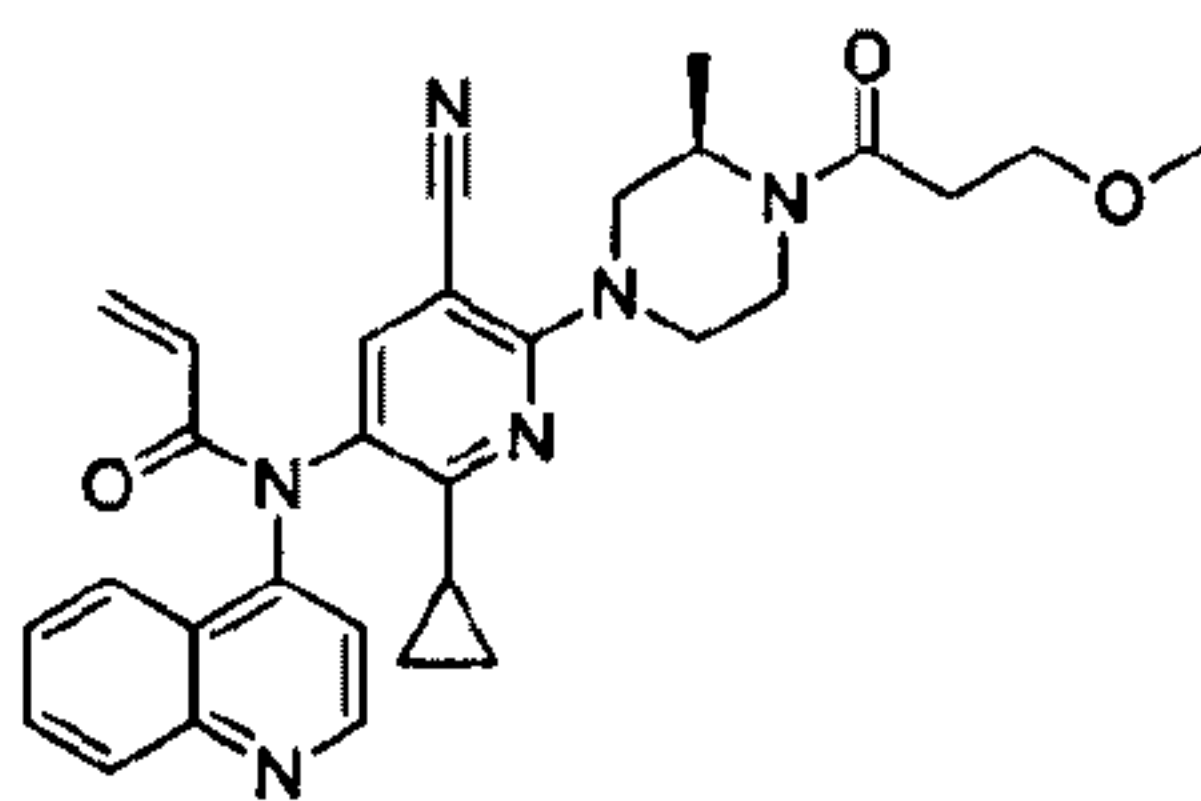
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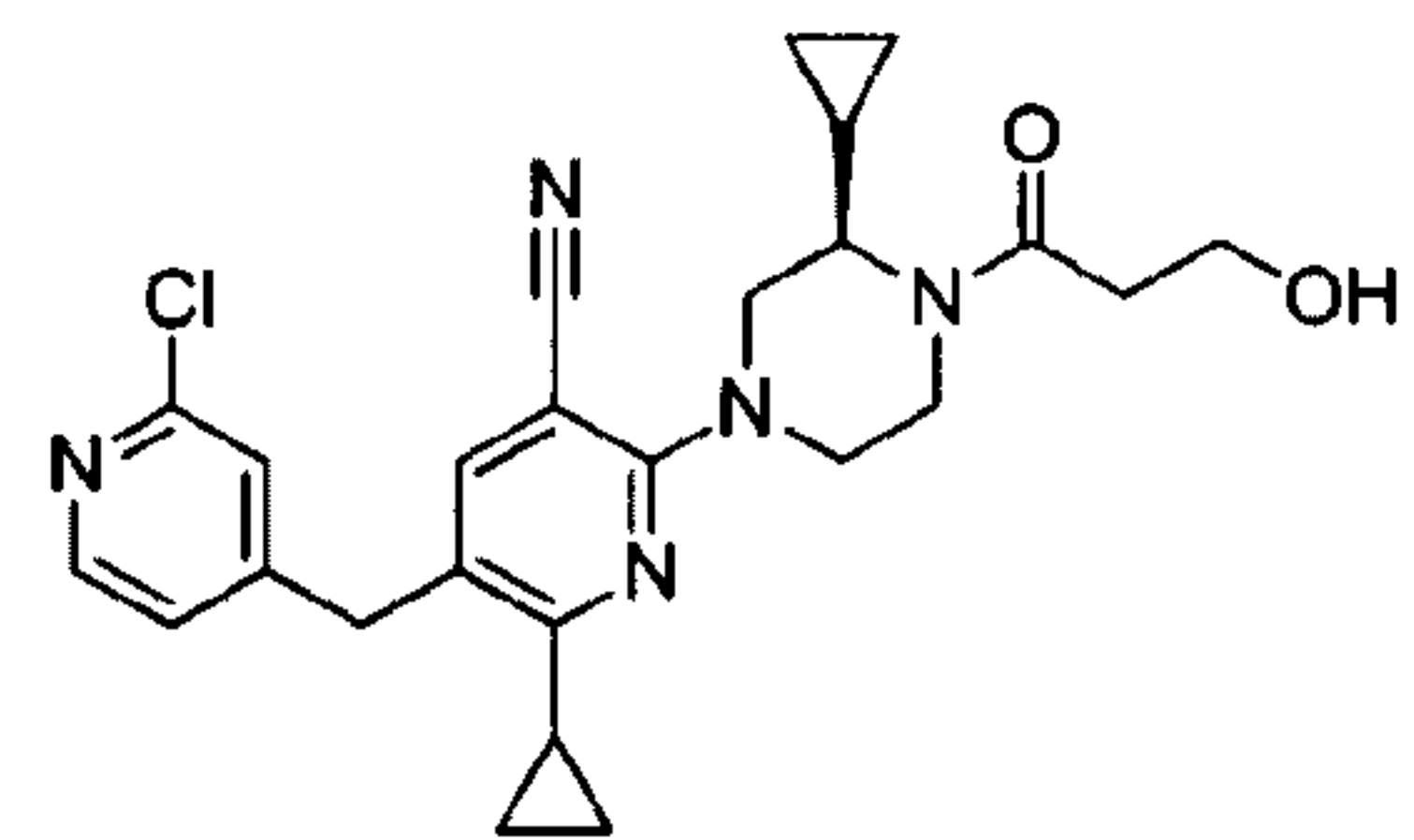
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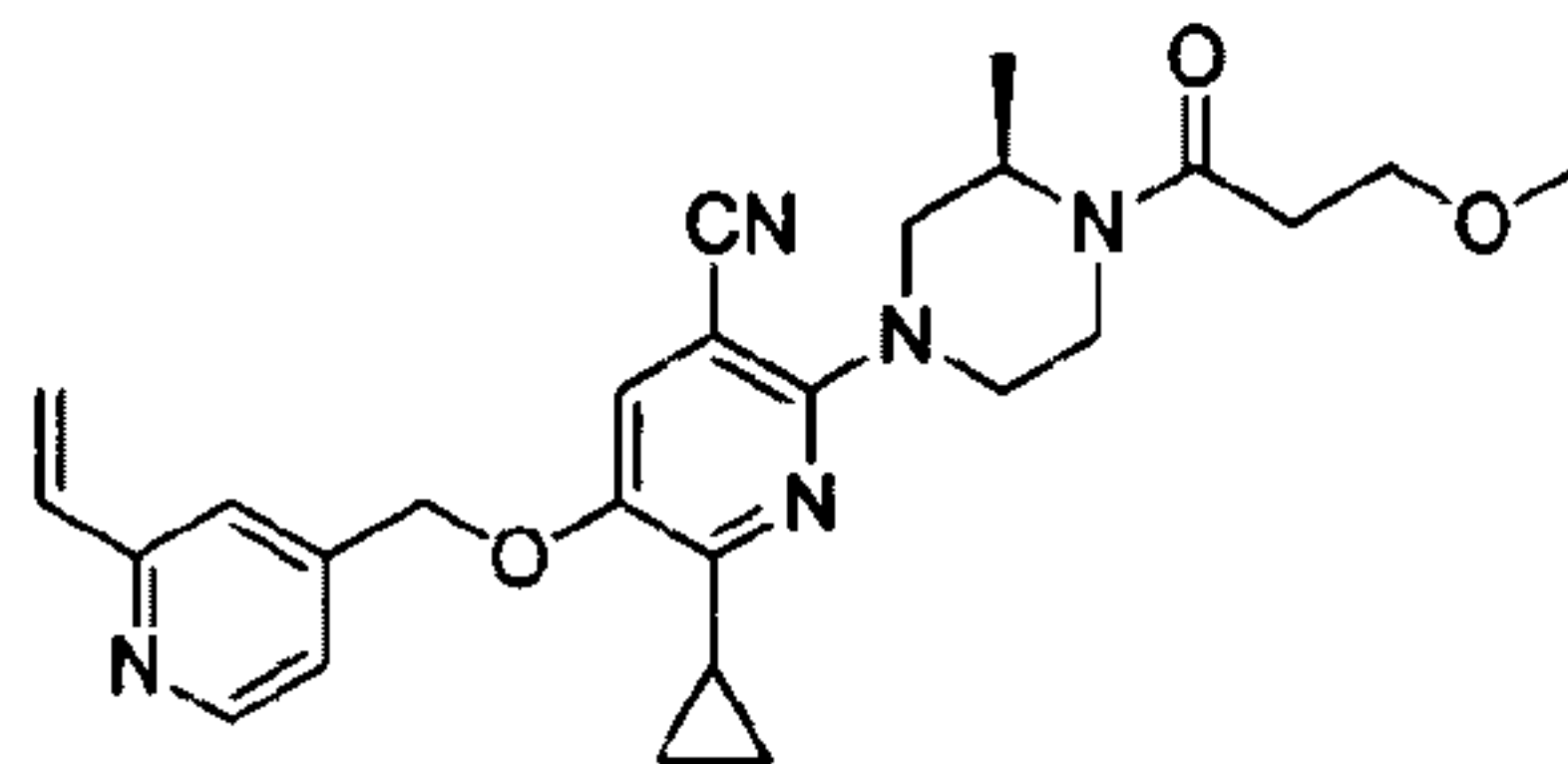
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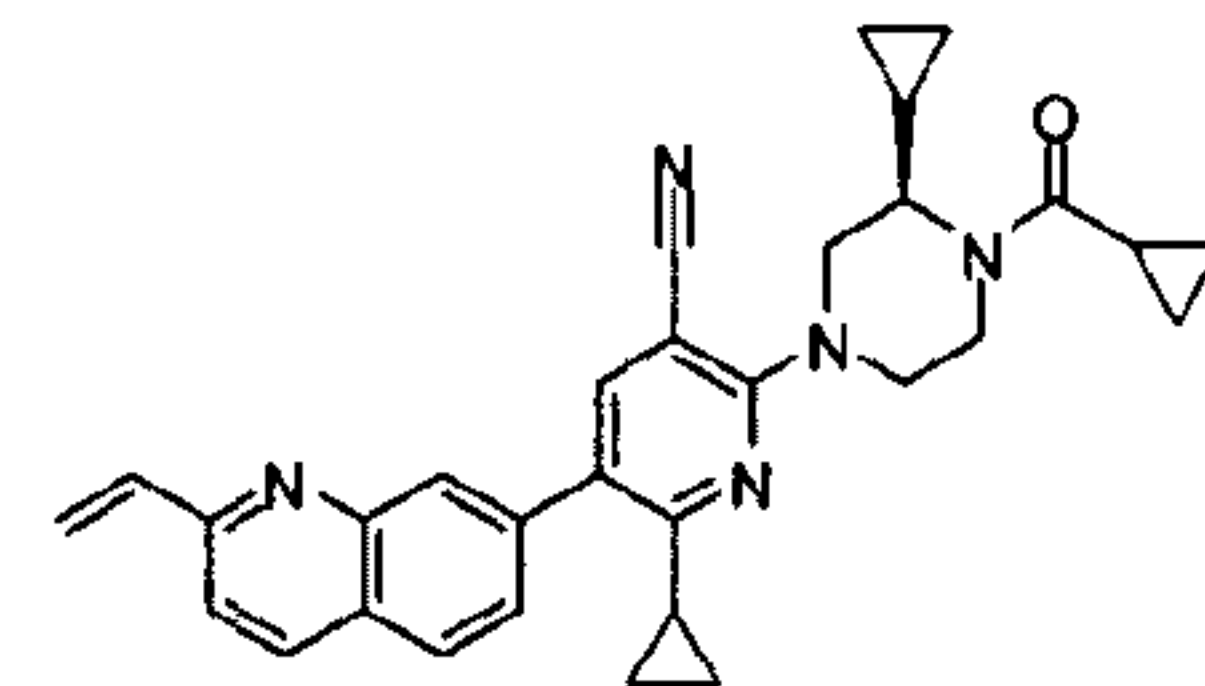
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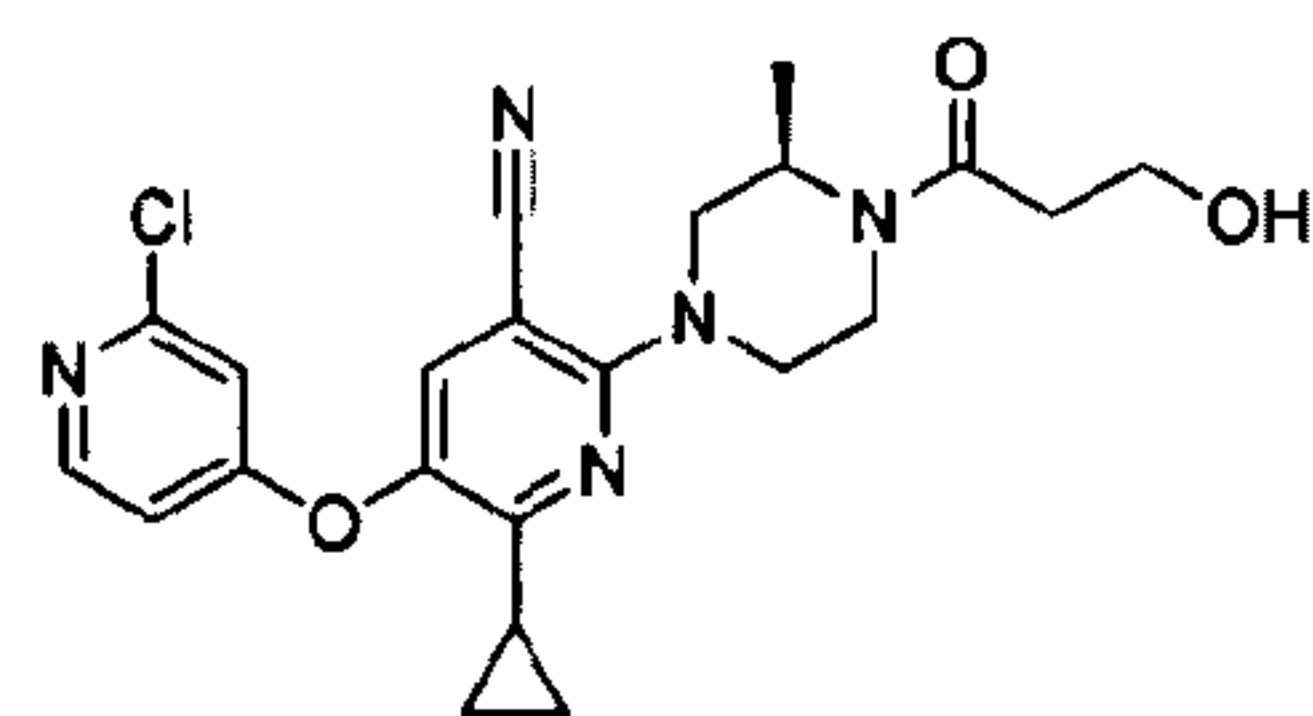
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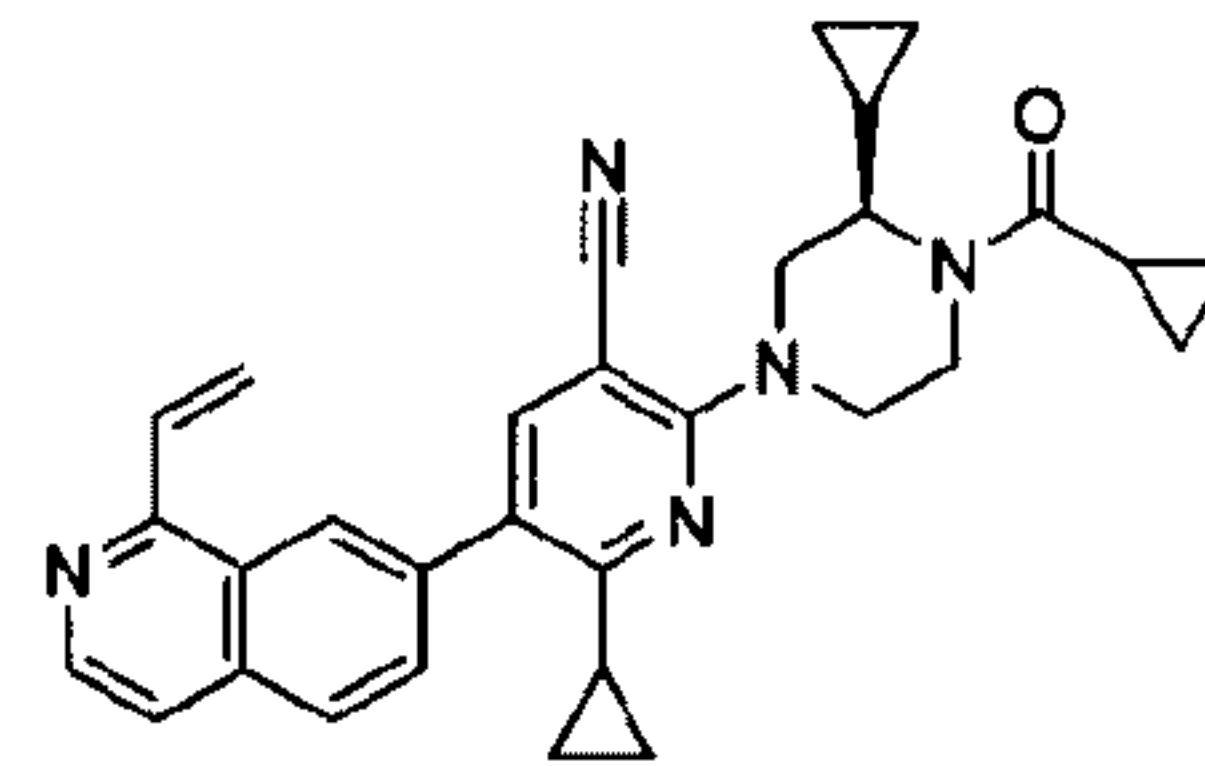
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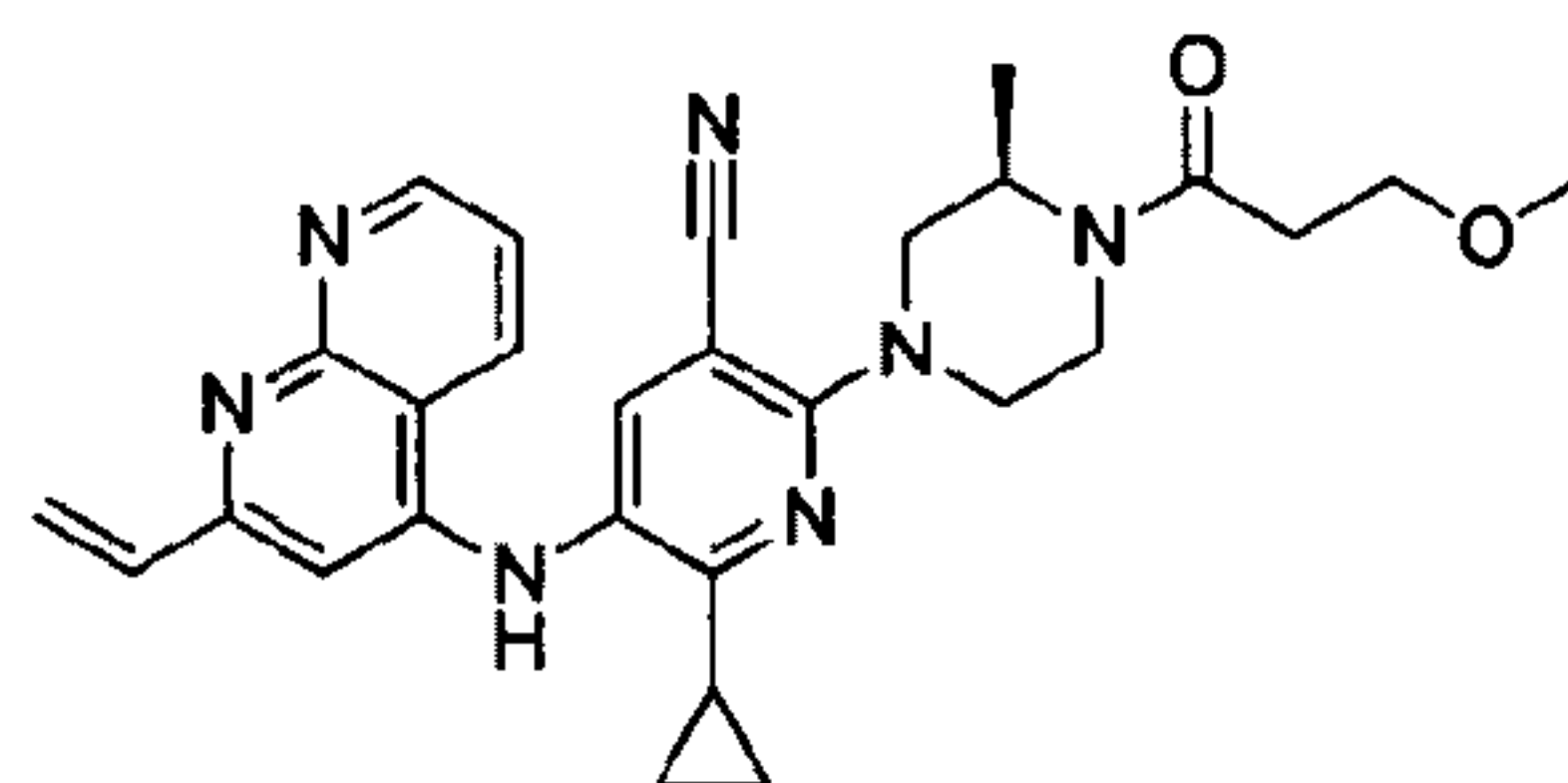
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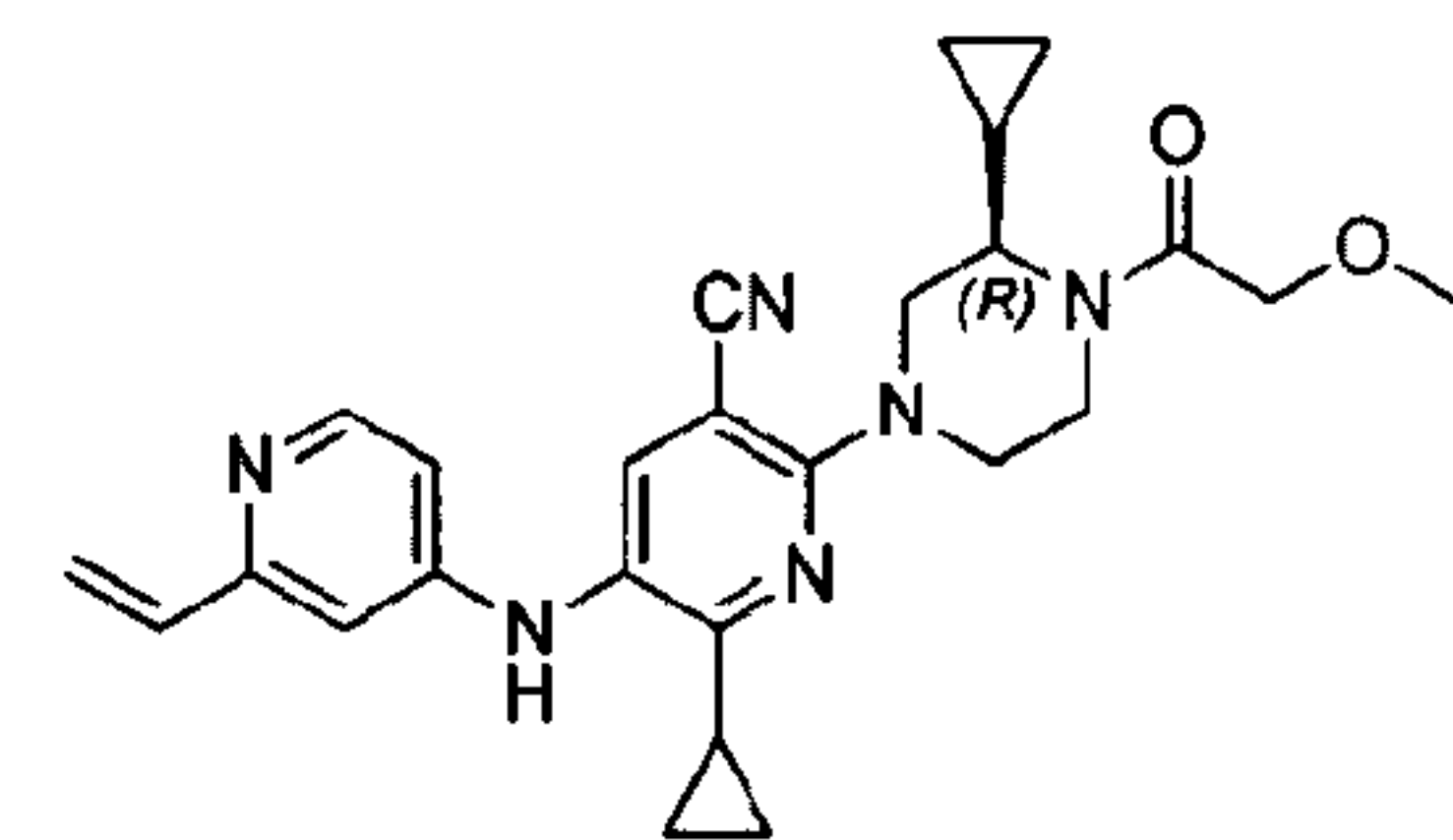
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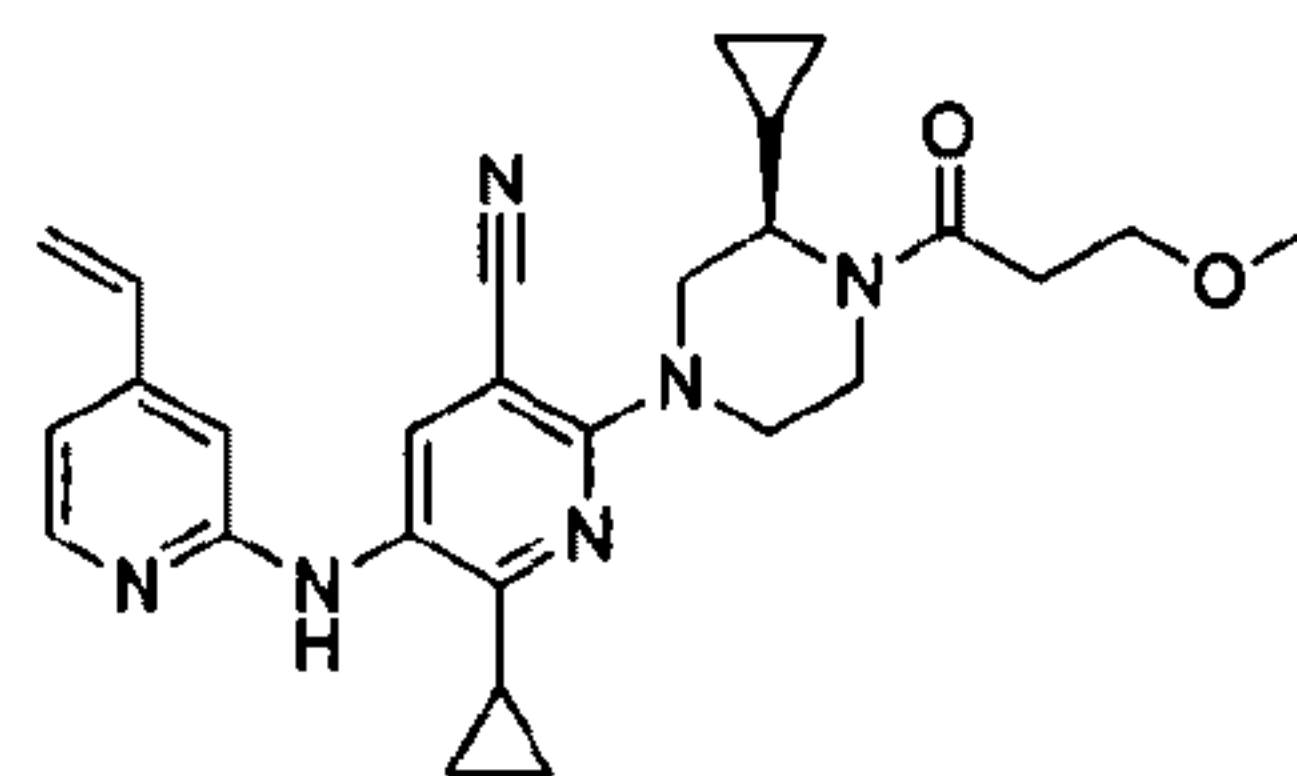
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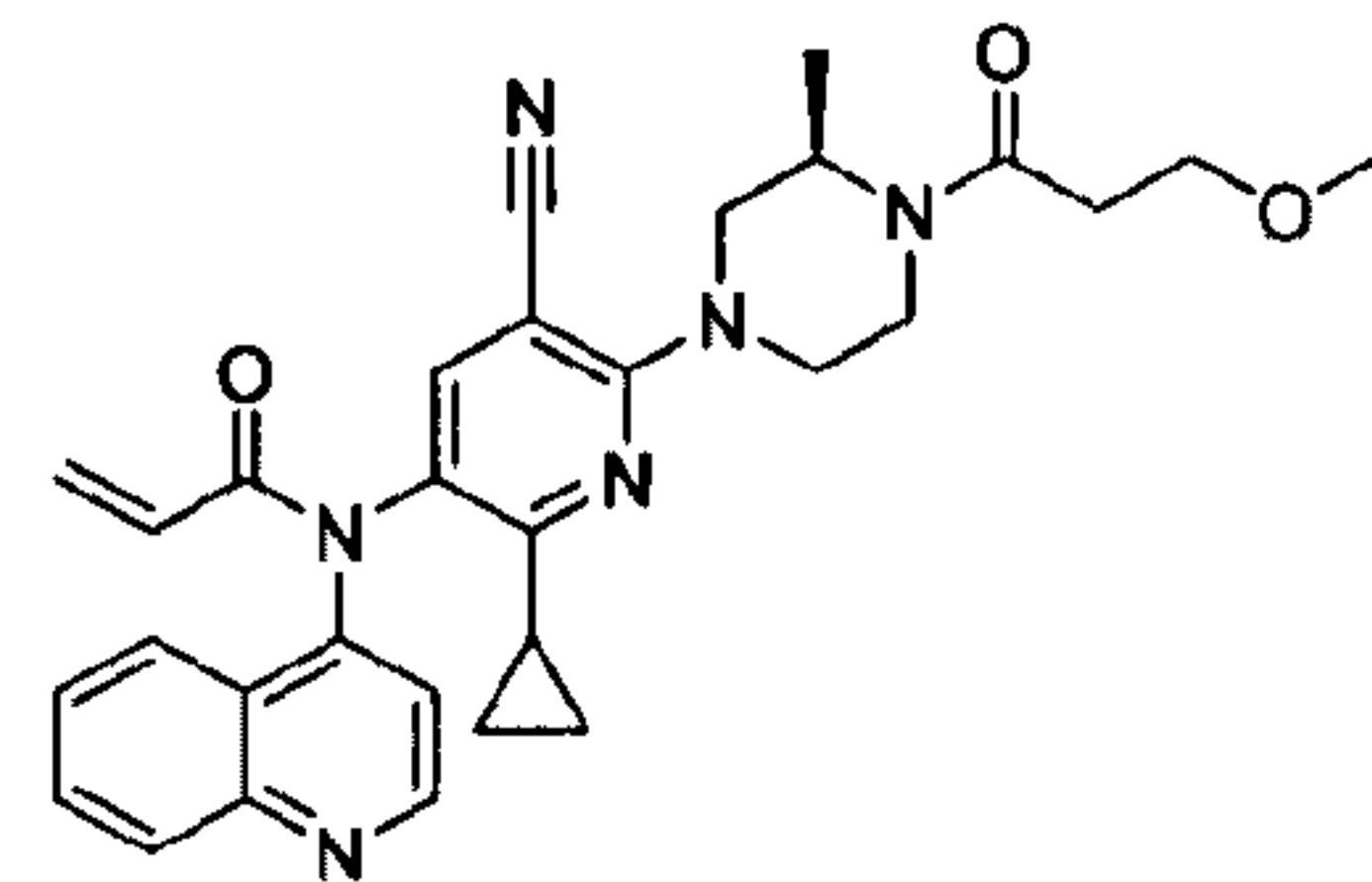
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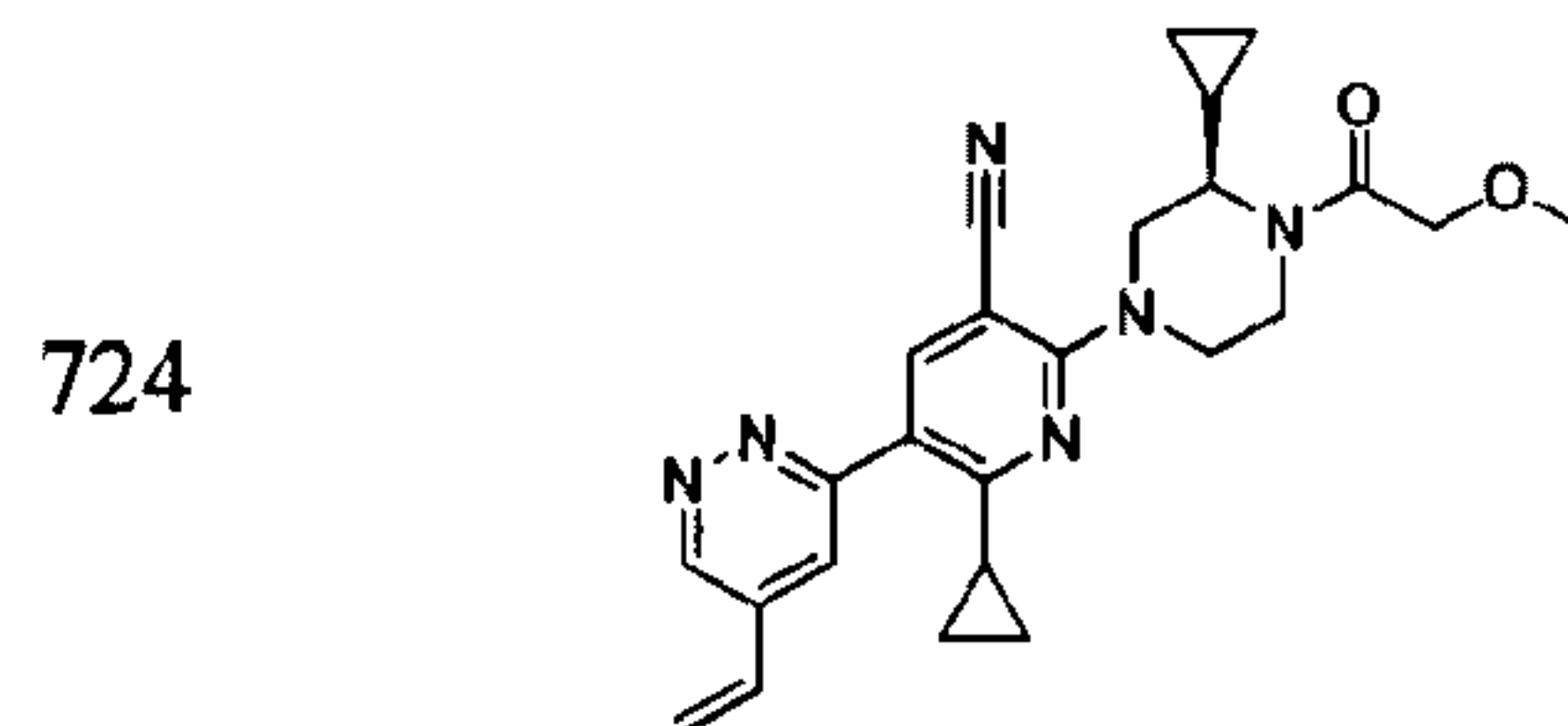
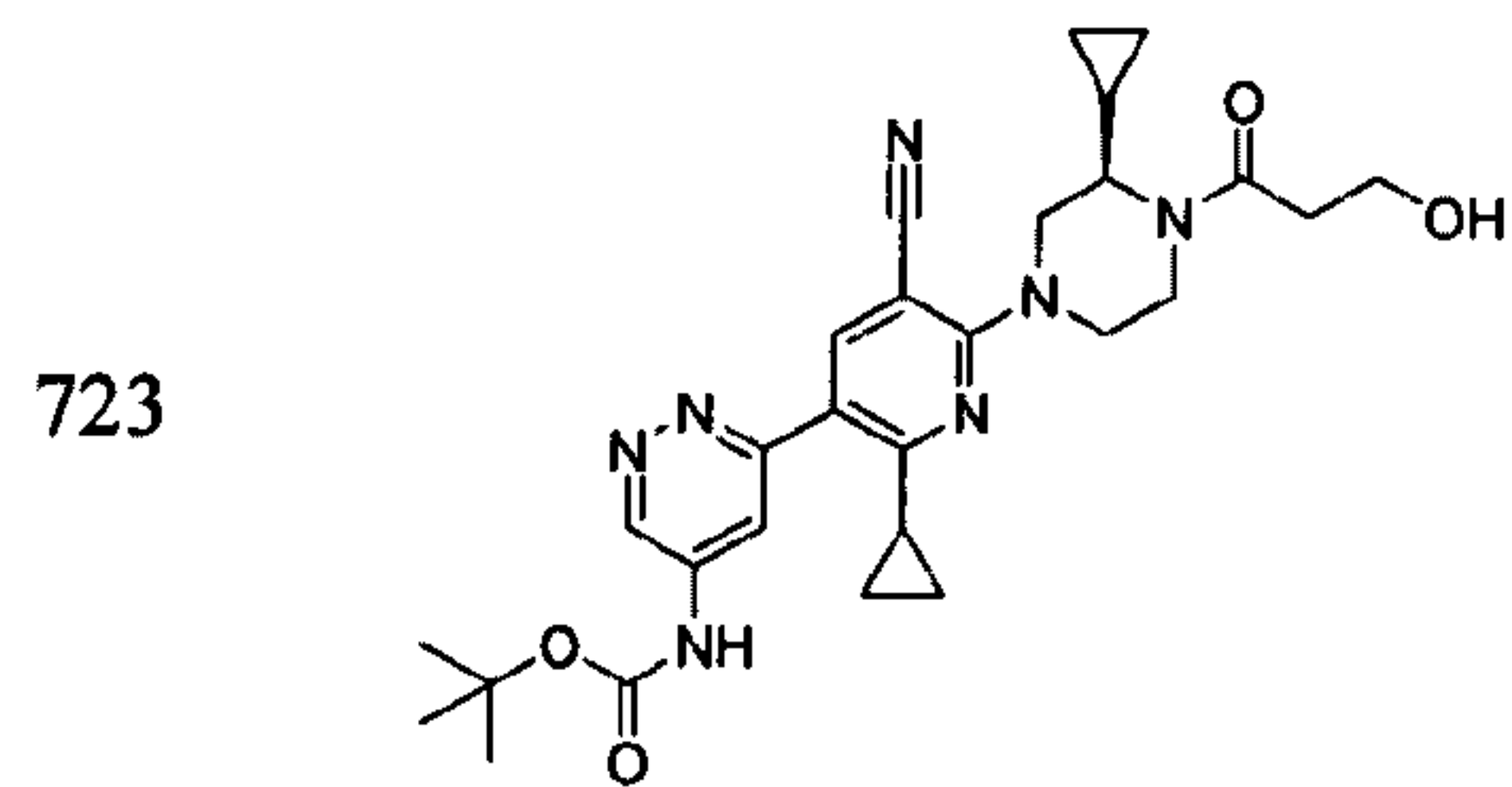
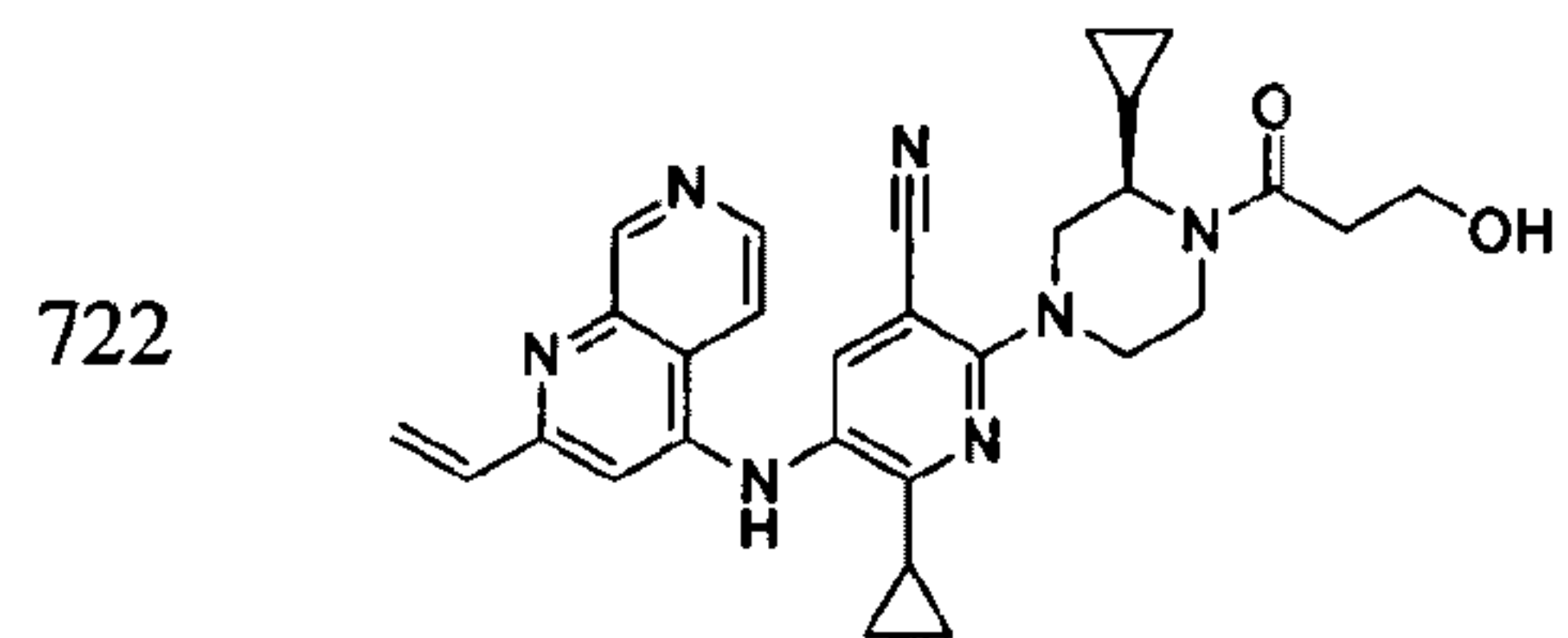
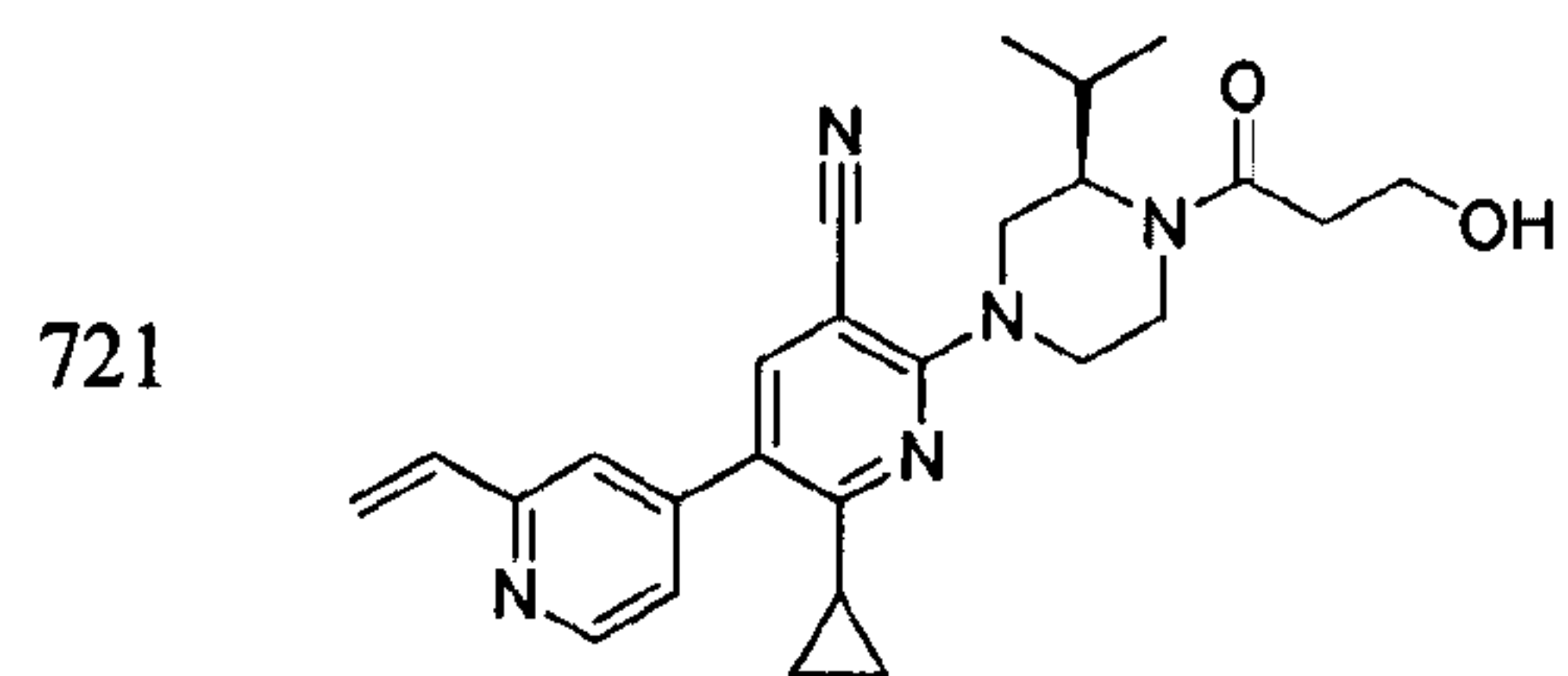
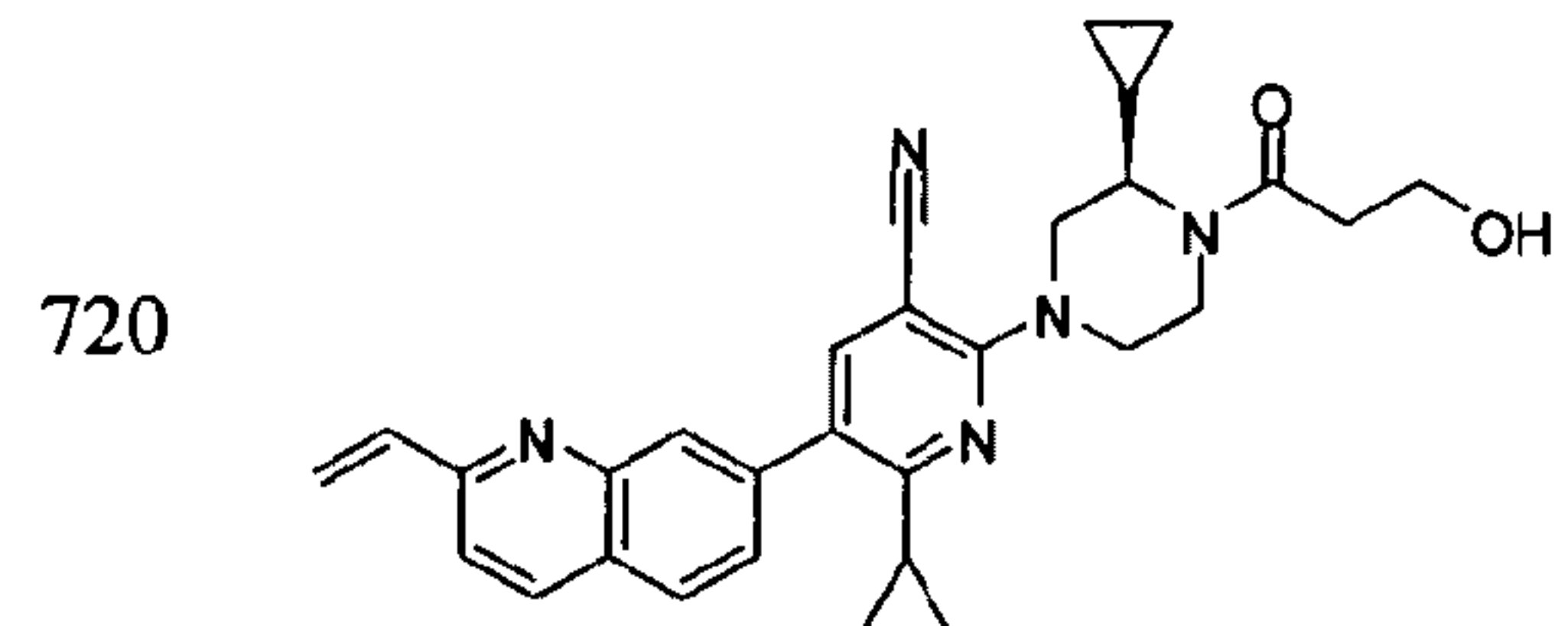
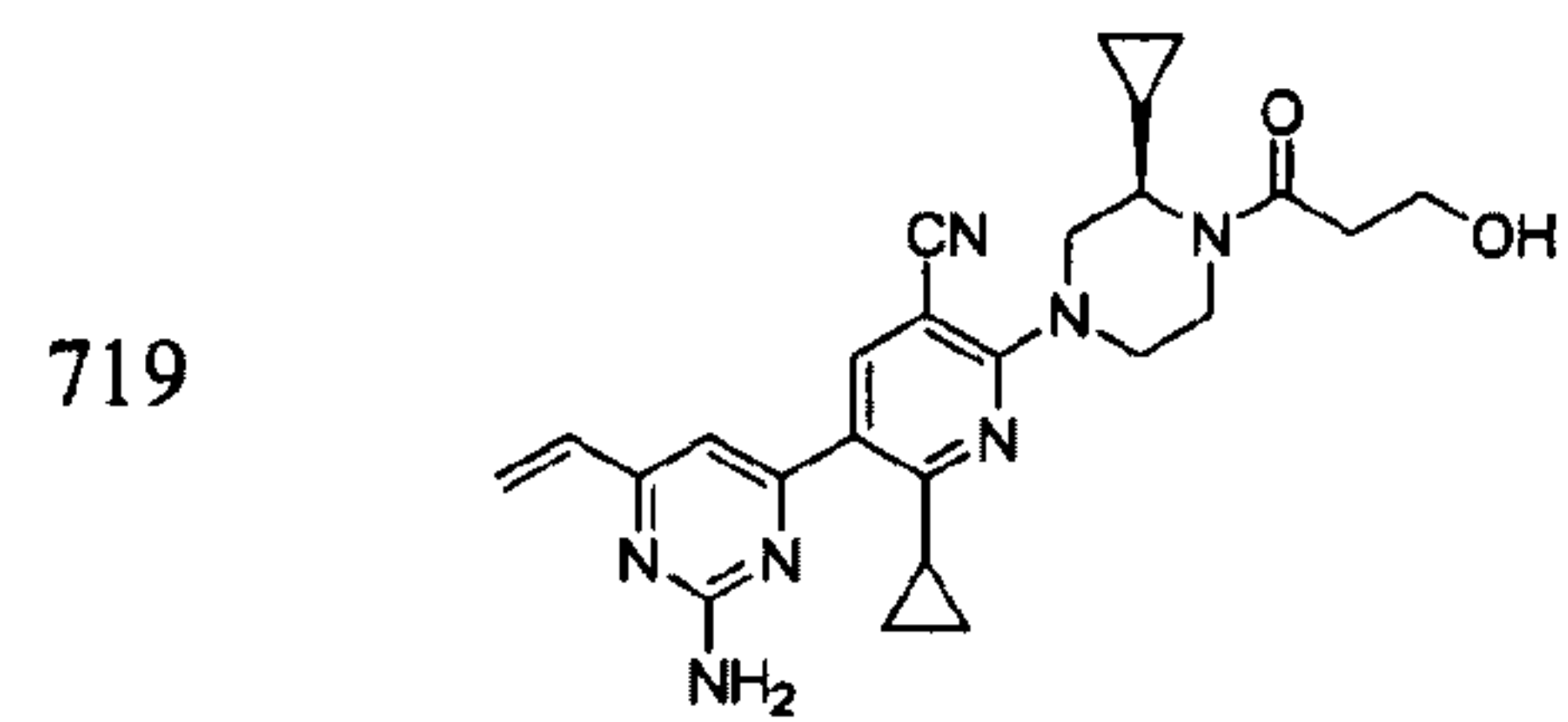
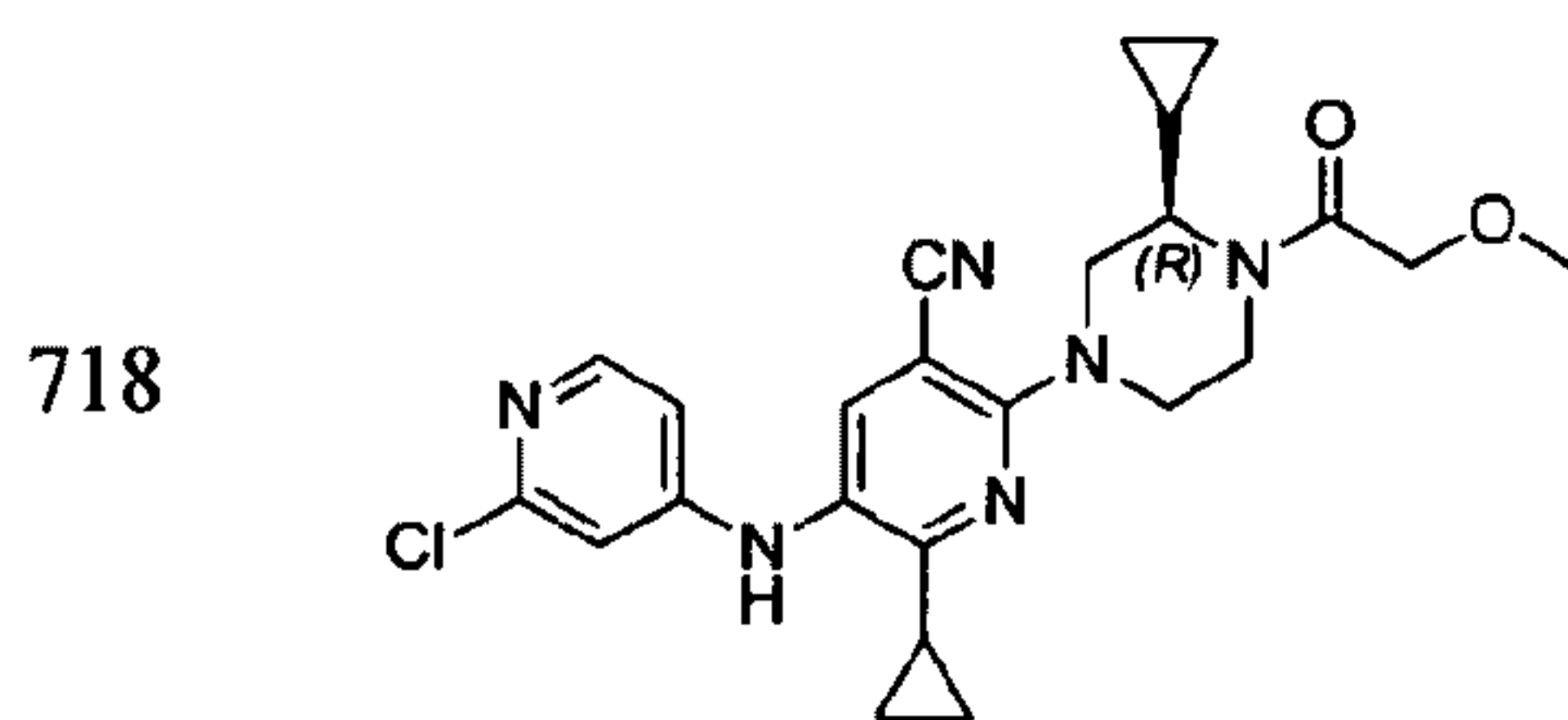
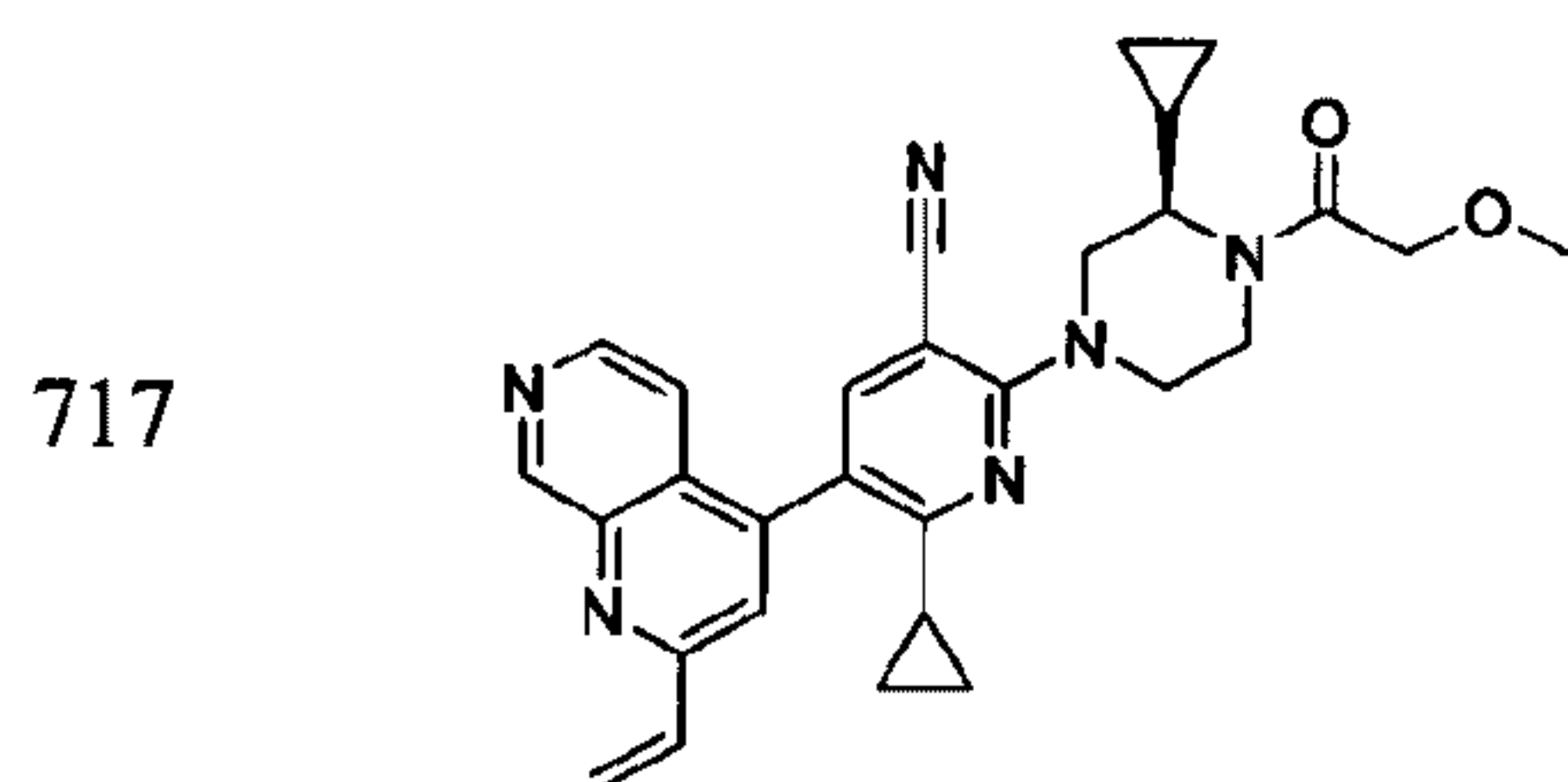
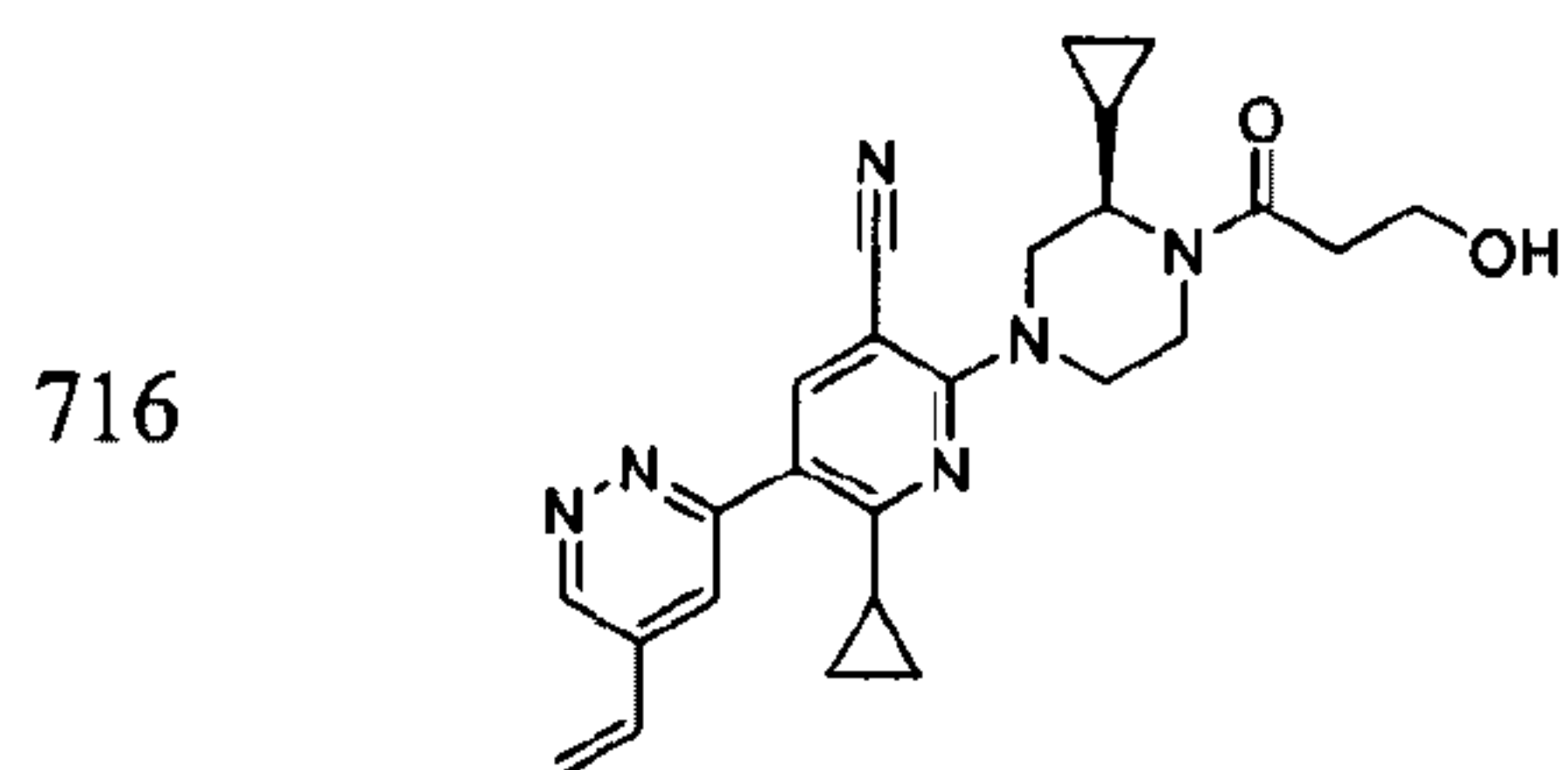
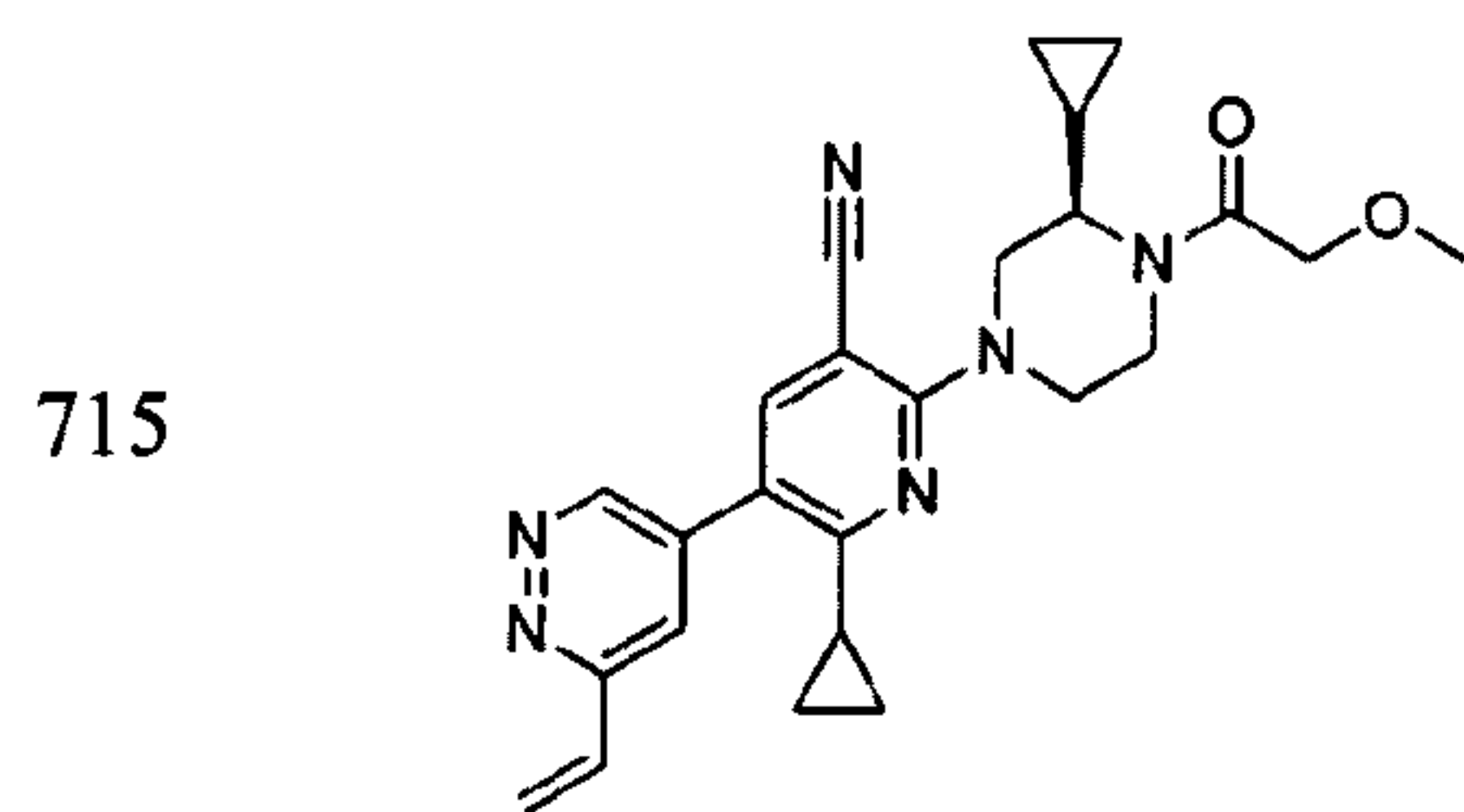
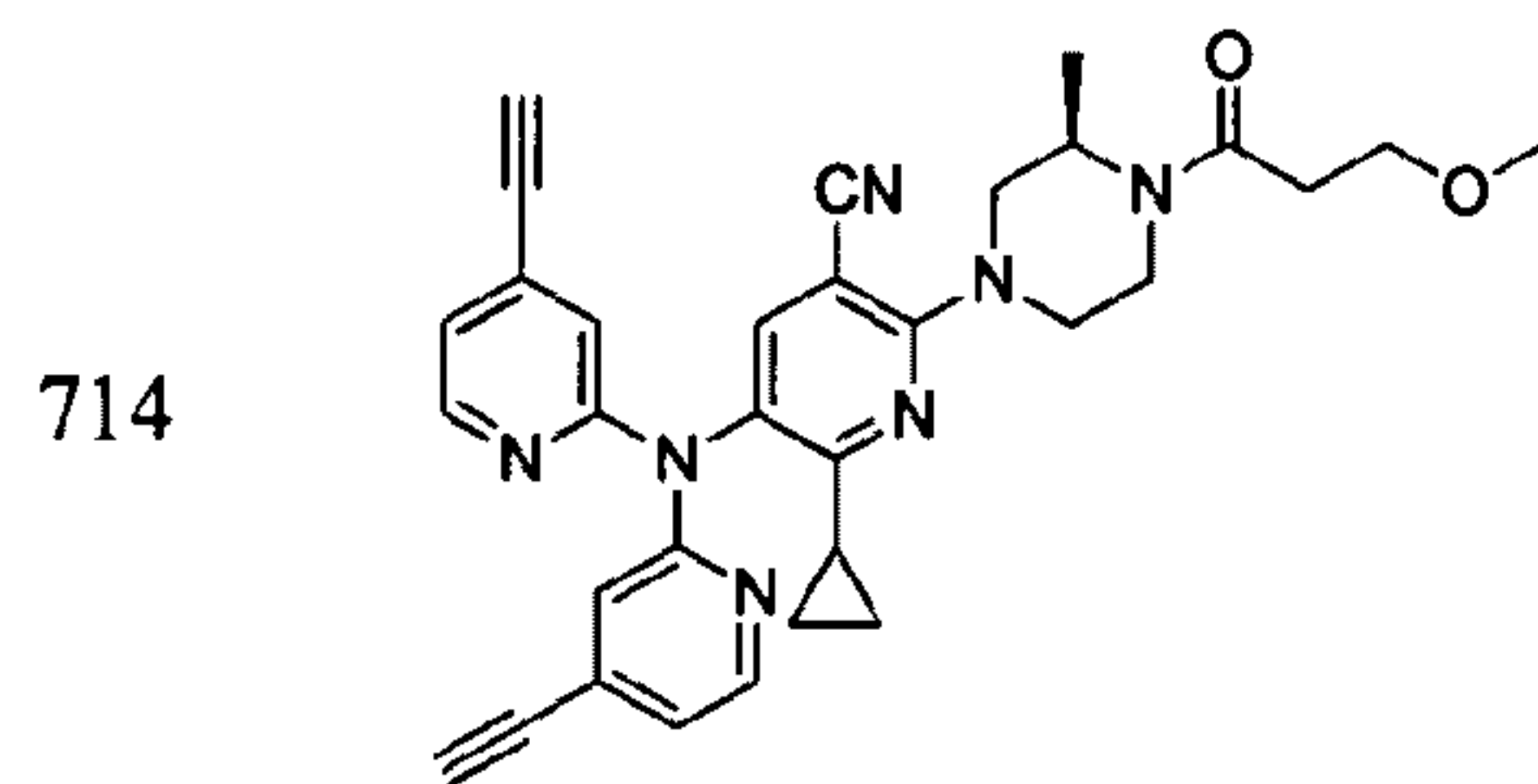
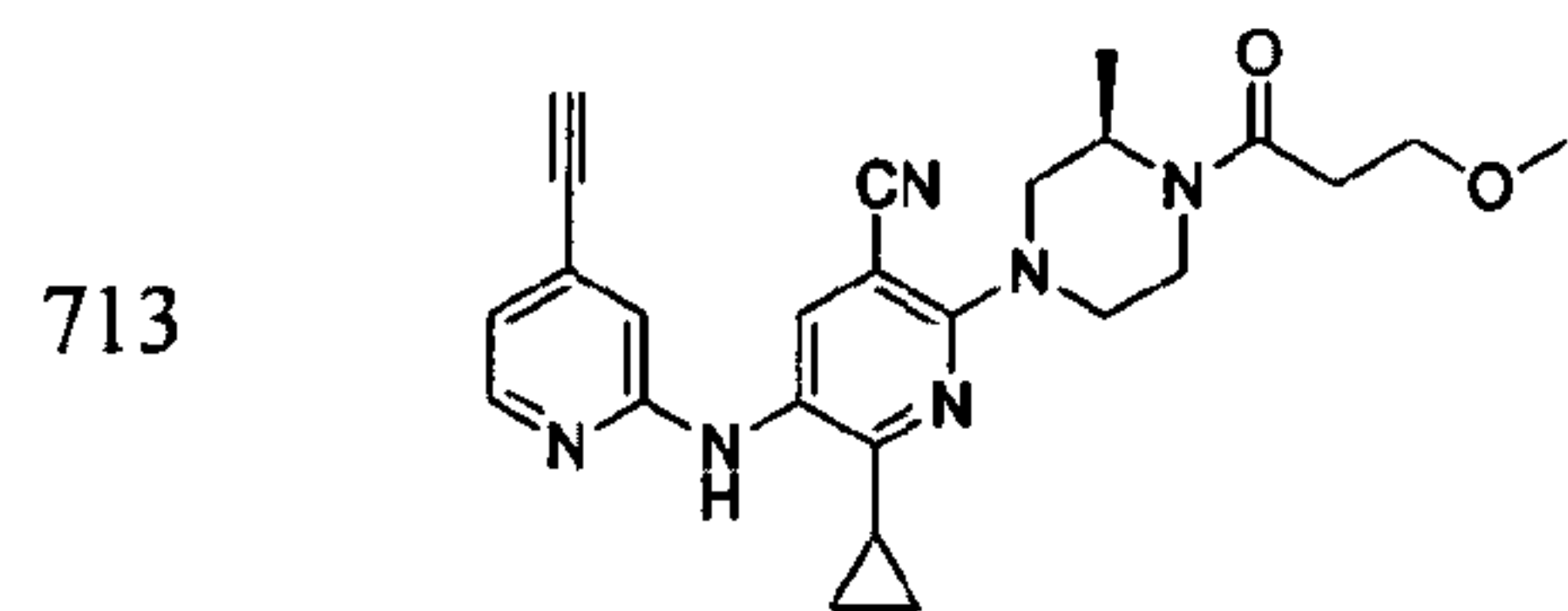


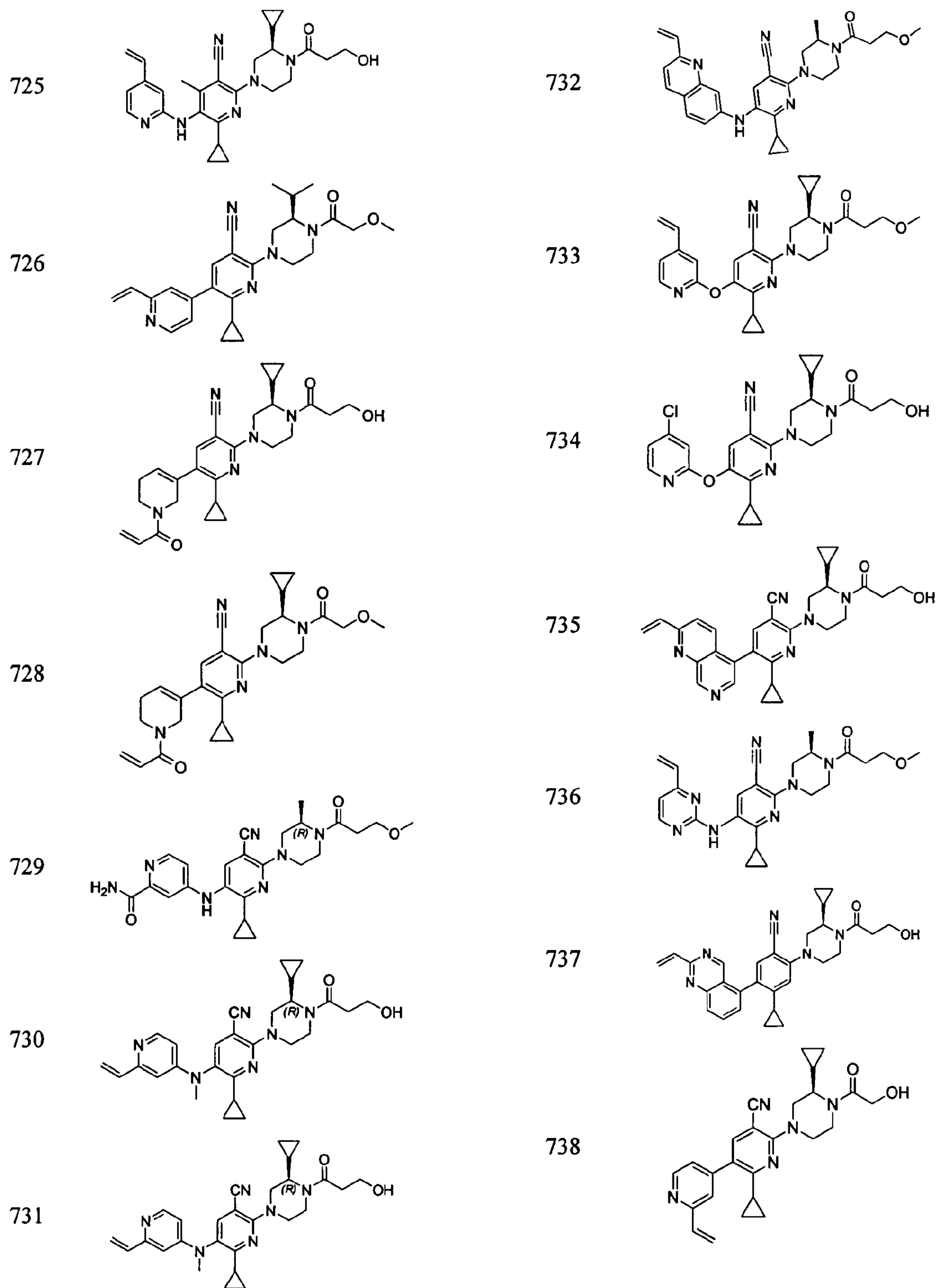
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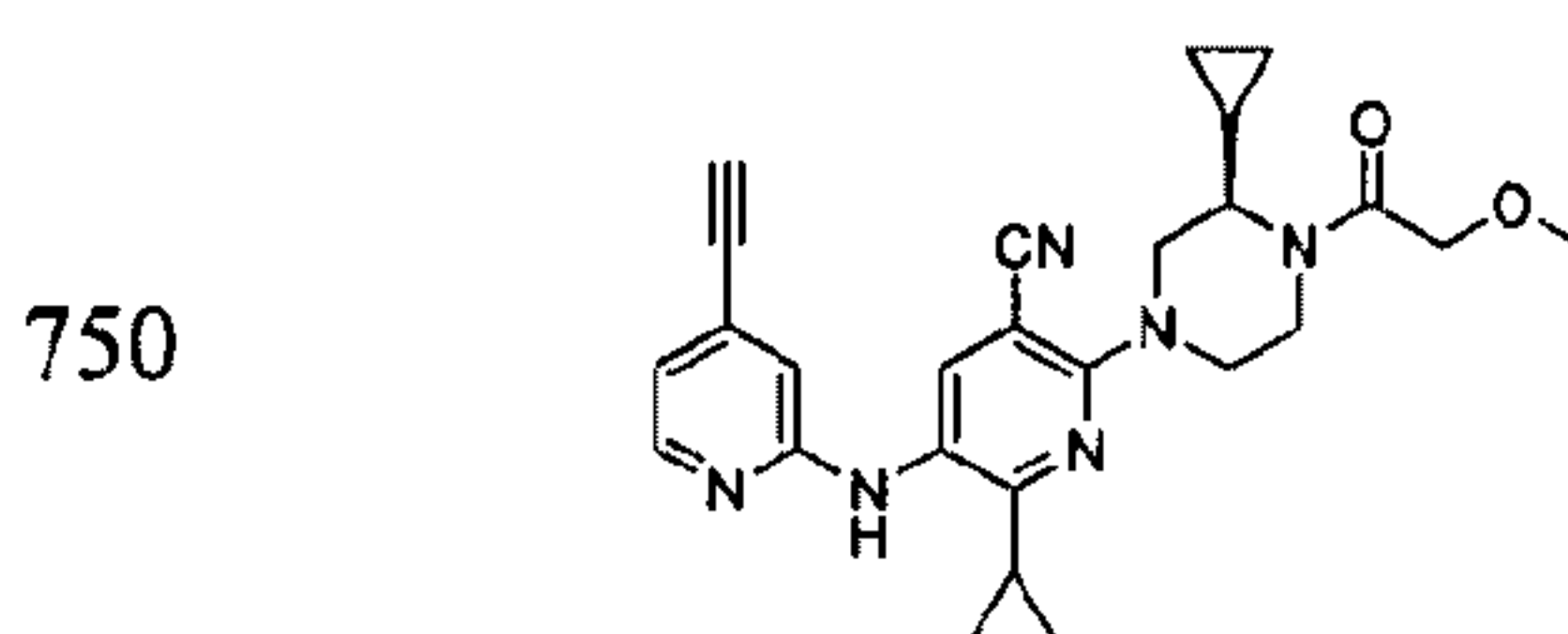
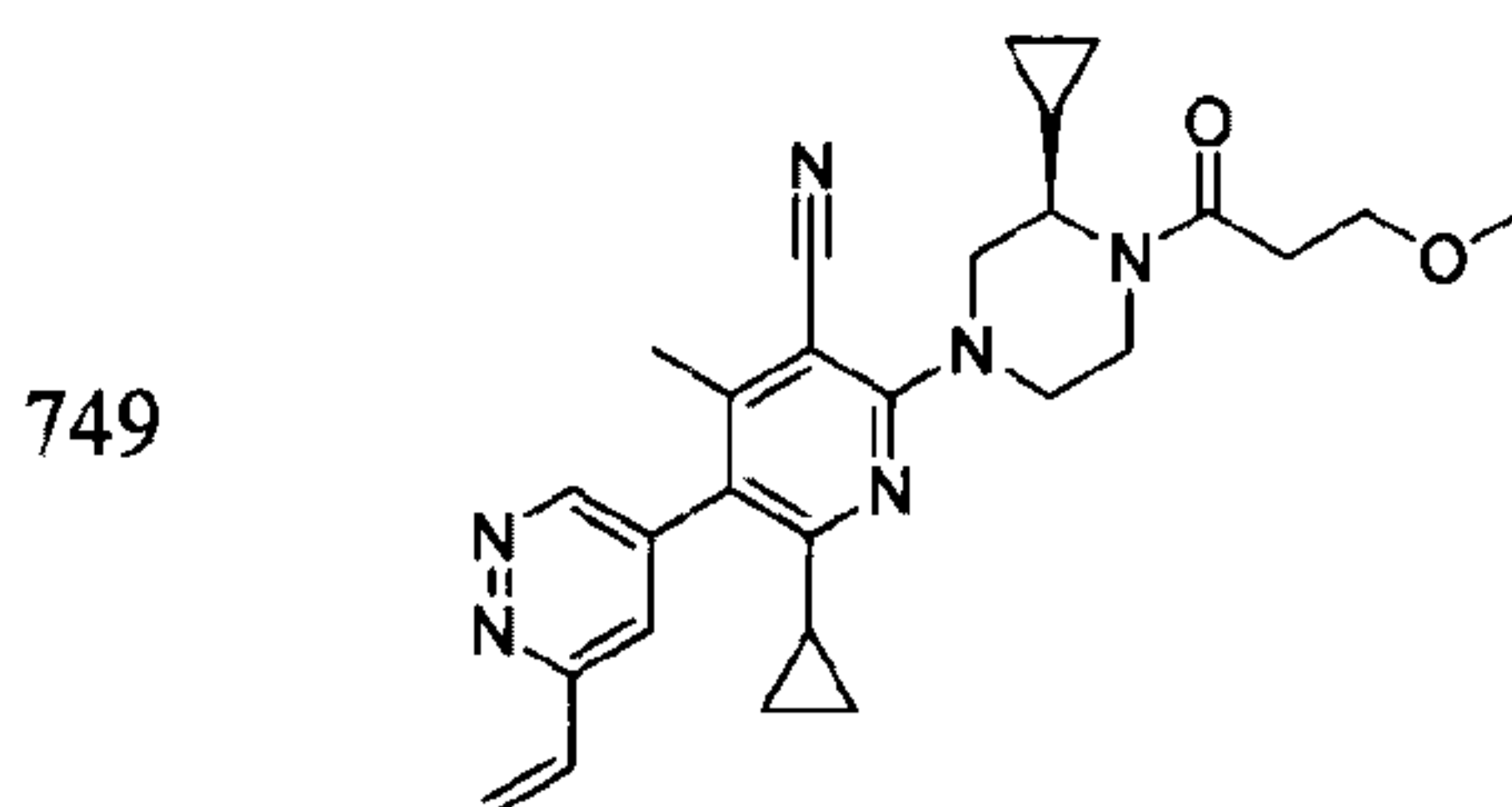
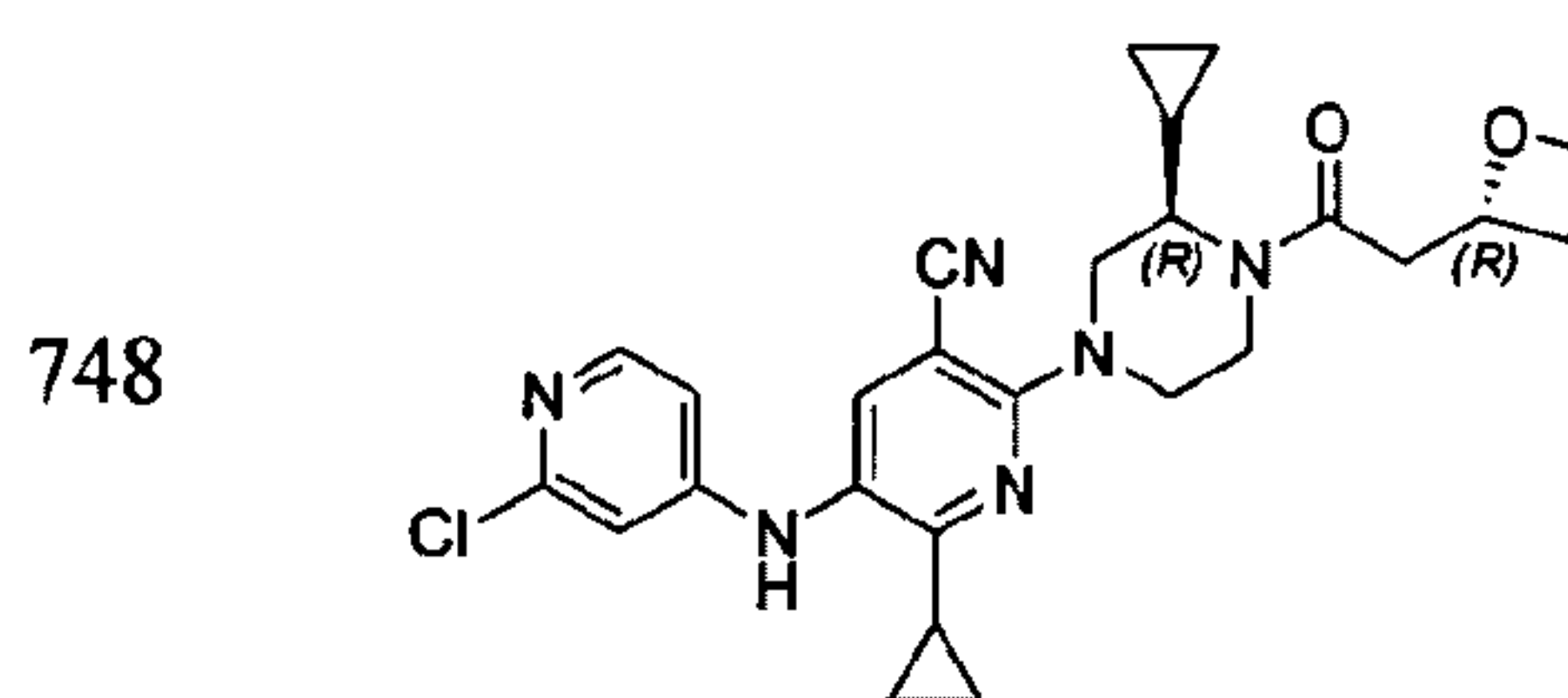
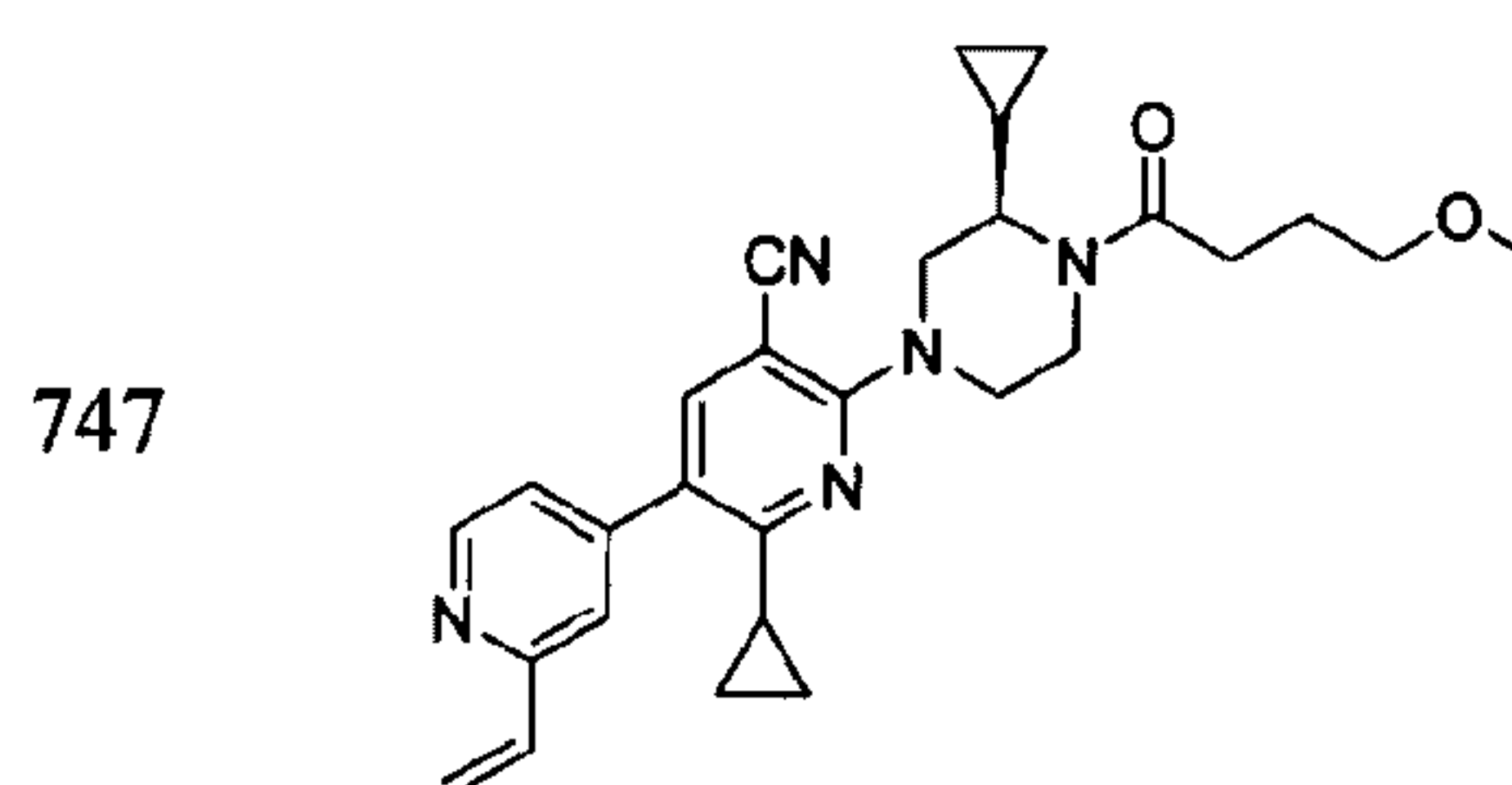
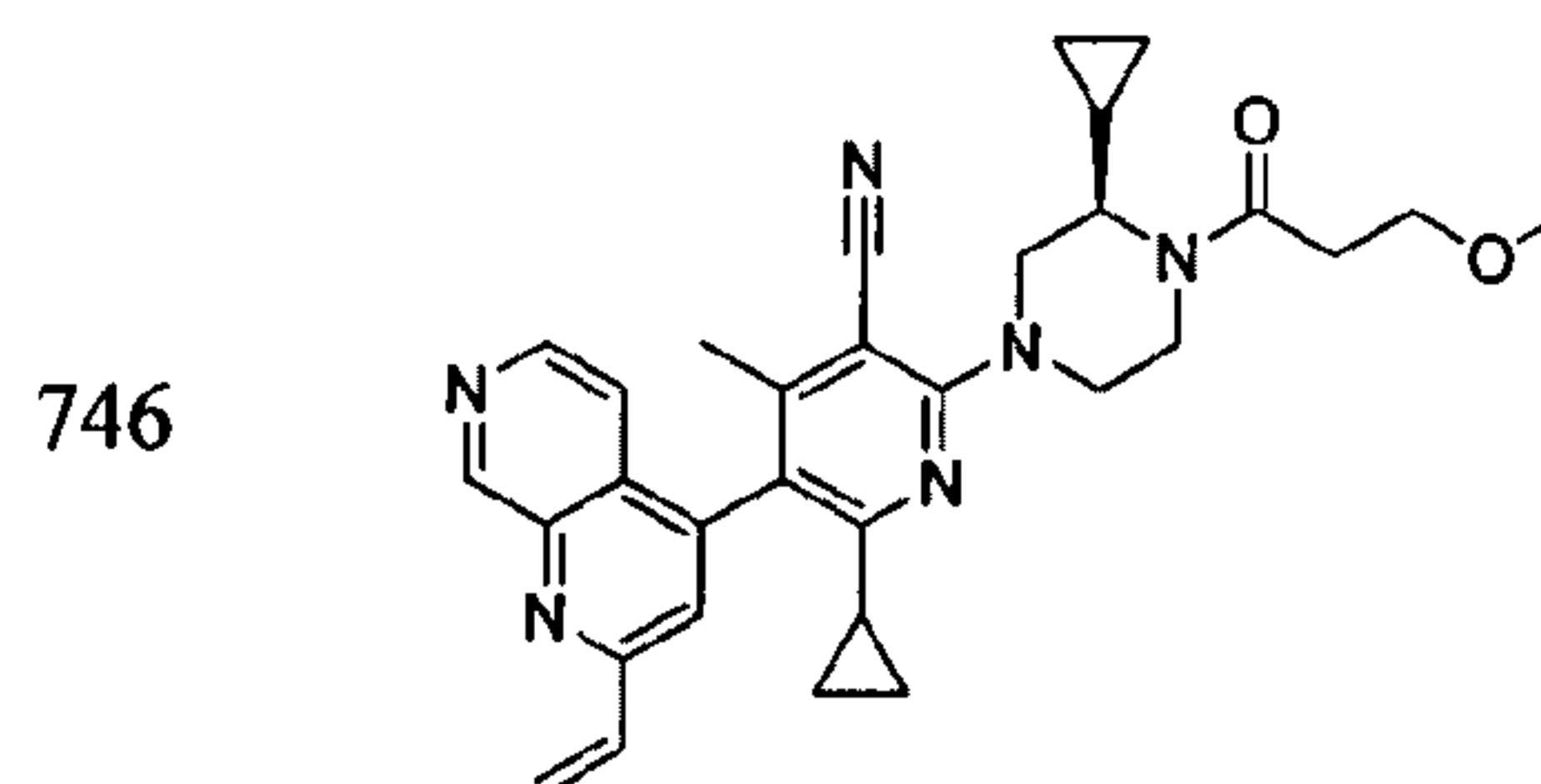
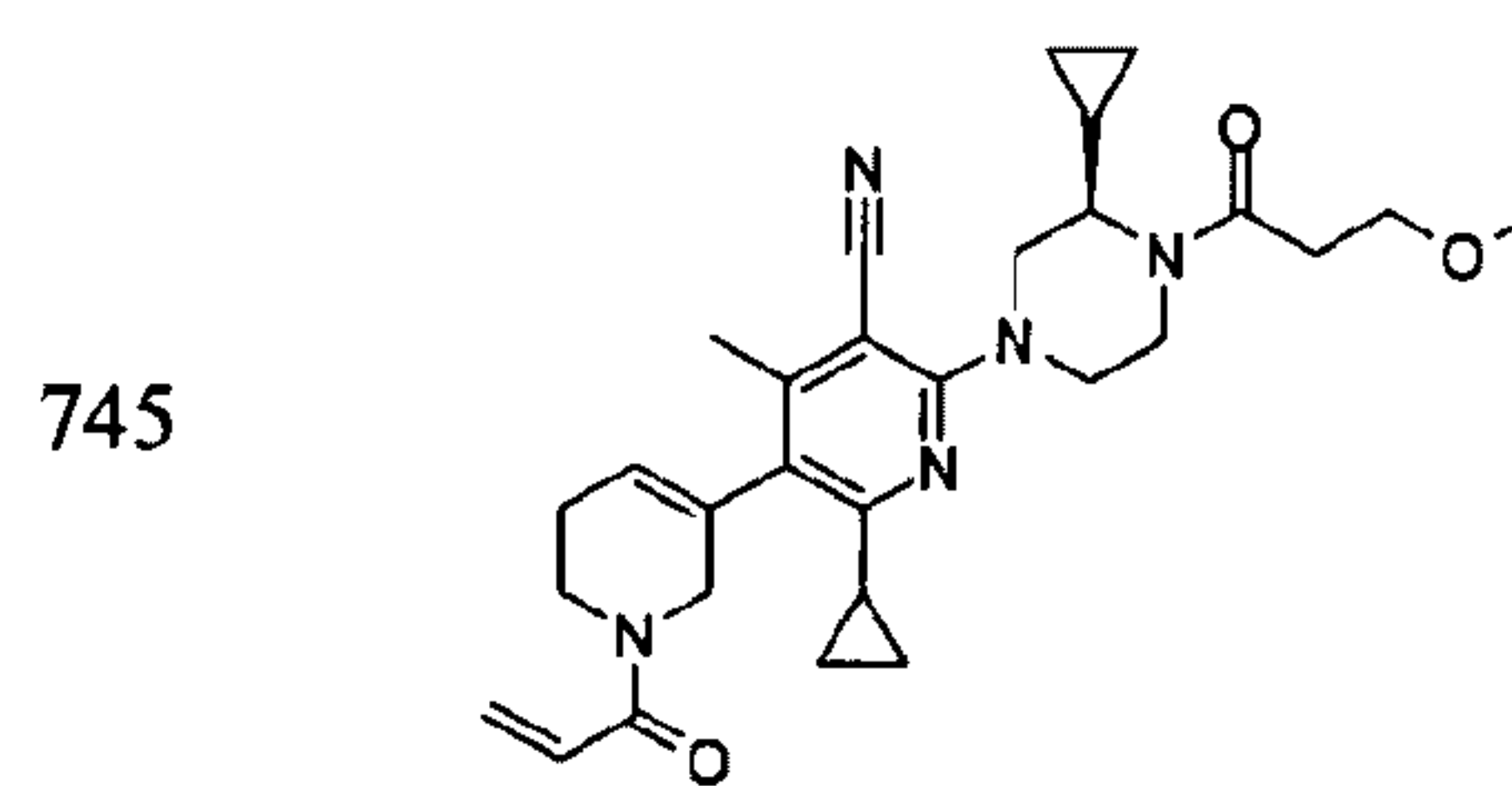
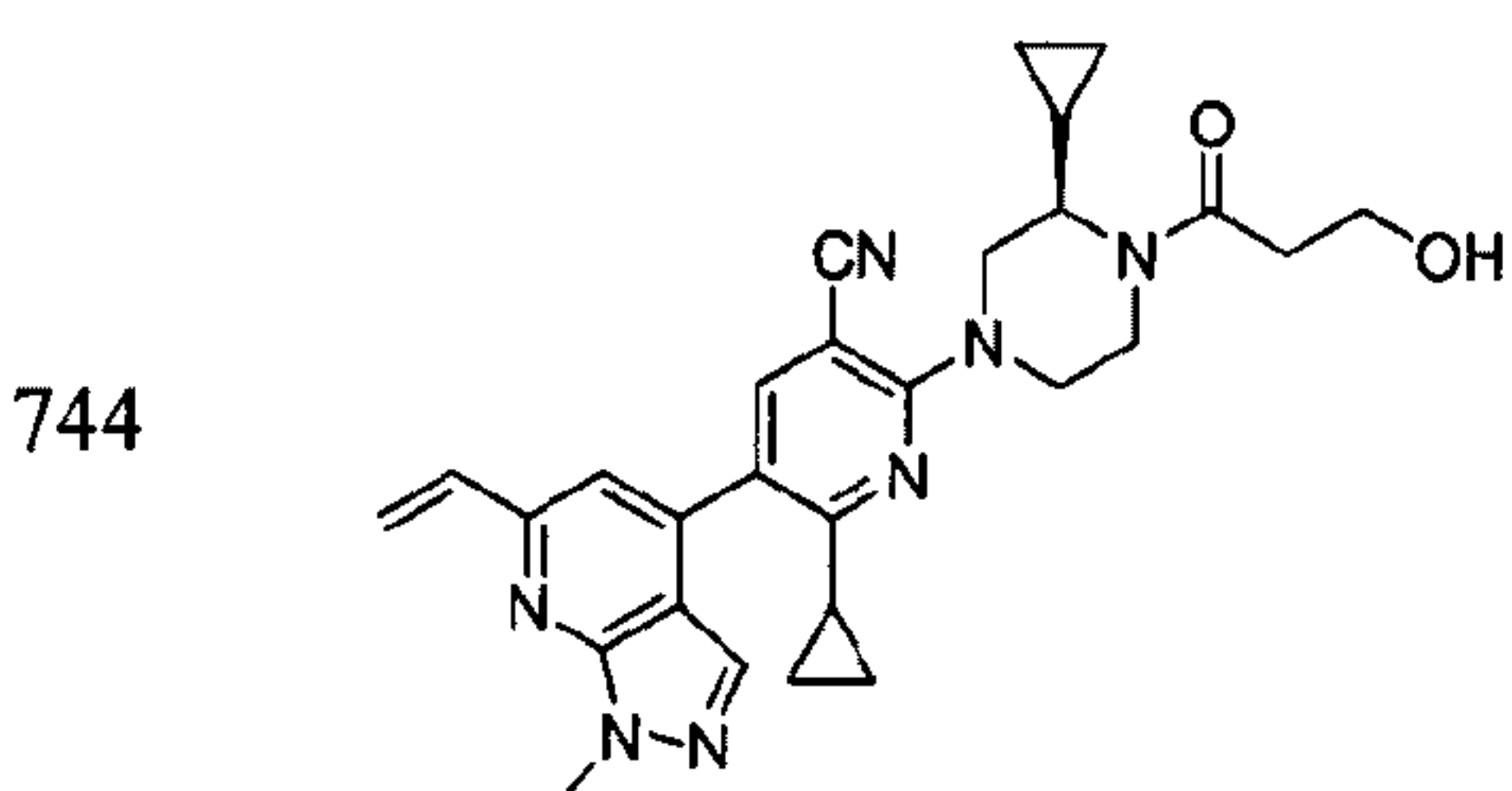
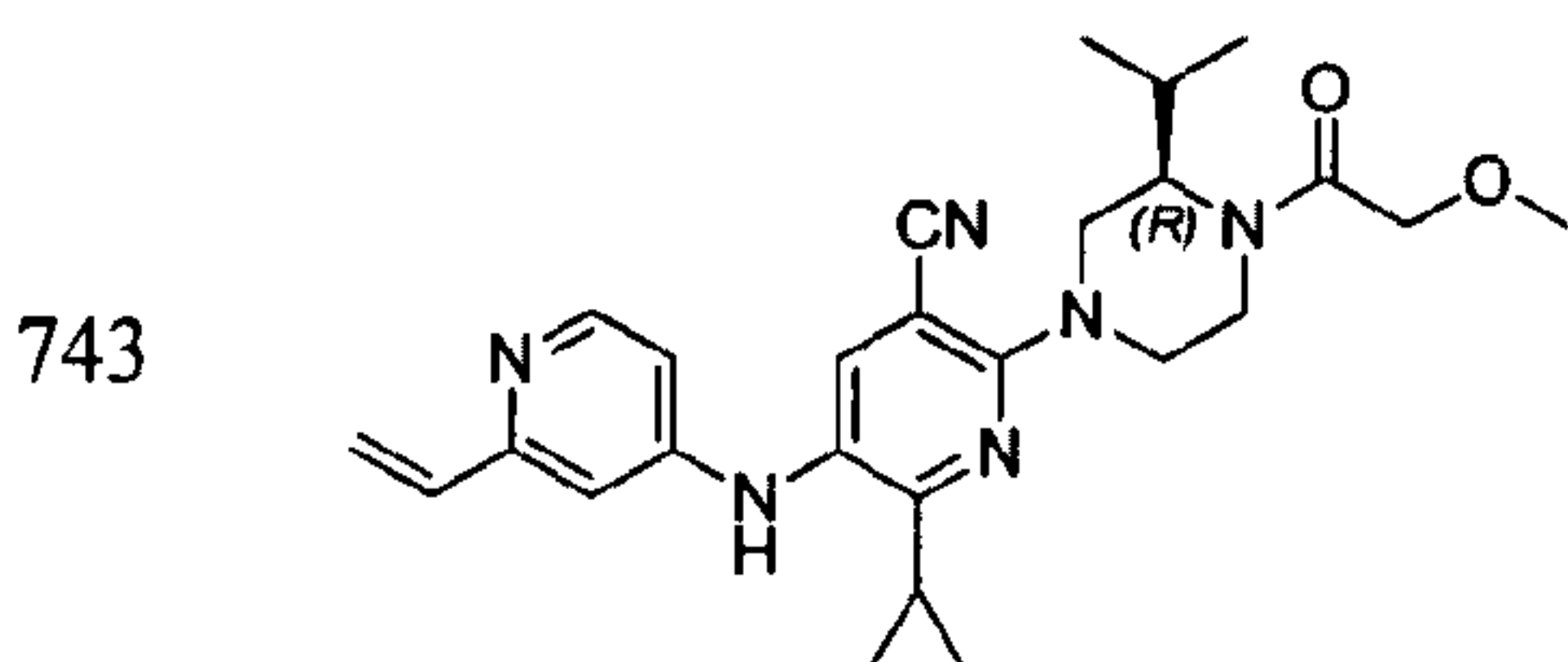
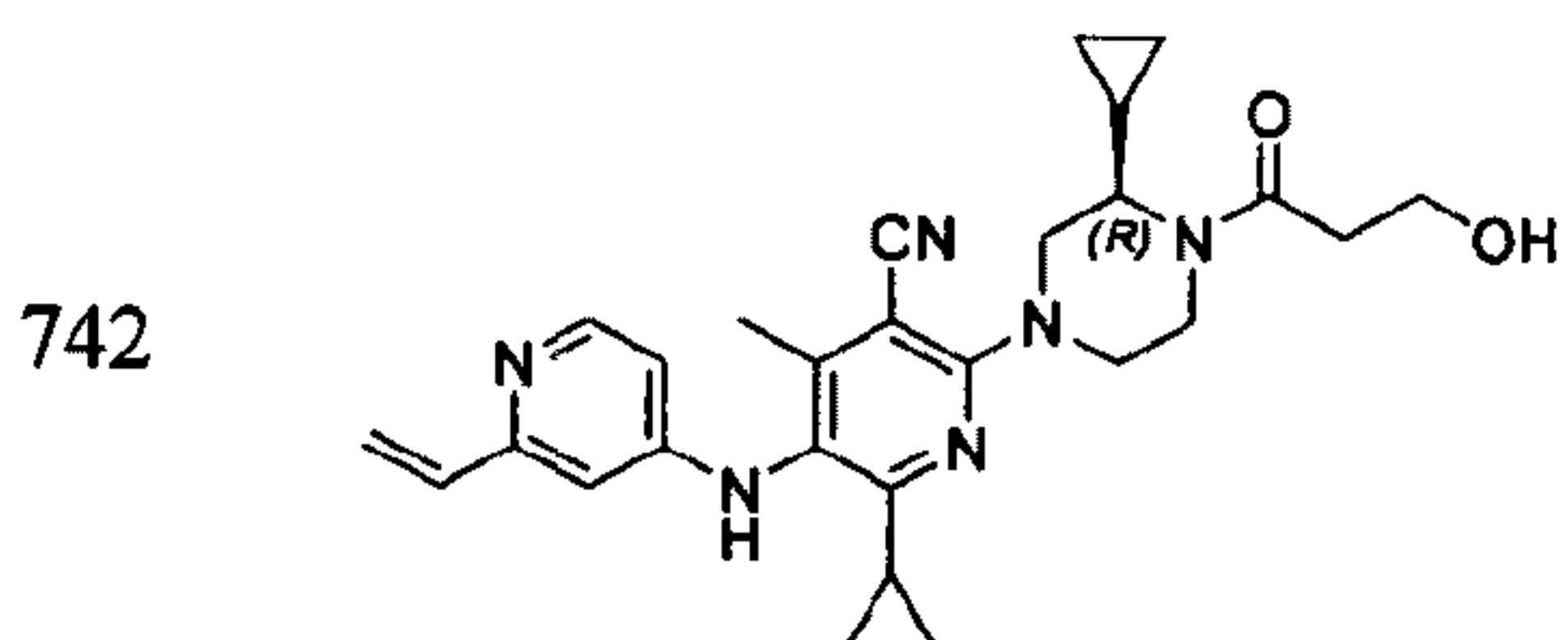
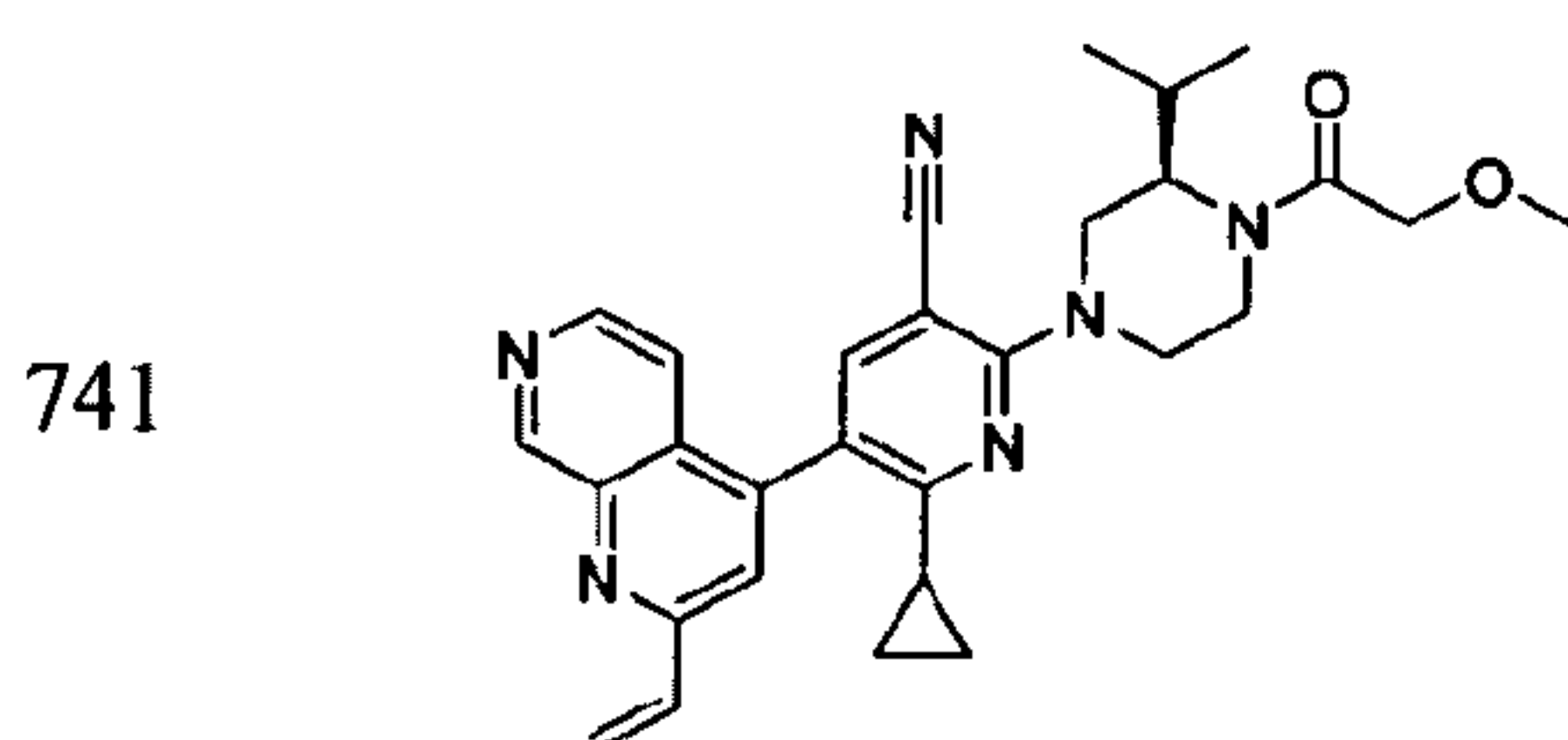
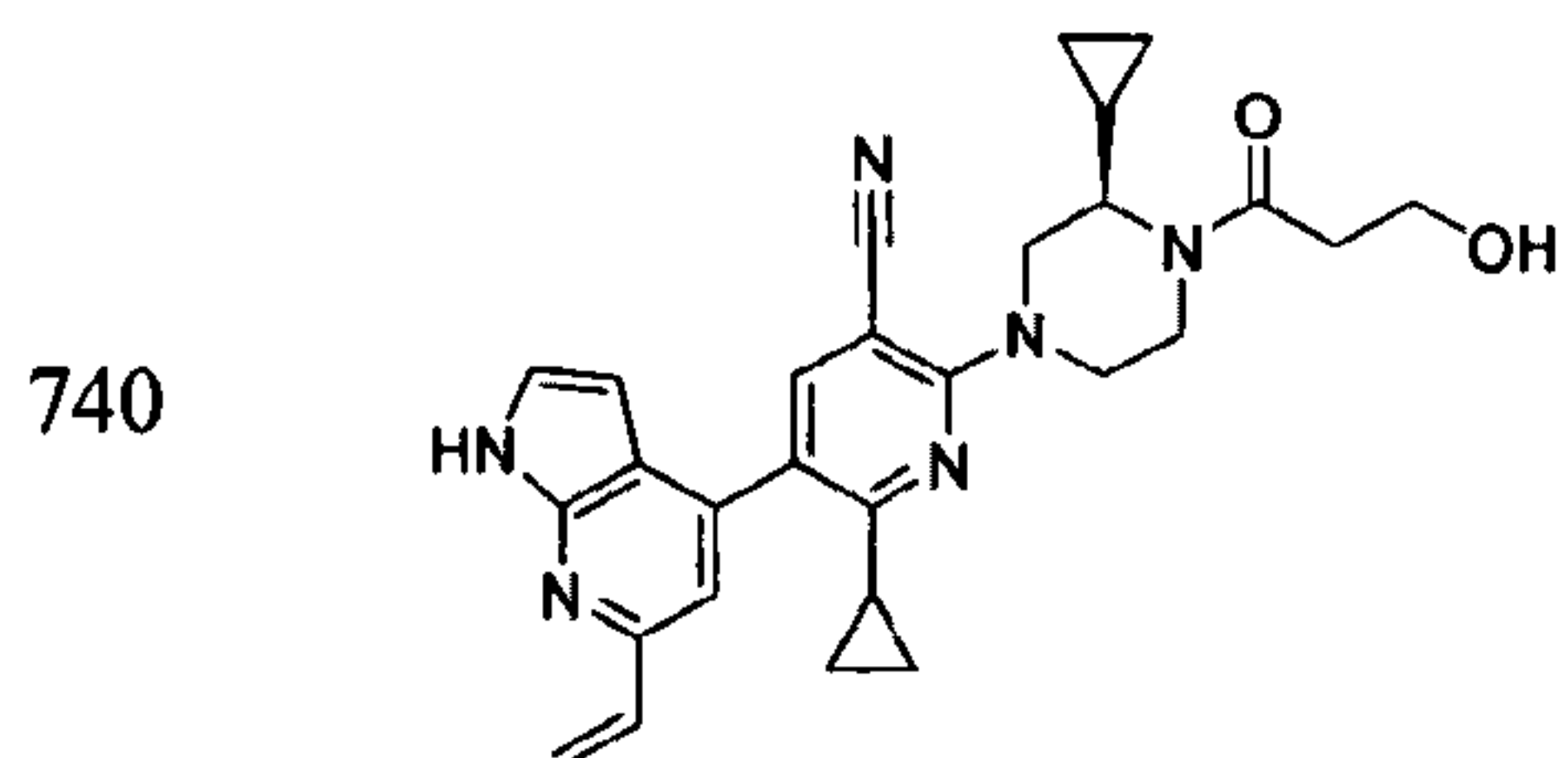
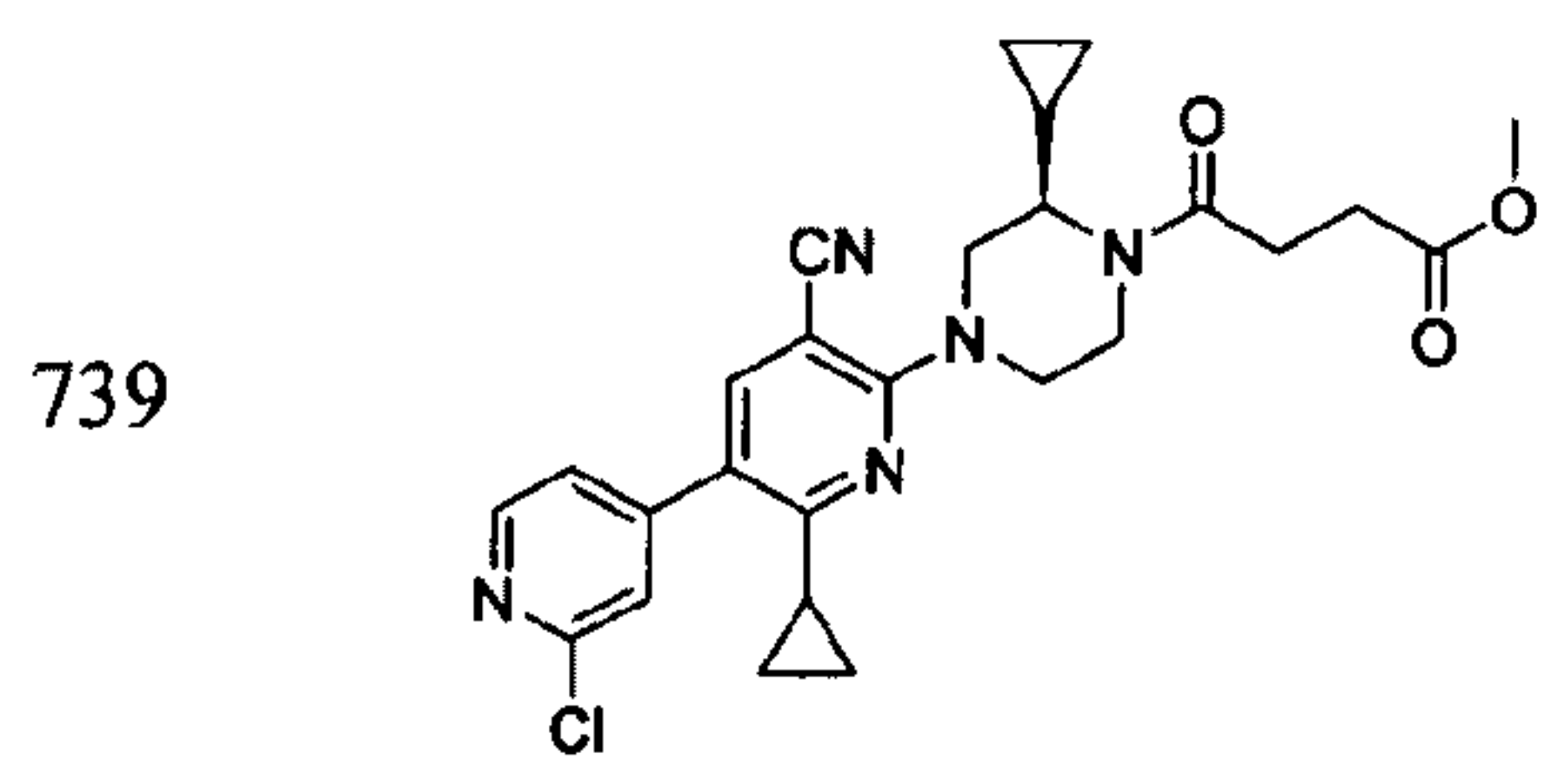


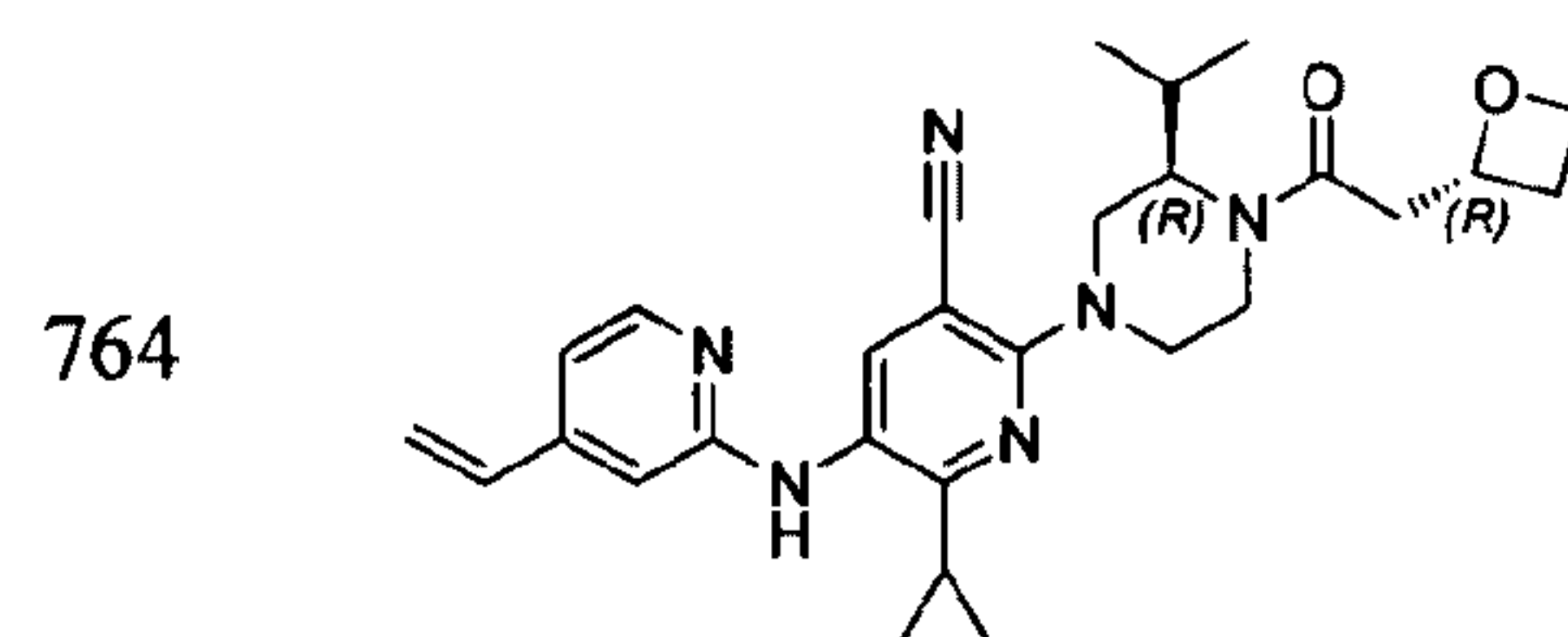
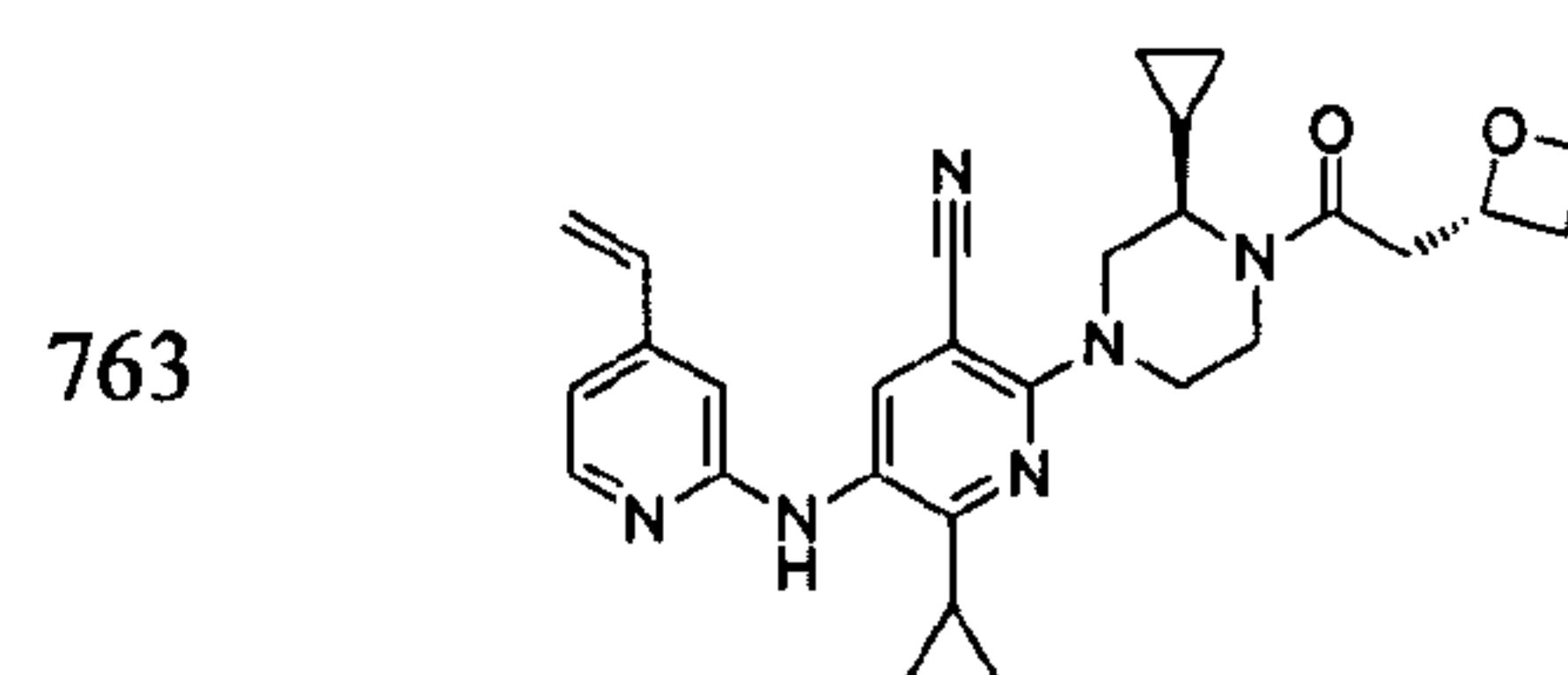
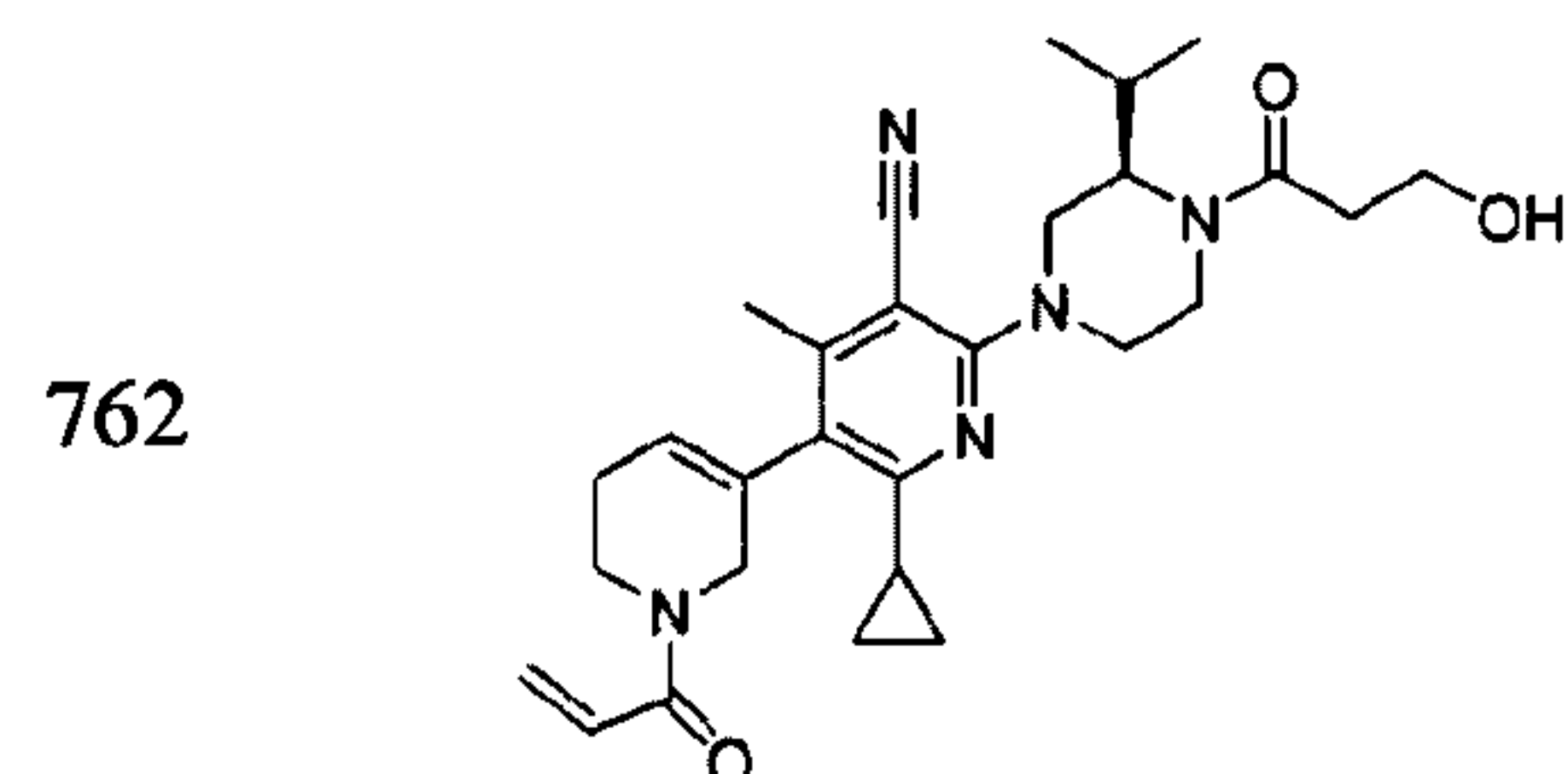
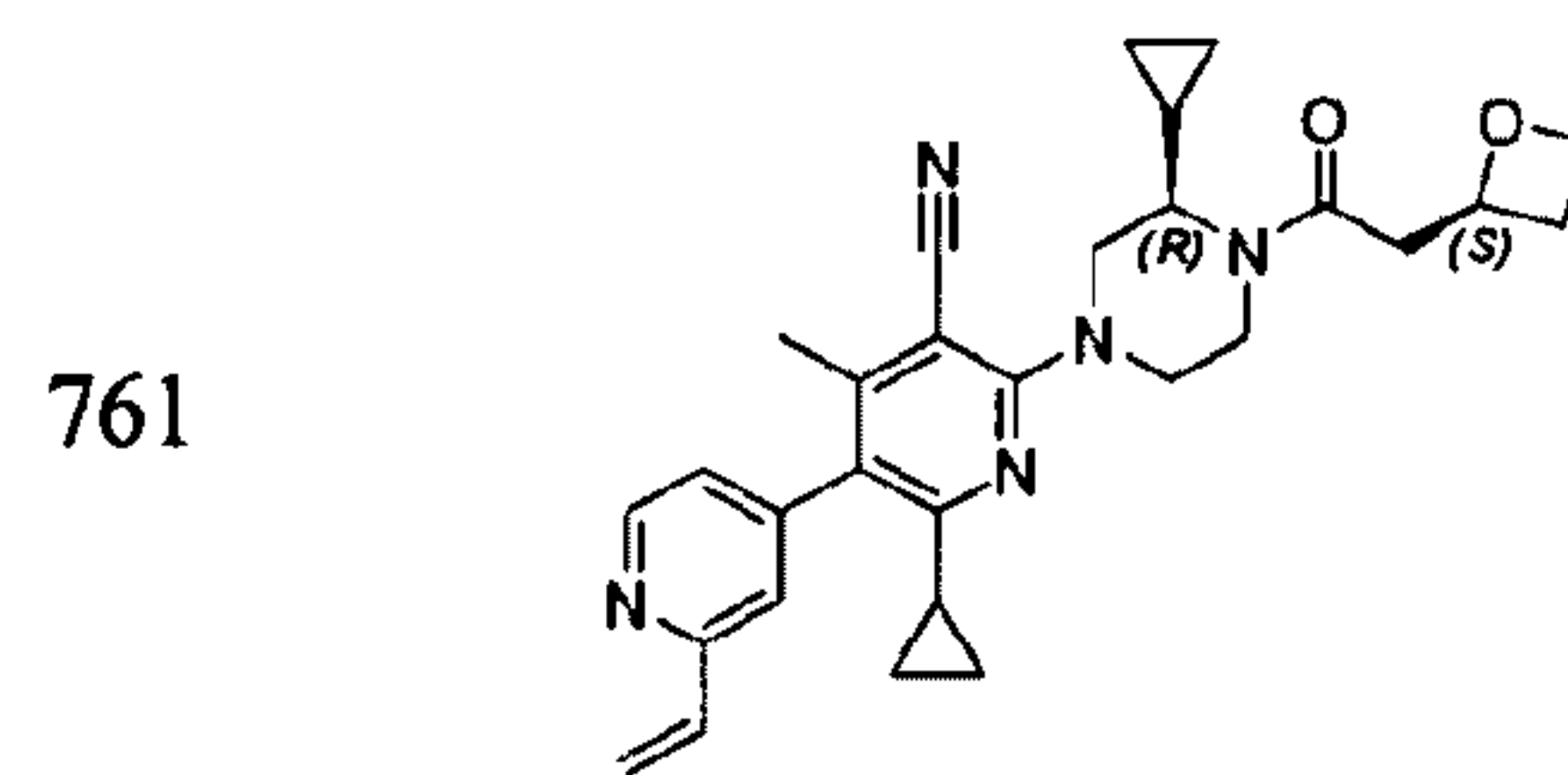
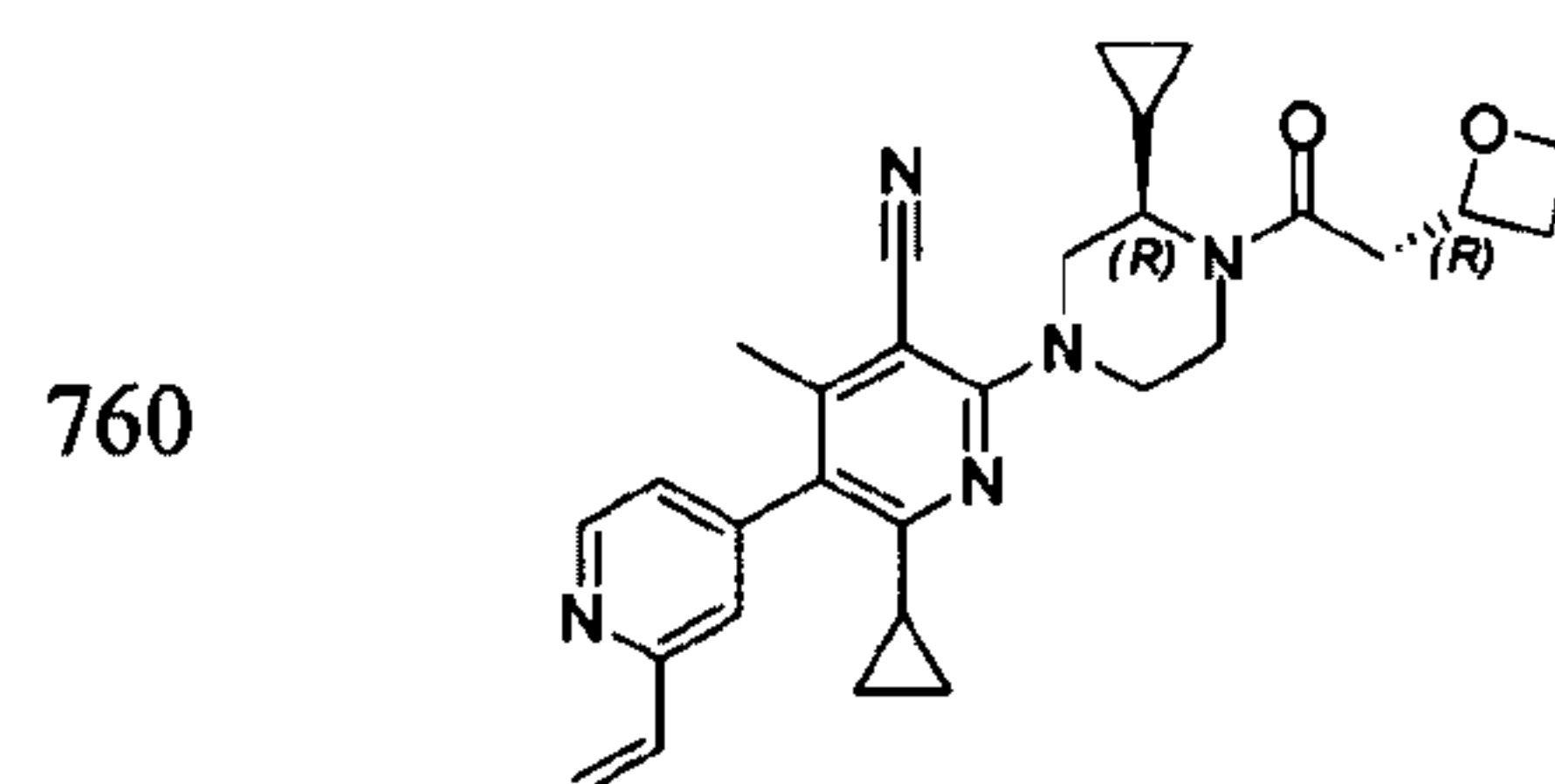
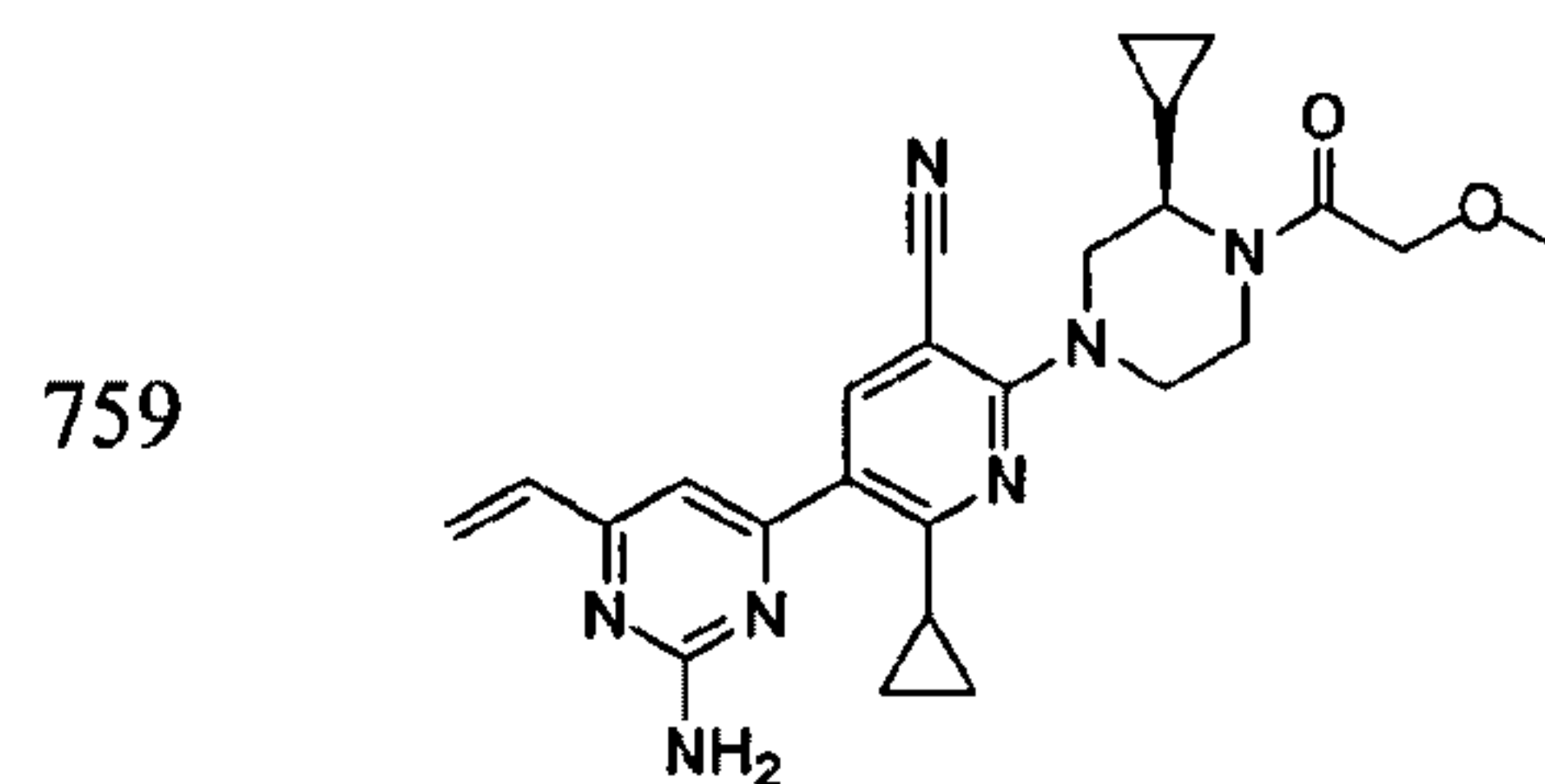
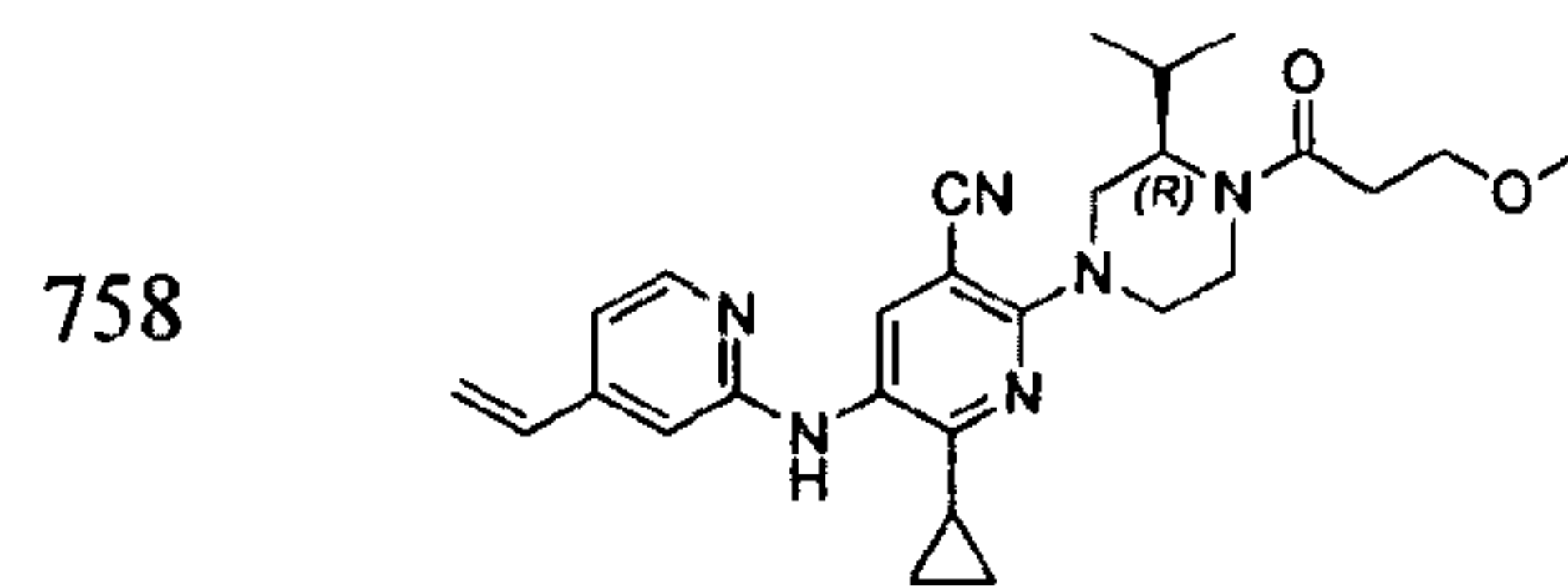
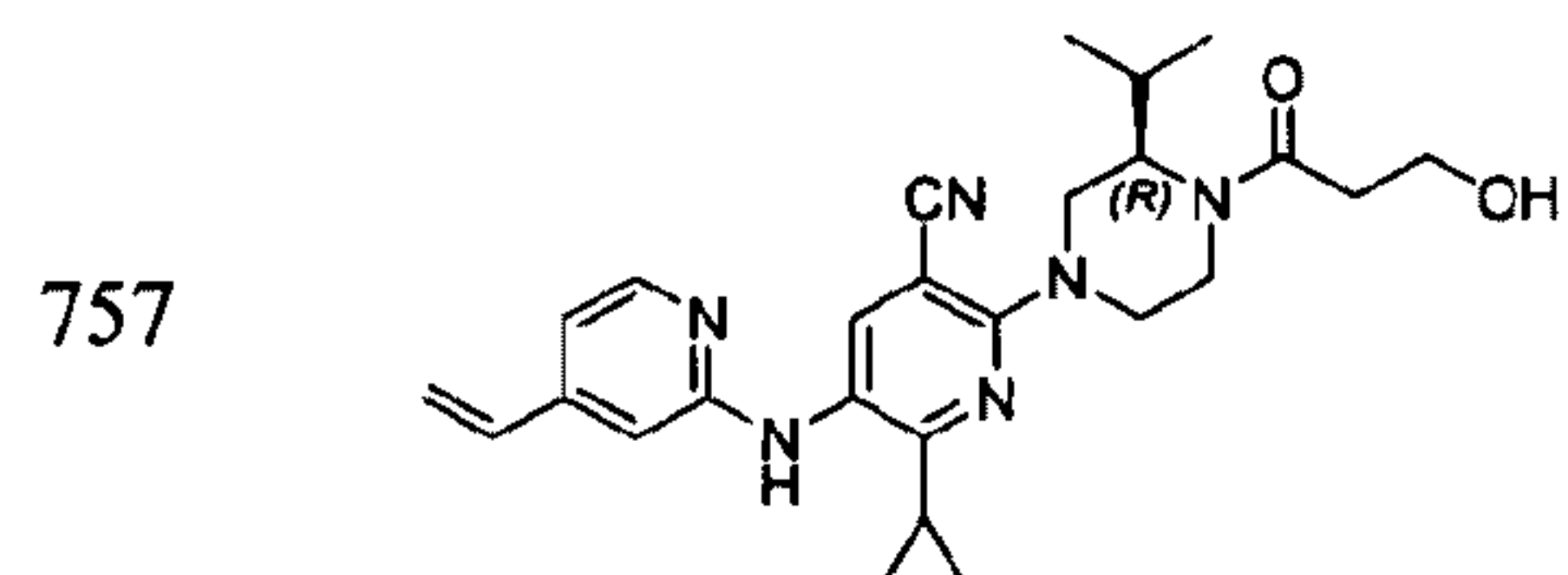
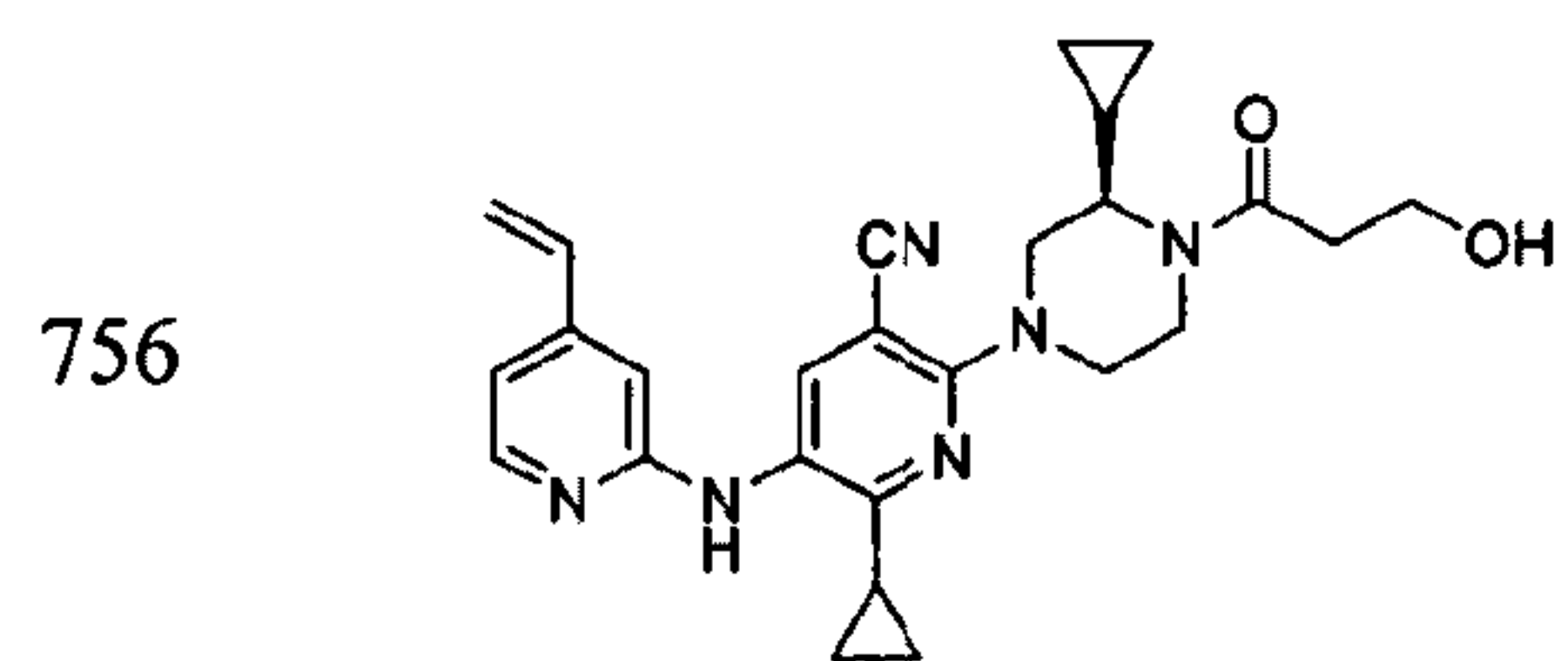
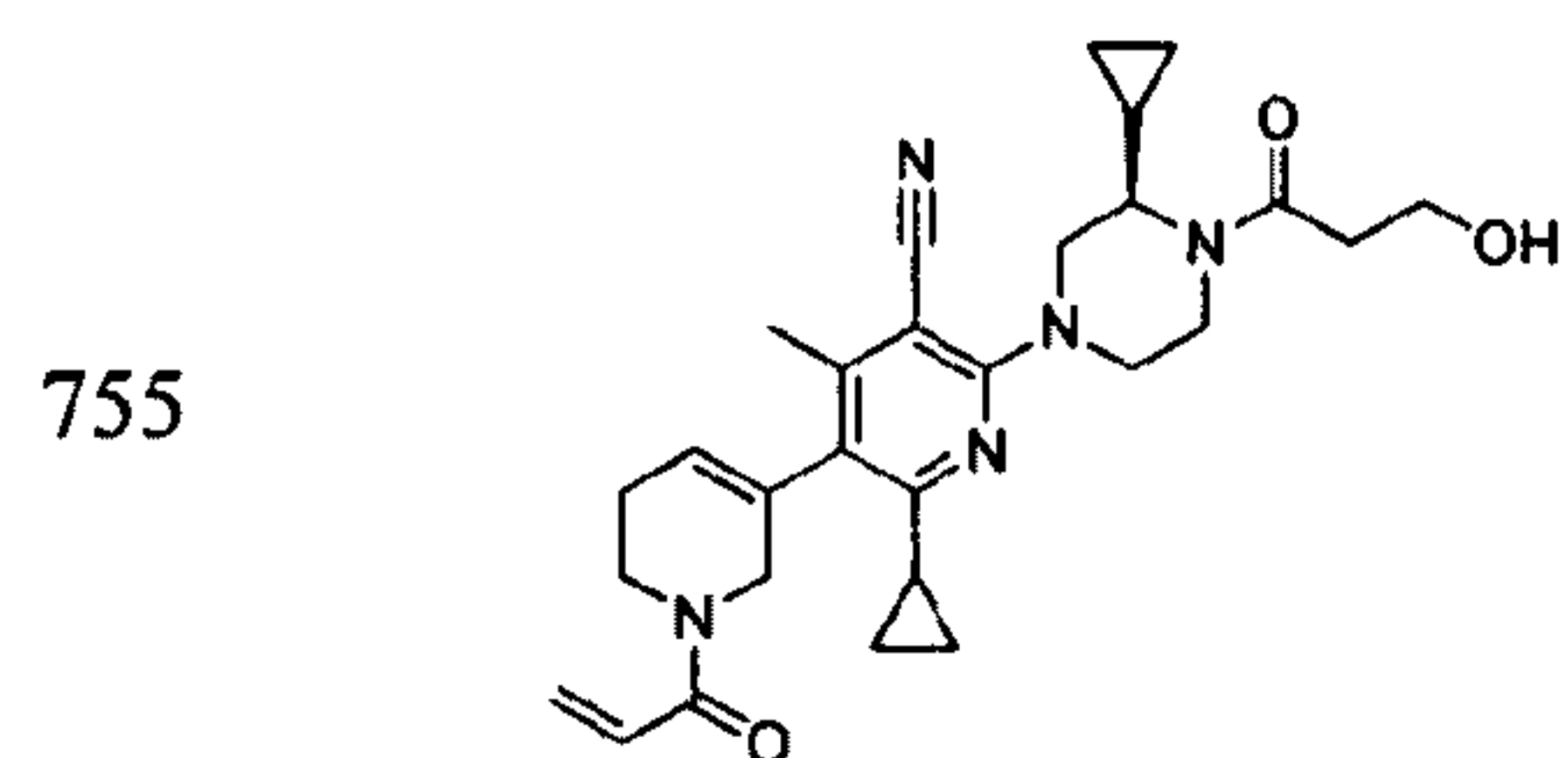
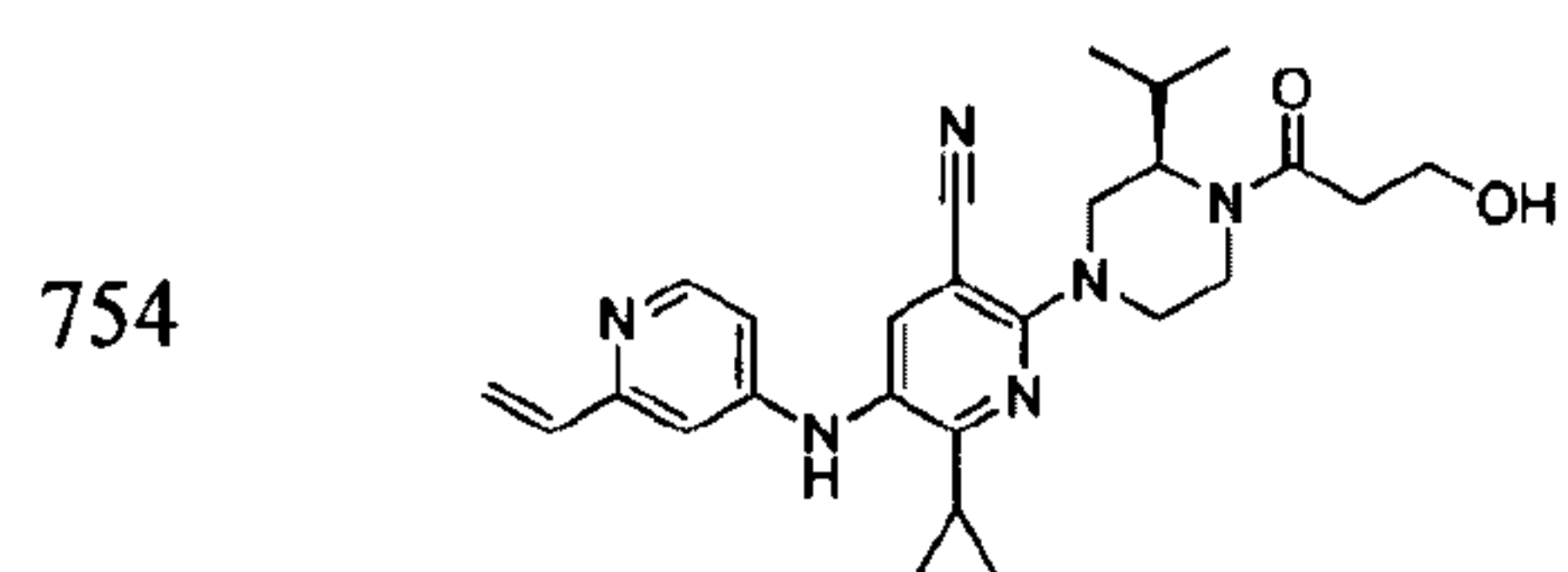
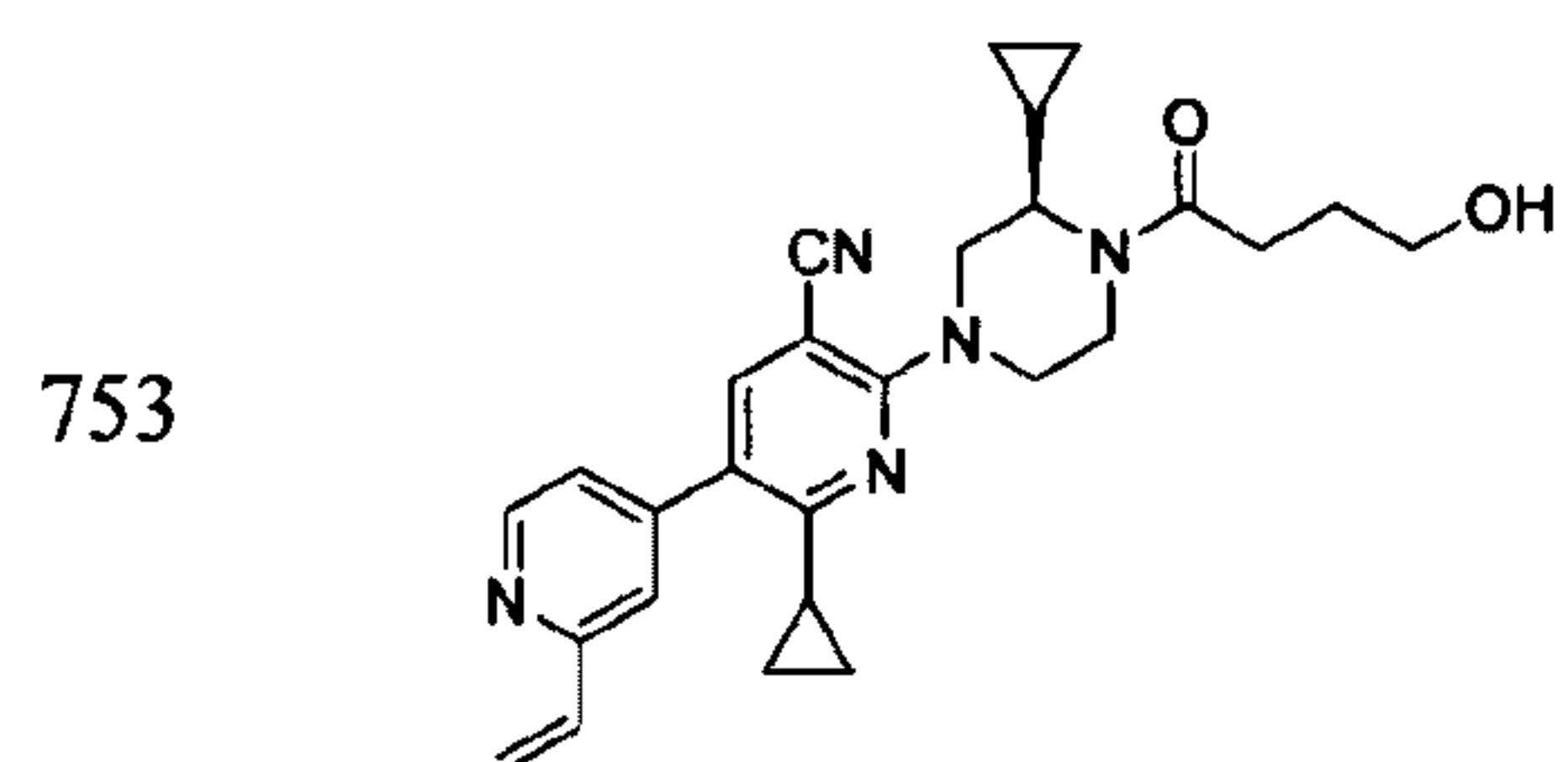
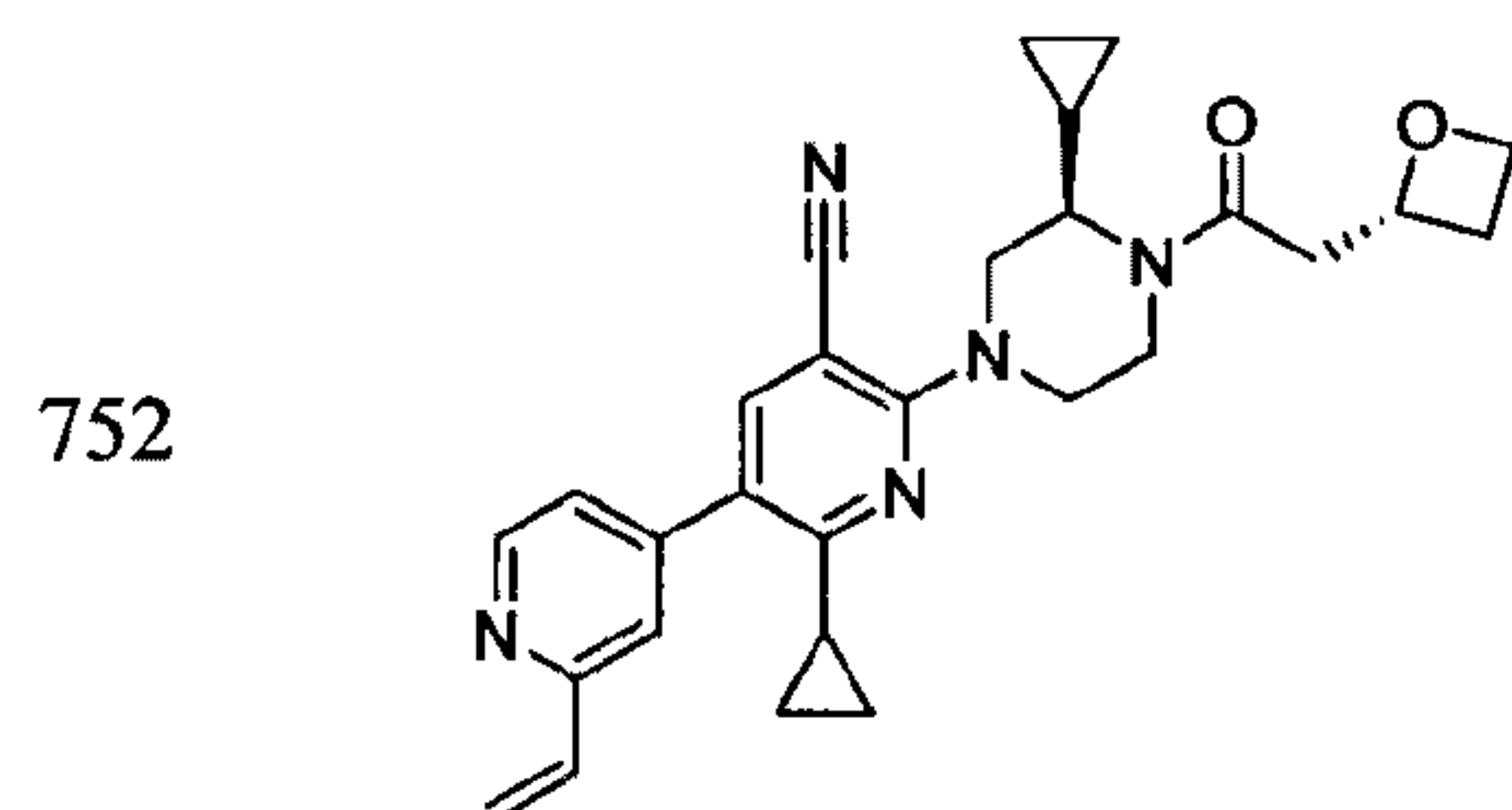
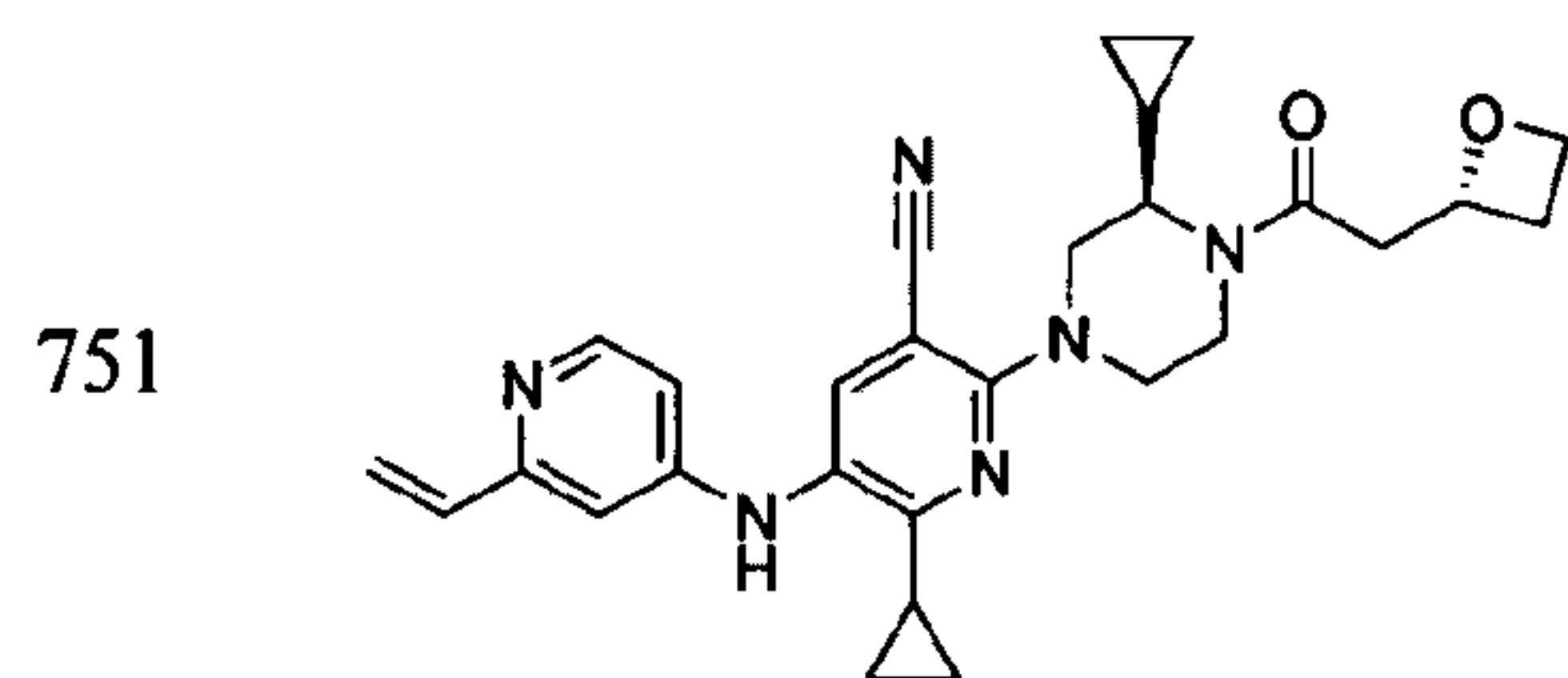
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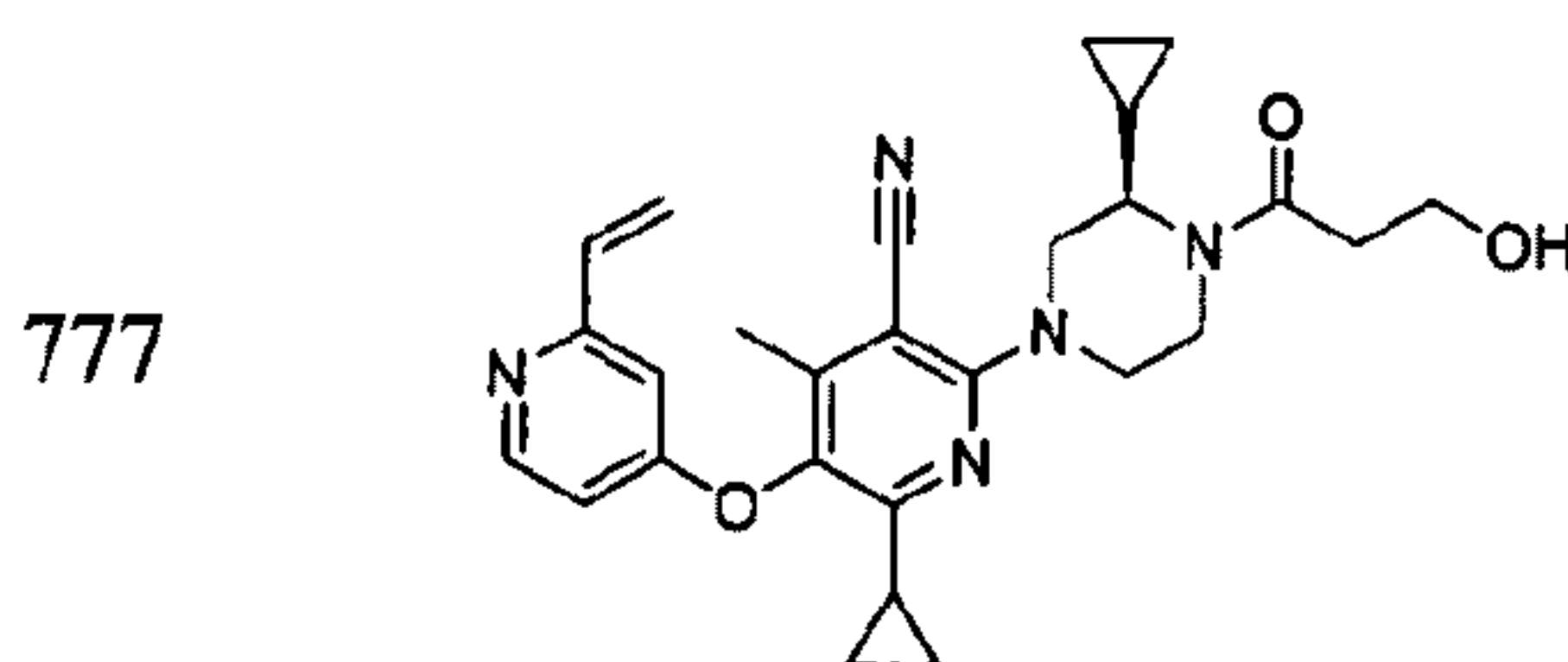
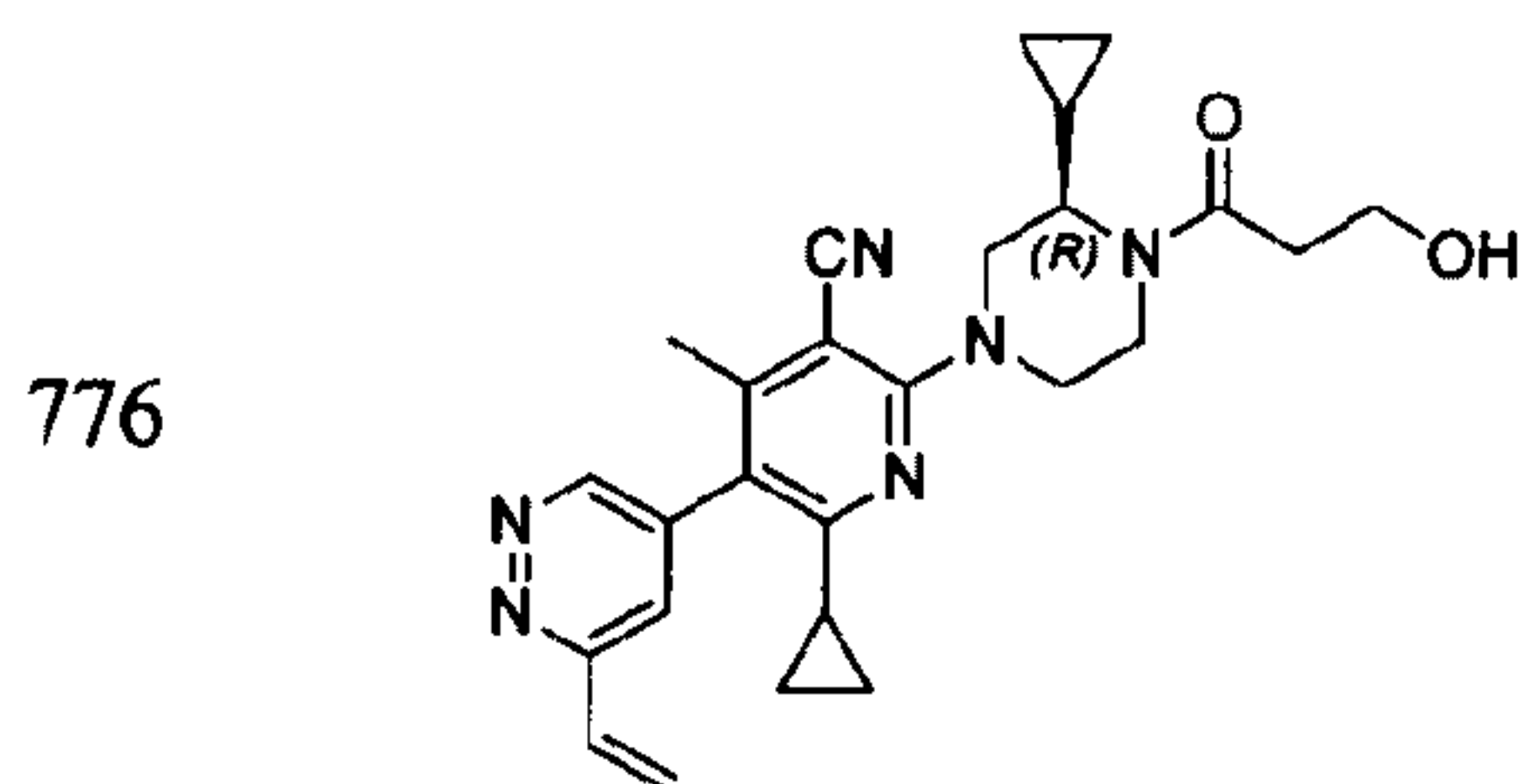
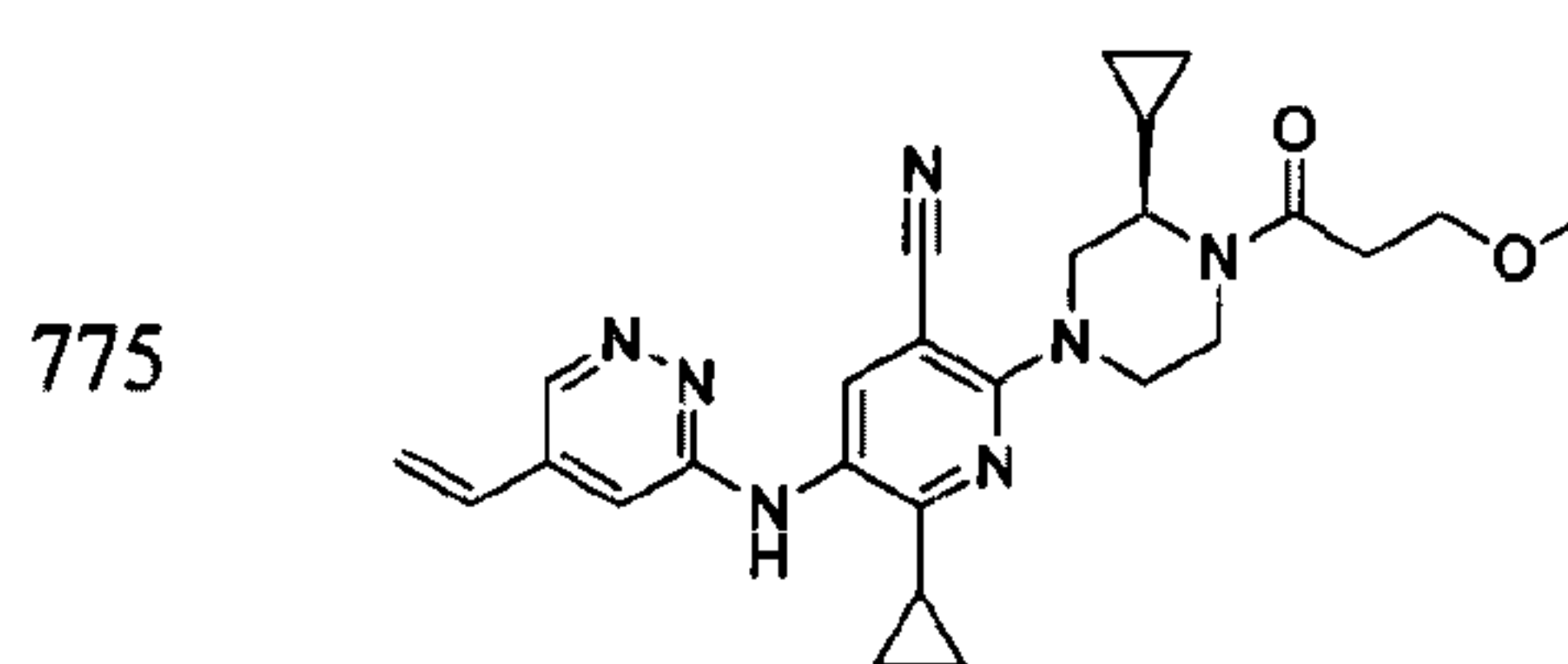
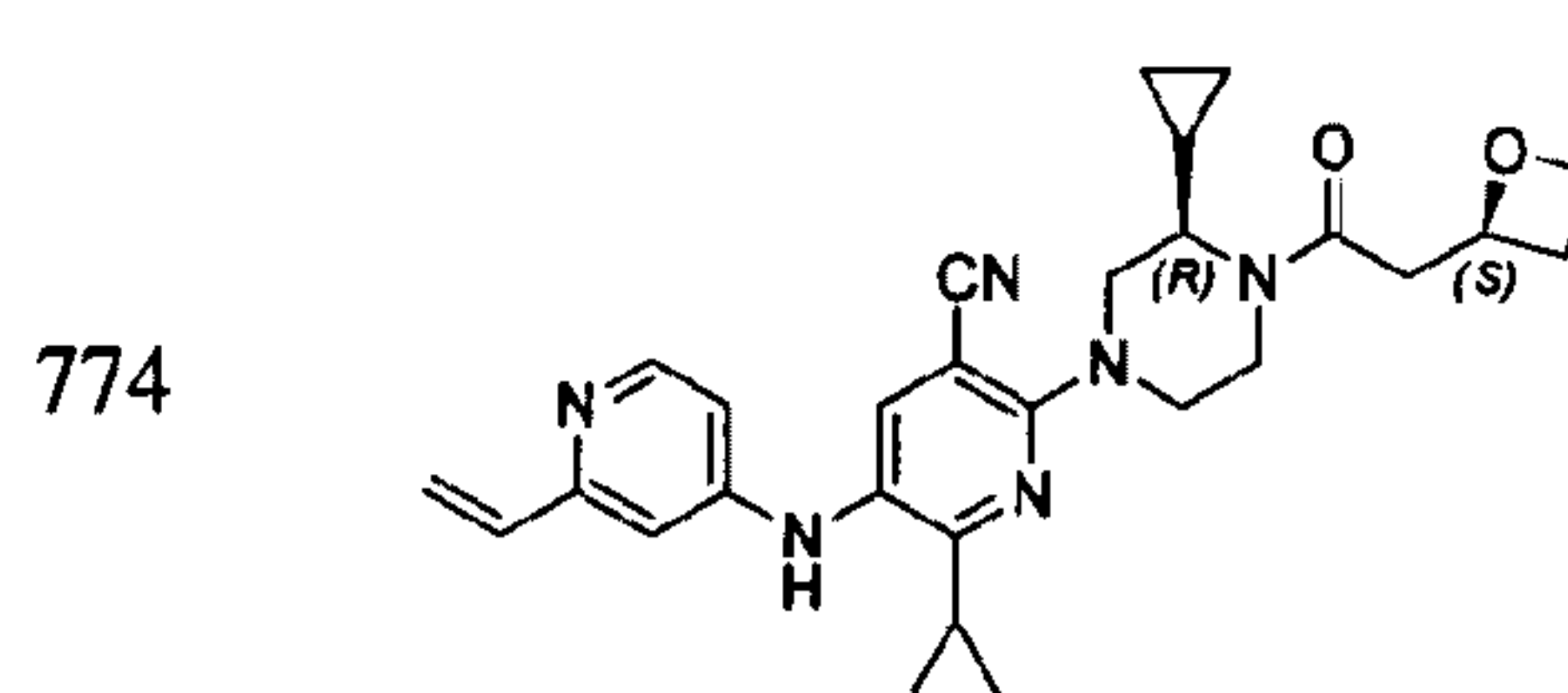
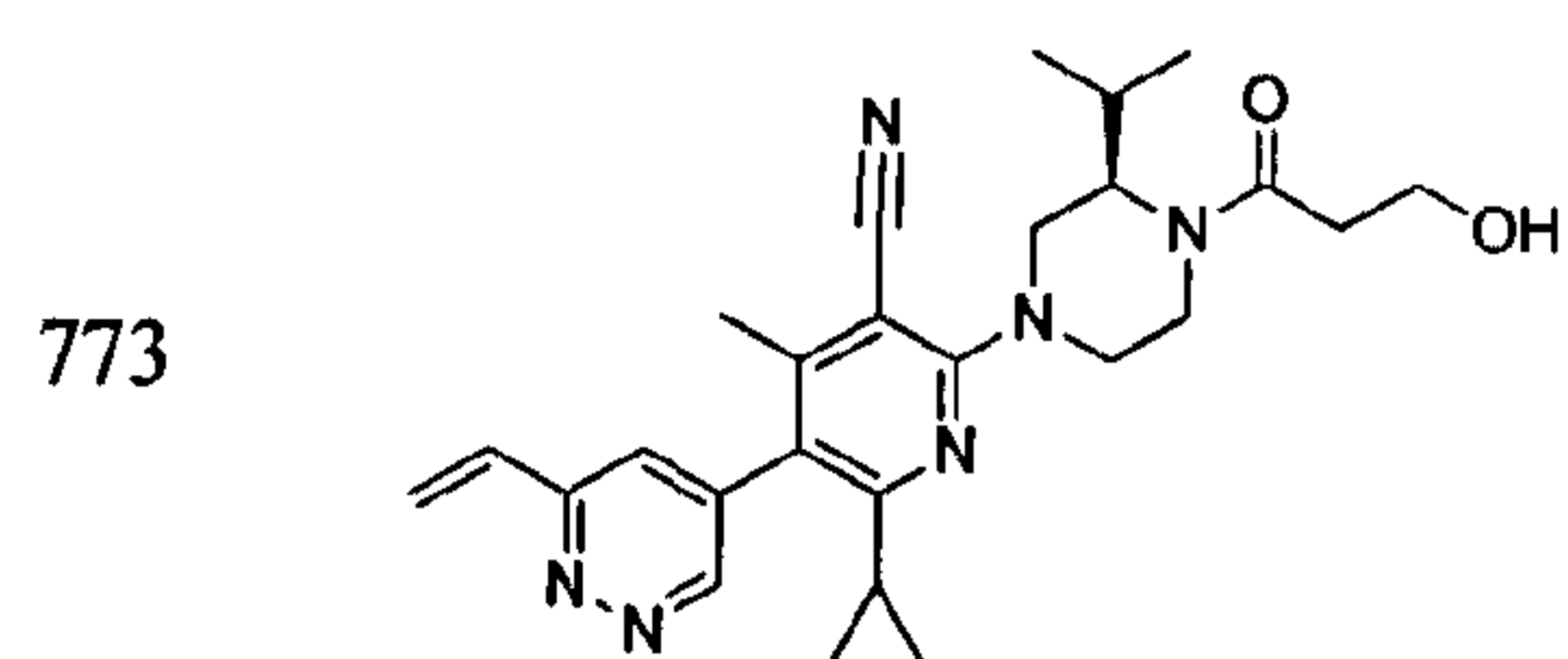
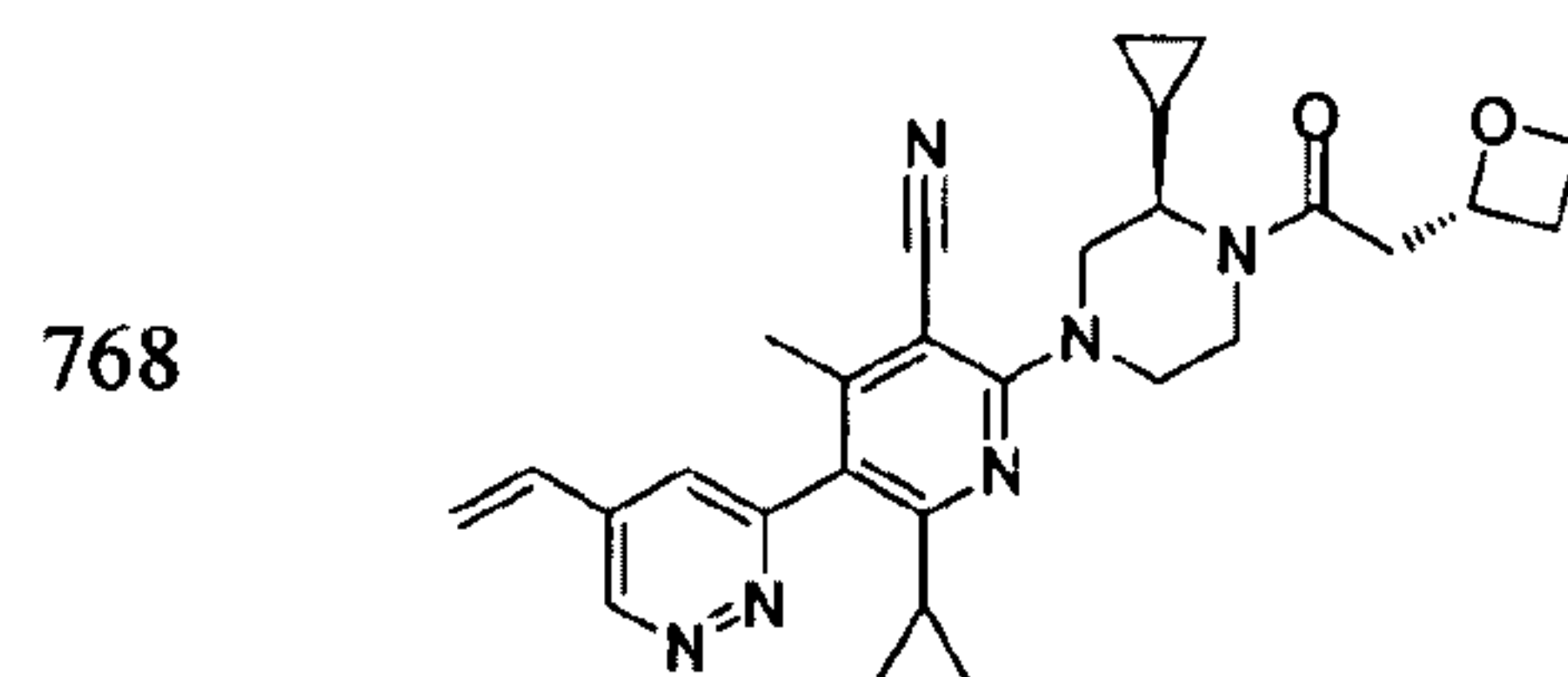
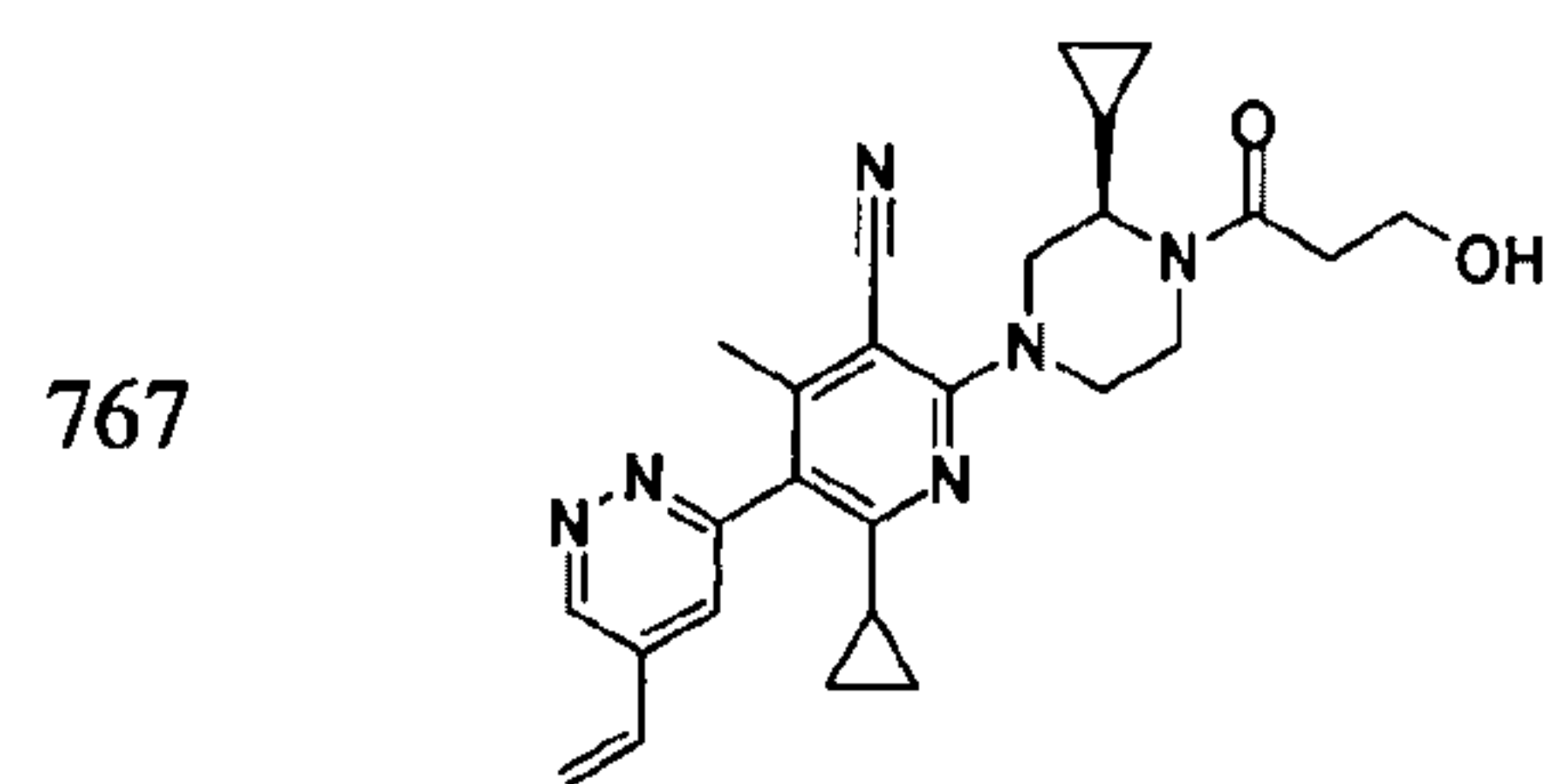
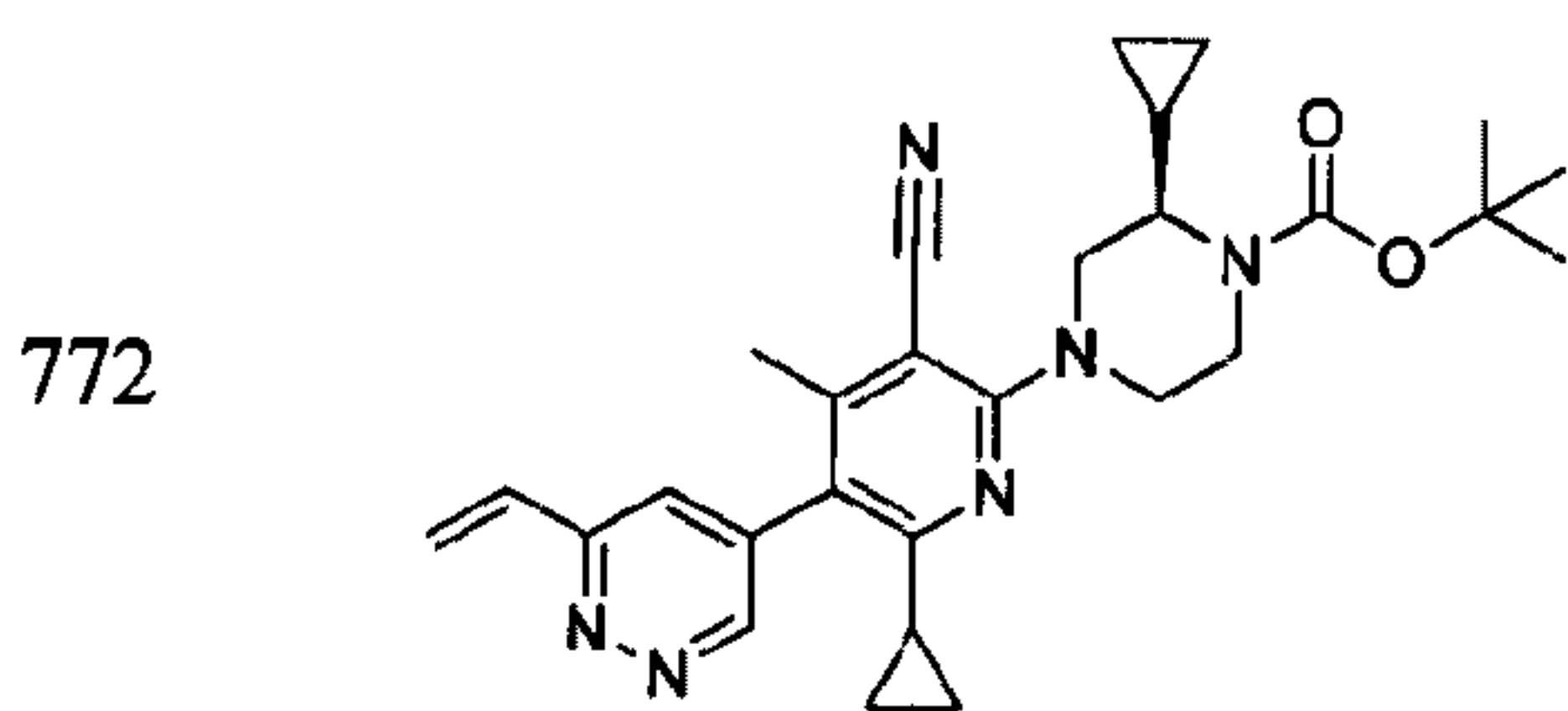
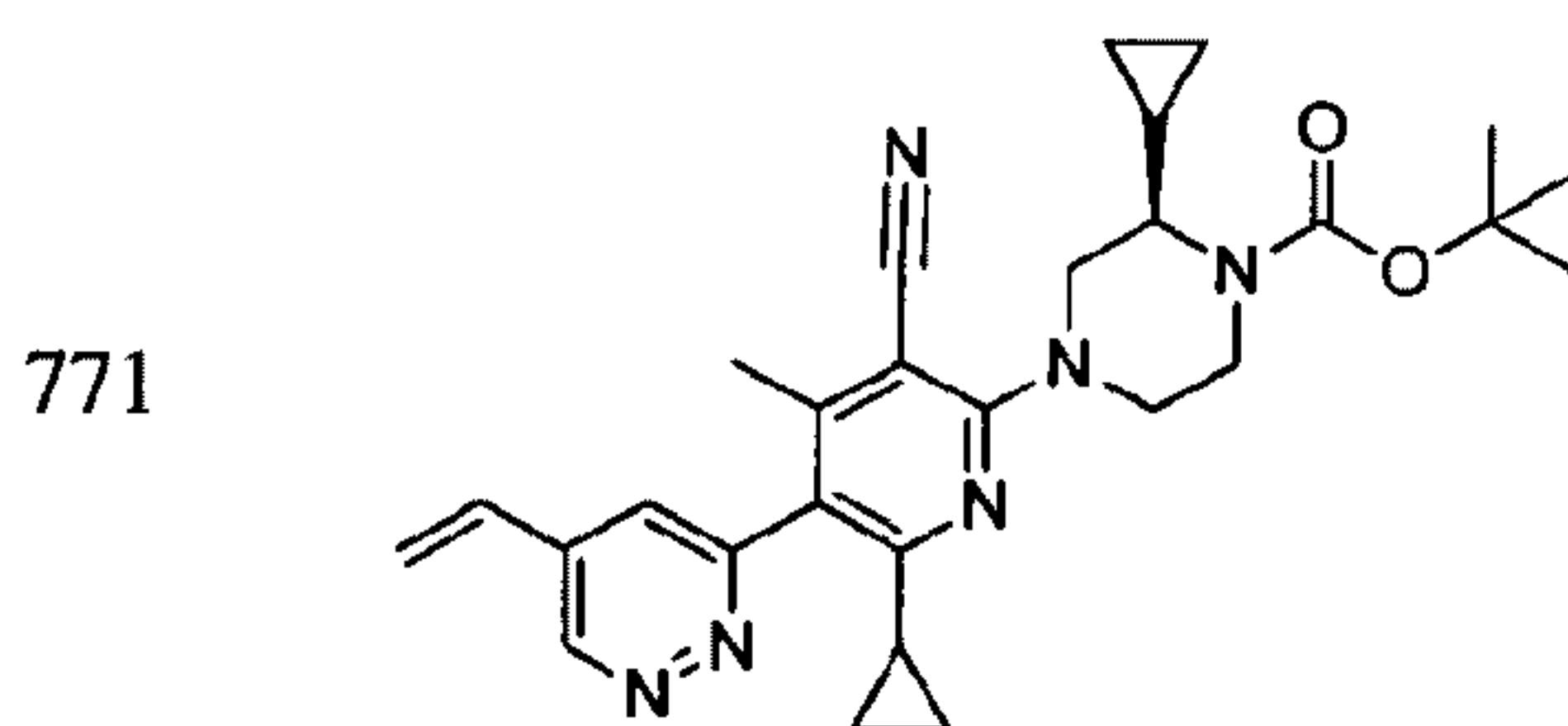
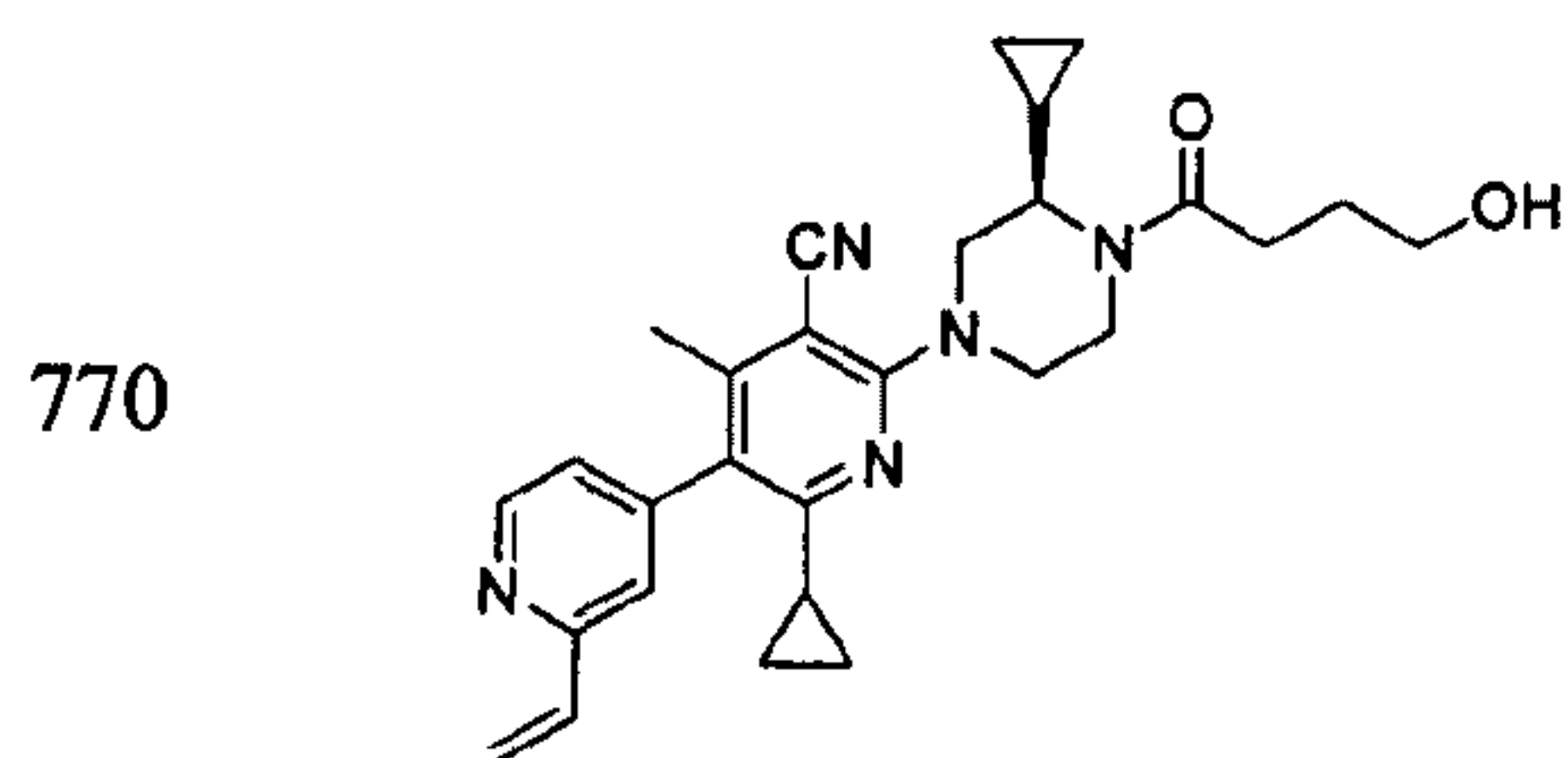
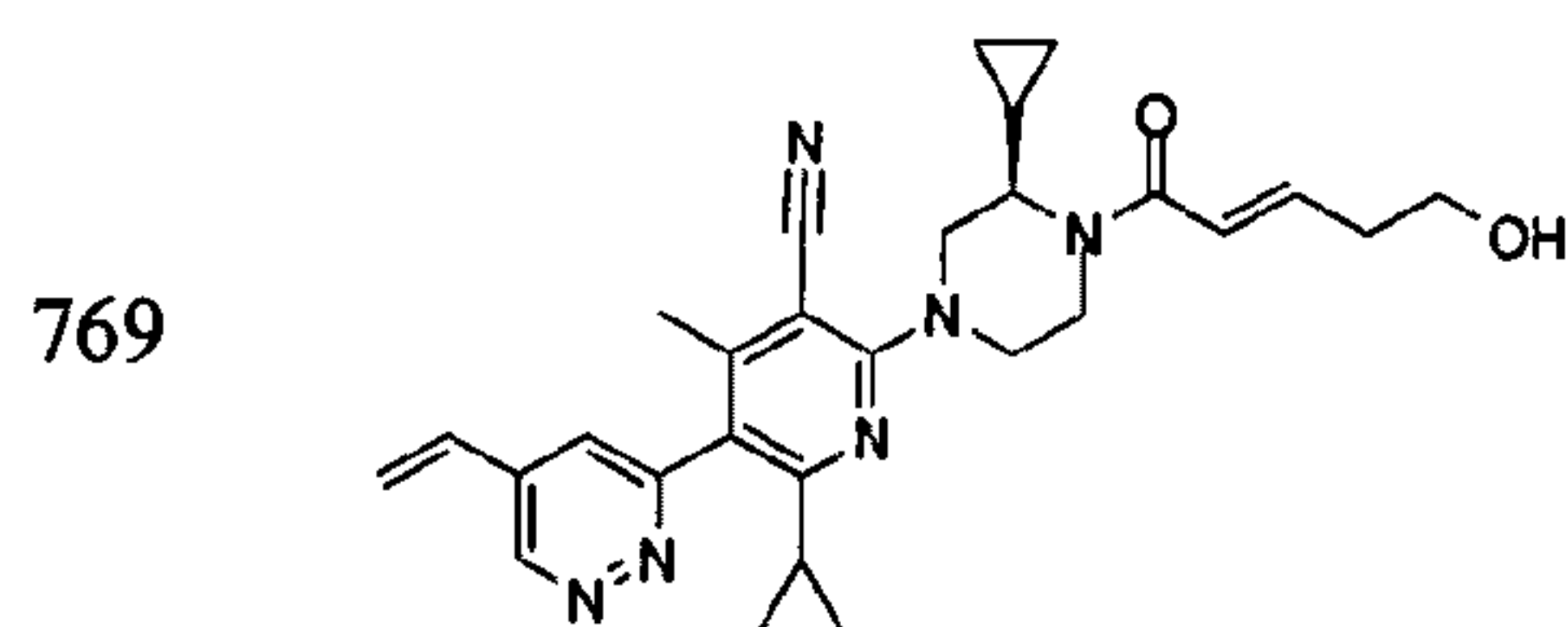
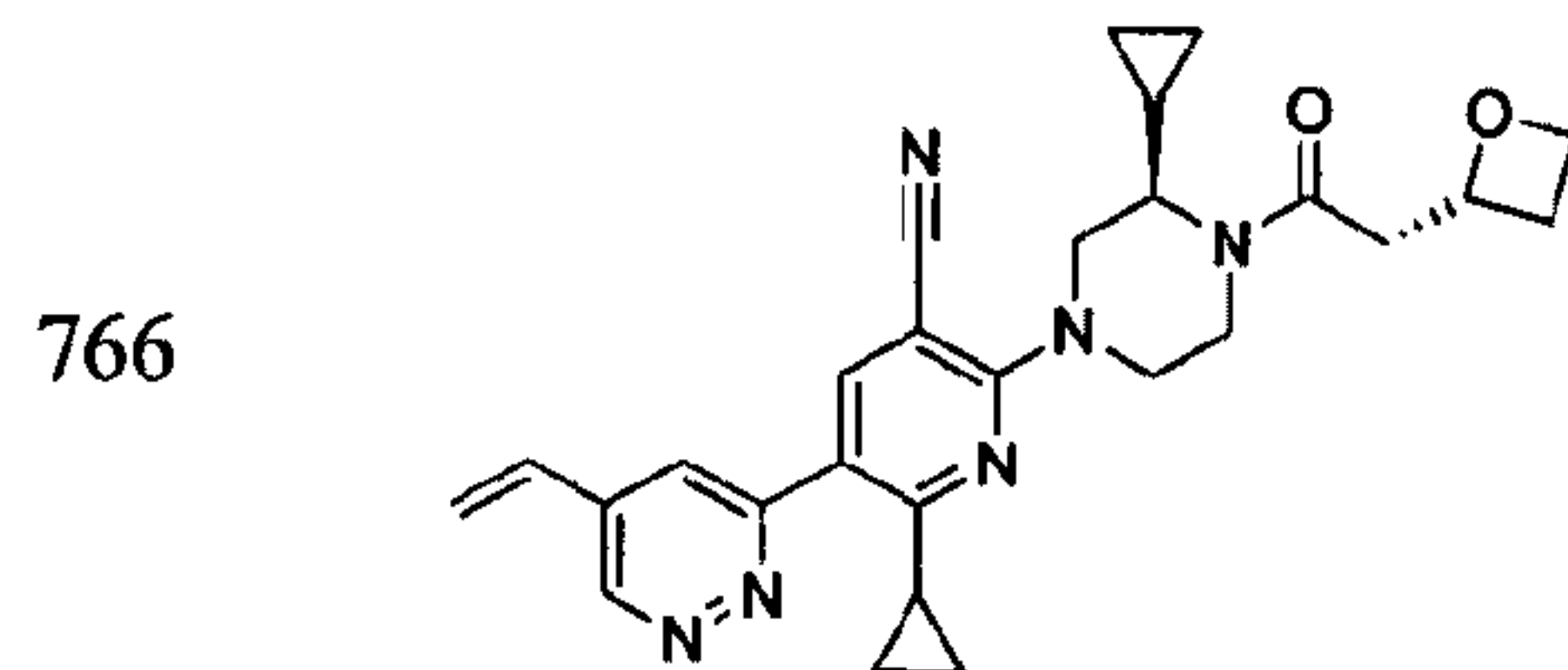
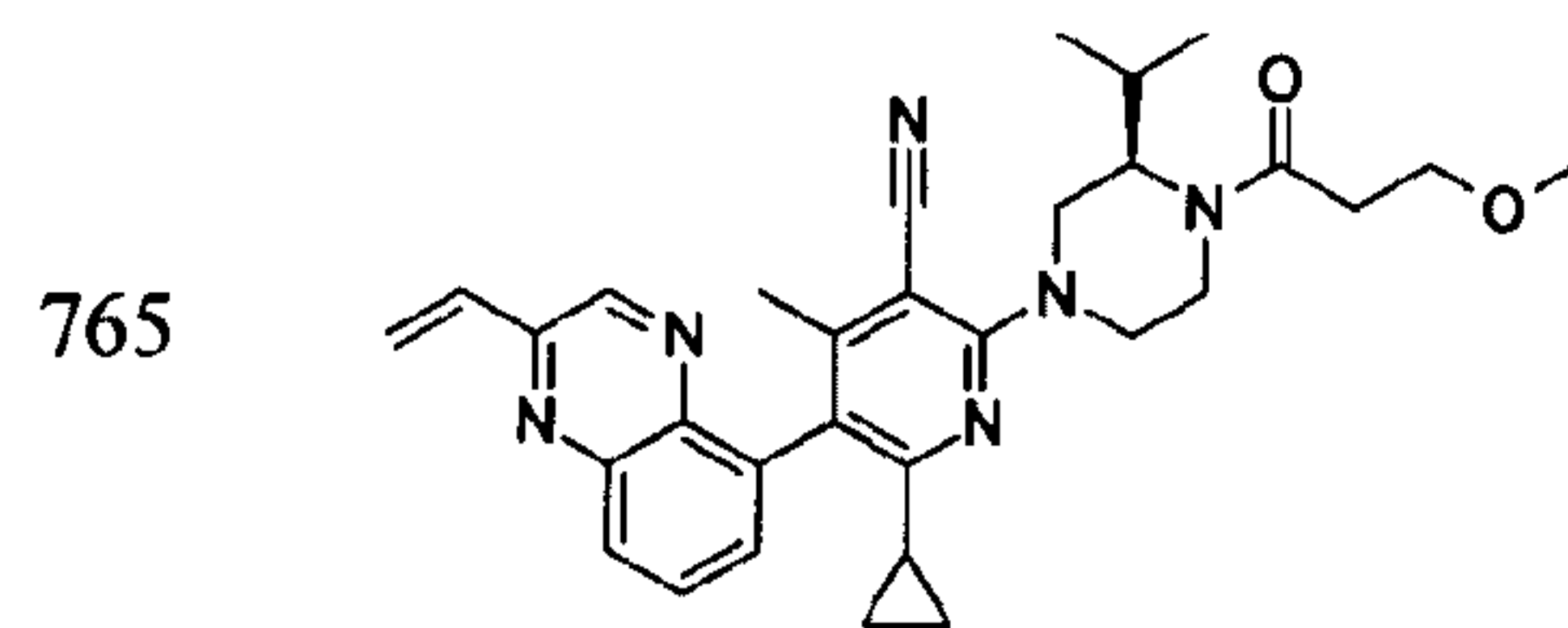


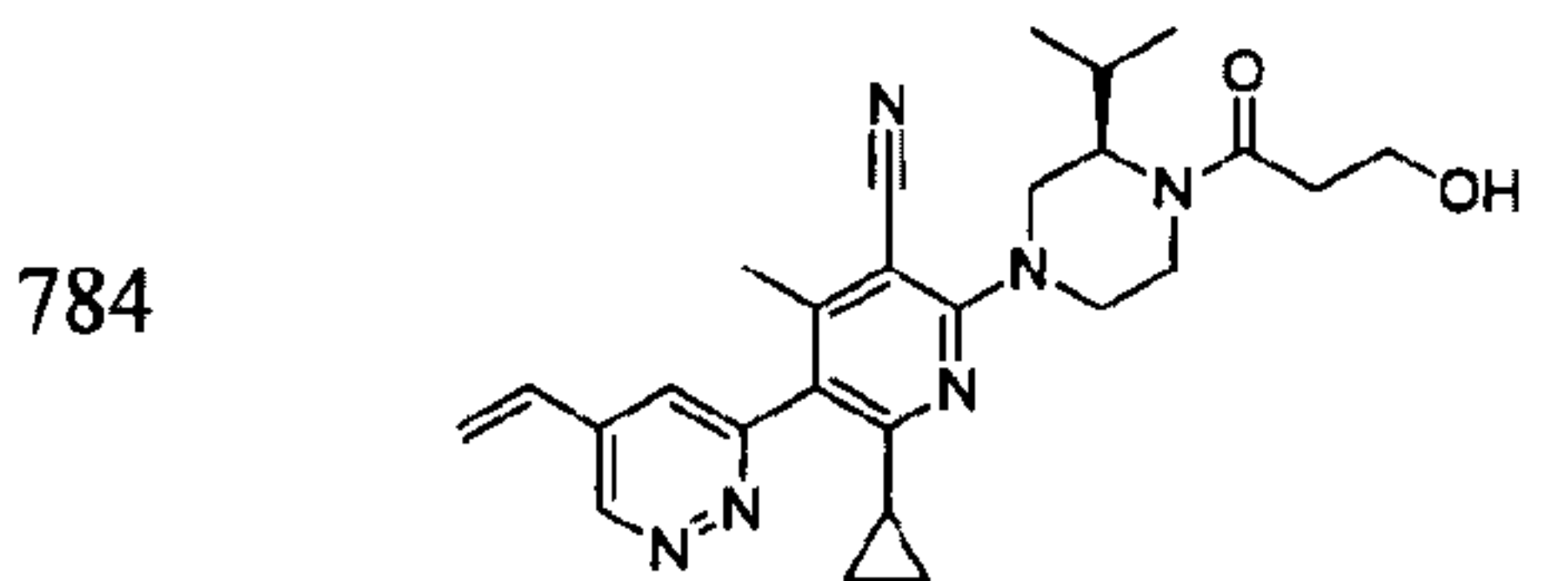
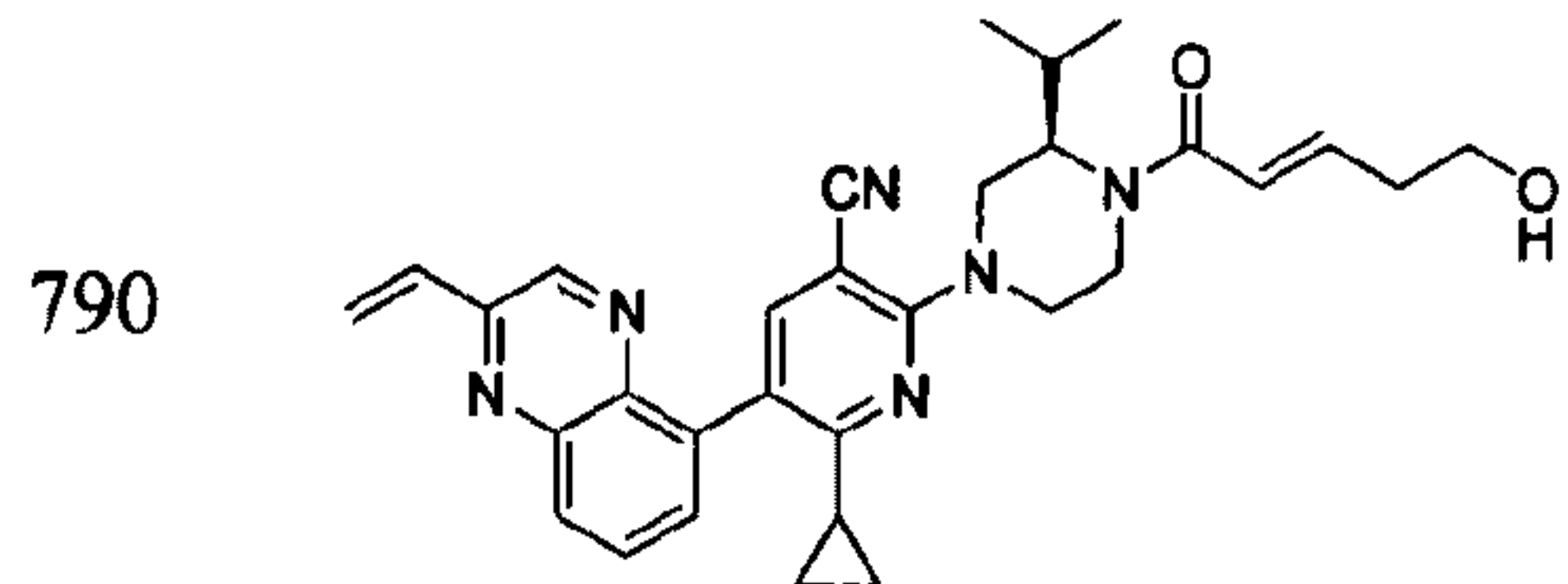
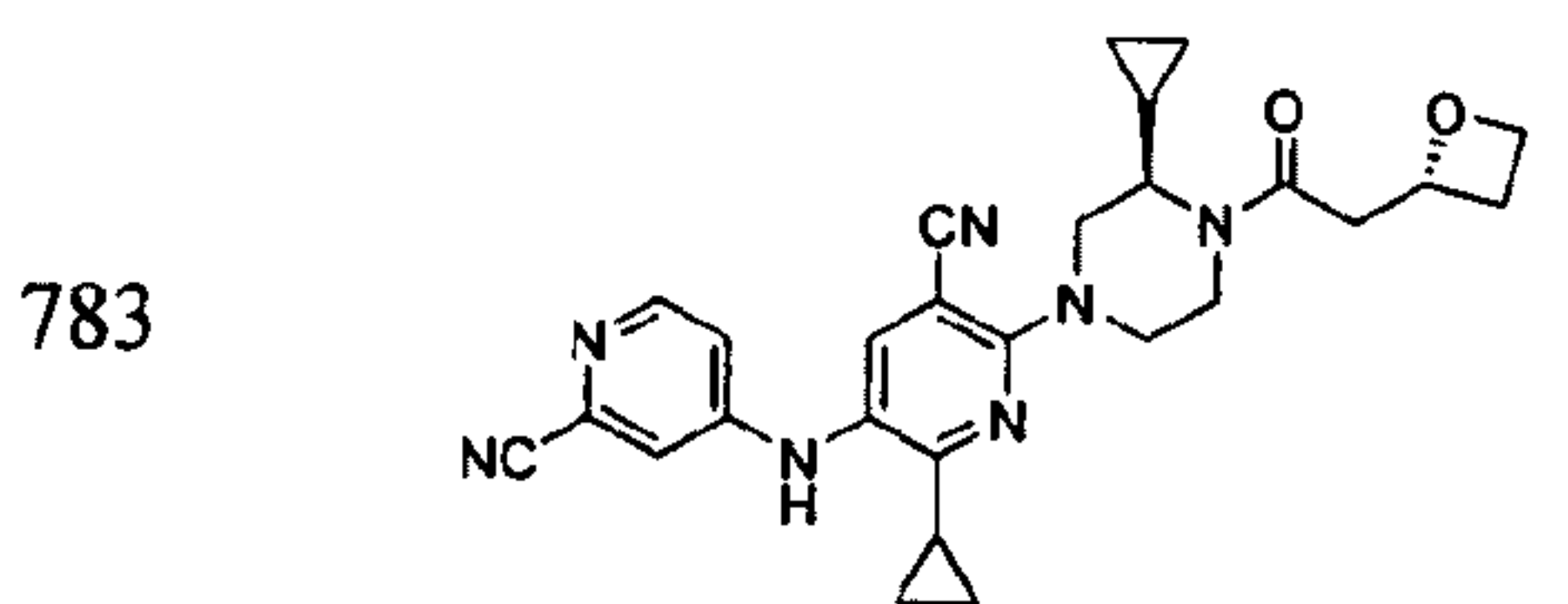
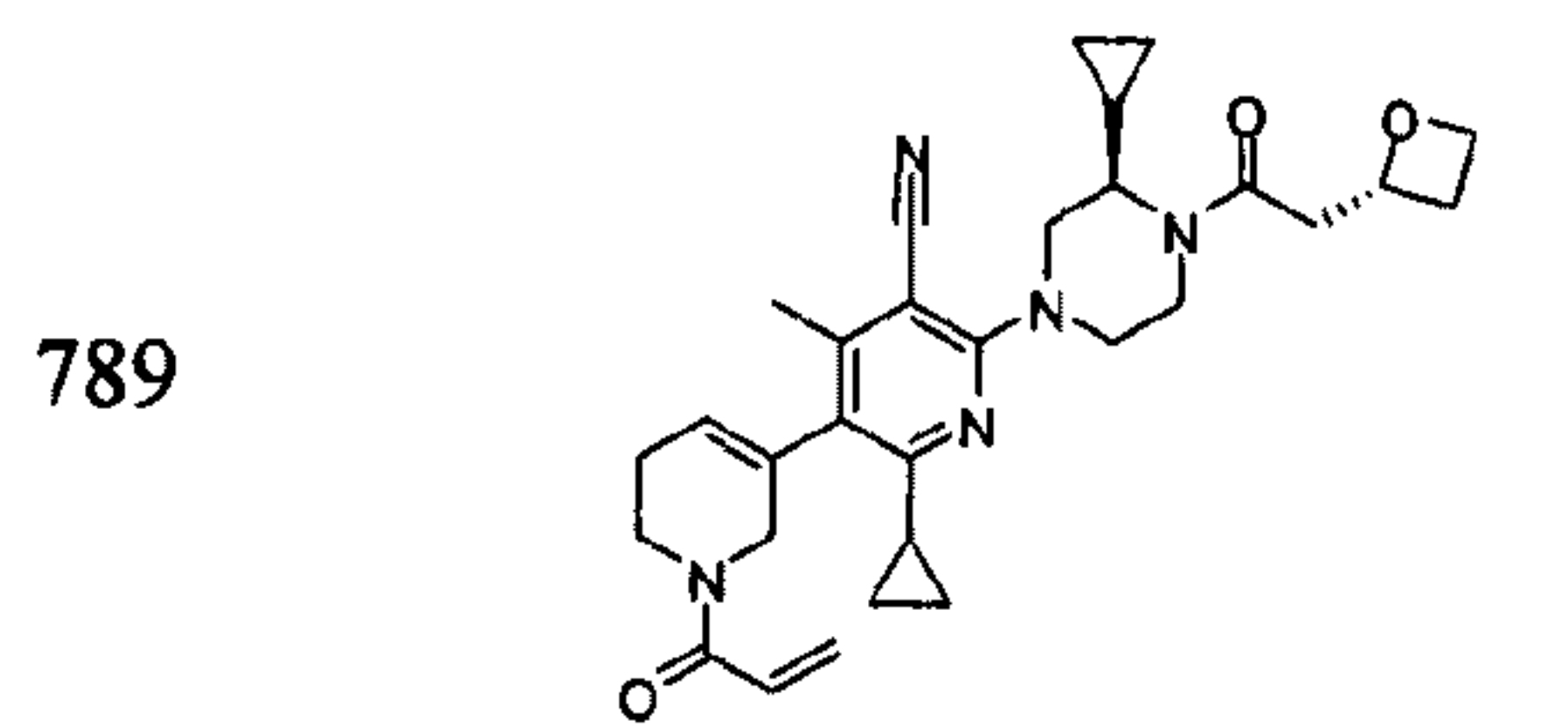
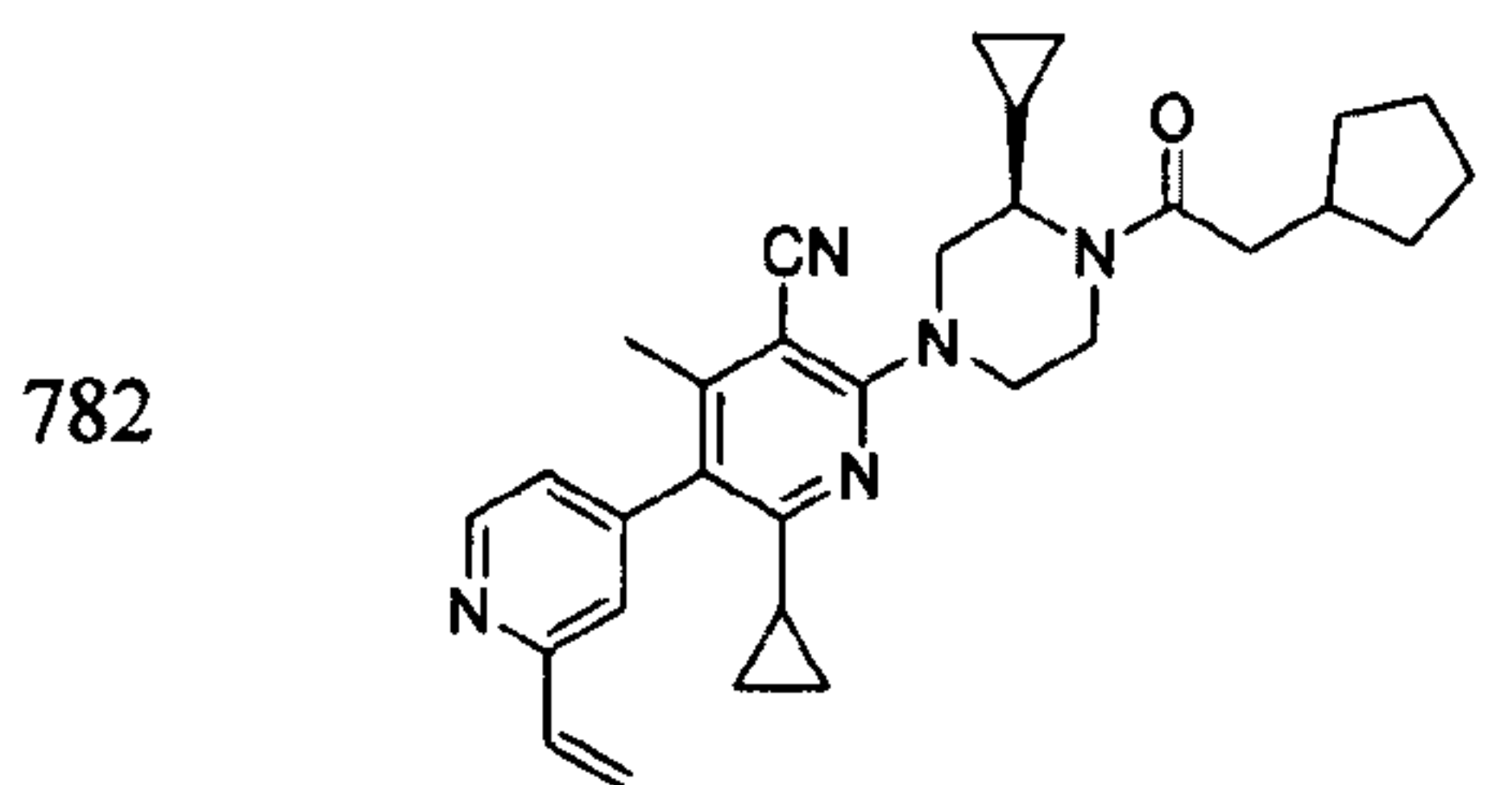
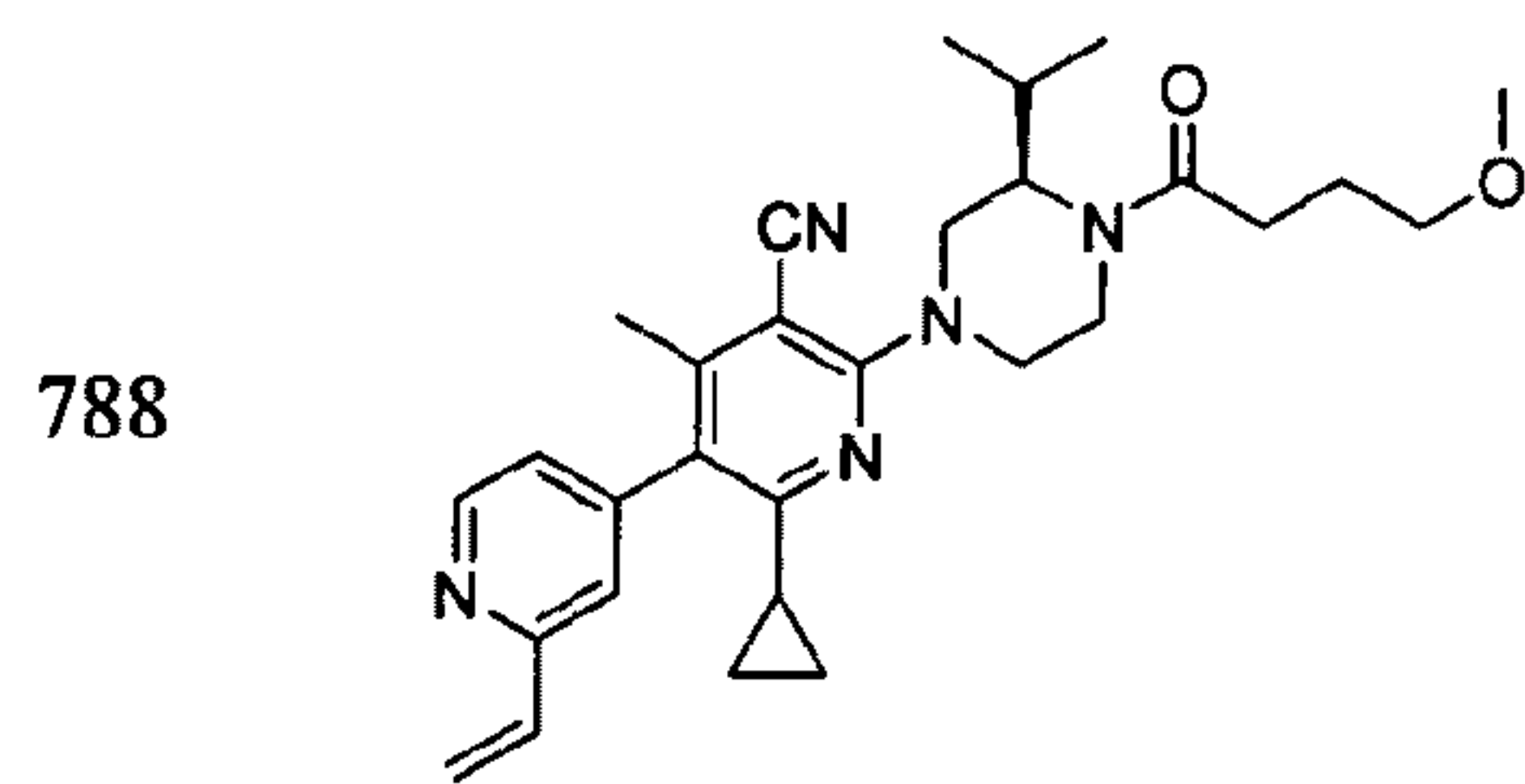
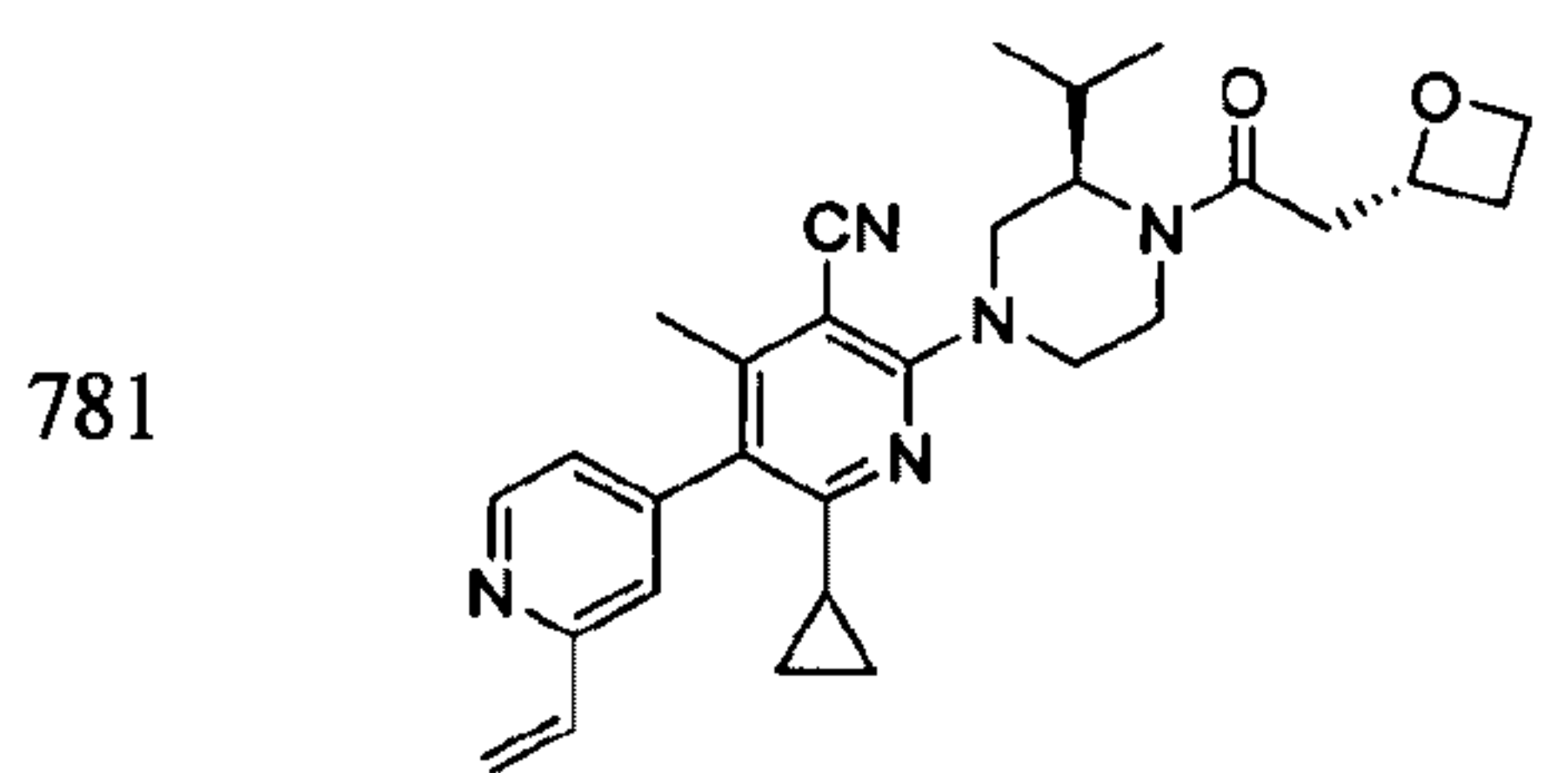
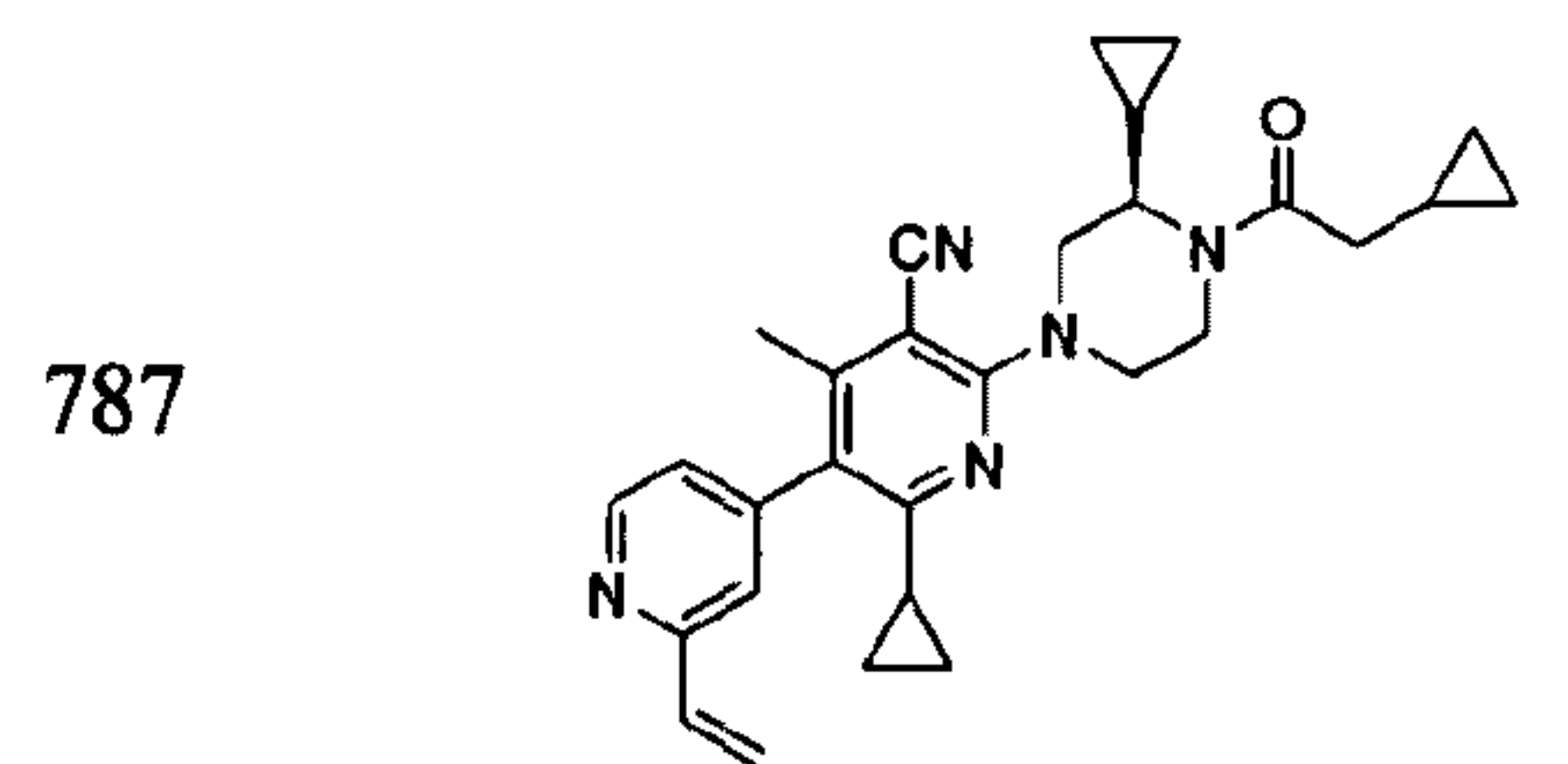
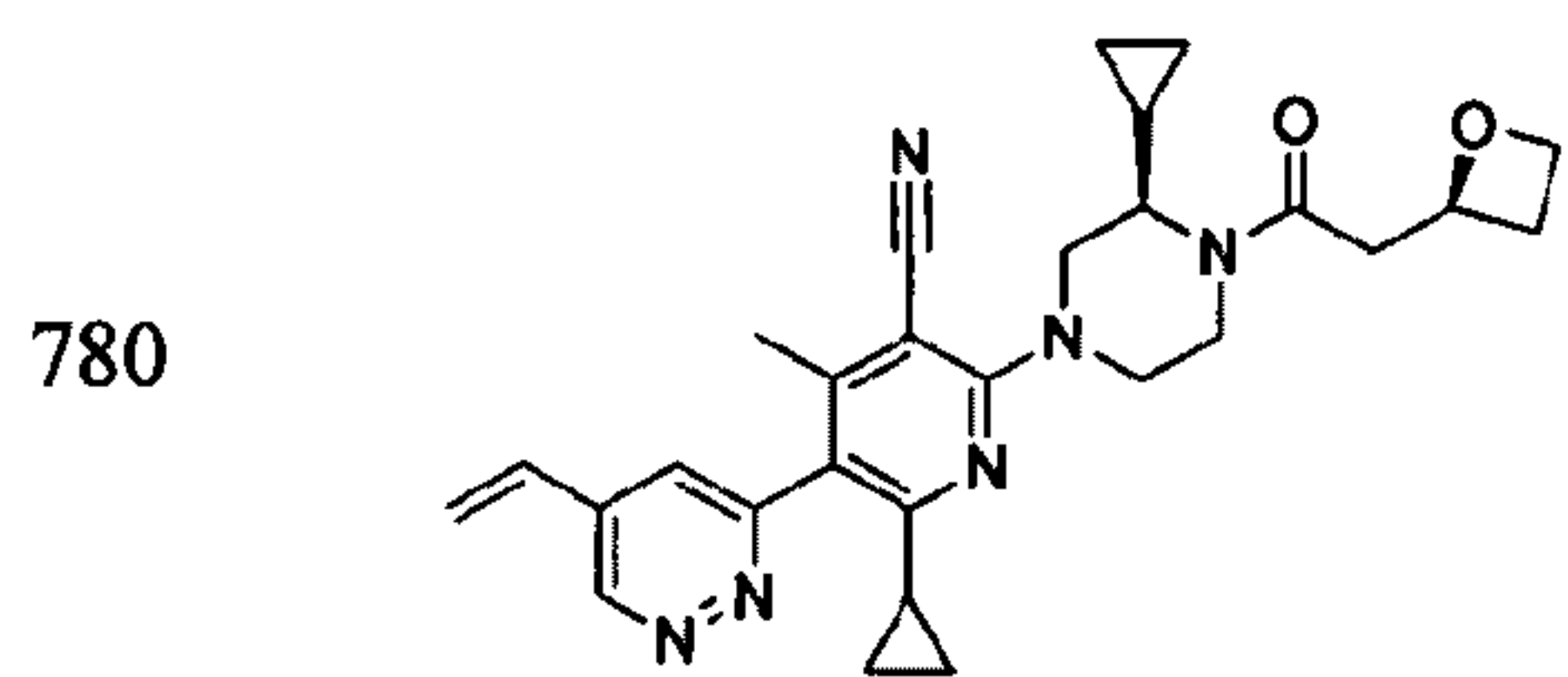
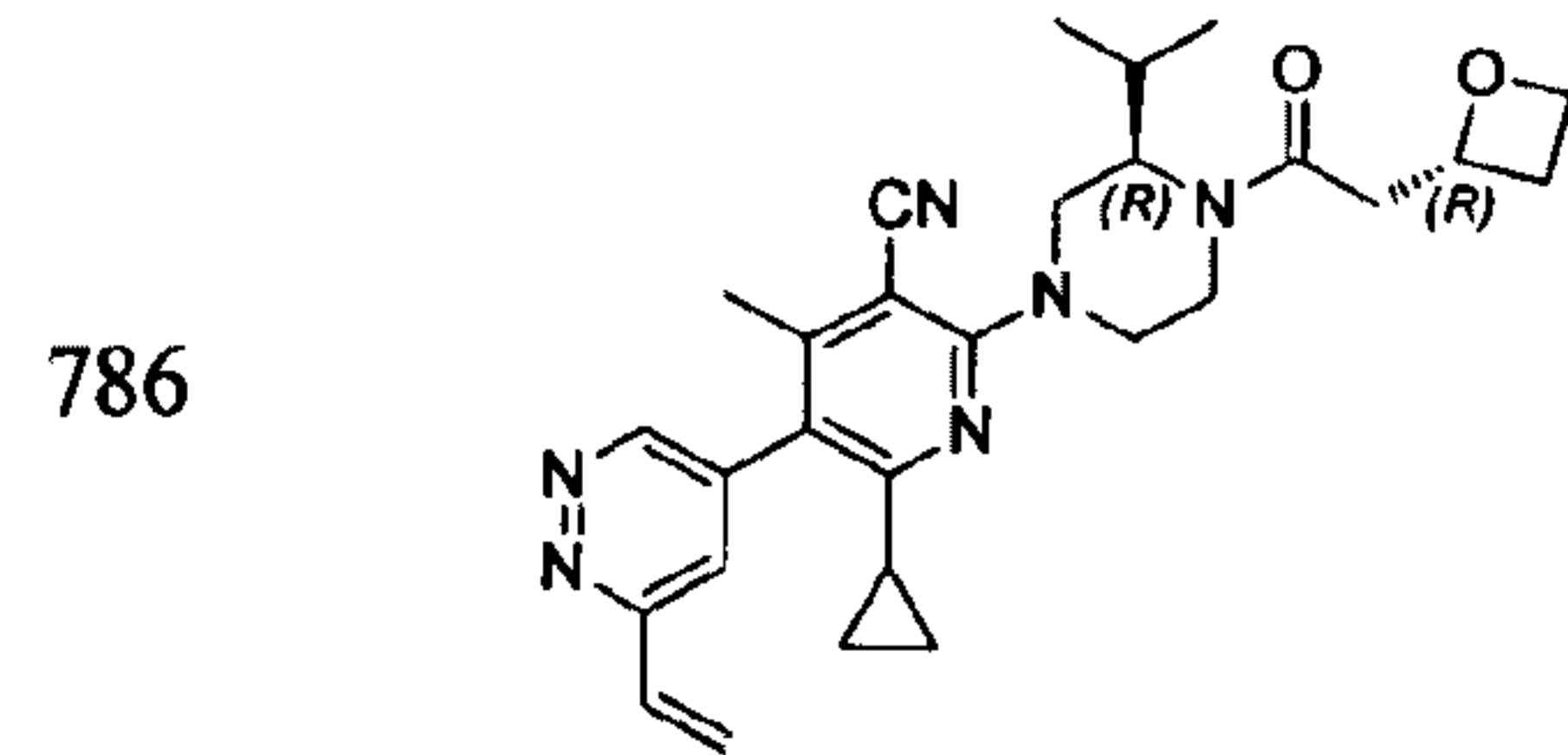
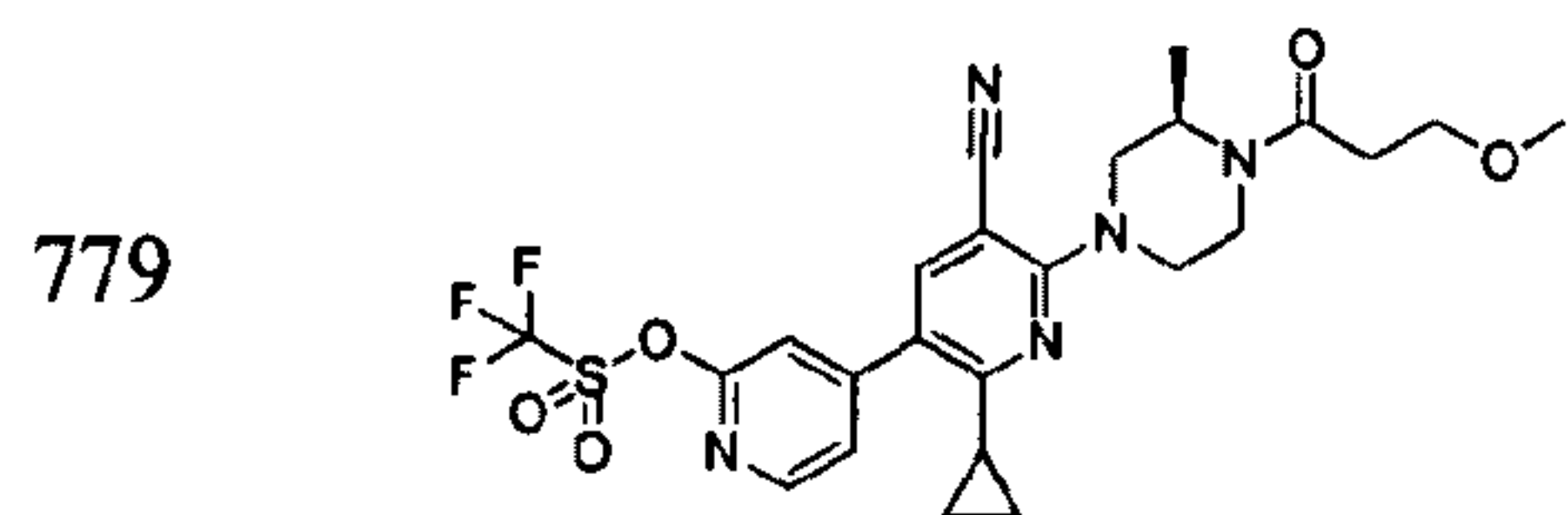
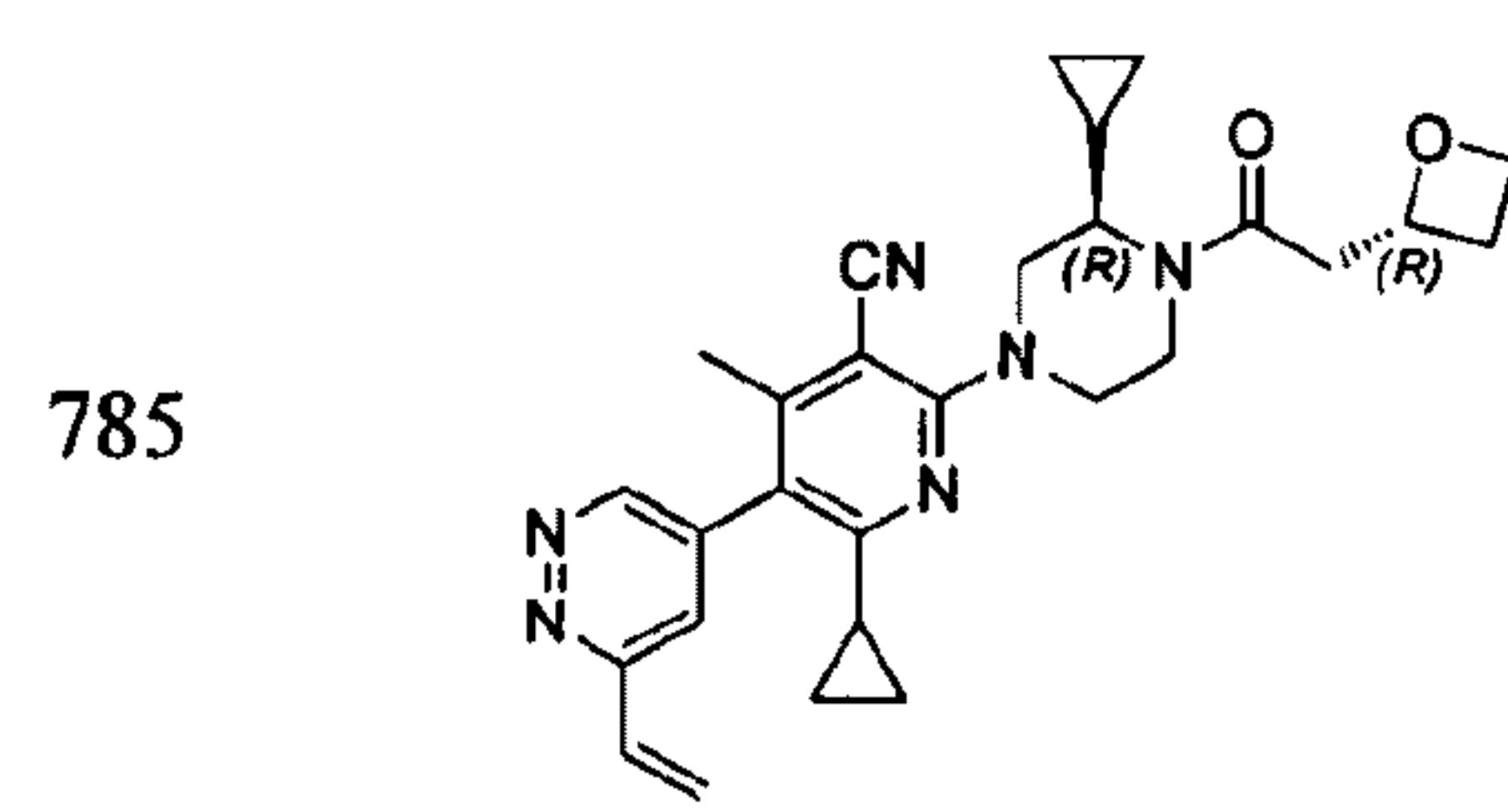
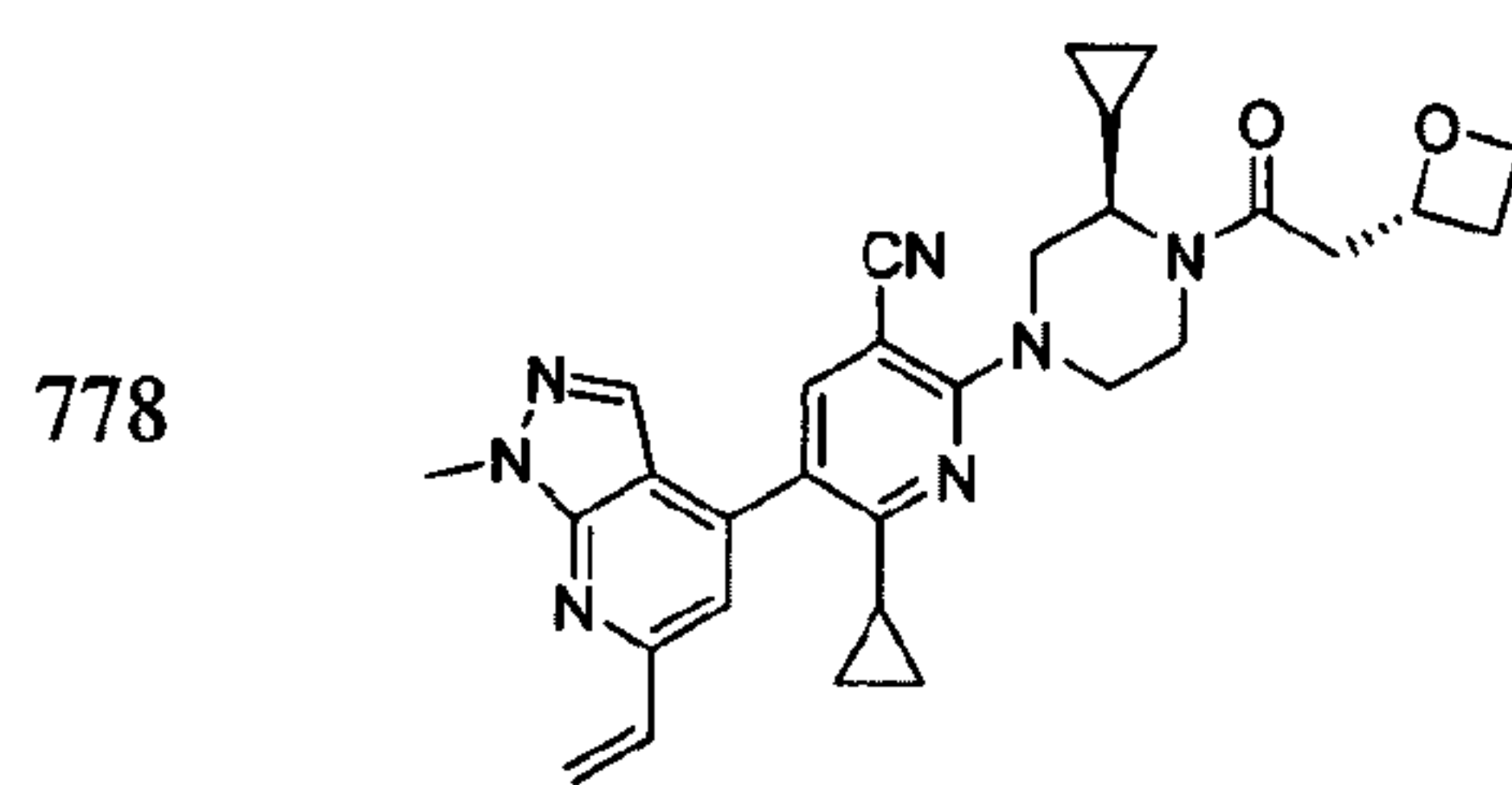


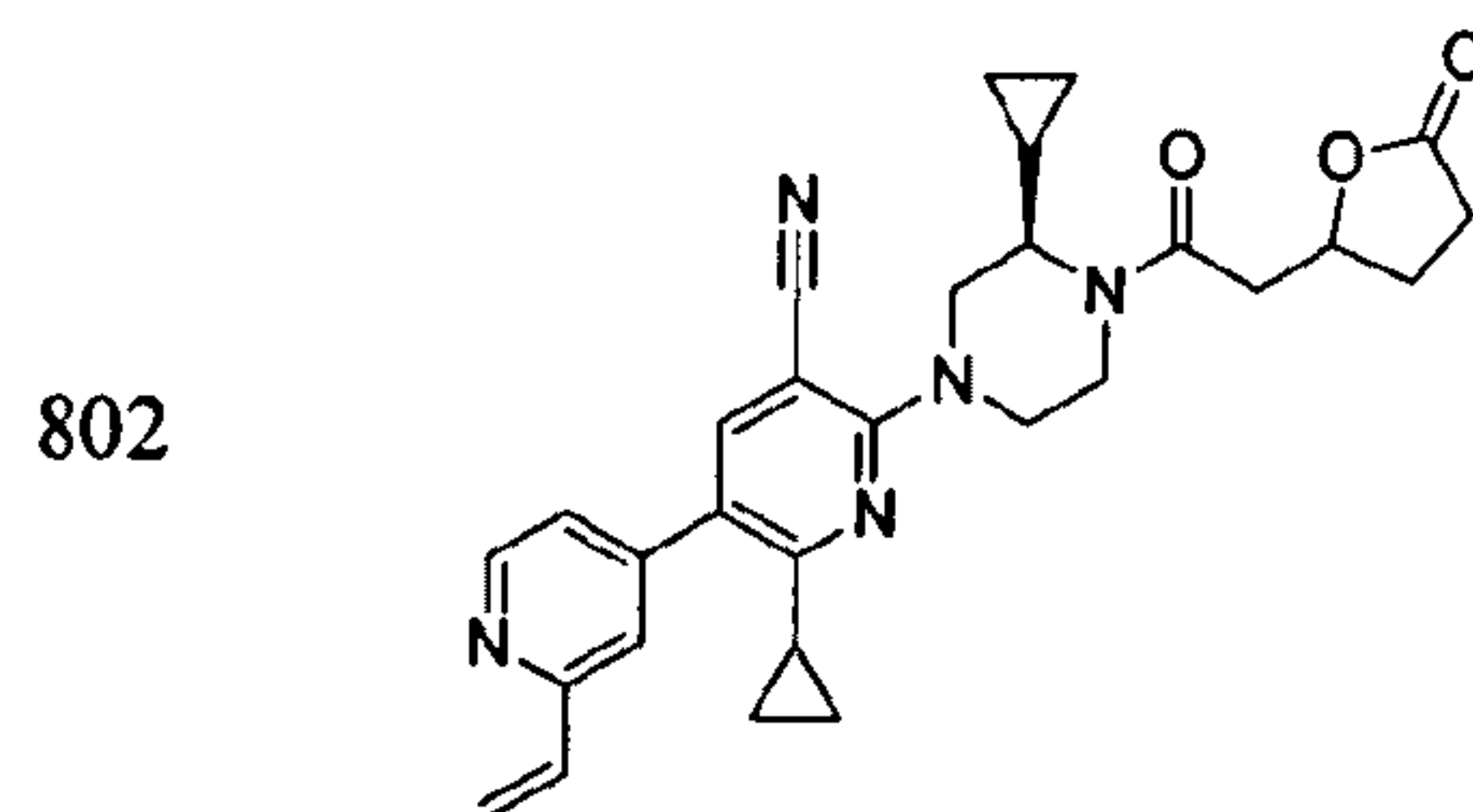
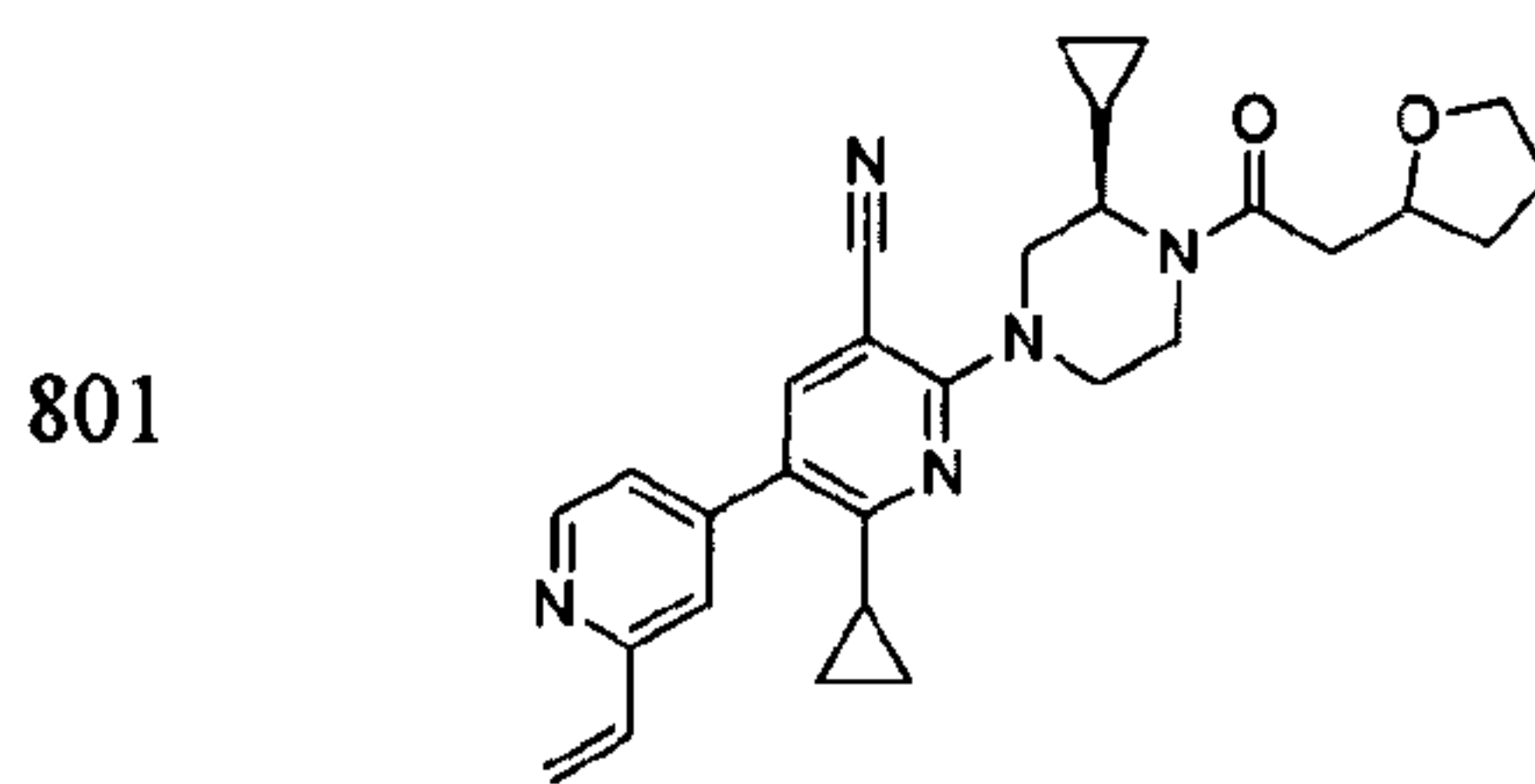
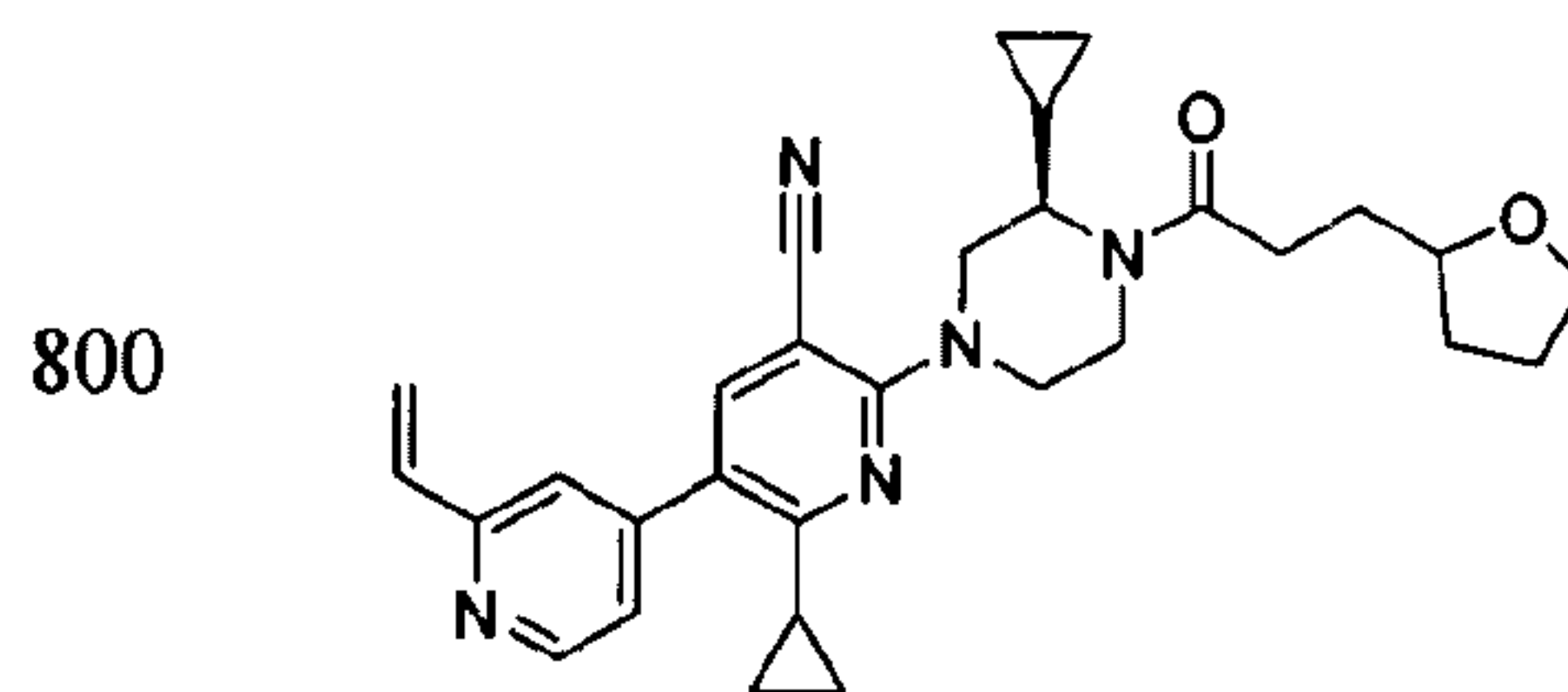
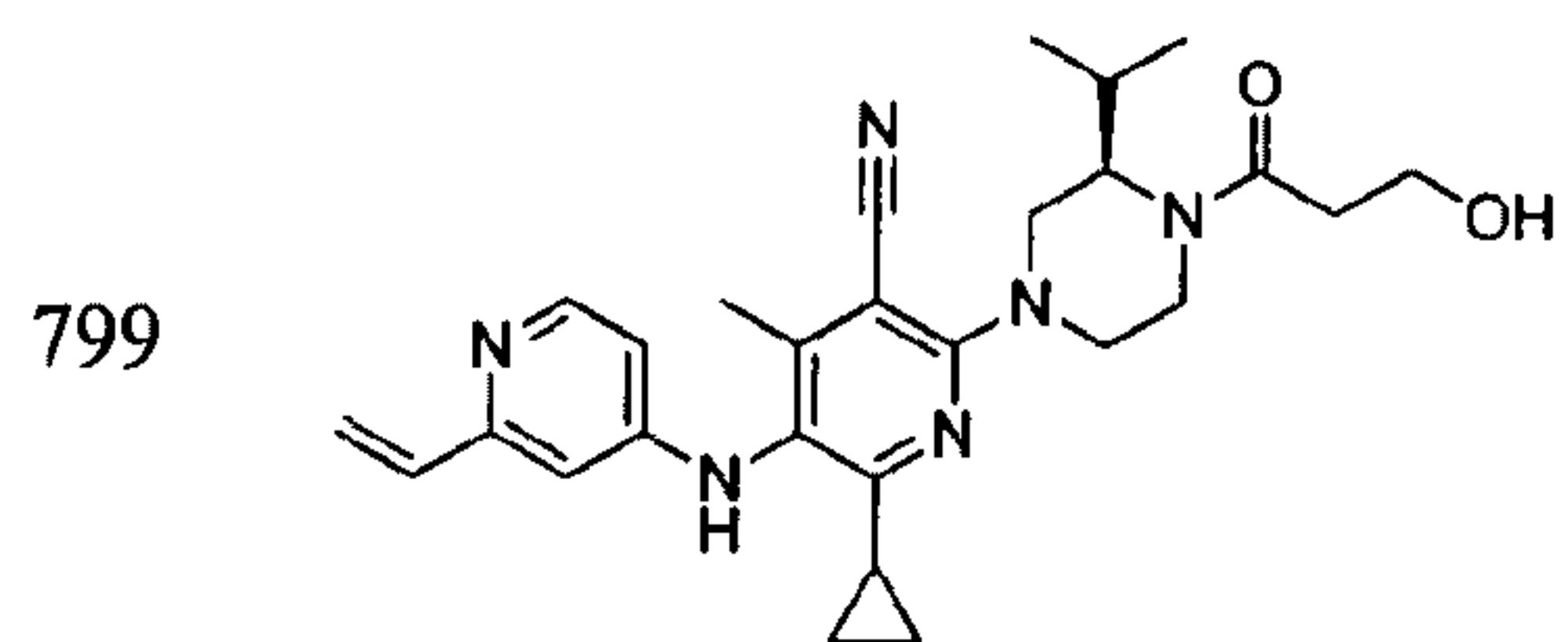
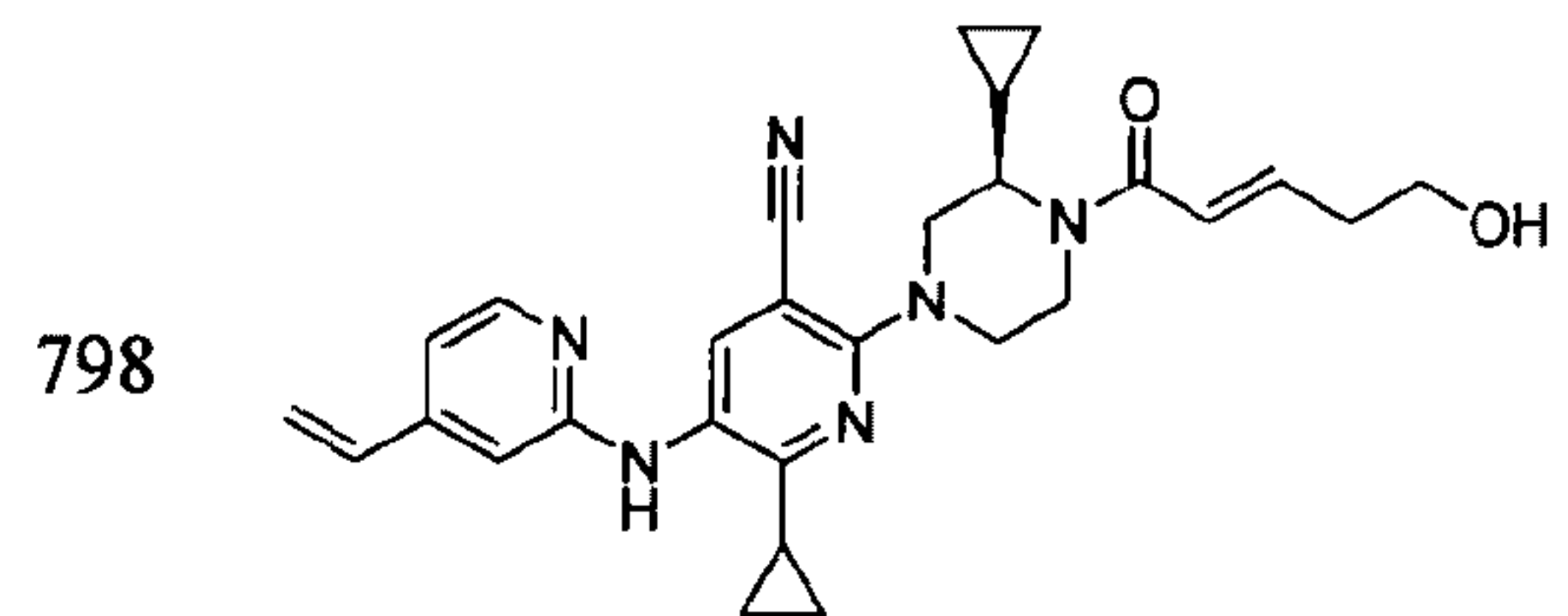
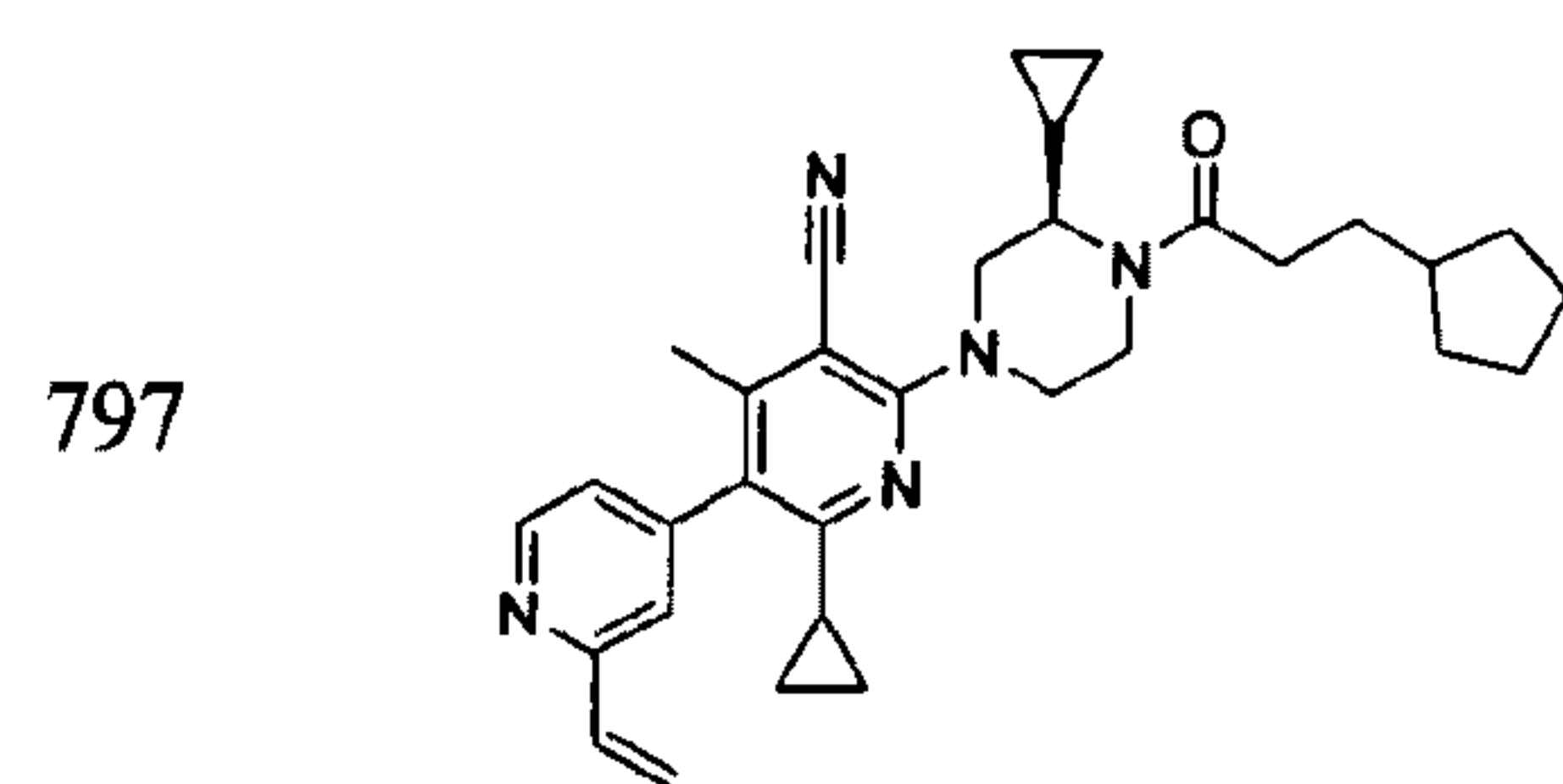
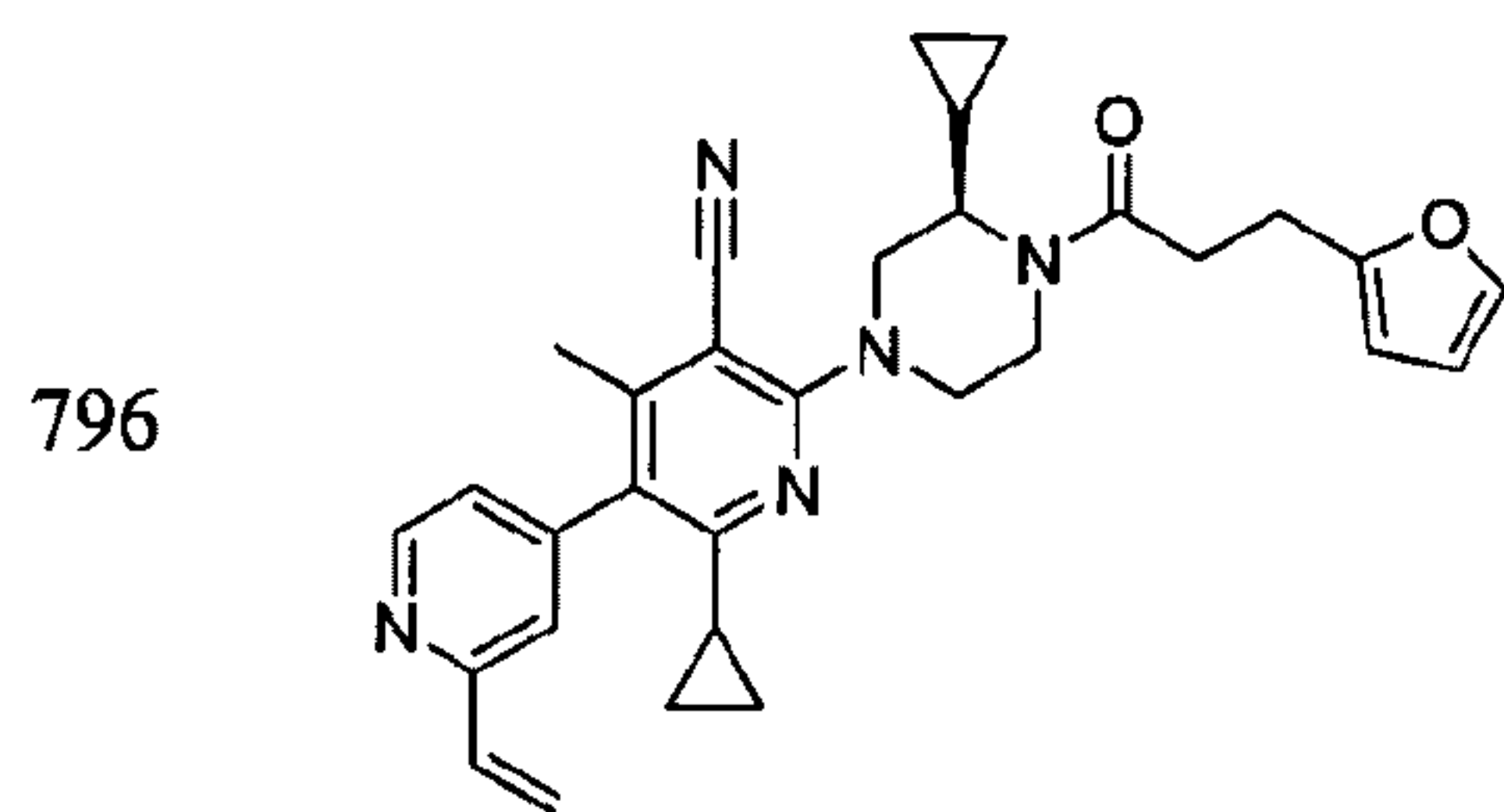
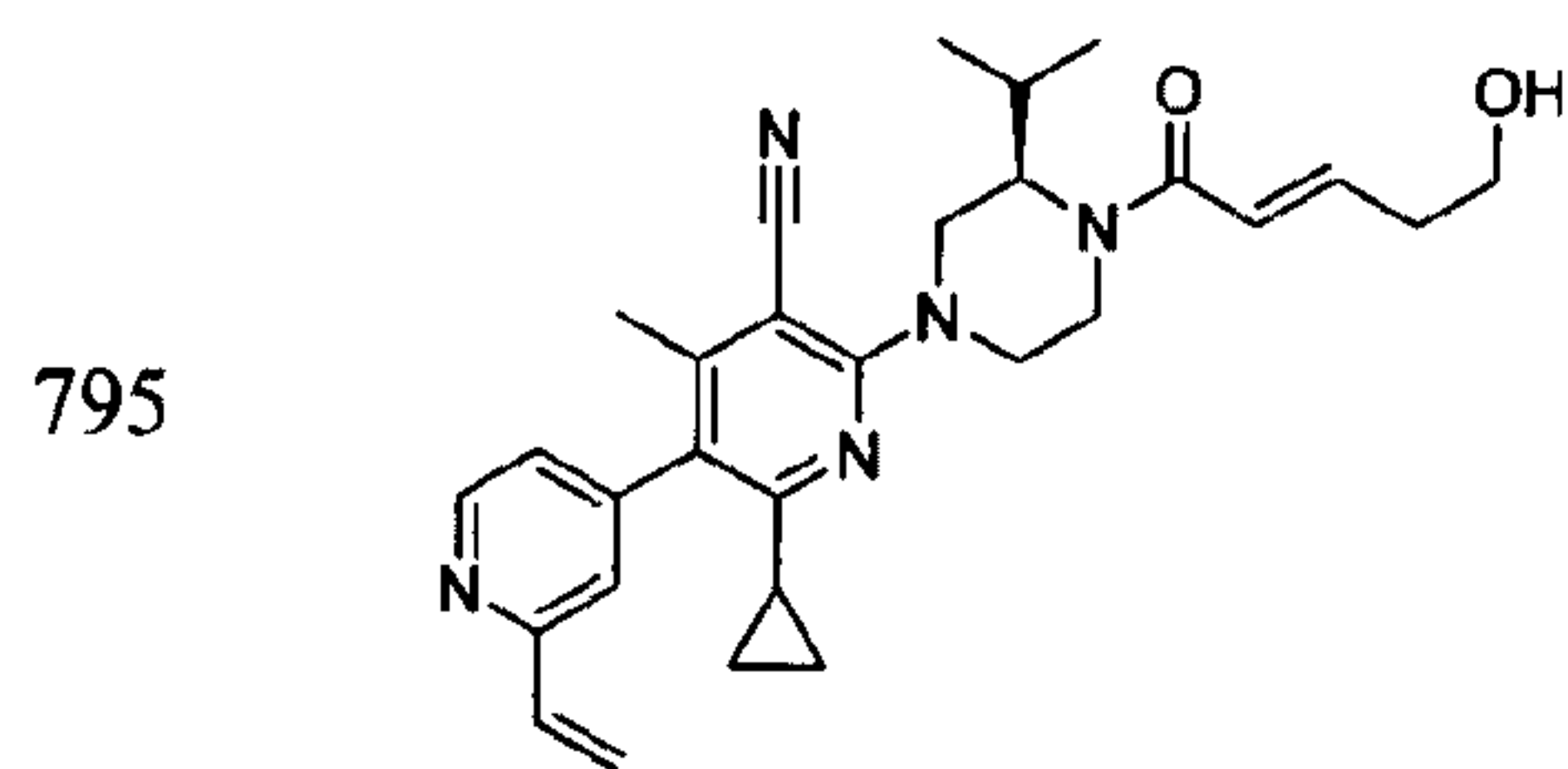
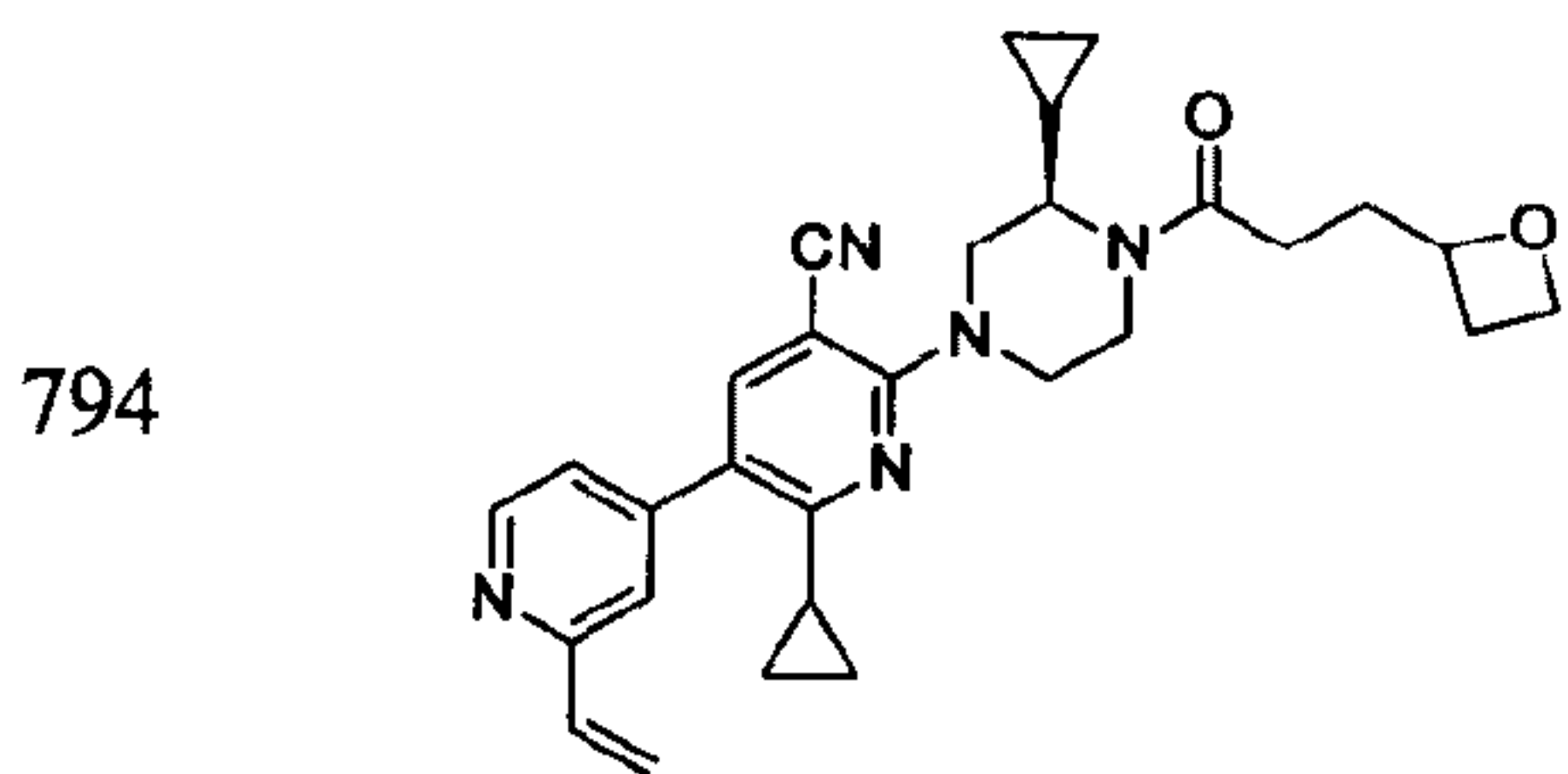
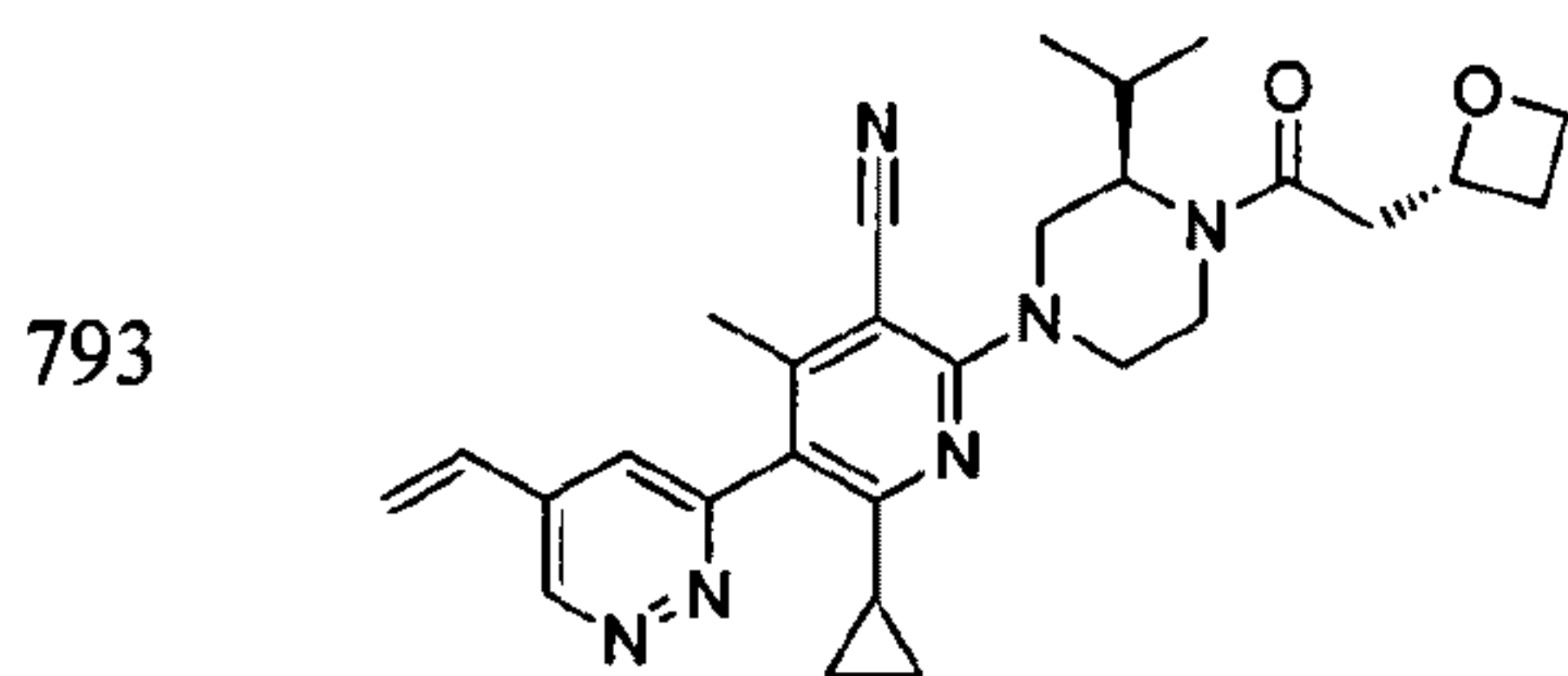
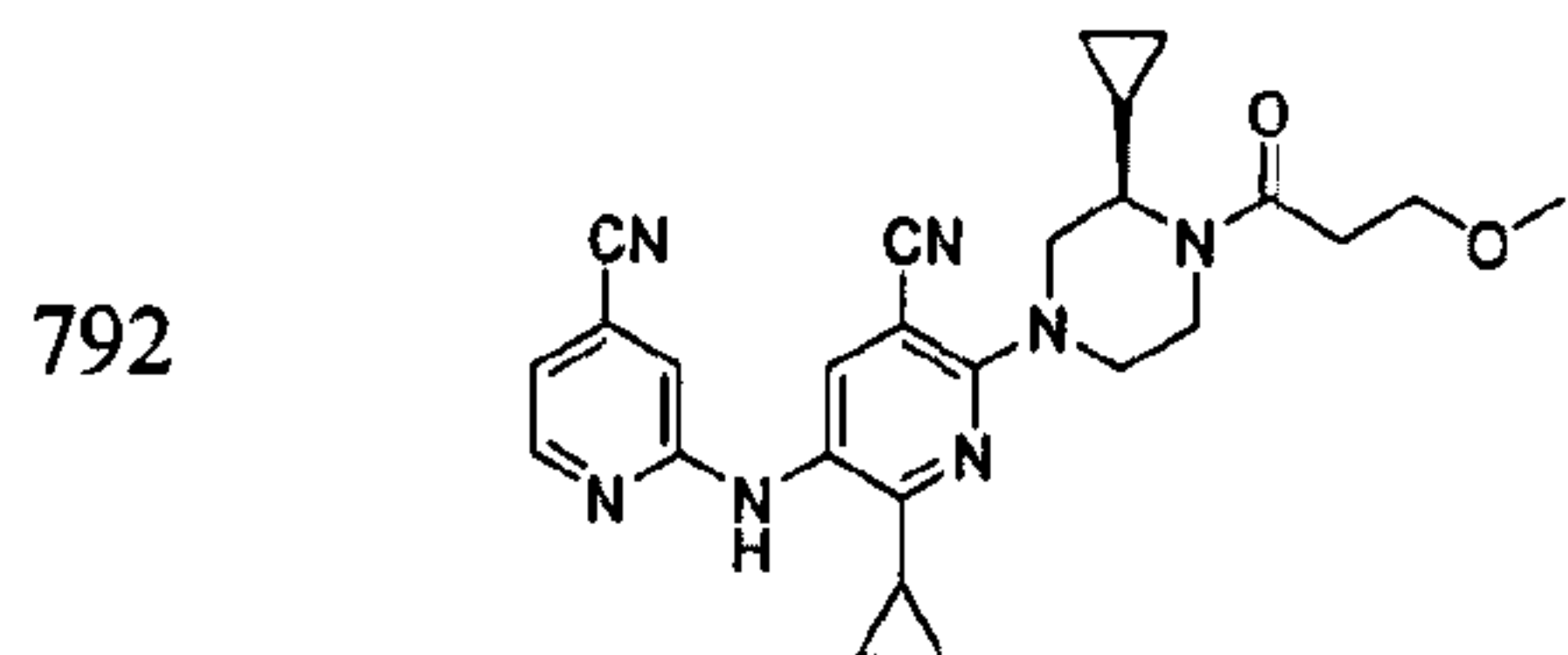
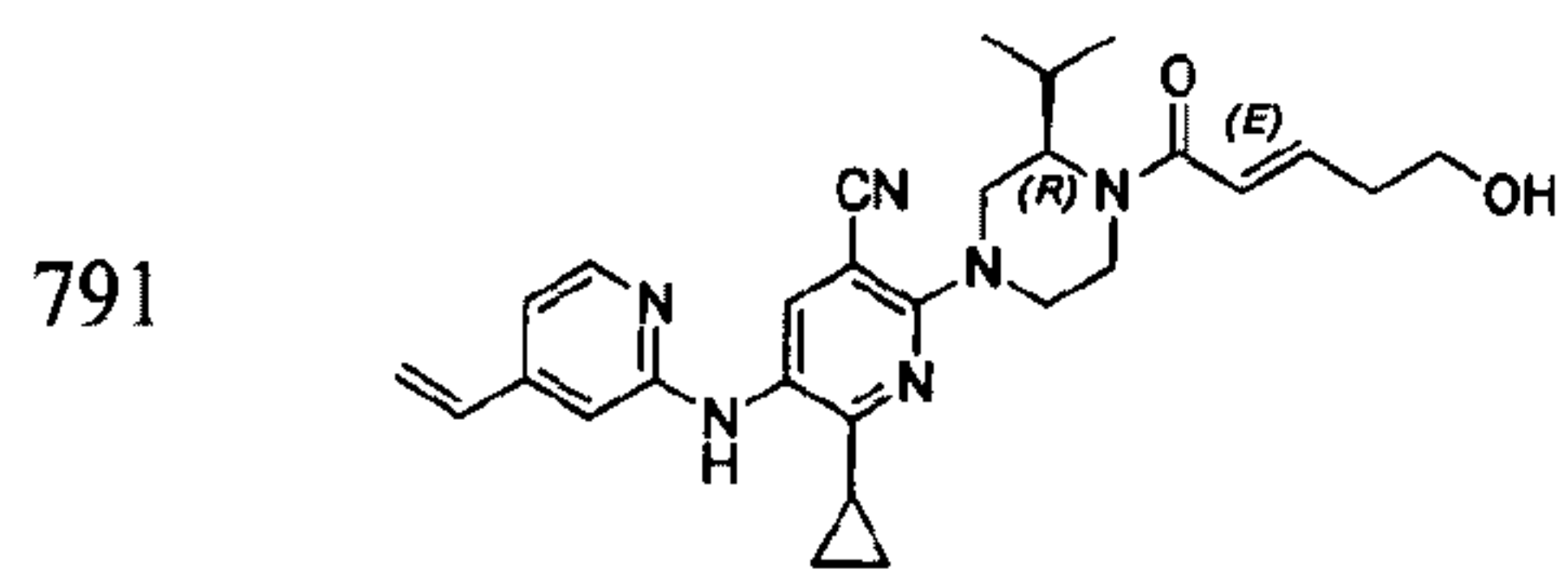


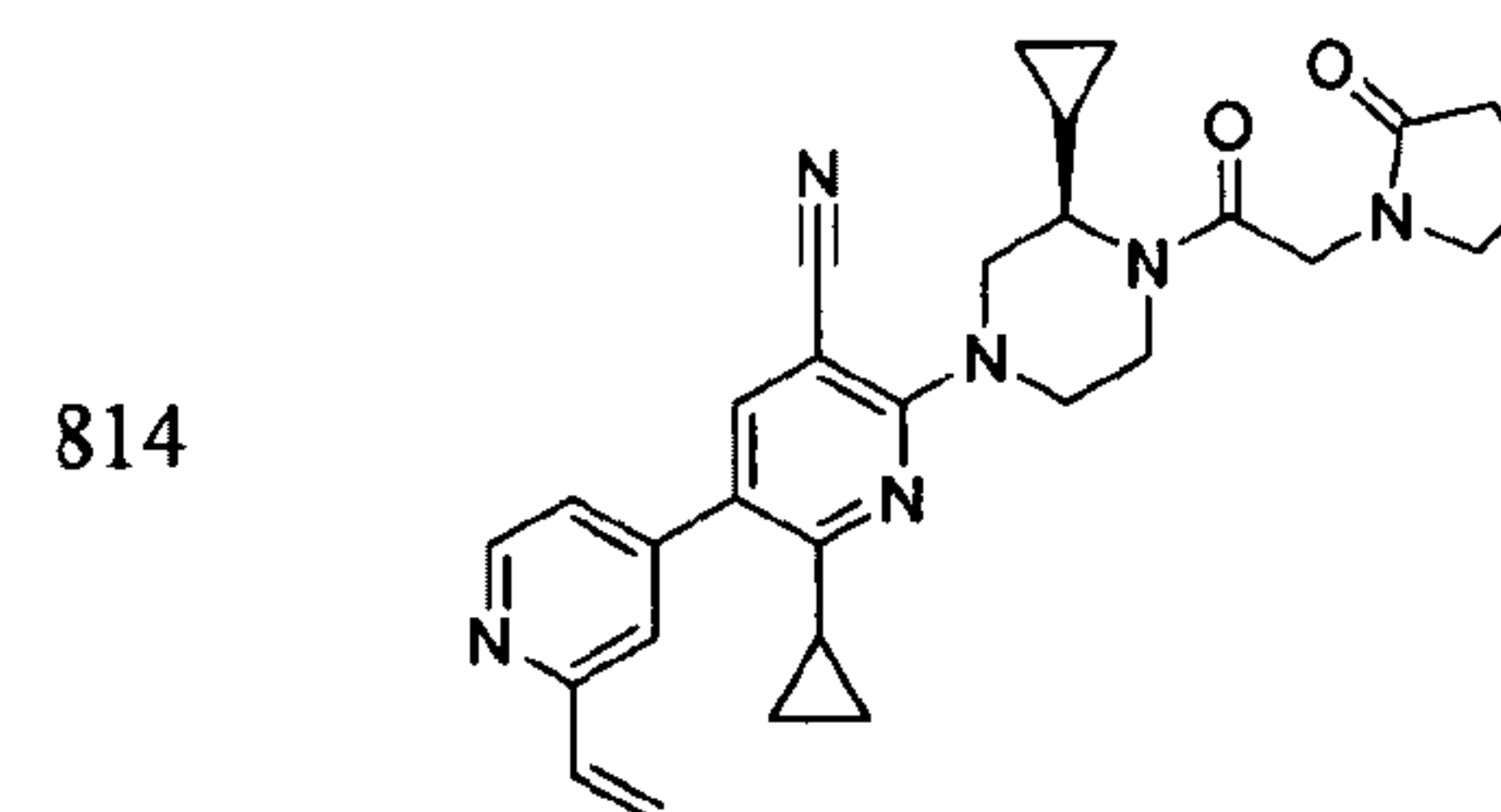
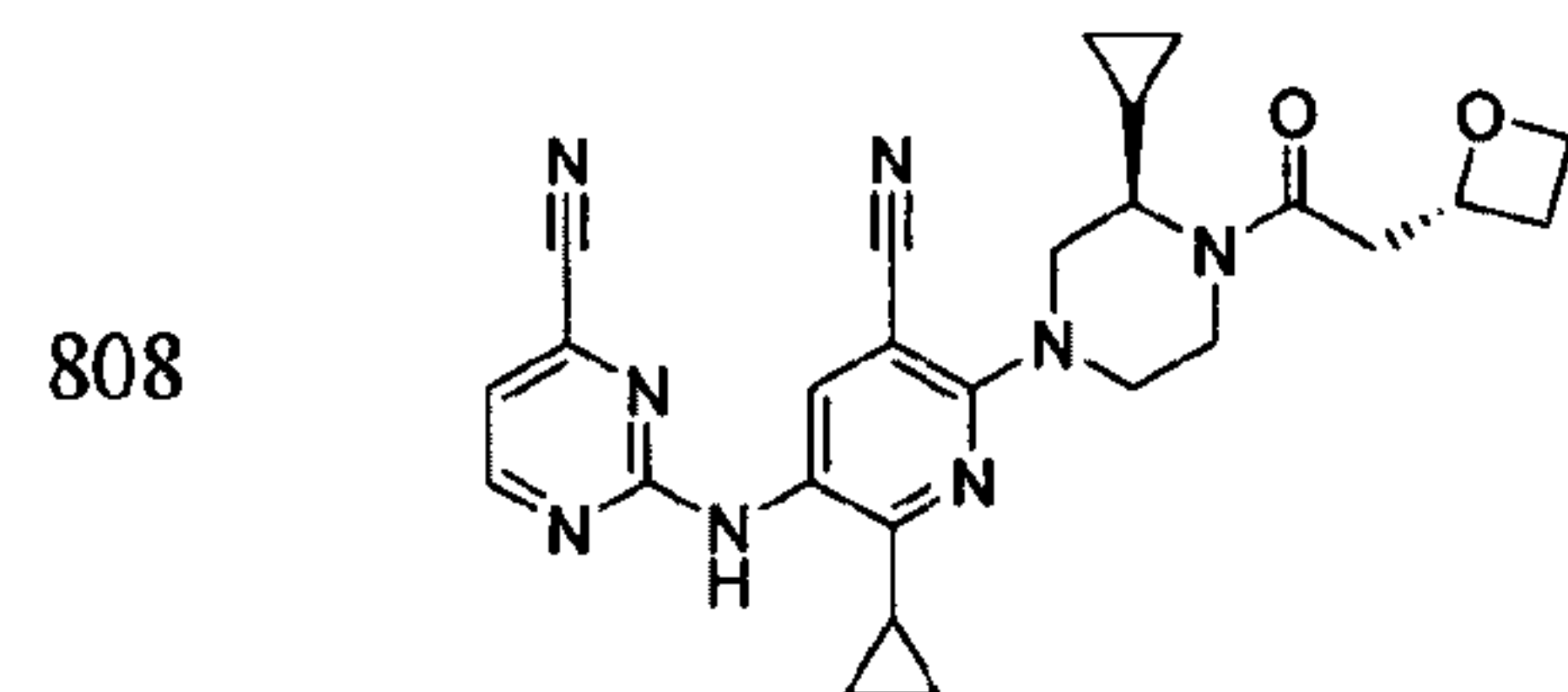
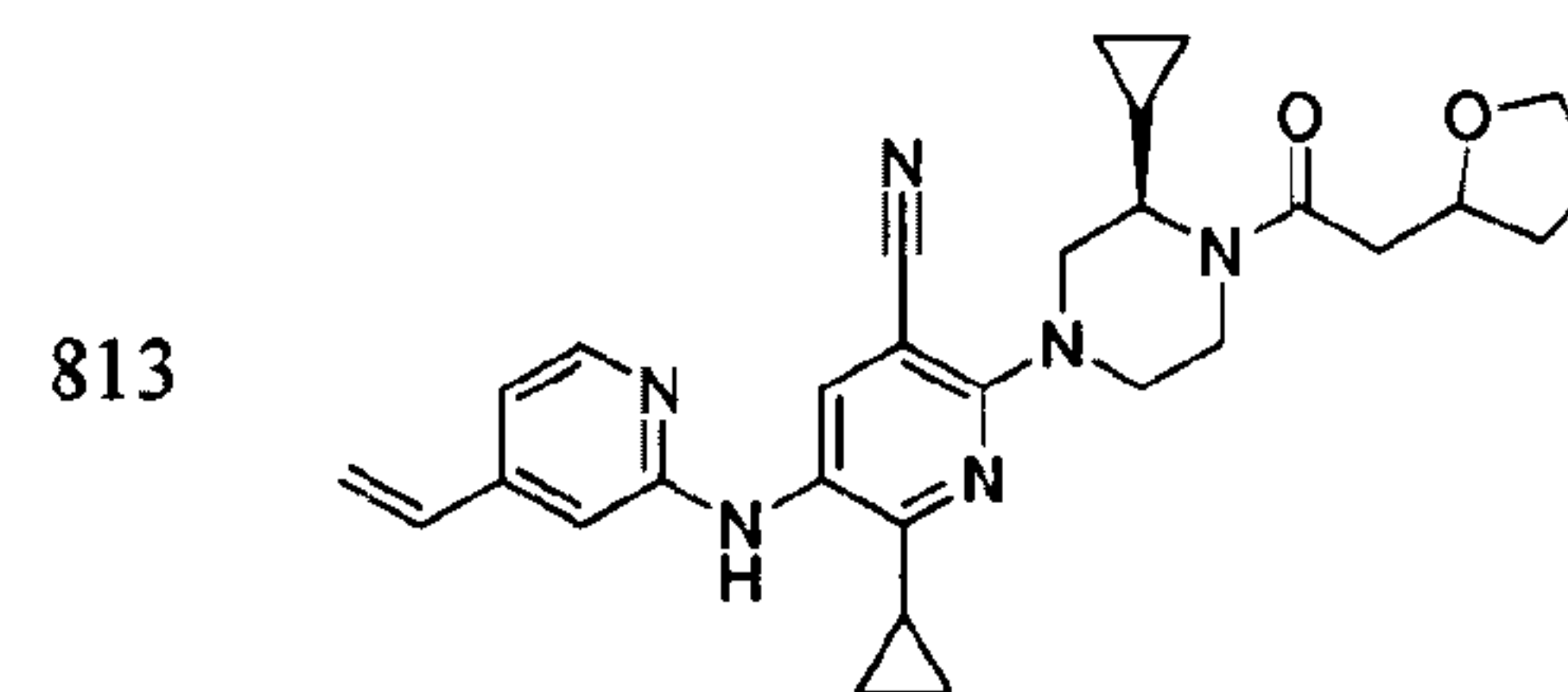
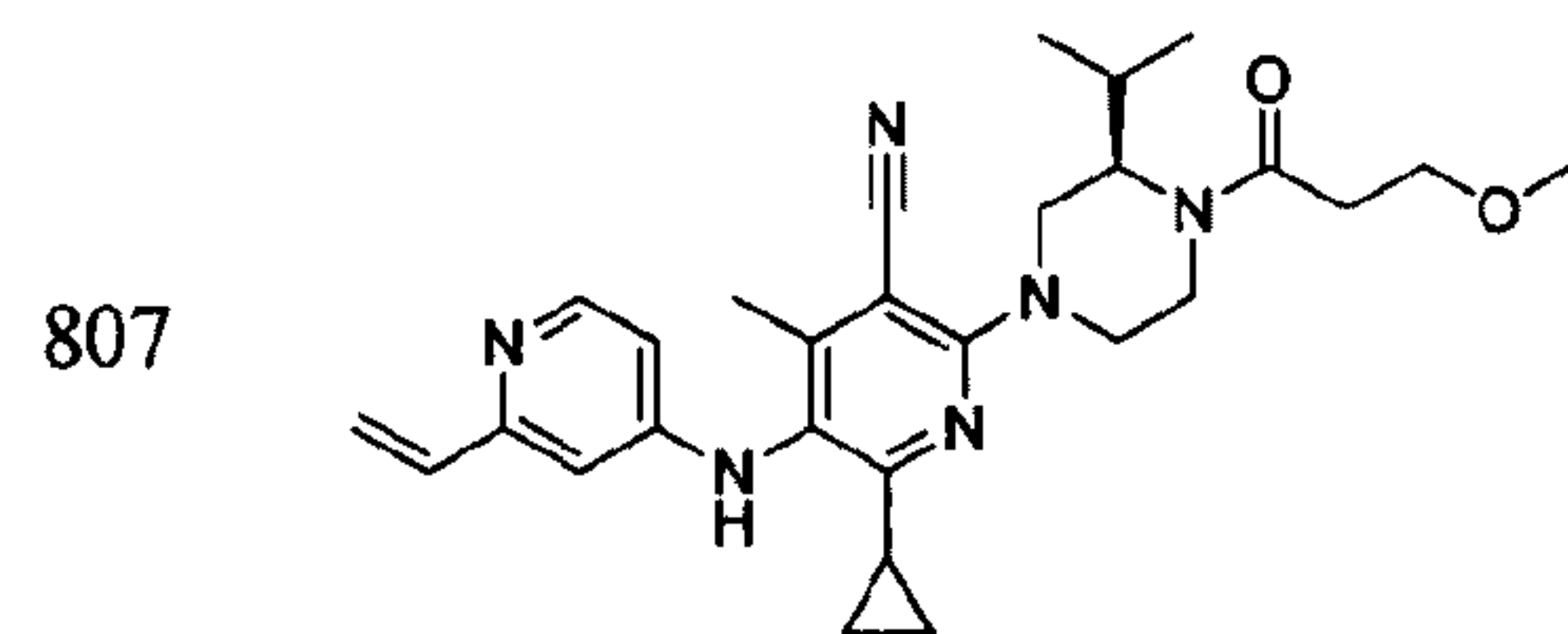
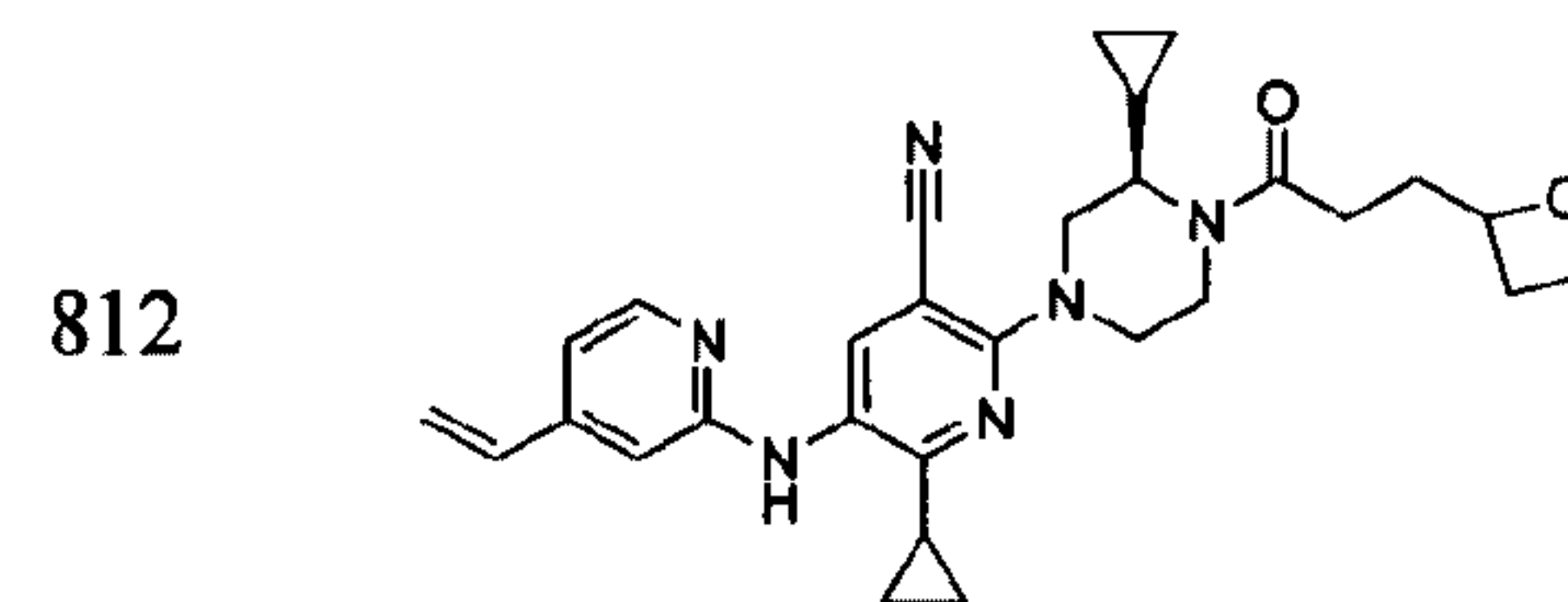
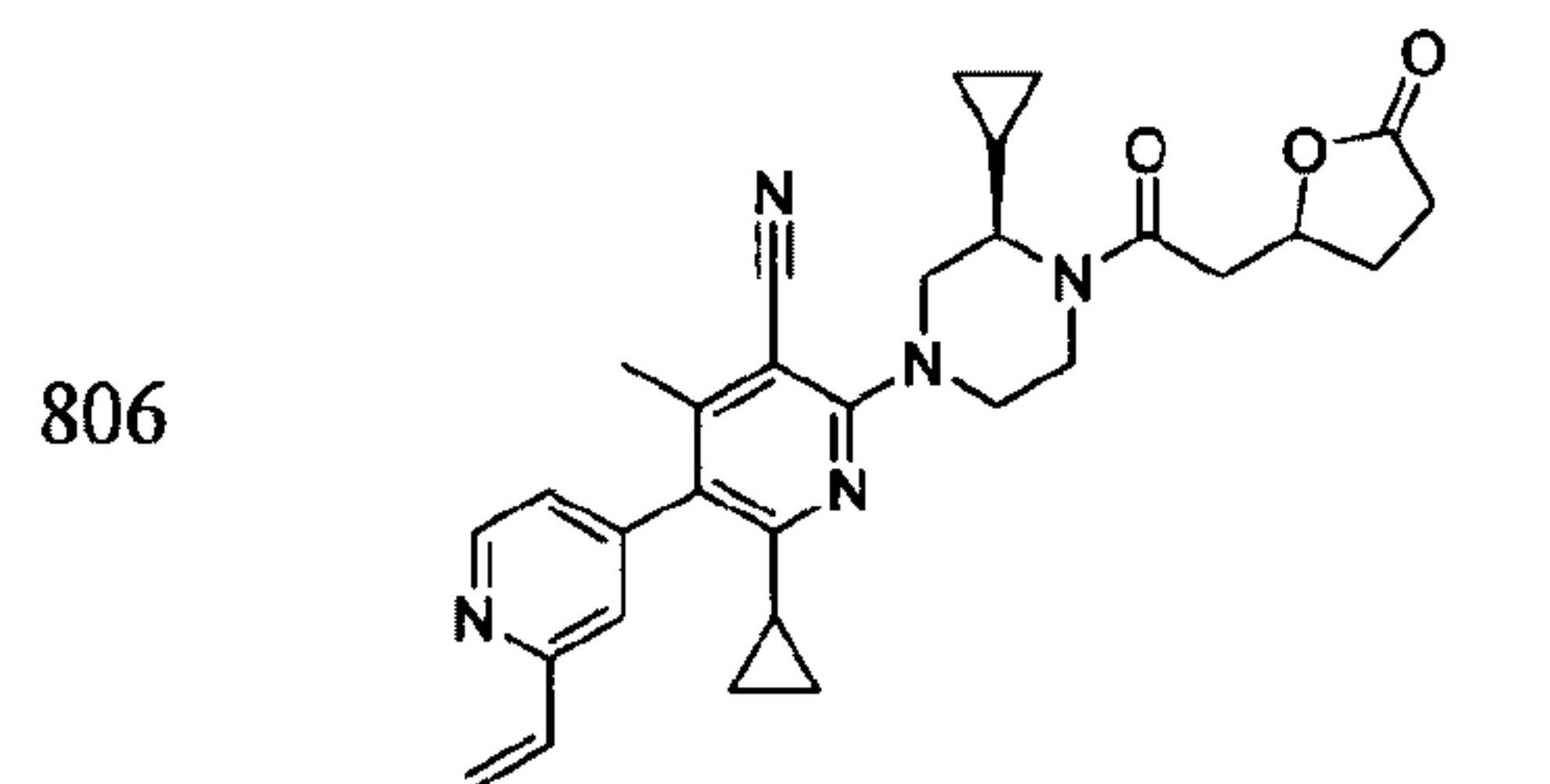
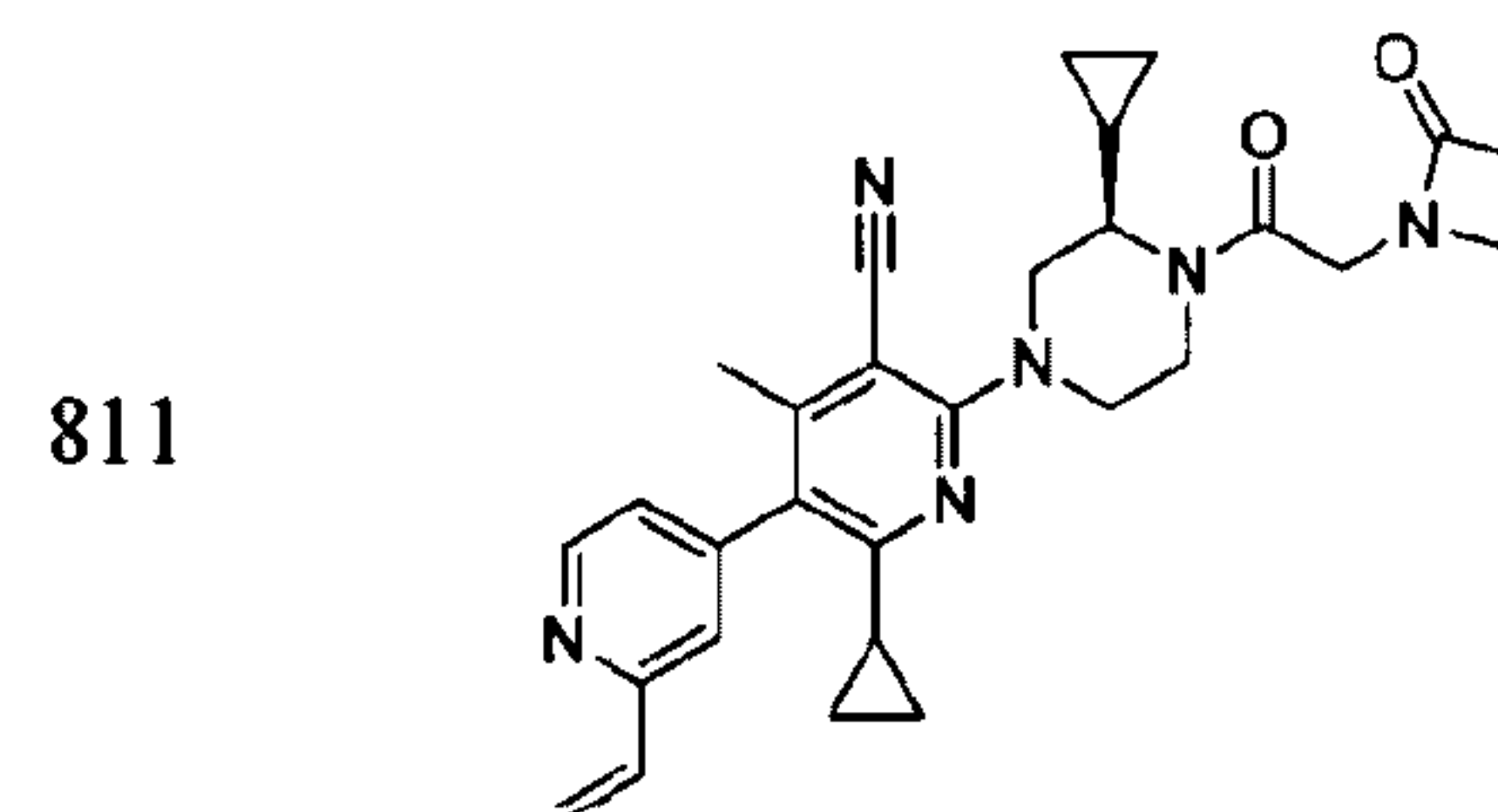
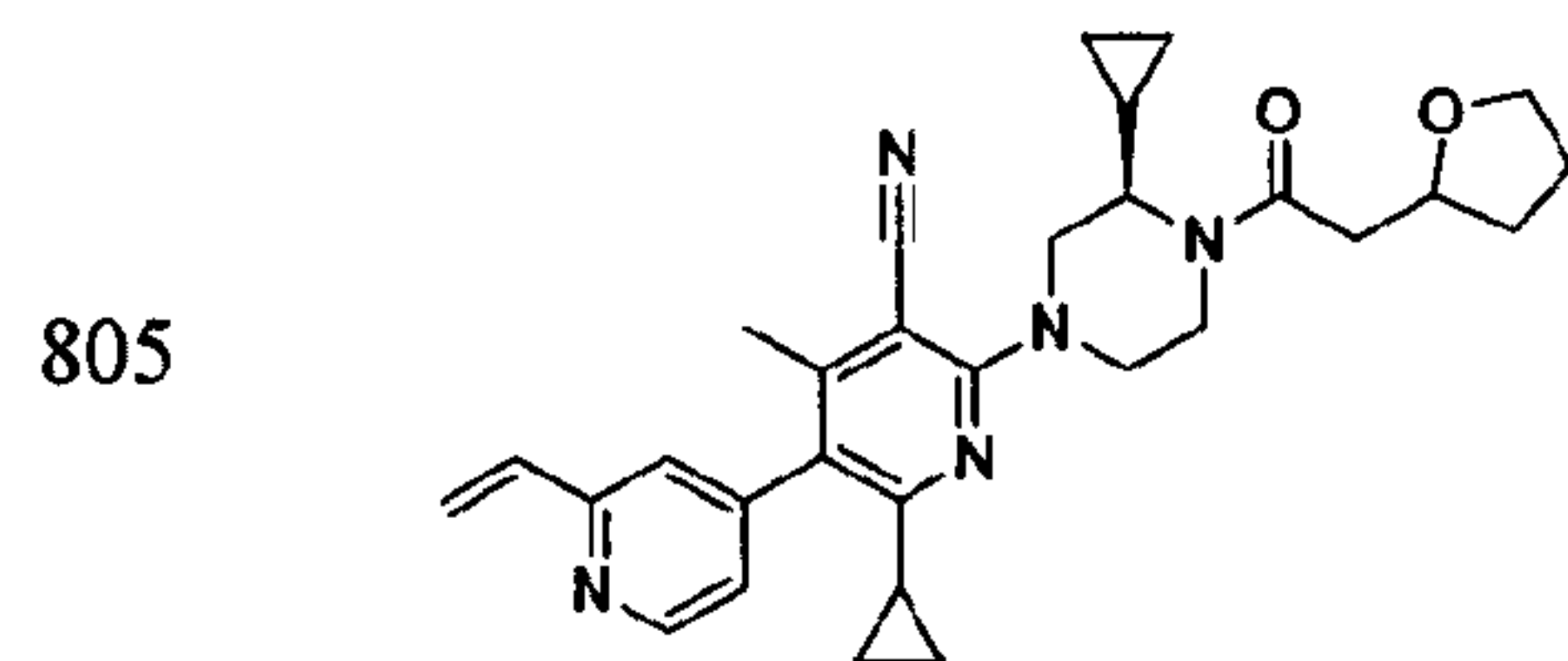
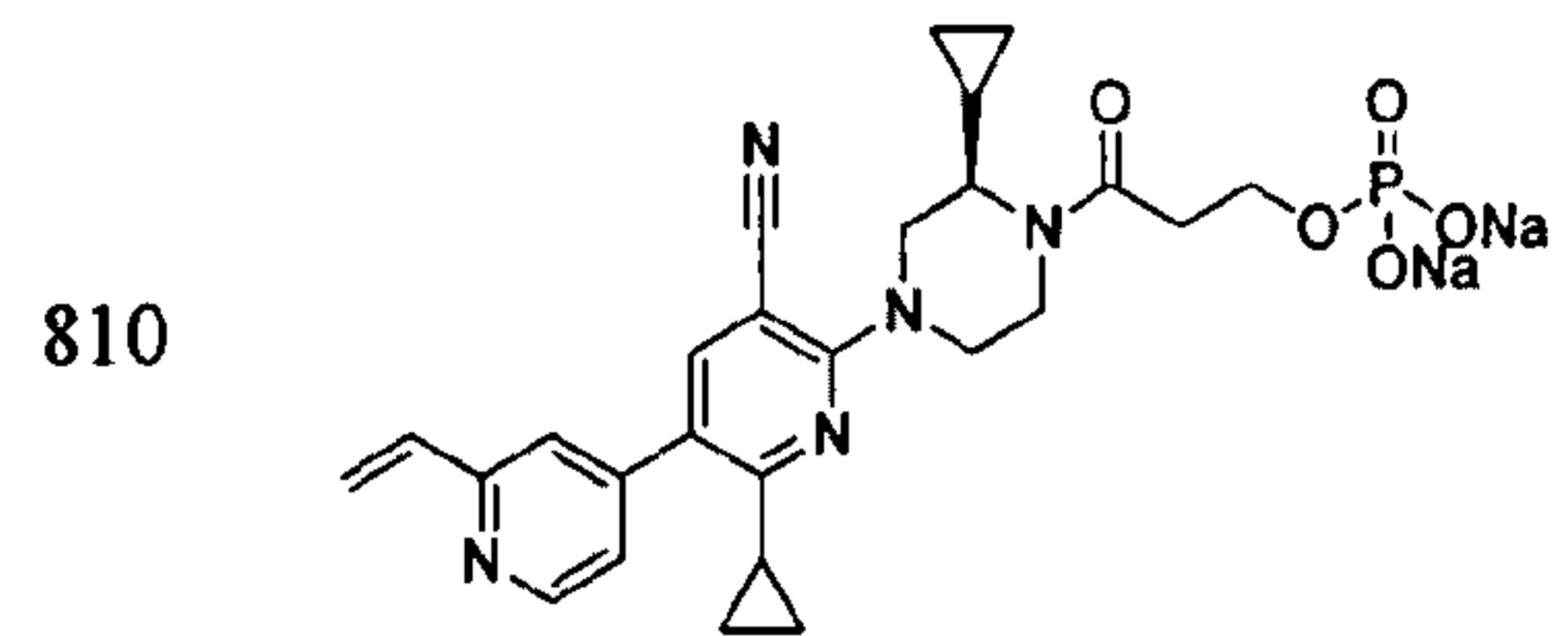
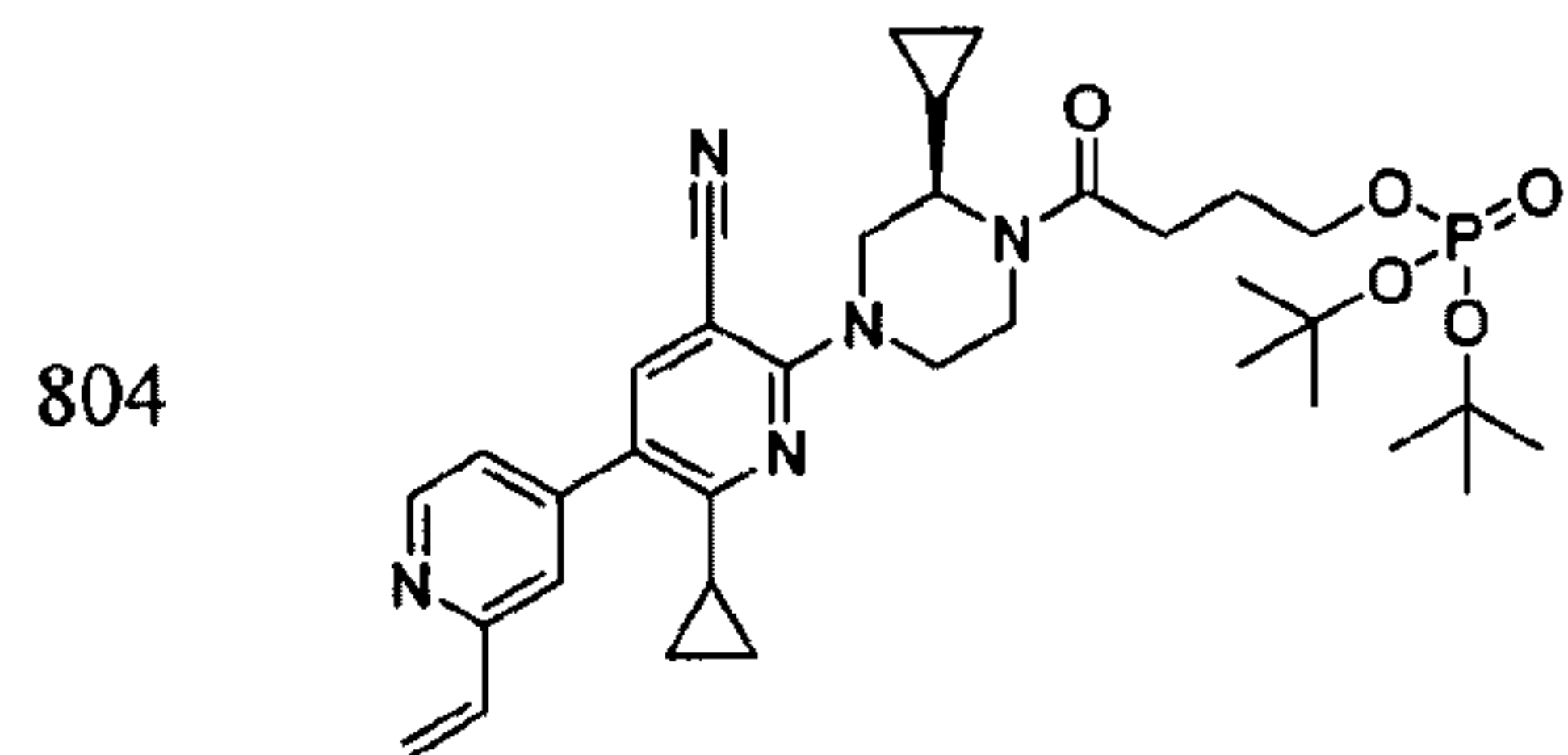
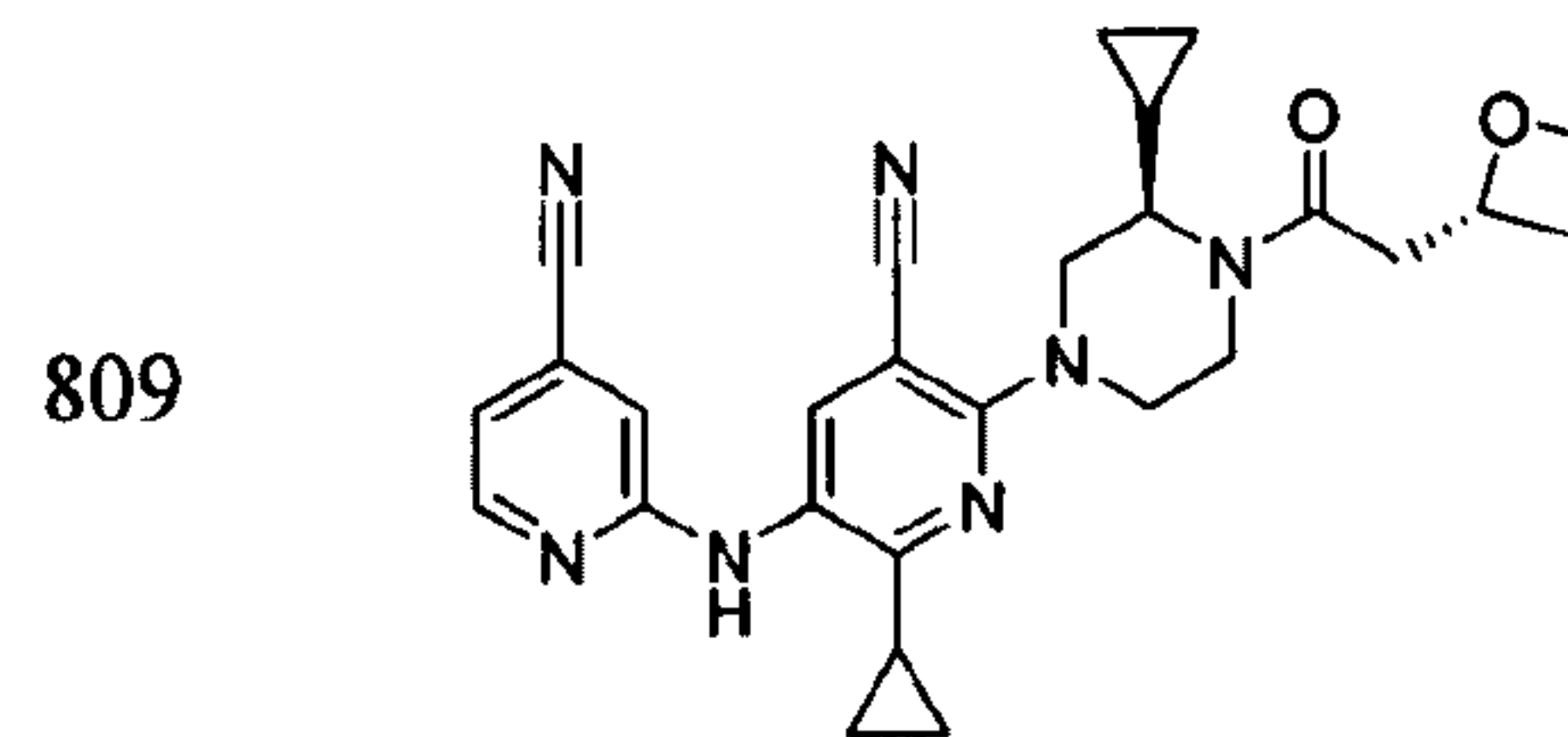
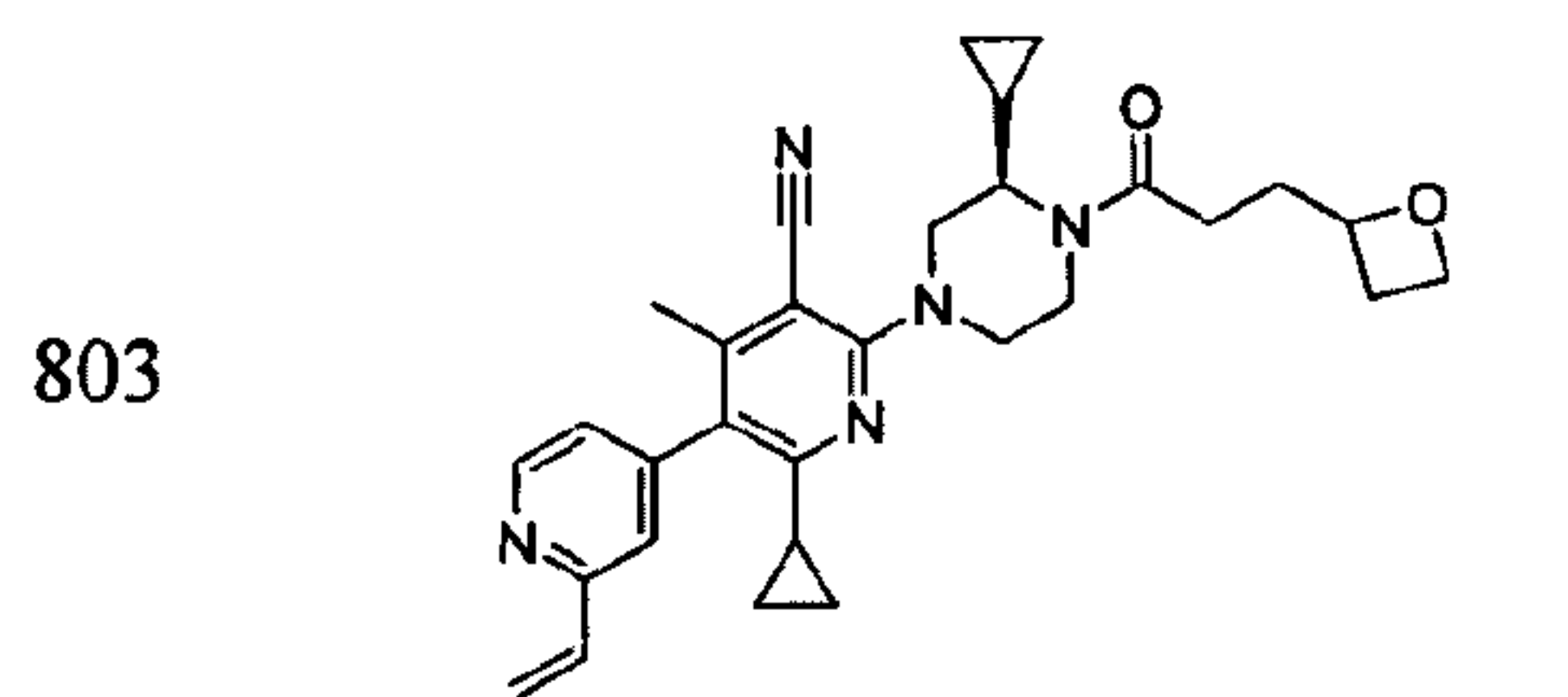


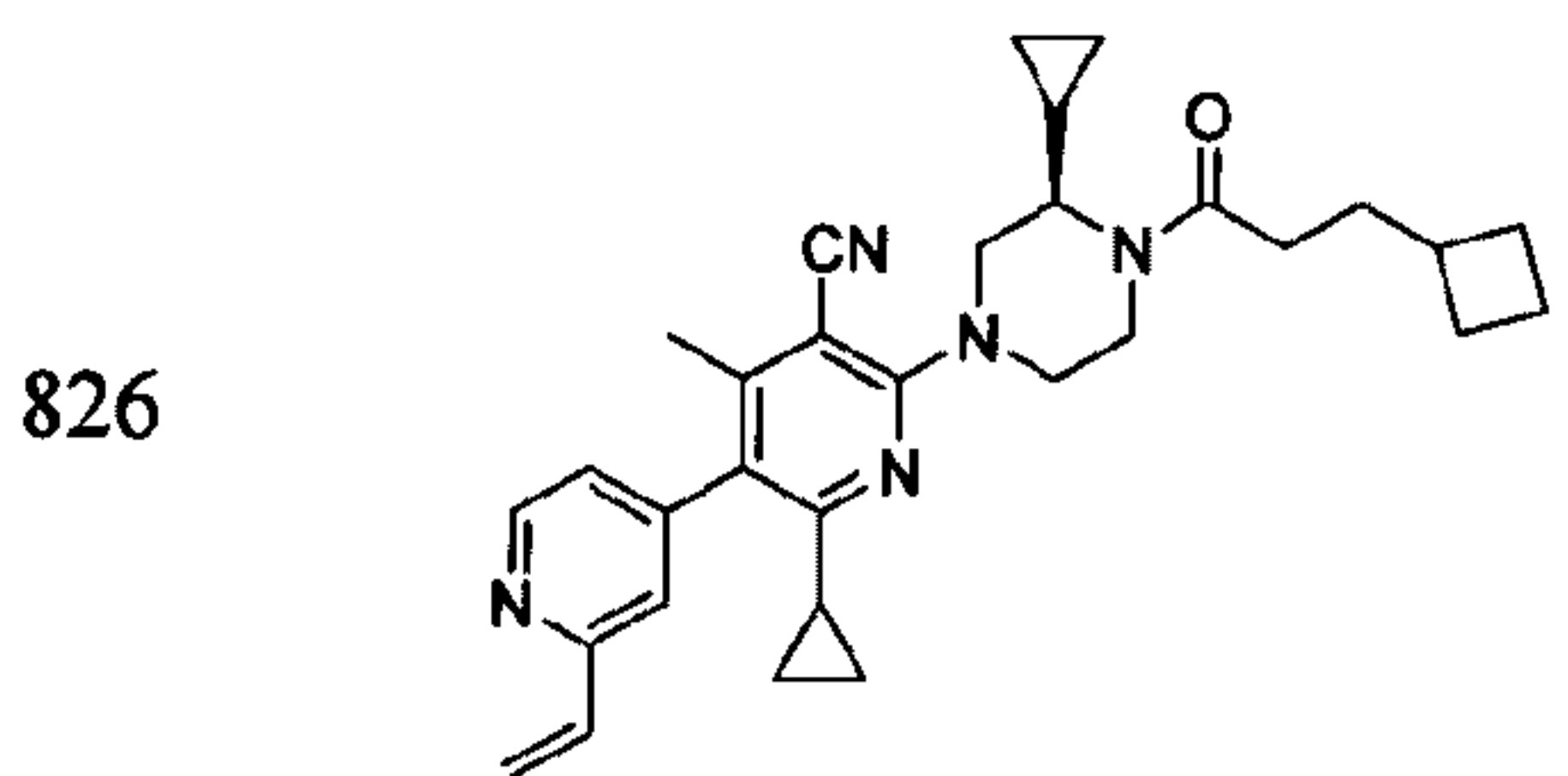
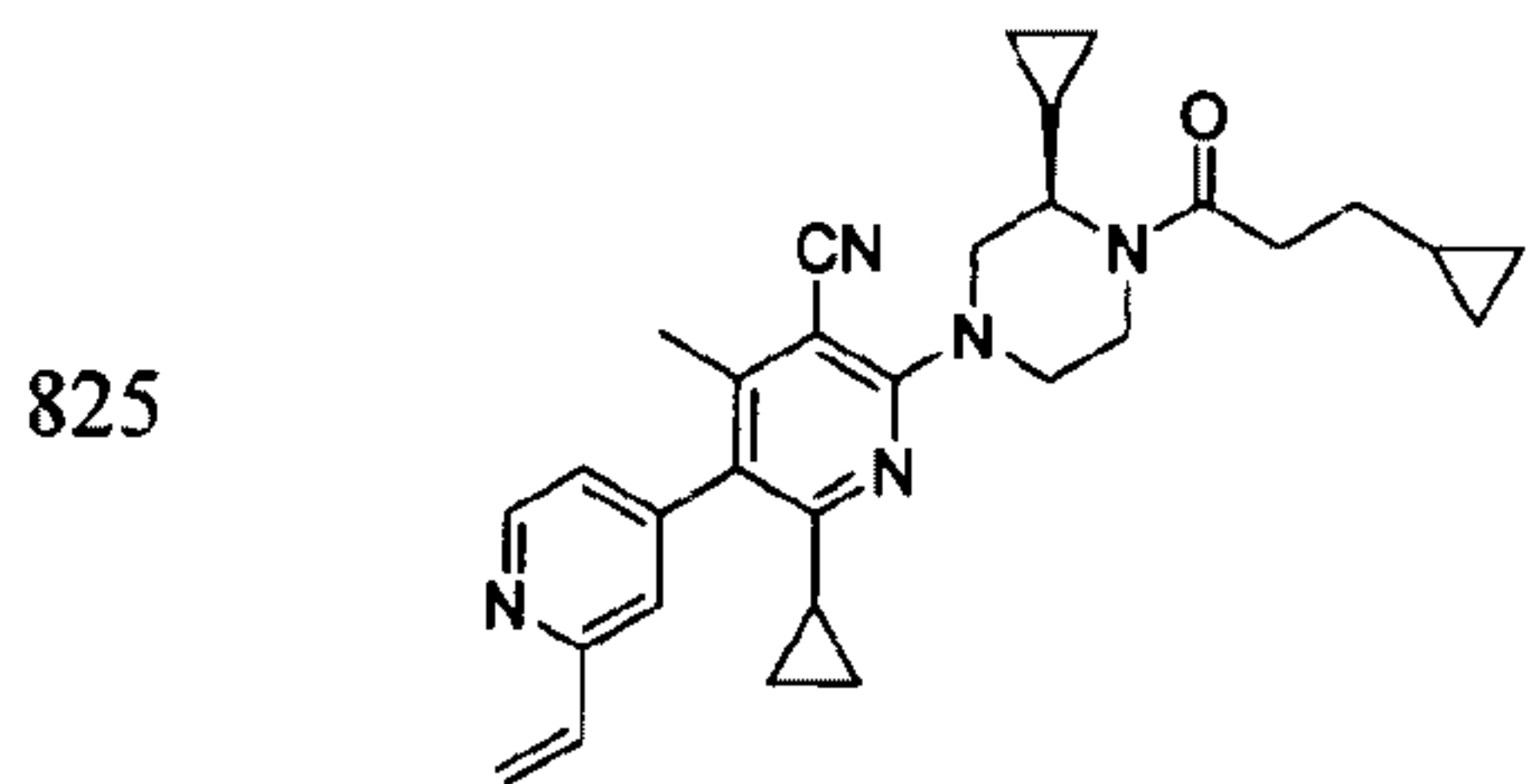
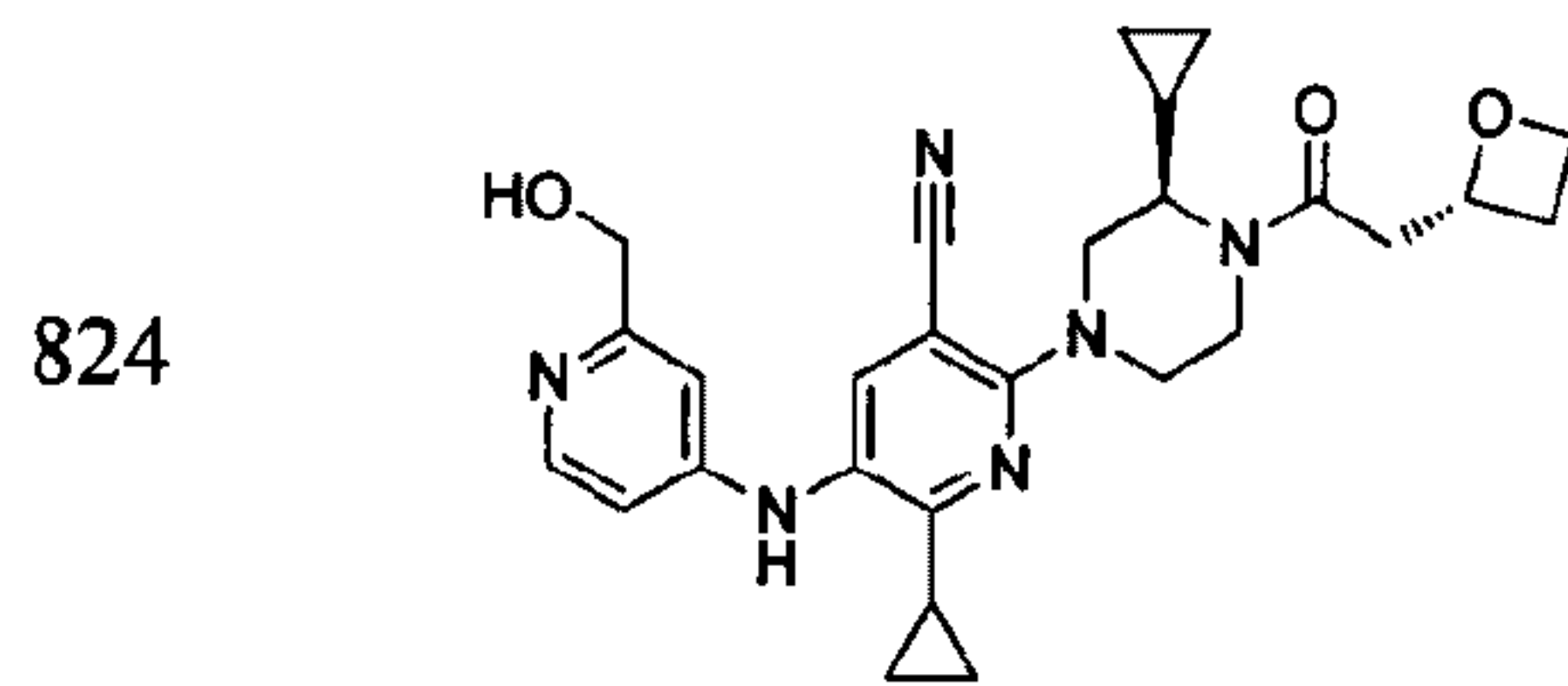
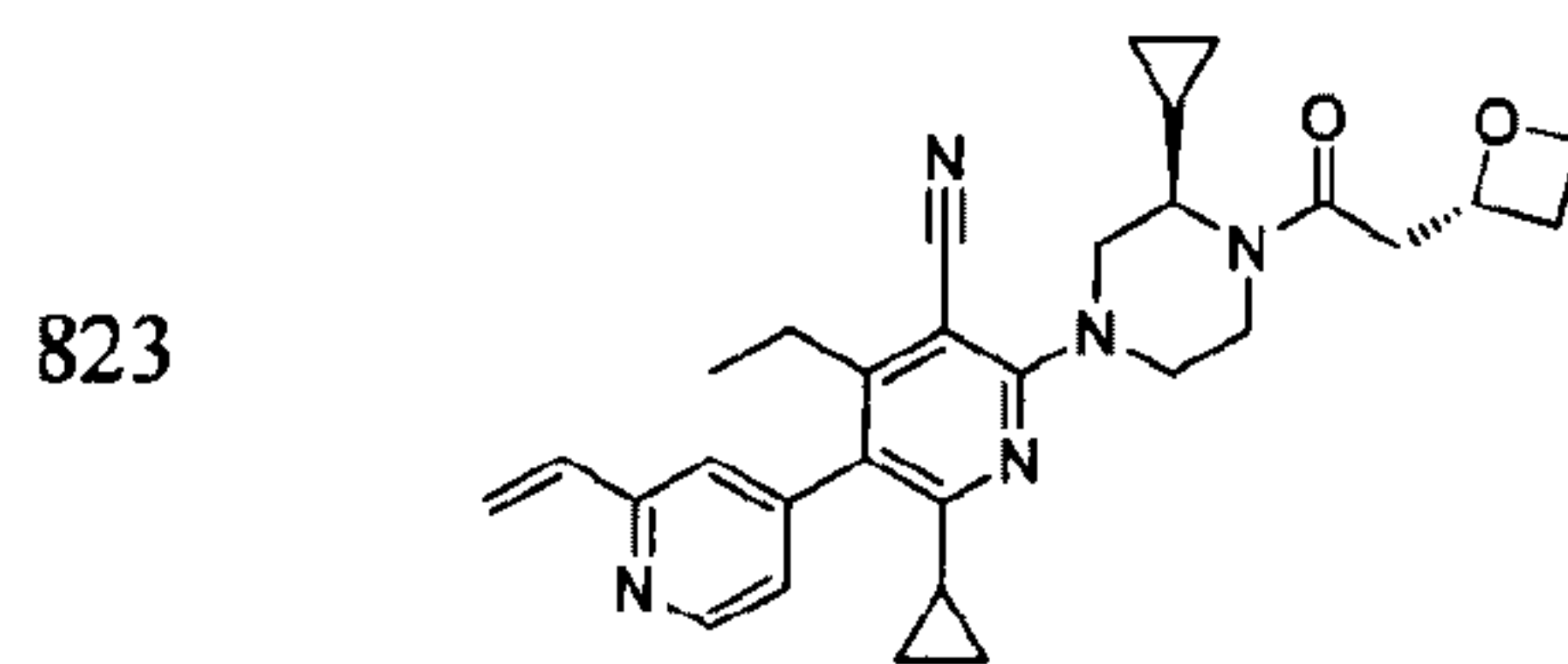
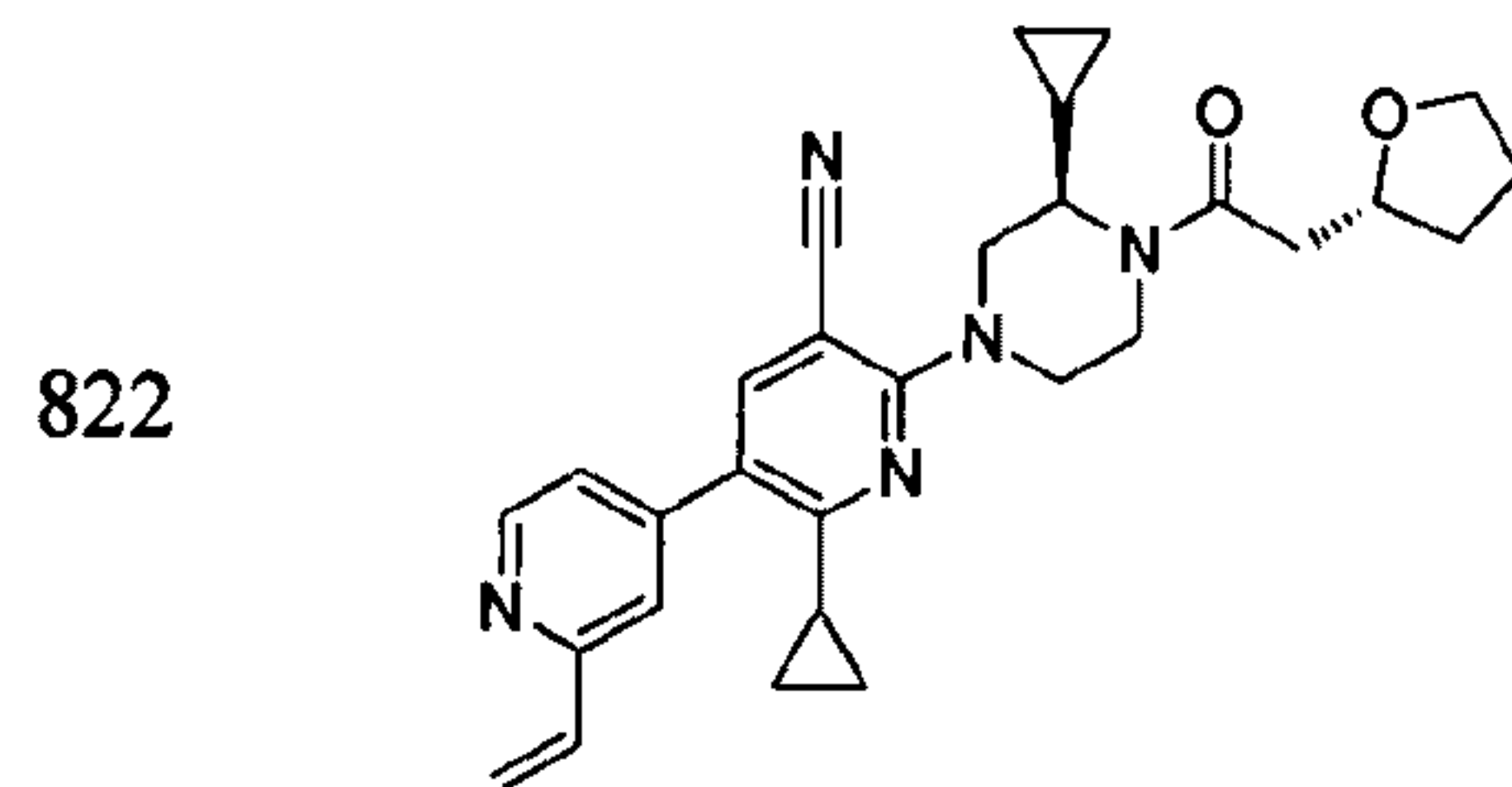
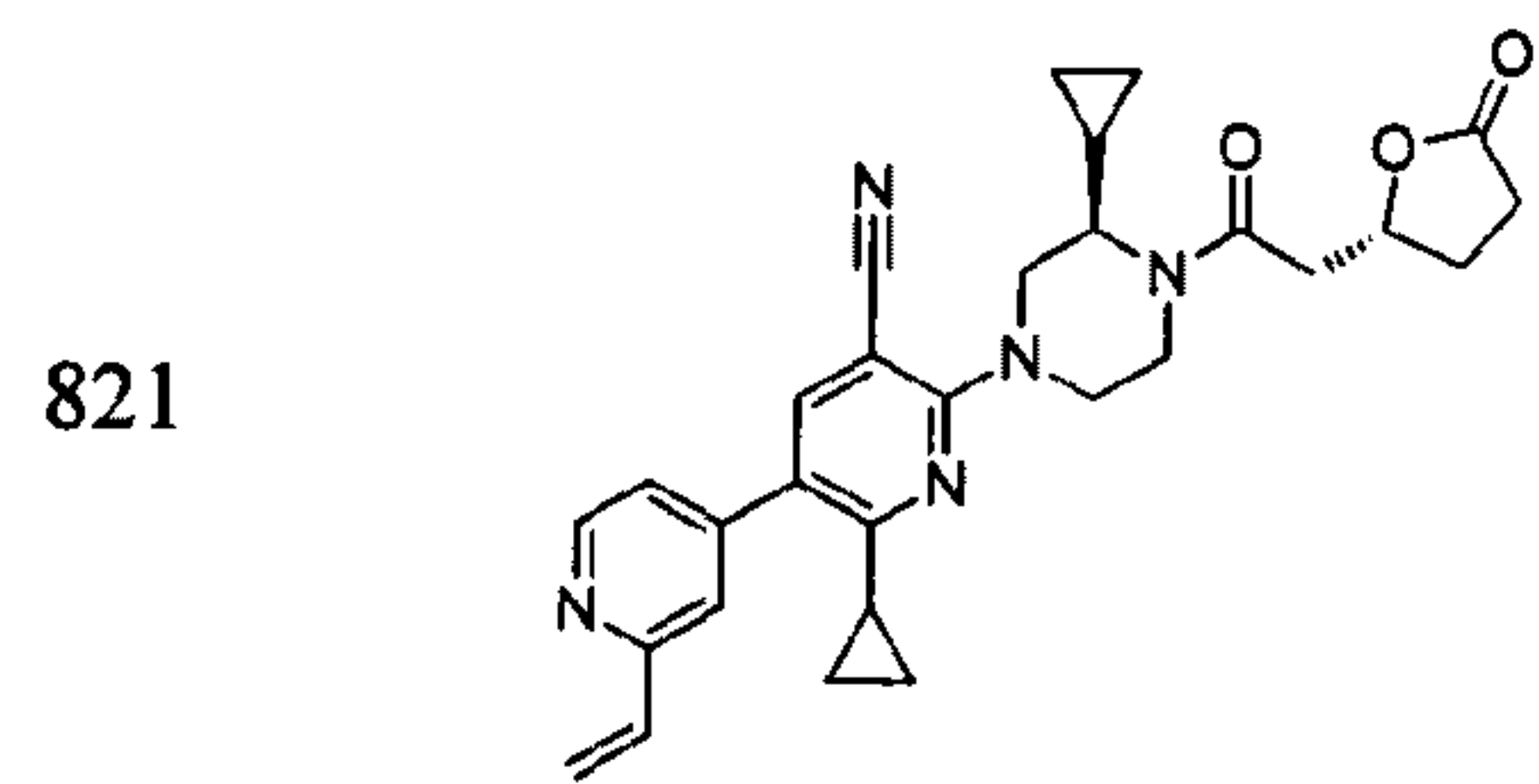
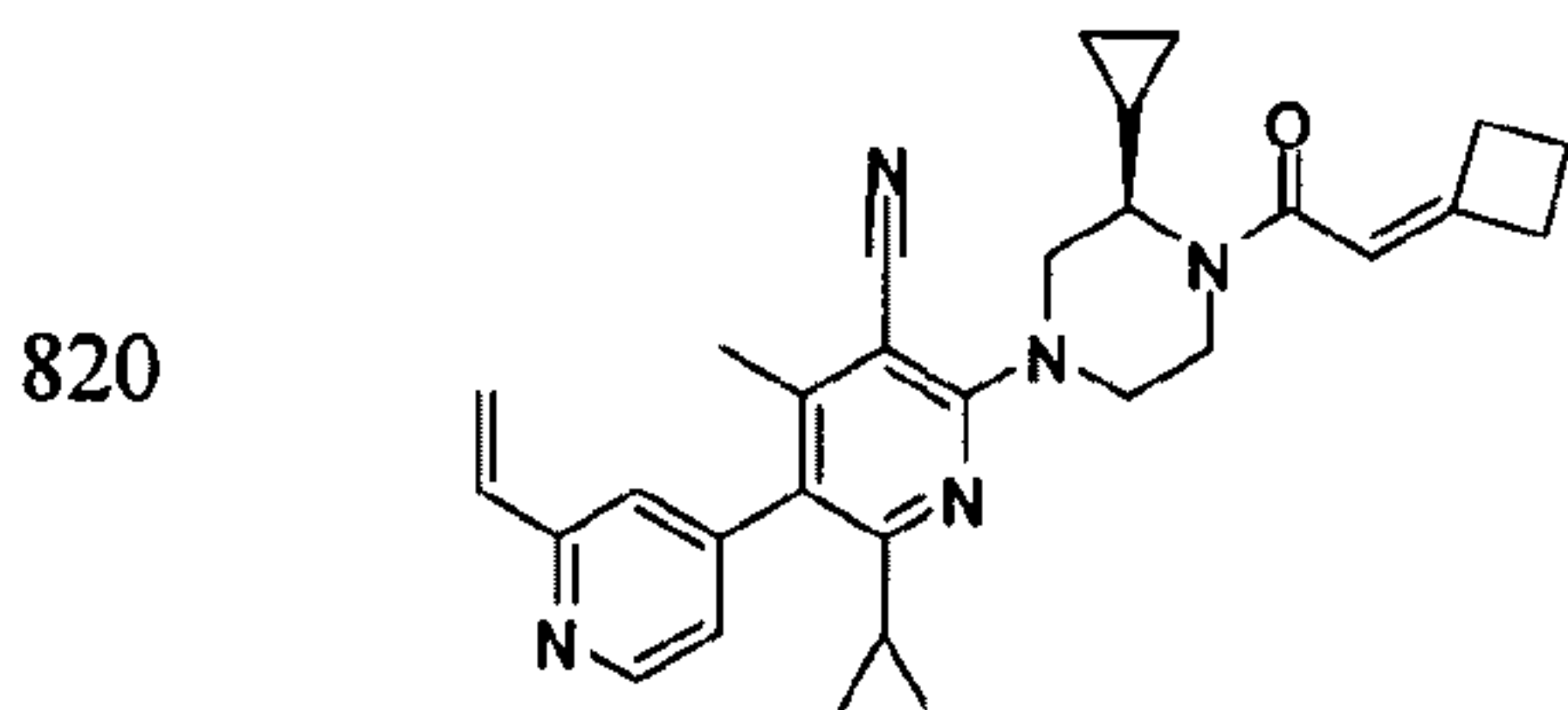
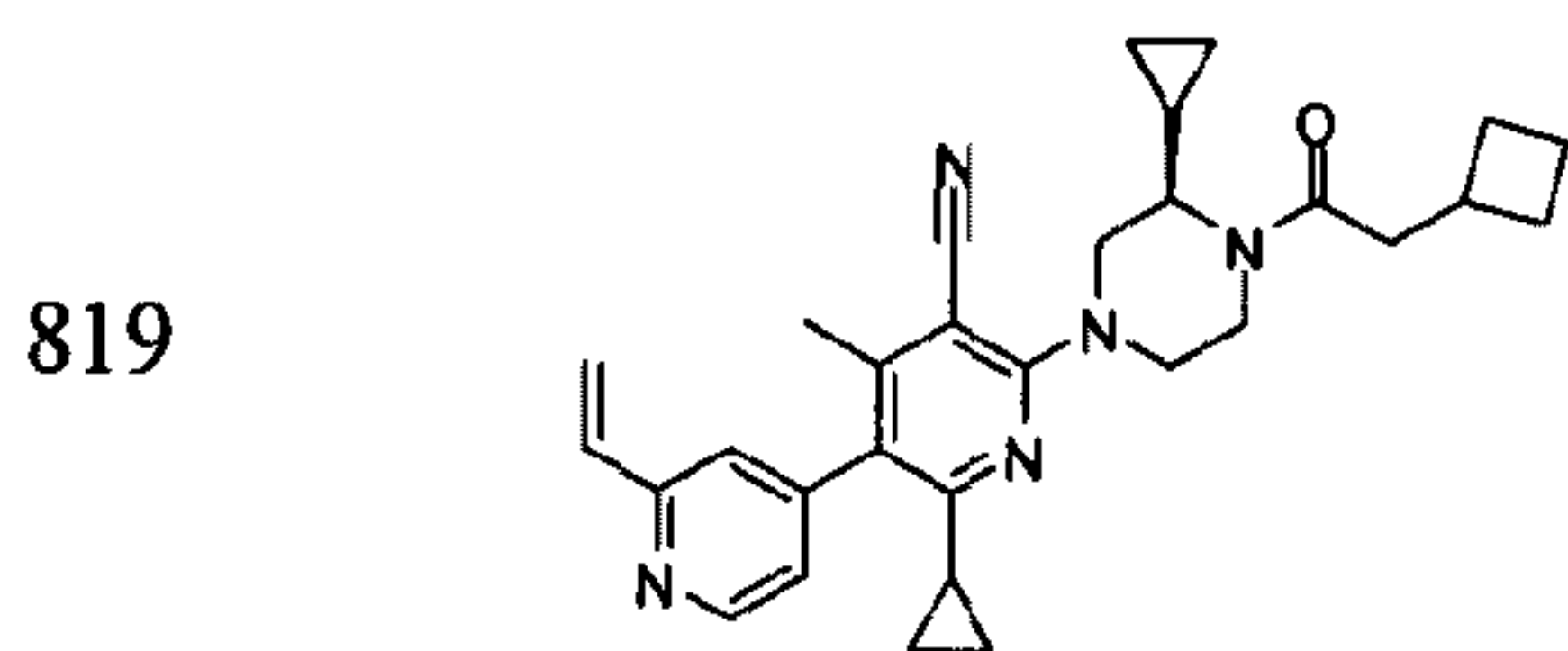
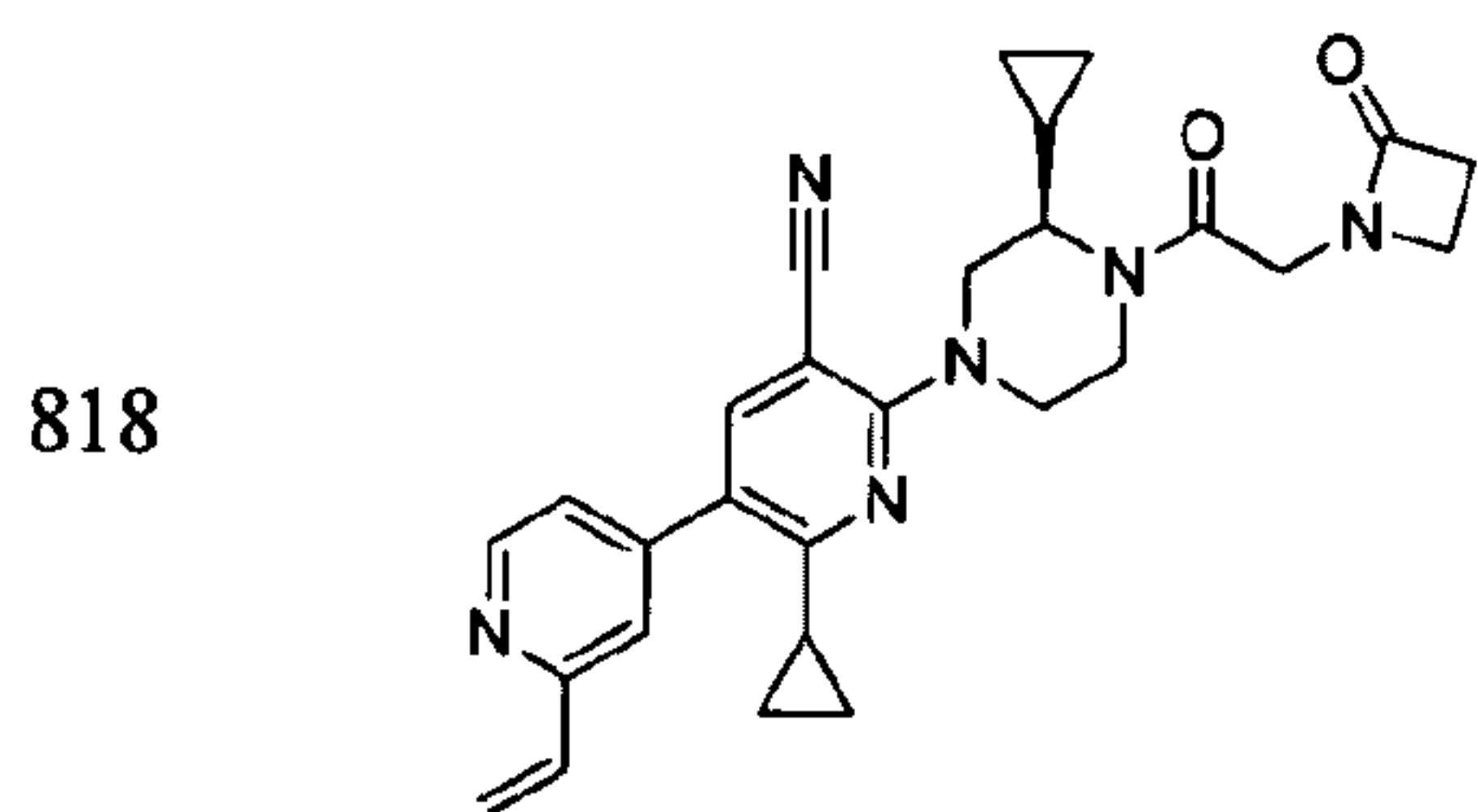
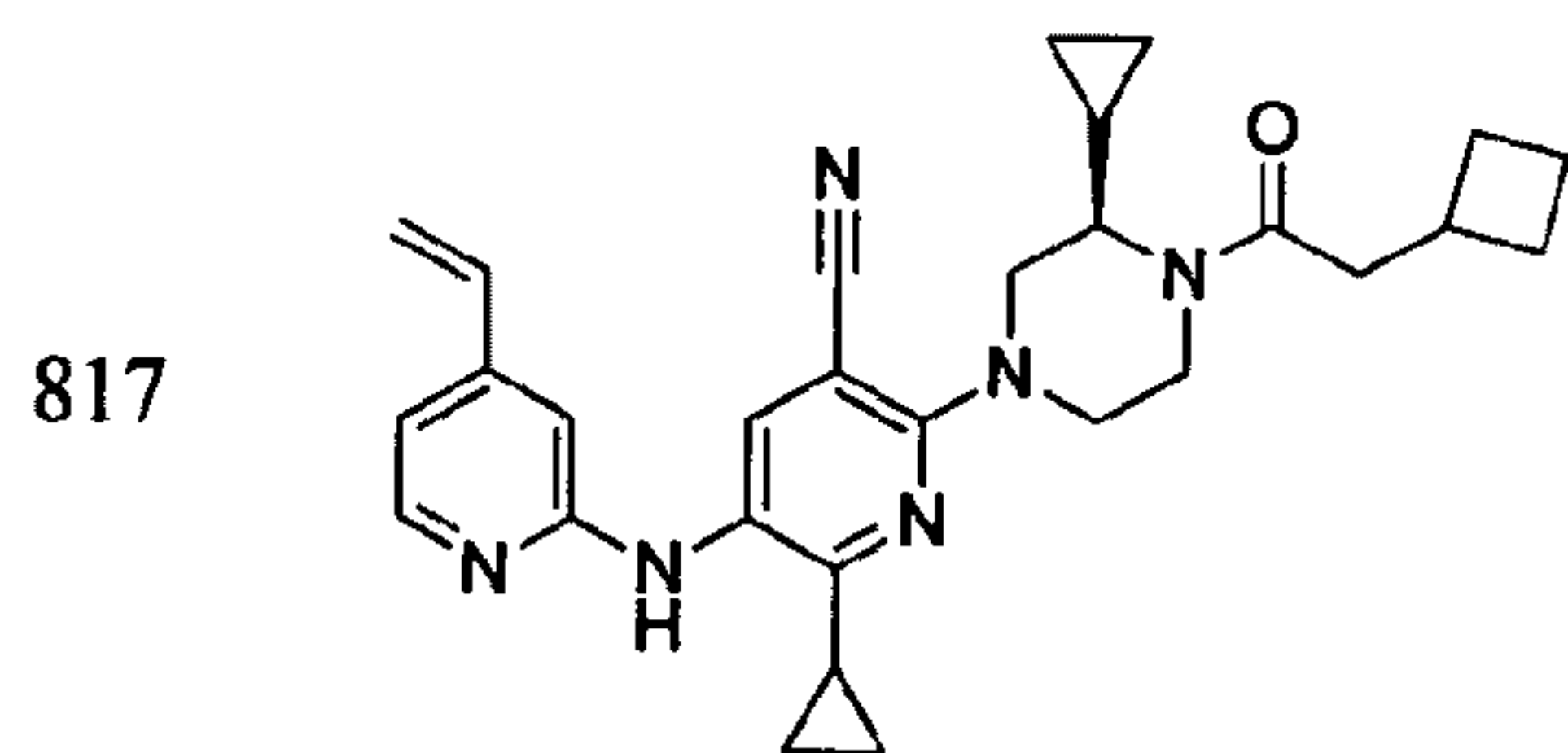
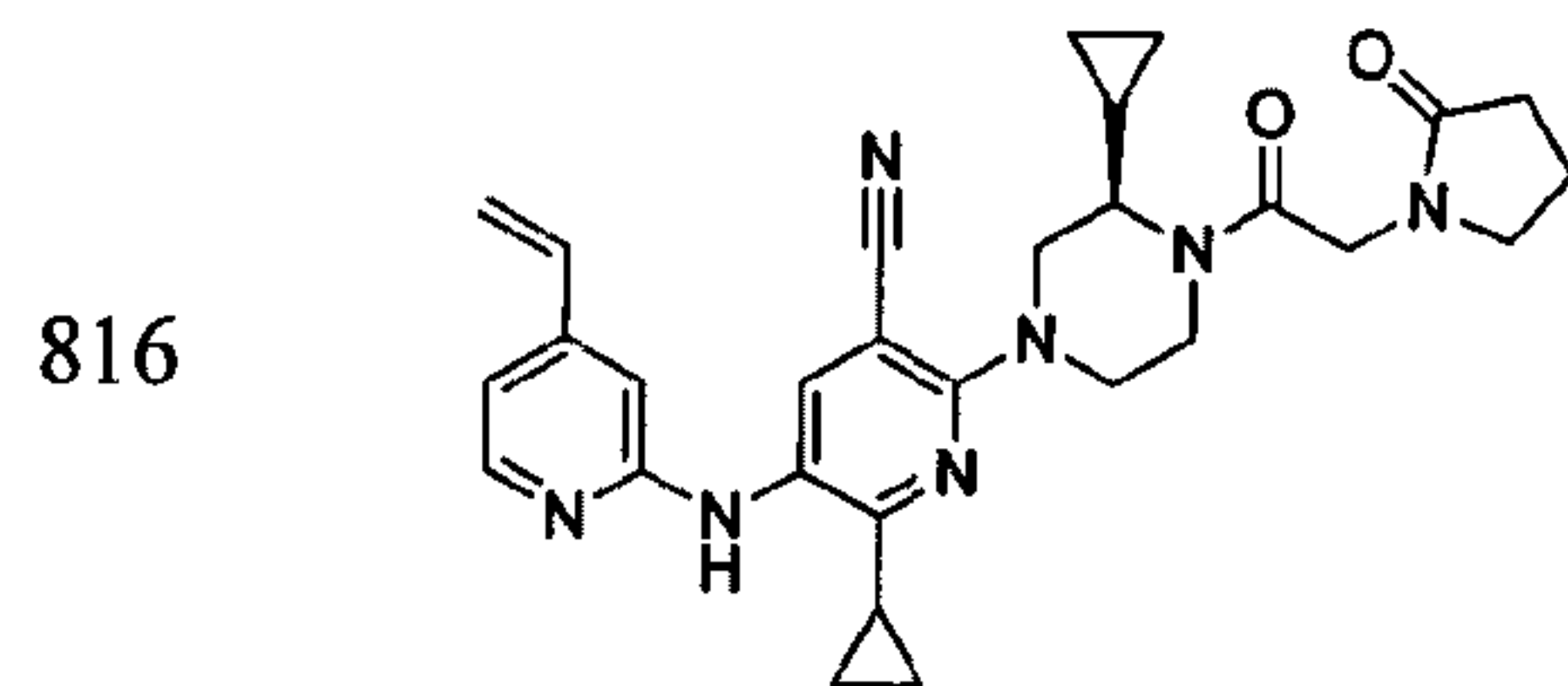
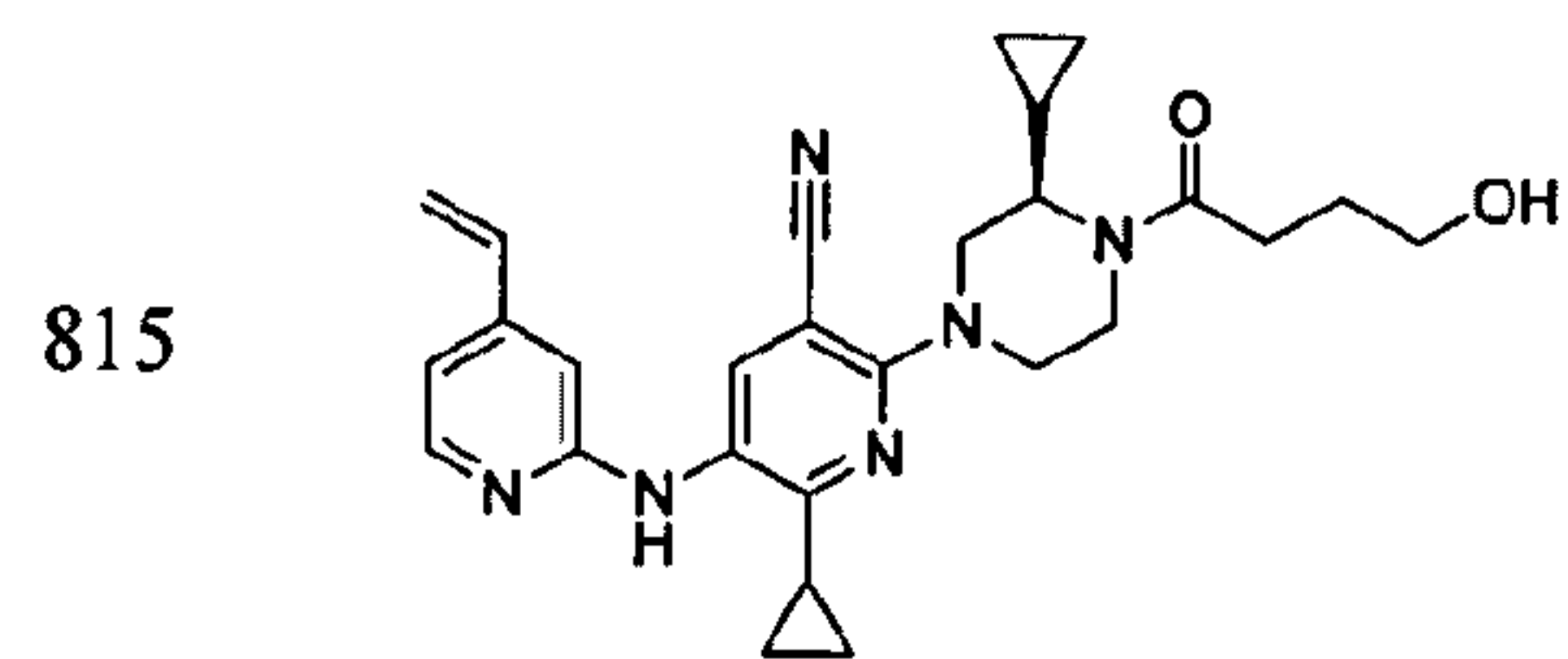


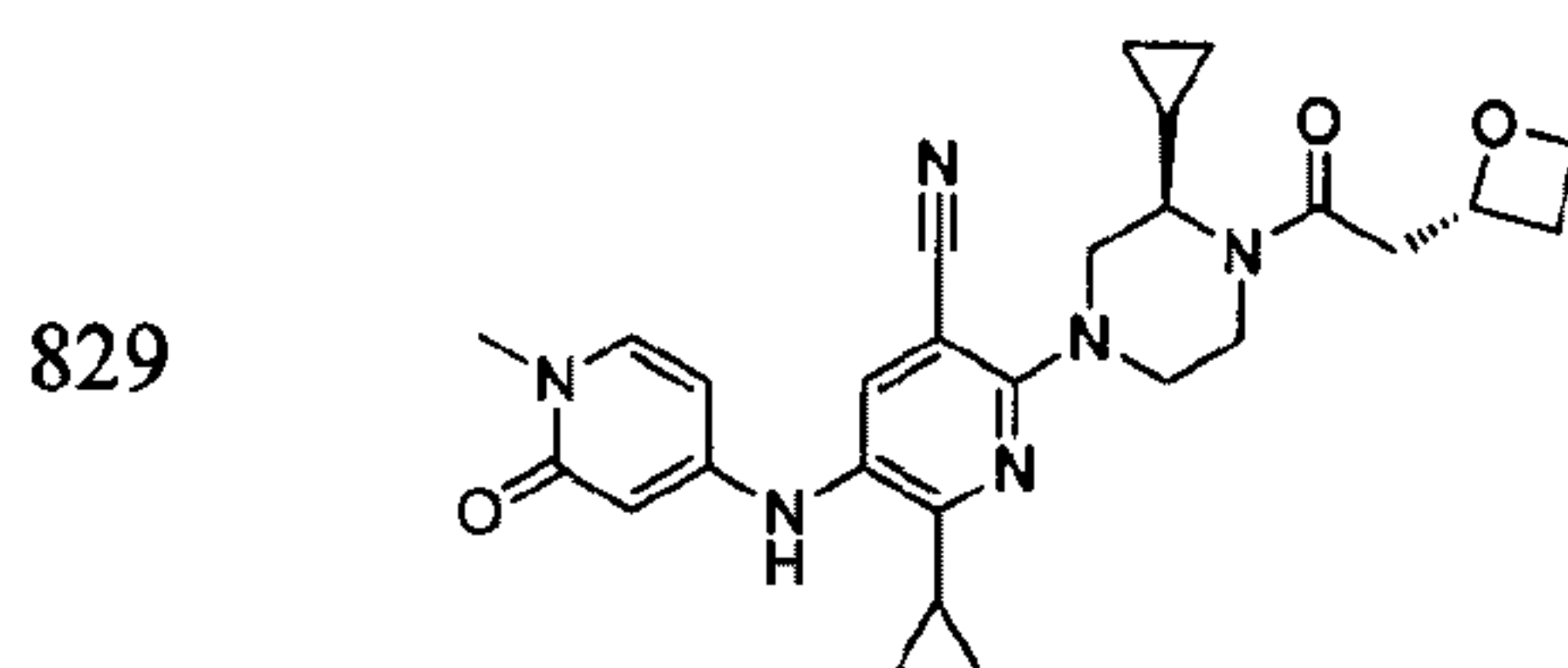
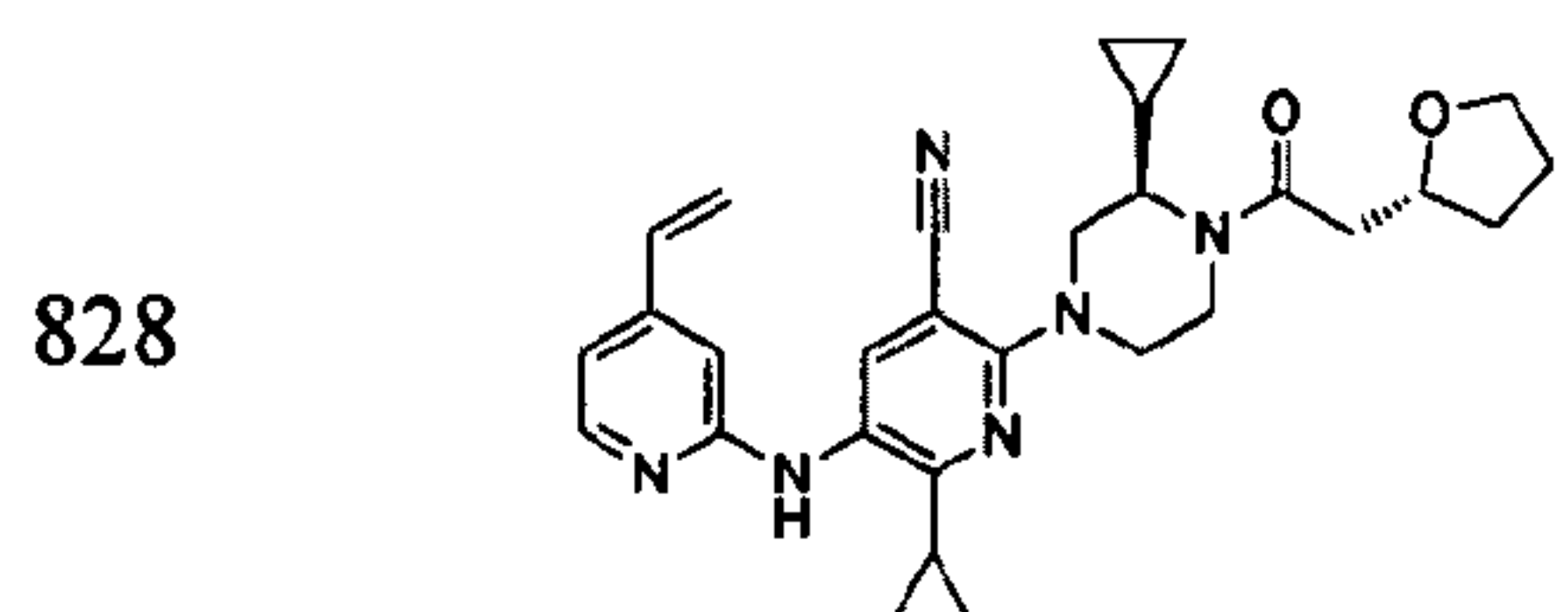
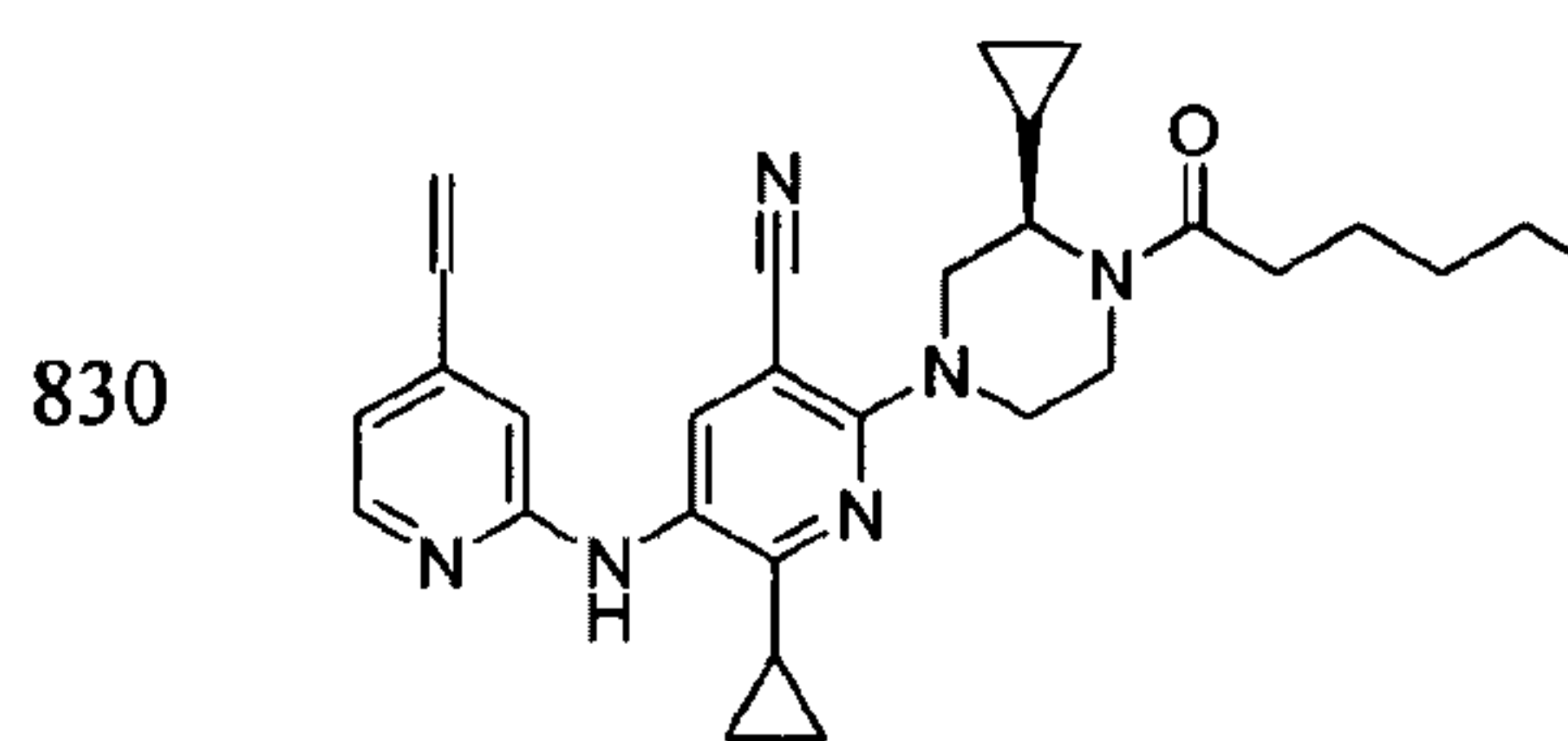
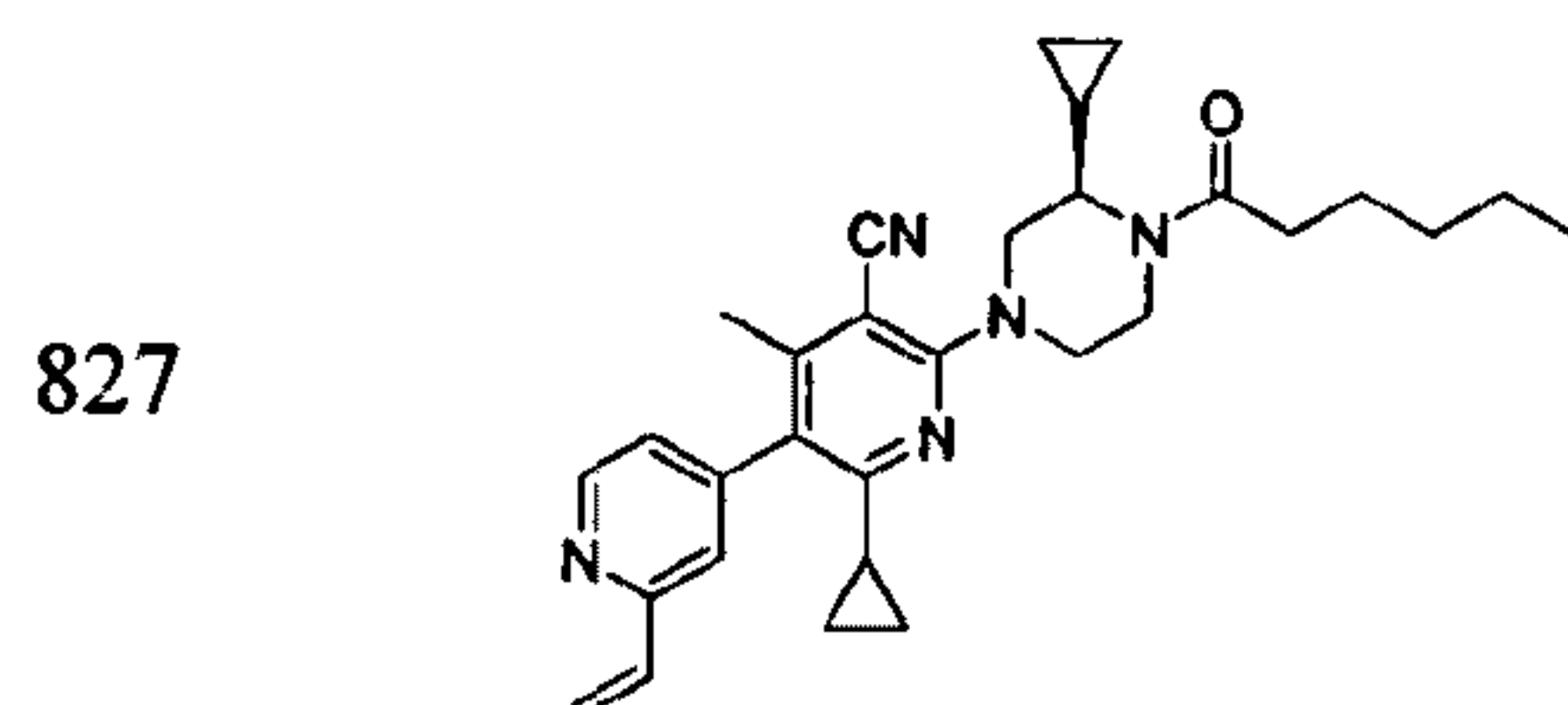












The compounds of this invention may contain one or more asymmetric centers and thus occur as racemates, racemic mixtures, scalemic mixtures, and diastereomeric mixtures, as well as single enantiomers or individual stereoisomers that are substantially free from another possible enantiomer or stereoisomer. The term “substantially free of other stereoisomers” as used herein means a preparation enriched in a compound having a selected stereochemistry at one or more selected stereocenters by at least about 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98%, or 99%. The term “enriched” means that at least the designated percentage of a preparation is the compound having a selected stereochemistry at one or more selected stereocenters. Methods of obtaining or synthesizing an individual enantiomer or stereoisomer for a given compound are known in the art and may be applied as practicable to final compounds or to starting material or intermediates.

The compounds of Formula I, II and IIa may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), and ^3H (T or tritium); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; and the like.

Unless otherwise indicated when a disclosed compound is named or depicted by a structure without specifying the stereochemistry and has one or more chiral centers, it is understood to represent all possible stereoisomers of the compound.

The compounds of this invention may also be represented in multiple tautomeric forms, in such instances, the invention expressly includes all tautomeric forms of the compounds described herein, even though only a single tautomeric form may be represented (e.g., alkylation of a ring system may result in alkylation at multiple sites, the invention expressly includes all such reaction products). All such isomeric forms of such compounds are expressly included in the present invention. All crystal forms of the compounds described herein are expressly included in the present invention.

It may be convenient or desirable to prepare, purify, and/or handle a corresponding salt of the active compound, for example, a pharmaceutically-acceptable salt. Examples of pharmaceutically acceptable salts are discussed in Berge *et al.*, 1977, "Pharmaceutically Acceptable Salts." J. Pharm. Sci. Vol. 66, pp. 1-19.

For example, if the compound is anionic, or has a functional group which may be anionic (e.g., -COOH may be -COO^-), then a salt may be formed with a suitable cation. Examples of suitable inorganic cations include, but are not limited to, alkali metal ions such as Na^+ and K^+ , alkaline earth cations such as Ca^{2+} and Mg^{2+} , and other cations such as Al^{3+} . Examples of suitable organic cations include, but are not limited to, ammonium ion (*i.e.*, NH_4^+) and substituted ammonium ions (e.g., NH_3R^+ , NH_2R^{2+} , NHR^{3+} , NR^{4+}). Examples of some suitable substituted ammonium ions are those derived from: ethylamine, diethylamine, dicyclohexylamine, triethylamine, butylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, benzylamine, phenylbenzylamine, choline, meglumine, and tromethamine, as well as amino acids, such as lysine and arginine. An example of a common quaternary ammonium ion is $\text{N}(\text{CH}_3)_4^+$.

If the compound is cationic, or has a functional group that may be cationic (e.g., -NH_2 may be -NH_3^+), then a salt may be formed with a suitable anion. Examples of suitable inorganic anions include, but are not limited to, those derived from the following inorganic acids: hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfurous, nitric, nitrous, phosphoric, and phosphorous.

Examples of suitable organic anions include, but are not limited to, those derived from the following organic acids: 2-acetoxybenzoic, acetic, ascorbic, aspartic, benzoic, camphorsulfonic, cinnamic, citric, edetic, ethanedisulfonic, ethanesulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, hydroxymaleic, hydroxynaphthalene carboxylic, isethionic, lactic, lactobionic, lauric, maleic, malic, methanesulfonic, mucic, oleic, oxalic, palmitic, pantoic, pantothenic, phenylacetic, phenylsulfonic, propionic, pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, toluenesulfonic, and valeric. Examples of suitable polymeric organic anions include, but are not limited to, those derived from the following polymeric acids: tannic acid, carboxymethyl cellulose.

Unless otherwise specified, a reference to a particular compound also includes salt forms thereof.

Compositions and routes of administration

The compounds utilized in the methods described herein may be formulated together with a pharmaceutically acceptable carrier or adjuvant into pharmaceutically acceptable compositions prior to be administered to a subject. In another embodiment, such pharmaceutically acceptable compositions further comprise additional therapeutic agents in amounts effective for achieving a modulation of disease or disease symptoms, including those described herein.

The term “pharmaceutically acceptable carrier or adjuvant” refers to a carrier or adjuvant that may be administered to a subject, together with a compound of this invention, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound.

Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d- α -tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone,

cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α -, β -, and γ -cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl- β -cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vCompound AGInally or via an implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleCompound AGInous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of

pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

The pharmaceutical compositions of this invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical compositions of this invention is useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions

of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

When the compositions of this invention comprise a combination of a compound of the formulae described herein and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about 1 to 100%, and more preferably between about 5 to 95% of the dosage normally administered in a monotherapy regimen. The additional agents may be administered separately, as part of a multiple dose regimen, from the compounds of this invention. Alternatively, those agents may be part of a single dosage form, mixed together with the compounds of this invention in a single composition.

The compounds described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular subject will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the subject's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a subject's condition, a maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Subjects may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

The pharmaceutical compositions described above comprising a compound of Structural Formula I, II or IIa or a compound described in any one of the embodiments herein, may further comprise another therapeutic agent useful for treating cancer.

Methods of Use

Provided is a method for inhibiting a mutant IDH1 activity comprising contacting a subject in need thereof a compound of Structural Formula I, II or IIa, a compound described in any one of the embodiments herein, or a pharmaceutically acceptable salt thereof. In one embodiment, the cancer to be treated is characterized by a mutant allele of IDH1 wherein the IDH1 mutation result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α -ketoglutarate to *R*(-)-2-hydroxyglutarate in a subject. In one aspect of this embodiment, the mutant IDH1 has an R132X mutation. In one aspect of this embodiment, the R132X mutation is selected from R132H, R132C, R132L, R132V, R132S and R132G. In another aspect, the R132X mutation is R132H or R132C. In yet another aspect, the R132X mutation is R132H.

Also provided are methods of treating a cancer characterized by the presence of a mutant allele of IDH1 comprising the step of administering to subject in need thereof (a) a compound of Structural Formula I, II or IIa, a compound described in any one of the embodiments herein, or a pharmaceutically acceptable salt thereof, or (b) a pharmaceutical composition comprising (a) and a pharmaceutically acceptable carrier.

In one embodiment, the cancer to be treated is characterized by a mutant allele of IDH1 wherein the IDH1 mutation result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α -ketoglutarate to *R*(-)-2-hydroxyglutarate in a patient. In one aspect of this embodiment, the IDH1 mutation is an R132X mutation. In another aspect of this embodiment, the R132X mutation is selected from R132H, R132C, R132L, R132V, R132S and R132G. In another aspect, the R132X mutation is R132 H or R132C. A cancer can be analyzed by sequencing cell samples to determine the presence and specific nature of (e.g., the changed amino acid present at) a mutation at amino acid 132 of IDH1.

Without being bound by theory, applicants believe that mutant alleles of IDH1 wherein the IDH1 mutation result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α -ketoglutarate to *R*(-)-2-hydroxyglutarate, and in particular R132H mutations of IDH1, characterize a subset of all types of cancers, without regard to their cellular nature or location in the body. Thus, the compounds and methods of this invention are useful to treat any type of cancer that is characterized by the presence of a mutant allele of IDH1 imparting such activity and in particular an IDH1 R132H or R132C mutation.

In one aspect of this embodiment, the efficacy of cancer treatment is monitored by measuring the levels of 2HG in the subject. Typically levels of 2HG are measured prior to treatment, wherein an elevated level is indicative of the use of the compound of Formula I to treat the cancer. Once the elevated levels are established, the level of 2HG is determined during the course of and/or following termination of treatment to establish efficacy. In certain embodiments, the level of 2HG is only determined during the course of and/or following termination of treatment. A reduction of 2HG levels during the course of treatment and following treatment is indicative of efficacy. Similarly, a determination that 2HG levels are not elevated during the course of or following treatment is also indicative of efficacy. Typically, these 2HG measurements will be utilized together with other well-known determinations of efficacy of cancer treatment, such as reduction in number and size of tumors and/or other cancer-associated lesions, improvement in the general health of the subject, and alterations in other biomarkers that are associated with cancer treatment efficacy.

2HG can be detected in a sample by LC/MS. The sample is mixed 80:20 with methanol, and centrifuged at 3,000 rpm for 20 minutes at 4 degrees Celsius. The resulting supernatant can

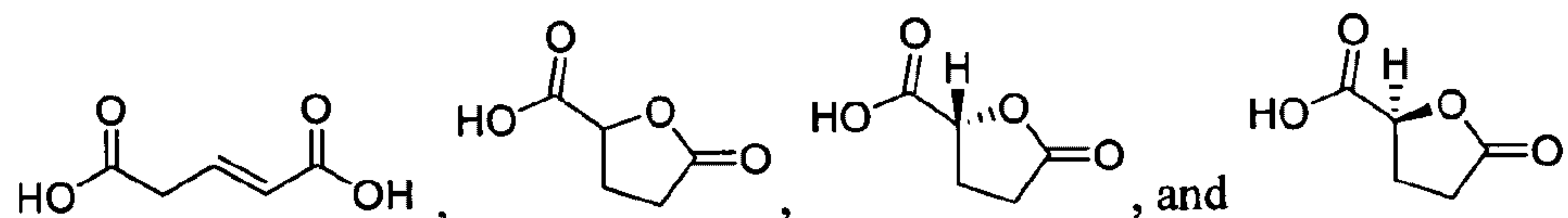
be collected and stored at -80 degrees Celsius prior to LC-MS/MS to assess 2-hydroxyglutarate levels. A variety of different liquid chromatography (LC) separation methods can be used. Each method can be coupled by negative electrospray ionization (ESI, -3.0 kV) to triple-quadrupole mass spectrometers operating in multiple reaction monitoring (MRM) mode, with MS parameters optimized on infused metabolite standard solutions. Metabolites can be separated by reversed phase chromatography using 10 mM tributyl-amine as an ion pairing agent in the aqueous mobile phase, according to a variant of a previously reported method (Luo *et al. J Chromatogr A* 1147, 153-64, 2007). One method allows resolution of TCA metabolites: $t = 0$, 50% B; $t = 5$, 95% B; $t = 7$, 95% B; $t = 8$, 0% B, where B refers to an organic mobile phase of 100% methanol. Another method is specific for 2-hydroxyglutarate, running a fast linear gradient from 50% -95% B (buffers as defined above) over 5 minutes. A Synergi Hydro-RP, 100mm $\times$ 2 mm, 2.1 μ m particle size (Phenomenex) can be used as the column, as described above. Metabolites can be quantified by comparison of peak areas with pure metabolite standards at known concentration. Metabolite flux studies from ^{13}C -glutamine can be performed as described, *e.g.*, in Munger *et al. Nat Biotechnol* 26, 1179-86, 2008.

In one embodiment 2HG is directly evaluated.

In another embodiment a derivative of 2HG formed in process of performing the analytic method is evaluated. By way of example such a derivative can be a derivative formed in MS analysis. Derivatives can include a salt adduct, *e.g.*, a Na adduct, a hydration variant, or a hydration variant which is also a salt adduct, *e.g.*, a Na adduct, *e.g.*, as formed in MS analysis.

In another embodiment a metabolic derivative of 2HG is evaluated. Examples include species that build up or are elevated, or reduced, as a result of the presence of 2HG, such as glutarate or glutamate that will be correlated to 2HG, *e.g.*, R-2HG.

Exemplary 2HG derivatives include dehydrated derivatives such as the compounds provided below or a salt adduct thereof:



In one embodiment the cancer is a tumor wherein at least 30, 40, 50, 60, 70, 80 or 90% of the tumor cells carry an IDH1 mutation, and in particular an IDH1 R132H or R132C mutation, at the time of diagnosis or treatment.

IDH1 R132X mutations are known to occur in certain types of cancers as indicated in Table 2, below.

Table 2. IDH mutations associated with certain cancers

<u>Cancer Type</u>	<u>IDH1 R132X Mutation</u>	<u>Tumor Type</u>
brain tumors	R132H	primary tumor
	R132C	primary tumor
	R132S	primary tumor
	R132G	primary tumor
	R132L	primary tumor
	R132V	primary tumor
fibrosarcoma	R132C	HT1080 fibrosarcoma cell line
Acute Myeloid Leukemia (AML)	R132H	primary tumor
	R132G	primary tumor
	R132C	primary tumor
Prostate cancer	R132H	primary tumor
	R132C	primary tumor
Acute lymphoblastic leukemia (ALL)	R132C	primary tumor
paragangliomas	R132C	primary tumor

IDH1 R132H mutations have been identified in glioblastoma, acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer, cholangiocarcinomas,

chondrosarcoma, myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN), colon cancer, and angio-immunoblastic non-Hodgkin's lymphoma (NHL). Accordingly, in one embodiment, the methods described herein are used to treat glioma (glioblastoma), acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer (NSCLC) or cholangiocarcinomas, chondrosarcoma, myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN) or colon cancer in a patient.

Accordingly in one embodiment, the cancer is a cancer selected from any one of the cancer types listed in Table 2, and the IDH R132X mutation is one or more of the IDH1 R132X mutations listed in Table 2 for that particular cancer type.

Treatment methods described herein can additionally comprise various evaluation steps prior to and/or following treatment with a compound of Structural Formula I, II or IIa or a compound described in any one of the embodiments described herein.

In one embodiment, prior to and/or after treatment with a compound of Structural Formula I, II or IIa or a compound described in any one of the embodiments described herein, the method further comprises the step of evaluating the growth, size, weight, invasiveness, stage and/or other phenotype of the cancer.

In one embodiment, prior to and/or after treatment with a compound of formula I or I-a or a compound described in any one of the embodiments described herein, the method further comprises the step of evaluating the IDH1 genotype of the cancer. This may be achieved by ordinary methods in the art, such as DNA sequencing, immuno analysis, and/or evaluation of the presence, distribution or level of 2HG.

In one embodiment, prior to and/or after treatment with a compound of formula I or I-a or a compound described in any one of the embodiments described herein, the method further comprises the step of determining the 2HG level in the subject. This may be achieved by spectroscopic analysis, *e.g.*, magnetic resonance-based analysis, *e.g.*, MRI and/or MRS measurement, sample analysis of bodily fluid, such as serum or spinal cord fluid analysis, or by analysis of surgical material, *e.g.*, by mass-spectroscopy.

Combination therapies

In some embodiments, the methods described herein comprise the additional step of co-administering to a subject in need thereof a second therapy *e.g.*, an additional cancer therapeutic agent or an additional cancer treatment. Exemplary additional cancer therapeutic agents include for example, chemotherapy, targeted therapy, antibody therapies, immunotherapy, and hormonal therapy. Additional cancer treatments include, for example: surgery, and radiation therapy. Examples of each of these treatments are provided below.

The term “co-administering” as used herein with respect to an additional cancer therapeutic agents means that the additional cancer therapeutic agent may be administered together with a compound of this invention as part of a single dosage form (such as a composition of this invention comprising a compound of the invention and an second therapeutic agent as described above) or as separate, multiple dosage forms. Alternatively, the additional cancer therapeutic agent may be administered prior to, consecutively with, or following the administration of a compound of this invention. In such combination therapy treatment, both the compounds of this invention and the second therapeutic agent(s) are administered by conventional methods. The administration of a composition of this invention, comprising both a compound of the invention and a second therapeutic agent, to a subject does not preclude the separate administration of that same therapeutic agent, any other second therapeutic agent or any compound of this invention to said subject at another time during a course of treatment. The term “co-administering” as used herein with respect to an additional cancer treatment means that the additional cancer treatment may occur prior to, consecutively with, concurrently with or following the administration of a compound of this invention.

In some embodiments, the additional cancer therapeutic agent is a chemotherapy agent. Examples of chemotherapeutic agents used in cancer therapy include, for example, antimetabolites (*e.g.*, folic acid, purine, and pyrimidine derivatives), alkylating agents (*e.g.*, nitrogen mustards, nitrosoureas, platinum, alkyl sulfonates, hydrazines, triazenes, aziridines, spindle poison, cytotoxic agents, topoisomerase inhibitors and others) and hypomethylating agents (*e.g.*, decitabine (5-aza-deoxycytidine), zebularine, isothiocyanates, azacitidine (5-azacytidine), 5-fluoro-2'-deoxycytidine, 5,6-dihydro-5-azacytidine and others). Exemplary agents include Aclarubicin, Actinomycin, Alitretinoin, Altretamine, Aminopterin, Aminolevulinic acid, Amrubicin, Amsacrine, Anagrelide, Arsenic trioxide, AsparCompound AGInase, Atrasentan, Belotecan, Bexarotene, bendamustine, Bleomycin, Bortezomib, Busulfan, Camptothecin, Capecitabine, Carboplatin, Carboquone, Carmofur, Carmustine, Celecoxib, Chlorambucil, Chloromethine, Cisplatin, Cladribine, Clofarabine, Crisantaspase, Cyclophosphamide, Cytarabine, Dacarbazine, Dactinomycin, Daunorubicin, Decitabine, Demecolcine, Docetaxel, Doxorubicin,

Efaproxiral, Elesclomol, Elsamitrucin, Enocitabine, Epirubicin, Estramustine, Etoposide, Floxuridine, Fludarabine, Fluorouracil (5FU), Fotemustine, Gemcitabine, Gliadel implants, Hydroxycarbamide, Hydroxyurea, Idarubicin, Ifosfamide, Irinotecan, Irofulven, Ixabepilone, Larotaxel, Leucovorin, Liposomal doxorubicin, Liposomal daunorubicin, Lonidamine, Lomustine, Lucanthone, Mannosulfan, Masoprocol, Melphalan, Mercaptopurine, Mesna, Methotrexate, Methyl aminolevulinate, Mitobronitol, Mitoguazone, Mitotane, Mitomycin, Mitoxantrone, Nedaplatin, Nimustine, Oblimersen, Omacetaxine, Ortataxel, Oxaliplatin, Paclitaxel, Pegaspargase, Pemetrexed, Pentostatin, Pirarubicin, Pixantrone, Plicamycin, Porfimer sodium, Prednimustine, Procarbazine, Raltitrexed, Ranimustine, Rubitecan, Sapacitabine, Semustine, Sitimagene ceradenovec, Strataplatin, Streptozocin, Talaporfin, Tegafur-uracil, Temoporfin, Temozolomide, Teniposide, Tesetaxel, Testolactone, Tetranitrate, Thiotepa, Tiazofurine, Tioguanine, Tipifarnib, Topotecan, Trabectedin, Triaziquone, Triethylenemelamine, Triplatin, Tretinoin, Treosulfan, Trofosfamide, Uramustine, Valrubicin, Verteporfin, Vinblastine, Vincristine, Vindesine, Vinflunine, Vinorelbine, Vorinostat, Zorubicin, and other cytostatic or cytotoxic agents described herein.

Because some drugs work better together than alone, two or more drugs are often given at the same time. Often, two or more chemotherapy agents are used as combination chemotherapy.

In some embodiments, the additional cancer therapeutic agent is a differentiation agent. Such differentiation agent includes retinoids (such as all-trans-retinoic acid (ATRA), 9-cis retinoic acid, 13-cis-retinoic acid (13-cRA) and 4-hydroxy-phenretinamide (4-HPR)); arsenic trioxide; histone deacetylase inhibitors HDACs (such as azacytidine (Vidaza) and butyrates (e.g., sodium phenylbutyrate)); hybrid polar compounds (such as hexamethylene bisacetamide ((HMBA)); vitamin D; and cytokines (such as colony-stimulating factors including G-CSF and GM-CSF, and interferons).

In some embodiments the additional cancer therapeutic agent is a targeted therapy agent. Targeted therapy constitutes the use of agents specific for the deregulated proteins of cancer cells. Small molecule targeted therapy drugs are generally inhibitors of enzymatic domains on mutated, overexpressed, or otherwise critical proteins within the cancer cell. Prominent examples are the tyrosine kinase inhibitors such as Axitinib, Bosutinib, Cediranib, dasatinib, erlotinib, imatinib, gefitinib, lapatinib, Lestaurtinib, Nilotinib, Semaxanib, Sorafenib, Sunitinib, and Vandetanib, and also cyclin-dependent kinase inhibitors such as Alvocidib and Seliciclib. Monoclonal antibody therapy is another strategy in which the therapeutic agent is an antibody which specifically binds to a protein on the surface of the cancer cells. Examples include the anti-HER2/neu antibody trastuzumab (HERCEPTIN®) typically used in breast cancer, and the anti-CD20 antibody rituximab and Tositumomab typically used in a variety of B-cell malignancies. Other exemplary antibodies include Cetuximab, Panitumumab, Trastuzumab, Alemtuzumab, Bevacizumab, Edrecolomab, and Gemtuzumab. Exemplary fusion proteins include Aflibercept and Denileukin difitox. In some embodiments, the targeted therapy can be used in combination with a compound described herein, e.g., a biguanide such as metformin or phenformin, preferably phenformin.

Targeted therapy can also involve small peptides as “homing devices” which can bind to cell surface receptors or affected extracellular matrix surrounding the tumor. Radionuclides which are attached to these peptides (e.g., RGDs) eventually kill the cancer cell if the nuclide decays in the vicinity of the cell. An example of such therapy includes BEXXAR®.

In some embodiments, the additional cancer therapeutic agent is an immunotherapy agent. Cancer immunotherapy refers to a diverse set of therapeutic strategies designed to induce the subject's own immune system to fight the tumor. Contemporary methods for generating an immune response against tumors include intravesicular BCG immunotherapy for superficial bladder cancer, and use of interferons and other cytokines to induce an immune response in renal cell carcinoma and melanoma subjects.

Allogeneic hematopoietic stem cell transplantation can be considered a form of immunotherapy, since the donor's immune cells will often attack the tumor in a graft-versus-tumor effect. In some embodiments, the immunotherapy agents can be used in combination with a compound or composition described herein.

In some embodiments, the additional cancer therapeutic agent is a hormonal therapy agent. The growth of some cancers can be inhibited by providing or blocking certain hormones. Common examples of hormone-sensitive tumors include certain types of breast and prostate cancers. Removing or blocking estrogen or testosterone is often an important additional treatment. In certain cancers, administration of hormone agonists, such as progestogens may be therapeutically beneficial. In some embodiments, the hormonal therapy agents can be used in combination with a compound or a composition described herein.

Other possible additional therapeutic modalities include imatinib, gene therapy, peptide and dendritic cell vaccines, synthetic chlorotoxins, and radiolabeled drugs and antibodies.

EXAMPLES

ABBREVIATIONS

anhy. - anhydrous	chromatography
aq. - aqueous	Hz - hertz
min - minute(s)	δ - chemical shift
mL - milliliter	<i>J</i> - coupling constant
mmol - millimole(s)	s - singlet
mol - mole(s)	d - doublet
MS - mass spectrometry	t - triplet
NMR - nuclear magnetic resonance	q - quartet
TLC - thin layer chromatography	m - multiplet
HPLC - high-performance liquid	br - broad

qd - quartet of doublets	Na ₂ CO ₃ - sodium carbonate
dquin - doublet of quintets	TFA - trifluoroacetic acid
dd - doublet of doublets	Na ₂ SO ₄ - sodium sulfate
dt - doublet of triplets	NaBH ₄ - sodium borohydride
CHCl ₃ - chloroform	NaHCO ₃ - sodium bicarbonate
DCM - dichloromethane	LiHMDS - lithium hexamethyldisilylamide
DMF - dimethylformamide	NaHMDS - sodium hexamethyldisilylamide
Et ₂ O - diethyl ether	LAH - lithium aluminum hydride
EtOH - ethyl alcohol	NaBH ₄ - sodium borohydride
EtOAc - ethyl acetate	LDA - lithium diisopropylamide
MeOH - methyl alcohol	Et ₃ N - triethylamine
MeCN - acetonitrile	DMAP - 4-(dimethylamino)pyridine
PE - petroleum ether	DIPEA - <i>N,N</i> -diisopropylethylamine
THF - tetrahydrofuran	NH ₄ OH - ammonium hydroxide
AcOH - acetic acid	EDCI - 1-ethyl-3-(3-
HCl - hydrochloric acid	dimethylaminopropyl)carbodiimide
H ₂ SO ₄ - sulfuric acid	HOBt - 1-hydroxybenzotriazole
NH ₄ Cl - ammonium chloride	HATU - <i>O</i> -(7-azabenzotriazol-1-yl)-
KOH - potassium hydroxide	<i>N,N,N',N'</i> -tetra-methyluronium
NaOH - sodium hydroxide	BINAP - 2,2'-bis(diphenylphosphanyl)-1,1'-
K ₂ CO ₃ - potassium carbonate	binaphthyl

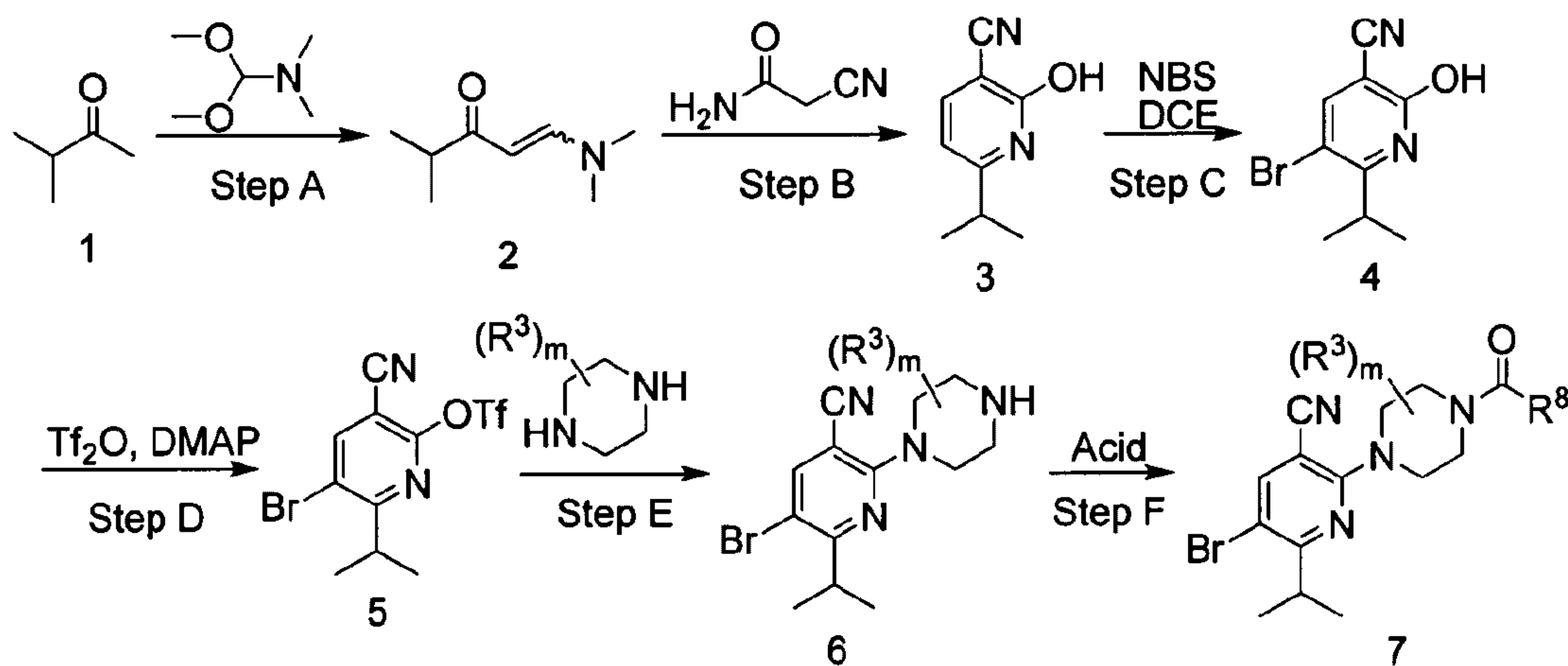
In the following examples, reagents were purchased from commercial sources (including Alfa, Acros, Sigma Aldrich, TCI and Shanghai Chemical Reagent Company), and used without further purification. Flash chromatography was performed on an Ez Purifier III using a column with silica gel particles of 200-300 mesh. Analytical and preparative thin layer chromatography plates (TLC) were HSGF 254 (0.15-0.2 mm thickness, Shanghai Anbang Company, China). Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker AMX-400 NMR (Bruker, Switzerland). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Mass spectra were run with electrospray ionization (ESI) from a Waters

LCT TOF Mass Spectrometer (Waters, USA). HPLC chromatographs were recorded on an Compound AGilent 1200 Liquid Chromatography (Compound AGilent, USA, column: Ultimate 4.6mmx50mm, 5 μ m, mobile phase A: 0.1% formic acid in water; mobile phase B: acetonitrile). Microwave reactions were run on an Initiator 2.5 Microwave Synthesizer (Biotage, Sweden).

For exemplary compounds disclosed in this section, the specification of a stereoisomer (e.g., an (R) or (S) stereoisomer) indicates a preparation of that compound such that the compound is enriched at the specified stereocenter by at least about 90%, 95%, 96%, 97%, 98%, or 99%.

Example 1 Preparation of (R)-5-bromo-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile. (R)-5-bromo-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (**7**, wherein R^{1a} is hydrogen; m is 1; R³ is 3-methyl; and R⁸ is methoxyethyl) was prepared according to general Scheme 1, below.

Scheme 1:



Step A: 1-(dimethylamino)-4-methylpent-1-en-3-one (2). To a solution of commercially available 3-methylbutan-2-one (**1**; 8.613 g, 100 mmol) in 150 mL of anhydrous DMF was added commercially available 1,1-dimethoxy-N,N-dimethylmethanamine (29.80 g, 250 mmol). The resulting mixture was stirred at 100°C overnight. After removal of DMF and excess of acetal, 14 g of title compound was obtained as a crude product and used in subsequent reaction without further purification. ¹H NMR (CHLOROFORM-d) δ 7.57 (d, J = 12.8 Hz, 1H), 5.05 (d, J = 12.5 Hz, 1H), 2.80 - 3.10 (m, 6H), 2.56 (dt, J = 13.7, 6.8 Hz, 1H), 1.06 - 1.14 (m, 6H).

Step B: 6-isopropyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3). 8.8 g of 1-(dimethylamino)-4-methylpent-1-en-3-one (**2**; 62 mmol) and 5.3 g of commercially available cyanoacetamide (62 mmol) in 24 mL of H₂O was treated with a premixed buffer solution of 0.7 mL of acetic acid, 1.8 mL of H₂O, and enough piperidine to make the buffer solution basic. The resulting solution was refluxed for 2 hrs and LC-MS showed the formation of desired product. After cooling to room temperature, the mixture was acidified with glacial acetic acid, and a brown yellowish precipitate was formed. The filter cake was washed with H₂O and air-dried to give 6.5 g of title compound. MS (ES) M+H expected 163.1, found 163.0. ¹H NMR (DMSO-d₆) δ 12.51 (br. s., 1H), 7.96 - 8.18 (m, 1H), 6.24 (d, J = 7.5 Hz, 1H), 2.83 (spt, J = 6.9 Hz, 1H), 1.19 (s, 29H), 1.17 (s, 3H).

Step C: 5-bromo-6-isopropyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (4). To a solution of 2-hydroxy-6-isopropylpyridine-3-carbonitrile (**3**; 3.0 g, 19 mmol) in 50 mL of DCE was added NBS (5 g, 28 mmol) at room temperature. The reaction mixture was then heated at reflux for 3 hours. After LC-MS showed the completion of reaction, the mixture was cooled to room temperature and poured into water and extracted with methylene chloride. The combined organic layer was dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. Column chromatography (4% MeOH/DCM) afforded 3.9 g of title compound as a brown solid. MS (ES) M+H expected 241.0, found 240.9. ¹H NMR (DMSO-d₆) δ 12.58 (br. s., 1H), 8.38 (s, 1H), 3.25 - 3.32 (m, 1H), 1.23 (s, 3H), 1.21 (s, 3H).

Step D: 5-bromo-3-cyano-6-isopropylpyridin-2-yl trifluoromethanesulfonate (5). To a solution of 5-bromo-2-hydroxy-6-isopropylpyridine-3-carbonitrile (**4**; 2.0 g, 8 mmol) in 20 mL of methylene chloride was added DMAP (100 mg, 0.8 mmol), and triethylamine (1.01 g, 10 mmol). The mixture was cooled to 0°C in an ice-water bath, and trifluoromethanesulfonic anhydride (2.82 g, 10 mmol) was added dropwise by syringe. The resulting reaction mixture was stirred at 0°C for 30 min before it was allowed to warm to room temperature and stirred for additional 2 hours. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% EtOAc/petroleum ether) to afford 2.8 g of title compound. ¹H NMR (CHLOROFORM-d) δ 8.22 (s, 1H), 3.57 (spt, J = 6.7 Hz, 1H), 1.28 (d, J = 6.8 Hz, 6H).

Step E: (R)-5-bromo-6-isopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6). A mixture of the above triflate **5** (1.68 g, 4.5 mmol), (R)-2-methylpiperazine (770 mg, 6.77 mmol), and

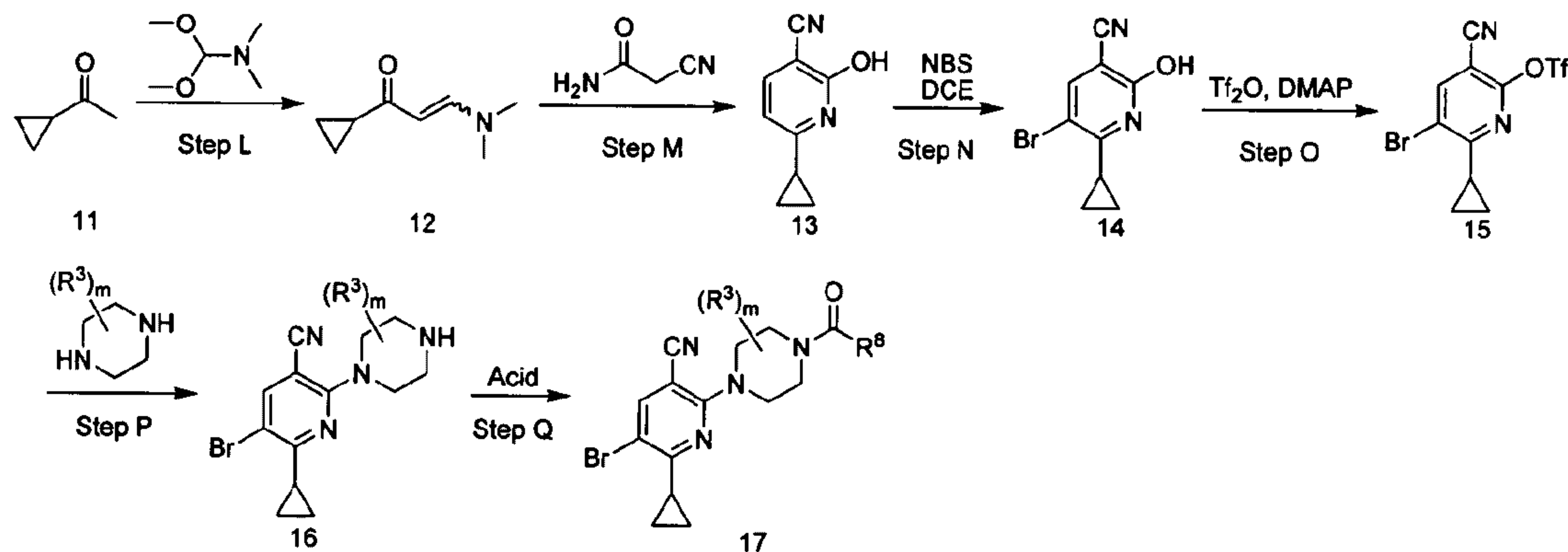
triethylamine (1.9 mL, 13.5 mmol) suspended in 5 mL of MeCN was subjected to microwave reaction at 175°C for 45 min. After the mixture was concentrated *in vacuo*, the residue was purified by column chromatography (10% DCM/MeOH) to afford 0.91 g of title compound as a light yellowish solid. MS (ES) M+H expected 323.1, found 323.0. ¹H NMR (CHLOROFORM-d) δ 7.79 (s, 1H), 4.35 - 4.40 (m, 0.5H), 4.32 - 4.35 (m, 1H), 4.30 (t, J = 2.4 Hz, 0.5H), 3.37 - 3.45 (m, 1H), 3.08 - 3.13 (m, 0.5H), 3.05 - 3.08 (m, 1H), 3.04 (d, J = 2.5 Hz, 0.5H), 2.96 - 3.01 (m, 1H), 2.89 - 2.96 (m, 1H), 2.65 - 2.74 (m, 1H), 1.21 (dd, J = 6.8, 0.8 Hz, 6H), 1.13 (d, J = 6.3 Hz, 3H).

Step F: (R)-5-bromo-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (7). To a 25 mL of round-bottom flask was added (R)-5-bromo-6-isopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6; 680 mg, 2.1 mmol), 3-methoxypropanoic acid (438 mg, 4.2 mmol), HATU (1.6g, 4.2 mmol), DIPEA (1.1 mL, 6.31 mmol) and 5 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature for 4 hours until TLC showed the completion of the reaction. After washing with Satd. NaHCO₃, brine, the combined organic layer was dried over anhy. Na₂SO₄ and concentrated *in vacuo*. Column chromatography purification (20% EtOAc/petroleum ether) afforded 550 mg of title compound as a light yellowish solid. MS (ES) M+H expected 409.1, found 409.0. ¹H NMR (CHLOROFORM-d) δ 7.83 (s, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J = 12.3 Hz, 0.5H), 4.19 - 4.39 (m, 3H), 3.76 - 3.85 (m, 0.5H), 3.73 (t, J = 6.4 Hz, 2H), 3.50 - 3.61 (m, 0.5H), 3.37 (s, 3H), 3.25 - 3.35 (m, 1H), 3.02 - 3.20 (m, 1H), 2.63 - 2.80 (m, 1H), 2.51 - 2.61 (m, 1H), 1.35 (d, J = 7.0 Hz, 1.5H), 1.25 (d, J = 6.3 Hz, 1.5H), 1.21 - 1.23 (m, 3H), 1.19 - 1.21 (m, 3H)

Other intermediates 7 were prepared by similar steps according to Scheme 1 and either: (1) replacing (R)-2-methylpiperazine in Step E with an alternately substituted or unsubstituted piperazine; and/or (2) replacing 3-methoxypropanoic acid in Step F with an alternate acid.

Example 2 Preparation of (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile. (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (**17**; wherein R^{1a} is hydrogen; R² is cyclopropyl; m is 1; R³ is 3-methyl; and R⁸ is methoxyethyl) was prepared according to general Scheme 2, below.

Scheme 2:



Step L: 1-cyclopropyl-3-(dimethylamino)prop-2-en-1-one (12). To a solution of commercially available 1-cyclopropylethanone (11; 8.584 g, 100 mmol) in 200 mL of anhydrous DMF was added 1,1-dimethoxy-N,N-dimethylmethanamine (29.80 g, 250 mmol). The resulting mixture was stirred at 100°C overnight. After removal of DMF and excess of acetal, 13.9 g of title compound was obtained as a crude product and used in subsequent reaction without further purification. ^1H NMR (CHLOROFORM- d) δ 7.56 (d, J = 12.8 Hz, 1H), 5.20 (d, J = 12.5 Hz, 1H), 2.78 - 3.08 (m, 6H), 1.79 (tt, J = 7.9, 4.5 Hz, 1H), 0.94 - 1.04 (m, 2H), 0.67 - 0.80 (m, 2H).

Step M: 6-cyclopropyl-2-hydroxynicotinonitrile (13). 3.532 g of 1-cyclopropyl-3-(dimethylamino)prop-2-en-1-one 12 and 2.032 g of cyanoacetamide in 10 mL of H_2O was treated with a premixed buffer solution of 0.33 mL of acetic acid, 0.82 mL of H_2O , and enough amount of piperidine to make solution basic. The resulting solution was refluxed for 2 hrs and LC-MS showed the formation of desired product 13. After cooling to room temperature, the mixture was acidified with glacial acetic acid, and a brown yellowish precipitated was formed. The thick brown slurry was filtered and filter cake was washed with H_2O and air-dried to give 1.30 g of title compound. MS (ES) $\text{M}+\text{H}$ expected 161.1, found 161.0. ^1H NMR (CHLOROFORM- d) δ 13.60 (br. s., 1H), 7.77 (d, J = 7.8 Hz, 1H), 5.91 (d, J = 7.8 Hz, 1H), 1.96 - 2.12 (m, 1H), 1.29 - 1.36 (m, 2H), 1.04 - 1.11 (m, 2H).

Step N: 5-bromo-6-cyclopropyl-2-hydroxynicotinonitrile (14). To a solution of 6-cyclopropyl-2-hydroxynicotinonitrile (13; 0.32 g, 2.0 mmol) in 5 mL of DCE was added NBS (0.534 g, 3.0 mmol) at room temperature. The reaction mixture was heated at reflux for 3 hours. After LC-MS showed completion of reaction, the reaction mixture was cooled to room temperature and poured into water. After extraction with methylene chloride (3 x 5 mL), the combined organic layer was

dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Column chromatography (4% MeOH/DCM) afforded 0.45 g of **14**. MS (ES) M+H expected 239.0, found 238.9. ^1H NMR (CHLOROFORM- d) δ 8.49-8.72 (br. s., 1H), 7.93 (s, 1H), 2.23 - 2.34 (m, 1H), 1.36 - 1.42 (m, 2H), 1.29 - 1.36 (m, 2H).

Step O: 5-bromo-3-cyano-6-cyclopropylpyridin-2-yl trifluoromethanesulfonate (15). To a 5-bromo-6-cyclopropyl-2-hydroxynicotinonitrile (**14**; 0.45 g, 1.882 mmol) in 10 mL of methylene chloride was added DMAP (23.2 mg, 0.19 mmol), and triethylamine (0.247 g, 2.45 mmol). The mixture was cooled to 0°C in an ice-water bath, and trifluoromethanesulfonic anhydride (0.69 g, 2.45 mmol) was added dropwise via syringe. The resulting reaction mixture was stirred at 0°C for 30 min before it was allowed to warm to room temperature and stirred for additional 2 hours. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% ethyl acetate/petroleum ether) to afford 537 mg of **15**. ^1H NMR (CHLOROFORM- d) δ 8.14 - 8.19 (m, 1H), 2.55 - 2.66 (m, 1H), 1.30 (dt, $J = 7.8, 3.1$ Hz, 2H), 1.21 - 1.27 (m, 2H).

Step P: (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (16). A mixture of above triflate **15** (1.68 g, 4.6 mmol), (R)-2-methylpiperazine (790 mg, 6.9 mmol), and triethylamine (1.9 mL, 13.8 mmol) suspended in 5 mL of MeCN was subjected to microwave reaction at 175°C for 60 min. After the mixture was concentrated under reduced pressure, the residue was extracted between ethyl acetate and water. The combined organic layer was then washed with aq. NaHCO_3 , brine, dried over anhy. Na_2SO_4 and concentrated *in vacuo* to give 1.26 g of crude **16**. MS (ES) M+H expected 321.1, found 321.2. ^1H NMR (CHLOROFORM- d) δ 7.78 (s, 1H), 4.14 - 4.24 (m, 2H), 3.09 - 3.14 (m, 1H), 3.02 - 3.07 (m, 1H), 2.96 - 3.00 (m, 2H), 2.71 (dd, $J = 12.9, 10.2$ Hz, 1H), 2.42 - 2.52 (m, 1H), 1.16 (d, $J = 6.3$ Hz, 3H), 1.08 (s, 2H), 1.07 (d, $J = 3.8$ Hz, 2H).

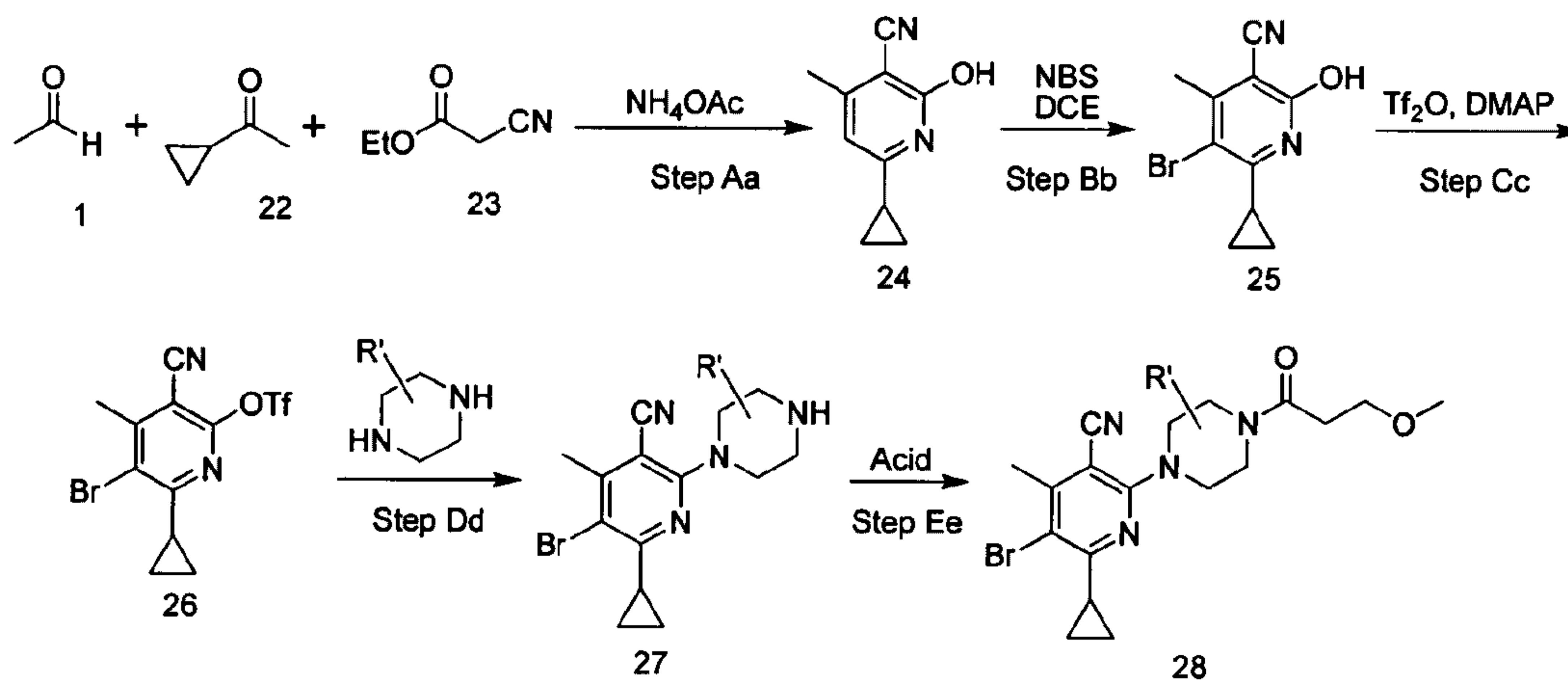
Step Q: (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (17). To a 25 mL of round-bottom flask was added (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (**16**; 1.26 g, 3.9 mmol), 3-methoxypropanoic acid (0.74 mL, 7.8 mmol), HATU (2.98 g, 7.8 mmol), DIPEA (2 mL, 11.76 mmol) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. Reaction mixture was

with Satd. NaHCO_3 and brine. The combined organic layer was then dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Column chromatography purification (30% EtOAc/petroleum ether) afforded 1.28 g of title compound as a white solid. MS (ES) $M+H$ expected 407.1, found 407.0. ^1H NMR (CHLOROFORM- d) δ 7.78 - 7.85 (m, 1H), 4.82 - 4.92 (m, 0.5H), 4.50 (d, $J = 13.6$ Hz, 0.5H), 4.18-4.21 (m, 2H), 4.07 - 4.16 (m, 1H), 3.75 - 3.82 (m, 0.5H), 3.70 - 3.75 (m, 2H), 3.45 - 3.55 (m, 0.5H), 3.36 (s, 3H), 3.15 - 3.27 (m, 1H), 2.92 - 3.14 (m, 1H), 2.67 - 2.78 (m, 1H), 2.51 - 2.61 (m, 1H), 2.40 - 2.51 (m, 1H), 1.34 (d, $J = 6.8$ Hz, 1.5H), 1.25 (d, $J = 2.5$ Hz, 1.5H), 1.09 (d, $J = 3.5$ Hz, 2H), 1.08 (s, 2H).

Other intermediates 17 were similarly prepared according to Scheme 2 by either: (1) replacing (R)-2-methylpiperazine in Step P with an alternately substituted or unsubstituted piperazine; and/or (2) replacing 3-methoxypropanoic acid in Step Q with an alternate acid.

Example 3 Preparation of (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile. (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (**28**; wherein R^{1a} is methyl; R^2 is cyclopropyl; m is 1; R^3 is 3-methyl; and R^8 is methoxyethyl) was prepared according to general Scheme 3, below.

Scheme 3:



Step Aa: 6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (24**).** To a suspension of ammonium acetate (140 g, 1.82 mol) in 400 mL of EtOH was added successively commercially available 1-cyclopropylethanone (**22**; 22.5 mL, 22.7 mmol), acetaldehyde (**21**; 10 g, 22.7 mmol), and ethyl cyanoacetate (**23**; 24.2 mL, 22.7 mmol). The resulting mixture was stirred at reflux temperature

for 2 hrs and subsequently at room temperature overnight. After the LC-MS showed the formation of the desired product, the solvent was removed under reduced pressure. Flash column chromatography (10% MeOH/DCM) afforded 1.3 g of **24** as a white solid. MS (ES) M+H expected 175.1, found 175.1. ¹H NMR (DMSO-d₆) δ 12.36 (br. s., 1H), 5.93 (s, 1H), 2.26 (s, 3H), 1.81 - 1.91 (m, 1H), 1.06 - 1.14 (m, 2H), 0.91 - 0.95 (m, 2H).

Step Bb: 5-bromo-6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (25). To a solution of 6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (**24**; 2.6 g, 15 mmol) in 10 mL of DCE was added NBS (4 g, 22.5 mmol) at room temperature. The reaction mixture was then heated at reflux for 3 hours. After LC-MS showed the completion of reaction, the mixture was cooled to room temperature and poured into water and extracted with methylene chloride. The combined organic layer was dried over anhy. Na₂SO₄ and concentrated *in vacuo*. Column chromatography (4% MeOH/DCM) afforded 4 g of **25** as a brown solid. MS (ES) M+H expected 253.0, found 253.0. ¹H NMR (CHLOROFORM-d) δ 2.68 (s, 3H), 1.79 - 1.88 (m, 1H), 1.03 - 1.09 (m, 2H), 0.93 - 1.01 (m, 2H).

Step Cc: 5-bromo-3-cyano-6-cyclopropyl-4-methylpyridin-2-yl trifluoromethanesulfonate (26). To a solution of 5-bromo-2-hydroxy-6-isopropylpyridinonitrile (**25**; 4.0 g, 14.6 mmol) in 20 mL of methylene chloride was added DMAP (178 mg, 1.46 mmol), and triethylamine (2.5 mL, 17.5 mmol). The mixture was cooled to 0°C in an ice-water bath, and trifluoromethanesulfonic anhydride (3.7 mL, 21.9 mmol) was added dropwise by syringe. The resulting reaction mixture was stirred at 0°C for 30 min then allowed to warm to room temperature and stirred overnight. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% EtOAc/petroleum ether) to afford 1.66 g of **26**. ¹H NMR (CHLOROFORM-d) δ 2.70 (s, 3H), 2.16 - 2.20 (m, 1H), 1.23-1.25 (m, 2H), 1.19- 1.22 (m, 2H).

Step Dd: (R)-5-bromo-6-cyclopropyl-4-methyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (27). A mixture of above triflate **26** (1.66 g, 4.3 mmol), (R)-2-methylpiperazine (738 mg, 6.46 mmol), and triethylamine (1.8 mL, 12.9 mmol) suspended in 5 mL of MeCN was subjected to microwave reaction at 150°C for 1 hour. After removal of solvent under reduced pressure, the residue was extracted between EtOAc and water. The organic layer was then washed with satd. aq. NaHCO₃ and brine, dried over anhy. Na₂SO₄ and concentrated *in vacuo*. Flash column

chromatography (10% DCM/MeOH) afforded 330 mg of **27** as a light yellowish solid. MS (ES) M+H expected 335.1, found 335.2. ¹H NMR (CHLOROFORM-d) δ 4.08 - 4.16 (m, 0.5H), 4.05 - 4.08 (m, 1H), 4.01 - 4.04 (m, 0.5H), 2.99 - 3.08 (m, 1H), 2.97 (d, J = 8.8 Hz, 2H), 2.88 - 2.95 (m, 1H), 2.58 - 2.65 (m, 1H), 2.55 - 2.57 (m, 3H), 1.77 (br. s., 1H), 1.12 (s, 1.5H), 1.10 (s, 1.5H), 1.05 - 1.09 (m, 2H), 1.00 - 1.05 (m, 2H).

Step Ee: *(R)*-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (**28**). To a 50 mL of round-bottom flask was added *(R)*-5-bromo-6-cyclopropyl-4-methyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (**27**; 1.12 g, 3.34 mmol), 3-methoxypropanoic acid (0.63 mL, 6.68 mmol), HATU (2.54 g, 6.68 mmol), DIPEA (3.8 g, 10 mmol) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. After washing the reaction mixture with Satd. NaHCO₃, brine, the organic layer was dried over anhy. Na₂SO₄ and concentrated *in vacuo*. Flash column chromatography (20% EtOAc/petroleum ether) afforded 1.7 g of **28** as a yellowish solid. MS (ES) M+H expected 421.1, found 421.3. ¹H NMR (CHLOROFORM-d) δ 4.90 (br. s., 0.5H), 4.52 (d, J = 13.6 Hz, 0.5H), 4.22 (br. s., 0.5H), 3.95 - 4.13 (m, 2H), 3.78 (br. s., 0.5H), 3.74 (t, J = 5.9 Hz, 2H), 3.50 - 3.61 (m, 0.5H), 3.38 (s, 3H), 3.07 - 3.24 (m, 1.5H), 2.90 - 3.06 (m, 1H), 2.65 - 2.79 (m, 1H), 2.60 (s, 3H), 2.52 - 2.63 (m, 1H), 2.17 - 2.21 (m, 1H), 1.37 (d, J = 6.5 Hz, 1.5H), 1.27 (d, J = 6.3 Hz, 1.5H), 1.09 (s, 2H), 1.05 - 1.08 (m, 2H).

Other intermediates **28** were similarly prepared according to Scheme 3 by either: (1) replacing *(R)*-2-methylpiperazine in Step Dd with an alternately substituted or unsubstituted piperazine; and/or (2) replacing 3-methoxypropanoic acid in Step Ee with an alternate acid.

Example 4 Preparation of *(R)*-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)-nicotinonitrile (Compound 189). A mixture of bromide **7** from Example 1 (26 mg, 0.06 mmol), 4-(trifluoromethyl)phenylboronic acid (17 mg, 0.089 mmol), Pd(PPh₃)₄ (3 mg, 0.003 mmol), and K₂CO₃ (16 mg, 0.119 mmol) suspended in 1 mL of DMF was subjected to microwave reaction at 150°C for 45 min. After the reaction, the reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography to afford 19 mg of Compound 189 as yellowish oil. MS (ES) M+H expected 475.2, found 475.1. ¹H

NMR (CHLOROFORM-d) δ 7.70 (d, J = 8.0 Hz, 2H), 7.60 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 4.93 (br. s., 0.5H), 4.56 (d, J = 11.0 Hz, 0.5H), 4.44 (d, J = 12.3 Hz, 1H), 4.32 - 4.39 (m, 1H), 4.28 (br. s., 0.5H), 3.83 (d, J = 13.3 Hz, 0.5H), 3.68 - 3.79 (m, 2H), 3.53 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.36 (br. s., 0.5H), 3.33 (br. s., 0.5H), 3.10 - 3.28 (m, 1.5H), 3.07 (dt, J = 13.3, 1 Hz, 1H), 2.65 - 2.80 (m, 1H), 2.52 - 2.65 (m, 1H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.30 (d, J = 6.3 Hz, 1.5H), 1.16 (d, J = 6.5 Hz, 6H).

Other Compounds of Formula II listed below, wherein R^{1b} is aryl or heteroaryl; and R² is isopropyl or cyclopropyl were similarly prepared using any of intermediates 7 (Scheme 1), 17 (Scheme 2), or 28 (Scheme 3) as starting material.

(R)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 185).

¹H NMR (CHLOROFORM-d) δ 7.70 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.47 - 7.56 (m, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 3.5 Hz, 1H), 6.48 - 6.55 (m, 1H), 4.86 - 4.96 (m, 1H), 4.43 - 4.59 (m, 2H), 4.38 (dt, J = 13.3, 2.0 Hz, 1H), 3.56 (br. s., 1H), 3.46 (dd, J = 13.3, 3.8 Hz, 1H), 3.28 (td, J = 12.4, 3.4 Hz, 1H), 3.07 (quin, J = 6.7 Hz, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.16 (dd, J = 6.7, 1.6 Hz, 6H). LC-MS : m/z 483.1(M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 187).

¹H NMR (CHLOROFORM-d) δ 7.76 (s, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.44 - 7.49 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 6.56 - 6.63 (m, 1H), 4.75 (br. s., 1H), 4.45 (d, J = 13.1 Hz, 1H), 4.35 - 4.42 (m, 2H), 3.42 - 3.64 (m, 1H), 3.31 - 3.41 (m, 1H), 3.18 (td, J = 12.5, 3.5 Hz, 1H), 3.07 (dt, J = 13.2, 6.6 Hz, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.16 (dd, J = 6.7, 1.9 Hz, 6H).. LC-MS : m/z 483.2 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 188).

¹H NMR (CHLOROFORM-d) δ 7.69 (d, J = 8.3 Hz, 2H), 7.59 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.22 (dd, J = 5.1, 1.1 Hz, 1H), 6.95 - 7.00 (m, 1H), 6.89 - 6.95 (m, 1H), 4.95 (br. s., 0.5H), 4.59 (d, J = 12.8 Hz, 0.5H), 4.19 - 4.48 (m, 3H), 3.89 - 4.06 (m, 2H), 3.82 (d, J = 13.6 Hz, 0.5H), 3.57 (t, J = 11.3 Hz, 0.5H), 3.20 - 3.38 (m, 1H), 3.08 - 3.20 (m, 1H), 3.00 - 3.08 (m, 1H), 1.35 (d, J = 6.5 Hz, 1.5H), 1.31 (d, J = 6.5 Hz, 1.5H), 1.15 (d, J = 6.5 Hz, 6H). LC-MS : m/z 513.1 (M+H)⁺.

(R)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-m-tolynicotinonitrile (Compound 190).

¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.51 (d, J = 1.0 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.01 - 7.09 (m, 3H), 6.51 (dd, J = 3.3, 1.8 Hz, 1H), 4.90 (br. s., 1H), 4.52 (d, J = 13.3 Hz, 1H), 4.42 (d, J = 13.8 Hz, 1H), 4.30 - 4.37 (m, 1H), 3.56 (br. s., 1H), 3.41 (dd, J = 13.2, 3.6 Hz, 1H), 3.24 (td, J = 12.4, 3.3 Hz, 1H), 3.15 (dt, J = 13.3, 6.7 Hz, 1H), 2.40 (s, 3H), 1.48 (d, J = 6.5 Hz, 3H), 1.15 (dd, J = 6.8, 2.3 Hz, 6H). LC-MS : m/z 429.1 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-m-tolynicotinonitrile (Compound 191).

¹H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.61 (s, 1H), 7.46 (t, J = 1.6 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.20 (d, J = 7.8 Hz, 1H), 7.00 - 7.08 (m, 2H), 6.59 (d, J = 1.0 Hz, 1H), 4.74 (br. s., 1H), 4.20 - 4.50 (m, 3H), 3.41 - 3.61 (m, 1H), 3.32 (dd, J = 13.1, 3.0 Hz, 1H), 3.08 - 3.19 (m, 2H), 2.40 (s, 3H), 1.45 (d, J = 6.8 Hz, 3H), 1.08 - 1.19 (m, 6H). LC-MS : m/z 429.1 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-5-m-tolynicotinonitrile (Compound 192).

¹H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.28 - 7.35 (m, 1H), 7.16 - 7.25 (m, 2H), 7.00 - 7.07 (m, 2H), 6.89 - 6.99 (m, 2H), 4.94 (br. s., 0.5H), 4.58 (d, J = 13.3 Hz, 0.5H), 4.33 - 4.43 (m, 1H), 4.19 - 4.33 (m, 2H), 3.90 - 4.05 (m, 2H), 3.80 (d, J = 13.3 Hz, 0.5H), 3.51 - 3.63 (m, 0.5H), 3.17 - 3.33 (m, 1H), 3.10 - 3.17 (m, 1H), 2.99 - 3.10 (m, 1H), 2.40 (s, 3H), 1.36 (d, J = 6.3 Hz, 1.5H), 1.32 (d, J = 6.8 Hz, 1.5H), 1.14 (d, J = 6.8 Hz, 6H). LC-MS : m/z 459.1 (M+H)⁺.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-m-tolynicotinonitrile (Compound 193).

¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 7.01 - 7.08 (m, 2H), 4.93 (br. s., 0.5H), 4.56 (d, J = 13.1 Hz, 0.5H), 4.30 - 4.44 (m, 2H), 4.19 - 4.30 (m, 1H), 3.81 (d, J = 13.6 Hz, 0.5H), 3.71 - 3.78 (m, 2H), 3.52 - 3.65 (m, 0.5H), 3.38 (s, 3H), 3.24 - 3.36 (m, 1H), 3.10 - 3.23 (m, 2H), 2.65 - 2.80 (m, 1H), 2.54 - 2.64 (m, 1H), 2.40 (s, 3H), 1.41 (d, J = 6.5 Hz, 1.5H), 1.31 (d, J = 6.8 Hz, 1.5H), 1.15 (d, J = 6.5 Hz, 6H). LC-MS : m/z 421.1 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-isopropylpiperazin-1-yl)-6-isopropyl-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 195).

¹H NMR (CHLOROFORM-d) δ 7.67 - 7.84 (m, 3H), 7.57 - 7.64 (m, 1H), 7.45 - 7.53 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 6.58 (s, 1H), 4.84 (d, J = 13.6 Hz, 1H), 4.49-4.69(m, 2H), 3.81 - 4.22 (m, 1H), 3.22-3.57 (br. s., 3H), 3.07 (dt, J = 13.3, 6.7 Hz, 1H), 2.19 - 2.38 (m, 1H), 1.18 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 0.88 - 1.05 (m, 6H). LC-MS : m/z 511.1 (M+H)⁺.

(R)-6-isopropyl-2-(3-isopropyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)-nicotinonitrile (Compound 196).

¹H NMR (CHLOROFORM-d) δ 7.64 - 7.75 (m, 2H), 7.55 - 7.62 (m, 1H), 7.37-7.46 (d, J = 8.5 Hz, 2H), 7.22 (ddd, J = 4.8, 3.2, 1.3 Hz, 1H), 6.87 - 7.02 (m, 2H), 4.68 - 4.82 (m, 1.5H), 4.35 - 4.54 (m, 1.5H), 3.81 - 4.11 (m, 3H), 3.63 (d, J = 10.3 Hz, 0.5H), 3.37 - 3.53 (m, 0.5H), 3.08 - 3.20 (m, 1H), 2.96 - 3.08 (m, 2H), 2.18 - 2.32 (m, 0.5H), 2.04 - 2.17 (m, 0.5H), 1.17 (dd, J = 6.7, 3.6 Hz, 3H), 1.13 (d, J = 6.5 Hz, 3H), 1.08 (dd, J = 11.0, 6.5 Hz, 3H), 0.87 - 0.93 (m, 1.5H), 0.85 (d, J = 6.8 Hz, 1.5H). LC-MS : m/z 541.1 (M+H)⁺.

(R)-6-isopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 197).

¹H NMR (CHLOROFORM-d) δ 7.66 - 7.76 (m, 2H), 7.59 (d, J = 2.3 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 4.68 - 4.84 (m, 1.5H), 4.47-4.5 (s, 1.5H), 3.88 (d, J = 13.6 Hz, 0.5H), 3.69 - 3.82 (m, 2H), 3.61 (d, J = 10.3 Hz, 0.5H), 3.42 - 3.52 (m, 0.5H), 3.38 (d, J = 2.8 Hz, 3H), 3.12 - 3.27 (m, 2H), 3.02 - 3.12 (m, 1H), 2.90 - 3.02 (m, 0.5H), 2.53 - 2.83 (m, 2H), 2.17 - 2.30 (m, 0.5H), 1.98 - 2.16 (m, 0.5H), 1.18 (d, J = 6.5 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.08 (dd, J = 6.5, 2.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 1.5H), 0.85 (d, J = 6.8 Hz, 1.5H). LC-MS : m/z 407.4 (M+H)⁺.

(R)-5-(4-fluorophenyl)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)nicotinonitrile (Compound 199).

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.17 - 7.24 (m, 2H), 7.08 - 7.16 (m, 2H), 6.38 (d, J = 1.8 Hz, 1H), 4.68 (br. s., 1H), 4.41 (d, J = 13.1 Hz, 1H), 4.36 (d, J = 13.1 Hz, 1H), 4.20-4.28 (d, J = 13.6 Hz, 1H), 3.39 - 3.59 (m, 1H), 3.25 - 3.37 (m, 1H), 3.03 - 3.18 (m, 2H), 2.41 (s, 3H), 1.41 (d, J = 6.5 Hz, 3H), 1.14 (dd, J = 6.8, 2.3 Hz, 6H). LC-MS : m/z 447.2 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-m-tolylnicotinonitrile (Compound 200).

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.29 (d, J = 2.0 Hz, 2H), 7.17 - 7.24 (m, 1H), 7.08 - 7.16 (m, 2H), 6.38 (d, J = 1.8 Hz, 1H), 4.68 (br. s., 1H), 4.41 (d, J = 13.1 Hz, 1H), 4.36 (d, J = 13.1 Hz, 1H), 4.20-4.28 (d, J = 13.6 Hz, 1H), 3.39 - 3.59 (m, 4H), 3.25 - 3.37 (m, 4H), 3.03 - 3.18 (m, 8H), 2.41 (s, 11H), 1.41 (d, J = 6.5 Hz, 11H), 1.14 (dd, J = 6.8, 2.3 Hz, 6H). LC-MS : m/z 443.3 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)-nicotinonitrile (Compound 201).

¹H NMR (CHLOROFORM-d) δ 7.70 (d, J = 8.0 Hz, 2H), 7.57 - 7.64 (m, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.27 - 7.32 (m, 1H), 6.35 - 6.42 (m, 1H), 4.68 (br. s., 1H), 4.34 - 4.53 (m, 2H), 4.20 - 4.34 (m, 1H), 3.48 (d, J = 4.8 Hz, 1H), 3.28 - 3.40 (m, 1H), 3.16 (td, J = 12.6, 3.4 Hz, 1H), 3.00 - 3.11 (m, 1H), 2.41 (s, 3H), 1.38 - 1.48 (m, 3H), 1.16 (dd, J = 6.8, 2.3 Hz, 6H). LC-MS : m/z 497.2 (M+H)⁺.

(R)-6-isopropyl-5-(4-isopropylphenyl)-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)nicotinonitrile (Compound 202).

¹H NMR (CHLOROFORM-d) δ 7.58 - 7.65 (m, 1H), 7.28 (d, J = 8.3 Hz, 3H), 7.11 - 7.20 (m, 2H), 6.37 (d, J = 2.0 Hz, 1H), 4.59-4.68 (br. s., 1H), 4.30 - 4.43 (m, 2H), 4.19 (br. s., 1H), 3.40 - 3.54 (m, 1H), 3.30 (dd, J = 12.8, 3.0 Hz, 1H), 3.14 - 3.22 (m, 1H), 3.06 - 3.14 (m, 1H), 2.96 (spt, J = 6.9 Hz, 1H), 2.41 (s, 3H), 1.39 - 1.45 (m, 3H), 1.30 (d, J = 7.0 Hz, 6H), 1.15 (dd, J = 6.8, 3.0 Hz, 6H). LC-MS : m/z 471.3 (M+H)⁺.

(R)-5-(furan-3-yl)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)nicotinonitrile (Compound 203).

¹H NMR (CHLOROFORM-d) δ 7.64 (s, 1H), 7.49 - 7.53 (m, 1H), 7.43 - 7.47 (m, 1H), 7.29 (d, J = 1.8 Hz, 1H), 6.45 (d, J = 0.8 Hz, 1H), 6.36 (d, J = 1.8 Hz, 1H), 4.68 (br. s., 1H), 4.39 (d, J = 13.1 Hz, 1H), 4.34 (d, J = 13.1 Hz, 1H), 4.18-4.26 (br. s., 1H), 3.38 - 3.56 (m, 1H), 3.22 - 3.35 (m, 2H), 3.11 (td, J = 12.6, 3.4 Hz, 1H), 2.36 - 2.47 (m, 3H), 1.39 (d, J = 6.5 Hz, 3H), 1.18 (dd, J = 6.7, 1.6 Hz, 6H). LC-MS : m/z 419.2 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-5-(furan-3-yl)-6-isopropylnicotinonitrile (Compound 204).

¹H NMR (CHLOROFORM-d) δ 7.72 - 7.77 (m, 1H), 7.64 (s, 1H), 7.50 (t, J = 1.8 Hz, 1H), 7.44 - 7.47 (m, 2H), 6.58 (dd, J = 1.8, 0.8 Hz, 1H), 6.45 (dd, J = 1.8, 0.8 Hz, 1H), 5.30 (s, 1H), 4.73 (br.

s., 1H), 4.38 (s, 1H), 4.41 (s, 1H), 4.31 (t, J = 2.1 Hz, 1H), 4.35 (t, J = 2.0 Hz, 1H), 3.48 (br. s., 1H), 3.32 (dd, J = 9.9, 3.1 Hz, 1H), 3.24 - 3.30 (m, 1H), 3.14 (td, J = 12.5, 3.5 Hz, 1H), 1.42 (d, J = 7.0 Hz, 3H), 1.19 (dd, J = 6.8, 1.0 Hz, 6H). LC-MS : m/z 405.2 (M+H)⁺.

(R)-5-(furan-3-yl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 205)

¹H NMR (CHLOROFORM-d) δ 7.63 (s, 1H), 7.50 (t, J = 1.8 Hz, 1H), 7.42 - 7.47 (m, 1H), 6.44 (dd, J = 1.8, 0.8 Hz, 1H), 4.92 (br. s., 0.5H), 4.54 (d, J = 13.1 Hz, 0.5H), 4.38 (dd, J = 12.2, 2.1 Hz, 1H), 4.17 - 4.35 (m, 2H), 3.80 (d, J = 13.1 Hz, 0.5H), 3.74 (t, J = 6.5 Hz, 2H), 3.51 - 3.62 (m, 0.5H), 3.36 - 3.39 (m, 3H), 3.23 - 3.35 (m, 2H), 3.06 - 3.17 (m, 1H), 2.64 - 2.80 (m, 1H), 2.51 - 2.63 (m, 1H), 1.38 (d, J = 6.3 Hz, 1.5H), 1.28 (d, J = 6.0 Hz, 1.5H), 1.19 (d, J = 6.8 Hz, 6H). LC-MS : m/z 397.2 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(4-isopropylphenyl)nicotinonitrile (Compound 206)

¹H NMR (CHLOROFORM-d) δ 7.72 - 7.77 (m, 1H), 7.61 (s, 1H), 7.46 (t, J = 1.6 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.12 - 7.19 (m, 2H), 6.59 (dd, J = 1.8, 0.8 Hz, 1H), 4.74 (br. s., 1H), 4.39 (d, J = 13.3 Hz, 1H), 4.33 (dt, J = 13.2, 1.9 Hz, 2H), 3.49 (br. s., 1H), 3.32 (dd, J = 13.2, 3.4 Hz, 1H), 3.08 - 3.23 (m, 2H), 2.96 (dt, J = 13.8, 6.9 Hz, 1H), 1.45 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 7.0 Hz, 6H), 1.15 (dd, J = 6.5, 2.3 Hz, 6H). LC-MS : m/z 457.2 (M+H)⁺.

(R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 207)

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.17 - 7.24 (m, 2H), 7.08 - 7.16 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J = 12.0 Hz, 0.5H), 4.40 (dd, J = 12.2, 1.9 Hz, 1H), 4.19 - 4.35 (m, 2H), 3.82 (d, J = 12.5 Hz, 0.5H), 3.69 - 3.78 (m, 2H), 3.53 - 3.63 (m, 0.5H), 3.38 (s, 3H), 3.26 - 3.35 (m, 1H), 3.13 - 3.22 (m, 1H), 3.03 - 3.12 (m, 1H), 2.65 - 2.81 (m, 1H), 2.53 - 2.64 (m, 1H), 1.40 (d, J = 6.3 Hz, 1.5H), 1.30 (d, J = 6.5 Hz, 1.5H), 1.14 (d, J = 6.8 Hz, 6H). LC-MS : m/z 425.2 (M+H)⁺.

(R)-6-isopropyl-5-(4-isopropylphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 208)

¹H NMR (CHLOROFORM-d) δ 7.59 - 7.65 (m, 1H), 7.29 - 7.33 (m, 2H), 7.14 - 7.22 (m, 2H), 4.95 (br. s., 0.5H), 4.58 (d, J = 13.1 Hz, 0.5H), 4.37 - 4.44 (m, 1H), 4.22 - 4.37 (m, 2H), 3.83 (d,

J = 13.3 Hz, 0.5H), 3.70 - 3.80 (m, 2H), 3.55 - 3.67 (m, 0.5H), 3.40 (s, 3H), 3.33 (t, J = 12.3 Hz, 1H), 3.15 - 3.25 (m, 2H), 2.98 (quin, J = 6.9 Hz, 1H), 2.67 - 2.83 (m, 1H), 2.55 - 2.67 (m, 1H), 1.43 (d, J = 5.8 Hz, 1.5H), 1.34 (m, 1.5H), 1.32 (d, J = 7.0 Hz, 6H), 1.17 (d, J = 6.8 Hz, 6H). LC-MS : m/z 449.2 (M+H)⁺.

(R)-5-(benzofuran-2-yl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 209).

¹H NMR (CHLOROFORM-d) δ 8.12 (s, 1H), 7.61 (dd, J = 7.7, 0.9 Hz, 1H), 7.48 - 7.56 (m, 1H), 7.32 (td, J = 7.7, 1.5 Hz, 1H), 7.24 - 7.29 (m, 1H), 6.78 - 6.88 (m, 1H), 4.93 (br. s., 0.5H), 4.38 - 4.64 (m, 2H), 4.27 (br. s., 0.5H), 3.83 (d, J = 12.8 Hz, 1H), 3.75 (br. s., 2H), 3.55 (quin, J = 6.7 Hz, 2H), 3.38 (s, 3H), 3.08 - 3.29 (m, 2H), 2.66 - 2.83 (m, 1H), 2.60 (br. s., 1H), 1.38 (d, J = 6.0 Hz, 1.5H), 1.33 (br. s., 1.5H), 1.28 (d, J = 6.5 Hz, 6H). LC-MS : m/z 447.1 (M+H)⁺.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(pyrimidin-5-yl)nicotinonitrile (Compound 210).

¹H NMR (CHLOROFORM-d) δ 9.23 - 9.28 (m, 1H), 8.69 (s, 2H), 7.62 (s, 1H), 4.94 (br. s., 0.5H), 4.56 (d, J = 9.5 Hz, 0.5H), 4.37 - 4.53 (m, 2H), 4.29 (br. s., 0.5H), 3.84 (d, J = 13.3 Hz, 0.5H), 3.68 - 3.79 (m, 2H), 3.52 - 3.64 (m, 0.5H), 3.40 - 3.46 (m, 0.5H), 3.38 (s, 3H), 3.20 - 3.32 (m, 1H), 3.16 (d, J = 9.5 Hz, 1H), 2.93 - 3.04 (m, 1H), 2.65 - 2.78 (m, 1H), 2.52 - 2.64 (m, 1H), 1.39 (d, J = 6.5 Hz, 1.5H), 1.29 (d, J = 6.8 Hz, 1.5H), 1.19 (dd, J = 6.7, 1.1 Hz, 6H). LC-MS : m/z 409.2 (M+H)⁺.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(naphthalen-2-yl)nicotinonitrile (Compound 211).

¹H NMR (CHLOROFORM-d) δ 7.83 - 7.97 (m, 3H), 7.66 - 7.77 (m, 2H), 7.49 - 7.60 (m, 2H), 7.36 (dd, J = 8.4, 1.6 Hz, 1H), 4.94 (br. s., 0.5H), 4.57 (d, J = 12.8 Hz, 0.5H), 4.42 (d, J = 12.8 Hz, 1H), 4.30 - 4.38 (m, 1H), 4.27 (br. s., 1H), 3.83 (d, J = 13.3 Hz, 0.5H), 3.69 - 3.79 (m, 2H), 3.54 - 3.65 (m, 0.5H), 3.39 (s, 3H), 3.29 - 3.38 (m, 1H), 3.18 - 3.24 (m, 1H), 3.06 - 3.17 (m, 1H), 2.66 - 2.83 (m, 1H), 2.52 - 2.65 (m, 1H), 1.42 (d, J = 7.3 Hz, 1.5H), 1.32 (d, J = 6.5 Hz, 1.5H), 1.17 (d, J = 6.8 Hz, 6H). LC-MS : m/z 457.1 (M+H)⁺.

(R)-6-isopropyl-5-(3-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 212).

¹H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.34 (t, J = 7.9 Hz, 1H), 6.92 (dd, J = 8.3, 1.8 Hz, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.74 - 6.79 (m, 1H), 4.93 (br. s., 0.5H), 4.56 (d, J = 12.8 Hz, 0.5H), 4.39 (d, J = 13.6 Hz, 1H), 4.21 - 4.34 (m, 2H), 3.84 (s, 3H), 3.79 (d, J = 8.0 Hz, 0.5H), 3.70 - 3.77 (m, 2H), 3.53 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.26 - 3.36 (m, 1H), 3.12 - 3.22 (m, 2H), 2.65 - 2.80 (m, 1H), 2.52 - 2.64 (m, 1H), 1.41 (d, J = 1.5 Hz, 4H), 1.31 (d, J = 6.5 Hz, 1.5H), 1.10 - 1.19 (m, 6H). LC-MS : m/z 437.1 (M+H)⁺.

(R)-2-isopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4'-bipyridine-5-carbonitrile (Compound 213)

¹H NMR (CHLOROFORM-d) δ 8.69 (d, J = 5.3 Hz, 2H), 7.61 (s, 1H), 7.22 (d, J = 5.5 Hz, 2H), 4.93 (br. s., 0.5H), 4.56 (d, J = 9.8 Hz, 0.5H), 4.34 - 4.51 (m, 2H), 4.28 (br. s., 1H), 3.83 (d, J = 13.3 Hz, 0.5H), 3.68 - 3.79 (m, 2H), 3.58 (t, J = 11.0 Hz, 0.5H), 3.38 (s, 3H), 3.14 - 3.28 (m, 2H), 3.03 - 3.14 (m, 1H), 2.65 - 2.83 (m, 1H), 2.52 - 2.65 (m, 1H), 1.39 (d, J = 6.3 Hz, 1.5H), 1.29 (d, J = 6.5 Hz, 1.5H), 1.18 (d, J = 6.5 Hz, 6H). LC-MS : m/z 408.1 (M+H)⁺.

(R)-6-isopropyl-5-(4-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 214)

¹H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.11 - 7.20 (m, 2H), 6.92 - 7.01 (m, 2H), 4.92 (br. s., 0.5H), 4.56 (d, J = 12.8 Hz, 0.5H), 4.37 (d, J = 12.5 Hz, 1H), 4.29 (d, J = 13.1 Hz, 2H), 3.86 (s, 3H), 3.81 (d, J = 13.6 Hz, 0.5H), 3.75 (br. s., 2H), 3.53 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.31 (t, J = 13.2 Hz, 1H), 3.11 - 3.20 (m, 2H), 2.66 - 2.82 (m, 1H), 2.52 - 2.64 (m, 1H), 1.41 (d, J = 6.0 Hz, 1.5H), 1.31 (d, J = 5.8 Hz, 1.5H), 1.14 (d, J = 6.8 Hz, 6H). LC-MS : m/z 437.3 (M+H)⁺.

(R)-5-(4-chlorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 215)

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.38 - 7.43 (m, 2H), 7.14 - 7.20 (m, 2H), 4.93 (br. s., 0.5H), 4.55 (d, J = 12.5 Hz, 0.5H), 4.40 (d, J = 12.8 Hz, 1H), 4.21 - 4.36 (m, 2H), 3.82 (d, J = 13.6 Hz, 0.5H), 3.69 - 3.78 (m, 2H), 3.53 - 3.63 (m, 0.5H), 3.38 (s, 3H), 3.27 - 3.37 (m, 1H), 3.11 - 3.23 (m, 1H), 3.02 - 3.11 (m, 1H), 2.65 - 2.81 (m, 1H), 2.53 - 2.64 (m, 1H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.30 (d, J = 6.8 Hz, 1.5H), 1.14 (d, J = 6.5 Hz, 6H). LC-MS : m/z 441.1 (M+H)⁺.

5-(4-ethylphenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 216)

¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.27 (s, 1H), 7.25 (s, 1H), 7.15 (d, J = 8.0 Hz, 2H), 4.93 (br. s., 0.5H), 4.56 (d, J = 12.5 Hz, 0.5H), 4.38 (d, J = 12.3 Hz, 1H), 4.30 (d, J = 12.3 Hz, 2H), 3.81 (d, J = 13.3 Hz, 0.5H), 3.75 (br. s., 2H), 3.51 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.31 (t, J = 13.6 Hz, 1H), 3.12 - 3.22 (m, 2H), 3.10 (d, J = 14.3 Hz, 0.5H), 2.77 (br. s., 0.5H), 2.71 (q, J = 7.5 Hz, 2H), 2.61 (br. s., 1H), 1.41 (d, J = 6.0 Hz, 1.5H), 1.32 (br. s., 1.5H), 1.29 (t, J = 7.5 Hz, 3H), 1.15 (d, J = 6.8 Hz, 6H). LC-MS : m/z 435.3 (M+H)⁺.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(naphthalen-1-yl)nicotinonitrile (Compound 217)

¹H NMR (CHLOROFORM-d) δ 7.92 (t, J = 7.4 Hz, 2H), 7.63 (s, 1H), 7.49 - 7.57 (m, 2H), 7.39 - 7.47 (m, 2H), 7.27 - 7.34 (m, 1H), 4.96 (br. s., 0.5H), 4.59 (d, J = 12.5 Hz, 0.5H), 4.45 (d, J = 13.3 Hz, 1H), 4.32 - 4.41 (m, 1H), 4.30 (br. s., 1H), 3.85 (d, J = 13.6 Hz, 0.5H), 3.70 - 3.81 (m, 2H), 3.55 - 3.67 (m, 0.5H), 3.39 (s, 3H), 3.07 - 3.27 (m, 2H), 2.67 - 2.76 (m, 2H), 2.53 - 2.66 (m, 1H), 1.45 (d, J = 5.5 Hz, 1.5H), 1.36 (d, J = 6.5 Hz, 1.5H), 1.06 (d, J = 6.5 Hz, 6H). LC-MS : m/z 457.3 (M+H)⁺.

(R)-5-(3-chlorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 218)

¹H NMR (CHLOROFORM-d) δ 7.56 - 7.61 (m, 1H), 7.35 - 7.39 (m, 2H), 7.21 - 7.25 (m, 1H), 7.11 - 7.14 (m, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J = 11.8 Hz, 0.5H), 4.42 (d, J = 12.5 Hz, 1H), 4.29 - 4.37 (m, 1H), 4.26 (br. s., 1H), 3.82 (d, J = 13.6 Hz, 0.5H), 3.68 - 3.78 (m, 2H), 3.53 - 3.65 (m, 0.5H), 3.38 (s, 3H), 3.28 - 3.37 (m, 1H), 3.12 - 3.24 (m, 1H), 3.04 - 3.12 (m, 1H), 2.65 - 2.80 (m, 1H), 2.50 - 2.64 (m, 1H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.30 (d, J = 6.5 Hz, 1.5H), 1.15 (d, J = 6.5 Hz, 6H). LC-MS : m/z 441.2 (M+H)⁺.

(R)-5-(3,4-dimethylphenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 220)

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.18 (d, J = 7.5 Hz, 1H), 7.00 (s, 1H), 6.97 (dd, J = 7.7, 1.6 Hz, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J = 13.1 Hz, 0.5H), 4.32 - 4.42 (m, 1H), 4.29 (d, J = 12.8 Hz, 1H), 3.78 - 3.85 (m, 0.5H), 3.71 - 3.77 (m, 2H), 3.53 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.24 - 3.35 (m, 1H), 3.17 (dt, J = 13.3, 6.7 Hz, 2H), 3.01 - 3.12 (m, 1H), 2.65 - 2.80 (m, 1H), 2.53 - 2.63 (m, 1H), 2.31 (d, J = 3.0 Hz, 6H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.31 (d, J = 6.8 Hz, 1.5H), 1.14 (d, J = 6.5 Hz, 6H). LC-MS : m/z 435.4 (M+H)⁺.

(R)-5-(3-fluoro-4-methylphenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 221).

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.23 (t, J = 8.0 Hz, 1H), 6.90 - 6.95 (m, 1H), 6.89 (dd, J = 5.8, 1.3 Hz, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J = 12.8 Hz, 0.5H), 4.21 - 4.45 (m, 3H), 3.81 (d, J = 13.3 Hz, 0.5H), 3.70 - 3.77 (m, 2H), 3.52 - 3.63 (m, 0.5H), 3.38 (s, 3H), 3.26 - 3.37 (m, 1H), 3.10 - 3.18 (m, 2H), 2.65 - 2.80 (m, 1H), 2.53 - 2.63 (m, 1H), 2.33 (d, J = 1.5 Hz, 3H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.30 (d, J = 6.5 Hz, 1.5H), 1.15 (d, J = 6.8 Hz, 6H). LC-MS : m/z 439.4 (M+H)⁺.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-phenylnicotinonitrile (Compound 222).

¹H NMR (CHLOROFORM-d) δ 7.56 - 7.61 (m, 1H), 7.35 - 7.39 (m, 3H), 7.21 - 7.25 (m, 2H), 4.93 (br. s., 0.5H), 4.55 (d, J = 11.8 Hz, 0.5H), 4.42 (d, J = 12.5 Hz, 1H), 4.29 - 4.37 (m, 1H), 4.26 (br. s., 1H), 3.82 (d, J = 13.6 Hz, 0.5H), 3.68 - 3.78 (m, 2H), 3.53 - 3.65 (m, 0.5H), 3.38 (s, 3H), 3.28 - 3.37 (m, 1H), 3.12 - 3.24 (m, 1H), 3.04 - 3.12 (m, 1H), 2.65 - 2.80 (m, 1H), 2.50 - 2.64 (m, 1H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.30 (d, J = 6.5 Hz, 1.5H), 1.15 (d, J = 6.5 Hz, 6H). LC-MS : m/z 407.4 (M+H)⁺.

(R)-5-(3,4-dimethoxyphenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 223).

¹H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 6.92 (d, J = 8.3 Hz, 1H), 6.78 (dd, J = 8.2, 1.9 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 4.88 - 4.96 (m, 0.5H), 4.55 (d, J = 13.1 Hz, 0.5H), 4.18 - 4.46 (m, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.78 - 3.86 (m, 0.5H), 3.71 - 3.78 (m, 2H), 3.52 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.31 (t, J = 10.8 Hz, 1H), 3.10 - 3.22 (m, 2H), 2.65 - 2.80 (m, 1H), 2.52 - 2.64 (m, 1H), 1.33 (s, 1.5H), 1.28 (s, 1.5H), 1.16 (d, J = 6.8 Hz, 6H). LC-MS : m/z 467.3 (M+H)⁺.

(R)-5-(benzo[d][1,3]dioxol-5-yl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 224).

¹H NMR (CHLOROFORM-d) δ 7.57 (s, 1H), 6.83 - 6.90 (m, 1H), 6.64 - 6.73 (m, 2H), 6.02 (s, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J = 12.5 Hz, 0.5H), 4.20 - 4.43 (m, 3H), 3.81 (d, J = 12.8 Hz, 0.5H), 3.74 (t, J = 6.3 Hz, 2H), 3.53 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.25 - 3.36 (m, 1H), 3.10 - 3.22 (m, 2H), 2.64 - 2.80 (m, 1H), 2.52 - 2.64 (m, 1H), 1.40 (d, J = 6.0 Hz, 1.5H), 1.30 (d, J = 6.5 Hz, 1.5H), 1.14 (d, J = 6.8 Hz, 6H). LC-MS : m/z 451.3 (M+H)⁺.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-(trifluoromethoxy)phenyl)nicotinonitrile (Compound 230).

¹H NMR (CHLOROFORM-d) δ 7.58 - 7.63 (m, 1H), 7.42 - 7.51 (m, 1H), 7.22 - 7.26 (m, 1H), 7.18 (dd, J = 7.8, 1.3 Hz, 1H), 7.11 (s, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J = 11.8 Hz, 0.5H), 4.27 - 4.46 (m, 3H), 3.78 - 3.88 (m, 0.5H), 3.75 (t, J = 6.4 Hz, 2H), 3.50 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.29 - 3.36 (m, 1H), 3.13 - 3.24 (m, 1H), 3.07 (dt, J = 13.3, 6.7 Hz, 1H), 2.65 - 2.81 (m, 1H), 2.52 - 2.64 (m, 1H), 1.40 (d, J = 6.3 Hz, 1.5H), 1.30 (d, J = 6.3 Hz, 1.5H), 1.16 (d, J = 6.5 Hz, 6H). LC-MS : m/z 491.3 (M+H)⁺.

(R)-5-(3-fluorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 231).

¹H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.39 (td, J = 8.0, 6.1 Hz, 1H), 7.05 - 7.13 (m, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.95 (dt, J = 9.4, 2.1 Hz, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J = 11.8 Hz, 0.5H), 4.26 - 4.45 (m, 3H), 3.82 (d, J = 13.1 Hz, 0.5H), 3.75 (t, J = 6.1 Hz, 2H), 3.51 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.27 - 3.35 (m, 1H), 3.16 - 3.23 (m, 1H), 3.09 - 3.14 (m, 1H), 2.65 - 2.81 (m, 1H), 2.60 (t, J = 5.9 Hz, 1H), 1.40 (d, J = 6.3 Hz, 1.5H), 1.30 (d, J = 6.5 Hz, 1.5H), 1.15 (d, J = 6.8 Hz, 6H). LC-MS : m/z 443.3 (M+H)⁺.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4-(trifluoromethoxy)phenyl)nicotinonitrile (Compound 232).

¹H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.27 (s, 4H), 4.93 (br. s., 0.5H), 4.49 - 4.61 (m, 0.5H), 4.26 - 4.47 (m, 3H), 3.82 (d, J = 13.6 Hz, 0.5H), 3.72 - 3.77 (m, 2H), 3.51 - 3.65 (m, 0.5H), 3.38 (s, 3H), 3.28 - 3.36 (m, 1H), 3.13 - 3.23 (m, 1H), 3.08 (dt, J = 13.3, 6.7 Hz, 1H), 2.65 - 2.80 (m, 1H), 2.60 (t, J = 5.9 Hz, 1H), 1.40 (d, J = 6.0 Hz, 1.5H), 1.30 (d, J = 6.5 Hz, 1.5H), 1.16 (d, J = 6.5 Hz, 6H). LC-MS : m/z 491.3 (M+H)⁺.

(R)-5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 233).

¹H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.27 (s, 4H), 4.93 (br. s., 0.5H), 4.49 - 4.61 (m, 0.5H), 4.26 - 4.47 (m, 3H), 3.82 (d, J = 13.6 Hz, 0.5H), 3.72 - 3.77 (m, 2H), 3.51 - 3.65 (m, 0.5H), 3.38 (s, 3H), 3.28 - 3.36 (m, 1H), 3.13 - 3.23 (m, 1H), 3.08 (dt, J = 13.3, 6.7 Hz, 1H), 2.65 - 2.80 (m, 1H), 2.60 (t, J = 5.9 Hz, 1H), 1.40 (d, J = 6.0 Hz, 1.5H), 1.30 (d, J = 6.5 Hz, 1.5H), 1.16 (d, J = 6.5 Hz, 6H). LC-MS : m/z 465.3 (M+H)⁺.

(R)-6-isopropyl-5-(isoquinolin-4-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 234).

¹H NMR (CHLOROFORM-d) δ 9.33 (s, 1H), 8.37 (s, 1H), 8.06 - 8.16 (m, 1H), 7.64 - 7.69 (m, 2H), 7.45 - 7.50 (m, 2H), 4.96 (br. s., 0.5H), 4.58 (br. s., 0.5H), 4.31 - 4.54 (m, 3H), 3.86 (d, J = 12.5 Hz, 0.5H), 3.76 (t, J = 6.4 Hz, 2H), 3.56 - 3.67 (m, 0.5H), 3.42 (d, J = 3.8 Hz, 1H), 3.36 - 3.40 (m, 3H), 3.08 - 3.33 (m, 1H), 2.65 - 2.78 (m, 2H), 2.54 - 2.64 (m, 1H), 1.44 (d, J = 4.5 Hz, 1.5H), 1.35 (d, J = 6.0 Hz, 1.5H), 1.05 - 1.11 (m, 6H). LC-MS : m/z 458.2 (M+H)⁺.

(R)-6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 219).

¹H NMR (CHLOROFORM-d) δ 7.57 (s, 1H), 7.31 - 7.39 (m, 2H), 7.27 (s, 1H), 7.10 - 7.18 (m, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.6 Hz, 0.5H), 4.07 - 4.33 (m, 3H), 3.77 - 3.84 (m, 0.5H), 3.71 - 3.76 (m, 2H), 3.48 - 3.60 (m, 0.5H), 3.36 - 3.41 (m, 3H), 3.25 (t, J = 10.4 Hz, 1H), 3.06 - 3.18 (m, 1H), 2.63 - 2.79 (m, 1H), 2.51 - 2.62 (m, 1H), 1.95 - 2.07 (m, 1H), 1.38 (d, J = 6.5 Hz, 1.5H), 1.28 (d, J = 6.8 Hz, 1.5H), 1.12 - 1.18 (m, 2H), 0.91 - 0.97 (m, 2H). LC-MS : m/z 423.3 (M+H)⁺.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-m-tolylnicotinonitrile (Compound 225).

¹H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.30 - 7.36 (m, 1H), 7.14 - 7.22 (m, 3H), 4.90 (br. s., 0.5H), 4.52 (d, J = 13.1 Hz, 0.5H), 3.80 - 4.36 (m, 3H), 3.80 (br. s., 0.5H), 3.74 (t, J = 6.3 Hz, 2H), 3.50 - 3.61 (m, 0.5H), 3.37 (s, 3H), 3.19 - 3.29 (m, 1H), 3.07 - 3.17 (m, 1H), 2.63 - 2.80 (m, 1H), 2.53 - 2.62 (m, 1H), 2.41 (s, 3H), 2.03 - 2.13 (m, 1H), 1.39 (d, J = 5.8 Hz, 1.5H), 1.29 (d, J = 6.5 Hz, 1.5H), 1.11 - 1.17 (m, 2H), 0.89 - 0.97 (m, 2H). LC-MS : m/z 419.3 (M+H)⁺.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4-(trifluoromethyl)phenyl)nicotinonitrile (Compound 226).

¹H NMR (CHLOROFORM-d) δ 7.71 (d, J = 8.0 Hz, 2H), 7.60 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 4.82 - 4.95 (m, 0.5H), 4.53 (d, J = 12.8 Hz, 0.5H), 4.17 - 4.39 (m, 3H), 3.80 (d, J = 13.6 Hz, 0.5H), 3.74 (t, J = 6.3 Hz, 2H), 3.49 - 3.62 (m, 0.5H), 3.37 (s, 3H), 3.24 - 3.33 (m, 1H), 3.03 - 3.15 (m, 1H), 2.63 - 2.80 (m, 1H), 2.51 - 2.62 (m, 1H), 1.93 - 2.02 (m, 1H), 1.38 (d, J = 6.5 Hz, 1.5H), 1.28 (d, J = 3.5 Hz, 1.5H), 1.14 - 1.20 (m, 2H), 0.93 - 0.99 (m, 2H). LC-MS : m/z 473.3 (M+H)⁺.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4-(trifluoromethoxy)phenyl)nicotinonitrile (Compound 227).

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.41 - 7.44 (m, 1H), 7.38 - 7.41 (m, 1H), 7.30 (s, 1H), 7.28 (s, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J = 11.5 Hz, 0.5H), 4.12 - 4.34 (m, 3H), 3.81 (br. s., 0.5H), 3.74 (t, J = 6.3 Hz, 2H), 3.55 (t, J = 11.4 Hz, 0.5H), 3.37 (s, 3H), 3.26 (br. s., 1H), 3.11 (br. s., 1H), 2.63 - 2.78 (m, 1H), 2.58 (d, J = 5.8 Hz, 1H), 1.95 - 2.05 (m, 1H), 1.38 (d, J = 5.8 Hz, 1.5H), 1.28 (d, J = 5.8 Hz, 1.5H), 1.13 - 1.18 (m, 2H), 0.93 - 0.99 (m, 2H). LC-MS : m/z 489.2 (M+H)⁺.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-(trifluoromethoxy)phenyl)-nicotinonitrile (Compound 228).

¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.27 (br. s., 1H), 7.21 - 7.26 (m, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J = 12.8 Hz, 0.5H), 4.17 - 4.36 (m, 3H), 3.77 - 3.86 (m, 0.5H), 3.74 (t, J = 6.1 Hz, 2H), 3.51 - 3.62 (m, 0.5H), 3.37 (s, 3H), 3.28 (t, J = 8.9 Hz, 1H), 3.12 (d, J = 10.8 Hz, 1H), 2.64 - 2.80 (m, 1H), 2.52 - 2.63 (m, 1H), 1.96 - 2.04 (m, 1H), 1.35 - 1.42 (m, 1.5H), 1.28 (d, J = 5.5 Hz, 1.5H), 1.14 - 1.20 (m, 2H), 0.93 - 1.01 (m, 2H). LC-MS : m/z 489.2 (M+H)⁺.

(R)-6-cyclopropyl-5-(3-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 229).

¹H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.41 (td, J = 7.8, 6.1 Hz, 1H), 7.14 - 7.19 (m, 1H), 7.04 - 7.13 (m, 2H), 4.90 (br. s., 0.5H), 4.52 (d, J = 13.1 Hz, 0.5H), 4.12 - 4.34 (m, 3H), 3.77 - 3.85 (m, 0.5H), 3.74 (t, J = 6.1 Hz, 2H), 3.48 - 3.61 (m, 0.5H), 3.37 (s, 3H), 3.26 (t, J = 9.4 Hz, 1H), 3.06 - 3.16 (m, 1H), 2.64 - 2.79 (m, 1H), 2.51 - 2.62 (m, 1H), 1.99 - 2.08 (m, 1H), 1.38 (d, J = 6.0 Hz, 1.5H), 1.28 (d, J = 6.5 Hz, 1.5H), 1.12 - 1.19 (m, 2H), 0.93 - 0.99 (m, 2H). LC-MS : m/z 423.3 (M+H)⁺.

(R)-6-cyclopropyl-5-(3-fluoro-4-methylphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 235).

¹H NMR (CHLOROFORM-d) δ 7.57 (s, 1H), 7.21 - 7.26 (m, 1H), 7.06 (s, 1H), 7.01 - 7.05 (m, 1H), 4.89 (br. s., 0.5H), 4.52 (d, J = 12.8 Hz, 0.5H), 4.11 - 4.33 (m, 3H), 3.80 (br. s., 0.5H), 3.74 (t, J = 6.3 Hz, 2H), 3.49 - 3.60 (m, 0.5H), 3.36 - 3.41 (m, 3H), 3.25 (t, J = 9.8 Hz, 1H), 3.03 - 3.15 (m, 1H), 2.63 - 2.79 (m, 1H), 2.51 - 2.61 (m, 1H), 2.32 (d, J = 1.5 Hz, 3H), 2.01 - 2.09 (m,

1H), 1.38 (d, J = 6.0 Hz, 1.5H), 1.26 - 1.30 (m, 1.5H), 1.12 - 1.17 (m, 2H), 0.92 - 0.97 (m, 2H).
LC-MS : m/z 437.3 (M+H)⁺.

(R)-6-cyclopropyl-5-(3-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 236).

¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.32 - 7.38 (m, 1H), 6.94 - 6.99 (m, 1H), 6.87 - 6.94 (m, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.1 Hz, 0.5H), 4.18-4.26 (m, J = 12.7 Hz, 3H), 3.84 (s, 3H), 3.81 (d, J = 5.5 Hz, 0.5H), 3.74 (t, J = 6.1 Hz, 2H), 3.55 (t, J = 11.0 Hz, 0.5H), 3.37 (s, 3H), 3.25 (t, J = 10.2 Hz, 1H), 3.03 - 3.15 (m, 1H), 2.63 - 2.79 (m, 1H), 2.51 - 2.62 (m, 1H), 2.05 - 2.15 (m, 1H), 1.39 (d, J = 6.0 Hz, 1.5H), 1.29 (d, J = 6.3 Hz, 1.5H), 1.11 - 1.18 (m, 2H), 0.91 - 0.96 (m, 2H). LC-MS : m/z 435.3 (M+H)⁺.

(R)-6-cyclopropyl-5-(3,4-dimethoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 237).

¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 6.92 - 6.95 (m, 2H), 6.88 (s, 1H), 4.89 (br. s., 0.5H), 4.53 (d, J = 14.1 Hz, 0.5H), 4.16 - 4.30 (m, 3H), 3.93 (s, 3H), 3.90 (s, 3H), 3.78 - 3.84 (m, 0.5H), 3.71 - 3.77 (m, 2H), 3.55 (br. s., 0.5H), 3.37 (s, 1H), 3.24 (br. s., 1H), 3.03-3.09 (m., 1H), 2.66 - 2.79 (m, 1H), 2.59 (br. s., 1H), 2.08 - 2.15 (m, 1.5H), 1.38 (br. s., 1.5H), 1.13 - 1.17 (m, 2H), 0.93 (dd, J = 8.0, 3.3 Hz, 2H). LC-MS : m/z 465.1 (M+H)⁺.

(R)-6-cyclopropyl-5-(isoquinolin-4-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 242).

¹H NMR (DMSO-d₆) δ 7.47 (dd, J = 5.0, 3.0 Hz, 1H), 7.17 (dd, J = 2.8, 1.3 Hz, 1H), 7.00 (dd, J = 5.0, 1.3 Hz, 1H), 4.91 (br. s., 0.5H), 4.55 (d, J = 10.8 Hz, 0.5H), 3.98 - 4.27 (m, 3H), 3.75 (q, J = 6.0 Hz, 2.5H), 3.53 - 3.63 (m, 0.5H), 3.40 (s, 3H), 3.11 - 3.25 (m, 1H), 2.94 - 3.06 (m, 1H), 2.69 - 2.81 (m, 1H), 2.67 (d, J = 7.3 Hz, 1H), 2.25 (s, 3H), 1.71 - 1.78 (m, 1H), 1.42 (d, J = 6.5 Hz, 1.5H), 1.32 (d, J = 6.8 Hz, 1.5H), 1.06 - 1.08 (m, 2H), 0.83 - 0.88 (m, 2H). LC-MS : m/z 456.2 (M+H)⁺.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(thiophen-3-yl)nicotinonitrile (Compound 246).

¹H NMR (CHLOROFORM-d) δ 7.64 (s, 1H), 7.41 (dd, J = 4.8, 3.0 Hz, 1H), 7.29 (dd, J = 3.0, 1.3 Hz, 1H), 7.18 (dd, J = 5.0, 1.3 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J = 13.6 Hz, 0.5H), 4.14 - 4.32 (m, 2.5H), 3.67 - 3.84 (m, 2.5H), 3.55 (br. s., 0.5H), 3.18 - 3.34 (m, 1H), 2.96 - 3.18 (m,

1.5H), 2.50 - 2.71 (m, 2H), 2.12 - 2.23 (m, 1H), 1.34 - 1.41 (m, 1.5H), 1.24 - 1.30 (m, 1.5H), 1.12 - 1.18 (m, 2H), 0.92 - 1.02 (m, 2H). LC-MS : m/z 411.3 (M+H)⁺.

(R)-5-(benzo[b]thiophen-2-yl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 247).

¹H NMR (CHLOROFORM-d) δ 7.82 - 7.87 (m, 1H), 7.78 - 7.82 (m, 1H), 7.77 (s, 1H), 7.33 - 7.42 (m, 2H), 7.32 (s, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J = 12.8 Hz, 0.5H), 4.24 - 4.39 (m, 3H), 3.70 - 3.80 (m, 2.5H), 3.35 - 3.41 (m, 3H), 3.29 (t, J = 9.8 Hz, 1H), 3.03 - 3.20 (m, 1.5H), 2.63 - 2.78 (m, 1H), 2.52 - 2.63 (m, 1H), 2.34 - 2.44 (m, 1H), 1.37 (d, J = 6.0 Hz, 1.5H), 1.23 - 1.29 (m, 1.5H), 1.15 - 1.21 (m, 2H), 0.95 - 1.06 (m, 2H). LC-MS : m/z 461.3 (M+H)⁺.

(R)-5-(3-chloro-4-fluorophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 248).

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.45 (dd, J = 6.9, 1.9 Hz, 1H), 7.22 - 7.28 (m, 2H), 4.92 (br. s., 0.5H), 4.54 (d, J = 12.8 Hz, 0.5H), 4.16 - 4.37 (m, 3H), 3.70 - 3.81 (m, 2.5H), 3.50 - 3.64 (m, 0.5H), 3.37 - 3.42 (m, 3H), 3.28 (t, J = 10.2 Hz, 1H), 3.12 (d, J = 11.0 Hz, 1H), 2.65 - 2.87 (m, 1H), 2.55 - 2.65 (m, 1H), 1.94 - 2.05 (m, 1H), 1.39 (d, J = 6.5 Hz, 1.5H), 1.28 (d, J = 4.0 Hz, 1.5H), 1.14 - 1.21 (m, 2H), 0.94 - 1.03 (m, 2H). LC-MS : m/z 457.3 (M+H)⁺.

(R)-6-cyclopropyl-5-(2-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 249). ¹H NMR (CHLOROFORM-d) δ 7.62 (s, 1H), 7.37 - 7.45 (m, 1H), 7.30 - 7.36 (m, 1H), 7.22 - 7.27 (m, 1H), 7.19 (t, J = 9.0 Hz, 1H), 4.92 (br. s., 0.5H), 4.54 (d, J = 13.3 Hz, 0.5H), 4.19 - 4.37 (m, 3H), 3.78 - 3.86 (m, 0.5H), 3.70 - 3.78 (m, 2H), 3.51 - 3.61 (m, 0.5H), 3.39 (s, 3H), 3.27 (t, J = 12.5 Hz, 1H), 3.02 - 3.16 (m, 1H), 2.65 - 2.82 (m, 1H), 2.54 - 2.64 (m, 1H), 1.83 - 1.90 (m, 1H), 1.41 (d, J = 6.3 Hz, 1.5H), 1.30 (d, J = 6.8 Hz, 1.5H), 1.12 - 1.19 (m, 2H), 0.92 - 0.98 (m, 2H). LC-MS : m/z 423.3 (M+H)⁺.

(R)-6-cyclopropyl-5-(2,4-difluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 250).

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.26 - 7.35 (m, 1H), 6.91 - 7.04 (m, 2H), 4.92 (br. s., 0.5H), 4.54 (d, J = 13.3 Hz, 0.5H), 4.18 - 4.37 (m, 3H), 3.78 - 3.85 (m, 0.5H), 3.71 - 3.78 (m, 2H), 3.51 - 3.62 (m, 0.5H), 3.39 (s, 3H), 3.23 - 3.33 (m, 1H), 3.14 (d, J = 10.5 Hz, 1H), 2.65 - 2.80 (m, 1H), 2.53 - 2.63 (m, 1H), 1.77 - 1.85 (m, 1H), 1.40 (d, J = 6.3 Hz, 1.5H), 1.30 (d, J = 6.5 Hz, 1.5H), 1.11 - 1.19 (m, 2H), 0.96 (dd, J = 7.8, 3.0 Hz, 2H). LC-MS : m/z 441.3 (M+H)⁺.

(R)-2-cyclopropyl-6'-methoxy-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,3'-bipyridine-5-carbonitrile (Compound 252).

¹H NMR (CHLOROFORM-d) δ 8.18 (d, J = 2.3 Hz, 1H), 7.60 (dd, J = 8.5, 2.5 Hz, 1H), 7.56 (s, 1H), 6.83 (d, J = 8.5 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J = 13.1 Hz, 0.5H), 4.15 - 4.36 (m, 3H), 3.96 - 4.02 (m, 3H), 3.76 - 3.86 (m, 0.5H), 3.74 (t, J = 6.3 Hz, 2H), 3.53 - 3.61 (m, 0.5H), 3.37 (s, 3H), 3.21 - 3.31 (m, 1H), 3.12 (d, J = 11.3 Hz, 1H), 2.63 - 2.80 (m, 1H), 2.51 - 2.62 (m, 1H), 1.93 - 2.04 (m, 1H), 1.38 (d, J = 6.0 Hz, 1.5H), 1.28 (d, J = 6.3 Hz, 1.5H), 1.12 - 1.19 (m, 2H), 0.92 - 1.00 (m, 2H). LC-MS : m/z 436.2 (M+H)⁺.

(R)-6-cyclopropyl-5-(1H-indol-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 253).

¹H NMR (CHLOROFORM-d) δ 8.28 (br. s., 1H), 7.66 (s, 1H), 7.63 (s, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.29 (t, J = 2.8 Hz, 1H), 7.20 (dd, J = 8.3, 1.8 Hz, 1H), 6.60 (t, J = 2.1 Hz, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J = 13.3 Hz, 0.5H), 4.12 - 4.33 (m, 3H), 3.81 (br. s., 0.5H), 3.75 (t, J = 6.4 Hz, 2H), 3.51 - 3.63 (m, 0.5H), 3.38 (s, 3H), 3.22 (d, J = 14.1 Hz, 1H), 3.01 - 3.17 (m, 1H), 2.66 - 2.81 (m, 1H), 2.62 (t, J = 5.8 Hz, 1H), 2.11 - 2.21 (m, 1H), 1.41 (d, J = 5.5 Hz, 1.5H), 1.31 (d, J = 6.3 Hz, 1.5H), 1.11 - 1.17 (m, 2H), 0.87 - 0.94 (m, 2H). LC-MS : m/z 444.3 (M+H)⁺.

(R)-6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 241).

¹H NMR (CHLOROFORM-d) δ 7.17 (s, 2H), 7.16 (d, J = 1.8 Hz, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.3 Hz, 0.5H), 4.03 - 4.22 (m, 3H), 3.79 (br. s., 0.5H), 3.74 (t, J = 6.3 Hz, 2H), 3.52 - 3.63 (m, 0.5H), 3.38 (s, 3H), 3.16 - 3.25 (m, 1H), 2.92 - 3.08 (m, 1H), 2.64 - 2.79 (m, 1H), 2.51 - 2.63 (m, 1H), 2.18 (s, 3H), 1.56 - 1.63 (m, 1H), 1.41 (d, J = 6.5 Hz, 1.5H), 1.31 (d, J = 6.5 Hz, 1.5H), 1.03 - 1.09 (m, 2H), 0.79 - 0.84 (m, 2H). LC-MS : m/z 437.2 (M+H)⁺.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-m-tolylnicotinonitrile (Compound 243).

¹H NMR (DMSO-d₆) δ 7.36 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 6.97 - 7.04 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J = 12.3 Hz, 0.5H), 4.24 (br. s., 0.5H), 4.03 - 4.19 (m, 2H), 3.76 (s, 0.5H), 3.75 (s, 2H), 3.55 - 3.64 (m, 0.5H), 3.40 (s, 3H), 3.11 - 3.26 (m, 1H), 2.93 - 3.08 (m, 1H), 2.68 - 2.80 (m, 1H), 2.61 (d, J = 11.0 Hz, 1H), 2.42 (s, 3H), 2.20 (s, 3H), 1.62 - 1.71 (m, 1H),

1.43 (d, J = 6.5 Hz, 1.5H), 1.34 (d, J = 6.0 Hz, 1.5H), 1.01 - 1.11 (m, 2H), 0.80 - 0.85 (m, 2H).

LC-MS : m/z 433.3 (M+H)⁺.

(R)-6-cyclopropyl-5-(3-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 251).

¹H NMR (CHLOROFORM-d) δ 7.37 (t, J = 7.8 Hz, 1H), 6.93 (dd, J = 8.3, 2.5 Hz, 1H), 6.78 (d, J = 7.5 Hz, 1H), 6.74 (s, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J = 12.8 Hz, 0.5H), 3.96 - 4.21 (m, 3H), 3.83 (s, 3H), 3.71 - 3.77 (m, 2H), 3.52 - 3.63 (m, 1H), 3.37 (s, 3H), 3.09 - 3.25 (m, 1H), 2.89 - 3.04 (m, 1H), 2.63 - 2.79 (m, 1H), 2.59 (br. s., 1H), 2.16 - 2.29 (m, 3H), 1.63 - 1.72 (m, 1H), 1.41 (d, J = 6.3 Hz, 1.5H), 1.29 - 1.33 (m, 1.5H), 1.06 (d, J = 7.3 Hz, 2H), 0.78 - 0.84 (m, 2H).

LC-MS : m/z 449.3 (M+H)⁺.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(4-(trifluoromethoxy)-phenyl)nicotinonitrile (Compound 255).

¹H NMR (CHLOROFORM-d) δ 7.31 - 7.36 (m, J = 8.0 Hz, 2H), 7.23 - 7.28 (m, J = 8.3 Hz, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J = 13.8 Hz, 0.5H), 4.01 - 4.22 (m, 2.5H), 3.69 - 3.85 (m, 2.5H), 3.53 - 3.67 (m, 0.5H), 3.36 - 3.43 (m, 3H), 3.12 - 3.28 (m, 1.5H), 2.94 - 3.12 (m, 1H), 2.66 - 2.83 (m, 1H), 2.61 (br. s., 1H), 2.16 - 2.22 (m, 3H), 1.54 - 1.65 (m, 1H), 1.39 - 1.46 (m, 1.5H), 1.32 (d, J = 6.3 Hz, 1.5H), 1.03 - 1.12 (m, 2H), 0.80 - 0.89 (m, 2H). LC-MS : m/z 503.3 (M+H)⁺.

6-cyclopropyl-5-(2,4-difluorophenyl)-2-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl- nicotinonitrile (Compound 256).

¹H NMR (CHLOROFORM-d) δ 7.16 - 7.25 (m, 1H), 6.93 - 7.07 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J = 13.3 Hz, 0.5H), 4.03 - 4.30 (m, 2.5H), 3.71 - 3.86 (m, 2.5H), 3.51 - 3.67 (m, 0.5H), 3.40 (s, 3H), 3.12 - 3.30 (m, 1.5H), 2.95 - 3.11 (m, 1H), 2.73 (td, J = 15.3, 7.3 Hz, 1H), 2.54 - 2.64 (m, 1H), 2.18 - 2.25 (m, 3H), 1.53 - 1.61 (m, 1H), 1.39 - 1.47 (m, 1.5H), 1.32 (t, J = 5.8 Hz, 1.5H), 1.03 - 1.17 (m, 2H), 0.82 - 0.93 (m, 2H). LC-MS : m/z 455.4 (M+H)⁺.

(R)-6-cyclopropyl-5-(3-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 257).

¹H NMR (CHLOROFORM-d) δ 7.41 - 7.51 (m, 1H), 7.12 (td, J = 8.5, 2.5 Hz, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J = 12.8 Hz, 0.5H), 4.04 - 4.22 (m, 2.5H), 3.72 - 3.84 (m, 2.5H), 3.53 - 3.67 (m, 0.5H), 3.40 (s, 3H), 3.12 - 3.29 (m, 1.5H), 2.93 - 3.11 (m, 1H), 2.66 - 2.83 (m, 1H), 2.61 (d, J = 6.3 Hz, 1H), 2.16 - 2.25 (m, 3H), 1.57 - 1.64 (m,

1H), 1.43 (d, J = 6.5 Hz, 1.5H), 1.33 (d, J = 6.8 Hz, 1.5H), 1.08 (t, J = 4.6 Hz, 2H), 0.80 - 0.91 (m, 2H). LC-MS : m/z 437.4 (M+H)⁺.

(R)-6-cyclopropyl-5-(3-fluoro-4-methylphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 258).

¹H NMR (CHLOROFORM-d) δ 7.23 - 7.33 (m, 2H), 6.89 (s, 1H), 6.87 (d, J = 3.5 Hz, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J = 13.3 Hz, 0.5H), 4.23 (br. s., 1H), 4.01 - 4.21 (m, 1.5H), 3.70 - 3.84 (m, 2.5H), 3.50 - 3.66 (m, 0.5H), 3.39 (s, 3H), 3.10 - 3.28 (m, 1.5H), 2.92 - 3.09 (m, 1H), 2.65 - 2.81 (m, 1H), 2.53 - 2.64 (m, 1H), 2.32 - 2.39 (m, 3H), 2.20 (s, 3H), 1.60 - 1.70 (m, 1H), 1.39 - 1.47 (m, 1.5H), 1.30 - 1.35 (m, 1.5H), 1.07 (t, J = 4.6 Hz, 2H), 0.83 (dt, J = 7.5, 3.5 Hz, 2H). LC-MS : m/z 451.4 (M+H)⁺.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(naphthalen-2-yl)nicotinonitrile (Compound 259).

¹H NMR (DMSO-d₆) δ 7.96 (d, J = 8.5 Hz, 1H), 7.91 - 7.95 (m, 1H), 7.88 (dd, J = 6.1, 3.4 Hz, 1H), 7.71 (s, 1H), 7.53 - 7.59 (m, 2H), 7.34 (dd, J = 8.4, 1.4 Hz, 1H), 4.94 (br. s., 0.5H), 4.57 (d, J = 13.3 Hz, 0.5H), 4.05 - 4.32 (m, 3H), 3.83 (br. s., 0.5H), 3.77 (t, J = 6.3 Hz, 2H), 3.56 - 3.67 (m, 0.5H), 3.41 (s, 3H), 3.17 - 3.29 (m, 1H), 2.96 - 3.12 (m, 1H), 2.67 - 2.83 (m, 1H), 2.55 - 2.65 (m, 1H), 2.23 (s, 3H), 1.63 - 1.71 (m, 1H), 1.45 (d, J = 5.8 Hz, 1.5H), 1.35 (d, J = 5.5 Hz, 1.5H), 1.05 - 1.14 (m, 2H), 0.77 - 0.83 (m, 2H). LC-MS : m/z 469.4 (M+H)⁺.

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-3,4'-bipyridine-5-carbonitrile (Compound 260).

¹H NMR (DMSO-d₆) δ 8.87 (br. s., 2H), 7.86 (br. s., 2H), 4.94 (br. s., 0.5H), 4.71 (s, 0.5H), 4.31 - 4.35 (s, 3H), 3.82 (br. s., 0.5H), 3.71 - 3.79 (m, 2H), 3.58 (br. s., 0.5H), 3.40 (s, 3H), 3.21 (br. s., 1H), 3.14 (br. s., 1H), 2.68 (br. s., 1H), 2.61 (br. s., 1H), 2.04 (br. s., 1H), 1.45 (d, J = 5.8 Hz, 1.5H), 1.35 (d, J = 5.5 Hz, 1.5H), 1.05 - 1.14 (m, 2H), 0.77 - 0.83 (m, 2H). LC-MS : m/z 420.5 (M+H)⁺.

(R)-5-(benzo[d][1,3]dioxol-5-yl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 261).

¹H NMR (DMSO-d₆) δ 6.91 (d, J = 8.0 Hz, 1H), 6.62 - 6.71 (m, 2H), 6.03 - 6.10 (m, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J = 13.6 Hz, 0.5H), 4.03 - 4.24 (m, 3H), 3.80 (br. s., 0.5H), 3.76 (t, J = 6.1 Hz, 2H), 3.59 (t, J = 11.7 Hz, 0.5H), 3.39 (s, 3H), 3.18 - 3.25 (m, 1H), 2.92 - 3.08 (m, 1H), 2.65 -

2.80 (m, 1H), 2.54 - 2.65 (m, 1H), 2.22 (s, 3H), 1.68 - 1.77 (m, 1H), 1.42 (d, J = 6.5 Hz, 1.5H), 1.33 (d, J = 6.5 Hz, 1.5H), 1.06 (t, J = 5.3 Hz, 2H), 0.84 (t, J = 6.1 Hz, 2H)

LC-MS : m/z 463.3 (M+H)⁺.

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methyl-5-(thiophen-3-yl)nicotinonitrile (Compound 262).

¹H NMR (DMSO-d₆) δ 7.47 (dd, J = 5.0, 3.0 Hz, 1H), 7.17 (dd, J = 2.8, 1.3 Hz, 1H), 7.00 (dd, J = 5.0, 1.3 Hz, 1H), 4.91 (br. s., 0.5H), 4.55 (d, J = 10.8 Hz, 0.5H), 3.98 - 4.27 (m, 3H), 3.75 (q, J = 6.0 Hz, 2.5H), 3.53 - 3.63 (m, 0.5H), 3.40 (s, 3H), 3.11 - 3.25 (m, 1H), 2.94 - 3.06 (m, 1H), 2.69 - 2.81 (m, 1H), 2.67 (d, J = 7.3 Hz, 1H), 2.25 (s, 3H), 1.71 - 1.78 (m, 1H), 1.42 (d, J = 6.5 Hz, 1.5H), 1.32 (d, J = 6.8 Hz, 1.5H), 1.06 - 1.08 (m, 2H), 0.83 - 0.88 (m, 2H). LC-MS : m/z 425.3 (M+H)⁺.

Example 5 Preparation of (R)-5-benzyl-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 239). A mixture of the bromide **7** from Example 1 (20mg, 0.049 mmol) and PdCl₂(dppf)·CH₂Cl₂ (4 mg, 0.005 mmol) in 1 mL of dry THF was stirred at room temperature for 5 min under nitrogen atmosphere. Benzyl zinc bromide (2 mL of 0.5M solution in THF, 0.098 mmol) was then added via a transfer needle, and the resulting reaction mixture was then refluxed for 4 h before the volatile was evaporated under reduced pressure. The black solid was applied to the top of a flash silica gel column, which was eluted with CH₂Cl₂ and then 8:1 CH₂Cl₂-EtOAc to obtain 5.1 mg of Compound 239 as a reddish solid. MS (ES) M+H expected 421.3, found 421.2. ¹H NMR (CHLOROFORM-d) δ 7.43 (s, 1H), 7.28 - 7.36 (m, 2H), 7.19 - 7.25 (m, 1H), 7.08 (d, J = 7.0 Hz, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.6 Hz, 0.5H), 4.16 - 4.36 (m, 3H), 3.91 (s, 2H), 3.79 (br. s., 0.5H), 3.73 (t, J = 6.5 Hz, 2H), 3.51 - 3.61 (m, 0.5H), 3.37 (s, 3H), 3.22 - 3.30 (m, 1H), 3.12 - 3.21 (m, 1H), 2.63 - 2.78 (m, 1H), 2.51 - 2.61 (m, 1H), 1.38 (d, J = 5.8 Hz, 1.5H), 1.28 - 1.32 (m, 1.5H), 1.12 (d, J = 6.5 Hz, 6H). Other Compounds of Formula II listed below, wherein R^{1b} is alkyl, -CH₂-aryl or -CH₂-heteroaryl; and R² is isopropyl or cyclopropyl were similarly prepared using any of intermediates **7** (Scheme 1), **17** (Scheme 2), or **28** (Scheme 3) as starting material.

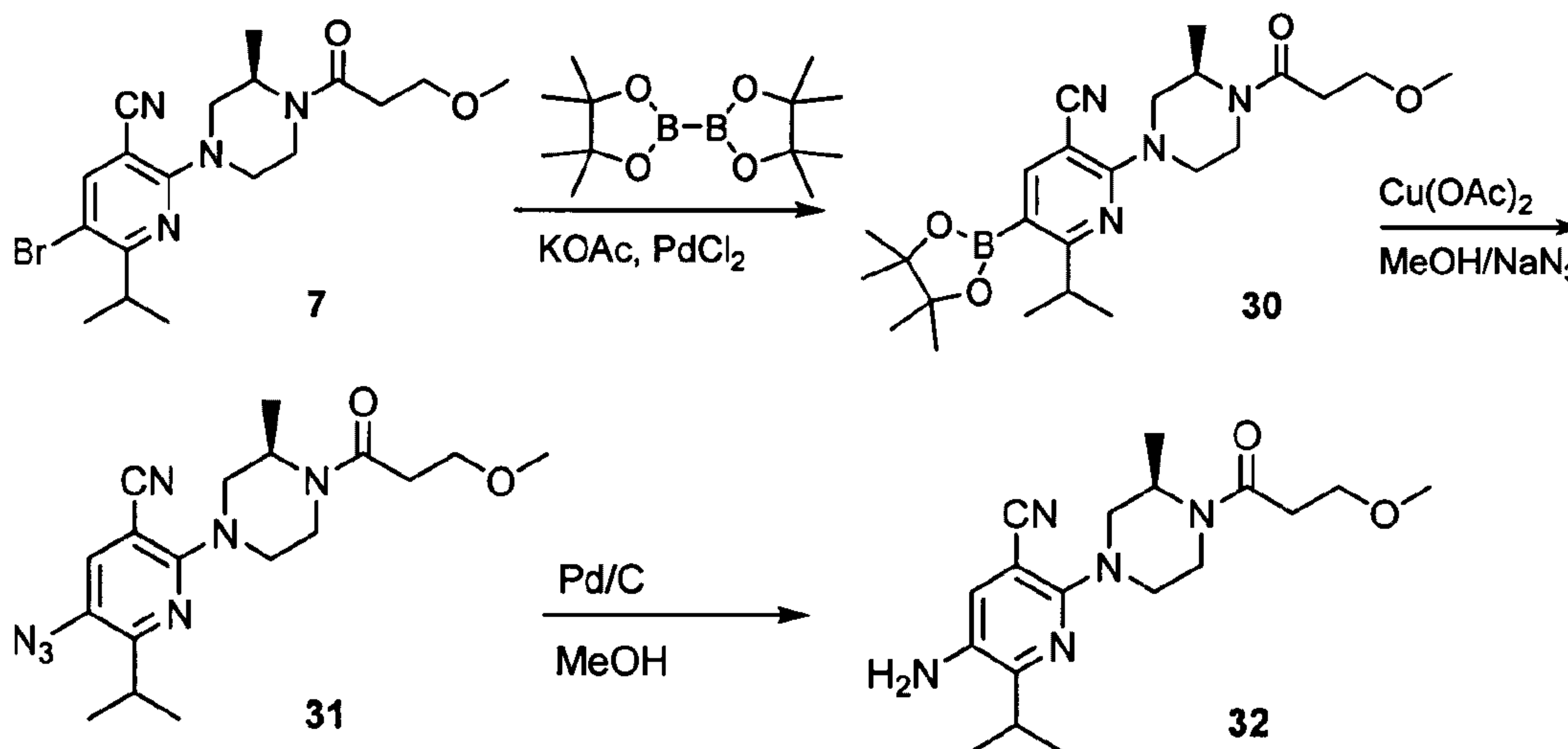
(R)-5-benzyl-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (Compound 245).

^1H NMR (CHLOROFORM- d) δ 7.29 - 7.35 (m, 2H), 7.24 (d, J = 7.5 Hz, 1H), 7.09 (d, J = 7.3 Hz, 2H), 4.91 (br. s., 0.5H), 4.54 (d, J = 14.1 Hz, 0.5H), 4.22 (br. s., 0.5H), 4.16 (s, 2H), 4.09 (d, J = 15.6 Hz, 1.5H), 3.97 - 4.05 (m, 1H), 3.69 - 3.82 (m, 2H), 3.53 - 3.63 (m, 1H), 3.36 - 3.42 (m, 3H), 3.15 (t, J = 13.9 Hz, 1H), 2.90 - 3.05 (m, 1H), 2.66 - 2.81 (m, 1H), 2.54 - 2.63 (m, 1H), 2.40 (s, 3H), 2.04 (dd, J = 8.0, 4.8 Hz, 1H), 1.42 (d, J = 6.8 Hz, 1.5H), 1.35 (br. s., 1.5H), 1.07 - 1.15 (m, 2H), 0.90 - 0.92 (m, 2H). LC-MS : m/z 433.3 ($M+H$) $^+$.

Example 6 Preparation of (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(methyl(2-(methyl amino)ethyl)amino)nicotinonitrile (Compound 238). (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(methyl(2-(methyl amino)ethyl)amino)nicotinonitrile (Compound 238) was prepared by mixing bromide 7 (30 mg, 0.074 mmol), CuI (0.7 mg, 0.004 mmol), K_2CO_3 (20 mg, 0.147 mmol), and *N*1,*N*2-dimethylethane-1,2-diamine (3.25 mg, 0.035 mmol) in a 5 mL microwave tube capped with a rubber septum. The tube was placed under vacuum and refilled with nitrogen three times. Piperidine (19 mg, 0.22 mmol) and DMSO (1 mL) were added to the tube and the rubber septum was quickly replaced with microwave tube cap. The reaction was heated in an oil bath at 120°C overnight before it was cooled, diluted with EtOAc, and filtered through a pad of Celite. The EtOAc was removed on a rotary evaporator. Compound 238 was obtained in 10 mg of quantity via preparative TLC (DCM: MeOH/10:1) separation. MS (ES) $M+H$ expected 417.3, found 417.5. ^1H NMR (CHLOROFORM- d) δ 7.56 (s, 1H), 4.91 (br. s., 0.5H), 4.53 (d, J = 12.3 Hz, 0.5H), 4.02 - 4.31 (m, 3H), 3.67 - 3.83 (m, 3H), 3.47 - 3.64 (m, 2H), 3.34 - 3.41 (m, 3H), 3.16 - 3.30 (m, 1H), 2.93 - 3.13 (m, 4H), 2.74 - 2.84 (m, 2H), 2.61 (s, 3H), 2.53 (s, 3H), 1.39 (d, J = 5.8 Hz, 1.5H), 1.30 - 1.34 (m, 1.5H), 1.17 (d, J = 6.5 Hz, 6H).

Example 7 Preparation of (R)-5-amino-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile. (R)-5-amino-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile was prepared according to Scheme 4.

Scheme 4:



(*R*)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (**30**). To a solution of (*R*)-5-bromo-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (**7**; 747 mg, 1.8 mmol) in DMF (8 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2 dioxaborolane) (563 mg, 2.2 mmol) and KOAc (538 mg, 5.5 mmol). The resulting mixture was stirred at room temperature for 5 min before addition of PdCl₂(dppf).CH₂Cl₂ (45 mg, 0.03 mmol). After flushing with nitrogen, the reaction mixture was heated at 85°C for 18 hours. LC-MS analysis indicated starting material still present, the temperature was raised to 120°C and stirred overnight. After cooling, the reaction mixture was diluted with water, and extracted with methylene chloride. The organic layer was then washed with brine, dried over anhy. Na₂SO₄, and concentrated *in vacuo*. Column chromatography (25% EtOAc/petroleum ether) afforded 334 mg of **30** as a white solid. MS (ES) M+H expected 457.3, found 457.4. ¹H NMR (CHLOROFORM-*d*) δ 8.16 (s, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J = 12.3 Hz, 0.5H), 4.19 - 4.39 (m, 3H), 3.76 - 3.85 (m, 0.5H), 3.73 (t, J = 6.4 Hz, 2H), 3.50 - 3.61 (m, 0.5H), 3.37 (s, 3H), 3.25 - 3.35 (m, 1H), 3.02 - 3.20 (m, 1H), 2.63 - 2.80 (m, 1H), 2.51 - 2.61 (m, 1H), 1.45 (d, J = 7.0 Hz, 1.5H), 1.35 (d, J = 6.3 Hz, 1.5H), 1.34 (s, 12H), 1.19-1.21 (dd, J = 6.8, 2.0 Hz, 3H), 1.23-1.25 (d, J = 6.8Hz, 3H).

(*R*)-5-azido-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (**31**). To a solution of above boronate **30** (10 mg, 0.022 mmol) and Cu(OAc)₂.H₂O (0.5 mg, 0.0025 mmol) in MeOH (0.2 mL) was added slowly NaN₃ (2.4 mg, 0.037 mmol) with stirring. After the

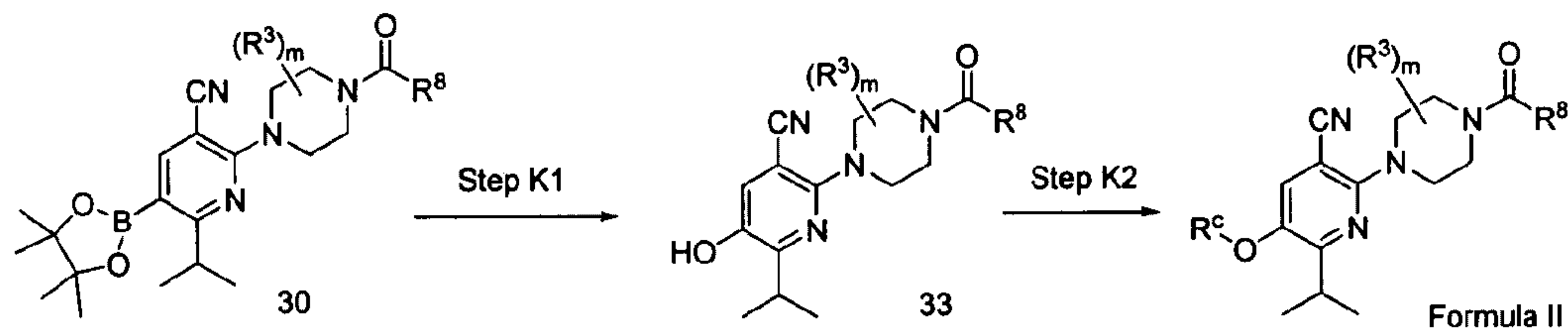
addition, the reaction mixture was heated to 50°C and stirred overnight. After cooling and dilution with water, the reaction mixture was extracted with methylene chloride. The organic layer was then washed with brine, dried over anhy. Na₂SO₄, and concentrated *in vacuo*. Column chromatography (25% ethyl acetate/petroleum ether) afforded 3.7 mg of **31** as a yellowish solid. MS (ES) M+H expected 372.2, found 372.3.

·-(*R*)-5-amino-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (**32**).

To a solution of above azide **31** (10 mg, 0.027 mmol) in 1 mL of MeOH was added 10% Pd/C (0.5 mg). The resulting mixture was purged with hydrogen and stirred at room temperature for 1h under hydrogen atmosphere. After LC-MS analysis showed the formation of desired product, the reaction mixture was filtered, the filtrate was concentrated *in vacuo*. Column chromatography (25% EtOAc/petroleum ether) afforded 9 mg of **32** as a pink solid. MS (ES) M+H expected 346.2, found 346.1. ¹H NMR (CHLOROFORM-*d*) δ 7.25 (s, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.1 Hz, 0.5H), 4.20 (br. s., 1H), 3.95 - 4.07 (m, 1H), 3.93 (br. s., 1H), 3.75 (br. s., 0.5H), 3.73 (t, J = 6.4 Hz, 2H), 3.52 - 3.63 (m, 0.5H), 3.37 (s, 3H), 3.02 - 3.21 (m, 2H), 2.88 - 3.02 (m, 1H), 2.62 - 2.78 (m, 1H), 2.59 (t, J = 5.8 Hz, 1H), 1.41 (d, J = 5.8 Hz, 1.5H), 1.31-1.32 (m, 1.5H), 1.26 (s, 6H).

Example 8 Preparation of (R)-5-(benzyloxy)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 254). Compound 254 was prepared according to general Scheme 5, below:

Scheme 5:



, wherein

R^c is -CH₂-aryl or -CH₂-heteroaryl.

Step K-1: (*R*)-5-hydroxy-6-isopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile. To a solution of boronate **30** from Example 7 (30 mg, 0.066 mmol) in 15 mL of THF, at room temperature, was added aq. NaOH solution (2.86 g, 0.07mmol). After stirring

for 5 min, a solution of 30% of H₂O₂ (2.43 mg, 0.07 mmol) was added. The reaction mixture was allowed to stir at room temperature for additional 30 min before it was adjusted to neutral pH and concentrated in *vacuo*. Column chromatography (50% EtOAc/petroleum ether) afforded 21 mg of **33**. MS (ES) M+H expected 347.2, found 347.3. ¹H NMR (METHANOL-d₄) δ 7.26 (s, 1H), 4.82 (br. s., 0.5H), 4.47 (d, J = 13.1 Hz, 0.5H), 4.39 (br. s., 0.5H), 3.95 (d, J = 13.1 Hz, 0.5H), 3.79 - 3.92 (m, 2H), 3.55 - 3.74 (m, 3H), 3.36 (s, 3H), 3.10 - 3.23 (m, 1H), 2.95 - 3.10 (m, 1H), 2.81 - 2.93 (m, 1H), 2.71 - 2.81 (m, 1H), 2.59 - 2.69 (m, 1H), 1.45 (d, J = 6.8 Hz, 1.5H), 1.36 (br. s., 1.5H), 1.23 (d, J = 6.8 Hz, 6H).

Step K-2: (R)-5-(benzyloxy)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 254). To a solution of (R)-5-hydroxy-6-isopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (**33**; 15 mg, 0.043 mmol) in 1 mL of THF was added 60% NaH (2.1 mg, 0.052 mmol) at 0°C. After stirring at room temperature for 30 min, benzyl bromide (8.9 mg, 0.052 mmol) was then added. The reaction mixture was stirred at 0°C for 30 min and then at room temperature overnight. After the reaction mixture was concentrated, preparative TLC separation of the crude (50% ethyl acetate/petroleum ether) afforded 6.5 mg of Compound 254 as a yellowish solid. MS (ES) M+H expected 437.3, found 437.4. ¹H NMR (CHLOROFORM-d) δ 7.33 - 7.43 (m, 5H), 7.23 (s, 1H), 5.02 (s, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.3 Hz, 0.5H), 4.21 (br. s., 0.5H), 4.02 - 4.09 (m, 1H), 3.90 - 4.02 (m, 1H), 3.65 - 3.85 (m, 3H), 3.51 - 3.61 (m, 0.5H), 3.42 - 3.51 (m, 1H), 3.37 (s, 3H), 3.09 - 3.23 (m, 1H), 2.91 - 3.07 (m, 1H), 2.63 - 2.78 (m, 1H), 2.51 - 2.62 (m, 1H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.31 (d, J = 6.5 Hz, 1.5H), 1.20 (d, J = 6.8 Hz, 6H).

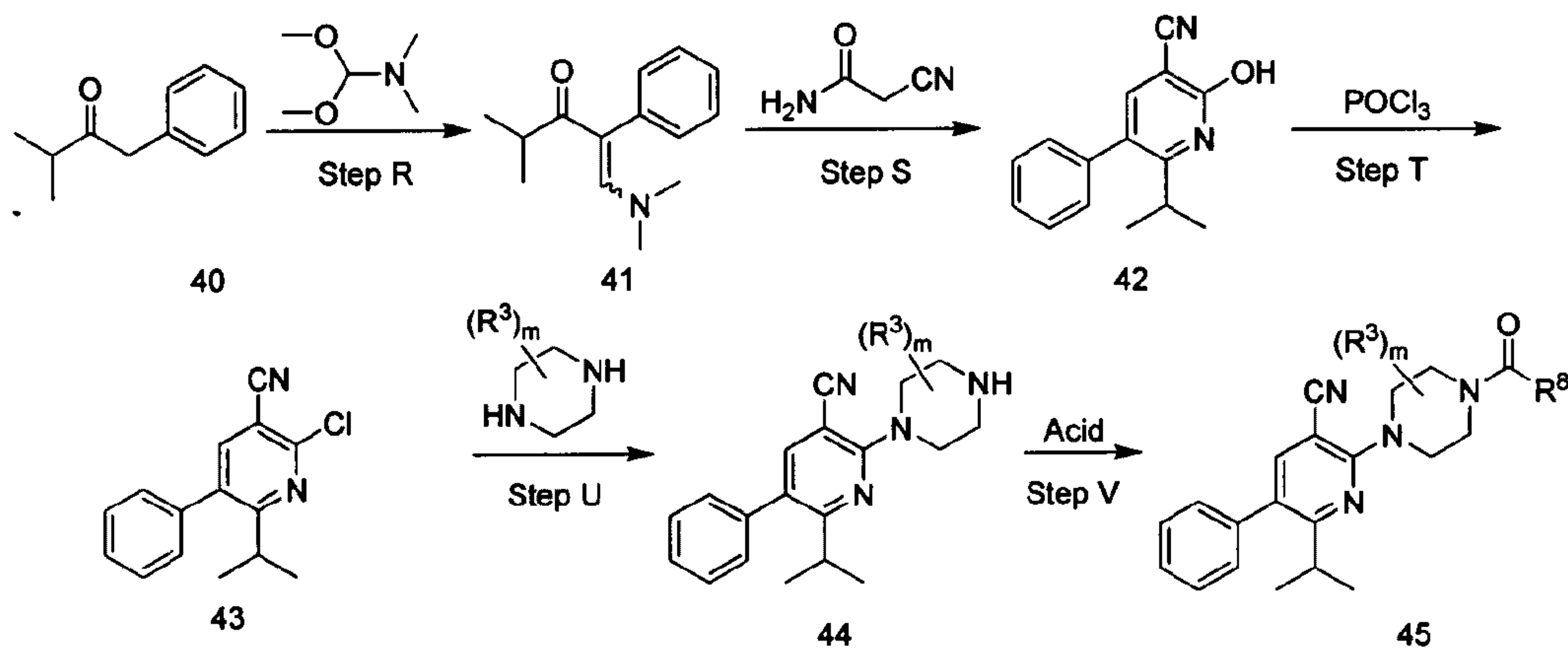
Other Compounds of Formula II listed below, wherein R^{1b} is -O-CH₂-aryl or -O-CH₂-heteroaryl; and R² is isopropyl or cyclopropyl were similarly prepared according to Scheme 5 by replacing (R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile **30** with alternate boronates prepared from any of intermediates **7** (Scheme 1), **17** (Scheme 2), or **28** (Scheme 3) using similar procedures set forth in Example 7 to prepare **30**.

(R)-5-(benzyloxy)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 254).

¹H NMR (CHLOROFORM-d) δ 7.33 - 7.43 (m, 5H), 7.23 (s, 1H), 5.02 (s, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.3 Hz, 0.5H), 4.21 (br. s., 0.5H), 4.02 - 4.09 (m, 1H), 3.90 - 4.02 (m, 1H), 3.65 - 3.85 (m, 3H), 3.51 - 3.61 (m, 0.5H), 3.42 - 3.51 (m, 1H), 3.37 (s, 3H), 3.09 - 3.23 (m, 1H), 2.91 - 3.07 (m, 1H), 2.63 - 2.78 (m, 1H), 2.51 - 2.62 (m, 1H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.31 (d, J = 6.5 Hz, 1.5H), 1.20 (d, J = 6.8 Hz, 6H). LC-MS : m/z 437.4 (M+H)⁺.

Example 9 Preparation of (R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 164). Compound 164 (45, wherein m is 1; R^3 is 3-methyl; and R^8 is 2-methylfuran-3-yl) was prepared according to the general scheme set forth below in general Scheme 6.

Scheme 6:



Step R: 1-(dimethylamino)-4-methyl-2-phenylpent-1-en-3-one (41). To a solution of 3-methyl-1-phenylbutan-2-one (40; 3.38 g, 20 mmol) in 40 mL of anhydrous DMF was added 1,1-dimethoxy-N,N-dimethylmethanamine (5.958 g, 50 mmol). The resulting mixture was stirred at 100°C overnight. After removal of DMF and excess of acetal, 4.3 g of 41 was obtained as a crude product and used in subsequent reaction without further purification. MS (ES) M+H expected 218.2, found 218.0.

Step S: 2-hydroxy-6-isopropyl-5-phenylnicotinonitrile (42). To a 20 mL of anhydrous DMF solution containing 960 mg of sodium hydride (22 mmol, 60% dispersion in mineral oil) was added dropwise a solution of crude 1-(dimethylamino)-4-methyl-2-phenylpent-1-en-3-one (41; 4.3 g, 20 mmol DMF solution), cyano acetamide (1.72 g, 20 mmol), and 2 mL of MeOH in 35 mL of DMF. After the addition was completed, the resulting mixture was stirred at 80°C

overnight. After removal of DMF under reduced pressure, the residue was re-dissolved in methylene chloride and washed with water, and brine. The organic layer was then dried over anhy. Na_2SO_4 and concentrated in vacuo. Flash column chromatography (1:10 ethyl acetate/petroleum ether) afforded 3.84 g of **42** as a white solid. MS (ES) M+H expected 239.1, found 239.0. ^1H NMR ($\text{DMSO}-d_6$) δ 8.03 (s, 1H), 7.43 - 7.50 (m, 2H), 7.37 - 7.43 (m, 1H), 7.30 - 7.33 (m, 1H), 7.29 (s, 1H), 2.85 - 2.97 (m, 1H), 1.21 (s, 3H), 1.20 (s, 3H).

Step T: 2-chloro-6-isopropyl-5-phenylnicotinonitrile (43). A mixture of 2-hydroxy-6-isopropyl-5-phenylnicotinonitrile (**42**; 2.3 g, 10 mmol), 5 mL of phosphoryl trichloride and one drop of DMF were heated to reflux overnight until LC-MS indicated the complete conversion to the product. After evaporation of excess of phosphoryl trichloride under reduced pressure, the residue was re-dissolved in methylene chloride and neutralized carefully with satd. aq. NaHCO_3 and washed subsequently with 1N HCl and brine. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography (1:5 ethyl acetate/petroleum ether) afforded 2.4 g of **43** as a yellowish solid. MS (ES) M+H expected 257.1, found 257.0. ^1H NMR ($\text{CHLOROFORM}-d$) δ 7.76 - 7.82 (m, 1H), 7.43 - 7.54 (m, 3H), 7.28 (br. s., 1H), 7.22 - 7.26 (m, 1H), 3.20 (spt, $J = 6.7$ Hz, 1H), 1.22 (s, 3H), 1.20 (s, 3H).

Step U: (R)-6-isopropyl-2-(3-methylpiperazin-1-yl)-5-phenylnicotinonitrile (44). A mixture of above chloride **43** (192.5 mg, 0.75 mmol), (R)-2-methylpiperazine (187.8 mg, 1.875 mmol), and triethylamine (0.261 mL, 1.875 mmol) suspended in 2 mL of acetonitrile was subjected to microwave reaction at 175°C for 45 min. After the reaction mixture was concentrated *in vacuo*, the residue was purified by flash column chromatography to give 184 mg of **44** as yellowish oil. MS (ES) M+H expected 321.2, found 321.1. ^1H NMR ($\text{CHLOROFORM}-d$) δ 7.56 - 7.66 (m, 1H), 7.34 - 7.51 (m, 3H), 7.19 - 7.28 (m, 2H), 4.31 - 4.59 (m, 2H), 3.11 - 3.27 (m, 3H), 3.01 - 3.11 (m, 2H), 2.84 (dd, $J = 12.8, 10.3$ Hz, 1H), 1.22 (d, $J = 6.3$ Hz, 3H), 1.15 (dd, $J = 6.7, 1.1$ Hz, 6H).

Step V: (R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 164). In a 5-mL of amber glass vial was placed (R)-6-isopropyl-2-(3-methylpiperazin-1-yl)-5-phenyl- nicotinonitrile (50 mg, 0.156 mmol), 2-methylfuran-3-carboxylic acid (39 mg, 0.312 mmol), EDCI (60 mg, 0.312 mmol), HOBt (42 mg, 0.312 mmol), triethylamine (40 mg, 0.312 mmol) and 2 mL of methylene chloride. The resulting

reaction mixture was stirred at room temperature overnight. The mixture was quenched with 1 N HCl aqueous solution, extracted with EtOAc three times. The combined organic layer was washed with satd. NaHCO₃ and brine, dried over anhy. Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by preparative TLC (EtOAc: petroleum ether/100:20) to afford 28 mg of the title compound as a white solid. MS (ES) M+H expected 429.2, found 429.1. ¹H NMR (METHANOL-d₄) δ 7.59 - 7.67 (m, 1H), 7.37 - 7.50 (m, 3H), 7.31 (d, J = 2.0 Hz, 1H), 7.21 - 7.28 (m, 2H), 6.39 (d, J = 2.0 Hz, 1H), 4.70 (br. s., 1H), 4.29 - 4.50 (m, 2H), 4.23 (br. s., 1H), 3.49 (br. s., 1H), 3.33 (dd, J = 12.9, 3.1 Hz, 1H), 3.08 - 3.23 (m, 2H), 2.40 - 2.47 (m, 3H), 1.43 (d, J = 6.8 Hz, 3H), 1.16 (dd, J = 6.8, 2.8 Hz, 6H).

Other Compounds of Formula II listed below, wherein R^{1a} is hydrogen; R^{1b} is optionally substituted phenyl; were similarly prepared according to Scheme 6 by replacing one or more of: (1) methyl-1-phenylbutan-2-one (40) with an alternate phenyl ketone as starting material; (2) (R)-2-methylpiperazine with an alternate piperazine in Step U; and (3) 2-methylfuran-3-carboxylic acid with an alternate acid in Step V.

2-(4-(furan-2-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 109).

¹H NMR (CHLOROFORM-d) δ 7.65 (s, 1H), 7.53 - 7.58 (m, 1H), 7.38 - 7.49 (m, 3H), 7.24 - 7.28 (m, 2H), 7.10 (d, J = 3.3 Hz, 1H), 6.54 (dd, J = 3.3, 1.8 Hz, 1H), 4.03 (br. s., 4H), 3.89 (dd, J = 6.4, 3.6 Hz, 4H), 3.17 (dt, J = 13.4, 6.7 Hz, 1H), 1.18 (d, J = 6.5 Hz, 6H). LC-MS : m/z 401.1 (M+H)⁺.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 119).

¹H NMR (CHLOROFORM-d) δ 7.62 - 7.69 (m, 1H), 7.54 (d, J = 0.8 Hz, 1H), 7.40 - 7.47 (m, 3H), 7.23 - 7.28 (m, 2H), 7.08 (d, J = 3.5 Hz, 1H), 6.53 (dd, J = 3.5, 1.8 Hz, 1H), 4.93 (br. s., 1H), 4.54 (d, J = 12.8 Hz, 1H), 4.45 (d, J = 12.3 Hz, 1H), 4.37 (d, J = 13.3 Hz, 1H), 3.58 (br. s., 1H), 3.44 (dd, J = 13.3, 3.8 Hz, 1H), 3.27 (td, J = 12.4, 3.4 Hz, 1H), 3.16 (dt, J = 13.3, 6.7 Hz, 1H), 1.50 (d, J = 6.8 Hz, 3H), 1.17 (dd, J = 6.7, 1.9 Hz, 6H). LC-MS : m/z 414.9 (M+H)⁺.

2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 120).

¹H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.64 (s, 1H), 7.40 - 7.51 (m, 4H), 7.24 - 7.28 (m, 2H), 6.61 (d, J = 1.3 Hz, 1H), 4.76 (br. s., 1H), 4.33 - 4.52 (m, 3H), 3.51 (s, 1H), 3.35 (dd, J = 13.2, 3.1 Hz, 1H), 3.12 - 3.22 (m, 2H), 1.47 (d, J = 6.8 Hz, 3H), 1.17 (dd, J = 6.5, 2.0 Hz, 6H). LC-MS : m/z 414.9 (M+H)⁺.

2-(4-(furan-3-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 124).

¹H NMR (CHLOROFORM-d) δ 7.76 - 7.81 (m, 1H), 7.65 (s, 1H), 7.36 - 7.51 (m, 4H), 7.23 - 7.28 (m, 2H), 6.62 (dd, J = 1.9, 0.9 Hz, 1H), 3.91 (br. s., 4H), 3.84 (br. s., 4H), 3.17 (dt, J = 13.4, 6.6 Hz, 1H), 1.17 (d, J = 6.8 Hz, 6H). LC-MS : m/z 401.1 (M+H)⁺.

2-(4-(1H-indole-3-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 125).

¹H NMR (CHLOROFORM-d) δ 8.97 (br. s., 1H), 7.74 - 7.81 (m, 1H), 7.64 (s, 1H), 7.53 (br. s., 1H), 7.38 - 7.50 (m, 4H), 7.28 - 7.31 (m, 1H), 7.24 - 7.28 (m, 3H), 3.94 (br. s., 4H), 3.85 (br. s., 4H), 3.16 (dt, J = 13.2, 6.6 Hz, 1H), 1.17 (d, J = 6.5 Hz, 6H). LC-MS : m/z 450.2 (M+H)⁺.

6-isopropyl-5-phenyl-2-(4-(2-phenylacetyl)piperazin-1-yl)nicotinonitrile (Compound 126).

¹H NMR (CHLOROFORM-d) δ 7.62 (s, 1H), 7.41 - 7.47 (m, 3H), 7.38 - 7.41 (m, 1H), 7.37 (s, 1H), 7.34 - 7.36 (m, 1H), 7.32 (s, 1H), 7.30 (s, 1H), 7.25 (d, J = 1.5 Hz, 1H), 7.24 (s, 1H), 3.84 - 3.89 (m, 2H), 3.83 (s, 2H), 3.73 - 3.78 (m, 2H), 3.64 - 3.68 (m, 2H), 3.58 - 3.63 (m, 2H), 3.15 (dt, J = 13.3, 6.7 Hz, 1H), 1.15 (d, J = 6.5 Hz, 6H). LC-MS : m/z 425.1 (M+H)⁺.

6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 139).

¹H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.37 - 7.51 (m, 4H), 7.33 - 7.37 (m, 2H), 7.29 - 7.33 (m, 2H), 7.22 - 7.27 (m, 2H), 4.62 (d, J = 13.6 Hz, 0.5H), 4.42 (d, J = 12.5 Hz, 0.5H), 4.19 - 4.35 (m, 2H), 3.81 (br. s., 1H), 3.76 (d, J = 13.1 Hz, 0.5H), 3.49 (t, J = 12.0 Hz, 0.5H), 2.91-3.29 (m, 3H), 1.31 (br. s., 3H), 1.15 (d, J = 6.8 Hz, 6H). LC-MS : m/z 439.2 (M+H)⁺.

2-((3S,5R)-3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 140).

¹H NMR (CHLOROFORM-d) δ 7.61 - 7.64 (m, 1H), 7.41 - 7.48 (m, 3H), 7.38 - 7.41 (m, 1H), 7.37 (s, 1H), 7.34 - 7.36 (m, 1H), 7.32 (s, 1H), 7.30 (s, 1H), 7.27 (d, J = 1.8 Hz, 1H), 7.23 - 7.26

(m, 1H), 4.90 (br. s., 1H), 4.46 (br. s., 2H), 4.20 (br. s., 1H), 3.82 (s, 2H), 3.12 - 3.22 (m, 2H), 3.11 (br. s., 1H), 1.43 (d, J = 7.0 Hz, 6H), 1.16 (d, J = 6.8 Hz, 6H). LC-MS : m/z 453.1 (M+H)⁺.

2-((3S,5R)-4-(furan-3-carbonyl)-3,5-dimethylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 141).

¹H NMR (CHLOROFORM-d) δ 7.77 (dd, J = 1.5, 0.8 Hz, 1H), 7.65 (s, 1H), 7.47 - 7.49 (m, 1H), 7.45 - 7.47 (m, 1H), 7.44 (s, 1H), 7.40 - 7.43 (m, 1H), 7.24 - 7.28 (m, 2H), 6.65 (dd, J = 1.9, 0.9 Hz, 1H), 4.71 (br. s., 2H), 4.47 (s, 1H), 4.50 (s, 1H), 3.27 (dd, J = 12.9, 4.1 Hz, 2H), 3.18 (dt, J = 13.3, 6.7 Hz, 1H), 1.55 (d, J = 7.0 Hz, 6H), 1.18 (d, J = 6.5 Hz, 6H). LC-MS : m/z 429.2 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 143).

¹H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.39 - 7.47 (m, 3H), 7.34 - 7.39 (m, 2H), 7.29 - 7.33 (m, 2H), 7.22 - 7.28 (m, 3H), 4.98 (br. s., 0.5H), 4.62 (d, J = 13.8 Hz, 0.5H), 4.42 (d, J = 12.0 Hz, 0.5H), 4.15 - 4.35 (m, 2H), 3.81 (br. s., 2H), 3.72 - 3.79 (m, 0.5H), 3.49 (t, J = 11.3 Hz, 0.5H), 3.29 (d, J = 10.0 Hz, 0.5H), 3.04 - 3.21 (m, 2.5H), 2.88 - 3.01 (m, 0.5H), 1.27 - 1.34 (m, 3H), 1.15 (d, J = 6.5 Hz, 6H). LC-MS : m/z 439.2 (M+H)⁺.

(S)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 144).

¹H NMR (CHLOROFORM-d) δ 7.74 - 7.80 (m, 1H), 7.64 (s, 1H), 7.36 - 7.52 (m, 4H), 7.27 (dd, J = 7.9, 6.4 Hz, 2H), 6.59 - 6.64 (m, 1H), 4.76 (br. s., 1H), 4.20 - 4.50 (m, 3H), 3.51 (br. s., 1H), 3.35 (dd, J = 13.3, 3.3 Hz, 1H), 3.06 - 3.24 (m, 2H), 1.47 (d, J = 6.8 Hz, 3H), 1.17 (dd, J = 6.5, 2.0 Hz, 6H). LC-MS : m/z 415.2 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 145).

¹H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.29 - 7.47 (m, 7H), 7.22 - 7.28 (m, 3H), 4.98 (br. s., 0.5H), 4.62 (d, J = 13.6 Hz, 0.5H), 4.42 (d, J = 12.8 Hz, 0.5H), 4.15 - 4.37 (m, 2H), 3.80 - 3.85 (m, 2H), 3.76 (d, J = 12.8 Hz, 0.5H), 3.49 (t, J = 11.2 Hz, 0.5H), 3.25 - 3.37 (m, 0.5H), 3.02 - 3.23 (m, 2.5H), 2.88 - 3.01 (m, 0.5H), 1.26 - 1.35 (m, 3H), 1.15 (d, J = 6.8 Hz, 6H). LC-MS : m/z 439.2 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 150).

¹H NMR (CHLOROFORM-d) δ 7.77 (dd, J = 1.5, 1.0 Hz, 1H), 7.63 - 7.66 (m, 1H), 7.38 - 7.50 (m, 4H), 7.23 - 7.28 (m, 2H), 6.61 (dd, J = 1.8, 0.8 Hz, 1H), 4.76 (br. s., 1H), 4.30 - 4.51 (m, 3H), 3.52 (br. s., 1H), 3.35 (dd, J = 13.2, 3.6 Hz, 1H), 3.06 - 3.24 (m, 2H), 1.47 (d, J = 6.8 Hz, 3H), 1.17 (dd, J = 6.8, 2.0 Hz, 6H). LC-MS : m/z 415.1 (M+H)⁺.

2-(4-(furan-3-carbonyl)-3-phenylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 153).

¹H NMR (CHLOROFORM-d) δ 7.59 - 7.74 (m, 1H), 7.56 (s, 1H), 7.33 - 7.50 (m, 8H), 7.29 (d, J = 7.3 Hz, 1H), 7.17 - 7.25 (m, 2H), 6.54 (br. s., 1H), 5.74 (br. s., 1H), 4.79 (br. s., 1H), 4.51 (br. s., 1H), 4.33 (d, J = 9.5 Hz, 1H), 3.95 (d, J = 11.5 Hz, 1H), 3.58 (br. s., 2H), 3.12 (spt, J = 6.6 Hz, 1H), 1.08 - 1.18 (m, 6H). LC-MS : m/z 477.1 (M+H)⁺.

2-(4-(furan-3-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 159).

¹H NMR (CHLOROFORM-d) δ 7.72 (br. s., 1H), 7.48 - 7.60 (m, 5H), 7.46 (br. s., 3H), 7.40 (br. s., 2H), 7.27 (br. s., 1H), 7.20 (d, J = 6.8 Hz, 1H), 6.77 (s, 1H), 6.59 (s, 1H), 5.14-5.37 (m, 1H), 4.25 (br. s., 2H), 3.87 (br. s., 3H), 3.64 (br. s., 1H), 2.81 - 2.95 (m, 1H), 1.16 (d, J = 6.5 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H). LC-MS : m/z 477.2 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-5-phenylnicotinonitrile (Compound 165).

¹H NMR (METHANOL-d₄) δ 7.62 (s, 1H), 7.35 - 7.57 (m, 3H), 7.21 - 7.28 (m, 3H), 6.87 - 7.11 (m, 2H), 4.60 (d, J = 13.3 Hz, 1H), 4.29 - 4.37 (m, 2H), 3.98 (s, 2H), 3.59 (t, J = 11.4 Hz, 1H), 3.04 - 3.27 (m, 4H), 1.36 (dd, J = 15.2, 5.9 Hz, 3H), 1.16 (d, J = 6.5 Hz, 6H). LC-MS : m/z 445.0 (M+H)⁺.

2-(4-(furan-2-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 166).

¹H NMR (CHLOROFORM-d) δ 7.54 - 7.56 (m, 2H), 7.52 (br. s., 3H), 7.43 (br. s., 2H), 7.24 - 7.30 (m, 3H), 7.20 (d, J = 7.3 Hz, 1H), 7.08 (d, J = 3.3 Hz, 1H), 6.77 (s, 1H), 6.52 (br. s., 1H), 5.31-5.37 (br. s., 1H), 4.40 (br. s., 1H), 4.32 (br. s., 1H), 3.85 - 4.03 (m, 2H), 3.79 (d, J = 13.1 Hz,

1H), 3.68 (d, J = 4.8 Hz, 1H), 2.87 (dt, J = 13.4, 6.8 Hz, 1H), 1.15 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.5 Hz, 3H). LC-MS : m/z 477.2 (M+H)⁺.

2-(4-(1H-indole-3-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 168).

¹H NMR (CHLOROFORM-d) δ 9.09 (br. s., 1H), 7.76 (br. s., 1H), 7.51 (s, 2H), 7.55 (s, 3H), 7.39 (br. s., 3H), 7.29 (s, 2H), 7.33 (s, 1H), 7.24 (br. s., 3H), 6.77 (br. s., 1H), 5.29 (br. s., 1H), 4.30 (d, J = 11.5 Hz, 1H), 4.18 (br. s., 1H), 3.93 (br. s., 3H), 3.64 (br. s., 1H), 2.89 (br. s., 1H), 1.16 (d, J = 5.8 Hz, 3H), 1.07 (d, J = 5.8 Hz, 3H). LC-MS : m/z 526.1 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-isopropylpiperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 170).

¹H NMR (CHLOROFORM-d) δ 7.74 (br. s., 1H), 7.61 (s, 1H), 7.47 (t, J = 1.6 Hz, 1H), 7.35 - 7.46 (m, 3H), 7.20 - 7.26 (m, 2H), 6.58 (s, 1H), 4.79 (d, J = 12.8 Hz, 1H), 4.54-4.68 (br. s., 1H), 4.45 (br. s., 1H), 3.8-4.07 (m, 1H), 3.56 - 3.74 (m, 1H), 3.19 (br. s., 1H), 3.06 - 3.18 (m, 3H), 1.52 - 1.59 (m, 3H), 1.40 - 1.48 (m, 3H), 1.17 (d, J = 6.8 Hz, 3H), 1.13 (d, J = 6.8 Hz, 3H). LC-MS : m/z 443.1 (M+H)⁺.

(R)-2-(3-ethyl-4-(furan-3-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 171).

¹H NMR (CHLOROFORM-d) δ 7.74 (s, 1H), 7.58 - 7.65 (m, 1H), 7.35 - 7.50 (m, 4H), 7.20 - 7.26 (m, 2H), 6.58 (dd, J = 1.8, 0.8 Hz, 1H), 5.02 (s, 1H), 4.69 (br. s., 1H), 4.50 (d, J = 13.1 Hz, 1H), 4.41 (d, J = 12.3 Hz, 1H), 4.23-4.31 (br. s., 1H), 3.46 - 3.86 (m, 2H), 3.27 (dd, J = 13.3, 3.3 Hz, 1H), 3.10 - 3.21 (m, 2H), 1.79 - 1.96 (m, 2H), 1.54 (d, J = 6.5 Hz, 1.5H), 1.45 (d, J = 6.5 Hz, 1.5H), 1.15 (dd, J = 6.8, 3.5 Hz, 6H). LC-MS : m/z 429.1 (M+H)⁺.

(R)-2-(3-ethyl-4-(furan-2-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 172).

¹H NMR (CHLOROFORM-d) δ 7.59 - 7.64 (m, 1H), 7.51 (dd, J = 1.8, 0.8 Hz, 1H), 7.36 - 7.46 (m, 3H), 7.21 - 7.26 (m, 2H), 7.02 - 7.10 (m, 1H), 6.51 (dd, J = 3.5, 1.8 Hz, 1H), 4.71 (br. s., 1H), 4.38 - 4.60 (m, 3H), 3.50 (br. s., 1H), 3.35 (dd, J = 13.3, 3.5 Hz, 1H), 3.22 (td, J = 12.5, 3.4 Hz, 1H), 3.08 - 3.18 (m, 1H), 1.90 - 2.06 (m, 1H), 1.83 (dqin, J = 14.2, 7.2 Hz, 1H), 1.15 (dd, J = 6.7, 3.1 Hz, 6H), 0.97 (t, J = 7.4 Hz, 3H). LC-MS : m/z 429.1 (M+H)⁺.

(R)-2-(3-ethyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 173).

¹H NMR (CHLOROFORM-d) δ 7.58 - 7.66 (m, 1H), 7.35 - 7.47 (m, 3H), 7.29 (d, J = 2.0 Hz, 1H), 7.21 - 7.26 (m, 2H), 6.32 - 6.41 (m, 1H), 4.59-4.80 (m, 1H), 4.50 (d, J = 13.1 Hz, 1H), 4.42 (br. s., 1H), 3.91-3.97 (br. s., 1H), 3.45-3.65 (m, 1H), 3.27 (dd, J = 13.1, 3.3 Hz, 1H), 3.05 - 3.19 (m, 2H), 2.41 (s, 3H), 1.86 - 1.95 (m, 1H), 1.79 (dt, J = 14.1, 7.0 Hz, 1H), 1.15 (dd, J = 6.8, 2.0 Hz, 6H), 0.87 - 0.99 (m, 3H). LC-MS : m/z 443.1 (M+H)⁺.

(R)-2-(3-ethyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-6-isopropyl-5-phenylnicotinonitrile (Compound 174).

¹H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.35 - 7.49 (m, 3H), 7.17 - 7.25 (m, 3H), 6.92 - 6.99 (m, 2H), 4.75 (br. s., 0.5H), 4.59 - 4.71 (m, 0.5H), 4.30 - 4.50 (m, 2H), 3.79 - 4.07 (m, 3H), 3.46 - 3.56 (m, 0.5H), 3.17 - 3.30 (m, 0.5H), 2.97 - 3.17 (m, 3H), 1.78 - 1.89 (m, 1H), 1.69 - 1.78 (m, 1H), 1.10 - 1.16 (m, 6H), 0.90 - 0.97 (m, 3H). LC-MS : m/z 459.1 (M+H)⁺.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-5,6-diphenylnicotinonitrile (Compound 117). Compound 117 was synthesized was synthesized was synthesized using 1,2-diphenylethanone as starting material.

¹H NMR (CHLOROFORM-d) δ 7.87 (s, 1H), 7.53 (dd, J = 1.5, 0.8 Hz, 1H), 7.37 - 7.44 (m, 2H), 7.27 - 7.35 (m, 6H), 7.12 - 7.19 (m, 2H), 7.06 - 7.12 (m, 1H), 6.53 (dd, J = 3.4, 1.9 Hz, 1H), 4.94 (br. s., 1H), 4.53 (t, J = 11.7 Hz, 2H), 4.36 - 4.46 (m, 1H), 3.62 (br. s., 1H), 3.44 - 3.54 (m, 1H), 3.26 - 3.37 (m, 1H), 1.52 (d, J = 6.5 Hz, 3H). LC-MS : m/z 448.9 (M+H)⁺.

2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-5,6-diphenylnicotinonitrile (Compound 118). Compound 118 was synthesized using 1,2-diphenylethanone as starting material.

¹H NMR (CHLOROFORM-d) δ 7.88 (s, 1H), 7.77 (s, 1H), 7.48 (s, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.27 - 7.33 (m, 6H), 7.13 - 7.16 (m, 2H), 6.61 (s, 1H), 4.71-4.79 (br. s., 1H), 4.47-4.50 (s, 1H), 4.38 (s, 1H), 4.41 (s, 1H), 3.48 - 3.64 (m, 1H), 3.38-3.42 (m, 1H), 3.21 (td, J = 12.4, 3.0 Hz, 1H), 1.49 (d, J = 6.5 Hz, 3H). LC-MS : m/z 448.9 (M+H)⁺.

2-(4-(furan-3-carbonyl)piperazin-1-yl)-5,6-diphenylnicotinonitrile (Compound 122).

Compound 122 was synthesized using 1,2-diphenylethanone as starting material.

^1H NMR (CHLOROFORM- d) δ 7.88 (s, 1H), 7.78 (s, 1H), 7.47 - 7.51 (m, 1H), 7.37 - 7.42 (m, 2H), 7.27 - 7.35 (m, 6H), 7.15 (dd, J = 6.5, 3.0 Hz, 2H), 6.62 (s, 1H), 3.92 (br. s., 4H), 3.89 (br. s., 4H). LC-MS : m/z 435.1 ($M+H$) $^+$.

5,6-diphenyl-2-(4-(2-phenylacetyl)piperazin-1-yl)nicotinonitrile (Compound 123)

Compound 123 was synthesized using 1,2-diphenylethanone as starting material.

^1H NMR (CHLOROFORM- d) δ 7.85 (s, 1H), 7.34 - 7.39 (m, 4H), 7.28 - 7.33 (m, 8H), 7.22 - 7.26 (m, 1H), 7.13 (dd, J = 6.5, 3.0 Hz, 2H), 3.85 - 3.91 (m, 2H), 3.79 - 3.84 (m, 4H), 3.66 (s, 4H). LC-MS : m/z 459.1 ($M+H$) $^+$.

(R)-5-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-

isopropylnicotinonitrile (Compound 161). Compound 161 was synthesized using 1-(3-fluorophenyl)-3-methylbutan-2-one as starting material.

^1H NMR (CHLOROFORM- d) δ 7.73 - 7.79 (m, 1H), 7.61 (s, 1H), 7.47 (t, J = 1.6 Hz, 1H), 7.35 - 7.44 (m, 1H), 7.06 - 7.13 (m, 1H), 7.00 - 7.04 (m, 1H), 6.96 (dt, J = 9.3, 2.1 Hz, 1H), 6.54 - 6.63 (m, 1H), 4.61 - 4.90 (m, 1H), 4.41 (s, 0.5H), 4.44 (s, 0.5H), 4.19 - 4.39 (m, 2H), 3.42-3.49 (br. s., 1H), 3.34 (dd, J = 13.2, 3.1 Hz, 1H), 3.14 - 3.23 (m, 1H), 3.06 - 3.14 (m, 1H), 1.44 (d, J = 6.8 Hz, 3H), 1.15 (dd, J = 6.8, 1.8 Hz, 6H). LC-MS : m/z 433.1 ($M+H$) $^+$.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(2-

methoxyphenyl)nicotinonitrile (Compound 175). Compound 175 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

^1H NMR (CHLOROFORM- d) δ 7.75 (s, 1H), 7.56 (s, 1H), 7.46 (t, J = 1.5 Hz, 1H), 7.34 - 7.41 (m, 1H), 7.06 - 7.12 (m, 1H), 7.01 (t, J = 7.3 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.55 - 6.62 (m, 1H), 4.74 (br. s., 1H), 4.18 - 4.46 (m, 3H), 3.77 (s, 3H), 3.49 (br. s., 1H), 3.31 (dd, J = 13.2, 3.1 Hz, 1H), 3.14 (td, J = 12.5, 3.0 Hz, 1H), 2.86 (quin, J = 6.7 Hz, 1H), 1.46 (d, J = 6.8 Hz, 3H), 1.15 (br. s., 3H), 1.04 (br. s., 3H). LC-MS : m/z 445.2 ($M+H$) $^+$.

(R)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-(2-

methoxyphenyl)nicotinonitrile (Compound 176). Compound 176 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

^1H NMR (CHLOROFORM- d) δ 7.56 (s, 1H), 7.50 - 7.53 (m, 1H), 7.34 - 7.41 (m, 1H), 7.07 - 7.13 (m, 1H), 7.03 - 7.06 (m, 1H), 6.99 - 7.02 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.51 (dd, J = 3.3, 1.8 Hz, 1H), 4.90 (br. s., 1H), 4.51 (d, J = 13.6 Hz, 1H), 4.41 (d, J = 13.8 Hz, 1H), 4.34 (d, J =

13.3 Hz, 1H), 3.77 (s, 3H), 3.57 (d, J = 10.5 Hz, 1H), 3.39 (dd, J = 13.1, 3.5 Hz, 1H), 3.23 (td, J = 12.4, 3.1 Hz, 1H), 2.86 (dt, J = 13.3, 6.7 Hz, 1H), 1.49 (d, J = 6.5 Hz, 3H), 1.16 (br. s., 3H), 1.05 (br. s., 3H). LC-MS : m/z 445.2 (M+H)⁺.

(R)-6-isopropyl-5-(2-methoxyphenyl)-2-(3-methyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)nicotinonitrile (Compound 177). Compound 177 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

¹H NMR (CHLOROFORM-d) δ 7.54 (s, 1H), 7.33 - 7.41 (m, 1H), 7.20 - 7.24 (m, 1H), 7.05 - 7.11 (m, 1H), 6.98 - 7.04 (m, 1H), 6.89 - 6.98 (m, 3H), 4.94 (br. s., 0.5H), 4.58 (d, J = 12.8 Hz, 0.2H), 4.17 - 4.46 (m, 3H), 3.91 - 4.04 (m, 2H), 3.76 (s, 3H), 3.56 (t, J = 11.2 Hz, 0.5H), 3.27 (d, J = 12.8 Hz, 0.5H), 3.13 - 3.23 (m, 1H), 2.98 - 3.11 (m, 1H), 2.85 (dt, J = 13.3, 6.7 Hz, 1H), 1.33 - 1.39 (m, 3H), 1.15 (br. s., 3H), 1.04 (br. s., 3H). LC-MS : m/z 475.2 (M+H)⁺.

(R)-6-isopropyl-5-(2-methoxyphenyl)-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)nicotino- nitrile (Compound 178). Compound 178 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

¹H NMR (CHLOROFORM-d) δ 7.52 - 7.59 (m, 1H), 7.34 - 7.41 (m, 1H), 7.29 (d, J = 1.8 Hz, 1H), 7.08 (dd, J = 7.3, 1.8 Hz, 1H), 7.01 (t, J = 7.2 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.38 (d, J = 1.8 Hz, 1H), 4.69 (br. s., 1H), 4.29 - 4.43 (m, 2H), 4.00 - 4.29 (m, 1H), 3.77 (s, 3H), 3.46 (br. s., 1H), 3.24 - 3.39 (m, 1H), 3.11 (td, J = 12.5, 3.0 Hz, 1H), 2.86 (spt, J = 6.6 Hz, 1H), 2.41 (s, 3H), 1.43 (d, J = 6.8 Hz, 3H), 1.12 - 1.19 (m, 3H), 1.04 (br. s., 3H). LC-MS : m/z 459.1 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-p-tolynicotinonitrile (Compound 179). Compound 179 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

¹H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.60 (s, 1H), 7.44 - 7.49 (m, 1H), 7.24 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.55 - 6.62 (m, 1H), 4.74 (br. s., 1H), 4.20 - 4.49 (m, 3H), 3.38 - 3.57 (m, 1H), 3.31 (dd, J = 13.1, 3.0 Hz, 1H), 3.07 - 3.22 (m, 2H), 2.37 - 2.46 (m, 3H), 1.45 (d, J = 6.8 Hz, 3H), 1.07 - 1.20 (m, 6H). LC-MS : m/z 429.1 (M+H)⁺.

(R)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-5-p-tolynicotinonitrile (Compound 180). Compound 180 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.50 - 7.53 (m, 1H), 7.24 (d, J = 7.8 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 3.5 Hz, 1H), 6.46 - 6.55 (m, 1H), 4.90 (br. s., 1H), 4.51 (d, J = 13.6 Hz, 1H), 4.42 (d, J = 14.1 Hz, 1H), 4.33 (dt, J = 13.3, 2.0 Hz, 1H), 3.57 (d, J = 10.3 Hz, 1H), 3.40 (dd, J = 13.2, 3.6 Hz, 1H), 3.18 - 3.30 (m, 1H), 3.09 - 3.18 (m, 1H), 2.41 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H), 1.07 - 1.20 (m, 6H). LC-MS : m/z 429.2 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-(thiophen-2-yl)acetyl)piperazin-1-yl)-5-p-tolynicotinonitrile (Compound 181). Compound 181 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

¹H NMR (CHLOROFORM-d) δ 7.58 (s, 1H), 7.20 - 7.25 (m, 3H), 7.12 (d, J = 7.8 Hz, 2H), 6.88 - 7.00 (m, 2H), 4.94 (br. s., 0.5H), 4.58 (d, J = 13.1 Hz, 0.5H), 4.32 - 4.43 (m, 1H), 4.27 (s, 1H), 4.30 (s, 1H), 3.91 - 4.05 (m, 2H), 3.80 (d, J = 13.6 Hz, 0.5H), 3.51 - 3.63 (m, 0.5H), 3.20 - 3.33 (m, 1H), 3.11 - 3.20 (m, 1H), 2.98 - 3.10 (m, 1H), 2.41 (s, 3H), 1.36 (d, J = 6.3 Hz, 1.5H), 1.32 (d, J = 6.8 Hz, 1.5H), 1.13 (d, J = 6.5 Hz, 6H). LC-MS : m/z 459.1 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-methylfuran-3-carbonyl)piperazin-1-yl)-5-p-tolynicotinonitrile (Compound 182). Compound 182 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.28 - 7.32 (m, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 6.36 - 6.41 (m, 1H), 4.69 (br. s., 1H), 4.38 (d, J = 13.3 Hz, 1H), 4.33 (d, J = 13.1 Hz, 1H), 4.23 (d, J = 12.0 Hz, 1H), 3.46 (br. s., 1H), 3.26 - 3.34 (m, 1H), 3.13 - 3.21 (m, 1H), 3.05 - 3.13 (m, 1H), 2.41 (s, 6H), 1.41 (d, J = 6.8 Hz, 3H), 1.14 (dd, J = 6.7, 3.4 Hz, 6H). LC-MS : m/z 443.2 (M+H)⁺.

(R)-6-isopropyl-5-(2-methoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 183). Compound 183 was synthesized using 1-(2-methoxyphenyl)-3-methylbutan-2-one as starting material.

¹H NMR (CHLOROFORM-d) δ 7.55 (s, 1H), 7.34 - 7.42 (m, 1H), 7.05 - 7.12 (m, 1H), 6.99 - 7.05 (m, 1H), 6.96 (d, J = 8.3 Hz, 1H), 4.93 (br. s., 0.5H), 4.55 (d, J = 13.1 Hz, 0.5H), 4.19 - 4.43 (m, 3H), 3.82 (d, J = 7.5 Hz, 0.5H), 3.76 (s, 3H), 3.70 - 3.76 (m, 2H), 3.54 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.30 (t, J = 13.3 Hz, 1H), 3.02 - 3.22 (m, 1H), 2.82 - 2.92 (m, 1H), 2.66 - 2.80 (m, 1H), 2.53 - 2.65 (m, 1H), 1.42 (d, J = 6.5 Hz, 1.5H), 1.32 (d, J = 6.5 Hz, 1.5H), 1.16 (br. s., 3H), 1.05 (br. s., 3H). LC-MS : m/z 437.1 (M+H)⁺.

(S)-5-(2-ethoxyphenyl)-2-(4-(furan-2-carbonyl)-2-methylpiperazin-1-yl)-6-

isopropylnicotinonitrile (Compound 184). Compound 184 was synthesized using 1-(2-ethoxyphenyl)-3-methylbutan-2-one as starting material.

¹H NMR (CHLOROFORM-d) δ 7.55 (s, 1H), 7.48 - 7.53 (m, 1H), 7.31 - 7.38 (m, 1H), 7.05 - 7.11 (m, 2H), 6.96 - 7.02 (m, 1H), 6.94 (d, J = 8.3 Hz, 1H), 6.45 - 6.56 (m, 1H), 4.77 (br. s., 1H), 4.53 (d, J = 11.3 Hz, 1H), 4.36 (d, J = 13.3 Hz, 1H), 4.23 - 4.33 (m, 1H), 4.02 (q, J = 6.8 Hz, 2H), 3.38 - 3.67 (m, 3H), 2.84 - 2.97 (m, 1H), 1.36 (d, J = 6.8 Hz, 3H), 1.27 - 1.30 (m, 3H), 1.24 - 1.27 (m, 6H). LC-MS : m/z 459.1 (M+H)⁺.

(R)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-p-tolynicotinonitrile

(Compound 198). Compound 198 was synthesized using 3-methyl-1-p-tolylbutan-2-one as starting material.

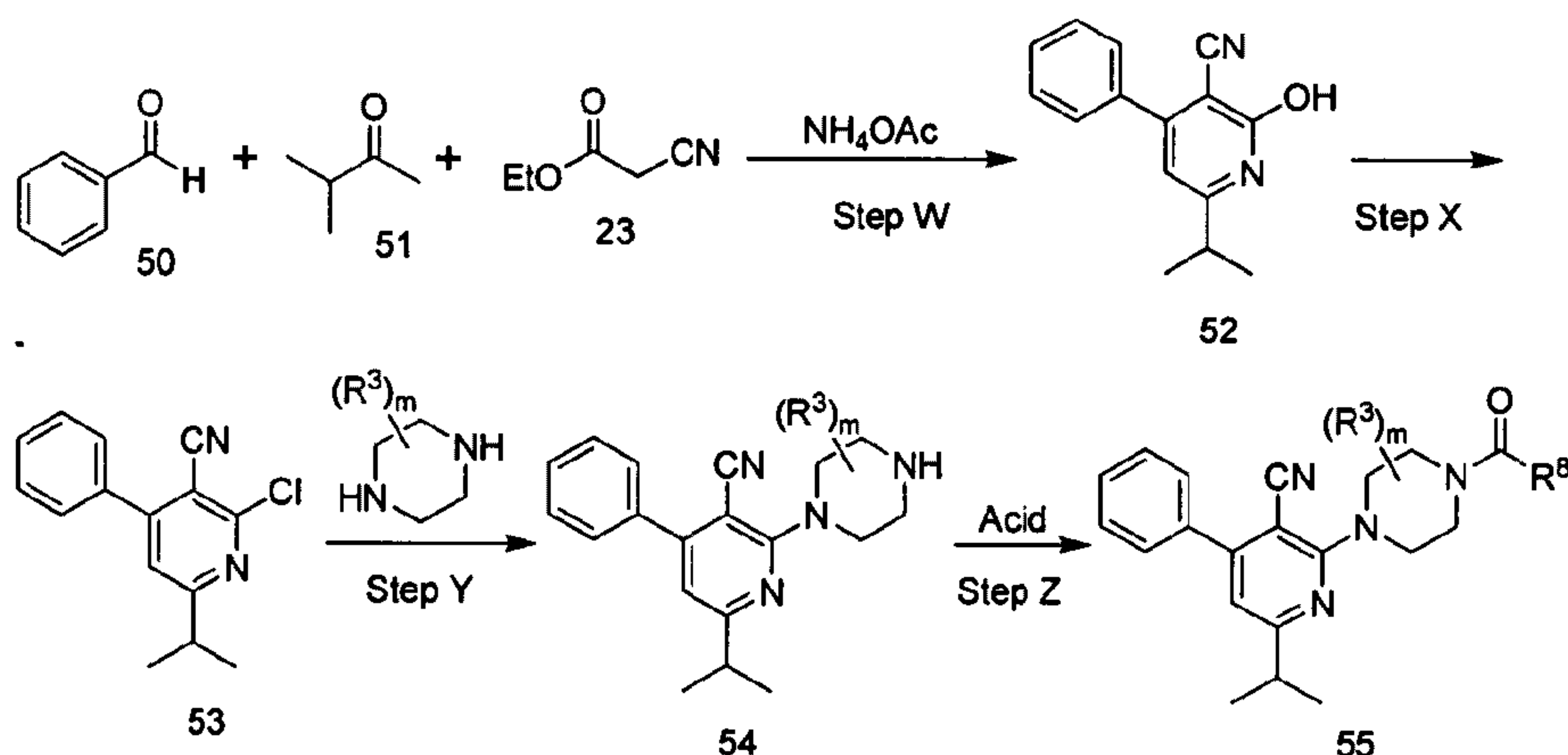
¹H NMR (CHLOROFORM-d) δ 7.59 (s, 1H), 7.23 (d, J = 7.8 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 4.92 (br. s., 0.5H), 4.55 (d, J = 12.8 Hz, 0.5H), 4.21 - 4.42 (m, 3H), 3.81 (d, J = 13.8 Hz, 0.5H), 3.69 - 3.77 (m, 6H), 3.53 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.31 (t, J = 12.3 Hz, 1H), 3.11 - 3.19 (m, 2H), 2.65 - 2.81 (m, 1H), 2.54 - 2.63 (m, 1H), 2.41 (s, 3H), 1.40 (d, J = 6.3 Hz, 1.5H), 1.31 (d, J = 6.5 Hz, 1.5H), 1.14 (d, J = 6.8 Hz, 6H). LC-MS : m/z 421.1 (M+H)⁺.

(R)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5,6-diphenylnicotinonitrile

(Compound 240). Compound 240 was synthesized using 1,2-diphenylethanone as starting material.

¹H NMR (CHLOROFORM-d) δ 7.84 (s, 1H), 7.33 - 7.40 (m, 2H), 7.26 - 7.33 (m, 4H), 7.20 - 7.25 (m, 2H), 7.08 - 7.16 (m, 2H), 4.94 (br. s., 0.5H), 4.56 (d, J = 12.8 Hz, 0.5H), 4.38 - 4.49 (m, 1H), 4.23 - 4.38 (m, 2H), 3.77 - 3.90 (m, 1H), 3.74 (t, J = 6.0 Hz, 2H), 3.54 - 3.64 (m, 0.5H), 3.37 (s, 3H), 3.34 (d, J = 6.3 Hz, 0.5H), 3.19 - 3.26 (m, 1H), 3.06 - 3.19 (m, 1H), 2.66 - 2.78 (m, 1H), 2.55 - 2.63 (m, 1H), 1.39 - 1.46 (m, 1.5H), 1.33 (d, J = 6.0 Hz, 1.5H). LC-MS : m/z 441.3 (M+H)⁺.

Example 10 Preparation of (R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 130). Compound 130 (**55**, wherein m is 1, R³ is methyl; and R⁸ is furan-3-yl) was synthesized according to general Scheme 7.
Scheme 7.



Step W: 2-hydroxy-6-isopropyl-4-phenylnicotinonitrile (52). To a suspension of ammonium acetate (31.46 g, 0.4 mol) in 200 mL of EtOH was added successively the 3-methyl-2-butanone (51; 5.38 mL, 50 mmol), benzaldehyde (50; 5.21 g, 50 mmol), and ethyl cyanoacetate (23; 5.6 mL, 50 mmol). The resulting mixture was stirred at reflux temperature for 3 hrs and subsequently at room temperature overnight. After the LC-MS showed the formation of the desired product, the precipitate formed was filtered and washed with EtOH (10 mL x 3 times) and hexane (10 mL x 3 times). After air-drying, 2.18 g of **52** was obtained as a white solid. MS (ES) M+H expected 239.1, found 239.0. ¹H NMR (CHLOROFORM-d) δ 7.61 - 7.70 (m, 2H), 7.51 - 7.58 (m, 3H), 6.33 (s, 1H), 3.06 (dt, J = 13.8, 6.9 Hz, 1H), 1.42 (d, J = 7.0 Hz, 6H).

Step X: 2-chloro-6-isopropyl-4-phenylnicotinonitrile (53). A mixture of 2-hydroxy-6-isopropyl-4-phenylnicotinonitrile **52**; (0.702 g, 2.94 mmol), 7 mL of phosphoryl trichloride and one drop of DMF were heated to reflux overnight until LC-MS indicated the complete conversion to the product. After evaporation of excess of phosphoryl trichloride under reduced pressure, the residue was re-dissolved in methylene chloride and neutralized carefully with satd. aq. NaHCO₃ and washed subsequently with 1N HCl and brine. The combined organic layer was dried over anhy. Na₂SO₄ and concentrated *in vacuo*. Flash column chromatography (1:5 ethyl acetate/petroleum ether) afforded 717 mg of **53** as a yellowish solid. MS (ES) M+H expected 257.1, found 257.0. ¹H NMR (CHLOROFORM-d) δ 7.52 - 7.64 (m, 5H), 7.26 (s, 1H), 3.09 - 3.21 (m, 1H), 1.37 (d, J = 7.0 Hz, 6H).

Step Y: (R)-6-isopropyl-2-(3-methylpiperazin-1-yl)-4-phenylnicotinonitrile (54). A mixture of above chloride **53** (192.6 mg, 0.75 mmol), (R)-2-methylpiperazine (150 mg, 1.5 mmol), and

triethylamine (0.21 mL, 1.5 mmol) suspended in 1.5 mL of acetonitrile was subjected to microwave reaction at 175°C for 45 min. After the reaction mixture was concentrated *in vacuo*, the residue was purified by flash column chromatography to give 197 mg of **54** as yellowish oil. MS (ES) M+H expected 321.2, found 321.1. ¹H NMR (CHLOROFORM-d) δ 7.54 - 7.60 (m, 2H), 7.47 - 7.53 (m, 3H), 6.71 (s, 1H), 4.21 - 4.35 (m, 2H), 3.03 - 3.18 (m, 4H), 2.99 (dt, J = 13.8, 6.9 Hz, 1H), 2.78 (dd, J = 12.7, 10.2 Hz, 1H), 1.30 (d, J = 7.0 Hz, 6H), 1.15 - 1.20 (m, 3H).

Step Z: (R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 130). In a 5-mL of amber glass vial was placed (R)-6-isopropyl-2-(3-methylpiperazin-1-yl)-4-phenyl- nicotinonitrile (**54**; 32 mg, 0.1 mmol), furan-3-carboxylic acid (22.4 mg, 0.312 mmol), EDCI (38.2 mg, 0.2 mmol), HOBt (27 mg, 0.2 mmol), triethylamine (35 μL, 0.2 mmol) and 1.5 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight. The mixture was quenched with 1 N HCl aqueous solution, extracted with EtOAc three times. The combined organic layer was washed with satd. NaHCO₃ and brine, dried over anhy. Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by preparative TLC (EtOAc: petroleum ether/20:100) to afford 23 mg of Compound 130 as a light yellowish solid. MS (ES) M+H expected 415.2, found 415.1. ¹H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.55 - 7.58 (m, 2H), 7.50 - 7.53 (m, 3H), 7.48 (t, J = 1.6 Hz, 1H), 6.79 (s, 1H), 6.60 - 6.62 (m, 1H), 4.76 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J = 13.1 Hz, 1H), 3.56 (br. s., 1H), 3.34 (dd, J = 12.9, 3.6 Hz, 1H), 3.17 (td, J = 12.5, 3.5 Hz, 1H), 3.01 (spt, J = 6.9 Hz, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.8 Hz, 6H).

Other Compounds of Formula II listed below, wherein R^{1a} is optionally substituted phenyl; and R^{1b} is hydrogen; were similarly prepared by general Scheme 7 replacing one or more of: (1) 3-methyl-2-butanone (**51**) with an alternate ketone as starting material; (2) benzaldehyde (**50**) with an alternate aldehyde as starting material; (3) (R)-2-methylpiperazine with an alternate piperazine in Step Y; and (4) 2-methylfuran-3-carboxylic acid with an alternate acid in Step Z. In addition, a compound wherein R^{1a} is isopropyl; R^{1b} is hydrogen and R² is phenyl was also prepared by the same method of general Scheme 7.

2-(4-benzoylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 100).

^1H NMR (DMSO- d_6) δ 7.54 - 7.59 (m, 2H), 7.50 - 7.54 (m, 3H), 7.47 (s, 5H), 6.80 (s, 1H), 4.01 (br. s., 2H), 3.74 - 3.89 (m, 3H), 3.66 (br. s., 3H), 3.01 (quin, $J = 6.8$ Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H). LC-MS : m/z 411.1 ($M+H$) $^+$.

2-((3S,5R)-4-benzoyl-3,5-dimethylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 101).

^1H NMR (DMSO- d_6) δ 7.53 - 7.58 (m, 2H), 7.49 - 7.53 (m, 3H), 7.40 - 7.47 (m, 5H), 6.79 (s, 1H), 4.54 (br. s., 2H), 4.24 (s, 1H), 4.27 (s, 1H), 3.28 (dd, $J = 13.1, 4.3$ Hz, 2H), 3.01 (dt, $J = 13.6, 6.9$ Hz, 1H), 1.52 (d, $J = 6.8$ Hz, 6H), 1.31 (d, $J = 7.0$ Hz, 6H). LC-MS : m/z 439.1 ($M+H$) $^+$.

2-((3S,5R)-4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 102).

^1H NMR (CHLOROFORM- d) δ 7.54 - 7.61 (m, 2H), 7.45 - 7.54 (m, 4H), 7.08 (d, $J = 3.5$ Hz, 1H), 6.78 (s, 1H), 6.52 (dd, $J = 3.5, 1.8$ Hz, 1H), 4.90 (br. s., 2H), 4.30 (s, 1H), 4.34 (s, 1H), 3.32 (dd, $J = 12.9, 4.4$ Hz, 2H), 3.01 (quin, $J = 6.9$ Hz, 1H), 1.60 (d, $J = 7.0$ Hz, 6H), 1.31 (d, $J = 7.0$ Hz, 6H). LC-MS : m/z 429.1 ($M+H$) $^+$.

2-(4-(furan-2-carbonyl)piperazin-1-yl)-4-isopropyl-6-phenylnicotinonitrile (Compound 103). Compound 103 was synthesized using isobutyraldehyde and acetophenone as starting materials.

^1H NMR (DMSO- d_6) δ 8.02 - 8.08 (m, 2H), 7.50 - 7.56 (m, 2H), 7.46 - 7.50 (m, 2H), 7.30 (s, 1H), 7.08 (dd, $J = 3.4, 0.6$ Hz, 1H), 6.53 (dd, $J = 3.3, 1.8$ Hz, 1H), 4.05 (br. s., 4H), 3.79 - 3.85 (m, 4H), 3.40 (dt, $J = 13.7, 6.8$ Hz, 1H), 1.38 (d, $J = 6.8$ Hz, 6H). LC-MS : m/z 400.8 ($M+H$) $^+$.

2-(4-(furan-2-carbonyl)piperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 104). Compound 104 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

^1H NMR (CHLOROFORM- d) δ 7.51 - 7.57 (m, 1H), 7.43 - 7.51 (m, 1H), 7.23 - 7.28 (m, 1H), 7.03 - 7.11 (m, 3H), 6.75 (s, 1H), 6.53 (dd, $J = 3.0, 1.5$ Hz, 1H), 4.02 (br. s., 4H), 3.89 (s, 3H), 3.74 - 3.82 (m, 4H), 3.00 (dt, $J = 13.8, 6.9$ Hz, 1H), 1.31 (d, $J = 6.8$ Hz, 6H). LC-MS : m/z 430.9 ($M+H$) $^+$.

2-(4-benzoylpiperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 105). Compound 105 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (DMSO-d₆) δ 7.43 - 7.50 (m, 6H), 7.25 (dd, J = 7.4, 1.6 Hz, 1H), 7.07 - 7.10 (m, 1H), 7.02 - 7.06 (m, 1H), 6.75 (s, 1H), 3.99 (br. s., 2H), 3.87 (s, 3H), 3.78 (br. s., 2H), 3.64 (br. s., 4H), 2.99 (dt, J = 13.8, 6.9 Hz, 1H), 1.31 (s, 3H), 1.29 (s, 3H). LC-MS : m/z 440.8 (M+H)⁺.

2-(4-(1H-indole-3-carbonyl)piperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 106). Compound 106 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 9.02 (br. s., 1H), 7.73 - 7.80 (m, 1H), 7.41 - 7.51 (m, 3H), 7.21 - 7.28 (m, 3H), 7.01 - 7.11 (m, 2H), 6.75 (s, 1H), 3.94 (br. s., 4H), 3.87 (s, 3H), 3.75 (br. s., 4H), 3.02 (dt, J = 13.7, 6.8 Hz, 1H), 1.31 (d, J = 6.8 Hz, 6H). LC-MS : m/z 480 (M+H)⁺.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 107).

¹H NMR (CHLOROFORM-d) δ 7.55 - 7.60 (m, 2H), 7.48 - 7.54 (m, 4H), 7.06 (dd, J = 3.5, 0.8 Hz, 1H), 6.77 (s, 1H), 6.52 (dd, J = 3.5, 1.8 Hz, 1H), 4.91 (br. s., 1H), 4.52 (d, J = 13.6 Hz, 1H), 4.29 - 4.36 (m, 1H), 4.23 (dt, J = 13.1, 2.1 Hz, 1H), 3.62 (br. s., 1H), 3.43 (dd, J = 13.1, 3.8 Hz, 1H), 3.26 (td, J = 12.4, 3.5 Hz, 1H), 3.00 (quin, J = 6.9 Hz, 1H), 1.50 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.8 Hz, 6H). LC-MS : m/z 415.1 (M+H)⁺.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-4-isopropyl-6-phenylnicotinonitrile (Compound 108). Compound 108 was synthesized using benzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 8.00 - 8.08 (m, 2H), 7.50 - 7.57 (m, 2H), 7.45 - 7.50 (m, 2H), 7.29 (s, 1H), 7.07 (dd, J = 3.5, 0.5 Hz, 1H), 6.52 (dd, J = 3.5, 1.8 Hz, 1H), 4.94 (br. s., 1H), 4.54 (d, J = 13.3 Hz, 1H), 4.34 (dd, J = 12.5, 2.3 Hz, 1H), 4.24 (dt, J = 13.1, 2.1 Hz, 1H), 3.65 (br. s., 1H), 3.41 - 3.46 (m, 1H), 3.38 - 3.41 (m, 1H), 3.25 (td, J = 12.4, 3.3 Hz, 1H), 1.53 (d, J = 6.8 Hz, 3H), 1.38 (d, J = 6.8 Hz, 6H). LC-MS : m/z 415.1 (M+H)⁺.

2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 110).

¹H NMR (CHLOROFORM-d) δ 8.00 - 8.06 (m, 2H), 7.77 (s, 1H), 7.50 (br. s., 1H), 7.48 (d, J = 4.3 Hz, 3H), 7.30 (s, 1H), 6.61 (s, 1H), 4.78 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J = 13.1 Hz, 1H), 3.58 (br. s., 1H), 3.40 (quin, J = 6.9 Hz, 1H), 3.33 (dd, J = 12.9, 3.1 Hz, 1H), 3.17 (td, J = 12.4, 3.3 Hz, 1H), 1.50 (d, J = 6.8 Hz, 3H), 1.38 (d, J = 6.8 Hz, 6H). LC-MS : m/z 415.0 (M+H)⁺.

2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-isopropyl-6-phenylnicotinonitrile (Compound 111). Compound 111 was synthesized using benzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.53 - 7.61 (m, 2H), 7.49 - 7.53 (m, 3H), 7.47 (s, 1H), 6.79 (s, 4H), 6.61 (s, 1H), 4.71-4.76 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J = 13.1 Hz, 1H), 3.56 (br. s., 1H), 3.34 (dd, J = 13.1, 3.3 Hz, 1H), 3.17 (td, J = 12.5, 3.4 Hz, 1H), 3.00 (dt, J = 13.7, 6.8 Hz, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 7.3 Hz, 6H). LC-MS : m/z 414.9 (M+H)⁺.

2-(4-(furan-3-carbonyl)piperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 113). Compound 113 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.42 - 7.53 (m, 2H), 7.25 (dd, J = 7.5, 1.5 Hz, 1H), 7.02 - 7.13 (m, 2H), 6.76 (s, 1H), 6.59 - 6.66 (m, 1H), 3.90 (br. s., 4H), 3.88 (s, 3H), 3.73 (br. s., 4H), 3.00 (dt, J = 13.7, 6.8 Hz, 1H), 1.30 (d, J = 6.8 Hz, 6H). LC-MS : m/z 431.0 (M+H)⁺.

4-(3-fluorophenyl)-2-(4-(furan-2-carbonyl)piperazin-1-yl)-6-isopropylnicotinonitrile (Compound 114). Compound 114 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.42 - 7.56 (m, 2H), 7.36 (dq, J = 7.7, 0.9 Hz, 1H), 7.17 - 7.27 (m, 2H), 7.09 (dd, J = 3.4, 0.9 Hz, 1H), 6.76 (s, 1H), 6.53 (dd, J = 3.5, 1.8 Hz, 1H), 4.03 (br. s., 4H), 3.83 (dd, J = 6.3, 4.0 Hz, 4H), 2.95 - 3.10 (m, 1H), 1.31 (d, J = 6.8 Hz, 6H). LC-MS : m/z 419.1 (M+H)⁺.

4-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)piperazin-1-yl)-6-isopropylnicotinonitrile (Compound 115). Compound 115 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.77 - 7.80 (m, 1H), 7.45 - 7.53 (m, 2H), 7.36 (dt, J = 7.7, 1.2 Hz, 1H), 7.17 - 7.28 (m, 2H), 6.77 (s, 1H), 6.62 (dd, J = 1.9, 0.6 Hz, 1H), 3.92 (br. s., 4H), 3.77 (br. s., 4H), 2.92 - 3.10 (m, 1H), 1.31 (d, J = 6.8 Hz, 6H). LC-MS : m/z 419.0 (M+H)⁺.

2-(4-(1H-indole-3-carbonyl)piperazin-1-yl)-4-(3-fluorophenyl)-6-isopropylnicotinonitrile (Compound 116). Compound 116 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.75 (d, J = 7.0 Hz, 1H), 7.40 - 7.63 (m, 3H), 7.36 (d, J = 7.8 Hz, 1H), 7.17 - 7.28 (m, 3H), 6.77 (s, 1H), 3.94 (br. s., 4H), 3.79 (br. s., 4H), 3.67 (s, 1H), 3.02 - 3.13 (m, 1H), 1.32 (d, J = 6.8 Hz, 6H). LC-MS : m/z 468.1 (M+H)⁺.

6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-4-phenylnicotinonitrile (Compound 121).

¹H NMR (CHLOROFORM-d) δ 7.48 - 7.58 (m, 5H), 7.33 - 7.39 (m, 3H), 7.30 (d, J = 1.5 Hz, 1H), 7.25 - 7.28 (m, 1H), 6.75 (s, 1H), 4.71 (s, 1H), 4.27 (br. s., 1H), 4.09 - 4.20 (m, 2H), 3.80 (br. s., 2H), 3.52 (s, 1H), 3.19-3.26 (s, 1H), 3.06 - 3.15 (m, 1H), 2.98 (dt, J = 13.7, 6.8 Hz, 1H), 1.40 (s, 3H), 1.30 (d, J = 4.5 Hz, 19H). LC-MS : m/z 439.2 (M+H)⁺.

4-(3-fluorophenyl)-2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 127). Compound 127 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.44 - 7.58 (m, 2H), 7.31 - 7.40 (m, 1H), 7.14 - 7.27 (m, 2H), 7.07 (d, J = 3.5 Hz, 1H), 6.74 (s, 1H), 6.53 (dd, J = 3.5, 1.8 Hz, 1H), 4.92 (br. s., 1H), 4.52 (d, J = 13.6 Hz, 1H), 4.34 (d, J = 10.5 Hz, 1H), 4.24 (dt, J = 13.1, 2.1 Hz, 1H), 3.62 (br. s., 1H), 3.45 (dd, J = 13.3, 3.8 Hz, 1H), 3.28 (td, J = 12.4, 3.4 Hz, 1H), 3.01 (dt, J = 13.6, 6.9 Hz, 1H), 1.44 - 1.54 (m, 3H), 1.31 (d, J = 6.8 Hz, 6H). LC-MS : m/z 433.0 (M+H)⁺.

4-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 128). Compound 128 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.73 - 7.81 (m, 1H), 7.44 - 7.56 (m, 2H), 7.35 (dt, J = 8.0, 1.1 Hz, 1H), 7.12 - 7.27 (m, 2H), 6.75 (s, 1H), 6.61 (dd, J = 1.8, 0.8 Hz, 1H), 4.77 (br. s., 1H), 4.31 (d, J = 12.0 Hz, 2H), 4.23 (d, J = 13.1 Hz, 1H), 3.57 (br. s., 1H), 3.36 (d, J = 10.0 Hz, 1H), 3.19

(td, J = 12.4, 3.5 Hz, 1H), 3.01 (dt, J = 13.5, 6.9 Hz, 1H), 1.46 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.8 Hz, 6H). LC-MS : m/z 433.1 (M+H)⁺.

2-(4-(1H-indole-3-carbonyl)-3-methylpiperazin-1-yl)-4-(3-fluorophenyl)-6-isopropylnicotinonitrile (Compound 129). Compound 129 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 8.85 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.40 - 7.54 (m, 3H), 7.35 (d, J = 7.8 Hz, 1H), 7.15 - 7.28 (m, 4H), 6.74 (s, 1H), 4.84 (br. s., 1H), 4.28 (t, J = 15.3 Hz, 3H), 3.59 (d, J = 11.8 Hz, 1H), 3.41 (d, J = 11.0 Hz, 1H), 3.21 (t, J = 10.8 Hz, 1H), 3.00 (dt, J = 13.8, 6.9 Hz, 1H), 1.45 (d, J = 6.5 Hz, 3H), 1.30 (d, J = 6.8 Hz, 6H). LC-MS : m/z 482.2 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 130).

¹H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.55 - 7.58 (m, 2H), 7.50 - 7.53 (m, 3H), 7.48 (t, J = 1.6 Hz, 1H), 6.79 (s, 1H), 6.60 - 6.62 (m, 1H), 4.76 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J = 13.1 Hz, 1H), 3.56 (br. s., 1H), 3.34 (dd, J = 12.9, 3.6 Hz, 1H), 3.17 (td, J = 12.5, 3.5 Hz, 1H), 3.01 (spt, J = 6.9 Hz, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.8 Hz, 6H). LC-MS : m/z 415.1 (M+H)⁺.

(R)-6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-4-phenylnicotinonitrile (Compound 131).

¹H NMR (CHLOROFORM-d) δ 7.52 - 7.57 (m, 2H), 7.47 - 7.52 (m, 3H), 7.29 - 7.41 (m, 4H), 7.24 - 7.28 (m, 1H), 6.75 (s, 1H), 4.98 (br. s., 0.5H), 4.62 (d, J = 13.3 Hz, 0.5H), 4.28 (d, J = 13.1 Hz, 1H), 4.06 - 4.20 (m, 2H), 3.81 (br. s., 2H), 3.70 - 3.79 (m, 0.5H), 3.54 (t, J = 11.3 Hz, 0.5H), 3.18 - 3.33 (m, 1H), 3.03 - 3.17 (m, 1H), 2.99 (dt, J = 13.8, 6.9 Hz, 1H), 1.33 (br. s., 3H), 1.29 (d, J = 7.0 Hz, 6H). LC-MS : m/z 439.1 (M+H)⁺.

(S)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 132).

¹H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.54 - 7.59 (m, 2H), 7.49 - 7.54 (m, 3H), 7.48 (t, J = 1.6 Hz, 1H), 6.79 (s, 1H), 6.59 - 6.63 (m, 1H), 4.76 (br. s., 1H), 4.28 (s, 1H), 4.31 (s, 1H), 4.22 (d, J = 13.3 Hz, 1H), 3.57 (br. s., 1H), 3.34 (dd, J = 13.2, 3.6 Hz, 1H), 3.17 (td, J = 12.5, 3.4 Hz, 1H), 3.01 (spt, J = 6.9 Hz, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.8 Hz, 6H). LC-MS : m/z 415.1 (M+H)⁺.

(S)-6-isopropyl-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)-4-phenylnicotinonitrile (Compound 133).

¹H NMR (CHLOROFORM-d) δ 7.53 - 7.56 (m, 2H), 7.47 - 7.53 (m, 3H), 7.33 - 7.39 (m, 2H), 7.29 - 7.33 (m, 2H), 7.24 - 7.28 (m, 1H), 6.75 (s, 1H), 4.98 (br. s., 0.5H), 4.62 (d, J = 13.3 Hz, 0.5H), 4.28 (d, J = 12.8 Hz, 1H), 4.08 - 4.20 (m, 2H), 3.81 (br. s., 2H), 3.70 - 3.79 (m, 0.5H), 3.54 (t, J = 11.3 Hz, 0.5H), 3.17 - 3.32 (m, 1H), 3.10 (t, J = 12.7 Hz, 1H), 2.98 (dt, J = 13.7, 6.8 Hz, 1H), 1.31 - 1.35 (m, 3H), 1.29 (d, J = 7.0 Hz, 6H). LC-MS : m/z 439.1 (M+H)⁺.

4-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)-3,5-dimethylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 134). Compound 134 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (DMSO-d₆) δ 7.77 (s, 1H), 7.45 - 7.53 (m, 2H), 7.35 (d, J = 8.3 Hz, 1H), 7.17 - 7.25 (m, 2H), 6.76 (s, 1H), 6.65 (d, J = 1.0 Hz, 1H), 4.71 (br. s., 1H), 4.31 (d, J = 12.8 Hz, 2H), 3.50 - 3.69 (m, 1H), 3.27 (dd, J = 13.2, 4.4 Hz, 2H), 3.01 (quin, J = 7.0 Hz, 1H), 1.56 (d, J = 7.0 Hz, 6H), 1.32 (s, 3H), 1.30 (s, 3H). LC-MS : m/z 447.1 (M+H)⁺.

2-(3,5-dimethyl-4-(2-phenylacetyl)piperazin-1-yl)-4-(3-fluorophenyl)-6-isopropylnicotinonitrile (Compound 135). Compound 135 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.43 - 7.55 (m, 1H), 7.12 - 7.40 (m, 8H), 6.74 (s, 1H), 4.90 (br. s., 1H), 4.26 (br. s., 3H), 3.82 (s, 2H), 3.14 (br. s., 2H), 3.00 (dt, J = 13.8, 6.9 Hz, 1H), 1.44 (d, J = 6.8 Hz, 6H), 1.30 (d, J = 6.8 Hz, 6H). LC-MS : m/z 471.1 (M+H)⁺.

4-(3-fluorophenyl)-2-(4-(furan-2-carbonyl)-3,5-dimethylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 136). Compound 136 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.45 - 7.55 (m, 2H), 7.32 - 7.38 (m, 1H), 7.15 - 7.28 (m, 2H), 7.08 (d, J = 3.5 Hz, 1H), 6.74 (s, 1H), 6.52 (dd, J = 3.5, 1.8 Hz, 1H), 4.90 (br. s., 2H), 4.34 (d, J = 13.1 Hz, 2H), 3.33 (dd, J = 13.1, 4.5 Hz, 2H), 2.93 - 3.08 (m, 1H), 1.59 (d, J = 7.0 Hz, 6H), 1.31 (d, J = 6.8 Hz, 6H). LC-MS : m/z 447.0 (M+H)⁺.

6-cyclohexyl-2-(4-(furan-2-carbonyl)piperazin-1-yl)-4-phenylnicotinonitrile (Compound 137). Compound 137 was synthesized using benzaldehyde and 1-cyclohexylethanone as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.46 - 7.61 (m, 6H), 7.08 (dd, J = 3.4, 0.9 Hz, 1H), 6.78 (s, 1H), 6.53 (dd, J = 3.4, 1.9 Hz, 1H), 4.03 (br. s., 4H), 3.76 - 3.86 (m, 4H), 2.66 (tt, J = 11.6, 3.3 Hz, 1H), 1.92 - 2.00 (m, 2H), 1.83 - 1.91 (m, 2H), 1.74 - 1.82 (m, 1H), 1.55 (qd, J = 12.3, 2.8 Hz, 2H), 1.41 (qt, J = 12.6, 3.1 Hz, 2H), 1.25 - 1.35 (m, 1H). LC-MS : m/z 441.0 (M+H)⁺.

6-cyclohexyl-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-phenylnicotinonitrile

(Compound 138). Compound 138 was synthesized using benzaldehyde and 1-cyclohexylethanone as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.43 - 7.61 (m, 6H), 6.77 (s, 1H), 6.61 (s, 1H), 4.76 (br. s., 1H), 4.29 (d, J = 12.3 Hz, 2H), 4.20 (d, J = 13.1 Hz, 1H), 3.56 (br. s., 1H), 3.33 (dd, J = 13.2, 3.1 Hz, 1H), 3.16 (td, J = 12.5, 3.1 Hz, 1H), 2.56 - 2.72 (m, 1H), 1.95 (d, J = 12.5 Hz, 2H), 1.87 (d, J = 12.8 Hz, 2H), 1.78 (d, J = 12.8 Hz, 1H), 1.49 - 1.60 (m, 2H), 1.46 (d, J = 6.5 Hz, 3H), 1.35 - 1.44 (m, 2H), 1.25 - 1.34 (m, 1H). LC-MS : m/z 455.1 (M+H)⁺.

6-cyclohexyl-2-((3S,5R)-4-(furan-3-carbonyl)-3,5-dimethylpiperazin-1-yl)-4-

phenylnicotinonitrile (Compound 142). Compound 142 was synthesized using benzaldehyde and 1-cyclohexylethanone as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.77 (s, 1H), 7.54 - 7.58 (m, 2H), 7.49 - 7.53 (m, 3H), 7.48 (t, J = 1.6 Hz, 1H), 6.79 (s, 1H), 6.65 (d, J = 2.0 Hz, 1H), 4.73 (br. s., 2H), 4.27 (d, J = 13.1 Hz, 2H), 3.25 (dd, J = 13.1, 4.5 Hz, 2H), 2.66 (tt, J = 11.6, 3.4 Hz, 1H), 1.95 (d, J = 12.5 Hz, 2H), 1.84 - 1.92 (m, 2H), 1.78 (d, J = 12.5 Hz, 1H), 1.57 (d, J = 7.0 Hz, 6H), 1.49 - 1.54 (m, 2H), 1.38 - 1.47 (m, 2H), 1.31 - 1.37 (m, 1H). LC-MS : m/z 469.1 (M+H)⁺.

6-isopropyl-4-(2-methoxyphenyl)-2-(4-(2-phenylacetyl)piperazin-1-yl)nicotinonitrile

(Compound 146). Compound 146 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.42 - 7.48 (m, 1H), 7.28 - 7.40 (m, 5H), 7.23 (dd, J = 7.5, 1.8 Hz, 1H), 7.01 - 7.10 (m, 2H), 6.73 (s, 1H), 3.83 - 3.90 (m, 5H), 3.82 (s, 2H), 3.62 - 3.70 (m, 4H), 3.49 - 3.56 (m, 2H), 2.91 - 3.03 (m, 1H), 1.29 (d, J = 6.8 Hz, 6H). LC-MS : m/z 455.2 (M+H)⁺.

2-(4-(furan-2-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-(2-

methoxyphenyl)nicotinonitrile (Compound 147). Compound 147 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.52 (dd, J = 1.8, 0.8 Hz, 1H), 7.41 - 7.48 (m, 1H), 7.25 (dd, J = 7.5, 1.8 Hz, 1H), 7.00 - 7.16 (m, 3H), 6.73 (s, 1H), 6.52 (dd, J = 3.5, 1.8 Hz, 1H), 4.91 (br. s., 1H), 4.51 (d, J = 12.3 Hz, 1H), 4.32 (d, J = 12.5 Hz, 1H), 4.22 (dt, J = 13.2, 2.0 Hz, 1H), 3.88 (s, 3H), 3.62 (br. s., 1H), 3.39 (dd, J = 13.2, 3.6 Hz, 1H), 3.22 (td, J = 12.4, 3.5 Hz, 1H), 3.00 (dt, J = 13.7, 6.8 Hz, 1H), 1.49 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 6.8 Hz, 6H). LC-MS : m/z 455.1 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-(2-methoxyphenyl)nicotinonitrile (Compound 148). Compound 148 was synthesized using 2-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.76 (dd, J = 1.5, 0.8 Hz, 1H), 7.40 - 7.51 (m, 2H), 7.22 - 7.28 (m, 1H), 7.01 - 7.11 (m, 2H), 6.70 - 6.76 (m, 1H), 6.61 (dd, J = 1.8, 0.8 Hz, 1H), 4.75 (br. s., 1H), 4.16 - 4.45 (m, 3H), 3.88 (s, 3H), 3.55 (br. s., 1H), 3.31 (dd, J = 12.9, 3.4 Hz, 1H), 3.14 (td, J = 12.5, 3.4 Hz, 1H), 3.00 (dt, J = 13.7, 6.8 Hz, 1H), 1.46 (d, J = 7.0 Hz, 3H), 1.30 (d, J = 6.8 Hz, 6H). LC-MS : m/z 445.2 (M+H)⁺.

6-isopropyl-4-(2-methoxyphenyl)-2-(3-methyl-4-(2-phenylacetyl)piperazin-1-yl)nicotinonitrile (Compound 149). Compound 149 was synthesized using 3-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.41 - 7.49 (m, 1H), 7.29 - 7.40 (m, 4H), 7.20 - 7.28 (m, 2H), 7.01 - 7.09 (m, 2H), 6.71 (s, 1H), 4.97 (br. s., 1H), 4.60 (d, J = 13.3 Hz, 1H), 4.25 (br. s., 1H), 4.16 (d, J = 13.3 Hz, 1H), 3.87 (s, 3H), 3.64 - 3.81 (m, 2H), 3.53 (t, J = 11.4 Hz, 1H), 3.14 - 3.29 (m, 1H), 2.85 - 3.14 (m, 2H), 1.62 (s, 3H), 1.29 (s, 6H). LC-MS : m/z 469.1 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-(3-methoxyphenyl)nicotinonitrile (Compound 151). Compound 151 was synthesized using 3-methoxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.76 (dd, J = 1.5, 0.8 Hz, 1H), 7.38 - 7.50 (m, 2H), 7.00 - 7.17 (m, 3H), 6.76 - 6.81 (m, 1H), 6.61 (dd, J = 1.9, 0.9 Hz, 1H), 4.76 (br. s., 1H), 4.29 (d, J = 12.8 Hz, 2H), 4.21 (d, J = 13.1 Hz, 1H), 3.84 - 3.92 (m, 3H), 3.56 (br. s., 1H), 3.33 (dd, J = 13.2, 3.6 Hz, 1H), 3.17 (td, J = 12.5, 3.4 Hz, 1H), 3.00 (dt, J = 13.7, 6.8 Hz, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 7.0 Hz, 6H). LC-MS : m/z 445.1 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-(3-hydroxyphenyl)-6-isopropylnicotinonitrile (Compound 152). Compound 152 was synthesized using 3-hydroxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.74 - 7.81 (m, 1H), 7.41 - 7.51 (m, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.11 (s, 1H), 7.05 (d, J = 7.5 Hz, 1H), 6.97 (dd, J = 8.2, 2.4 Hz, 1H), 6.79 (s, 1H), 6.57 - 6.64 (m, 1H), 4.79 (br. s., 1H), 4.15 - 4.44 (m, 3H), 3.59 (br. s., 1H), 3.34 (d, J = 10.5 Hz, 1H), 3.17 (td, J = 12.5, 3.1 Hz, 1H), 2.93 - 3.04 (m, 1H), 1.47 (d, J = 6.8 Hz, 3H), 1.27 - 1.31 (m, 6H). LC-MS : m/z 431.2 (M+H)⁺.

2-(4-(furan-3-carbonyl)-3-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 154).

¹H NMR (CHLOROFORM-d) δ 7.61 (br. s., 1H), 7.50 - 7.54 (m, 2H), 7.46 - 7.50 (m, 3H), 7.37 - 7.43 (m, 3H), 7.34 (t, J = 7.7 Hz, 2H), 7.22 - 7.27 (m, 1H), 6.67 (s, 1H), 6.52 (br. s., 1H), 5.75 (br. s., 1H), 4.57 (br. s., 2H), 4.29 (d, J = 11.5 Hz, 1H), 4.00 (d, J = 11.0 Hz, 1H), 3.60 - 3.74 (m, 1H), 3.55 (d, J = 10.5 Hz, 1H), 2.94 (dt, J = 13.6, 6.8 Hz, 1H), 1.25 - 1.27 (m, 3H), 1.23 (d, J = 7.0 Hz, 3H). LC-MS : m/z 477.1 (M+H)⁺.

2-(4-(furan-2-carbonyl)-3-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 155).

¹H NMR (CHLOROFORM-d) δ 7.51 - 7.55 (m, 2H), 7.46 - 7.50 (m, 4H), 7.45 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.20 - 7.25 (m, 1H), 6.92 - 7.07 (m, 1H), 6.68 (s, 1H), 6.45 (br. s., 1H), 5.95 (t, J = 4.5 Hz, 1H), 4.63 (s, 1H), 4.66 (s, 1H), 4.33 (d, J = 11.0 Hz, 1H), 4.06 (dd, J = 13.6, 4.0 Hz, 1H), 3.69 (br. s., 1H), 3.56 - 3.65 (m, 1H), 2.97 (dt, J = 13.7, 6.8 Hz, 1H), 1.24 - 1.28 (m, 6H). LC-MS : m/z 477.1 (M+H)⁺.

(R)-4-(3-fluorophenyl)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 156). Compound 156 was synthesized using 3-fluorobenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.77 (dd, J = 1.5, 1.0 Hz, 1H), 7.43 - 7.53 (m, 2H), 7.35 (dq, J = 7.7, 0.9 Hz, 1H), 7.12 - 7.28 (m, 2H), 6.67 - 6.80 (m, 1H), 6.61 (dd, J = 1.9, 0.9 Hz, 1H), 4.76 (br. s., 1H), 4.17 - 4.45 (m, 3H), 3.56 (br. s., 1H), 3.36 (dd, J = 13.1, 3.5 Hz, 1H), 3.18 (td, J = 12.5, 3.5 Hz, 1H), 2.95 - 3.07 (m, 1H), 1.46 (d, J = 6.8 Hz, 3H), 1.29 - 1.32 (m, 6H). LC-MS : m/z 433.1 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-(2-hydroxyphenyl)-6-isopropylnicotinonitrile (Compound 157). Compound 157 was synthesized using 2-hydroxybenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 8.01 (dd, J = 8.2, 1.4 Hz, 1H), 7.73 - 7.77 (m, 1H), 7.50 - 7.60 (m, 1H), 7.46 (t, J = 1.6 Hz, 1H), 7.31 - 7.37 (m, 2H), 7.21 (s, 1H), 6.60 (dd, J = 1.6, 0.6 Hz, 1H), 4.71 (br. s., 1H), 4.25 (br. s., 1H), 4.07 (d, J = 13.3 Hz, 1H), 3.98 (d, J = 13.8 Hz, 1H), 3.71 (br. s., 1H), 3.45 - 3.56 (m, 1H), 3.15 - 3.26 (m, 1H), 3.06 (dt, J = 13.7, 6.8 Hz, 1H), 1.32 - 1.37 (m, 9H). LC-MS : m/z 432.2 (M+H)⁺.

(R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropyl-4-o-tolylnicotinonitrile (Compound 158). Compound 158 was synthesized using 2-methylbenzaldehyde and 3-methylbutan-2-one as starting materials.

¹H NMR (CHLOROFORM-d) δ 7.72 - 7.79 (m, 1H), 7.47 (t, J = 1.6 Hz, 1H), 7.29 - 7.40 (m, 3H), 7.19 (d, J = 6.8 Hz, 1H), 6.65 (s, 1H), 6.60 (dd, J = 1.9, 0.9 Hz, 1H), 4.75 (br. s., 1H), 4.17 - 4.46 (m, 3H), 3.42 - 3.67 (m, 1H), 3.34 (dd, J = 13.1, 3.5 Hz, 1H), 3.16 (td, J = 12.5, 3.5 Hz, 1H), 2.92 - 3.03 (m, 1H), 2.24 (s, 3H), 1.45 (d, J = 6.3 Hz, 3H), 1.30 (d, J = 6.8 Hz, 6H). LC-MS : m/z 429.1 (M+H)⁺.

2-(4-(furan-3-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 160).

¹H NMR (CHLOROFORM-d) δ 7.69 (br. s., 1H), 7.64 (s, 1H), 7.45 (br. s., 2H), 7.36 - 7.44 (m, 4H), 7.31 (br. s., 2H), 7.16 - 7.26 (m, 3H), 6.57 (br. s., 1H), 5.37 (br. s., 1H), 4.15 (d, J = 9.8 Hz, 2H), 3.96 (d, J = 8.8 Hz, 4H), 2.98 - 3.12 (m, 1H), 1.13 (d, J = 6.8 Hz, 6H). LC-MS : m/z 477.2(M+H)⁺.

(R)-2-(3-cyano-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylpyridin-4-yl)phenyl acetate (Compound 162). Compound 162 was synthesized from (R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-(2-hydroxyphenyl)-6-isopropylnicotinonitrile (Compound 157) by reaction with acetyl chloride.

¹H NMR (METHANOL-d₄) δ 7.76 (s, 1H), 7.39 - 7.58 (m, 3H), 7.31 (t, J = 1.9 Hz, 1H), 7.24 (dd, J = 7.7, 1.9 Hz, 1H), 6.78 (s, 1H), 6.61 (d, J = 1.3 Hz, 1H), 4.76 (br. s., 1H), 4.17 - 4.44 (m, 3H), 3.56 (br. s., 1H), 3.34 (dd, J = 12.9, 3.4 Hz, 1H), 3.17 (td, J = 12.5, 3.5 Hz, 1H), 2.93 - 3.06 (m,

1H), 2.27 - 2.43 (m, 3H), 1.46 (d, J = 6.8 Hz, 3H), 1.30 (d, J = 7.0 Hz, 6H). LC-MS : m/z 473.1 (M+H)⁺.

(R)-4-(2-ethoxyphenyl)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-6-isopropylnicotinonitrile (Compound 163). Compound 163 was synthesized from (R)-2-(4-(furan-3-carbonyl)-3-methylpiperazin-1-yl)-4-(2-hydroxyphenyl)-6-isopropylnicotinonitrile (Compound 157) by treatment with NaH/DMF followed by ethyl bromide quench.

¹H NMR (METHANOL-d₄) δ 7.76 (s, 1H), 7.37 - 7.51 (m, 2H), 6.98 - 7.16 (m, 3H), 6.79 (s, 1H), 6.57 - 6.64 (m, 1H), 4.76 (br. s., 1H), 4.17 - 4.45 (m, 3H), 4.12 (q, J = 7.0 Hz, 2H), 3.56 (br. s., 1H), 3.34 (dd, J = 12.9, 3.6 Hz, 1H), 3.17 (td, J = 12.4, 3.3 Hz, 1H), 3.00 (quin, J = 6.9 Hz, 1H), 1.47 (dt, J = 6.8, 3.5 Hz, 6H), 1.30 (d, J = 6.8 Hz, 6H). LC-MS : m/z 459.1 (M+H)⁺.

2-(4-(furan-2-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 167).

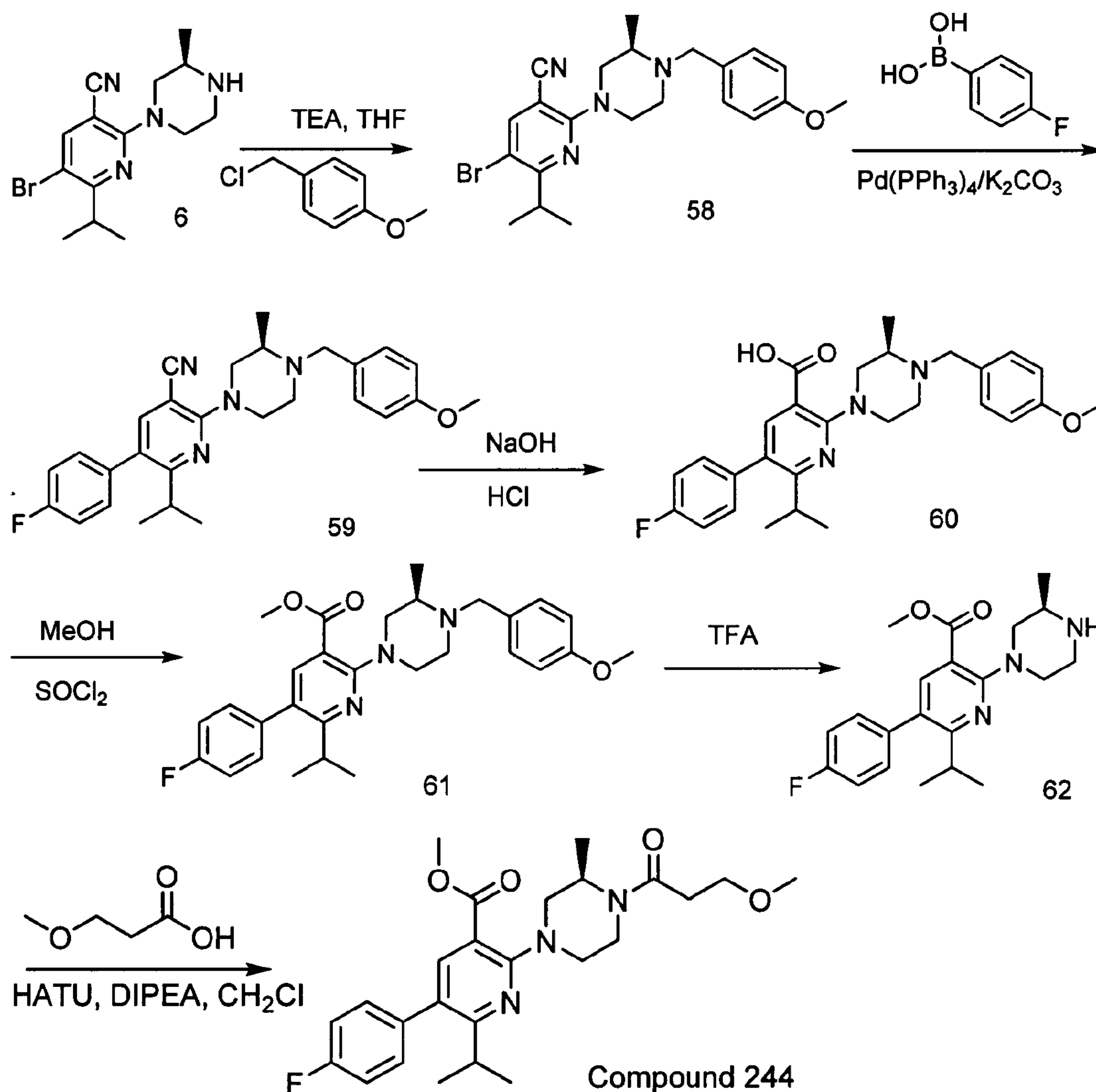
¹H NMR (CHLOROFORM-d) δ 7.64 (s, 1H), 7.52 (s, 1H), 7.36 - 7.48 (m, 5H), 7.31 (br. s., 2H), 7.22 (d, J = 6.5 Hz, 3H), 7.07 (d, J = 3.0 Hz, 1H), 6.52 (br. s., 1H), 5.37-5.59 (br. s., 1H), 4.17 (br. s., 3H), 3.98 (br. s., 2H), 3.92 (br. s., 1H), 3.00 - 3.12 (m, 1H), 1.13 (d, J = 6.5 Hz, 3H), 0.79 (br. s., 3H). LC-MS : m/z 477.1(M+H)⁺.

2-(4-(1H-indole-3-carbonyl)-2-phenylpiperazin-1-yl)-6-isopropyl-4-phenylnicotinonitrile (Compound 169).

¹H NMR (CHLOROFORM-d) δ 9.00 (br. s., 1H), 7.71 (d, J = 6.3 Hz, 1H), 7.64 (s, 1H), 7.42 (d, J = 7.3 Hz, 6H), 7.24 - 7.34 (m, 4H), 7.22 (d, J = 6.3 Hz, 4H), 5.53 (br. s., 1H), 4.13 - 4.35 (m, 2H), 4.01 (br. s., 2H), 3.76 - 3.96 (m, 2H), 3.00 - 3.13 (m, 1H), 1.14 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H). LC-MS : m/z 526.1 (M+H)⁺.

Example 11 Preparation of (R)-methyl 5-(4-fluorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinate (Compound 244). Compound 244 was prepared according to Scheme 8.

Scheme 8.



Step 1: (R)-5-bromo-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinonitrile (**58**). To a solution of (R)-5-bromo-6-isopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (**6**; Example 1; 1 g, 3.10 mmol) and triethylamine (375 mg, 3.72 mmol) in 20 mL THF was added 1-(chloromethyl)-4-methoxybenzene (485 mg, 3.10 mmol) dropwise at 0°C. The reaction mixture was stirred at 0°C for 4 hrs before warmed up to room temperature and quenched by adding 20 mL of water. Solvent was removed under reduced pressure and the residue was extracted with EtOAc (3 x 20 mL). The combined organic layer was then washed with brine, dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography separation (20%

EtOAc/petroleum ether) then afforded 1.3 g of **58** as thick brown oil. MS (ES) M+H expected 443.1, found 443.2

Step 2: (R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinonitrile (59). To a solution of (R)-5-bromo-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)-nicotinonitrile (**58**; 1 g, 2.18 mmol) and 4-fluorophenylboronic acid (610 mg, 4.36 mmol) in 5 mL of DMF was added Pd(PPh₃)₄ (340 mg 0.218 mmol) and K₂CO₃ (360 mg, 2.62 mmol) under nitrogen protection. The reaction was subjected to microwave reaction at 150°C for 1 hour. After dilution with 20 mL of water, the mixture was extracted with EtOAc (3 x 20mL). The combined organic layer was washed with brine, dried over anhy. Na₂SO₄ and concentrated *in vacuo*. Flash column chromatography separation (20% EtOAc/petroleum ether) then afforded 600 mg of **59** as thick brown oil. MS (ES) M+H expected 459.3, found 459.2.

Step 3: (R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinic acid (60)

To a solution of (R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinonitrile (600 mg, 1.31 mmol) in 20 mL of ethanol was added 20 mL 50% aq. NaOH solution. The reaction mixture was heated to 120°C overnight, and then acidified with 2N aq. HCl to pH<6. Ethanol was removed under reduced pressure and the residue was washed with water several times and filtered. After air-drying, 500 mg of crude title compound was obtained as a yellowish solid. MS (ES) M+H expected 478.2, found 478.2.

Step 4: (R)-methyl-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinate (61).

To a 25 mL of round-bottom flask was charged with 10 mL of methanol. After cooling at 0°C, 1 mL of thionyl chloride was added dropwise and the solution was stirred at room temperature for 30 min, before adding (R)-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-yl)nicotinic acid (500 mg, 1.05 mmol) slowly. The resulting mixture was then heated to reflux temperature for 2 hrs. After removing the volatile under reduced pressure, 500 mg of crude title compound was obtained and used without further purification. MS (ES) M+H expected 492.3, found 492.2.

Step 5: (R)-methyl 5-(4-fluorophenyl)-6-isopropyl-2-(3-methylpiperazin-1-yl)nicotinate (62).
(R)-methyl-5-(4-fluorophenyl)-6-isopropyl-2-(4-(4-methoxybenzyl)-3-methylpiperazin-1-

yl)nicotinate (**61**; 500 mg, 1.02 mmol) was dissolved in 15 mL of 2,2,2-trifluoroacetic acid. The mixture was heated to reflux overnight. After removal of excess of TFA under reduced pressure, the residue was re-dissolved in methylene chloride and washed with satd. NaHCO₃, brine. The organic layer was then dried over anhy. Na₂SO₄, and concentrated *in vacuo*. 300 mg of title compound was obtained as yellowish oil and used subsequently without further purification. MS (ES) M+H expected 372.2, found 372.2.

Step 6: (R)-methyl 5-(4-fluorophenyl)-6-isopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinate (Compound 244).

¹H NMR (CHLOROFORM-d) δ 7.84 (s, 1H), 7.20 - 7.25 (m, 2H), 7.06 - 7.15 (m, 2H), 4.86 (br. s., 0.5H), 4.43 (d, J = 12.5 Hz, 0.5H), 4.21 (d, J = 6.0 Hz, 0.5H), 3.92 (d, J = 13.1 Hz, 0.5H), 3.87 (s, 3H), 3.81 (d, J = 16.3 Hz, 1H), 3.74 (t, J = 6.7 Hz, 3H), 3.64 (br. s., 1H), 3.37 (s, 3H), 3.18 - 3.34 (m, 1H), 2.96 - 3.15 (m, 2H), 2.64 - 2.80 (m, 1H), 2.60 (br. s., 1H), 1.34 - 1.40 (m, 1.5H), 1.29 - 1.32 (m, 1.5H), 1.17 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 6.5 Hz, 3H). LC-MS : m/z 458.2 (M+H)⁺.

Example 12. Assays for IDH1 R132H Inhibitors.

Assays were conducted in a volume of 76 μ l assay buffer (150 mM NaCl, 10 mM MgCl₂, 20 mM Tris pH 7.5, 0.03% bovine serum albumin) as follows in a standard 384-well plate: To 25 μ l of substrate mix (8 μ M NADPH, 2 mM aKG), 1 μ l of test compound was added in DMSO. The plate was centrifuged briefly, and then 25 μ l of enzyme mix was added (0.2 μ g/ml IDH1 R132H) followed by a brief centrifugation and shake at 100 RPM. The reaction was incubated for 50 minutes at room temperature, then 25 μ l of detection mix (30 μ M resazurin, 36 μ g/ml) was added and the mixture further incubated for 5 minutes at room temperature. The conversion of resazurin to resorufin was detected by fluorescent spectroscopy at Ex544 Em590 c/o 590.

Certain of the compounds of Formula I set forth in Tables 1 and 5 were tested in this assay and the results set forth below in Table 3. As used in Table 3, "A" refers to an inhibitory activity against IDH1 R132H with an IC₅₀ $\leq$ 1.0 μ M; "B" refers to an inhibitory activity against IDH1 R132H with an IC₅₀ greater than 1 μ M and $\leq$ 5 μ M; "C" refers to an inhibitory activity against IDH1 R132H with an IC₅₀ greater than 5 μ M and $\leq$ 15 μ M.

Table 3. IDH1 R132H Inhibition by Compounds of Formula I.

Cmpd No.	IC ₅₀	Cmpd No.	IC ₅₀	Cmpd No.	IC ₅₀	Cmpd No.	IC ₅₀
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Cmpd No.	IC ₅₀
100	C
101	B
102	B
103	C
104	C
105	B
106	C
107	B
108	C
109	C
110	B
111	C
113	C
114	B
115	B
116	C
117	C
118	C
119	C
120	B
121	C
122	C
123	C
124	C
125	C
126	B
127	C
128	B
129	C
130	B
131	B
132	B
133	B
134	B
135	B
136	C
137	C
138	B
139	B
140	B
141	C
142	B

Cmpd No.	IC ₅₀
143	B
144	B
145	B
146	C
147	C
148	B
149	B
150	B
151	B
152	B
153	C
154	C
155	C
156	B
157	C
158	B
159	C
160	C
161	B
162	B
163	B
164	B
165	B
166	C
167	B
168	B
169	B
170	B
171	B
172	C
173	B
174	B
175	B
176	B
177	B
178	B
179	B
180	B
181	B
182	A
183	B
184	B

Cmpd No.	IC ₅₀
185	B
187	A
188	B
189	B
190	C
191	A
192	B
193	B
195	B
196	B
197	B
198	B
199	B
200	B
201	B
202	B
203	B
204	B
205	B
206	B
207	A
208	B
209	B
210	C
211	B
212	A
213	B
214	B
215	B
216	B
217	B
218	B
219	A
220	B
221	B
222	A
223	A
224	A
225	A
226	A
227	A
228	B

Cmpd No.	IC ₅₀
229	A
230	B
231	B
232	B
233	B
234	A
235	A
236	A
237	B
238	B
239	B
240	B
241	A
242	A
243	A
244	B
245	B
246	A
247	B
248	A
249	A
250	A
251	A
252	A
253	A
254	B
255	A
256	A
257	A
258	A
259	A
260	A
261	A
262	A

Certain of the compounds of Formula I set forth in Table 5 were tested in this assay and the assay in Example 13 and the results set forth below in Table 4. As used in Table 4, “A1” refers to an inhibitory activity against IDH1 R132H with an $IC_{50} \leq 0.5 \mu M$ or an IC_{50} for inhibition of 2-HG production $\leq 0.5 \mu M$; “B1” refers to an inhibitory activity against IDH1 R132H with an IC_{50} greater than $0.5 \mu M$ and $\leq 1 \mu M$ or an IC_{50} for inhibition of 2-HG production greater than $0.5 \mu M$ and $\leq 1 \mu M$; “C1” refers to an inhibitory activity against IDH1 R132H with an IC_{50} greater than $1 \mu M$ and $\leq 10 \mu M$ or an IC_{50} for inhibition of 2-HG production greater than $1 \mu M$ and $\leq 10 \mu M$; and “D1” refers to an inhibitory activity against IDH1 R132H with an IC_{50} greater than $10 \mu M$ or an IC_{50} for inhibition of 2-HG production greater than $10 \mu M$.

Table 4.

Cmpd No.	IDH1R 132H IC_{50} (μM)	HT1080 IC_{50} (μM)	U87R132H IC_{50} (μM)
263	A1	B1	C1
264	B1	C1	C1
265	A1	C1	C1
266	A1	C1	C1
267	B1	C1	C1
268	B1	C1	C1
269	A1	C1	C1
270	B1	C1	C1
271	A1	C1	C1
272	B1	C1	C1
273	B1		
274	B1	C1	C1
275	A1	C1	C1
276	A1	C1	C1
277	A1	C1	C1
278	B1	C1	C1
279	B1	C1	C1
280	A1	C1	C1
281	B1		
282	B1		
283	A1	B1	C1
284	B1		
285	A1	B1	C1
286	A1	A1	A1
287	A1	C1	C1
288	A1	A1	A1
289	A1		

Cmpd No.	IDH1R 132H IC_{50} (μM)	HT1080 IC_{50} (μM)	U87R132H IC_{50} (μM)
290	A1		
291	B1		
292	A1	B1	C1
293	A1	C1	C1
294	A1	B1	B1
295	A1	B1	B1
296	A1	B1	B1
297	A1	B1	C1
298	B1		
299	A1	B1	B1
300	B1		
301	A1	C1	C1
302	A1	C1	C1
303	A1	C1	C1
304	A1	C1	B1
305	B1		
306	B1		
307	A1	C1	C1
308	A1	C1	C1
309	A1	B1	B1
310	B1		
311	B1		
312	A1	B1	C1
313	A1	C1	B1
314	B1		
315	A1	A1	B1
316	B1		

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
317	B1		
318	A1		
319	A1		
320	A1	B1	A1
321	A1	B1	A1
322	A1		
323	A1	B1	B1
324	B1		
325	A1	A1	A1
326	A1	B1	A1
327	B1		
328	A1		
329	B1		
330	A1	A1	A1
331	A1		
332	B1		
333	A1		
334	B1		
335	A1	B1	A1
336	B1		
337	B1		
338	A1		
339	B1		
340	A1	B1	B1
341	A1		
342	A1	A1	A1
343	A1	A1	A1
344	B1		
345	A1	C1	B1
346	A1	C1	B1
347	A1	A1	A1
348	A1		
349	B1		
350	A1	C1	B1
351	A1	C1	B1
352	A1	C1	B1
353	A1	B1	B1
354	B1		
355	B1		
356	A1	C1	C1
357	B1		
358	A1		
359	A1		

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
360	A1	C1	C1
361	A1	C1	B1
362	A1		
363	A1	C1	B1
364	A1	B1	A1
365			
366			
367			
368	B1		
369	B1		
370	B1		
371	B1		
372	A1		
373	A1	C1	B1
374	A1	C1	B1
375	B1		
376	A1	C1	B1
377	A1	B1	A1
378	A1		
379	B1		
380	A1	B1	B1
381	A1	A1	A1
382	A1	A1	B1
383	A1	C1	C1
384	A1	B1	B1
385	B1		
386	A1	C1	B1
387	A1	A1	A1
388	A1	C1	B1
389	A1	A1	A1
390	A1	A1	A1
391	A1	B1	B1
392	A1		
393	A1	C1	B1
394	B1		
395	B1		
396	A1		
397	A1		
398	A1	C1	B1
399	B1		
400	B1	C1	C1
401	B1	C1	C1
402	A1		

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
403	A1	B1	B1
404	B1		
405	A1		
406	A1	C1	C1
407	A1	A1	A1
408	A1	B1	A1
409	A1	A1	A1
410	A1	A1	A1
411	A1	B1	B1
412	A1	C1	B1
413	B1		
414	B1		
415	A1	C1	C1
416	B1	C1	B1
417	A1	A1	A1
418	A1	A1	A1
419	A1	A1	A1
420	A1	C1	C1
421	B1		
422	B1		
423	B1		
424	A1	B1	B1
425	B1	C1	C1
426	B1	C1	C1
427	A1	A1	A1
428	A1	A1	B1
429	A1	C1	C1
430	C1		
431	B1	B1	B1
432	B1	C1	C1
433	A1	A1	A1
434	A1	C1	C1
435	B1		
436	A1	B1	B1
437	B1		
438	A1	C1	B1
439	A1	A1	
440	A1		
441	B1		
442	A1	A1	A1
443	A1	A1	A1
444	A1	A1	A1
445	A1	C1	

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
446	A1	A1	C1
447	B1	C1	C1
448	A1	C1	C1
449	B1	C1	C1
450	B1		
451	A1	C1	C1
452	A1	C1	C1
453	A1	B1	A1
454	A1	A1	A1
455	B1		
456	A1	A1	A1
457	A1	B1	B1
458	A1	B1	B1
459	A1	A1	A1
460	A1		
461	B1		
462	B1	C1	C1
463	A1	C1	C1
464	B1		
465	B1		
466	A1	C1	B1
467	B1		
468	A1	C1	C1
469	A1	C1	C1
470	A1	C1	C1
471	A1		
472	A1	A1	A1
473	A1	C1	B1
474	A1		
475	A1	B1	A1
476	A1	B1	A1
477	B1		
478	B1		
479	B1		
480	A1	A1	A1
481	A1	A1	A1
482	A1		
483	A1	C1	B1
484	B1		
485	A1	A1	A1
486	B1		
487	A1		
488	A1	A1	B1

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
489	B1		
490	B1		
491	A1	B1	
492	B1	B1	
493	B1		
494	A1		
495	B1		
496	B1	B1	A1
497	A1		
498	A1	A1	A1
499	B1	C1	C1
500	A1	A1	A1
501	B1		
502	B1		
503	A1		
504	B1		
505	A1		
506	B1		
507	B1		
508	A1	A1	A1
509	B1		
510	B1		
511	A1	B1	
512	A1		
513	B1		
514	A1	A1	
515	B1	C1	
516	A1	B1	
517	A1	B1	
518	A1	A1	A1
519	B1		
520	B1	A1	
521	A1		
522	B1	C1	
523	B1		
524	A1		
525	A1		
526	B1	A1	A1
527	A1	A1	A1
528	A1	B1	A1
529	A1	B1	
530	A1	A1	A1
531	A1		

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
532	A1		
533	B1	C1	
534	A1		
535	A1	A1	
536	A1	A1	
537	A1	B1	
538	A1		
539	A1	C1	
540	A1		
541	A1	A1	A1
542	A1	A1	A1
543	B1		
544	A1	B1	
545	B1		
546	A1	A1	A1
547	A1	A1	A1
548	B1		
549	A1		
550	B1	A1	A1
551	A1	A1	A1
552	A1		
553	A1	A1	
554	A1		
555	A1	B1	
556	A1		
557	A1	B1	
558	A1	A1	A1
559	A1	C1	
560	A1	C1	
561	A1	A1	A1
562	A1	A1	A1
563	A1	A1	
564	A1		
565	A1	B1	B1
566	A1	B1	
567	B1		
568	A1	A1	A1
569	A1	A1	
570	A1	A1	
571	A1	A1	
572	A1	A1	
573	A1	A1	A1
574	A1	A1	

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
575	A1	A1	
576	B1	A1	
577	A1	A1	
578	A1	A1	
579	A1	A1	A1
580	A1	A1	A1
581	A1	A1	A1
582	A1	C1	
583	B1		
584	B1		
585	A1	A1	A1
586	A1		
587	A1	A1	A1
588	A1	A1	
589	A1	A1	A1
590	A1	A1	A1
591	A1	A1	A1
592	A1	A1	A1
593	B1		
594	A1	A1	
595	A1	A1	A1
596	A1	A1	
597	A1	A1	A1
598	A1	B1	
599	A1	A1	A1
600	B1	B1	
601	A1		
602	A1	A1	
603	A1	A1	A1
604	A1	A1	
605	A1	A1	A1
606	A1	A1	
607	A1	A1	
608	A1	A1	A1
609	A1	A1	A1
610	A1	A1	A1
611	A1	A1	A1
612	A1	A1	A1
613	A1	A1	A1
614	A1		
615	A1	A1	A1
616	A1		
617	A1	A1	A1

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
618	A1	A1	A1
619	A1	A1	
620	A1	A1	
621	A1	A1	B1
622	B1	C1	
623	B1		
624	A1	A1	
625	A1	A1	A1
626	A1	A1	A1
627	A1	A1	A1
628	A1	A1	A1
629	A1	A1	A1
630	B1		
631	A1	A1	A1
632	A1		
633	A1	A1	A1
634	A1	A1	A1
635	A1	A1	A1
636	A1	A1	A1
637	A1	A1	A1
638	A1	A1	A1
639	A1	A1	A1
640	A1		
641	A1		
642	A1	A1	A1
643	A1	A1	B1
644	A1	A1	A1
645	A1	A1	A1
646	A1		
647	A1	A1	A1
648	A1	A1	A1
649	A1	A1	A1
650	A1		A1
651	A1		A1
652	A1	A1	A1
653	A1	A1	
654	A1	A1	A1
655	A1	A1	
656	B1		
657	A1	A1	A1
658	A1		A1
659	A1		
660	A1	A1	A1

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
661	A1		
662	A1	A1	
663	A1	A1	A1
664	A1	A1	
665	A1		
666	A1	A1	A1
667	A1	A1	A1
668	A1	B1	
669	A1	A1	
670	A1	A1	A1
671	A1		
672	B1	C1	
673	B1		
674	A1	A1	A1
675	A1	C1	B1
676	A1	A1	A1
677	A1	A1	
678	A1	A1	A1
679	A1	A1	
680	A1	A1	
681	A1	A1	A1
682	A1		
683	A1		
684	A1	A1	
685	C1		
686	A1	A1	A1
687	A1		B1
688	A1	A1	A1
689	A1	A1	A1
690	A1	A1	A1
691	A1	A1	A1
692	A1	A1	A1
693	A1	A1	A1
694	A1	B1	A1
695	A1	A1	A1
696	A1	A1	A1
697	A1	A1	A1
698	A1	A1	A1
699	A1		
700		A1	A1
701	A1		
702	A1	C1	C1
703	A1	A1	A1

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
704	A1		
705	A1	A1	A1
706	A1	A1	A1
707	A1	A1	A1
708	A1		C1
709	A1	A1	A1
710	A1	A1	A1
711	A1	A1	A1
712	A1	C1	
713	A1	A1	A1
714	A1	A1	A1
715	A1	A1	A1
716	A1	A1	A1
717	A1	A1	A1
718	A1	B1	A1
719	A1	A1	A1
720	A1	A1	A1
721	A1	A1	A1
722	A1	A1	A1
723	A1		
724	A1	A1	A1
725	A1	A1	A1
726	A1	A1	A1
727	A1	A1	A1
728	A1	A1	A1
729	A1		
730	A1	A1	A1
731	A1		
732	A1	A1	A1
733	A1	B1	A1
734	A1		
735	A1	A1	A1
736	A1	A1	A1
737	A1	B1	B1
738	A1	A1	A1
739	A1		
740	A1	A1	A1
741	A1	A1	A1
742	A1	A1	A1
743	A1	A1	A1
744	A1	A1	A1
745	A1	A1	A1
746	A1	A1	A1

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
747	A1	A1	A1
748	A1	A1	A1
749	A1	A1	A1
750	A1	A1	A1
751	A1	A1	A1
752	A1	A1	A1
753	A1	A1	A1
754	A1	A1	A1
755	A1	A1	A1
756	A1	A1	A1
757	A1		A1
758	A1		A1
759	A1		A1
760	A1	A1	A1
761	A1	A1	A1
762	A1	A1	A1
763	A1	A1	A1
764	A1	A1	A1
765	A1	A1	A1
766	A1	A1	A1
767	A1	A1	A1
768	A1	A1	A1
769	A1	A1	A1
770	A1	A1	A1
771	A1	A1	A1
772	B1		
773	A1		A1
774	A1	A1	A1
775	A1	A1	A1
776	A1	A1	A1
777	A1	A1	A1
778	A1	A1	A1
779	C1		
780	A1		
781	A1	A1	A1
782	A1	A1	A1
783		A1	A1
784	A1	A1	A1
785	A1	A1	A1
786	A1	A1	A1
787	A1	A1	A1
788	A1	A1	A1
789	A1	A1	A1

Cmpd No.	IDH1R 132H IC50 (μM)	HT1080 IC50 (μM)	U87R132H IC50 (μM)
790	A1		
791	A1		
792	A1	C1	C1
793	A1	A1	A1
794	A1	A1	A1
795	A1		
796	A1	A1	A1
797	A1	A1	A1
798	A1		
799	A1	A1	A1
800	A1	A1	A1
801	A1	A1	A1
802	A1		
803	A1	A1	A1
804	A1	A1	B1
805	A1	A1	A1
806	A1	A1	A1
807	A1	A1	
808	A1	A1	
809	A1	A1	
810	B1	A1	A1
811	A1	A1	A1
812	A1	A1	A1
813	A1	A1	A1
814	B1		
815	A1	A1	
816	B1		
817	A1	A1	
818	A1	A1	
819	A1	A1	
820	A1		
821	A1		
822	A1	A1	
823	A1	A1	
824	A1		
825	A1		
826	A1		
827	A1		
828	A1		
829	A1		
830	A1		

In some embodiments, the invention provides a compound selected from any one of compound numbers 182, 187, 191, 207, 212, 219, 222, 223, 224, 225, 226, 227, 229, 234, 235, 236, 241, 242, 243, 246, 248, 249, 250, 251, 252, 253, 255, 256, 257, 258, 259, 260, 261, and 262.

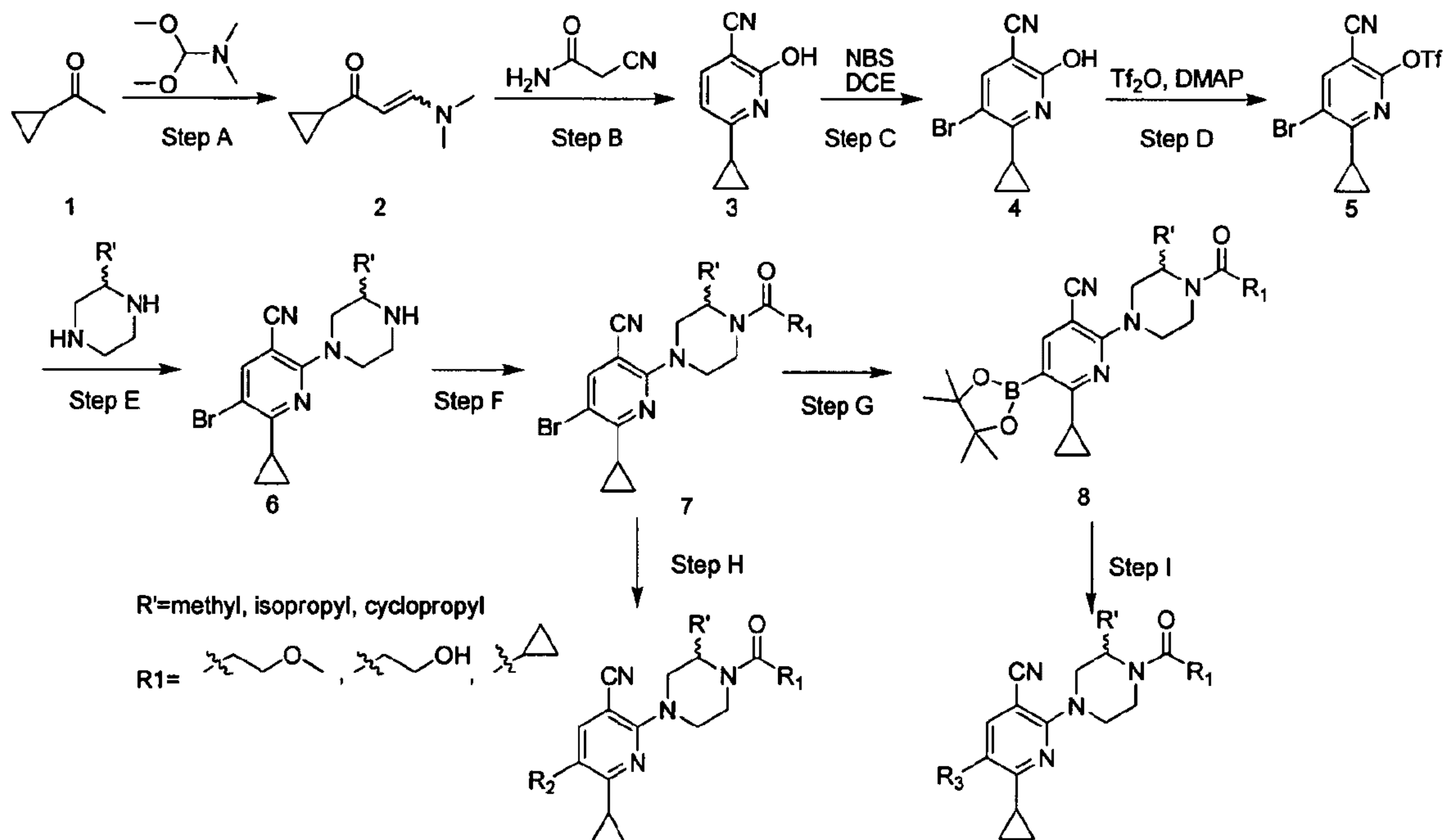
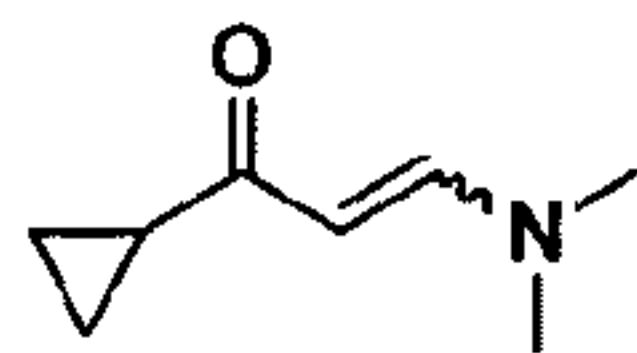
In some embodiments, the invention provides a compound selected from any one of compound numbers 263, 265, 266, 269, 271, 275, 276, 277, 280, 283, 285, 286, 287, 288, 289, 290, 292, 293, 294, 295, 296, 297, 299, 301, 302, 303, 304, 307, 308, 309, 312, 313, 315, 318, 319, 320, 321, 322, 323, 325, 326, 328, 330, 331, 333, 335, 338, 340, 341, 342, 343, 345, 346, 347, 348, 350, 351, 352, 353, 356, 358, 359, 360, 361, 362, 363, 364, 372, 373, 374, 376, 377, 378, 380, 381, 382, 383, 384, 386, 387, 388, 389, 390, 391, 392, 393, 396, 397, 398, 402, 403, 405, 406, 407, 408, 409, 410, 411, 412, 415, 417, 418, 419, 420, 424, 427, 428, 429, 433, 434, 436, 438, 439, 440, 442, 443, 444, 445, 446, 448, 451, 452, 453, 454, 456, 457, 458, 459, 460, 463, 466, 468, 469, 470, 471, 472, 473, 474, 475, 476, 480, 481, 482, 483, 485, 487, 488, 491, 494, 497, 498, 500, 503, 505, 508, 511, 512, 514, 516, 517, 518, 521, 524, 525, 527, 528, 529, 530, 531, 532, 534, 535, 536, 537, 538, 539, 540, 541, 542, 544, 546, 547, 549, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 568, 569, 570, 571, 572, 573, 574, 575, 577, 578, 579, 580, 581, 582, 585, 586, 587, 588, 589, 590, 591, 592, 594, 595, 596, 597, 598, 599, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 624, 625, 626, 627, 628, 629, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 773, 774, 775, 776, 777, 778, 780, 781, 782, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 811, 812, 813, 815, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, and 830.

Example 13. Cellular Assays for IDH1m (R132H or R132C) Inhibitors.

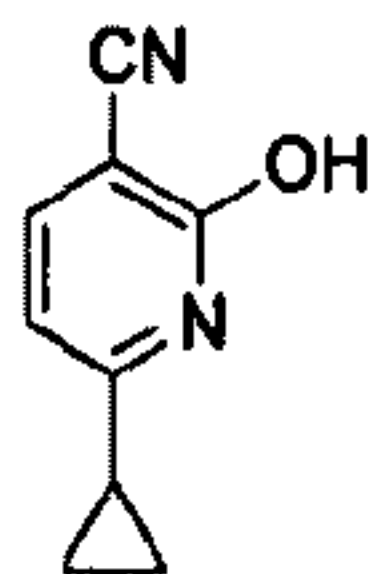
Cells (e.g., HT1080 or U87MG) are grown in T125 flasks in DMEM containing 10% FBS, 1x penicillin/streptomycin and 500ug/mL G418. They are harvested by trypsin and seeded into 96 well white bottom plates at a density of 5000 cell/well in 100 ul/well in DMEM with 10% FBS. No cells are plated in columns 1 and 12. Cells are incubated overnight at 37°C in 5% CO₂. The next day compounds are made up at 2x concentration and 100ul are added to each cell well. The final concentration of DMSO is 0.2% and the DMSO control wells are plated in row G. The plates are then placed in the incubator for 48 hours. At 48 hours, 100µl of media is removed from each well and analyzed by LC-MS for 2-HG concentrations. The cell plate is placed back in the incubator for another 24 hours. At 72 hours post compound addition, 10 mL/plate of Promega Cell Titer Glo reagent is thawed and mixed. The cell plate is removed from the incubator and allowed to equilibrate to room temperature. Then 100ul of reagent is added to each well of media. The cell plate is then placed on an orbital shaker for 10 minutes and then allowed to sit at room temperature for 20 minutes. The plate is then read for luminescence with an integration time of 500ms.

The IC₅₀ for inhibition of 2-HG production (concentration of test compound to reduce 2HG production by 50% compared to control) in these two cell lines for various compounds of formula I is set forth in Table 4 above.

EXAMPLE 14. Preparation of 2,3,5,6-Tetrasubstituted Pyridines.

General procedure 1:**Step A: 1-cyclopropyl-3-(dimethylamino)prop-2-en-1-one (2)**

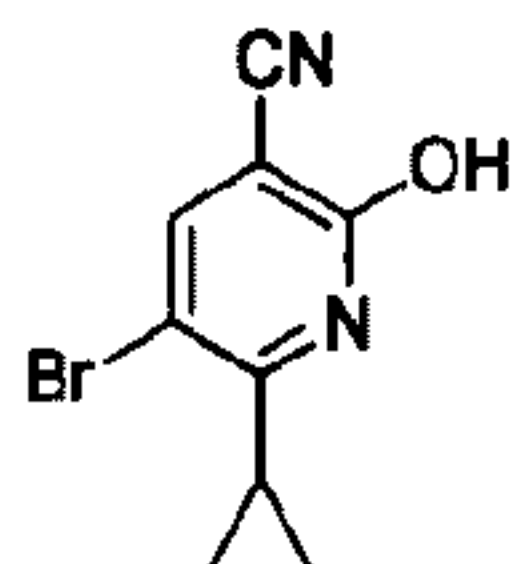
To a solution of 1-cyclopropylethanone (100 g, 1.2 mol) in anhydrous DMF (1300 mL) was added DMFDMA (300 g, 2.5 mol). The resulting mixture was stirred at 100 °C overnight. The solvent was removed in vacuum to give crude **2** (110 g) as yellow solid. ^1H NMR (CHLOROFORM- d) δ 7.56 (d, $J = 12.8$ Hz, 1H), 5.20 (d, $J = 12.5$ Hz, 1H), 2.78 - 3.08 (m, 6H), 1.79 (tt, $J = 7.9, 4.5$ Hz, 1H), 0.94 - 1.04 (m, 2H), 0.67 - 0.80 (m, 2H).

Step B: 6-cyclopropyl-2-hydroxynicotinonitrile (3)

To a mixture of 1-cyclopropyl-3-dimethylamino-propenone (315 g, 2.3 mol) and cyanoacetamide (270 g, 2.3 mol) in a buffer solution of 47.4 mL of acetic acid and 1485 mL of water was added piperidine to adjust to pH 9. The mixture was then heated at reflux for 2 hours,

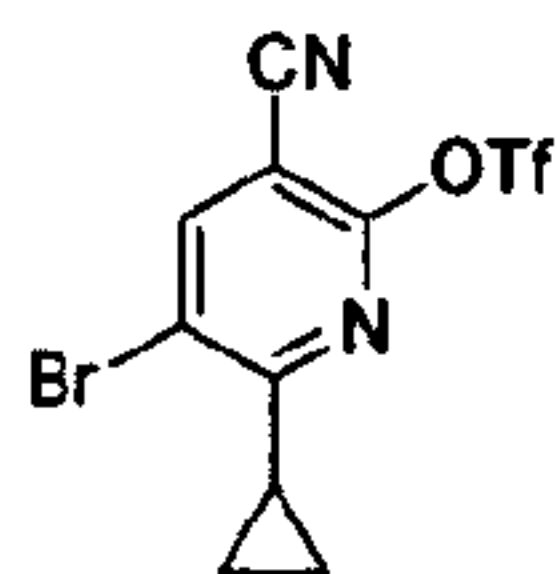
cooled and acidified by 6N HCl to pH 5 below 25 degree. The yellow precipitate was filtered, washed with water and dried to give **3** as a white solid (561 g). MS (ES) M+H expected 161.1, found 161.0. ¹H NMR (CHLOROFORM-d) δ 13.60 (br. s., 1H), 7.77 (d, J = 7.8 Hz, 1H), 5.91 (d, J = 7.8 Hz, 1H), 1.96 - 2.12 (m, 1H), 1.29 - 1.36 (m, 2H), 1.04 - 1.11 (m, 2H).

Step C: 5-bromo-6-cyclopropyl-2-hydroxynicotinonitrile (4)



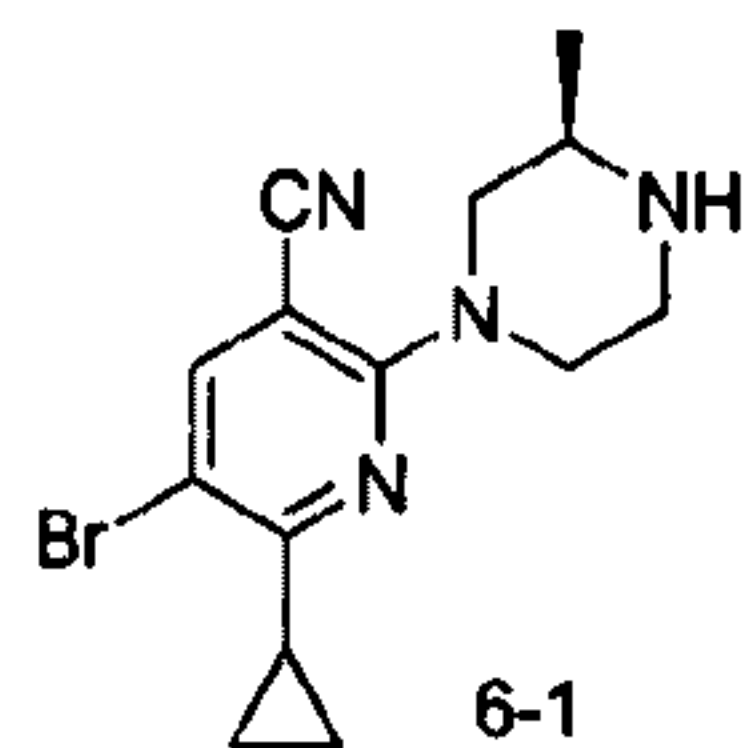
A mixture of 6-cyclopropyl-2-hydroxynicotinonitrile (561 g, 3.6 mol) and NBS (624 g, 5.4 mol) in DCE (4500 mL) was heated at reflux for 3 hrs. The mixture was cooled to room temperature and the precipitate was filtered, washed with water and dried to give crude **4** (473 g) as a white solid. MS (ES) M+H expected 239.0, found 238.9. ¹H NMR (CHLOROFORM-d) δ 8.49-8.72 (br. s., 1H), 7.93 (s, 1H), 2.23 - 2.34 (m, 1H), 1.36 - 1.42 (m, 2H), 1.29 - 1.36 (m, 2H).

Step D: 5-bromo-3-cyano-6-cyclopropylpyridin-2-yl trifluoromethanesulfonate (5)

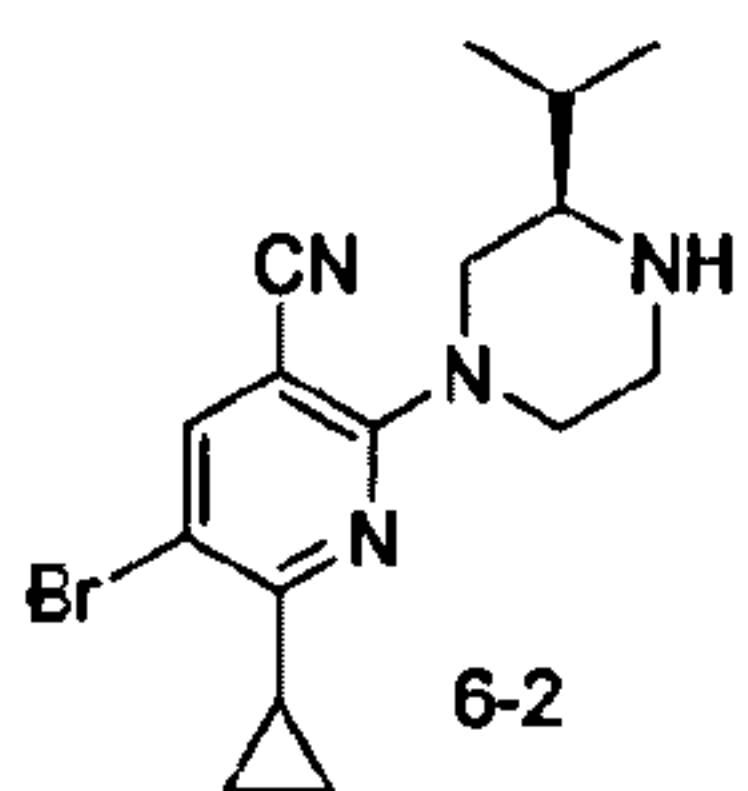


To a 1L flask were added 5-bromo-4-cyclopropyl-2-hydroxybenzonitrile (47.6 g, 0.2 mol), pyridine (32 g, 0.4 mol) and Cat. DMAP (500 mg) in DCM (300 mL), and the mixture was cooled to 0°C, and trifluoromethanesulfonic anhydride (59 g, 0.21 mol) in DCM (100 mL) was added dropwise. After addition, the mixture was stirred for another 1h. TLC (PE:EtOAc = 10:1) showed conversion of starting material to product. After reaction, diluted with DCM (300 mL), and washed with 1N HCl. The organic layer was dried over Na₂SO₄ and concentrated *in vacuo* afforded the title compound (70 g) as a yellow solid. ¹H NMR (CHLOROFORM-d) δ 8.14 - 8.19 (m, 1H), 2.55 - 2.66 (m, 1H), 1.30 (dt, J = 7.8, 3.1 Hz, 2H), 1.21 - 1.27 (m, 2H).

Step E: Exemplified by (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (6-1) (R'=methyl)

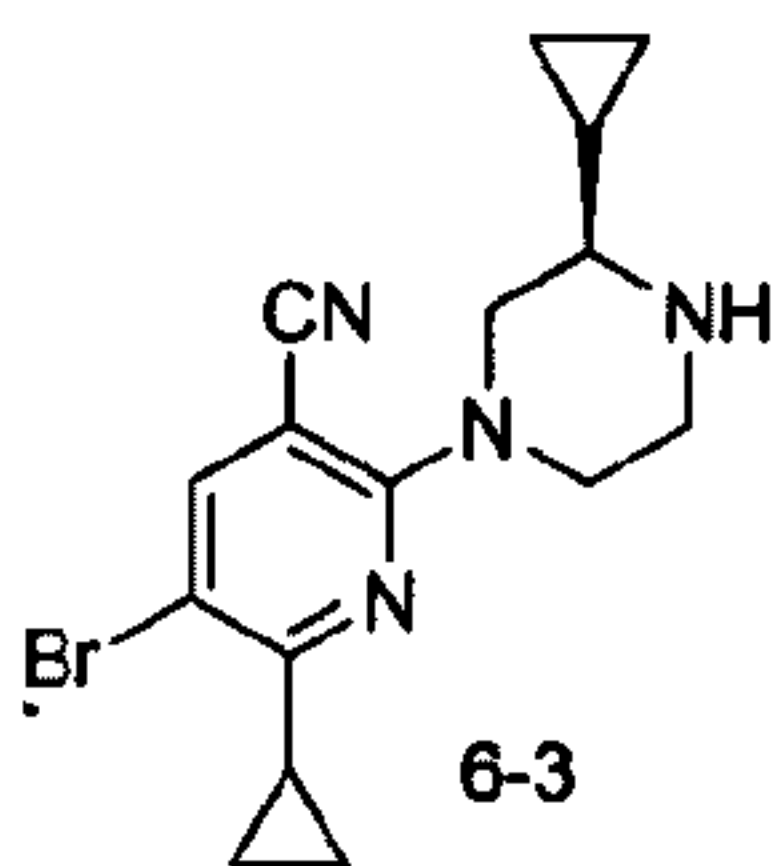


A mixture of above triflate **5** (1.68 g, 4.6mmol), (R)-2-methylpiperazine (790 mg, 6.9 mmol), and triethylamine (1.9 mL, 13.8 mmol) suspended in 5 mL of MeCN was heated at 70°C for 2 h. After the mixture was concentrated under reduced pressure, the residue was extracted between ethyl acetate and water. The combined organic layer was then washed with aq. NaHCO₃, brine, dried over anhy. Na₂SO₄ and concentrated *in vacuo* to give 1.26 g of crude title compound. MS (ES) M+H expected 321.1, found 321.2. ¹H NMR (CHLOROFORM-d) δ 7.78 (s, 1H), 4.14 - 4.24 (m, 2H), 3.09 - 3.14 (m, 1H), 3.02 - 3.07 (m, 1H), 2.96 - 3.00 (m, 2H), 2.71 (dd, J = 12.9, 10.2 Hz, 1H), 2.42 - 2.52 (m, 1H), 1.16 (d, J = 6.3 Hz, 3H), 1.08 (s, , 2H), 1.07 (d, J = 3.8 Hz, 2H).



(R)-5-bromo-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)nicotinonitrile (6-2)

(R'=isopropyl) was synthesized by the same procedure described above except using (R)-2-isopropylpiperazine instead of (R)-2-methylpiperazine. MS (ES) M+H expected 349.1, found 349.2. ¹H NMR (CHLOROFORM-d) δ 7.79 (s, 1H), 4.14 - 4.24 (m, 2H), 3.09 - 3.14 (m, 1H), 3.02 - 3.07 (m, 1H), 2.96 - 3.00 (m, 2H), 2.71 (dd, 1H), 2.12 - 2.22 (m, 1H), 1.26 (d, 6H), 1.08 (d, , 2H), 1.07 (d, 2H).

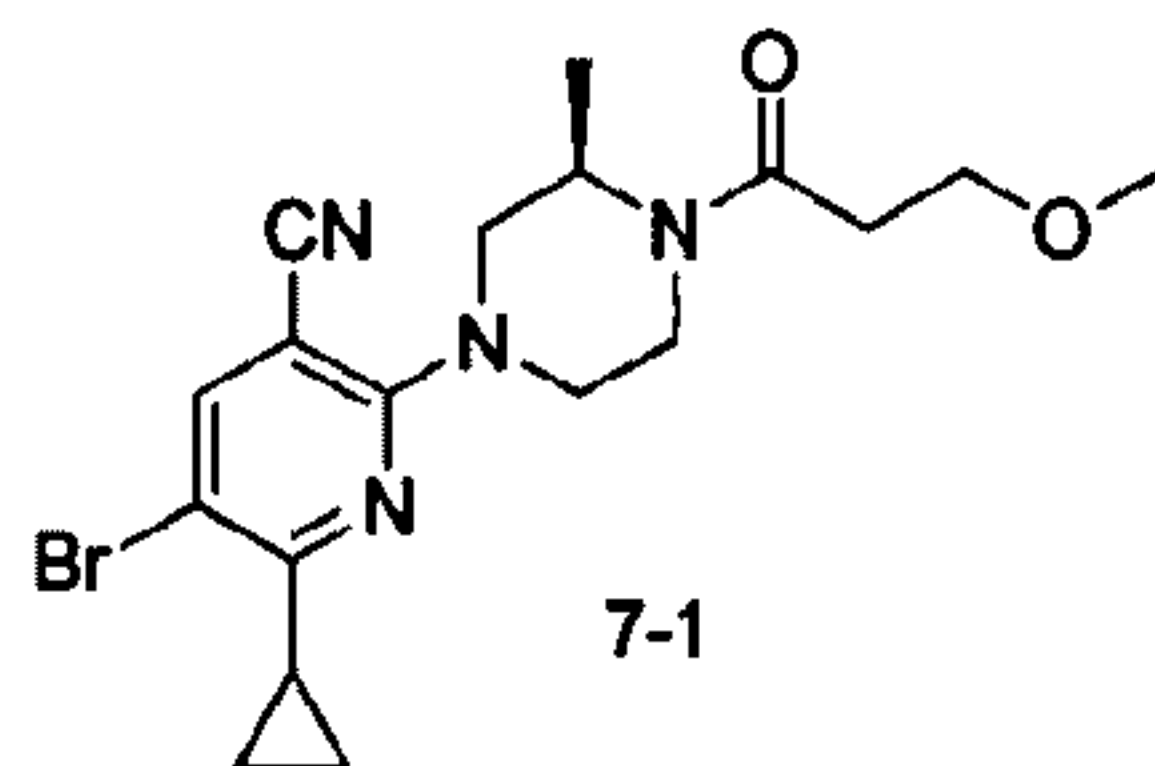


(R)-5-bromo-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)nicotinonitrile (6-3)

(R'=cyclopropyl) was synthesized by the same procedure described above except using (R)-2-cyclopropylpiperazine (building block 1) instead of (R)-2-methylpiperazine. MS (ES) M+H

expected 347.1, found 349.1. ^1H NMR (CHLOROFORM- d) δ 7.77 (s, 1H), 4.14 - 4.24 (m, 2H), 3.09 - 3.14 (m, 1H), 3.02 - 3.07 (m, 1H), 2.96 - 3.00 (m, 2H), 2.71 (dd, 1H), 2.12 - 2.24 (m, 1H), 1.25 (d, 2H), 1.16 (d, 2H), 1.08 (d, 2H), 1.07 (d, 2H).

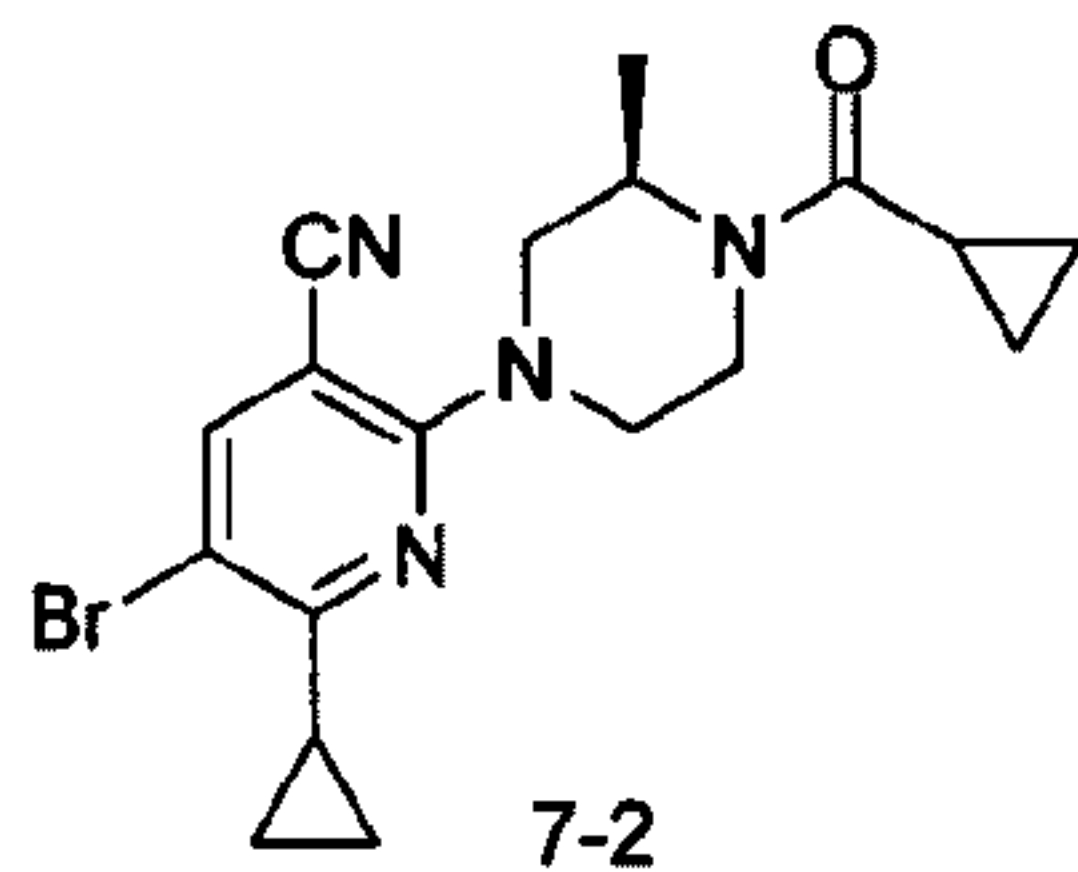
Step F, method 1: Exemplified by (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (**7-1**) (R' =methyl, R_1 =c)



To a 25 mL of round-bottom flask was added (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl) nicotinonitrile (**6-1**) (1.26 g, 3.9 mmol), 3-methoxypropanoic acid (0.74 mL, 7.8 mmol), HATU (2.98 g, 7.8 mmol), DIPEA (2 mL, 11.76 mmol) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. Reaction mixture was with satd. NaHCO_3 and brine. The combined organic layer was then dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Column chromatography purification (30% EtOAc/petroleum ether) afforded 1.28 g of title compound as a white solid. MS (ES) $M+H$ expected 407.1, found 407.0. ^1H NMR (CHLOROFORM- d) δ 7.78 - 7.85 (m, 1H), 4.82 - 4.92 (m, 0.5H), 4.50 (d, J = 13.6 Hz, 0.5H), 4.18-4.21 (m, 2H), 4.07 - 4.16 (m, 1H), 3.75 - 3.82 (m, 0.5H), 3.70 - 3.75 (m, 2H), 3.45 - 3.55 (m, 0.5H), 3.36 (s, 3H), 3.15 - 3.27 (m, 1H), 2.92 - 3.14 (m, 1H), 2.67 - 2.78 (m, 1H), 2.51 - 2.61 (m, 1H), 2.40 - 2.51 (m, 1H), 1.34 (d, J = 6.8 Hz, 1.5H), 1.25 (d, J = 2.5 Hz, 1.5H), 1.09 (d, J = 3.5 Hz, 2H), 1.08 (s, 2H).

Step F, method 2: Exemplified by (R)-5-bromo-2-(4-(cyclopropanecarbonyl)-3-

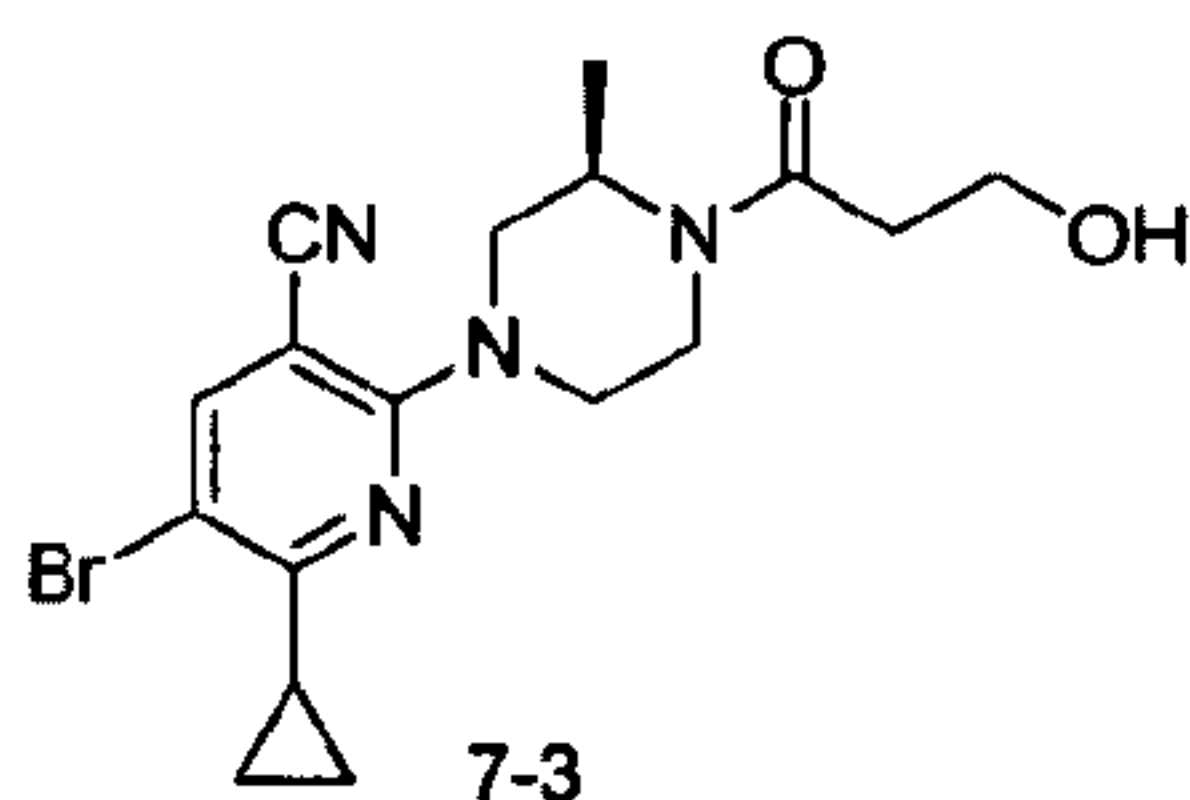
methylpiperazin-1-yl) -6-cyclopropylnicotinonitrile (**7-2**) (R' =methyl, R_1 =)



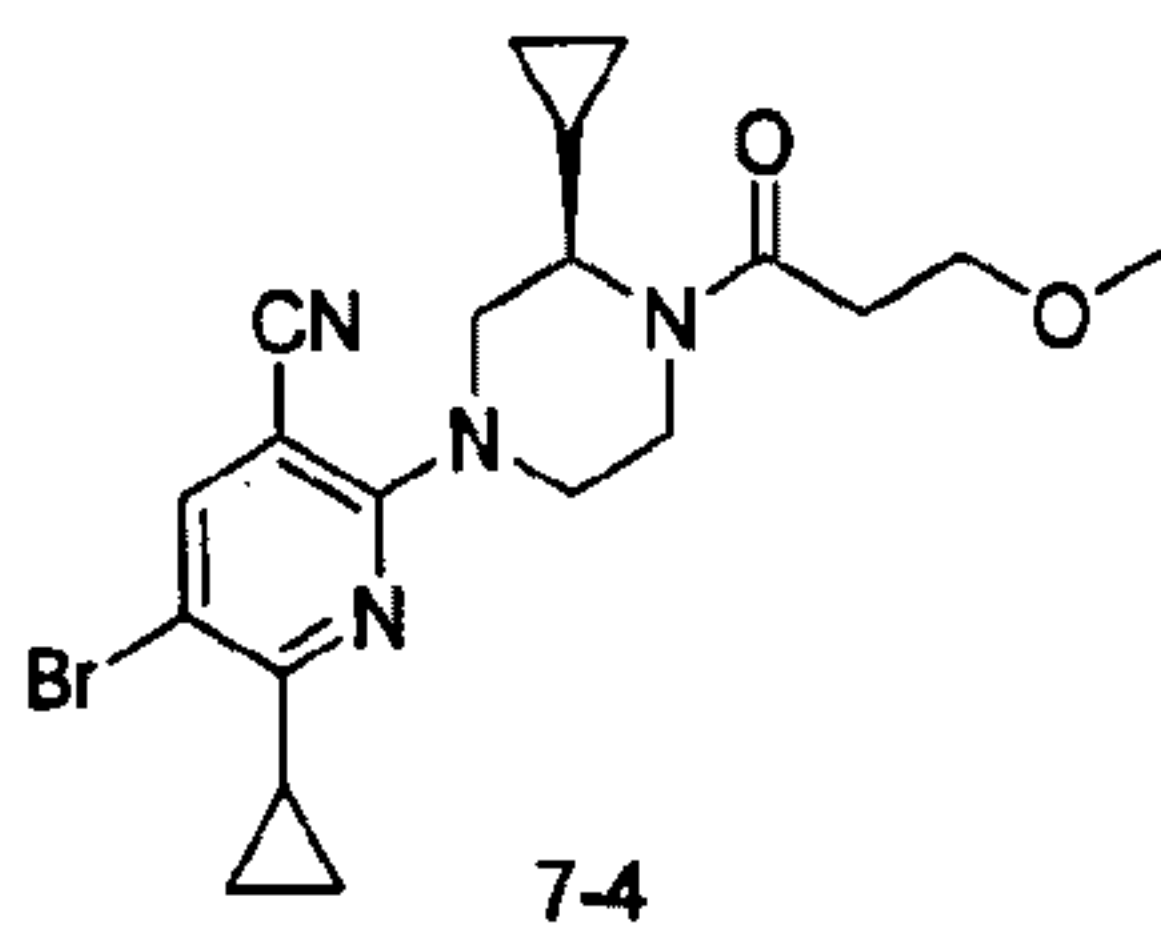
To a 25 mL of round-bottom flask was added (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl) nicotinonitrile (**6-1**) (1 g, 3.2 mmol), cyclopropanecarbonyl chloride (0.4

mL, 3.3 mmol), DIPEA (0.4 mL, 3.4 mmol) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. Reaction mixture was with Satd. NaHCO_3 and brine. The combined organic layer was then dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Column chromatography purification (10% EtOAc/petroleum ether) afforded 1.1 g of title compound as a white solid. MS (ES) $M+H$ expected 389.1, found 389.0. ^1H NMR (CHLOROFORM- d) δ 7.85 (s, 1H), 4.18-4.21 (m, 2H), 4.07 - 4.16 (m, 1H), 3.70 - 3.75 (m, 2H), 3.15 - 3.27 (m, 1H), 2.92 - 3.14 (m, 1H), 2.67 - 2.78 (m, 1H), 2.51 - 2.61 (m, 1H), 2.40 - 2.51 (m, 1H), 1.34 (d, $J = 6.8$ Hz, 1.5H), 1.25 (d, $J = 2.5$ Hz, 1.5H), 1.25 - 1.36 (m, 4H), 1.09 (d, 2H), 1.08 (d, 2H).

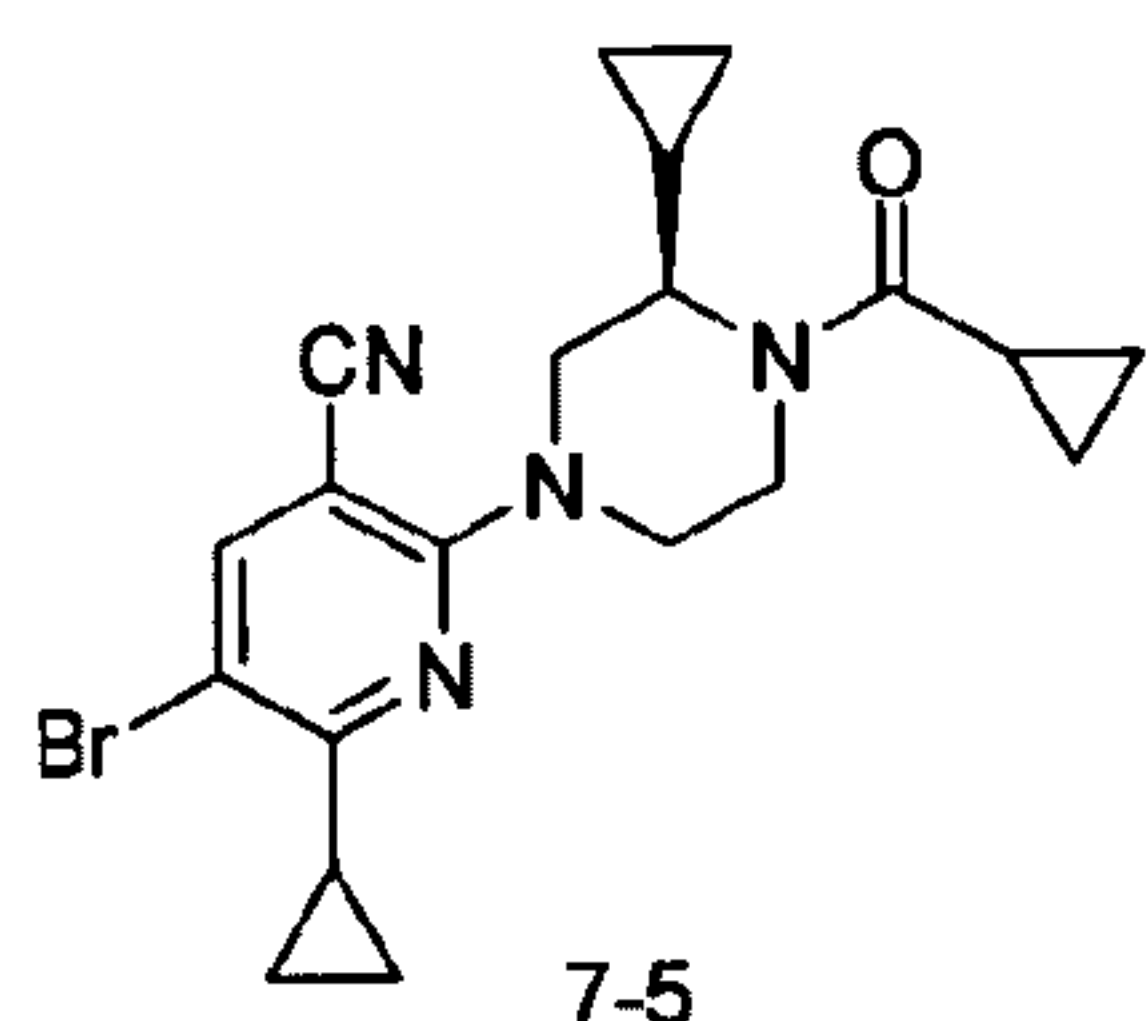
Step F, method 3: Exemplified by (R)-5-bromo-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (**7-3**) (R' =methyl, $R1 = \text{CH}_2\text{CH}_2\text{OH}$)



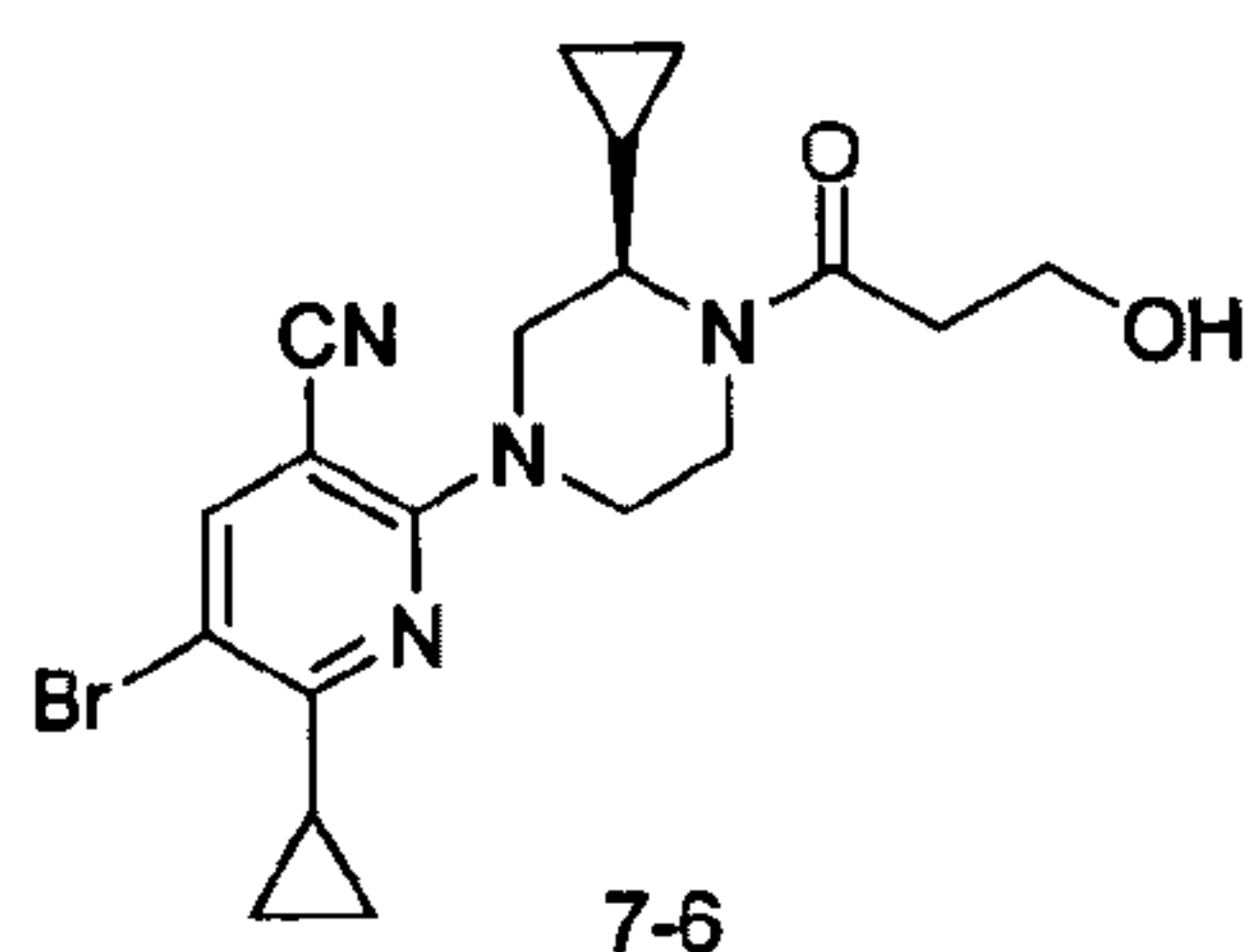
To a 25 mL of round-bottom flask was added (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl) nicotinonitrile (**6-1**) (2 g, 6.2 mmol), sodium 2 - carboxyethanolate (0.70 g, 6.4 mmol), DIPEA (2 mL, 11.5 mmol) and 10 mL of DMF. The resulting reaction mixture was stirred at room temperature for 5 h until TLC showed the completion of the reaction. Reaction mixture was washed with water and brine. The combined organic layer was then dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Column chromatography purification (50% EtOAc/petroleum ether) afforded 1.2 g of title compound as a white solid. MS (ES) $M+H$ expected 393.1, found 393.1. ^1H NMR (CHLOROFORM- d) δ 7.85 (m, 1H), 4.88 - 4.97 (m, 0.5H), 4.75 (d, $J = 13.6$ Hz, 0.5H), 4.29-4.48 (m, 2H), 4.11 - 4.20 (m, 1H), 3.70 - 3.75 (m, 2H), 3.45 - 3.55 (m, 2H), 3.15 - 3.27 (m, 1H), 2.92 - 3.14 (m, 1H), 2.67 - 2.78 (m, 1H), 2.51 - 2.61 (m, 1H), 2.40 - 2.51 (m, 1H), 1.34 (d, $J = 6.8$ Hz, 1.5H), 1.25 (d, $J = 2.5$ Hz, 1.5H), 1.09 (d, $J = 3.5$ Hz, 2H), 1.08 (s, 2H).



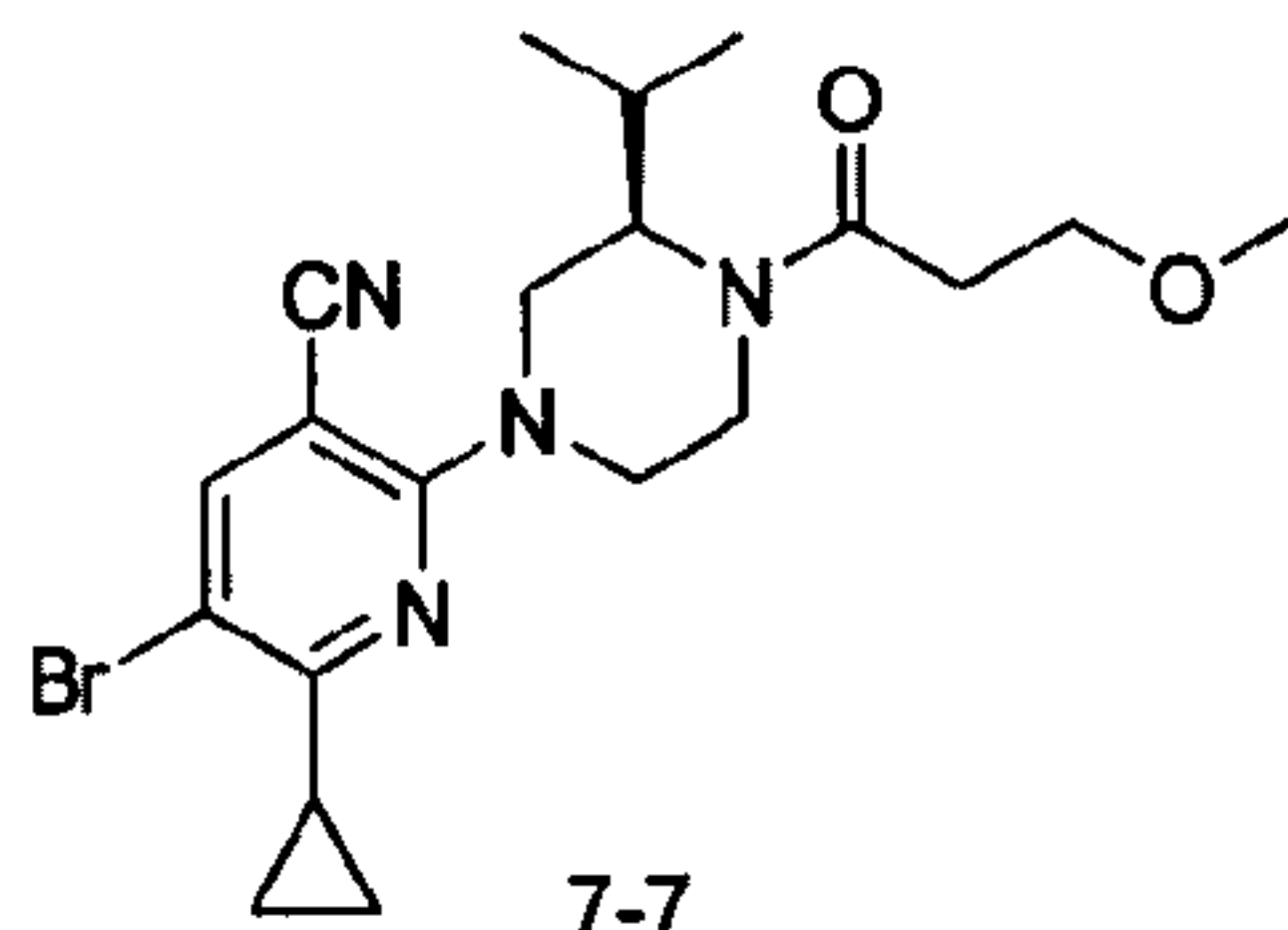
(R)-5-bromo-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (7-4) was synthesized by method 1 in step F except using 6-3 as the starting material instead of 6-1. MS (ES) M+H expected 433.1, found 433.3.



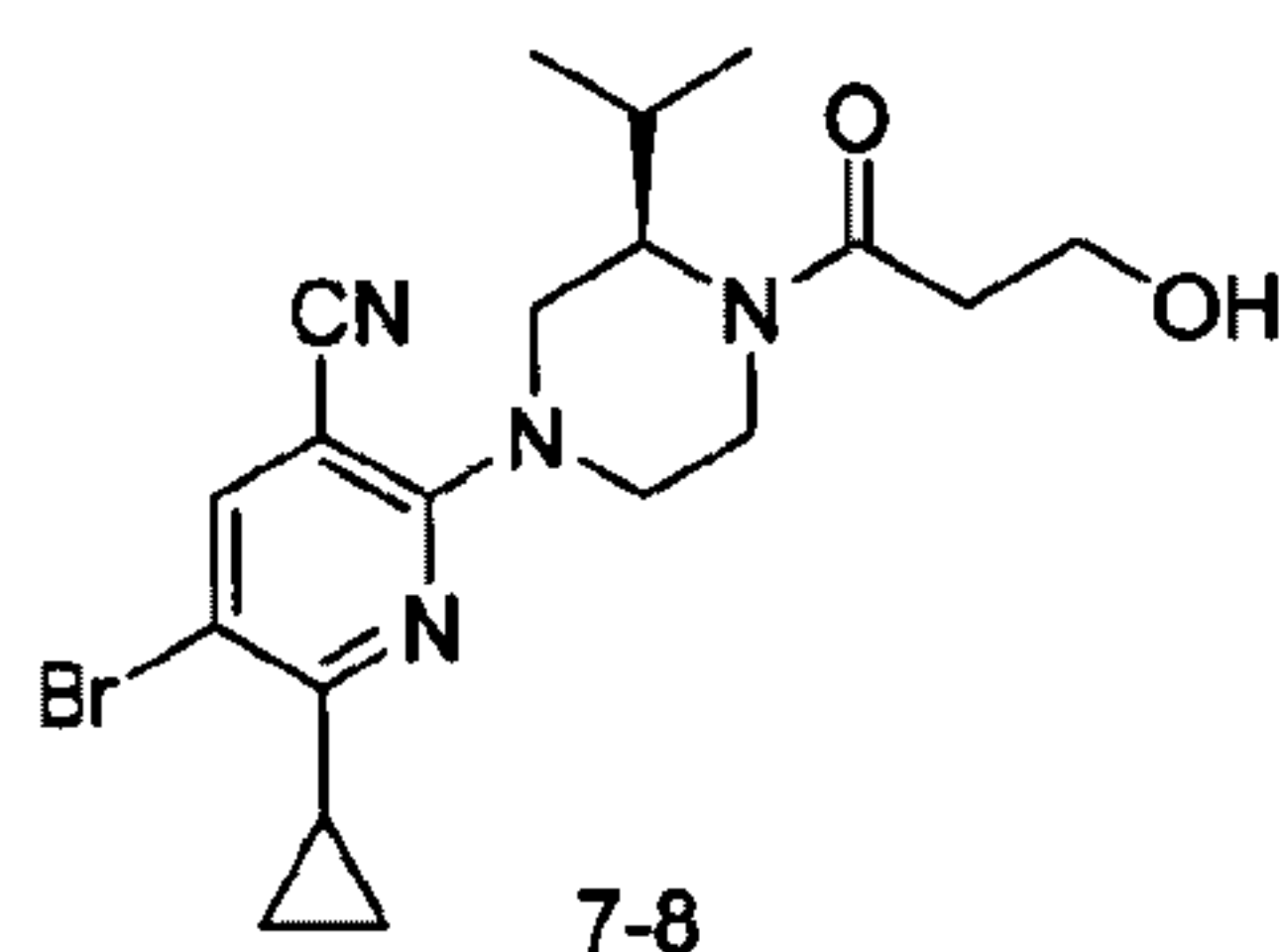
(R)-5-bromo-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropylnicotinonitrile (7-5) was synthesized by method 2 in step F except using 6-3 as the starting material instead of 6-1. MS (ES) M+H expected 415.1, found 415.1.



(R)-5-bromo-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)nicotinonitrile (7-6) was synthesized by method 3 in step F except using 6-3 as the starting material instead of 6-1. MS (ES) M+H expected 419.1, found 419.1. ¹H NMR (CHLOROFORM-d) δ 7.85 (m, 1H), 4.87 - 4.97 (m, 0.5H), 4.77 (d, J = 13.6 Hz, 0.5H), 4.29 - 4.48 (m, 2H), 4.11 - 4.20 (m, 1H), 3.70 - 3.75 (m, 2H), 3.45 - 3.55 (m, 2H), 3.15 - 3.27 (m, 1H), 2.92 - 3.14 (m, 1H), 2.67 - 2.78 (m, 1H), 2.51 - 2.61 (m, 1H), 2.40 - 2.51 (m, 1H), 1.34 (d, J = 6.8 Hz, 2H), 1.25 (d, 2H), 1.09 (d, J = 3.5 Hz, 2H), 1.08 (s, 2H).

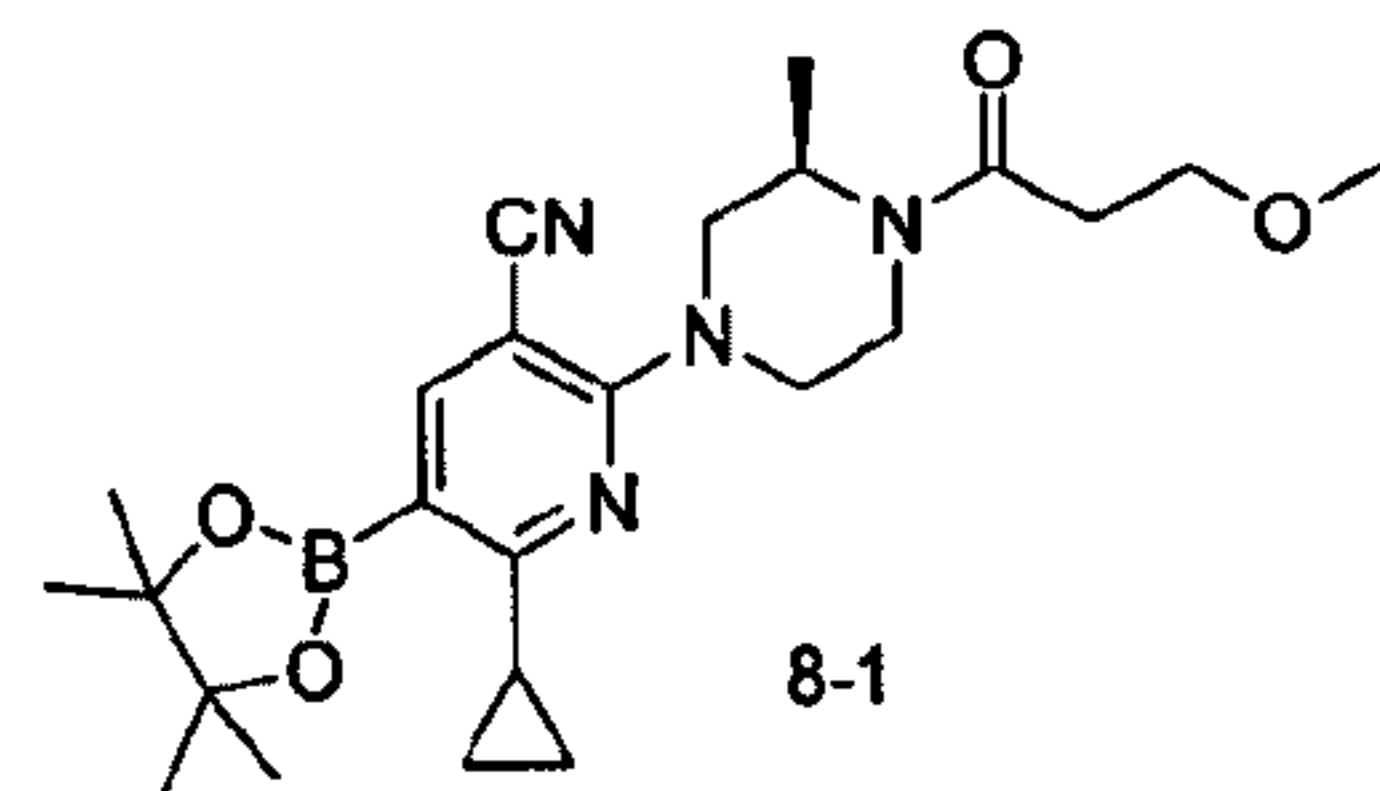


(R)-5-bromo-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (7-7) was synthesized by method 1 in step F except using 6-2 as the starting material instead of 6-1. MS (ES) M+H expected 434.1, found 435.1.



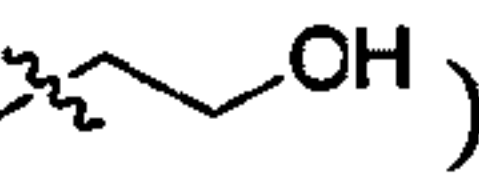
(R)-5-bromo-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)nicotinonitrile (7-8) was synthesized by method 1 in step F except using 6-2 as the starting material instead of 6-1. MS (ES) M+H expected 421.1, found 421.6.

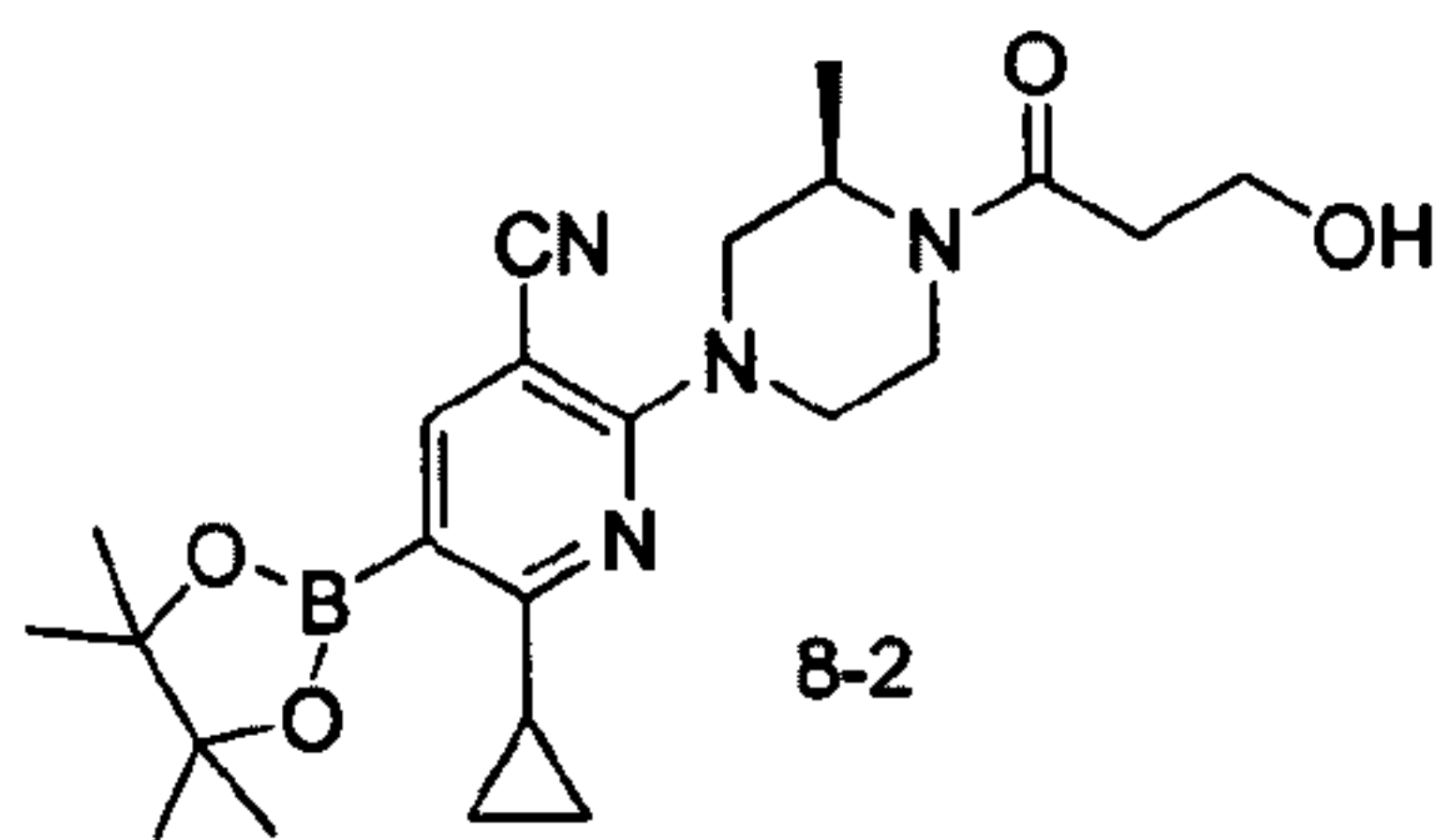
Step G, method 1: Exemplified by (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (8-1) (R'=methyl, R1=c)



To a solution of (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinonitrile (7-1) (747 mg, 1.8 mmol) in DMF (8 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2 dioxaborolane) (563 mg, 2.2 mmol) and KOAc (538 mg, 5.5 mmol). The resulting mixture was stirred at room temperature for 5 min before addition of PdCl₂(dppf).CH₂Cl₂ (45 mg, 0.03 mmol). After flushing with nitrogen, the reaction mixture was heated at 85°C for 18 hours. After cooling, the reaction mixture was diluted with water, and extracted with methylene chloride. The organic layer was then washed with brine, dried over

anhy. Na₂SO₄, and concentrated *in vacuo*. Column chromatography (25% EtOAc/petroleum ether) afforded 334 mg of title compound as a white solid. MS (ES) M+H expected 455.3, found 455.2.

Step G, method 2: Exemplified by (R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nicotinonitrile (R'=methyl, R1= )



1.4 g of (R)-5-bromo-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (**7-3**) (3.3 mmol), 2.12 g of 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (8.34 mmol), 0.7 g of KOAc (7.4 mmol), 154 mg of Xphos (0.32 mmol) and 308 mg of Pd₂(dba)₃ (0.33 mmol) in 20 mL of dioxane in a round bottom flask was stirred under N₂ at 75°C overnight. Then the mixture was cooled to room temperature. Concentrated, purified by column chromatography (petroleum ether: ethyl acetate from 3:1 to 1:1) to give 670 mg of title compound. MS (ES) M+H expected 441.2, found 441.2.

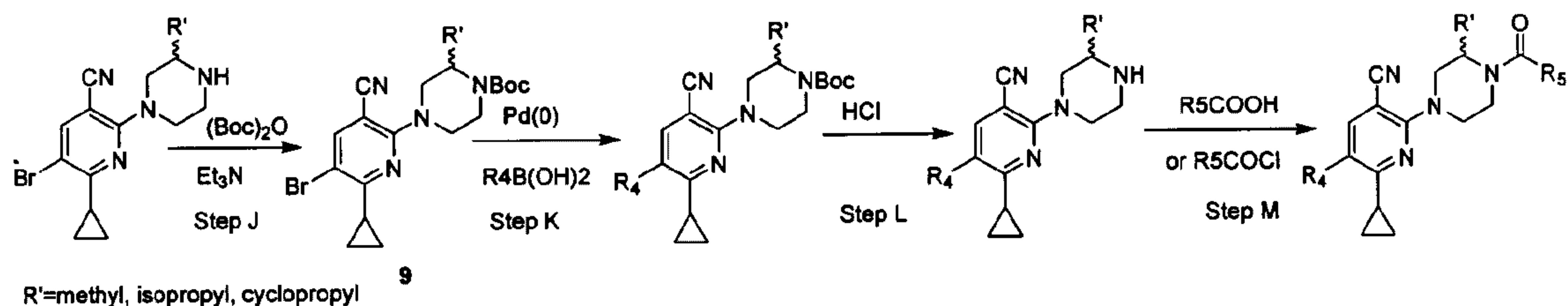
General procedure 1, Step H: Exemplified by (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(thiophen-2-yl)nicotinonitrile (**Compound 273**)

A mixture of **7-1** (26 mg, 0.06 mmol), thiophen-2-ylboronic acid (14 mg, 0.089 mmol), Pd(PPh₃)₄ (3 mg, 0.003 mmol), and K₂CO₃ (16 mg, 0.119 mmol) suspended in 1 mL of DMF was subjected to microwave reaction at 150°C for 45 min. After the reaction was complete, the reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography to afford 19 mg of title compound as yellowish oil. ¹H NMR (CHLOROFORM-d) δ 7.70 (s, 1H), 7.38 (dd, J = 3.9, 2.4 Hz, 1H), 7.07 - 7.14 (m, 2H), 4.90 (br. s., 0.5H), 4.52 (d, J = 13.1 Hz, 0.5H), 4.15 - 4.41 (m, 2.5H), 3.67 - 3.89 (m, 2.5H), 3.47 - 3.63 (m, 0.5H), 3.34 - 3.43 (m, 3H), 3.20 - 3.33 (m, 1H), 2.99 - 3.17 (m, 1.5H), 2.63 - 2.81 (m, 1H), 2.50 - 2.62 (m, 1H), 2.26 - 2.36 (m, 1H), 1.37 (d, J = 6.3 Hz, 1.5H), 1.27 (d, J = 6.8 Hz, 1.5H), 1.10 - 1.18 (m, 2H), 0.94 - 1.05 (m, 2H). LC-MS: m/z 411.1 (M+H)⁺.

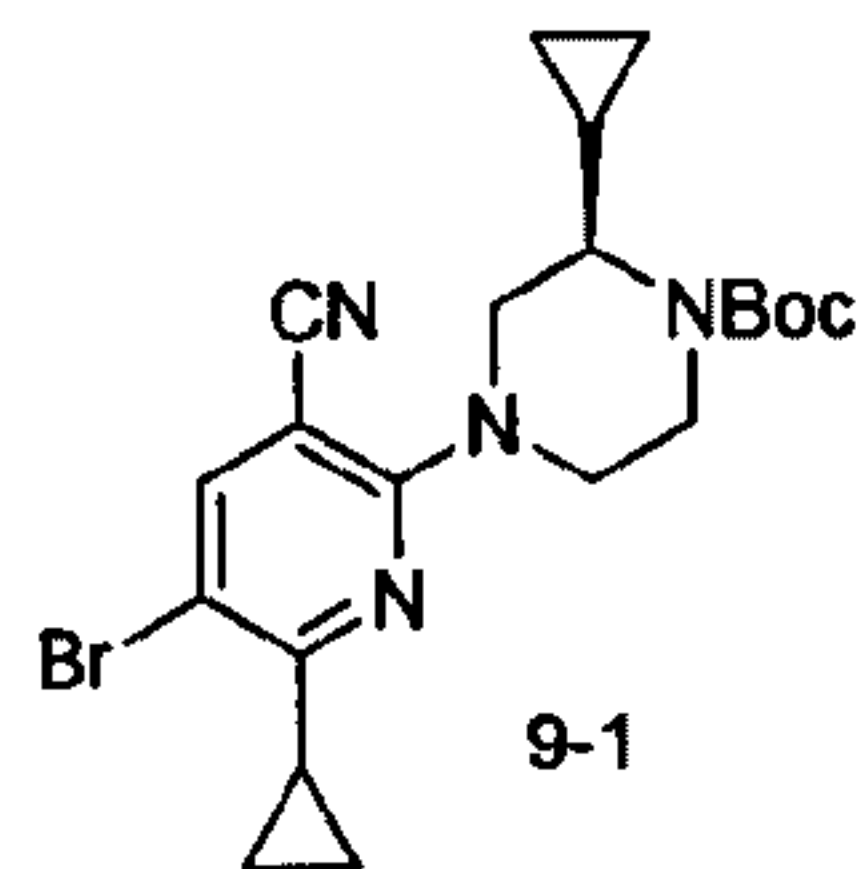
Step I: Exemplified by (R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinazolin-5-yl)nicotinonitrile (**Compound 603**)

To a solution of **8-1** (95 mg, 0.197 mmol), 5-chloro-2-vinylquinazoline (25 mg, 0.131 mmol), Xphos (7 mg, 0.013 mmol), $\text{Pd}_2(\text{dba})_3$ (6 mg, 0.007 mmol) and $\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$ (105 mg, 0.393 mmol) was stirred at 100°C for 16 hours, the mixture was partitioned between EtOAc and water, the organic was washed with water, brine and concentrated to give the crude which was purified by column chromatography to give 25 mg of the product. ^1H NMR ($\text{CHLOROFORM-}d$) δ 9.16 (d, $J = 3.0$ Hz, 1H), 8.05 (d, $J = 8.5$ Hz, 1H), 7.95 (dd, $J = 8.5, 7.3$ Hz, 1H), 7.66 (s, 1H), 7.45 - 7.58 (m, 1H), 7.06 (dd, $J = 17.2, 10.4$ Hz, 1H), 6.80 (dd, $J = 17.3, 1.5$ Hz, 1H), 5.80 - 5.96 (m, 1H), 4.87 - 5.02 (m, 0.5H), 4.56 (d, $J = 12.0$ Hz, 0.5H), 4.35 - 4.44 (m, 2.5H), 3.84 (d, $J = 12.8$ Hz, 0.5H), 3.69 - 3.79 (m, 2H), 3.52 - 3.65 (m, 0.5H), 3.30 - 3.43 (m, 4H), 3.05 - 3.24 (m, 1.5H), 2.65 - 2.81 (m, 1H), 2.48 - 2.64 (m, 1H), 1.50 - 1.59 (m, 1H), 1.30 - 1.44 (m, 3H), 1.13 - 1.22 (m, 2H), 0.84 - 0.89 (m, 2H). LC-MS: m/z 483.2 ($\text{M}+\text{H}$) $^+$

General procedure 2:



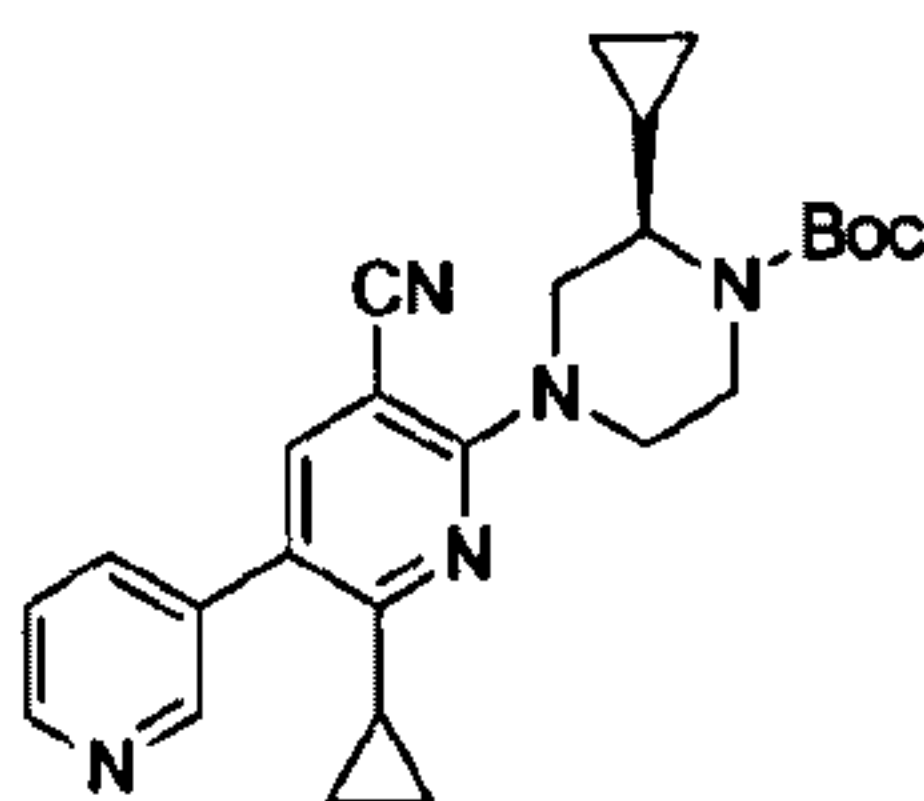
Step J: Exemplified by (R)-tert-butyl 4-(5-bromo-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (**9-1**, $\text{R}' = \text{cyclopropyl}$)



To a solution of **6-3** (1 g, 2.24 mmol) in DCM (8 mL) was added $(\text{Boc})_2\text{O}$ (0.5 g, 2.26 mmol) and Et_3N (0.1 mL). The resultant solution was stirred at room temperature for 2 h. The reaction mixture was diluted with water. The organic layer was then washed with brine, dried

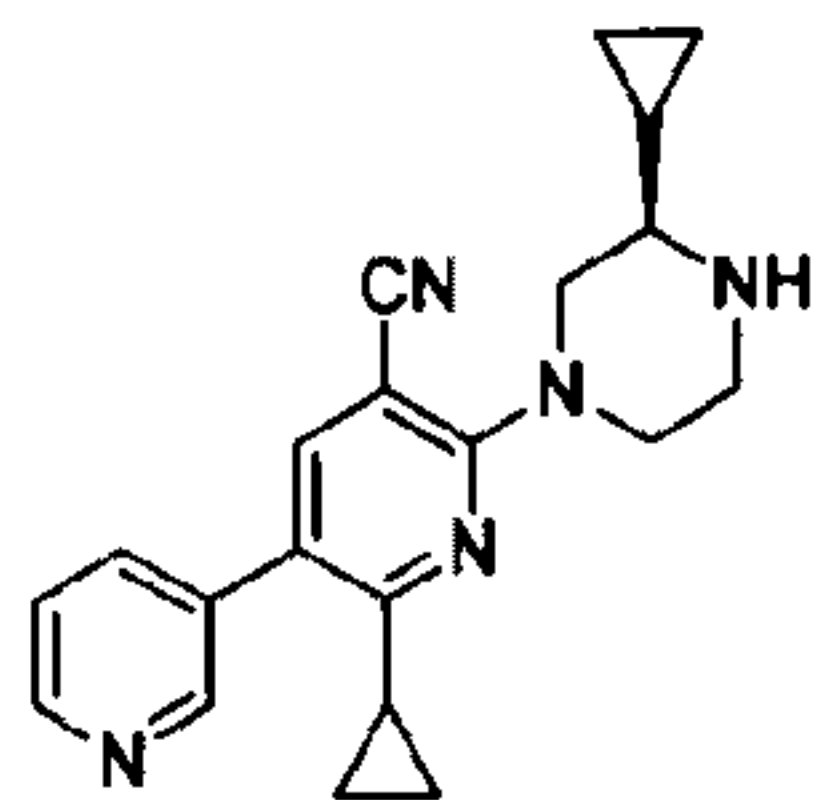
over anhy. Na_2SO_4 , and concentrated *in vacuo* to give the title compound as a white solid (1.5 g), which can be used directly for the next step. ^1H NMR (CHLOROFORM- d) δ 7.85 (s, 1H), 4.14 - 4.24 (m, 2H), 3.29 - 3.34 (m, 1H), 3.12 - 3.18 (m, 1H), 2.96 - 3.00 (m, 2H), 2.71 (dd, 1H), 2.12 - 2.24 (m, 1H), 1.5 (s, 9H), 1.25 (d, 2H), 1.16 (d, 2H), 1.08 (d, 2H), 1.07 (d, 2H).

Step K: Exemplified by (R)-tert-butyl 4-(5-cyano-2-cyclopropyl-[3,3'-bipyridin]-6-yl)-2-cyclopropyl piperazine-1-carboxylate ($\text{R}'=\text{cyclopropyl}$, $\text{R}_4=3\text{-pyridinyl}$)



To a solution of (R)-tert-butyl 4-(5-bromo-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (150 mg, 0.33 mmol) in 2 mL of dioxane and 0.5 mL water was added pyridin-3-ylboronic acid (45.6 mg, 0.37 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (24 mg, 0.033 mmol), CsF (100 mg, 0.66 mmol). The resulting mixture was stirred at 100°C under N_2 atmosphere and microwaved for 1 h. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% EtOAc/petroleum ether) to afford 100 mg title compound. MS (ES) $\text{M}+\text{H}$ expected 446.2, found 446.3.

Step L: Exemplified by (R)-2-cyclopropyl-6-(3-cyclopropylpiperazin-1-yl)-[3,3'-bipyridine]-5-carbonitrile ($\text{R}'=\text{cyclopropyl}$, $\text{R}_4=3\text{-pyridinyl}$)



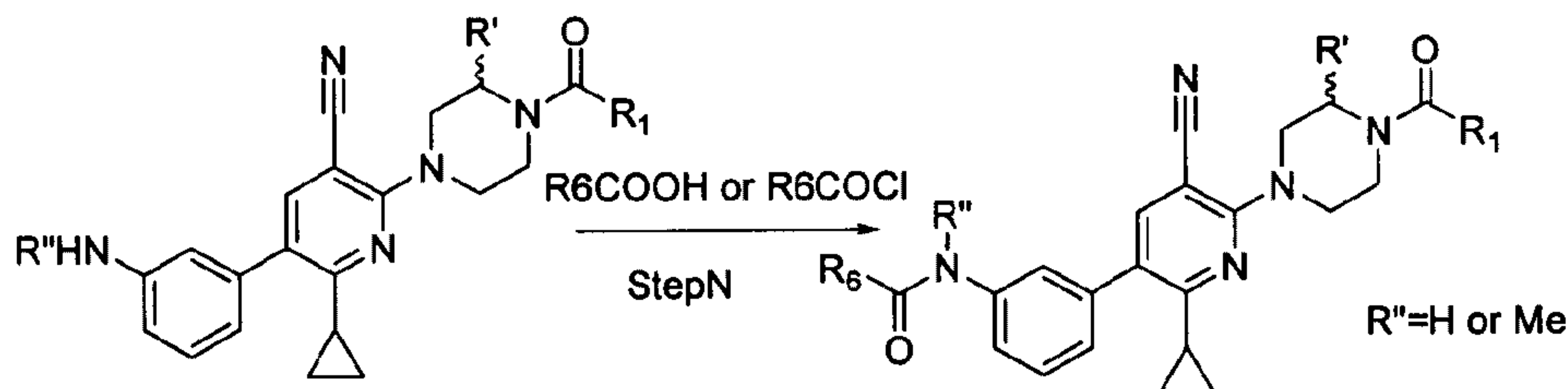
To a solution of (R)-tert-butyl 4-(5-cyano-2-cyclopropyl-[3,3'-bipyridin]-6-yl)-2-cyclopropyl piperazine-1-carboxylate (100 mg, 0.22 mmol) in 3 mL of DCM was added TFA (1 mL). The resulting mixture was stirred at room temperature for 2h. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and basified with Na_2CO_3 solution to $\text{pH}=8$. Then the solution was extracted with DCM (10 mL x 3).

The organic layer was dried and concentrated and purified by Prep-HPLC (5% DCM/MeOH) to get 70 mg title compound. MS (ES) M+H expected 346.2, found 346.2.

General procedure 2, Step M: Exemplified by (R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-[3,3'-bipyridine]-5-carbonitrile (**Compound 524**)

To a solution of (R)-2-cyclopropyl-6-(3-cyclopropylpiperazin-1-yl)-[3,3'-bipyridine]-5-carbonitrile (70 mg, 0.2 mmol) in 10 mL DCM was added 3,3,3-trifluoropropanoic acid (31 mg, 0.24 mmol), and triethylamine (1mL), HOBT (54 mg, 0.4 mmol), EDCI (76.8 mg, 0.4 mmol). The resulting reaction mixture was stirred at r.t. overnight. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by Prep-HPLC (50% EtOAc/petroleum ether) to get 25 mg title compound. ¹H NMR (CHLOROFORM-d) δ 8.56 - 8.77 (m, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.65 (s, 1H), 7.44 (dd, J = 7.7, 4.9 Hz, 1H), 4.56 (d, J = 13.1 Hz, 1H), 4.44 (d, J = 13.1 Hz, 1H), 4.12 (br. s., 1H), 3.63 - 3.86 (m, 2H), 3.32 (d, J = 9.3 Hz, 2H), 3.20 (d, J = 13.1 Hz, 1H), 3.11 (d, J = 11.8 Hz, 1H), 1.99 (td, J = 8.0, 3.8 Hz, 1H), 1.11 - 1.23 (m, 3H), 1.01 (dd, J = 7.5, 3.5 Hz, 2H), 0.77 - 0.95 (m, 2H), 0.66 (br. s., 1H), 0.50 (d, J = 5.0 Hz, 2H) LC-MS: m/z 445.4 (M+H)⁺.

General procedure 3:



Method 1: Exemplified by (R)-2-chloro-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetamide (**Compound 403**) (R''=H, R1=CH₂CH₂OC(=O)CH₃)

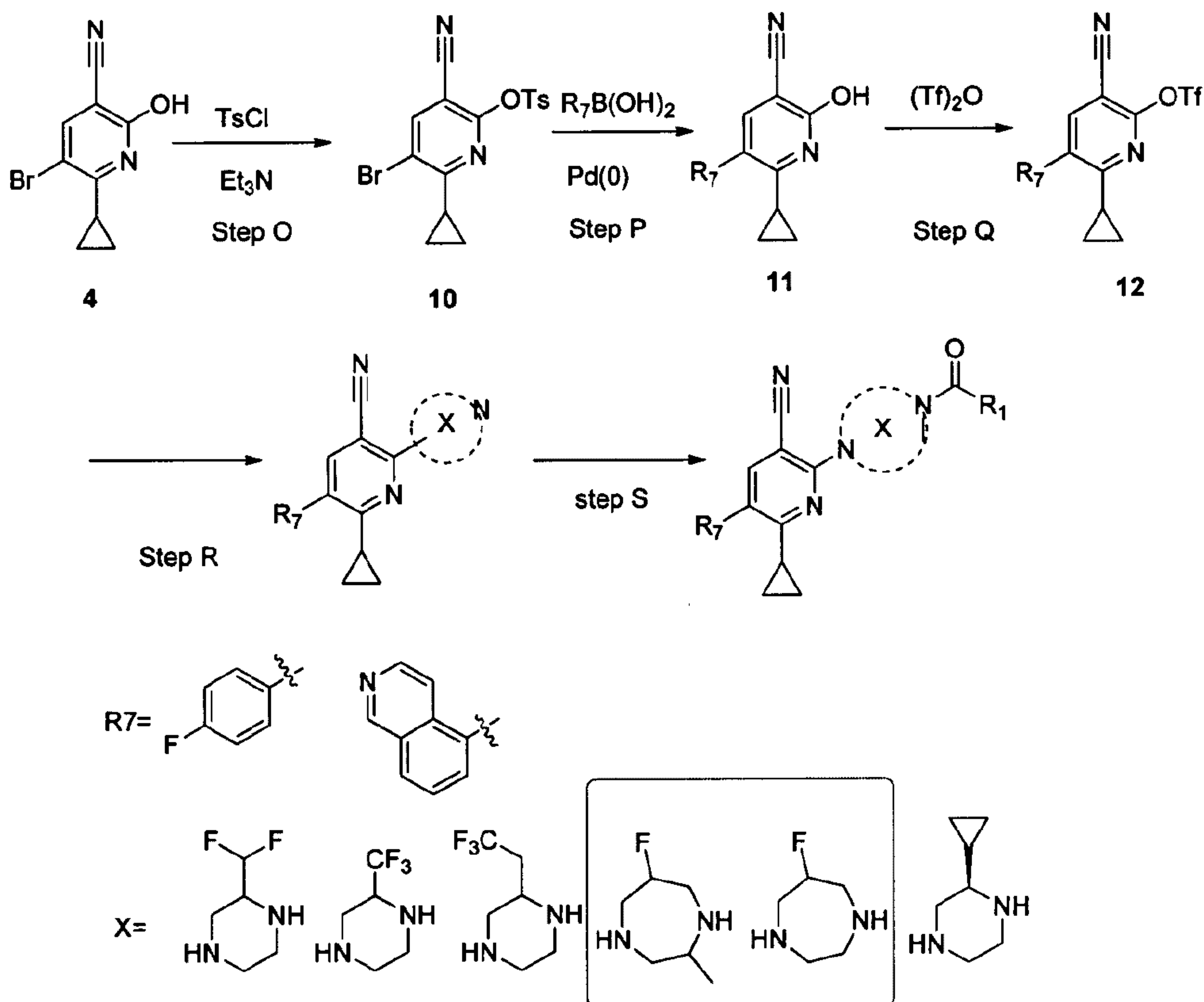
To a solution of (R)-5-(3-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methyl piperazin-1-yl) nicotinonitrile (50 mg, 0.119 mmol) and 2-chloroacetyl chloride (15 mg, 0.131 mmol) in 2 ml of DCM was added dropwise TEA (24 mg, 0.238 mmol) at 0°C, then the mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was

partitioned between EtOAc and water. The organic layer was dried over Na₂SO₄ and concentrated to give the crude which was purified by prep-TLC to give 20 mg of the product. ¹H NMR (CHLOROFORM-d) δ 8.34 (s, 1H), 7.66 - 7.75 (m, 1H), 7.62 (s, 1H), 7.50 - 7.55 (m, 1H), 7.42 - 7.48 (m, 1H), 7.22 (d, J = 7.8 Hz, 1H), 4.92 (s, 0.5H), 4.50-4.54 (m, 0.5H), 4.29 - 4.33 (m, 1H), 4.26 (m, 1H), 4.21-4.25 (m, 0.5H), 3.71 - 3.84 (m, 2.5H), 3.52-3.57 (m, 0.5H), 3.39 (s, 3H), 3.21 - 3.32 (m, 1H), 3.13 (d, J = 11.3 Hz, 1H), 3.05 (d, J = 12.3 Hz, 0.5H), 2.66 - 2.81 (m, 1H), 2.54 - 2.65 (m, 1H), 2.07 - 2.12 (m, 1H), 1.40 (d, J = 6.3 Hz, 1H), 1.28 - 1.31 (m, 2H), 1.14 - 1.19 (m, 2H), 0.94 - 1.00 (m, 2H). LC-MS: m/z 496.2 (M+H)⁺.

Method 2: Exemplified by (R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)propionamide (**Compound 424**)

To a 25 mL of round-bottom flask was added (R)-5-(3-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methyl piperazin-1-yl) nicotinonitrile (50 mg, 0.119 mmol), propionic acid (0.1 mL), HATU (20 mg), DIPEA (0.05 mL) and 10 mL of methylene chloride. The resulting reaction mixture was stirred at room temperature overnight until TLC showed the completion of the reaction. Reaction mixture was with satd. NaHCO₃ and brine. The combined organic layer was then dried over anhy. Na₂SO₄ and concentrated *in vacuo*. Column chromatography purification (30% EtOAc/petroleum ether) afforded 45 mg of title compound as a white solid. ¹H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 4.89 (s, 0.5H), 4.52 (d, J = 13.3 Hz, 0.5H), 4.14 - 4.35 (m, 2.5H), 3.67 - 3.85 (m, 2.5H), 3.49 - 3.62 (m, 0.5H), 3.37 (s, 3H), 3.17 - 3.32 (m, 1H), 2.93 - 3.17 (m, 1.5H), 2.63 - 2.81 (m, 1H), 2.52 - 2.63 (m, 1H), 2.37 - 2.49 (m, 2H), 2.05 - 2.13 (m, 1H), 1.38 (d, J = 6.5 Hz, 1H), 1.22 - 1.31 (m, 5H), 1.14 (dt, J = 7.4, 3.6 Hz, 2H), 0.88 - 1.01 (m, 2H). LC-MS: m/z 476.3 (M+H)⁺.

General procedure 4:

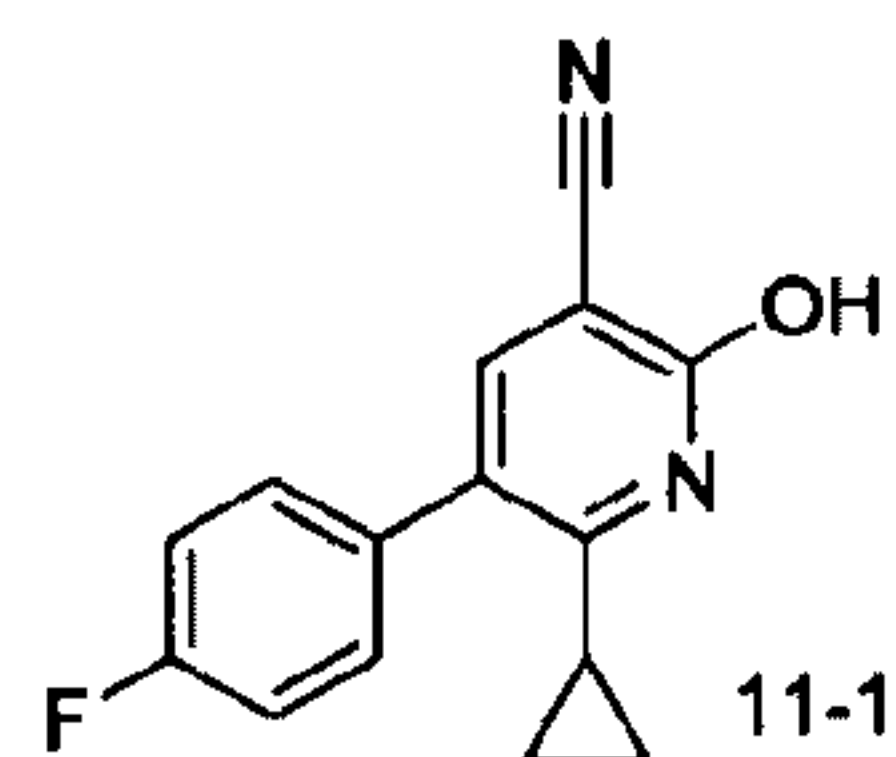


Step O: 5-bromo-3-cyano-6-cyclopropylpyridin-2-yl 4-methylbenzenesulfonate (10)

To a solution of 4 (2.37 g, 10 mmol) in THF (20 mL) was added TsCl (1.9 g, 11 mmol) and Et₃N (1 mL). The reaction was stirred at room temperature for 2 h. The resultant solution was partitioned between DCM and water. The organic layer was dried over Na₂SO₄ and concentrated to give the crude which was purified by column chromatography to give 2.6 g of 10.

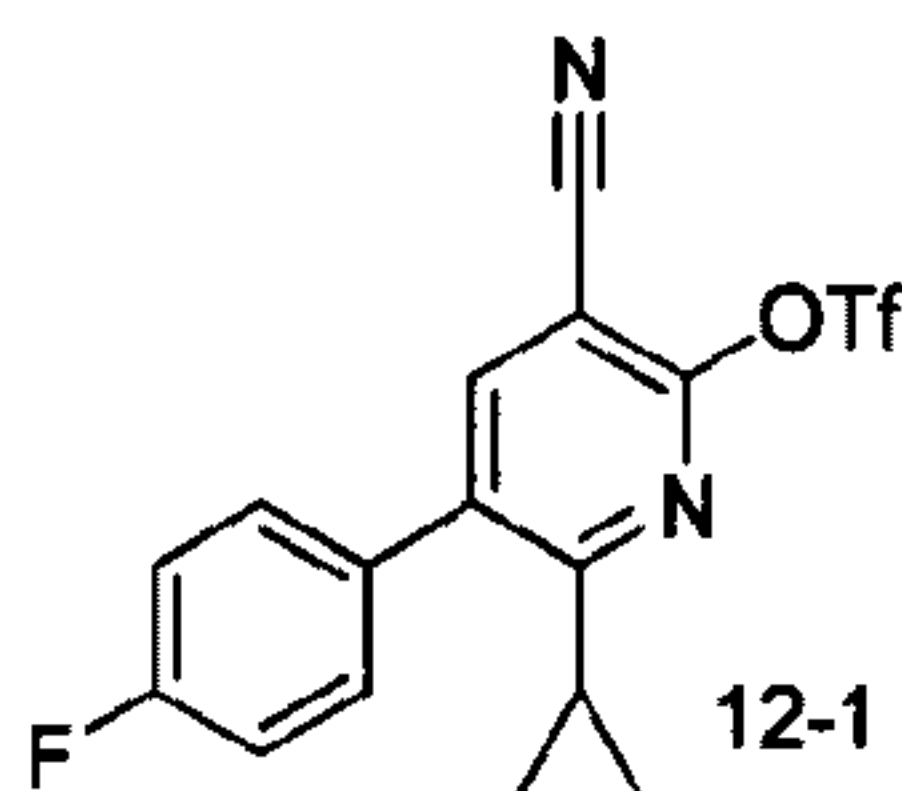
¹H NMR (CHLOROFORM-d) δ 7.86 (s, 1H), 7.35 - 7.46 (m, 2H), 7.11 - 7.25 (m, 2H), 1.99 - 2.17 (m, 1H), 1.21 - 1.38 (m, 2H), 1.00 - 1.20 (m, 2H). LC-MS: m/z 393.0 (M+H)⁺.

Step P: Exemplified by 6-cyclopropyl-5-(4-fluorophenyl)-2-hydroxynicotinonitrile (11-1)



A mixture of **10** (2.6 g, 11 mmol), 4-fluorophenylboronic acid (1.4 g, 10 mmol), Pd(PPh₃)₄ (30 mg), and K₂CO₃ (16 mg, 0.119 mmol) suspended in 10 mL of DMF was subjected to microwave reaction at 150°C for 45 min. After the reaction, the reaction mixture was concentrated *in vacuo*, and the residue was purified by column chromatography to afford 1.9 g of title compound as a yellow solid. LC-MS: m/z 255.0 (M+H)⁺

Step Q:

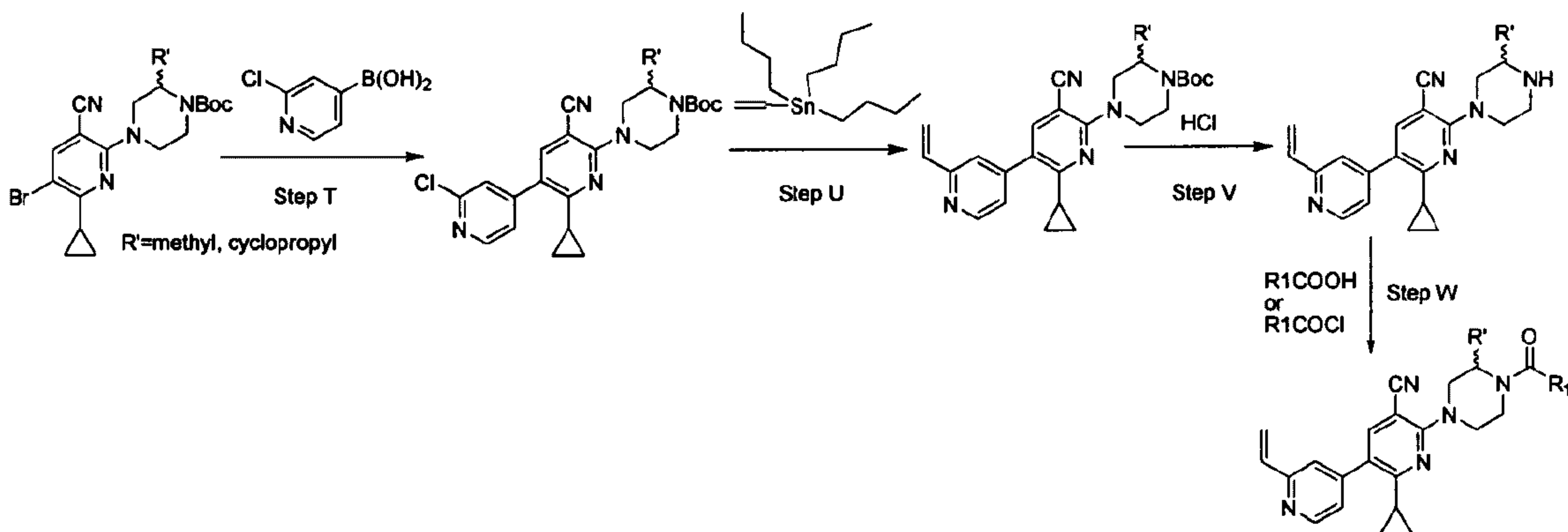


3-cyano-6-cyclopropyl-5-(4-fluorophenyl)pyridin-2-yl trifluoromethanesulfonate. ¹H NMR (CHLOROFORM-d) δ: 7.87 (s, 1H), 7.32 - 7.57 (m, 2H), 7.13 - 7.24 (m, 2H), 1.99 - 2.17 (m, 1H), 1.21 - 1.38 (m, 2H), 1.00 - 1.20 (m, 2H). LC-MS: m/z 387.1 (M+H)⁺.

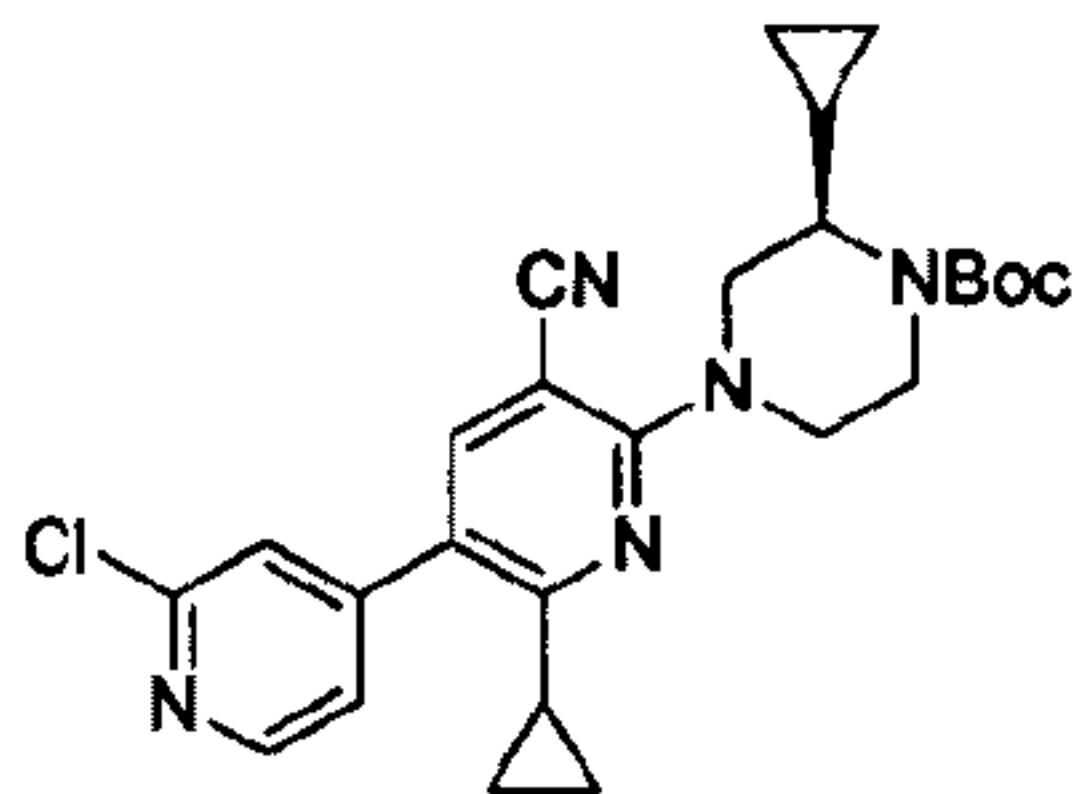
Step R: The same procedure as General procedure 1, step E except using **12-1** as the starting material instead of **5** and the suitable building blocks described in the “building block” section.

Step S: The same procedure as General procedure 1, step G except using the suitable building blocks described in the “building block” section.

General procedure 5:

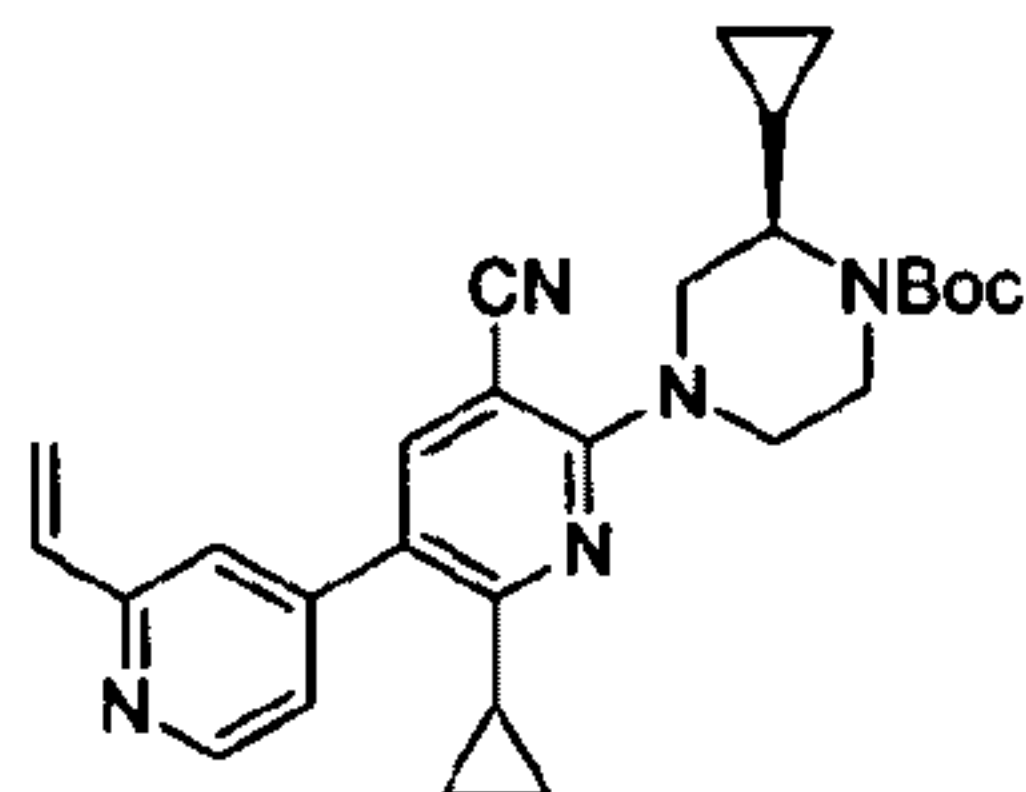


Step T: Exemplified by (R)-tert-butyl 4-(2'-chloro-5-cyano-2-cyclopropyl-3,4'-bipyridin-6-yl)-2-cyclopropylpiperazine-1-carboxylate



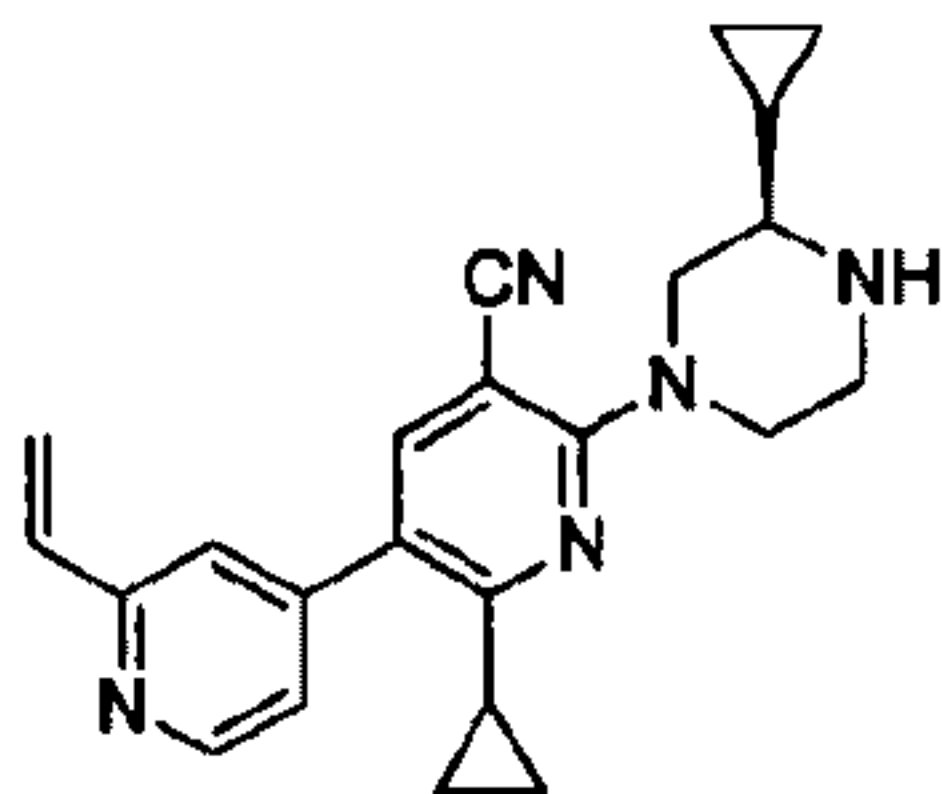
To a 25 mL flask was added with 9-1 (1000 mg 2.235 mmol), 2-chloropyridin-4-ylboronic acid (457 mg, 2.906 mmol), $\text{Pd}(\text{PPh}_3)_4$ (120 mg, 0.1 mmol), K_2CO_3 (926 mg, 6.705 mmol), and 4 mL DMF. The resultant mixture was stirred at 150°C for 5 h. After washing with satd. NaHCO_3 , brine, the combined organic layer was dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Column chromatography purification (20% EtOAc/petroleum ether) afforded 640 mg of title compound. ^1H NMR (CHLOROFORM- d) δ . 8.48 (d, $J = 5.0$ Hz, 1H), 7.62 (s, 1H), 7.39 - 7.47 (m, 1H), 7.32 (dd, $J = 5.1, 1.3$ Hz, 1H), 4.59 (d, $J = 12.9$ Hz, 1H), 4.45 (d, $J = 13.2$ Hz, 1H), 4.09 (d, $J = 13.5$ Hz, 1H), 3.50 (d, $J = 9.1$ Hz, 1H), 3.34 - 3.43 (m, 1H), 3.27 (dd, $J = 13.2, 3.8$ Hz, 1H), 3.11 (td, $J = 12.5, 3.7$ Hz, 1H), 1.94 - 2.06 (m, 1H), 1.77 (br. s., 2H), 1.50 (s, 9H), 1.34 (br. s., 1H), 1.04 (dd, $J = 7.9, 3.2$ Hz, 2H), 0.56 - 0.63 (m, 2H), 0.50 (dd, $J = 8.5, 3.5$ Hz, 1H), 0.32 - 0.42 (m, 1H).

Step U: Exemplified by (R)-tert-butyl 4-(5-cyano-2-cyclopropyl-2'-vinyl-3,4'-bipyridin-6-yl)-2-cyclopropyl piperazine-1-carboxylate



To a flask was added with (R)-tert-butyl 4-(2'-chloro-5-cyano-2-cyclopropyl-3,4'-bipyridin-6-yl)-2-cyclopropylpiperazine-1-carboxylate (640 mg 1.33 mmol), tributyl(vinyl)stannane (550 mg, 1.73 mmol), $\text{Pd}(\text{PPh}_3)_4$ (120 mg, 0.1 mmol), K_2CO_3 (460 mg, 3.33 mmol), and 4 mL DMF. The resultant mixture was stirred at 150°C for 5 h. After washing with satd. NaHCO_3 , brine, the combined organic layer was dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Column chromatography purification (20% EtOAc/petroleum ether) afforded the compound. LC-MS: m/z 472.2 ($\text{M}+\text{H}$) $^+$.

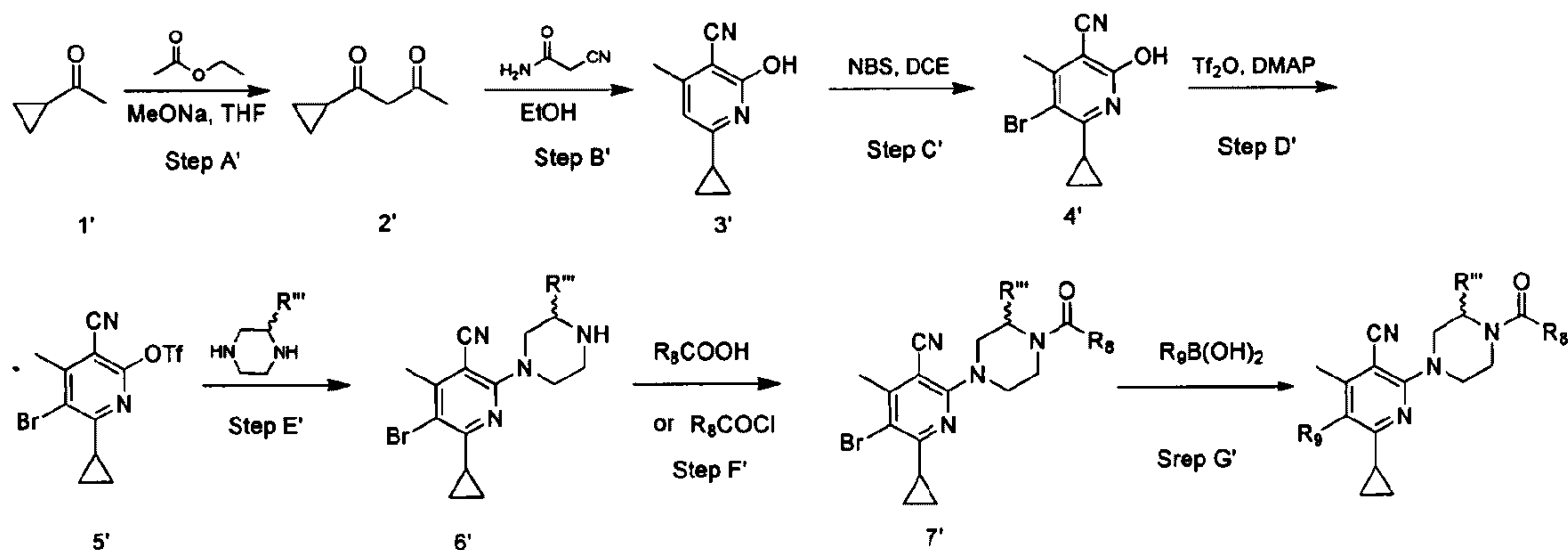
Step V: (R)-2-cyclopropyl-6-(3-cyclopropylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile



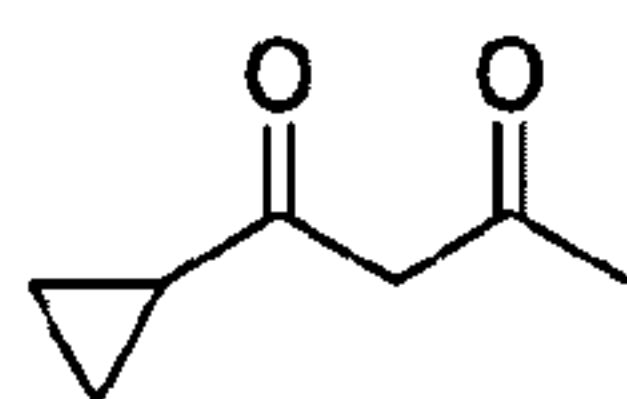
To a flask was added (R)-tert-butyl 4-(5-cyano-2-cyclopropyl-2'-vinyl-3,4'-bipyridin-6-yl)-2-cyclopropylpiperazine-1-carboxylate and 12mL EtOH/HCl (1M). The resulting reaction mixture was stirred at 0°C for 30 minutes until TLC showed the completion of the reaction, which was concentrated *in vacuo* to afford a product as light yellowish solid. ¹H NMR (CHLOROFORM-d) δ: 8.65 (d, J = 5.0 Hz, 1H), 7.62 (s, 1H), 7.38 (s, 1H), 7.23 (dd, J = 5.0, 1.8 Hz, 1H), 6.89 (dd, J = 17.3, 10.9 Hz, 1H), 6.29 (dd, J = 17.6, 1.2 Hz, 1H), 5.57 (dd, J = 10.9, 1.2 Hz, 1H), 4.50 (d, J = 12.9 Hz, 1H), 4.36 (d, J = 13.2 Hz, 1H), 3.28 (br. s., 1H), 3.22 (d, J = 12.3 Hz, 1H), 3.10 (br. s., 1H), 2.95 (br. s., 1H), 1.96 - 2.06 (m, 1H), 1.21 (t, J = 4.1 Hz, 1H), 0.95 - 1.07 (m, 3H), 0.92 (br. s., 1H), 0.62 (d, J = 7.9 Hz, 2H), 0.40 (d, J = 4.7 Hz, 2H).

Step W: The same procedure as General procedure 1, step G except using the suitable building blocks described in the “building block” section.

General Procedure 6:

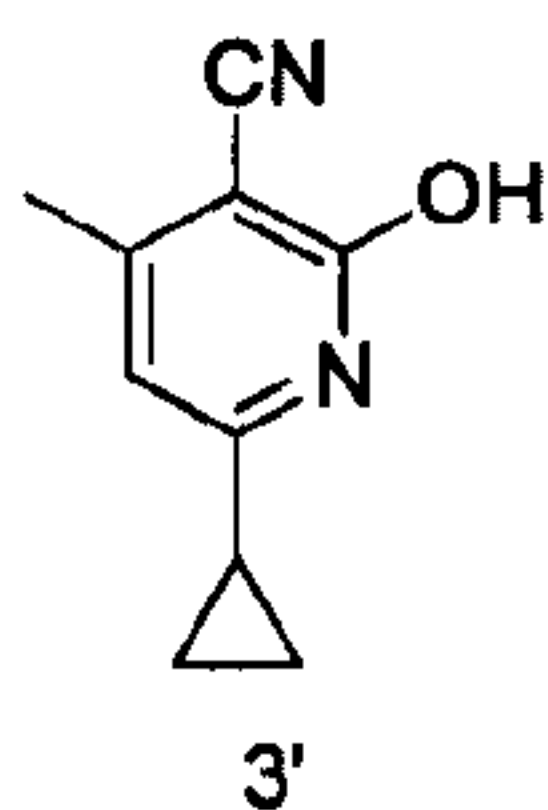


Step A': 1-cyclopropylbutane-1,3-dione



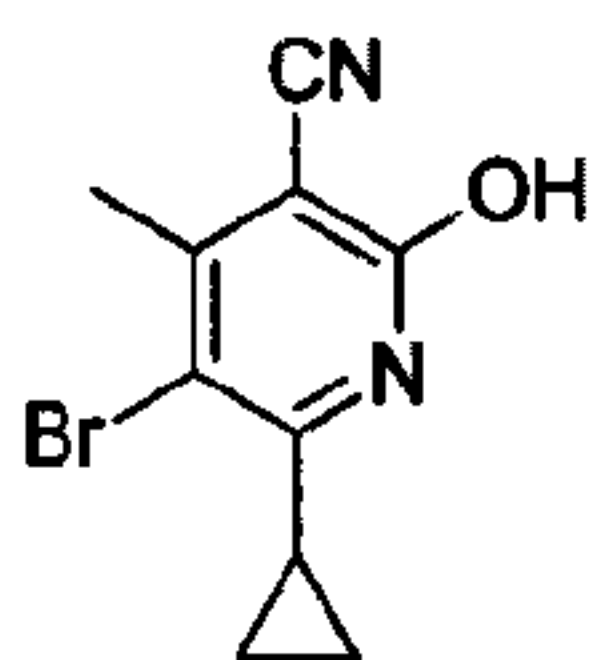
A mixture of CH₃ONa (75.65 g, 1.25 mol) and 1-cyclopropylethanone (105.0 g, 1.25 mol) in THF (1000 mL) was stirred at 35°C for 1 h and followed by addition of ethyl acetate (110.0 g, 1.25 mol) dropwise. After stirring at 50°C for 4 hrs, the solvent was removed under reduced pressure and the residue was dissolved in H₂O (500 mL) and adjusted to pH 3.5 with citric acid. The mixture was extracted by ethyl acetate (500 mL × 3). The combined organic layers were concentrated in vacuum to give 1-cyclopropylbutane-1,3-dione (110.0 g, yield 69%) as a yellow oil. ¹H NMR (CHLOROFORM-d) δ 0.83-0.95(m, 2H), 1.06-1.10(m, 2H), 1.54-1.63(m, 1H), 2.00(s, 3H).

Step B': 6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile

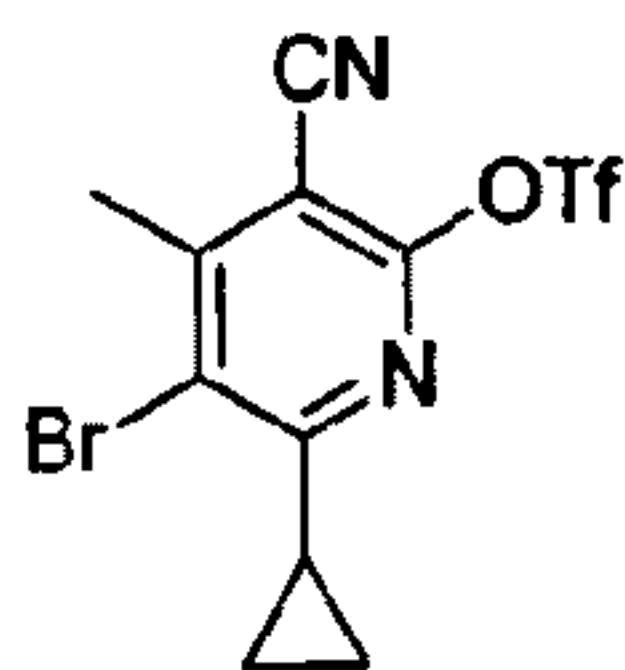


A mixture of 1-cyclopropylbutane-1,3-dione (126.0 g, 1.0 mol) and 2-cyanoacetamide (88.0 g, 1.0 mol) and piperidine (60 mL) in EtOH (1500 mL) was stirred at reflux for 4 hrs. The reaction mixture was filtered, washed with PE (200 mL) and dried in vacuum to give 6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (90.0 g, 52%) as a white solid. ¹H NMR (DMSO-d₆) δ 12.36 (br. s., 1H), 5.93 (s, 1H), 2.26 (s, 3H), 1.81 - 1.91 (m, 1H), 1.06 - 1.14 (m, 2H), 0.91 - 0.95 (m, 2H).

Step C': 5-bromo-6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile

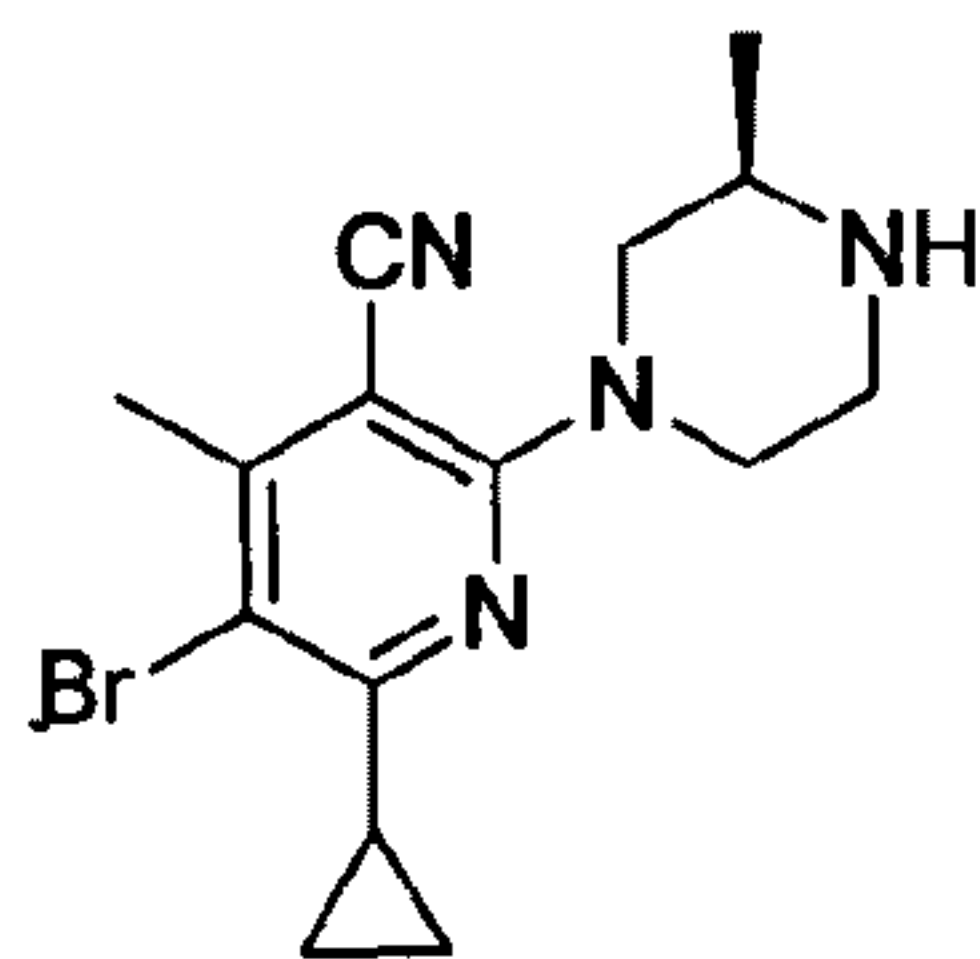


A mixture of 6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (90.0 g, 0.52 mol) and NBS (100.0 g, 0.57 mol) in DCE (1500 mL) was stirred at reflux temperature for 4 hrs. The reaction mixture was filtered and the residue was washed with DCE (200 mL) and dried in vacuum to give 5-bromo-6-cyclopropyl-2-hydroxy-4-methylnicotinonitrile (100.0 g, 76%) as a white solid. MS (ES) M+H expected 253.0, found 253.0. ¹H NMR (CHLOROFORM-d) δ 2.68 (s, 3H), 1.79 - 1.88 (m, 1H), 1.03 - 1.09 (m, 2H), 0.93 - 1.01 (m, 2H).

Step D': 5-bromo-3-cyano-6-cyclopropyl-4-methylpyridin-2-yl trifluoromethane-sulfonate

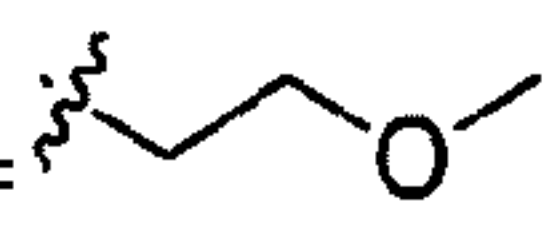
To a solution of 5-bromo-2-hydroxy-6-isopropylnicotinonitrile (40 g, 0.15 mol) in 200 mL of methylene chloride was added DMAP (1.78 g, 14.6 mmol), and triethylamine (25 mL, 175 mmol). The mixture was cooled to 0°C in an ice-water bath, and trifluoromethanesulfonic anhydride (37 mL, 0.21 mol) was added dropwise by syringe. The resulting reaction mixture was stirred at 0°C for 30 min then allowed to warm to room temperature and stirred overnight. After TLC showed the complete conversion of starting material to product, the reaction mixture was concentrated and purified by column chromatography (20% EtOAc/petroleum ether) to afford 55 g of title compound. ¹H NMR (CHLOROFORM-d) δ 2.70 (s, 3H), 2.16 - 2.20 (m, 1H), 1.23 - 1.25 (m, 2H), 1.19 - 1.22 (m, 2H)

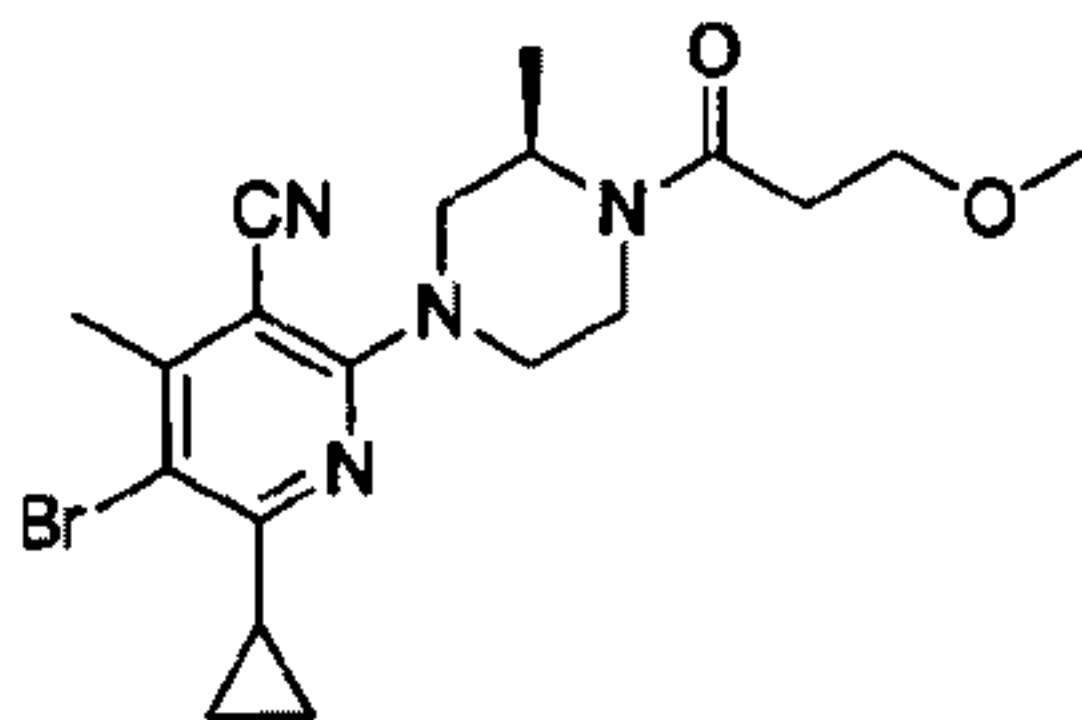
Step E': Exemplified by (R)-5-bromo-6-cyclopropyl-4-methyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (R'''=methyl)



A mixture of 5-bromo-3-cyano-6-cyclopropyl-4-methylpyridin-2-yl trifluoromethanesulfonate (50.0 g, 0.13 mol) and (R)-2-methylpiperazine (15.6 g, 0.16 mol) and Et₃N (26.0 g, 0.26 mol) in THF (500 mL) was stirred at 80°C overnight. The resulting mixture concentrated in vacuum to give (R)-5-bromo-6-cyclopropyl-4-methyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (34.8 g, 80%) as a white solid. ¹H NMR (CHLOROFORM-d) δ 4.08 - 4.16 (m, 0.5H), 4.05 - 4.08 (m, 1H), 4.01 - 4.04 (m, 0.5H), 2.99 - 3.08 (m, 1H), 2.97 (d, J = 8.8 Hz, 2H), 2.88 - 2.95 (m, 1H), 2.58 - 2.65 (m, 1H), 2.55 - 2.57 (m, 3H), 1.77 (br. s., 1H), 1.12 (s, 1.5H), 1.10 (s, 1.5H), 1.05 - 1.09 (m, 2H), 1.00 - 1.05 (m, 2H).

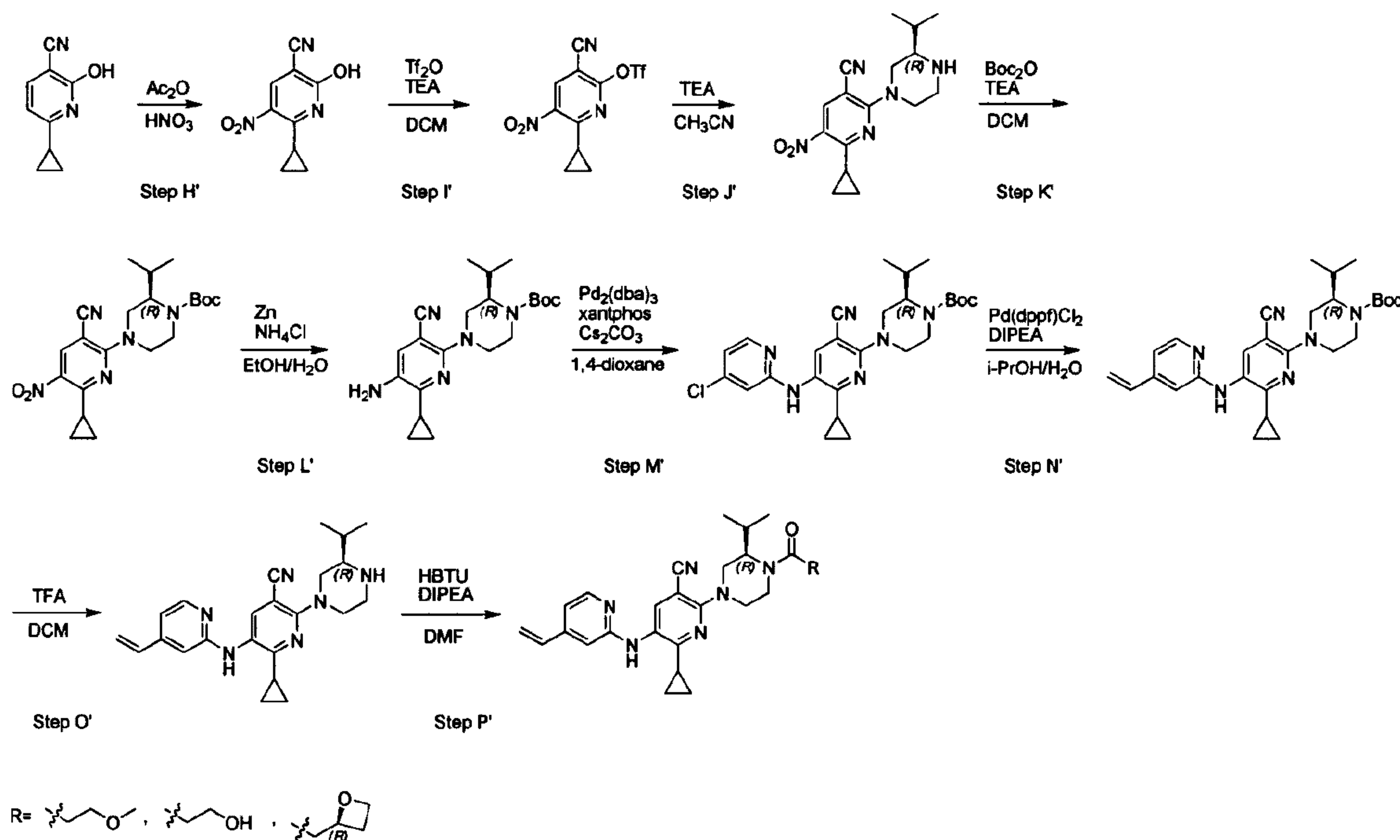
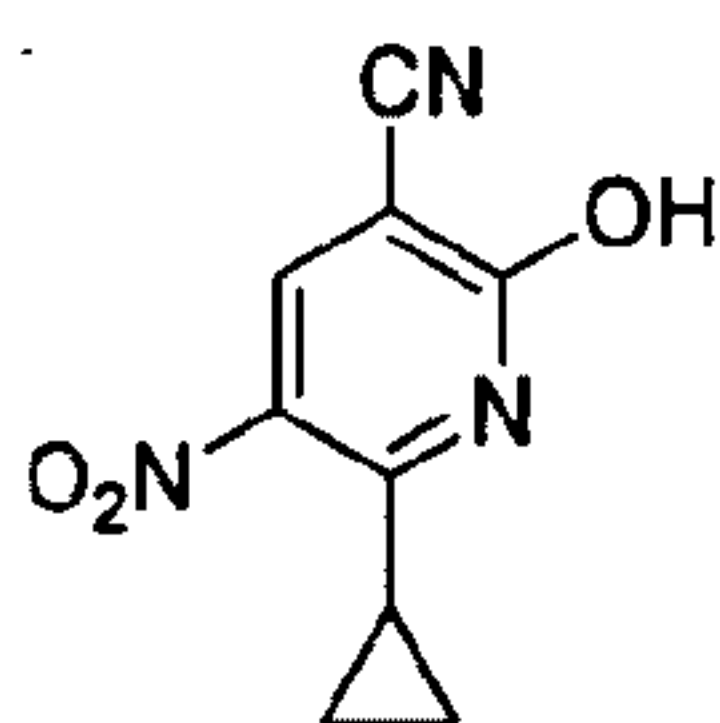
Step F': preparation of (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazine-1-yl)nicotinonitrile

zin-1-yl)-4-methylnicotinonitrile (R'''=methyl, R8= ).



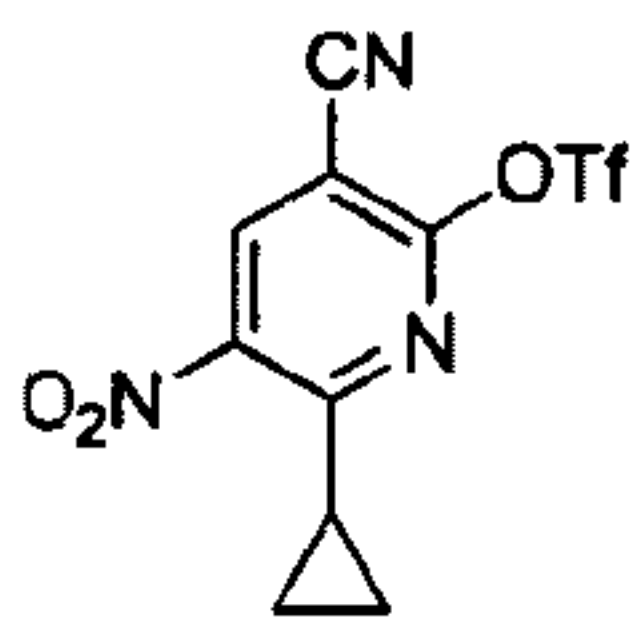
A mixture of (R)-5-bromo-6-cyclopropyl-4-methyl-2-(3-methyl piperazin-1-yl)nicotinonitrile (34.8 g, 0.1 mol) and 3-methoxypropanoic acid (16.0 g, 0.15 mol) in pyridine (500 mL) was stirred at 0°C for 30 min, and followed by addition of POCl₃ (28.7 g, 0.19 mol) dropwise. The resulting mixture was stirred at 20°C for 2 hrs. The reaction mixture was concentrated and purified by chromatography to give (R)-5-bromo-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-4-methylnicotinonitrile (25.0 g, 59%) as yellow oil. ¹H NMR (CHLOROFORM-d) δ 4.90 (br. s., 0.5H), 4.52 (d, J = 13.6 Hz, 0.5H), 4.22 (br. s., 0.5H), 3.95 - 4.13 (m, 2H), 3.78 (br. s., 0.5H), 3.74 (t, J = 5.9 Hz, 2H), 3.50 - 3.61 (m, 0.5H), 3.38 (s, 3H), 3.07 - 3.24 (m, 1.5H), 2.90 - 3.06 (m, 1H), 2.65 - 2.79 (m, 1H), 2.60 (s, 3H), 2.52 - 2.63 (m, 1H), 2.17 - 2.21 (m, 1H), 1.37 (d, J = 6.5 Hz, 1.5H), 1.27 (d, J = 6.3 Hz, 1.5H), 1.09 (s, 2H), 1.05 - 1.08 (m, 2H).

Step G' was similar to Step H in **general procedure 1**.

General procedure 7:**Step H': 6-cyclopropyl-2-hydroxy-5-nitronicotinonitrile**

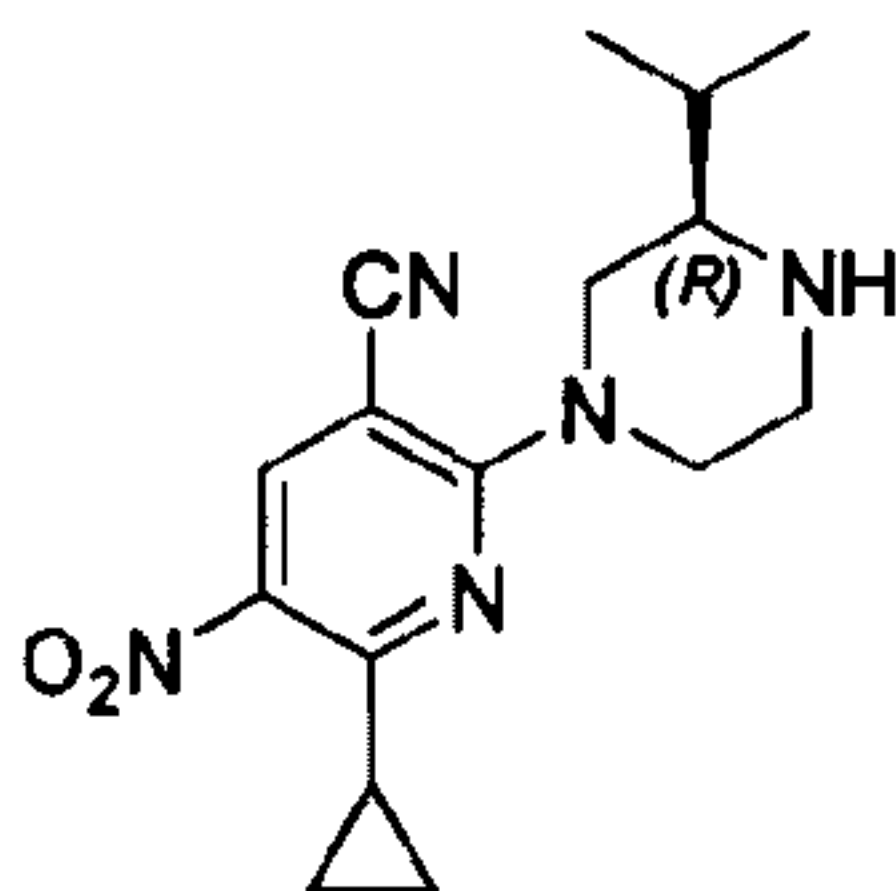
To a solution of 6-cyclopropyl-2-hydroxynicotinonitrile (20 g, 0.125 mmol) in Ac_2O (110 mL) was added dropwise HNO_3 (15 mL) at $0^\circ\text{C} \sim 40^\circ\text{C}$ for 30 mins. After the addition, the reaction mixture was stirred at r.t. for 3 hrs. The mixture was cooled to 0°C and the solid was collected by filtration. The solid was washed with brine dried under vacuum to give the title compound (15.5 g, 60.4%) as a pale yellow solid. ^1H NMR (CHLOROFORM-d) δ 10.71 (s, 1H), 8.68 (s, 1H), 3.13 (tt, $J = 8.6, 5.6$ Hz, 1H), 1.57 – 1.52 (m, 2H), 1.44 – 1.37 (m, 2H). LC-MS: m/z 205.9 ($\text{M}+\text{H}$) $^+$

Step I': 3-cyano-6-cyclopropyl-5-nitropyridin-2-yl trifluoromethanesulfonate



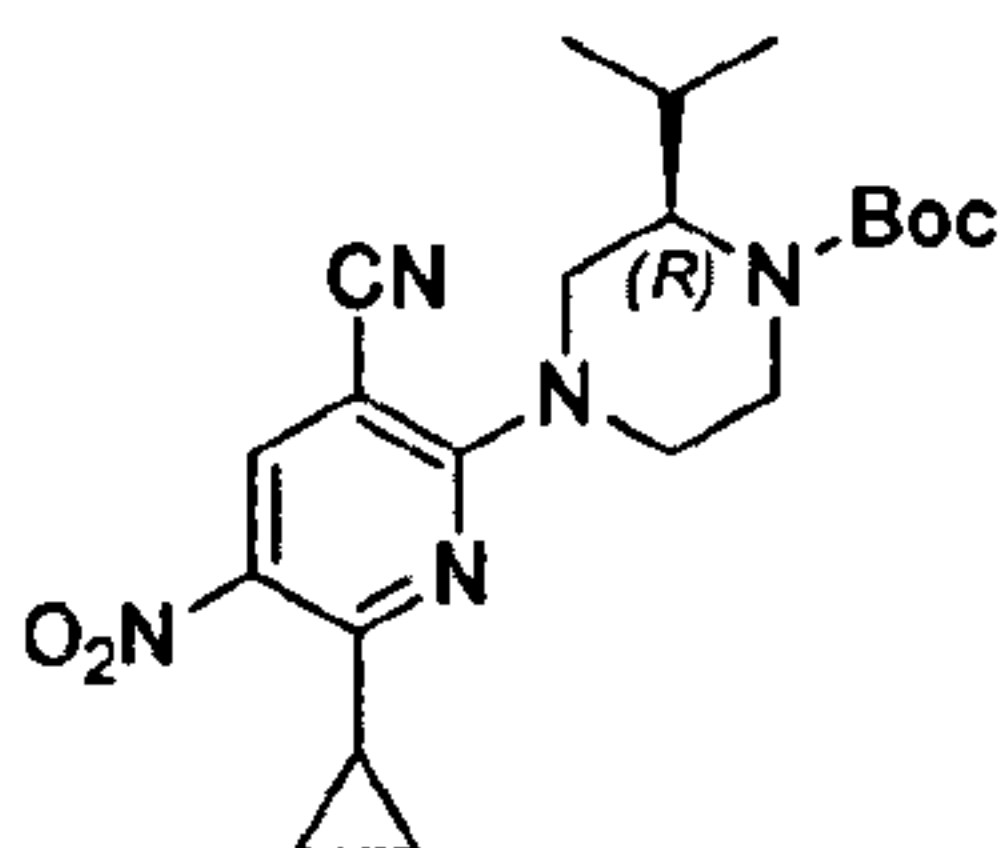
To a solution of 6-cyclopropyl-2-hydroxy-5-nitronicotinonitrile (7.6 g, 37.7 mmol) in DCM (150 mL) was added DMAP (30.0 mg) and TEA (7.5 g, 74.1 mmol) at r.t.. Then $\text{ Tf}_2\text{O}$ (15.7 g, 55.6 mmol) was added dropwise to the above solution at $-40\text{ }^{\circ}\text{C}$ for 30 min. The reaction mixture was stirred at $-40\text{ }^{\circ}\text{C}$ for 2hs. The mixture was quenched with water at $-40\text{ }^{\circ}\text{C}$. The mixture was then extracted with EtOAc (50 mL X 2). The combined organic layer was washed with brine, dried over Na_2SO_4 . The organic phase was filtered and the filtrate was concentrated in vacuum to give the title compound (12.5 g, crude) as a pale yellow solid. LC-MS: m/z 337.5 $(\text{M}+\text{H})^+$

Step J': (R)-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)-5-nitronicotinonitrile



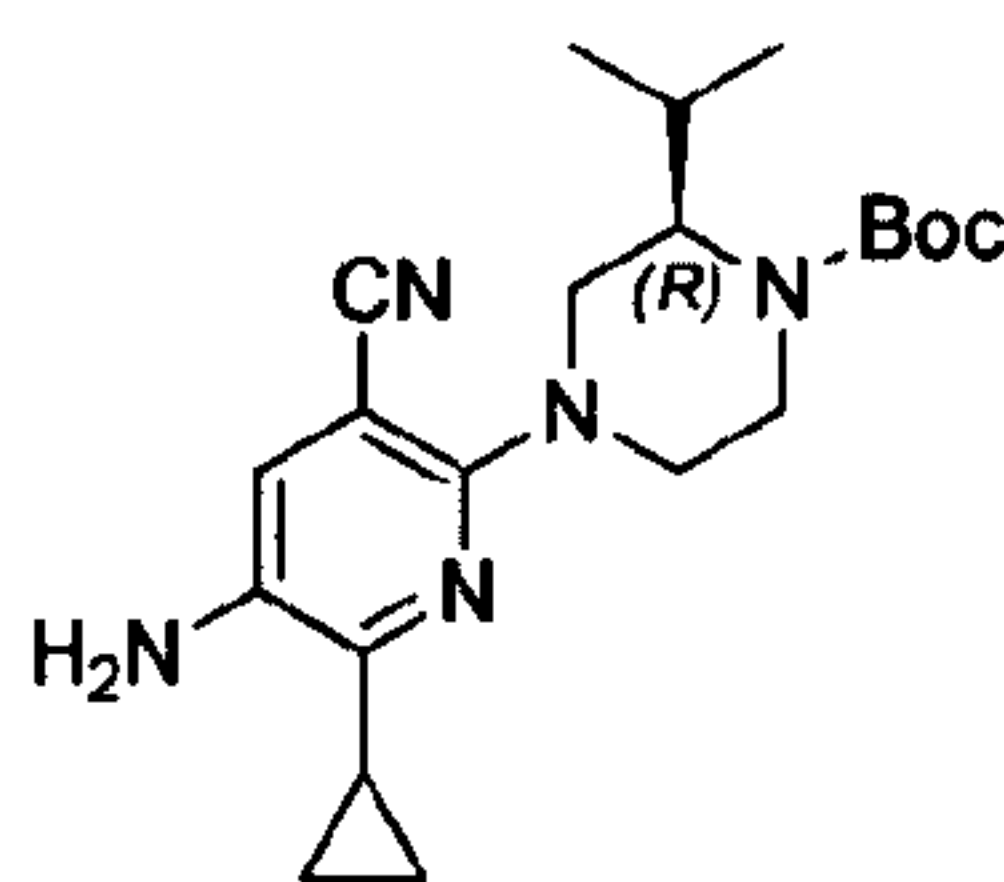
To a solution of 3-cyano-6-cyclopropyl-5-nitropyridin-2-yl trifluoromethanesulfonate (10.9 g, 32.3 mmol) and (R)-2-isopropylpiperazine (3.45 g, 27.0 mmol) in CH_3CN (100 mL) was added TEA (6.5 g, 64.7 mmol) at r.t.. The reaction mixture was heated and stirred at $85\text{ }^{\circ}\text{C}$ for 3 hrs. The mixture was concentrated *in vacuo* and the residue was extracted with EtOAc (50 mL X 2). The combined organic layer was washed with brine, dried over Na_2SO_4 . The organic phase was filtered and the filtrate was concentrated in vacuum to give the title compound (8.5 g, crude) as a brown solid. LC-MS: m/z 316.6 $(\text{M}+\text{H})^+$

Step K': (R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-nitropyridin-2-yl)-2-isopropylpiperazine-1-carboxylate



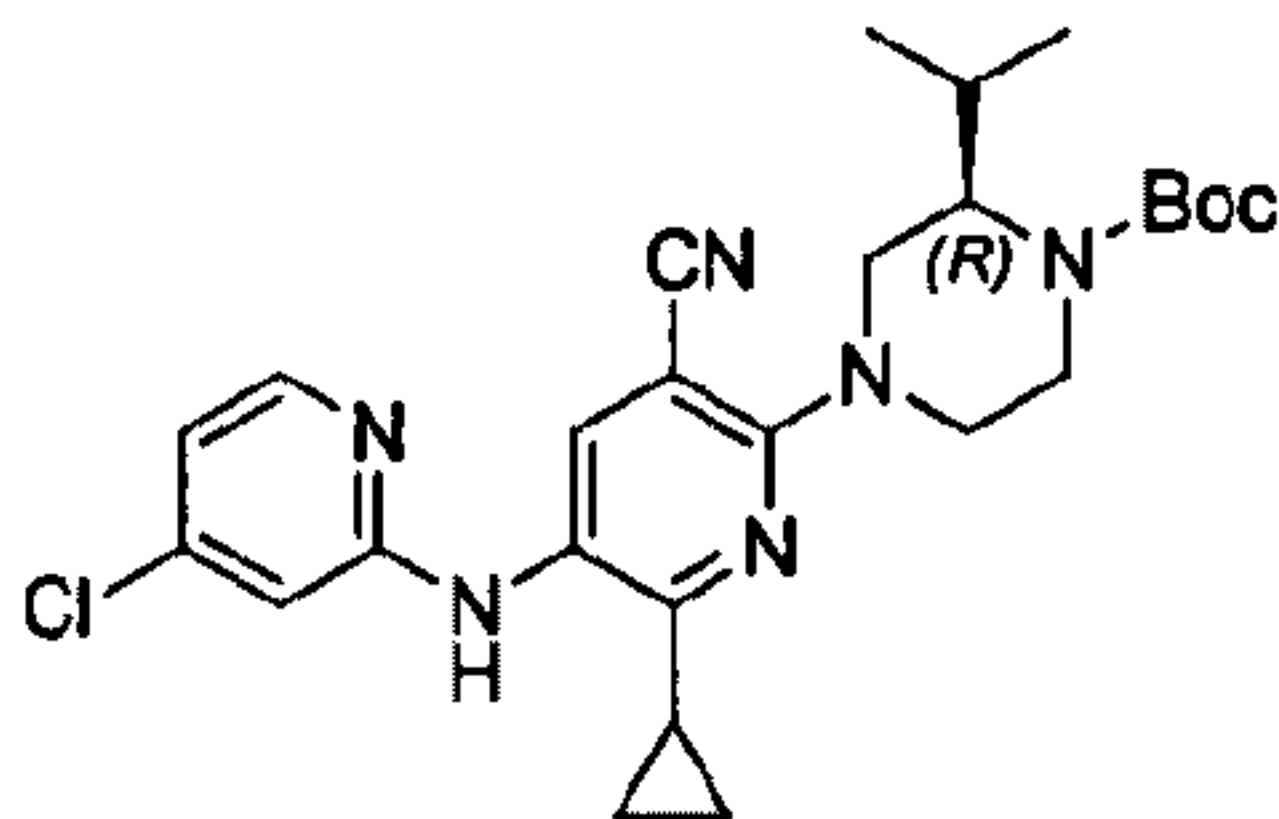
To a solution of (R)-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)-5-nitronicotinonitrile (8.52 g, 26.2 mmol) and Boc anhydride (8.5 g, 39.3 mmol) in DCM (50 mL) was added TEA (3.9 g, 39.3 mmol) at r.t.. The reaction mixture was stirred at 30 °C for 3 hrs. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM : MeOH) to afford the title compound (10.4 g, 95 %) as a yellow liquid. ¹H NMR (CHLOROFORM-d) δ 8.51 (s, 1H), 4.74 (d, J = 13.7 Hz, 1H), 4.55 (d, J = 13.1 Hz, 1H), 3.88 (s, 1H), 3.37 – 3.23 (m, 2H), 3.11 (ddd, J = 10.5, 7.7, 5.7 Hz, 2H), 1.86 (tdd, J = 13.3, 8.5, 4.9 Hz, 1H), 1.49 (s, 9H), 1.27 (d, J = 2.3 Hz, 2H), 1.26 – 1.17 (m, 4H), 1.01 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H).

Step L': (R)-tert-butyl 4-(5-amino-3-cyano-6-cyclopropylpyridin-2-yl)-2-isopropylpiperazine-1-carboxylate



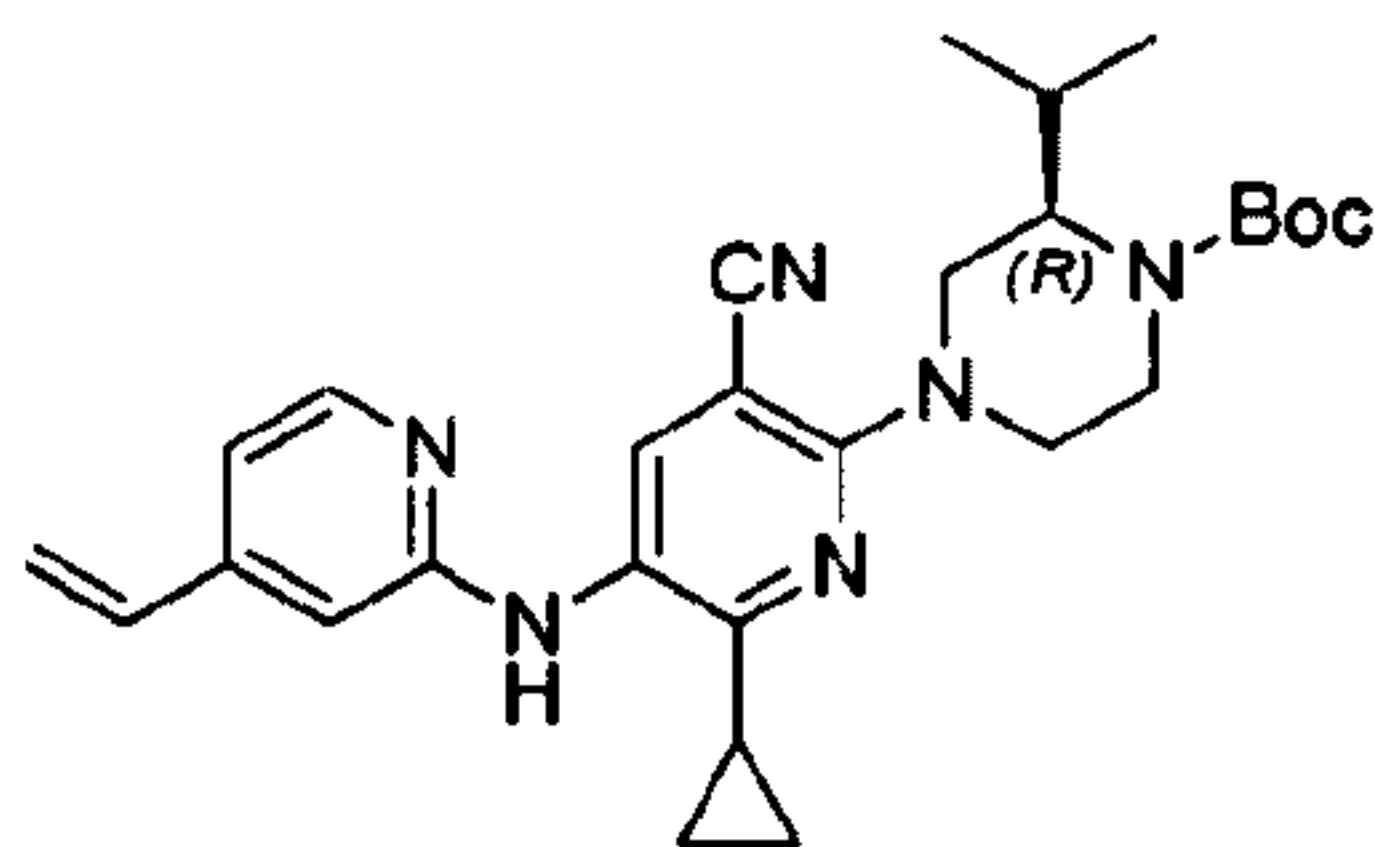
To a solution of (R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-nitropyridin-2-yl)-2-isopropylpiperazine-1-carboxylate (19 g, 45.8 mmol) in EtOH (200 mL) and H₂O (100 mL) was added Zinc (30 g, 458 mmol) and NH₄Cl (24.5 g, 458 mmol) at r.t.. The reaction mixture was stirred at 40 °C overnight. The mixture was filtered through a pad of silica and the filtrate was extracted with EtOAc (100 mL X 2). The combined organic layer was washed with brine, dried over Na₂SO₄. The organic phase was filtered and the filtrate was concentrated in vacuum to give the title compound (13.1 g, 74.3%) as a yellow solid. ¹H NMR (CHLOROFORM-d) δ: 7.10 (d, J = 2.9 Hz, 1H), 4.02 (t, J = 19.0 Hz, 3H), 3.81 (t, J = 16.8 Hz, 3H), 3.13 (td, J = 12.8, 2.4 Hz, 1H), 2.99 – 2.86 (m, 2H), 2.25 (tt, J = 12.9, 6.5 Hz, 1H), 1.97 – 1.83 (m, 1H), 1.49 (d, J = 2.2 Hz, 9H), 1.13 – 1.06 (m, 2H), 1.06 – 1.01 (m, 2H), 0.98 (t, J = 9.2 Hz, 3H), 0.87 (t, J = 6.6 Hz, 3H). LC-MS: m/z 386.6 (M+H)⁺

Step M': (R)-tert-butyl 4-(5-((4-chloropyridin-2-yl)amino)-3-cyano-6-cyclopropylpyridin-2-yl)-2-isopropylpiperazine-1-carboxylate



To a solution of (R)-tert-butyl 4-(5-amino-3-cyano-6-cyclopropylpyridin-2-yl)-2-isopropylpiperazine-1-carboxylate (600 mg, 81.6 mmol) and 2-bromo-4-chloropyridine (390.3 mg, 2.03 mmol) in 1,4-dioxane (15 mL) was added $\text{Pd}_2(\text{dba})_3$ (142.7 mg, 0.156 mmol) and Xantphos (135.3 mg, 0.234 mmol) and Cs_2CO_3 (1.02 g, 3.12 mmol) at r.t. under N_2 . The resulting mixture was heated and stirred at 115°C under N_2 in microwave for 1 h. The solvent was removed in vacuum and the residue was purified via reverse phase silica gel column chromatography (MeOH : H_2O) to afford the title compound (137 mg, 18%) as a pale yellow solid. ^1H NMR (CHLOROFORM- d) δ : 8.07 (d, $J = 5.4$ Hz, 1H), 7.72 (d, $J = 3.3$ Hz, 1H), 6.75 (dd, $J = 5.5, 1.7$ Hz, 1H), 6.39 (d, $J = 1.6$ Hz, 1H), 6.25 (s, 1H), 4.45 (d, $J = 13.2$ Hz, 1H), 4.26 (d, $J = 9.2$ Hz, 1H), 4.21 – 3.61 (m, 2.5H), 3.11 (dt, $J = 13.5, 6.8$ Hz, 2.5H), 2.22 – 1.98 (m, 2H), 1.52 – 1.47 (m, 9H), 1.28 (s, 1H), 1.14 (dt, $J = 8.1, 4.5$ Hz, 1H), 1.08 (dd, $J = 9.7, 4.7$ Hz, 1H), 1.01 (dd, $J = 10.9, 5.2$ Hz, 4H), 0.90 (d, $J = 6.8$ Hz, 3H). LC-MS: m/z 497.6 ($\text{M}+\text{H}$) $^+$

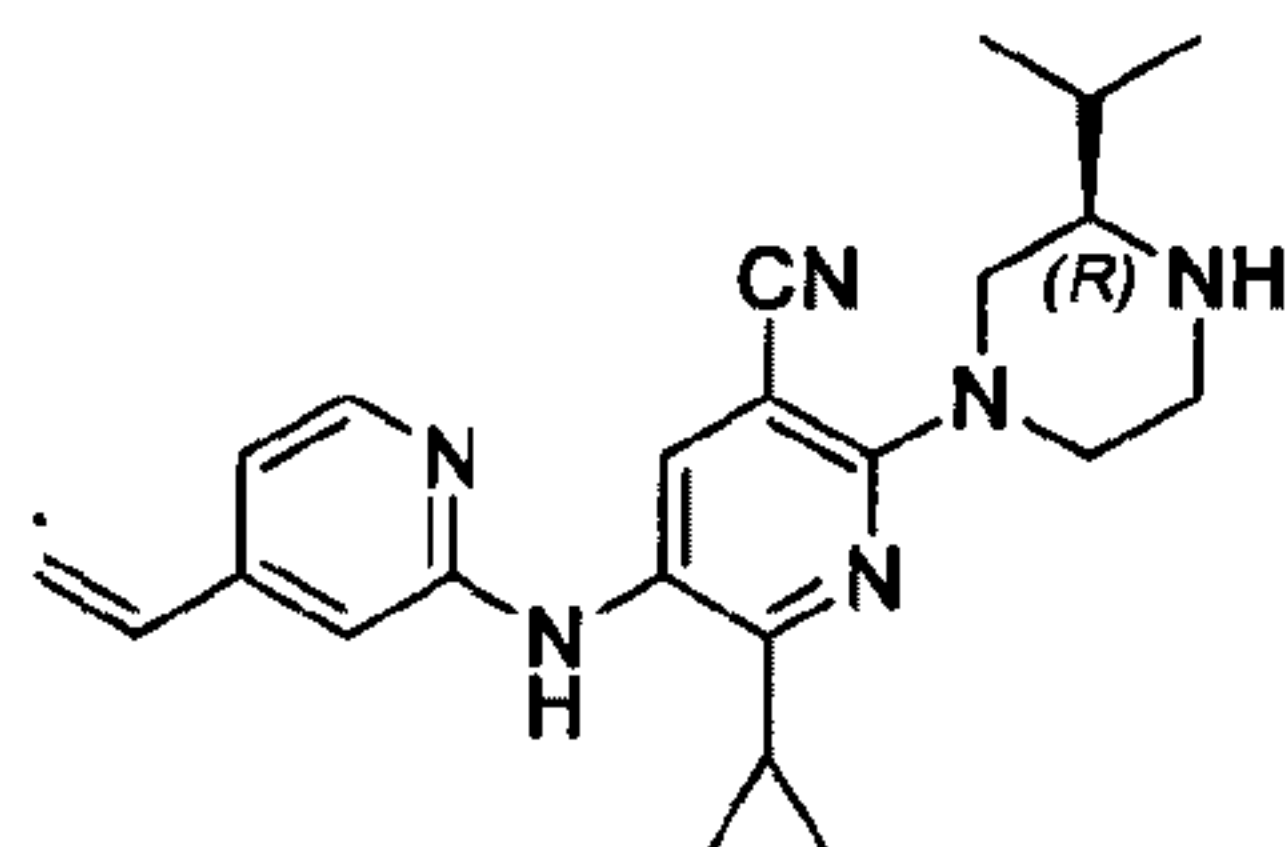
Step N $^{\circ}$: (R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-((4-vinylpyridin-2-yl)amino)pyridin-2-yl)-2-isopropylpiperazine-1-carboxylate



To a solution of (R)-tert-butyl 4-(5-((4-chloropyridin-2-yl)amino)-3-cyano-6-cyclopropylpyridin-2-yl)-2-isopropylpiperazine-1-carboxylate (600 mg, 1.21 mmol) in isopropanol (15 mL) and H_2O (3 mL) was added Vinyltrifluoroboric acid potassium salt (324.2 mg, 2.42 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (98.7 mg, 0.121 mmol) and DIPEA (312.2 mg, 2.42 mmol) at r.t. under N_2 . The reaction mixture was heated and stirred at 125°C under N_2 in microwave for 1.5 h. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM : MeOH) to afford the title compound (513 mg, 87%) as a yellow solid.

LC-MS: m/z 489.6 ($M+H$)⁺

Step O': (R)-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile



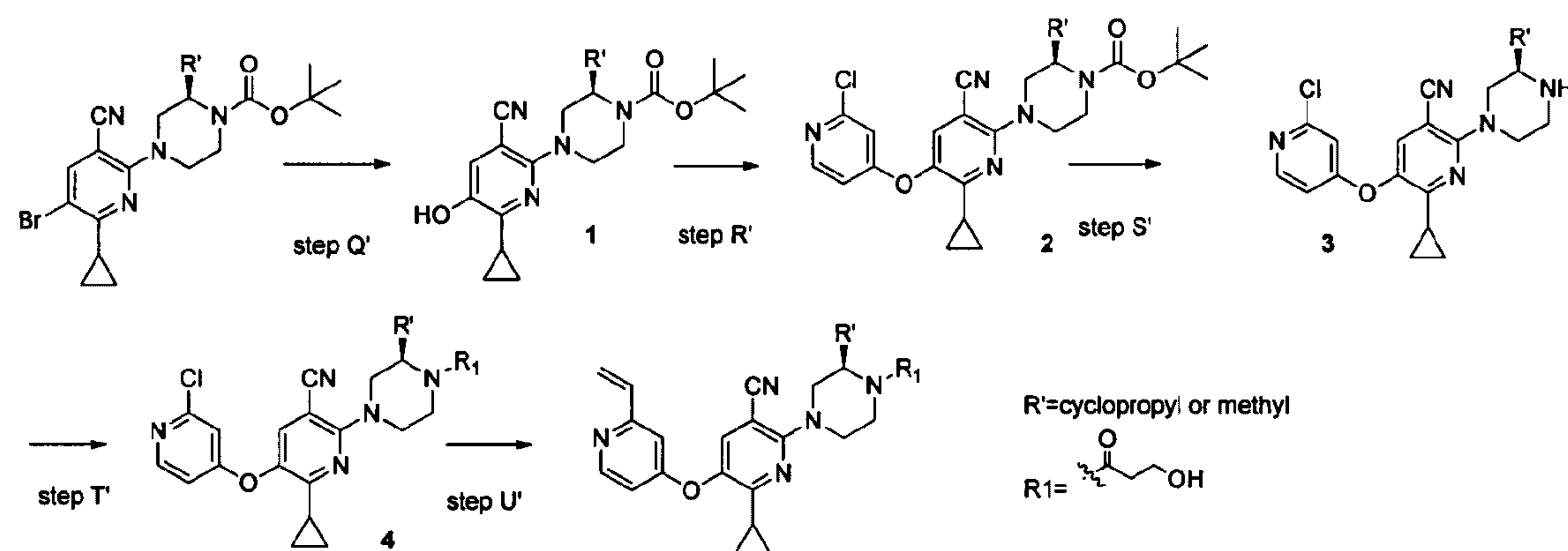
To a solution of (R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-((4-vinylpyridin-2-yl)amino)pyridin-2-yl)-2-isopropylpiperazine-1-carboxylate (513 mg, 1.05 mmol) in anhydrous DCM (10 mL) was added TFA (5 mL) at r.t. The reaction mixture was stirred at r.t. for 2hs. The solvent was removed in vacuum and the residue was adjusted to pH > 7.0. The residue mixture was extracted with EtOAc (15 mL X 2). The combined organic layer was washed with brine, dried over Na₂SO₄. The organic phase was filtered and the filtrate was concentrated in vacuum to give out the title compound (crude, 406 mg) as a yellow liquid. ¹H NMR (CHLOROFORM-d) δ : 7.99 (d, J = 6.6 Hz, 1H), 7.72 (s, 1H), 7.04 (dd, J = 6.6, 1.3 Hz, 1H), 6.64 (dd, J = 17.4, 10.8 Hz, 1H), 6.47 (s, 1H), 6.12 (d, J = 17.5 Hz, 1H), 5.81 (d, J = 10.8 Hz, 1H), 5.24 (s, 1H), 4.59 (d, J = 13.9 Hz, 1H), 4.45 (d, J = 14.3 Hz, 1H), 3.63 – 3.48 (m, 2H), 3.30 (dd, J = 14.1, 11.1 Hz, 2H), 3.18 (s, 1H), 2.15 – 2.01 (m, 2H), 1.28 (d, J = 4.8 Hz, 1H), 1.16 (dd, J = 10.2, 6.9 Hz, 8H), 1.12 – 1.09 (m, 1H). LC-MS: m/z 389.5 ($M+H$)⁺

Step P': (R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-isopropylpiperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile (**Compound 757**)

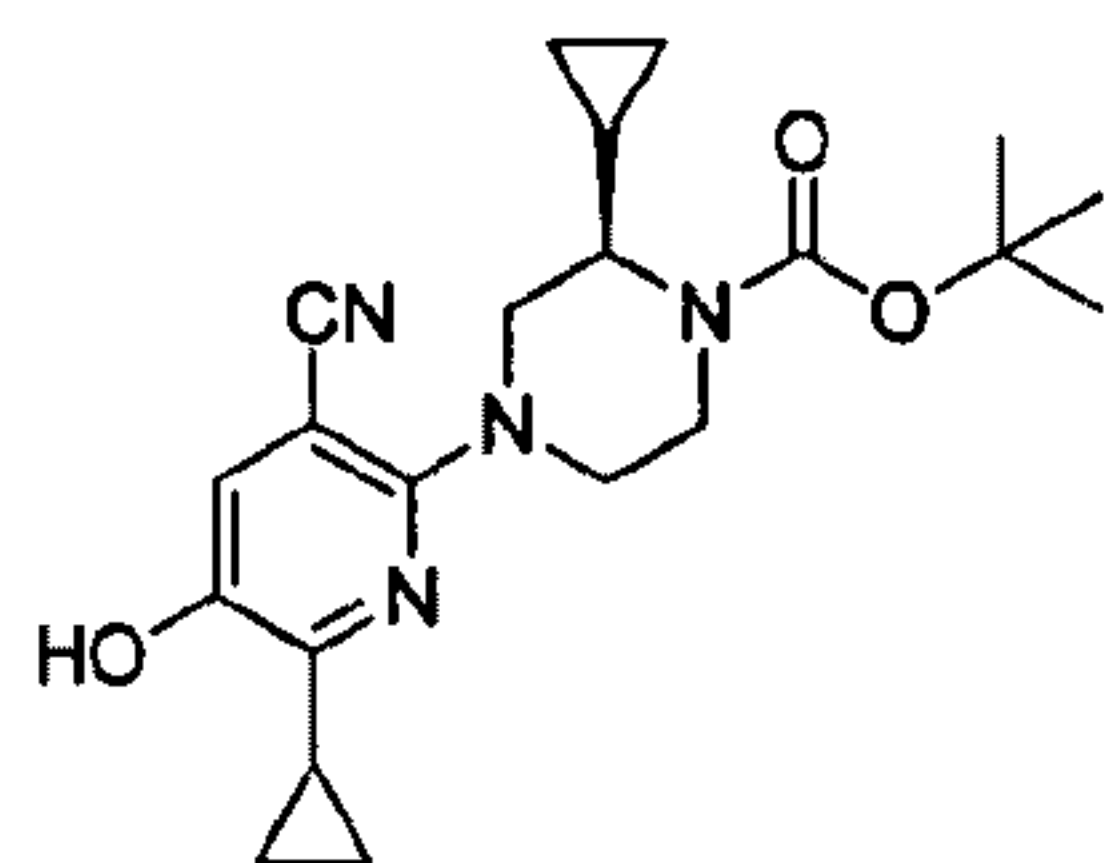
To a solution of (R)-6-cyclopropyl-2-(3-isopropylpiperazin-1-yl)-5-((4-vinylpyridin-2-yl)amino)nicotinonitrile (300 mg, 0.77 mmol) in DMF (15 mL) was added sodium 3-hydroxypropanoate (208.8 mg, 1.55 mmol), HATU (442.5 mg, 1.2 mmol) and DIPEA (200 mg, 1.55 mmol) at r.t.. The reaction mixture was stirred at r.t. for 3hs. The solvent was removed in vacuum and the residue was purified via silica gel column chromatography (DCM: MeOH) to afford the title compound (138 mg, 38.8%) as a pale yellow solid. ¹H NMR (CHLOROFORM-d) δ : 8.12 (d, J = 5.4 Hz, 1H), 7.85 (d, J = 5.5 Hz, 1H), 6.84 (d, J = 5.4 Hz, 1H), 6.59 (dd, J = 17.6, 10.8 Hz, 1H), 6.46 (s, 1H), 6.42 (s, 1H), 5.91 (d, J = 17.5 Hz, 1H), 5.48 (d, J = 10.9 Hz, 1H),

4.69 (d, $J = 10.4$ Hz, 0.5H), 4.44 (d, $J = 12.6$ Hz, 1.5H), 4.31 – 4.23 (m, 1H), 3.93 (s, 2H), 3.75 (d, $J = 13.5$ Hz, 0.5H), 3.51 – 3.38 (m, 2H), 3.14 – 2.97 (m, 2H), 2.61 (dt, $J = 5.7, 4.8$ Hz, 2H), 2.36 – 2.25 (m, 0.5H), 2.19 (ddd, $J = 12.9, 8.1, 4.9$ Hz, 1H), 1.29 (t, $J = 16.6$ Hz, 1H), 1.18 – 0.97 (m, 7H), 0.95 – 0.88 (m, 1.5H), 0.86 (d, $J = 6.8$ Hz, 1.5H). LC-MS: m/z 461.6 ($M+H$)⁺

General procedure 8

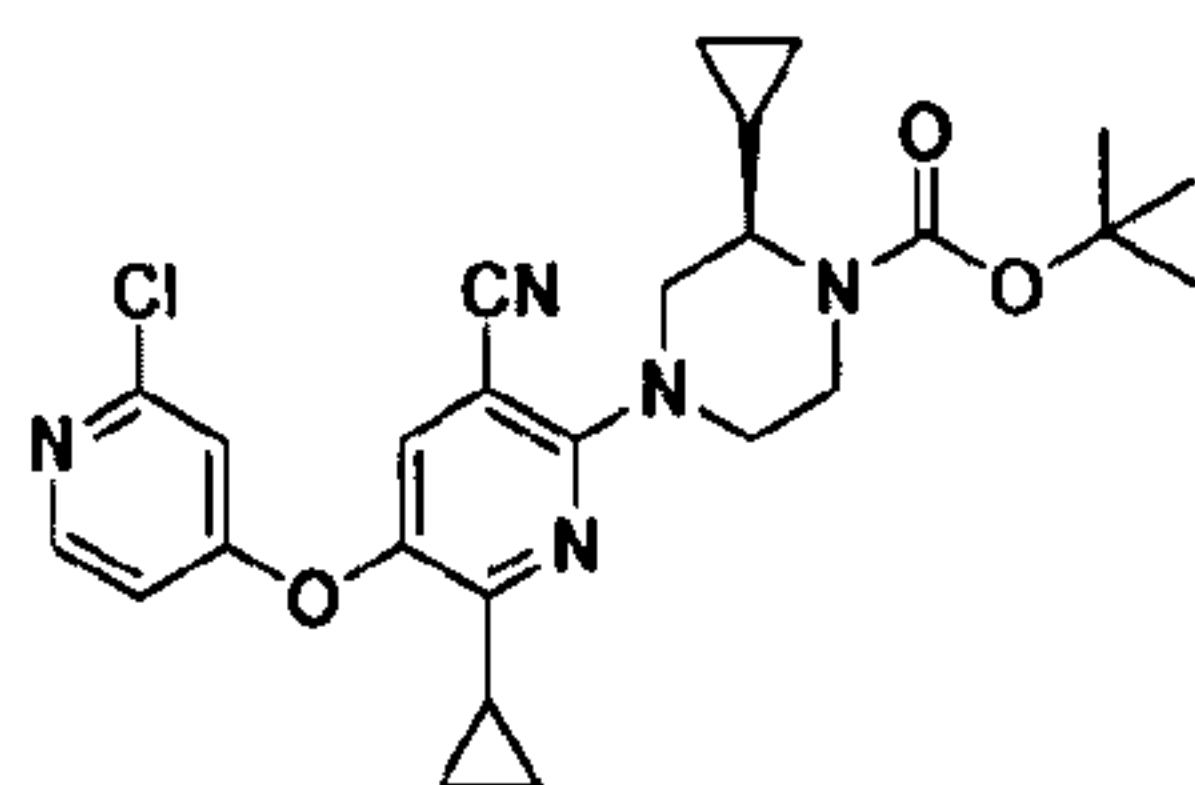


Step Q': ((R)-tert-butyl 4-(3-cyano-6-cyclopropyl-5-hydroxypyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate



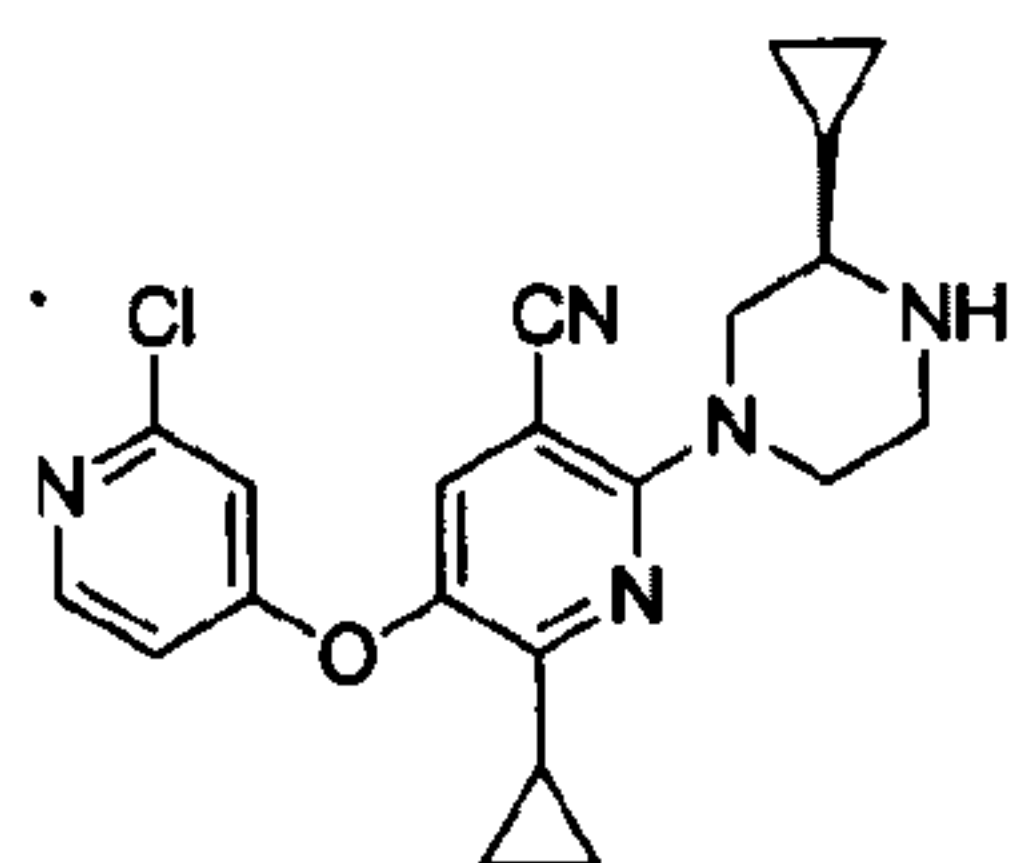
To a mixture of (R)-tert-butyl 4-(5-bromo-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (0.35 g, 1.0 mmol), potassium hydroxide (0.22 g, 4 mmol) in a 50 mL flask was added $\text{Pd}_2(\text{dba})_3$ (0.092 g, 0.1 mmol), t-Bu-Xphos (0.082g, 0.2 mol). Then 10 mL 1,4-dioxane and 1.0 mL water was added, the mixture was stirred at 80 °C for 16 hours, cooled and acidified with 2N HCl to pH 6 (temperature held below 25 °C). Then the mixture was extracted with ethyl acetate (15 mL X2), the organic phase was combined and concentrated to give brown oil, which was further purified by silica gel chromatography (PE:EA=3:1), to give 0.16 g of (**1**) as a white solid (41% yield). LC-MS: m/z 386.0 ($M+H$)⁺

Step R': (R)-tert-butyl 4-(5-(2-chloropyridin-4-yloxy)-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate



A mixture of (R)-tert-butyl 4-(5-bromo-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropyl piperazine-1-carboxylate (0.16 g, 0.41 mmol), 2-chloro-4-iodopyridine (0.15 g, 0.62 mmol), 9 mg Cu(I)Br (0.06 mmol) and 12 mg 2,2,6,6-tetramethylheptane-3,5-dione (0.06 mmol), 0.28 g Cs₂CO₃ was heated under microwave in 4 mL DMSO for 30 min. The mixture was cooled to room temperature and washed with water and purified by silica gel chromatography (DCM: MeOH = 20: 1) to give 0.10 g of (2) as a yellow solid (52% yield). LC-MS: m/z 486.0 (M+H)⁺

Step S': (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl)nicotinonitrile



A mixture of (R)-tert-butyl 4-(5-(2-chloropyridin-4-yloxy)-3-cyano-6-cyclopropylpyridin-2-yl)-2-cyclopropylpiperazine-1-carboxylate (0.10 g, 0.21 mmol) and TFA (0.35 mL) was stirred in DCM (10 mL) for 2 hrs. The solvent was removed and the residue was basified with NaHCO₃ solution and extracted with DCM (10 mL), the organic phase was separated and concentrated to give a yellow solid (3) (0.075 g, 0.19 mmol, crude yield 90%). LC-MS: m/z 397.1 (M+H)⁺

Step T': (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl) piperazin-1-yl) nicotinonitrile (**Compound 694**)

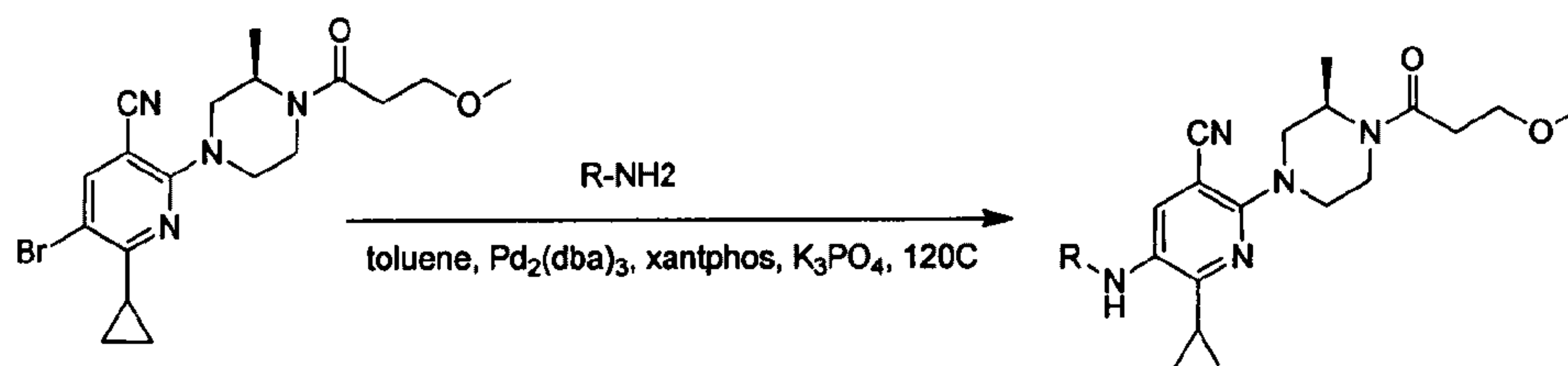
A mixture of (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropylpiperazin-1-yl) nicotinonitrile (0.35 g, 0.88 mmol), sodium 3-hydroxypropanoate (0.10 g, 0.88 mmol),

HATU (0.50 g, 1.32 mmol) and 0.23 g DIEA (1.76 mmol) was stirred in 8 mL DMF for 4 hrs. Then the mixture was quenched by adding 6 mL water and extracted with EA (15 mL X2), the organic phase was combined and concentrated to give a yellow oil, which was further purified by silica gel chromatography (DCM:MeOH = 20 : 1) to give 0.10 g of product as a yellow solid (52% yield). ¹H NMR (CHLOROFORM-d) δ: 8.30 (d, J = 5.6 Hz, 1H), 7.48-7.49 (m, 0.5H), 6.81 (dt, J = 5.6, 2.0 Hz, 2H), 4.70 (s, 1H), 4.41 (d, J = 13.0 Hz, 1H), 4.29 (d, J = 13.0 Hz, 1H), 4.12 (dd, J = 18.6, 7.4 Hz, 1H), 3.93 (s, 2H), 3.84 – 3.67 (m, 1H), 3.18 (d, J = 12.8 Hz, 1H), 3.13 – 2.99 (m, 1H), 2.61 (s, 2H), 2.32 – 2.22 (m, 0.5H), 2.02 (t, J = 4.6 Hz, 1H), 1.35 (s, 1H), 1.29 (d, J = 9.4 Hz, 3H), 1.14 (dd, J = 7.4, 3.0 Hz, 2H), 1.04 (dt, J = 7.9, 3.1 Hz, 2H), 0.66-0.67 (m, 2H), 0.46-0.51 (m, 2H). LC-MS: m/z 468.1 (M+H)⁺

Step U': (R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(2-vinylpyridin-4-yloxy)nicotinonitrile (Compound 692)

A mixture of (R)-5-(2-chloropyridin-4-yloxy)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxy propanoyl) piperazin-1-yl)nicotinonitrile (**4**) 0.35 g, (0.75 mmol), potassium trifluoro(vinyl)borate (0.15 g, 1.1 mmol), PdCl₂dppf (80 mg, 0.075 mmol) and DIEA (0.24 mL, 1.5 mmol) was heated in isopropanol at reflux at 85⁰C under nitrogen for 5 hrs. Then mixture was then concentrated under reduced pressure to give a yellow solid which was further purified by silica chromatography (PE/EA/MeOH=150/120/8) to give 0.19 g of product as a white solid (55% yield). ¹H NMR (CHLOROFORM-d) δ: 8.47 (d, J = 5.6 Hz, 1H), 7.48 -7.49(m, 0.5 H), 6.86 (d, J = 2.3 Hz, 1H), 6.77 (dd, J = 17.4, 10.8 Hz, 1H), 6.66 (dd, J = 5.6, 2.4 Hz, 1H), 6.22 (dd, J = 17.4, 0.9 Hz, 1H), 5.53 (dd, J = 10.8, 0.8 Hz, 1H), 4.68 (d, J = 11.7 Hz, 1H), 4.38 (d, J = 12.9 Hz, 1H), 4.30 – 4.22 (m, 1H), 4.15 – 4.04 (m, 1H), 3.92 (s, 2H), 3.75 (d, J = 20.7 Hz, 1H), 3.47 (d, J = 21.7 Hz, 1H), 3.25 – 3.12 (m, 1H), 3.09 – 2.95 (m, 1H), 2.60 (s, 2H), 2.32 – 2.22 (m, 0.5 H), 2.11 – 2.05 (m, 1H), 1.37 (d, J = 20.5 Hz, 1H), 1.27 (d, J = 2.0 Hz, 1H), 1.16 – 1.10 (m, 2H), 1.01 (ddd, J = 10.1, 6.7, 3.3 Hz, 2H), 0.65 (t, J = 33.7 Hz, 2H), 0.45-0.48 (m, 2H). LC-MS: m/z 460.1 (M+H)⁺

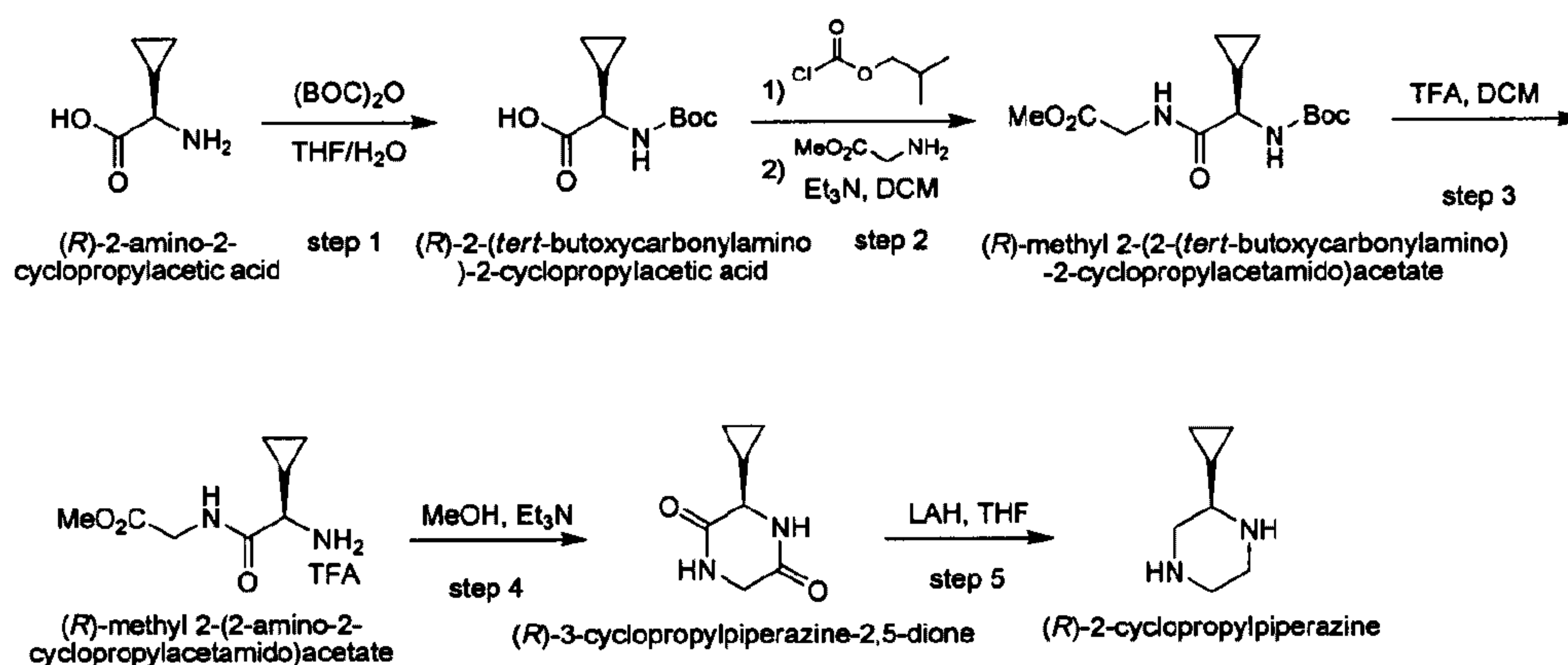
General Procedure 9:



Core 7-1 (120 mg, 0.295 mmol) and amine (0.295 mmol) were dissolved in toluene (2 mL). K₃PO₄ (125.0 mg, 0.590 mmol), Xantphos (cat.) and Pd₂(dba)₃(cat.) were added to above mixture under N₂. The mixture was shaken at 120°C for 16 hrs. The crude product was purified by prep-HPLC.

EXAMPLE 15: Building Blocks Syntheses

Building block 1: (*R*)-2-cyclopropylpiperazine:



Step 1: To a solution of (*R*)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-vinylquinazolin-5-yl)nicotinonitrile (100 g, 0.87 mol) in water (1250 ml), NaHCO₃ (175 g, 2.08 mol) was added at room temperature, then a solution of (Boc)₂O in THF (1250 mL) was added and the reaction mixture was heated to reflux overnight. Then the resulting mixture was concentrated to remove THF under reduced pressure. EtOAc (1250 mL) was added to the residue and the resulting mixture was cooled to 5°C and then adjusted to pH 3 with saturated aqueous NaHSO₄. The layers were separated and the aqueous was extracted with EtOAc (1000 mL x 3). The combined EtOAc layers were washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure to give (*R*)-2-(tert-butoxycarbonylamino)-2-

cyclopropylacetic acid (165 g, yield 88 %). ¹H NMR (MeOD 400MHz) δ 3.16-3.14 (d, J=8.8, 1H), 1.11 (s, 9H), 0.73-0.78 (m, 1H), 0.28-0.2 (m, 3H), 0.18-0.15 (m, 1H) 100 ee%.

Step 2: Isobutyl chloroformate (81.6 g, 0.6 mol) was added over 1 hr to a stirred mixture of (R)-2-(tert-butoxycarbonylamino)-2-cyclopropylacetic acid (129 g, 0.6 mol) and Et₃N (67 g, 0.66 mol) in DCM (1000 mL) at 0°C - 5°C and the reaction mixture was stirred 1 hr at 0°C - 5°C. In a separate flask, a mixture of glycine methyl ester hydrochloride (82.8 g, 0.66 mol), Et₃N (73 g, 0.72 mol) and DCM (1000 mL) was stirred for 1 hr and the mixture was then added to the flask over 2 hrs. After the addition was complete, the mixture was stirred overnight at room temperature for 40 hrs and then washed with water and brine, dried with Na₂SO₄, concentrated under reduced pressure and the residue was purified by column chromatography to give (R)-methyl 2-(2-(tert-butoxycarbonylamino)-2-cyclopropyl acetamido)acetate (100 g, yield 58 %) as white solid. 100ee%. ¹H NMR (DMSO 400MHz) δ 8.2-8.16 (t, J=5.6, 1H), 6.66-6.86 (d, J=8.8, 9H), 3.71-3.92 (m, 2H), 3.62 (s, 3H), 3.46-3.51 (t, J=8.4, 1H), 1.36 (s, 9H), 0.97-1.01 (m, 1H), 0.38-0.44 (m, 3H), 0.25-0.28 (m, 1H).

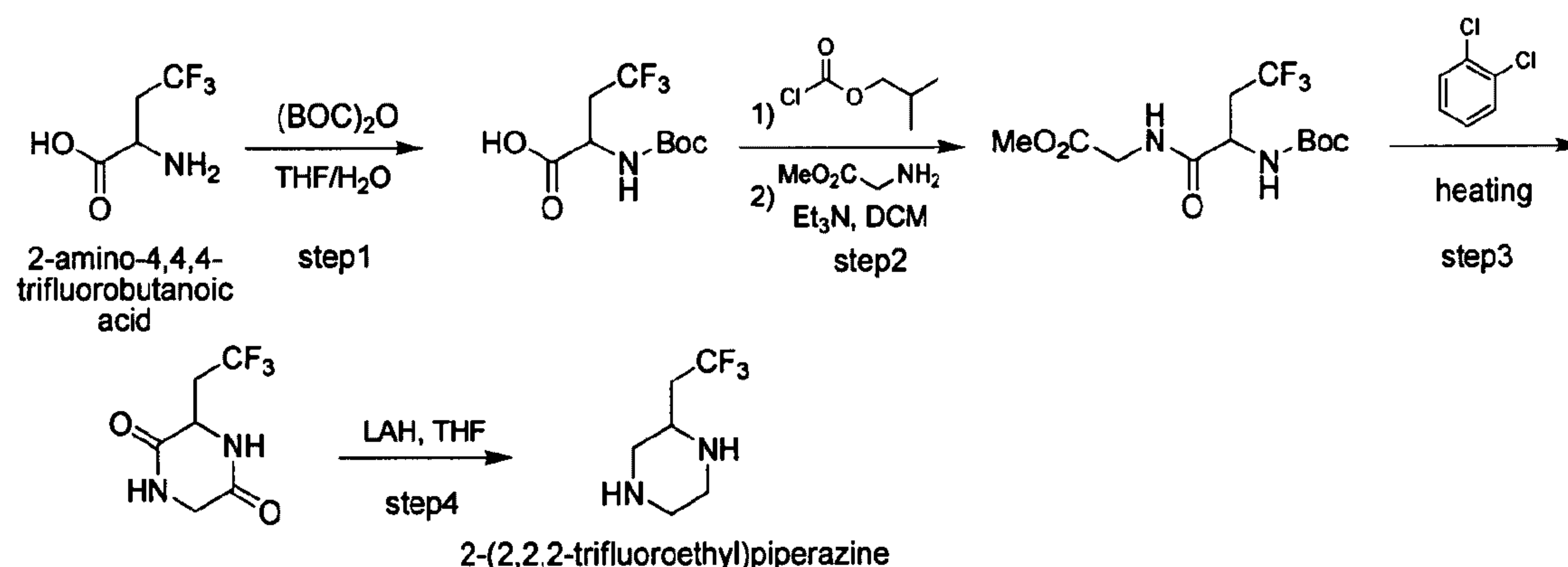
Step 3: To a solution of (R)-methyl 2-(2-(tert-butoxycarbonylamino)-2-cyclopropylacetamido)acetate (290 g, 1.014 mol) in DCM (1740 mL), TFA (870 mL) was added dropwise at 0°C. The reaction solution was stirred overnight at room temperature. The resulting solution was concentrated under reduced pressure to give (R)-methyl 2-(2-amino-2-cyclopropylacetamido)acetate (511 g crude).

Step 4: To a solution (R)-methyl 2-(2-amino-2-cyclopropylacetamido)acetate (255.5 g crude, 0.507 mol) in MeOH (1250 mL), Et₃N (750 mL, 10.78 mol) was added dropwise at 0°C. Then the reaction solution was stirred two days at room temperature. The resulting mixture was filtered and the precipitate was washed with MTBE and dried by high vacuum to give (R)-3-cyclopropylpiperazine-2,5-dione (60 g, yield 76.9 %). ¹H NMR (DMSO 400MHz) δ 7.98 (s, 1H), 7.74 (s, 1H), 3.68-6.64 (d, J=17.6, 1H), 3.30-3.36 (m, 1H), 2.9-2.93 (dd, J=3.2, 1H), 0.87-0.92 (m, 1H), 0.21-0.27 (m, 3H), 0.18-0.21 (m, 1H).

Step 5: To a suspension mixture of (R)-3-cyclopropylpiperazine-2,5-dione (30 g, 0.195 mmol) in THF (1000 mL), AlLiH₄ (45g, 1.184 mol) was added in portions over 1.5 hrs at 0°C. Then the reaction mixture was heated to 70°C overnight. After cooling, water (45 mL) was added dropwise at 0°C and then a solution of KOH (45 mL, 1%) was added dropwise at 0°C. The

resulting mixture was filtered and the residue was washed with EtOAc and MeOH (3:1) and the filtrate was concentrated under reduced pressure to give crude product. Then the crude product was washed with DCM and the filtrate was concentrated under reduced pressure to give (R)-2-cyclopropylpiperazine (18.5 g, yield 75.5 %). 99.5 ee%. ^1H NMR (MeOD 400MHz) δ 2.9-2.96 (m, 1H), 2.8-2.88 (m, 1H), 2.7-2.8(m, 1H), 2.55-2.68 (m, 2H), 2.4-2.5 (q, J=10.4, 1H), 1.65-1.73 (m, 1H), 0.55-0.67 (m, 1H), 0.35-0.45 (m, 2H), 0.05-0.25 (m, 2H).

Building block 2: 2-(2,2,2-trifluoroethyl)piperazine



Step 1: To a solution of 2-amino-4,4,4-trifluorobutanoic acid (450 mg, 3 mmol) in 5 mL H_2O and 5 mL THF was added NaHCO_3 (504 mg, 6 mmol), followed by a solution of di-tert-butyl dicarbonate (650 mg, 3 mmol) in THF (3 mL). The resulting mixture was stirred at 80°C overnight. After removal of THF, poured into water and extracted with methylene chloride. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. 723 mg of 2-(tert-butoxycarbonylamino)-4,4,4-trifluorobutanoic acid was obtained as a crude product and used in subsequent reaction without further purification. MS (ES) $\text{M}+\text{H}$ expected 258, found 258. ^1H NMR (CHLOROFORM-d) δ 5.25 (d, J = 7.8 Hz, 1H), 4.40 - 4.67 (m, 1H), 2.60 - 2.90 (m, 2H), 1.46 (s, 9H).

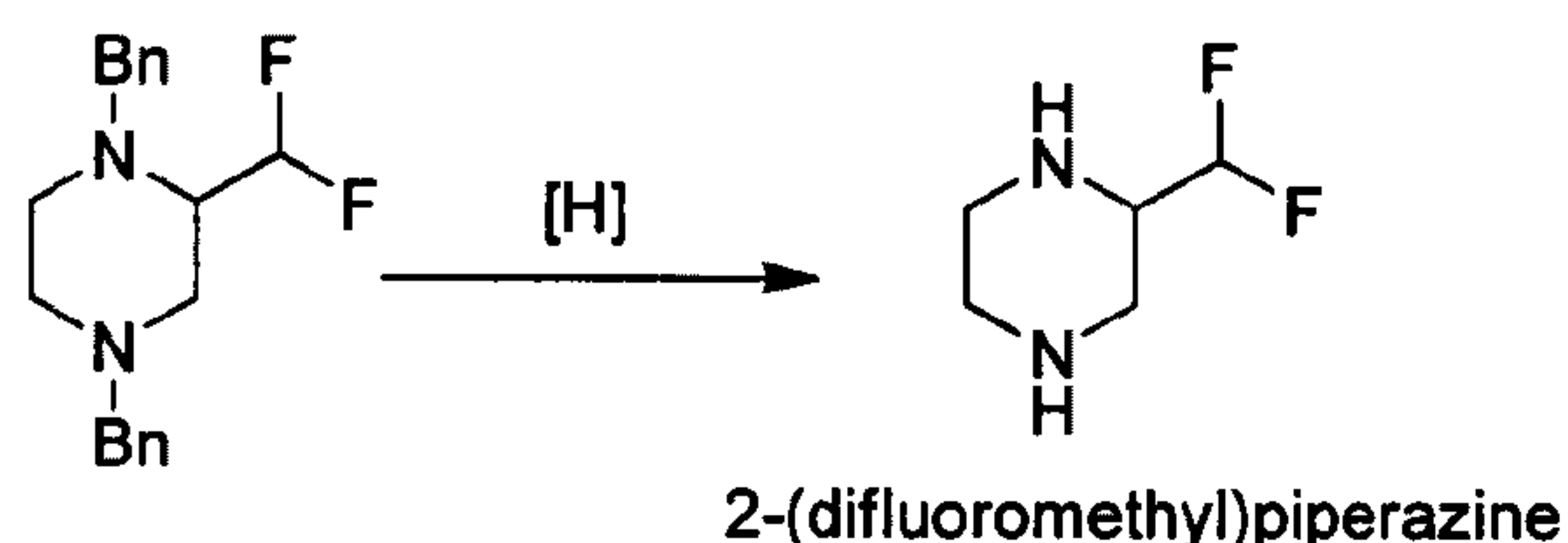
Step 2: To a 25 mL of round-bottom flask was added 2-(tert-butoxycarbonylamino)-4,4,4-trifluorobutanoic acid (723 mg, 2.8 mmol), Et_3N (560 mg, 5.6 mmol), isobutyl chloroformate (380 mg, 2.8 mmol) in 5 mL methylene chloride. The resulting reaction mixture was stirred at 0°C for 0.5 hours. And methyl 2-aminoacetate (352 mg, 2.8 mmol) was added. The resulting mixture

was stirred at room temperature overnight. After washing with Satd. NaHCO_3 , brine, the combined organic layer was dried over anhy. Na_2SO_4 and concentrated *in vacuo*. 900 mg of methyl 2-(2-(tert-butoxycarbonylamino)-4,4,4-trifluorobutanamido)acetate was obtained as a crude product and used in subsequent reaction without further purification. MS (ES) $M+H$ expected 329.1, found 329.0. ^1H NMR (CHLOROFORM-d) δ 7.11 (br. s., 1H), 5.28 (br. s., 1H), 4.44 - 4.67 (m, 1H), 3.84 - 4.07 (m, 2H), 3.69 - 3.83 (s, 3H), 2.72 - 2.95 (m, 1H), 2.42 - 2.64 (m, 1H), 1.38 - 1.50 (m, 9H).

Step 3: A mixture of methyl 2-(2-(tert-butoxycarbonylamino)-4,4,4-trifluorobutanamido)acetate (900 mg, 2.7 mmol) in 5 mL 1,2-dichlorobenzene was heated to 180°C overnight. The mixture was cooled down and was added MTBE (5 mL). A brown yellowish precipitate was formed. The filter cake was washed with MTBE and air-dried to give 200 mg of 3-(2,2,2-trifluoroethyl)piperazine-2,5-dione. ^1H NMR (DMSO-d_6) δ 8.28 (d, $J = 9.3$ Hz, 2H), 4.00 - 4.26 (m, 1H), 3.68 - 3.87 (m, 2H), 2.66 - 2.88 (m, 2H).

Step 4: To a flask was added 3-(2,2,2-trifluoroethyl)piperazine-2,5-dione (200 mg, 1 mmol) in THF (5 mL), and LAH (2.5 mL, 6 mmol) was added dropwise under N_2 at 0°C . And the mixture was heated to 65°C overnight. After reaction, the mixture was cooled down. And 0.23 mL H_2O was added followed by 0.2x3 mL 10% NaOH and 0.46 mL H_2O , and the mixture was filtered. The cake washed with EtOAc. The organic phase was concentrated to give 2-(2,2,2-trifluoroethyl)piperazine 140 mg, which was used without further purification. ^1H NMR (CHLOROFORM-d) δ 2.75 - 3.02 (m, 7H), 2.52 (dd, $J = 11.7, 9.9$ Hz, 1H), 2.10 - 2.17 (m, 2H).

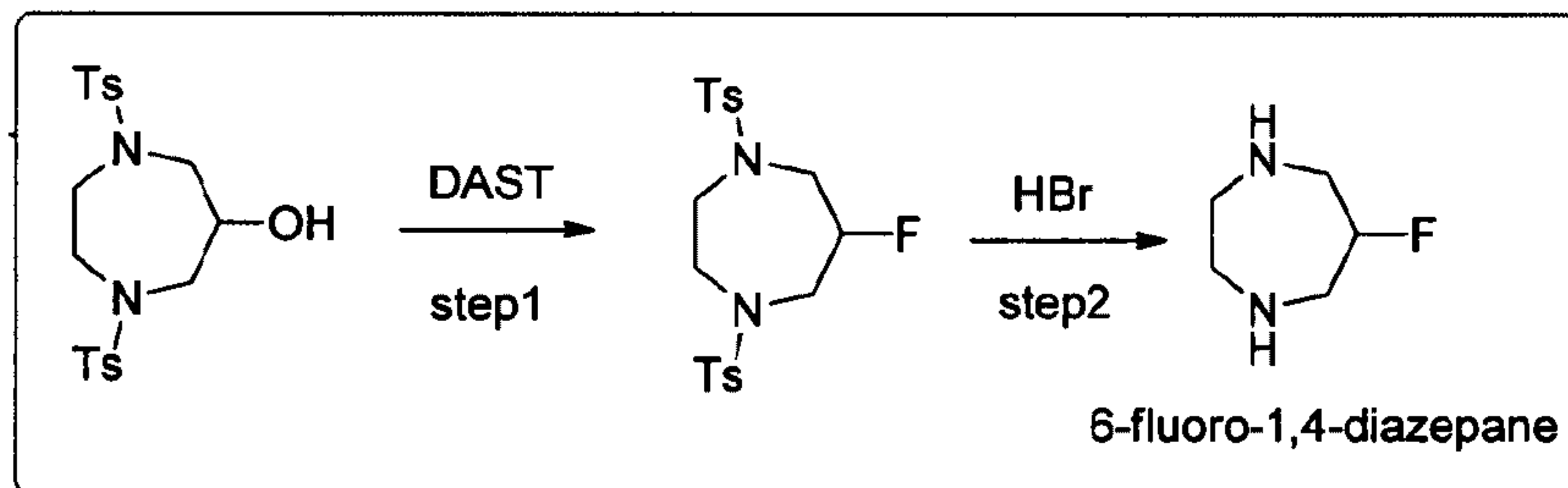
Building block 3: 2-(difluoromethyl)piperazine



To a solution of 1,4-dibenzyl-2-(difluoromethyl)piperazine (synthesized according to *Synthetic Communications*, 2011, vol. 41, # 14, 2031 - 2035) (80 mg, 0.253 mmol) in 40 mL of EtOH was added $\text{Pd}(\text{OH})_2/\text{C}$ (15 mg). The resulting mixture was hydrogenated under 50 Psi at r.t. for

two days. The reaction mixture was filtered, and the filtrate was concentrated to afford 2-(difluoromethyl)piperazine, which was used directly without further purification. LC-MS: m/z 137.1 (M+H)⁺

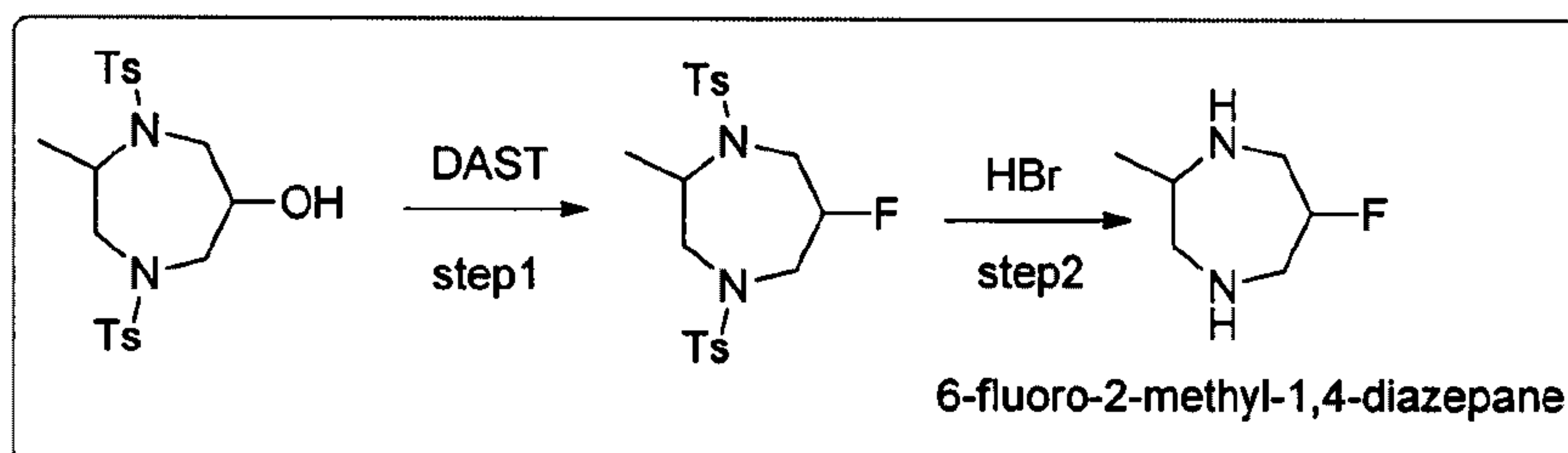
Building block 4: 6-fluoro-1,4-diazepane



Step 1: To a solution of 1,4-ditosyl-1,4-diazepan-6-ol (synthesized according to *Synthesis*, 2003, 2, 223 - 226) (200 mg, 0.47 mmol) in 5 mL of DCM was added DAST (190 mg, 1.18 mmol). The resulting mixture was stirred at r.t. overnight. The reaction mixture was quenched with aq NaHCO₃. The aqueous layer was extracted with DCM and the combined organic phases were dried and concentrated. The residue was purified by prep-TLC to afford 6-fluoro-1,4-ditosyl-1,4-diazepane (120 mg). ¹H NMR (CHLOROFORM-d) δ 7.66 - 7.71 (m, 4H), 7.34 (d, J = 8.0 Hz, 4H), 5.02-4.92 (m, 1H), 3.60 (dd, J = 18.1, 5.3 Hz, 4H), 3.34 - 3.53 (m, 4H), 2.46 (s, 6H).

Step 2: A suspension of 6-fluoro-1,4-ditosyl-1,4-diazepane (82 mg, 0.19 mmol) in HOAc-HBr (3 mL, 30 wt%) was heated to 100 °C for 3 mins in a pressure tube using microwave irradiation. The solvent was removed in vacuum and the residue triturated with Et₂O, washed with Et₂O to give 6-fluoro-1,4-diazepane, which was used directly without further purification. LC-MS: m/z 119.1 (M+H)⁺

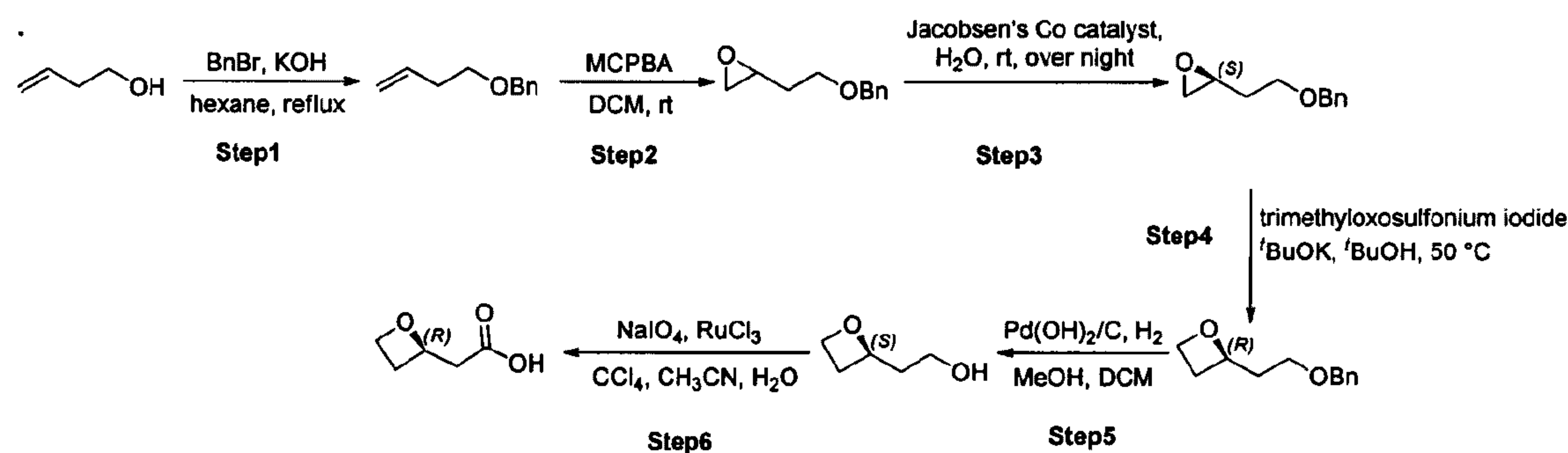
Building block 5: 6-fluoro-2-methyl-1,4-diazepane



Step 1: 6-fluoro-2-methyl-1,4-ditosyl-1,4-diazepane (120 mg) was obtained from 2-methyl-1,4-ditosyl-1,4-diazepan-6-ol (synthesized according to *Synthesis*, 2003, 2, 223 – 226) (200 mg, 0.47 mmol) (200 mg) by the method similar to 6-fluoro-1,4-ditosyl-1,4-diazepane. ^1H NMR (CHLOROFORM- d) δ 7.62 - 7.75 (m, 4H), 7.30 - 7.37 (m, 4H), 5.00-4.84(m, 1H), 4.09 - 4.37 (m, 2H), 3.73 - 3.95 (m, 1H), 3.37 - 3.62 (m, 2H), 3.12 - 3.32 (m, 1H), 3.05 (ddd, $J = 13.6, 7.2, 4.0$ Hz, 1H), 2.43 - 2.46 (m, 6H), 1.05 - 1.14 (m, 3H).

Step 2: 6-fluoro-2-methyl-1,4-diazepane was obtained from 6-fluoro-2-methyl-1,4-ditosyl-1,4-diazepane by the method similar to 6-fluoro-1,4-ditosyl-1,4-diazepane. LC-MS: m/z 133.1 (M+H) $^+$

Building block 6: 2-(oxetan-2-yl)acetic acid



Step 1: A mixture of 3-buten-1-ol (18.03 g, 0.25 mol), TEA (2.4 mL, 0.02 mol) and sodium hydroxide (15 g, 0.38 mol) in hexane (200 mL) was stirred at 50 °C for 0.5 h. Benzyl bromide (32.7 mL, 0.27 mol) in hexane (50 mL) was added dropwise over a period of 0.5 h. Afterwards, the resulting mixture was heated to reflux overnight (oil temperature: 85 °C). The precipitate was removed via filtration and washed with ethyl acetate twice. The combined organic phase was washed with brine and dried over sodium sulfate. Such obtained product was pure enough for the next reaction step. Yield: 38.21 g, 94.2%, colorless oil. ^1H NMR (400 MHz, CDCl_3) δ 7.46-7.29

(m, 6H), 5.89 (ddt, $J = 17.0, 10.1, 6.7$ Hz, 1H), 5.21 - 5.03 (m, 2H), 4.56 (s, 2H), 3.57 (t, $J = 6.8$ Hz, 2H), 2.43 (qd, $J = 6.7, 1.1$ Hz, 2H).

Step 2: To solution of ((but-3-en-1-yloxy)methyl)benzene (38.21 g, 0.24 mol) in dichloromethane (400 mL) was added mCPBA (77.15 g, 0.38 mol) at -20 °C as solid in portions. Afterwards, the resulting suspension was allowed to warm to rt and stirred overnight. The precipitate was filtered off and washed with dichloromethane. Afterwards, the combined organic phase was washed with saturated NaHCO₃ and Na₂SO₃ and brine. The white precipitate was occurred while removing solvents under reduced pressure. More n-hexane was added and the most appeared white solid was filtered off. This procedure was repeated third times. The crude product was subjected to column chromatography on silica gel using a mixture of ethyl acetate with petroleum ether as eluent (EtOAc:PE=1/50 to 1/5) to afford the title compound. Yield: 35.26 g, 84.0%, pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.29 (m, 5H), 4.56 (s, 2H), 3.73 - 3.59 (m, 2H), 3.15 - 3.06 (m, 1H), 2.85 - 2.77 (m, 1H), 2.55 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.95 (dddd, $J = 13.4, 7.2, 6.2, 4.7$ Hz, 1H), 1.81 (dq, $J = 14.3, 5.9$ Hz, 1H). LC-MS: m/z 220.0 (M+CH₃CN)⁺.

Step 3: To a round bottom flask charged with HOAc (60.1 mg, 1.0 mol%) in toluene (20 mL) was added Jacobsen salen Co(II) catalyst (0.30 g, 0.5 mol%) at rt and the resulting solution was stirred at rt for 0.5 h while the flask is open to air in order to absorb oxygen. The volatiles were removed under reduced pressure to give rise to a dark solid. Racemic epoxide (17.82 g, 100 mmol) was added neat, followed by the addition of distilled water (1.0 mL, 56 mmol) dropwise at 0 °C. The resulting reaction mixture was allowed to warm to rt slowly and stirred at rt overnight. The reaction mixture was diluted with n-hexane and then passed through a pad of celite. Epoxide was obtained by using petroleum ether and diol was obtained by using a mixture of methanol with dichloromethane (1/30). The obtained epoxide (red oil) was distilled and the desired product was obtained at 145-165°C (oil temperature); similarly, the diol was obtained at 185-205°C (oil temperature). Yield of epoxide: 7.83 g, 43.9%, pale yellow oil; Yield of diol: 8.46 g, 43.1%, bright yellow oil. For chiral epoxide: ¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.29 (m, 5H), 4.56 (s, 2H), 3.73 - 3.59 (m, 2H), 3.15-3.06 (m, 1H), 2.85 - 2.77 (m, 1H), 2.55 (dd, $J = 5.0, 2.7$ Hz, 1H), 1.95 (dddd, $J = 13.4, 7.2, 6.2, 4.7$ Hz, 1H), 1.81 (dq, $J = 14.3, 5.9$ Hz, 1H). LC-MS: m/z 220.0 (M+CH₃CN)⁺. For chiral diol: ¹H NMR (400 MHz, CDCl₃) δ 7.41 - 7.29 (m,

5H), 4.53 (s, 2H), 3.94 (s, 1H), 3.86 - 3.41 (m, 5H), 3.18 (s, 1H), 1.91 - 1.66 (m, 2H). LC-MS: m/z 219.0 ($M+Na$)⁺. ee>99%.

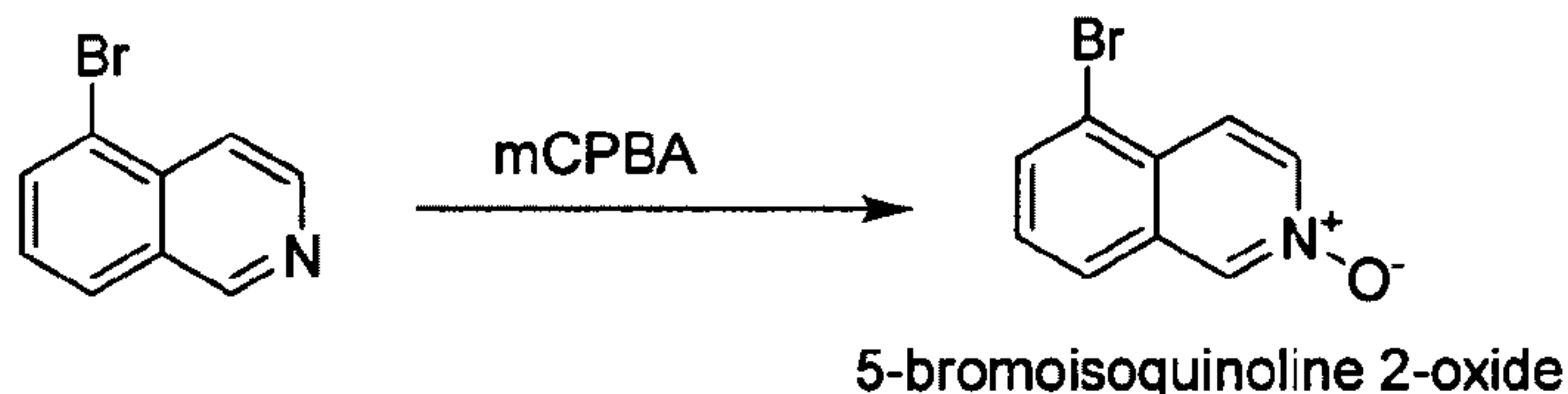
Step 4: A mixture of potassium tert-butoxide (1.68 g, 15 mmol) and trimethyloxosulphonium iodide (3.30 g, 15 mmol) in tert-butoxide (35 mL) was stirred at 50 °C for 1 h. A solution of chiral epoxide (0.89 g, 5 mmol) in tert-butoxide (15 mL) was added dropwise while keeping the temperature around 50 °C. Afterwards, the resulting reaction mixture was stirred at 50 °C overnight. The precipitate was removed via filtration and washed with ethyl acetate. The combined organic phase was dried under reduced pressure and diluted with ethyl acetate. The diluted solution was washed with brine and dried over sodium sulfate. The crude product was subjected to column chromatography on silica gel using EtOAc:PE = 1/10 as eluent to afford the title compound. Yield: 0.55 g, 57.7%; colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.29 (m, 5H), 5.09-4.94 (m, 1H), 4.70 (dd, J = 14.0, 7.8 Hz, 1H), 4.62-4.38 (m, 3H), 3.67-3.51 (m, 2H), 2.72 (dq, J = 13.9, 7.8 Hz, 1H), 2.43 (dt, J = 10.7, 7.6 Hz, 1H), 2.16 (td, J = 13.3, 5.8 Hz, 1H), 2.02 (td, J = 13.6, 6.0 Hz, 1H). LC-MS: m/z 234.1 ($M+CH_3CN$)⁺. ee>99%.

Step 5: A mixture of (R)-2-(2-(benzyloxy)ethyl)oxetane (4.35 g, 22.63 mmol) and palladium hydroxide on carbon (20%, with 50% of water, 0.80 g, 2.5 mol%) in methanol (50 mL) and dichloromethane (15 mL) was stirred at rt overnight with an input of hydrogen gas. The precipitate was removed via filtration through a pad of celite and washed with dichloromethane. The combined organic phase was dried using water pump at 30 °C and was confirmed pure enough for the next reaction. Yield: 2.28 g, 98.7%; colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 5.09 (qd, J = 7.5, 4.6 Hz, 1H), 4.70 (td, J = 8.0, 6.0 Hz, 1H), 4.57 (dt, J = 9.1, 5.9 Hz, 1H), 3.82 (ddd, J = 11.8, 7.3, 4.6 Hz, 1H), 3.74 (ddd, J = 11.1, 6.5, 4.9 Hz, 1H), 3.11- 2.77 (m, 1H), 2.77- 2.62 (m, 1H), 2.45 (ddt, J = 11.0, 9.1, 7.4 Hz, 1H), 2.13-1.98 (m, 1H), 1.91 (ddt, J = 14.3, 7.3, 4.7 Hz, 1H). ee>99%.

Step 6: To a mixture of oxetane (3.10 g, 30.48 mmol), sodium periodate (19.56 g, 91.44 mmol), water (30 mL), acetonitrile (60 mL) and carbon tetrachloride (30 mL) was added ruthenium trichloride plus three water (79.7 mg, 1 mol%) at 0-5 °C. Afterwards, the resulting mixture was allowed to warm to rt and stirred at this temperature for 2 h. The precipitate was removed via filtration through a pad of celite and washed with diethyl ether (around 100 mL x 5). The combined organic phase was washed with brine (50 mL x 3) and then dried using water pump at

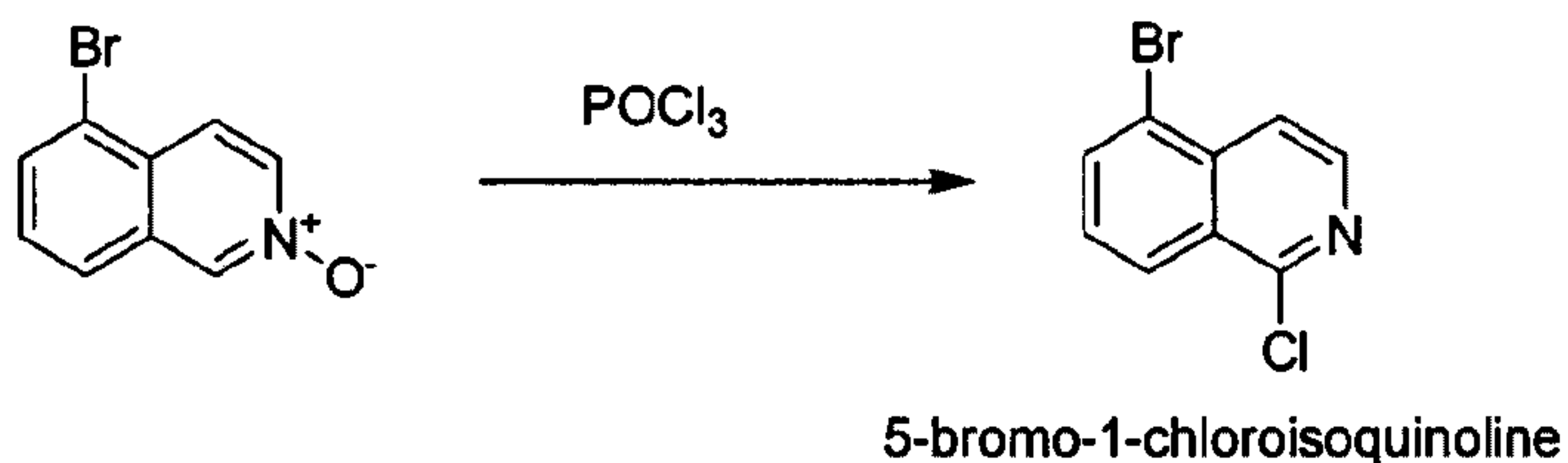
35 °C and was confirmed pure enough for the next reaction. Yield: 2.26 g, 63.8%; light yellow oil. ^1H NMR (400 MHz, methanol- d_4) δ 5.26-5.15 (m, 1H), 4.69 (ddd, $J = 8.3, 7.8, 5.9$ Hz, 1H), 4.58 (dt, $J = 9.2, 5.9$ Hz, 1H), 2.88-2.70 (m, 3H), 2.51 (ddt, $J = 11.2, 9.1, 7.3$ Hz, 1H). ee>99%.

Building block 7: 5-bromoisoquinoline 2-oxide



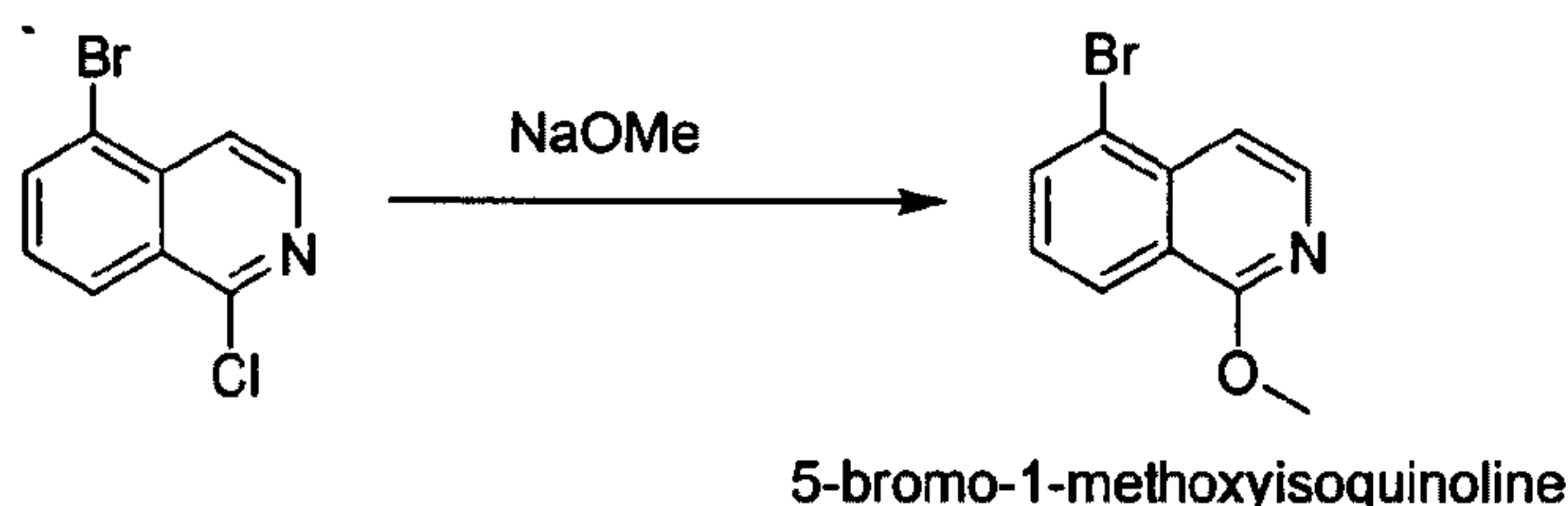
To a solution of 5-bromoisoquinoline (1.5 g, 7.2 mmol) in dichloromethane (20 mL) was added mCPBA (1.5 g, 8.6 mmol) at room temperature all at once. The reaction mixture was stirred at room temperature for 2h. Then the mixture was washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4 . The solvent was removed and the residue was purified by column chromatography over silica gel (EtOAc) to give 0.97g of title compound as a pale yellow solid. ^1H NMR (CHLOROFORM- d) δ 8.71 - 8.80 (m, 1H), 8.22 (dd, $J = 7.3, 1.5$ Hz, 1H), 8.06 (d, $J = 7.3$ Hz, 1H), 7.81 - 7.91 (m, 1H), 7.70 (d, $J = 8.2$ Hz, 1H), 7.43 - 7.54 (m, 1H). LC-MS: m/z 222.9 ($\text{M}+\text{H}$) $^+$

Building block 8: 5-bromo-1-chloroisoquinoline



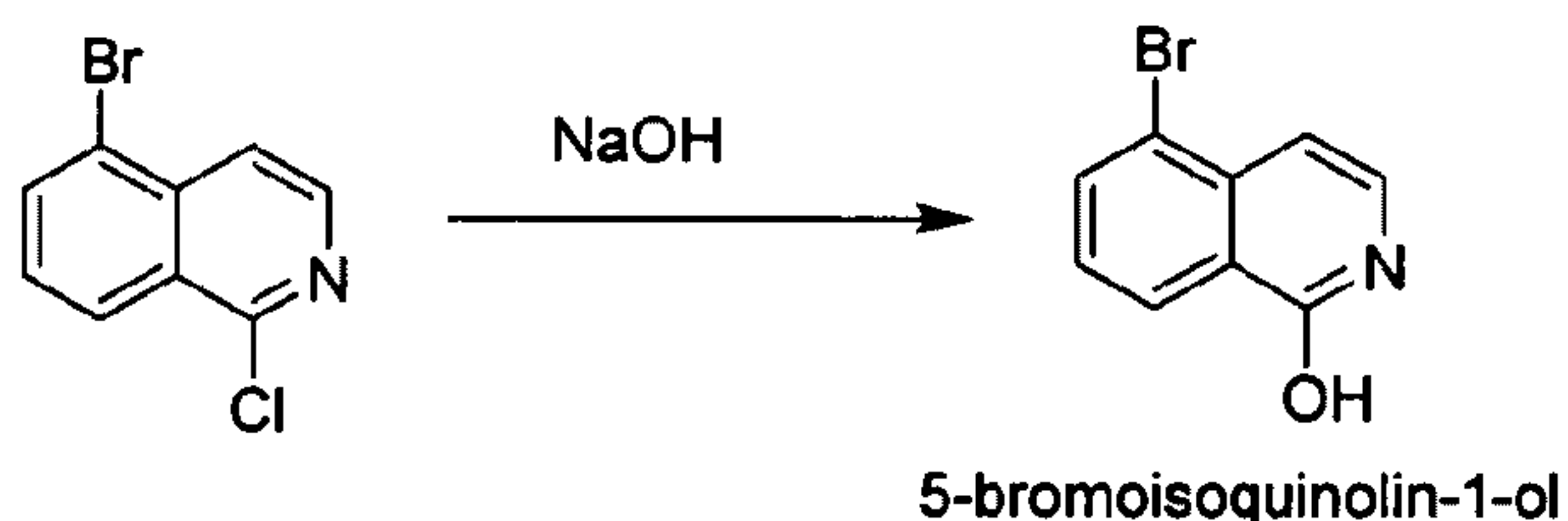
To a solution of 5-bromoisoquinoline 2-oxide (0.4 g, 2.4mmol) in CHCl_3 (10mL) was added POCl_3 (0.7 mL, 3eq). Then the mixture was refluxed for 2h. After cooling to room temperature, the reaction mixture was poured into ice-water, neutralized with saturated NaHCO_3 (aq), extracted with EtOAc. The solvent was removed and 0.45 g crude product was obtained which was used in next step with further purification. ^1H NMR (CHLOROFORM-d) δ 8.33 - 8.44 (m, 2H), 8.02 - 8.08 (m, 1H), 8.00 (d, $J = 5.6$ Hz, 1H), 7.52 - 7.61 (m, 1H). LC-MS: m/z 242.9 ($\text{M}+\text{H}$) $^+$.

Building block 9: 5-bromo-1-methoxyisoquinoline



To a solution of 5-bromo-1-chloroisoquinoline (1.2 g, 5.0 mmol) in methanol (10mL) was added NaOMe (324 mg, 6.0 mmol). The mixture was refluxed for 2h. The solvent was removed and the residue was purified by column chromatography over silica gel (10-20% EtOAc/petroleum ether) to obtain 600 mg of title compound as a white solid. ^1H NMR (DMSO-d_6) δ 8.26 (d, $J = 8.3$ Hz, 1H), 8.12 (d, $J = 6.0$ Hz, 1H), 7.95 (dd, $J = 7.5, 1.0$ Hz, 1H), 7.58 (d, $J = 6.0$ Hz, 1H), 7.41 (t, $J = 7.9$ Hz, 1H), 4.17 (s, 3H). LC-MS: m/z 237.0 ($\text{M}+\text{H}$) $^+$

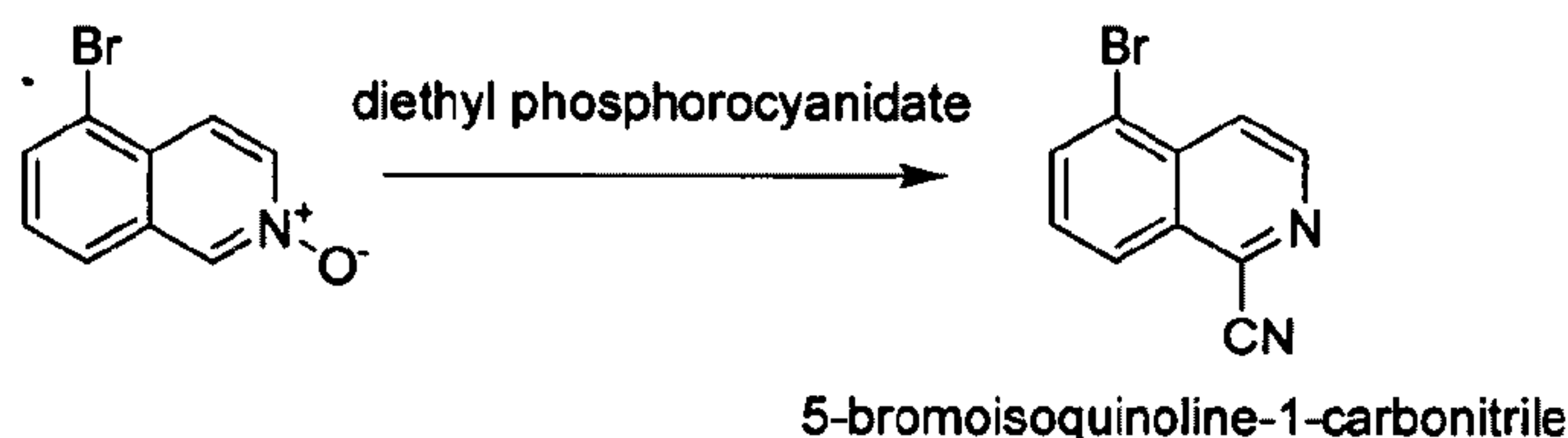
Building block 10: 5-bromo-1-methoxyisoquinoline



To a suspension of 5-bromo-1-chloroisoquinoline (300 mg, 1.2 mmol) in water (10mL) was added NaOH (240 mg, 6 mmol). The mixture was refluxed for 2h. After cooling to room temperature, the pH of the mixture was adjusted to 7 with 2N HCl. The precipitate was filtered

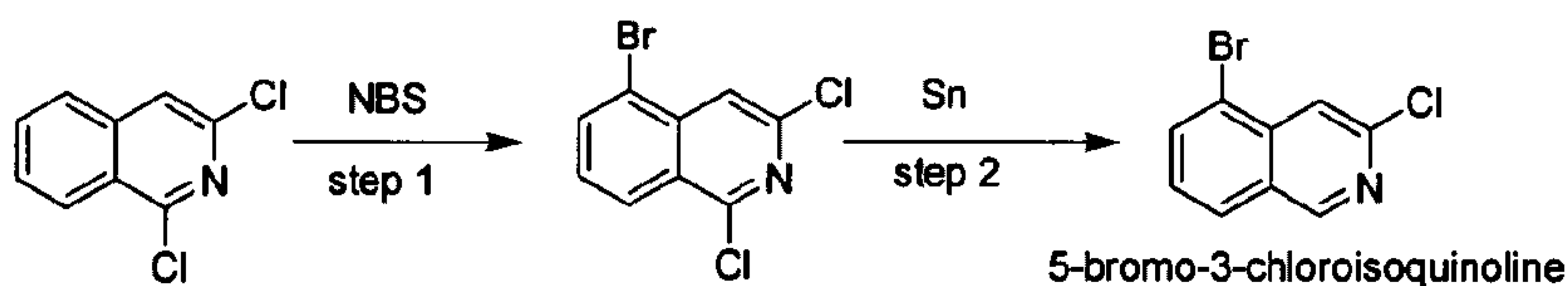
and dried to get 205 mg crude product as a white solid which was used directly in next step. LC-MS: m/z 222.9 ($M+H$)⁺

Building block 11: 5-bromo-1-methoxyisoquinoline



A mixture of 5-bromoisoquinoline 2-oxide (224 mg, 1.0 mmol), diethyl phosphorocyanidate (489 mg, 3.0 mmol) and Et₃N (101mg, 1.0 mmol) in CH₃CN (5 mL) was heated at 150°C for 1.5h in a microwave oven. After cooling to room temperature, the precipitate was filtered and dried to obtain 110 mg product as a yellow solid. ¹H NMR (CHLOROFORM-d) δ 8.79 (d, J = 5.8 Hz, 1H), 8.38 (d, J = 8.5 Hz, 1H), 8.29 (d, J = 5.8 Hz, 1H), 8.14 (d, J = 7.5 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H). LC-MS: m/z 231.9 ($M+H$)⁺

Building block 12: 5-bromo-3-chloroisoquinoline

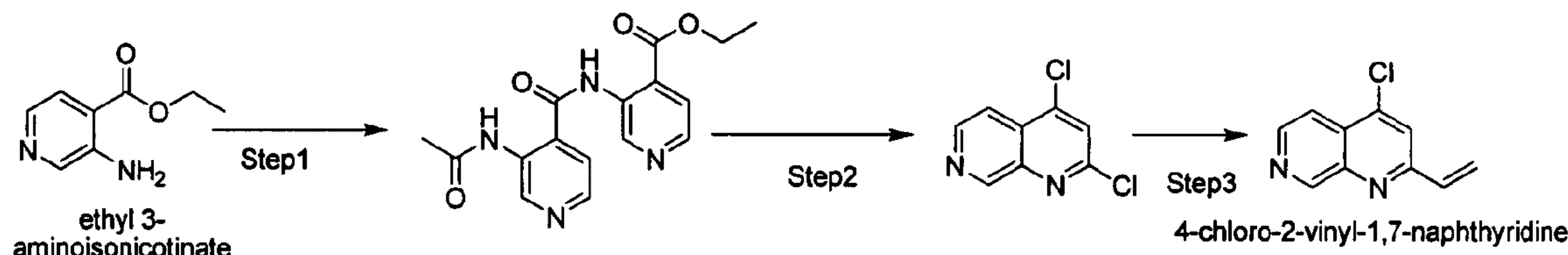


Step 1: To a solution of 1,3-dichloroisoquinoline (4 g, 20.2mmol) in CH₃CN (100 mL) was added H₂SO₄ (4 mL), followed by NBS (4.4g, 24.2mmol). The mixture was stirred at room temperature for 90h. Then the precipitate was collected by filtration, washed with water, dried to afford 3.4 g of 5-bromo-1,3-dichloroisoquinoline as a pale yellow solid. ¹H NMR (CHLOROFORM-d) δ 8.33 (d, J = 8.5 Hz, 1H), 8.03 - 8.10 (m, 2H), 7.56 (dd, J = 8.4, 7.7 Hz, 1H).LC-MS: m/z 276.9 ($M+H$)⁺

Step 2: To a suspension of 5-bromo-1,3-dichloroisoquinoline (3 g, 10.8 mmol) in AcOH (30 mL) and conc. HCl (6 mL) was added Sn powder (3.86 g, 32.4mmol). The mixture was stirred at 60°C for 20 min. After cooling to room temperature, the mixture was neutralized with NaOH (aq), filtered through celite. The filtrate was extracted with EtOAc (2 x 30mL). The solvent was removed and the residue was purified by column chromatography over silica gel (5-10%

EtOAc/petroleum ether) to afford 0.8 g of 5-bromo-3-chloroisoquinoline as a white solid. ^1H NMR (CHLOROFORM- d) δ 9.04 (s, 1H), 8.04 (s, 1H), 7.90 - 8.02 (m, 2H), 7.47 (t, $J = 7.9$ Hz, 1H).

Building block 13: 4-chloro-2-vinyl-1,7-naphthyridine



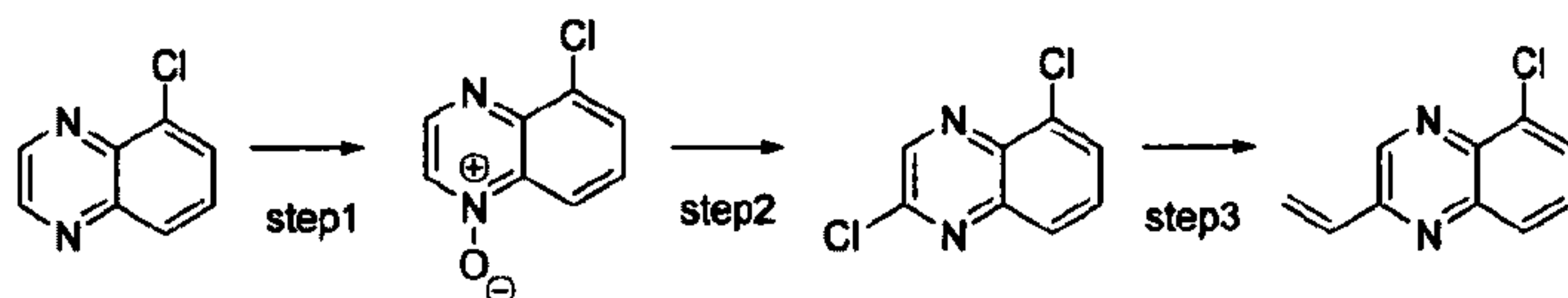
Step 1: To a stirred solution of ethyl-2-aminonicotinate (1 g, 6.02 mmol) and ethyl acetate (13 g, 147.7 mmol) in 15 mL of anhydrous THF was added sodium tert-butoxide (1.45 g, 15.1 mmol) portionwise over 1 min. The resulting mixture was stirred at room temperature for 40 mins and at 100°C for 4 hours. After this time the reaction was cooled to r.t. and evaporated in vacuo. The resulting solid was dissolved in water (20 mL) and neutralized to pH 7 with 1.0M aqueous HCl. The resulting solid was filtered and dried under vacuum overnight to give ethyl 3-(3-acetamidonicotinamido)isonicotinate as a tan solid (0.58 g, 59%). LC-MS: m/z 329.1 ($\text{M}+\text{H}^+$) ^1H NMR (CHLOROFORM- d) δ : 11.96 (s, 1H), 10.74 (br. s., 1H), 10.12 (s, 1H), 9.99 (s, 1H), 8.56 (d, $J = 5.3$ Hz, 1H), 8.59 (d, $J = 5.0$ Hz, 1H), 7.89 - 7.96 (m, 1H), 7.66 (d, $J = 5.3$ Hz, 1H), 4.51 (q, $J = 7.0$ Hz, 2H), 2.24 - 2.33 (m, 3H), 2.19 (s, 2H), 1.43 - 1.54 (t, 3H).

Step 2: A stirred solution of ethyl 3-(3-acetamidonicotinamido)isonicotinate (400 mg, 2.47 mmol) in phosphorus oxychloride (2.5 mL) was heated to 120°C for 3 hours. After this time the reaction was cooled to r.t. and evaporated in vacuo. The resulting residue was carefully basified to pH > 10 with an aqueous solution of Na_2CO_3 and the resulting solid was filtered, washed with water and dried under vacuum to give 2,4-dichloro-1,7-naphthyridine (200mg, 83%). ^1H NMR (CHLOROFORM- d) δ : 9.48 (s, 1H), 8.79 (d, $J = 5.9$ Hz, 1H), 8.01 (d, $J = 5.9$ Hz, 1H), 7.74 (s, 1H). LC-MS: m/z 200 ($\text{M}+\text{H}^+$)

Step 3: To 5 mg $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$ in a reaction tube under nitrogen were added 3 mL isopropanol, 1mL water, 93.6 mg (0.8 mmol) DIPEA, 52 mg (0.39 mmol) potassium vinyl trifluoroborate and 78 mg (0.39 mmol) 4-chloro-2-vinyl-1,7-naphthyridine. The reaction solution was heated to 100°C for half hour under microwave irradiation. The reaction mixture was

extracted into ethyl acetate, washed several times with water and purified by prepTLC (petrol: ethyl acetate=1:1) to give 4-chloro-2-vinyl-1,7-naphthyridine 50 mg (66.8%). ^1H NMR (CHLOROFORM- d) δ : 9.51 (d, J = 0.6 Hz, 1H), 8.70 (d, J = 5.6 Hz, 1H), 7.98 - 8.04 (m, 1H), 7.89 (s, 1H), 7.02 (dd, J = 17.6, 10.9 Hz, 1H), 6.41 (d, J = 17.6 Hz, 1H), 5.83 (d, J = 11.2 Hz, 1H). LC-MS: m/z 191.6 ($M+H$) $^+$

Building block 14: 5-chloro-2-vinylquinoxaline

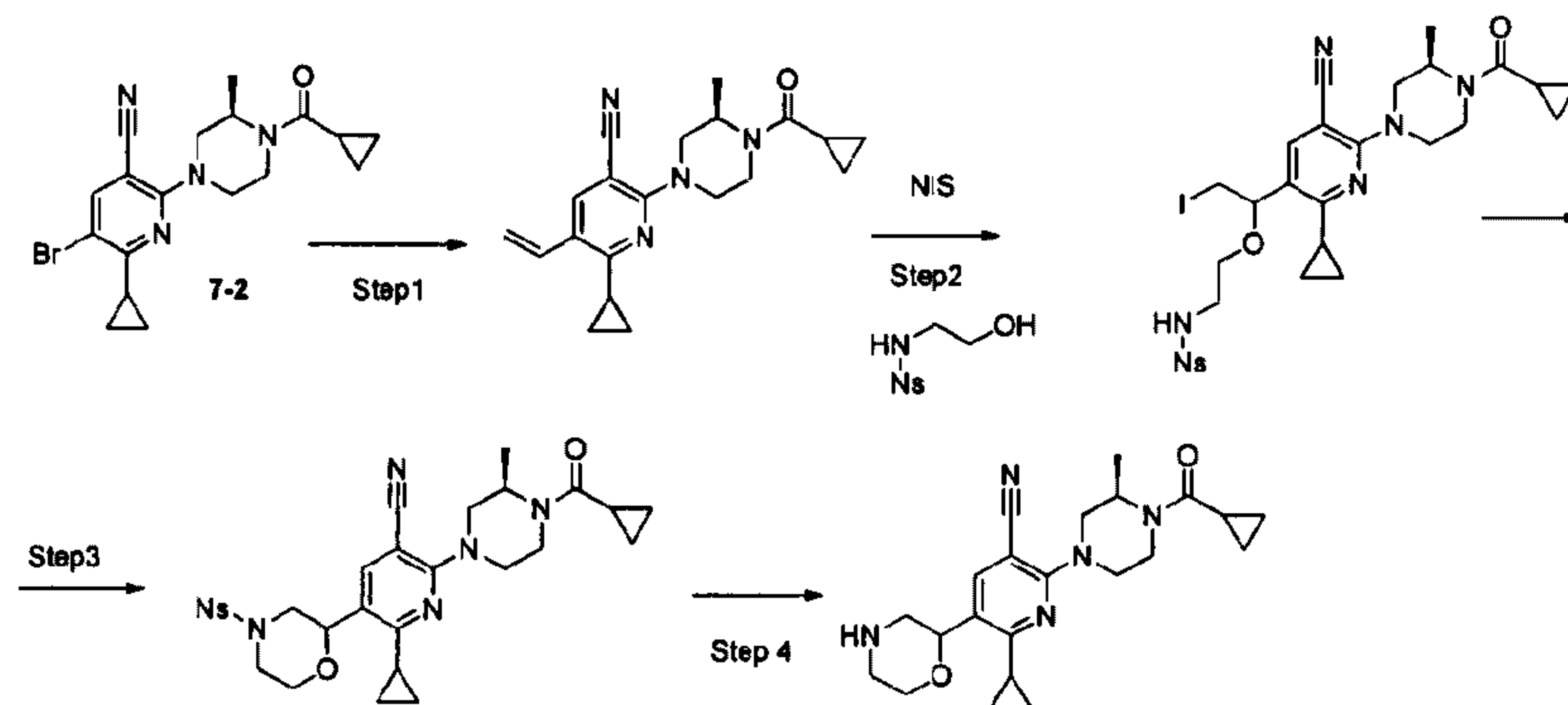


Step 1: To a solution of 5-chloroquinoxaline (1.4 g, 8.54 mmol) in 50 mL of dichloromethane was added mCPBA (1.62 g, 9.39 mmol). The resulting mixture was stirred at room temperature overnight. After removal of dichloromethane, the crude product obtained was purified by doing column chromatography (100% DCM) to afford 1.5 g of 5-chloroquinoxaline 1-oxide as a white solid.

Step 2: To a solution of 5-chloroquinoxaline 1-oxide (450 mg, 2.5 mmol) in 5 mL of chloroform was added POCl_3 (1.9 g, 12.5 mmol) slowly. The resulting mixture was heated to 80°C and held stirring at 80°C overnight. After removal of chloroform and excess POCl_3 , the crude product obtained was purified by doing column chromatography (5% PE/EA) to afford 240 mg of 2,5-dichloroquinoxaline as a white solid. MS (ES) $M+H$ expected 198, found 199. ^1H NMR (CHLOROFORM- d) δ : 8.89 (s, 1H), 7.98 (d, 1H), 7.92 (d, 1H), 7.76 (t, 1H).

Step 3: To a flask was added 2,5-dichloroquinoxaline (315 mg, 1.59 mmol), potassium trifluoro(vinyl)borate (234 mg, 1.75 mmol), PdCl_2DPPF (130 mg, 0.16 mmol), K_2CO_3 (442 mg, 3.18 mmol), propan-2-ol (4 mL), and H_2O (1 mL), the mixture was degassed with N_2 , then heated to 90 °C with stirring for about 3 hrs. TLC (5% PE/EA) showed the consumption of the starting material and new spot appeared. The mixture was then filtered through celite, the cake was washed with ethyl acetate. The filtrate was concentrated *in vacuo*, the residue was purified by column chromatography (1-5% PE/EA) to afford 256 mg of 5-chloro-2-vinylquinoxaline as a white solid. ^1H NMR (CHLOROFORM- d) δ : 9.10 (s, 1H), 8.02 (d, 1H), 7.85 (d, 1H), 7.71 (t, 1H), 7.09 (q, 1H), 6.57 (d, 1H), 5.89 (d, 1H). MS (ES) $M+H$ expected 190, found 191.

Building block 15: 2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(morpholin-2-yl)nicotinonitrile



Step 1: A mixture of 7-2 (500 mg, 1.28 mmol), Potassium vinyltrifluoroborate (258 mg, 1.93 mmol), TEA (650 mg, 6.4 mmol) and Pd(dppf)Cl₂ (52 mg, 0.064 mmol) in i-PrOH and water was heated at 100°C under microwave irradiation for 0.5 hr. The reaction mixture was concentrated and the residue was purified by column chromatography (50% PE/EA) to afford 420 mg of title compound. ¹H NMR (CHLOROFORM-d) δ 7.80 (s, 1H), 6.99 (dd, J = 17.3, 10.8 Hz, 1H), 5.58 (dd, J = 17.3, 0.8 Hz, 1H), 5.36 (dd, J = 11.0, 0.8 Hz, 1H), 4.86 (br. s., 0.5H), 4.53 (br. s., 0.5H), 4.44 (br. s., 0.5H), 4.09-4.29 (m, 2.5H), 3.65 (br. s., 0.5H), 3.41 (br. s., 0.5H), 3.12-3.24 (m, 2H), 2.14 - 2.26 (m, 1H), 1.76 (br. s., 1H), 1.25-1.42 (m, 3H), 1.10 - 1.17 (m, 2H), 0.96 - 1.10 (m, 4H), 0.82 (dd, J = 7.8, 1.8 Hz, 2H).

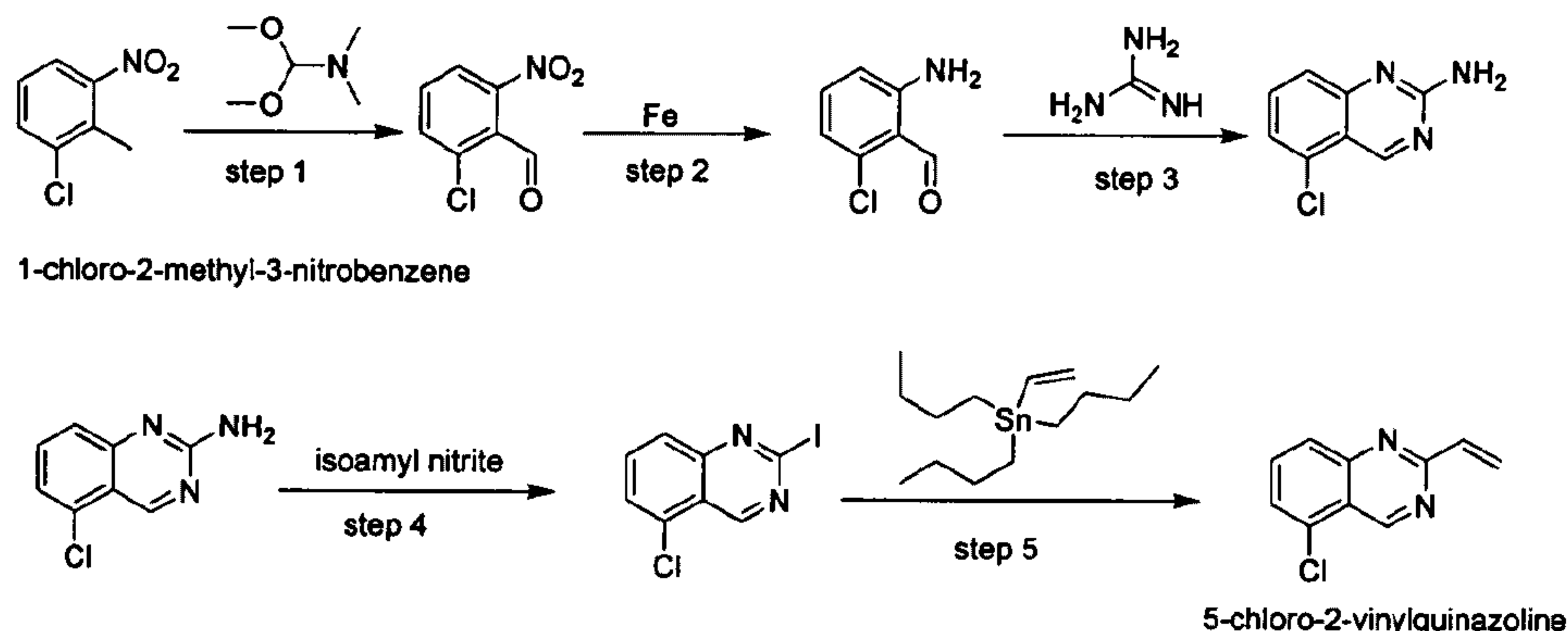
Step 2: A mixture of (R)-2-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-vinylnicotinonitrile (200 mg, 0.59 mmol), N-(2-hydroxyethyl)-4-nitrobenzenesulfonamide (174 mg, 0.71 mmol, synthesized in accordance with Organic Letters, 2011, 13, # 4, p. 728 - 731), and NIS (159 mg, 0.71 mmol) suspended in 10 mL of MeCN was stirred at r.t. for 2 hrs. After the mixture was concentrated *in vacuo*, the residue was purified by column chromatography (50% PE/EA) to afford 100 mg of N-(2-(1-(5-cyano-6-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropyl pyridin-3-yl)-2-iodoethoxy)ethyl)-4-nitrobenzenesulfonamide as a light yellowish solid. ¹H NMR (CHLOROFORM-d) δ 8.36 - 8.45 (m, J = 8.8 Hz, 2H), 8.08 - 8.17 (m, J = 8.8 Hz, 2H), 7.60 (s, 1H), 5.57 (br. s., 1H), 4.83 (br. s., 0.5H), 4.60 - 4.71 (m, 1H), 4.53 (br. s., 0.5H), 4.40 (br. s.,

0.5H), 4.19 - 4.34 (m, 2.5H), 3.54 - 3.72 (m, 1H), 3.15 - 3.48 (m, 8H), 1.88 - 1.98 (m, 1H), 1.75 (br. s., 1H), 1.34-1.40 (m, 3H), 1.00 - 1.18 (m, 6H), 0.81 (d, J = 7.8 Hz, 2H).

Step 3: A mixture of N-(2-(1-(5-cyano-6-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)-2-iodoethoxy)ethyl)-4-nitrobenzenesulfonamide (100 mg, 0.14 mmol), K₂CO₃ (97 mg, 0.71 mmol) in 10 mL of MeCN was stirred at r.t. overnight. After the mixture was filtered, *the* filtrate was concentrated and the residue was purified by column chromatography (50% PE/EA) to afford 66 mg of 2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(4-((4-nitrophenyl)sulfonyl)morpholin-2-yl)nicotinonitrile as a light yellowish solid. ¹H NMR (CHLOROFORM-d) δ 8.39 - 8.49 (m, J = 8.5 Hz, 2H), 7.90 - 8.02 (m, J = 8.3 Hz, 2H), 7.70 (s, 1H), 4.91 (dd, J = 10.2, 2.1 Hz, 1H), 4.84 (br. s., 0.5H), 4.52 (br. s., 0.5H), 4.42 (br. s., 0.5H), 4.16 (dd, J = 11.8, 2.5 Hz, 4H), 3.86 - 4.00 (m, 2H), 3.76 (d, J = 11.5 Hz, 1H), 3.61 (br. s., 0.5H), 3.14 - 3.38 (m, 3H), 2.52 - 2.69 (m, 1H), 1.97 - 2.09 (m, 1H), 1.74 (br. s., 1H), 1.28 - 1.48 (m, 3H), 1.19 - 1.25 (m, 2H), 1.11 - 1.19 (m, 2H), 1.04 - 1.11 (m, 2H), 0.81 (d, J = 7.5 Hz, 2H).

Step 4: A mixture of 2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(4-((4-nitrophenyl)sulfonyl)morpholin-2-yl)nicotinonitrile (50 mg, 0.075 mmol), butane-1-thiol (3 d) and LiOH.H₂O (20 mg) in 10 mL of MeCN was stirred at r.t. overnight. After the mixture was filtered, the filtrate was concentrated and the residue was purified by column chromatography (10% DCM/MeOH) to afford 21 mg of 2-((R)-4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-6-cyclopropyl-5-(morpholin-2-yl)nicotinonitrile. ¹H NMR (CHLOROFORM-d) δ 7.81 (br. s., 1H), 4.96 (br. s., 1H), 4.34 - 4.63 (m, 1H), 4.14 (br. s., 3H), 3.97 (br. s., 1H), 3.46 (br. s., 3H), 3.32 (br. s., 2H), 3.09 (br. s., 3H), 2.75 (br. s., 1H), 2.09 (br. s., 1H), 1.74 (br. s., 1H), 1.26 (br. s., 5H), 1.03 (br. s., 4H), 0.80 (br. s., 2H).

Building block 16: 5-chloro-2-vinylquinazoline



Step 1: To a solution of 1-chloro-2-methyl-3-nitrobenzene (10.0 g, 58.3 mmol) in 150 mL of anhydrous DMF was added 1,1-dimethoxy-N,N-dimethylmethanamine (21.0 g, 175 mmol). The resulting mixture was stirred at 140 °C for 16 hours. After cooling to 0 °C, the mixture was added slowly a solution of NaIO₄ (37.4 g, 175 mmol) in H₂O and DMF. The mixture was stirred for another 6 hours. The mixture was filtered and partitioned between EtOAc and water. The organic layer was washed with water and dried over Na₂SO₄ and concentrated to give the crude which was purified by column to afford 6.5 g of 2-chloro-6-nitrobenzaldehyde. ¹H NMR (CHLOROFORM-d) δ 10.39 (s, 1H), 7.95 - 8.04 (m, 1H), 7.74 - 7.80 (m, 1H), 7.64 (t, J = 8.0 Hz, 1H). LC-MS: m/z 186.0 (M+H)⁺

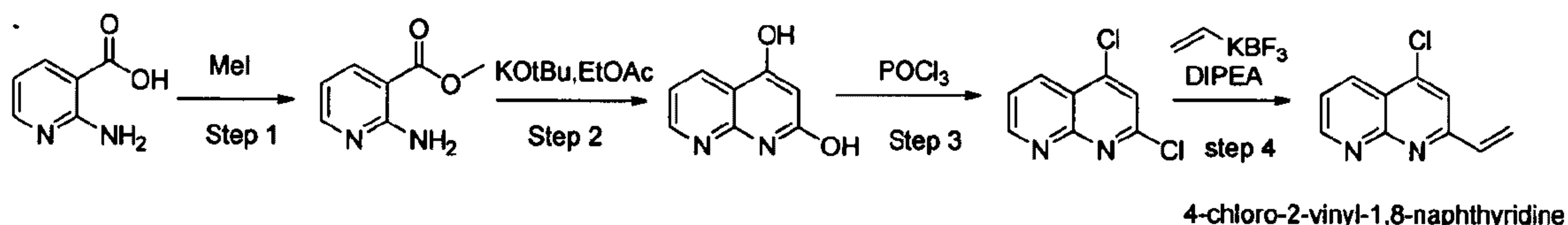
Step 2: To a solution of 2-chloro-6-nitrobenzaldehyde (1 g, 0.0054 mmol) in ethanol was added Fe (1.8 g, 0.032 mmol), AcOH (10 ml) and 2N aqueous HCl (5 mL). The resulting mixture was stirred at 25 °C for 2 hours. The mixture was filtered and the filtrate was partitioned between DCM and water, the organic layer was washed with water and brine, concentrated to give 2-amino-6-chlorobenzaldehyde under 25 °C which was without purification for next step. LC-MS: m/z 156.01 (M+H).

Step 3: The mixture of compound 2-amino-6-chlorobenzaldehyde (2.8 g, 0.018 mol), guanidine (3.43 g, 0.36 mol) and Na₂CO₃ (3.82 g, 0.36 mol) in naphthalene was stirred at 180 °C for 2 hours. After cooling to room temperature, the mixture was filtered and the solid was washed with water and DCM to give the yellow solid 5-chloroquinazolin-2-amine which was used without purification for next step. ¹H NMR (DMSO-d₆) δ 9.28 (s, 1H), 7.65 (dd, J = 8.5, 7.8 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.16 (s, 2H). LC-MS: m/z 180.0 (M+H).

Step 4: The mixture of 5-chloroquinazolin-2-amine (2.2 g, 12.2 mmol), isoamyl nitrite (4.30 g, 36.7 mmol), CuI (1.17 g, 6.12 mmol) and CH₂I₂ (16.4 g, 61.2 mmol) in THF was stirred at 60°C for 72 hours. After cooling to room temperature, the mixture was filtered and the filtrate was partitioned between EtOAc and water, the organic layer was washed with water and brine, dried over Na₂SO₄. Then the organic layer was concentrate to give the crude which was purified by column to give 5-chloro-2-iodoquinazoline as yellow solid. ¹H NMR (CHLOROFORM-d) δ 9.46 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.86 (dd, J = 8.5, 7.5 Hz, 1H), 7.72 (dd, J = 7.4, 1.1 Hz, 1H). LC-MS: m/z 291.1 (M+H).

Step 5: The mixture of 5-chloro-2-iodoquinazoline (1.3 g, 4.48 mmol), potassium vinyltrifluoroborate (600 mg, 4.48 mmol), Pd(dppf)Cl₂ (165 mg, 0.224 mmol) and CsF (2.04 g, 13.4 mmol) in dioxane/H₂O was stirred at 80°C for 16 hours. After cooling to room temperature, the mixture was partitioned between EtOAc and water. The organic layer was washed with water, brine and dried over Na₂SO₄, concentrated to give the crude which was purified by column to give 500 mg of 5-chloro-2-vinylquinazoline as yellow solid. ¹H NMR (CHLOROFORM-d) δ 9.75 (s, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.63 (d, J = 7.5 Hz, 1H), 7.06 (dd, J = 17.2, 10.4 Hz, 1H), 6.85 (dd, J = 17.3, 1.8 Hz, 1H), 5.90 (dd, J = 10.5, 1.5 Hz, 1H). LC-MS: m/z 191.0 (M+H).

Building block 17: 4-chloro-2-vinyl-1,8-naphthyridine



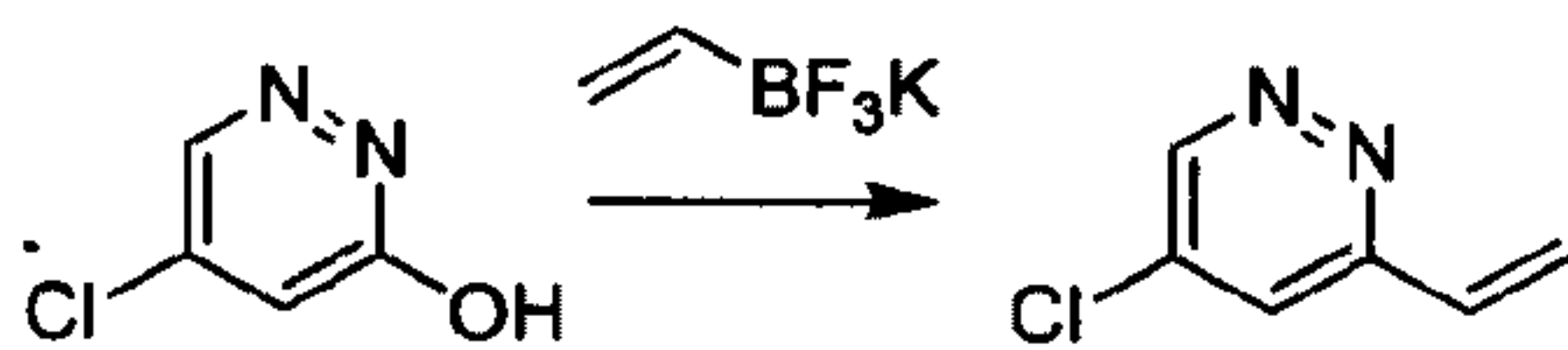
Step 1: A mixture of 25 g of 2-aminonicotinic acid (0.18 mol), 25 g of K₂CO₃ (0.18 mol) in 250 mL of DMF was stirred at 140°C for 30 minutes, then cooled to 10°C in ice/H₂O, 11 mL of MeI (0.18 mol) was added at 10°C dropwise, the mixture was stirred at room temperature overnight. The mixture was filtered, the filtrate was concentrated, residue was dissolved in EtOAc, and filtered again through a pad of silica gel, the filtrate was concentrated to give 15 g of methyl 2-aminonicotinate. ¹H NMR (400MHz, CHLOROFORM-d) δ: 7.67 (d, J = 7.0 Hz, 1 H), 7.69 (d, J = 7.8 Hz, 1 H), 7.60 - 7.44 (m, 1 H), 3.54 (br. s., 3 H).

Step 2: To methyl 2-aminonicotinate (7.48 g, 49 mmol) in EtOAc/THF (150 mL/ 150mL) was added 13.8 g of KtOBu (123 mmol) in portions slowly at room temperature, and the mixture was stirred at room temperature for 50 minutes before it was refluxed for 4 hours. After cooling to room temperature, the mixture was concentrated, the residue was dissolved in 200 mL of H₂O, pH was adjusted to pH=7 with 1N HCl with vigorous stirring, the resulting suspension was filtered, the solid obtained was dried in vacuum to give 7 g of 1,8-naphthyridine-2,4-diol.

Step 3: A mixture of 8.0 g of 1,8-naphthyridine-2,4-diol (49 mmol) in 80 mL of POCl₃ was refluxed for 1.5 hour, excessive POCl₃ was removed under reduced pressure, the residue was poured into satd NaHCO₃ slowly with vigorous stirring, the mixture was extracted with EtOAc, and the organic layers were dried over Na₂SO₄, concentrated to give 2 g of 2,4-dichloro-1,8-naphthyridine, which was used in the subsequent reaction without further purification. ¹H NMR (400MHz, CHLOROFORM-d) δ : 9.21 - 9.12 (m, 1 H), 8.59 (dd, J = 1.8, 8.3 Hz, 1 H), 7.67 - 7.58 (m, 2 H).

Step 4: 100 mg of 2,4-dichloro-1,8-naphthyridine (0.5 mmol), 68 mg of potassium vinyltrifluoroborate (0.5 mmol), 130 mg of DIPEA (1 mmol) in *i*PrOH/H₂O (3 mL/ 1 mL) was added Pd(dppf)₂Cl₂, then the mixture was stirred at 105°C in a sealed tube for 1 hour. When TLC (Petroleum ether: Ethyl acetate = 3:1) indicated the completion of the reaction, the mixture was cooled to room temperature, filtered through a pad of celite, the filtrate was concentrated to give 120 mg of crude 4-chloro-2-vinyl-1,8-naphthyridine, and was used in the subsequent reaction without further purification. ¹H NMR (400MHz, CHLOROFORM-d) δ : 9.17 (dd, J = 1.8, 4.3 Hz, 1 H), 8.58 (dd, J = 1.9, 8.4 Hz, 1 H), 7.62 - 7.49 (m, 2 H), 7.13 - 6.94 (m, 1 H), 6.52 (d, J = 17.6 Hz, 1 H), 5.81 (d, J = 10.8 Hz, 1 H).

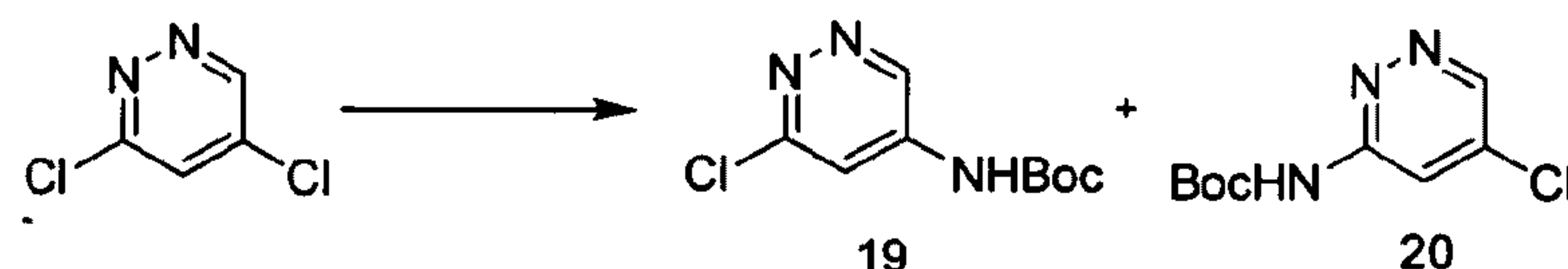
Building block 18: 5-chloro-3-vinylpyridazine



The mixture of 5-chloropyridazin-3-ol (500 mg, 3.36 mmol), potassium vinyltrifluoroborate (450 mg, 3.36 mmol), Pd(dppf)Cl₂ (124 mg, 0.168 mmol) and CsF (1.5 g, 10.07 mmol) in dioxane/H₂O (8 mL/ 2 mL) was stirred at 100 °C for 16 hours. The mixture was diluted with EtOAc (50 mL) and filtered. The filtrate was partitioned between EtOAc (50 mL) and water (30

mL), the organic layer was washed with water (30 mL), brine and dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 200 mg of the product. ^1H NMR (CHLOROFORM- d) δ 9.06 (d, $J = 2.3$ Hz, 1H), 7.60 (d, $J = 2.3$ Hz, 1H), 7.02 (dd, $J = 17.8, 11.0$ Hz, 1H), 6.32 (d, $J = 17.6$ Hz, 1H), 5.77 (d, $J = 10.9$ Hz, 1H). LC-MS : m/z 141.0 ($\text{M}+\text{H}$) $^+$

Building block 19 and 20: tert-butyl 6-chloropyridazin-4-ylcarbamate and tert-butyl 5-chloropyridazin-3-ylcarbamate

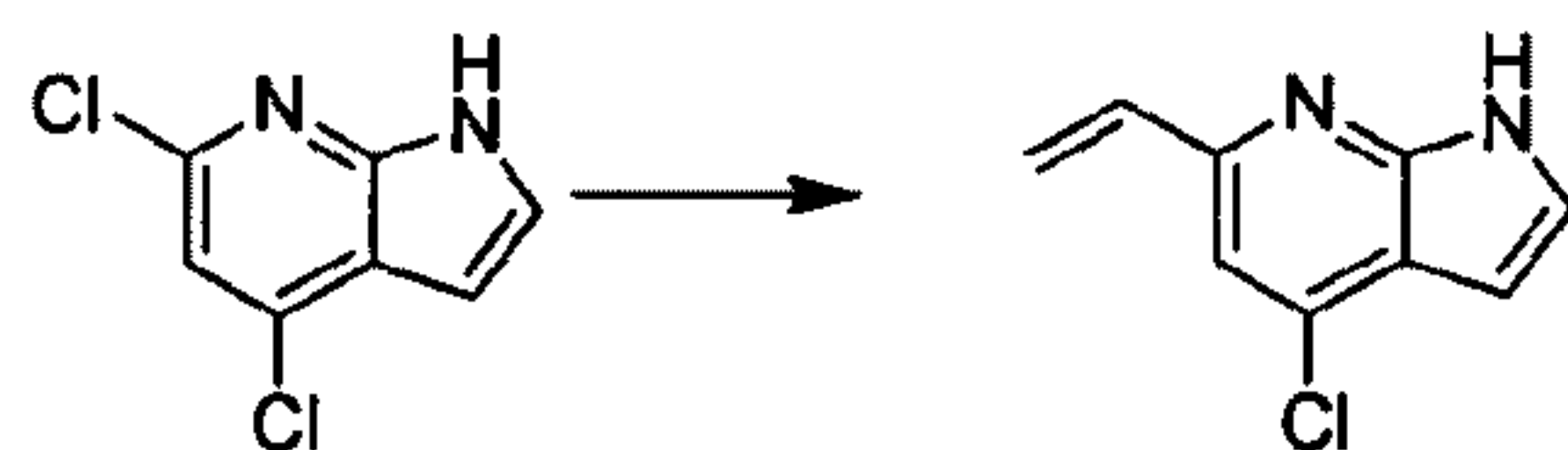


The mixture of 3,5-dichloropyridazine (400 mg, 2.68 mmol), BocNH_2 (314 mg, 2.68 mmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (99 mg, 0.134 mmol), Xantphos (155 mg, 0.268 mmol) and Cs_2CO_3 (2.61 g, 8.05 mmol) in toluene was stirred at 80°C for 16 hours. The mixture was diluted with EtOAc (50 mL) and filtered. The filtrate was partitioned between EtOAc (50 mL) and water (30 mL), the organic layer was washed with water (30 mL), brine and dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 150 mg of the product 19 and 120 mg of 20.

tert-butyl 6-chloropyridazin-4-ylcarbamate ^1H NMR (CHLOROFORM- d) δ 8.86 (d, $J = 2.0$ Hz, 1H), 8.37 (d, $J = 2.3$ Hz, 1H), 8.12 (br. s., 1H), 1.56 (s, 9H). LC-MS : m/z 230.1 ($\text{M}+\text{H}$) $^+$

tert-butyl 5-chloropyridazin-3-ylcarbamate ^1H NMR (CHLOROFORM- d) δ 8.94 (s, 1H), 8.04 (s, 1H), 7.37 (br. s., 1H), 1.48 - 1.63 (s, 9H). LC-MS : m/z 230.1 ($\text{M}+\text{H}$) $^+$

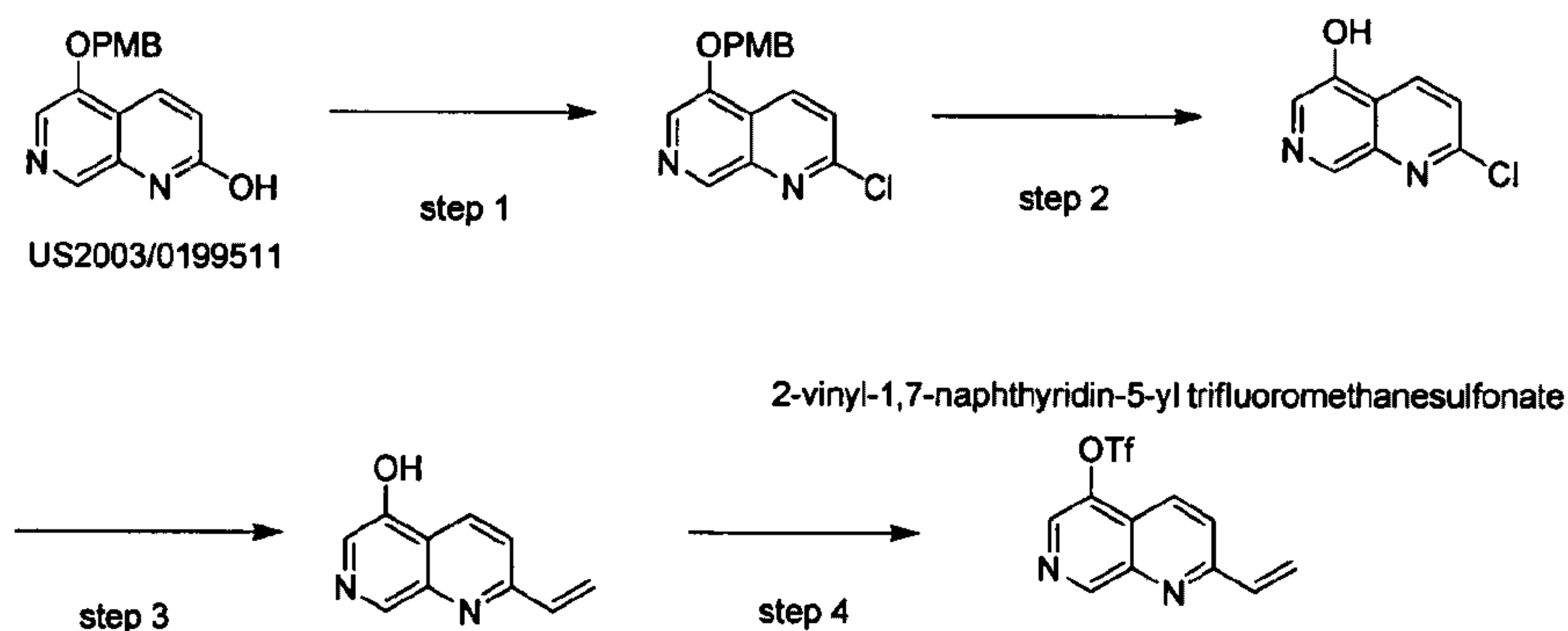
Building block 21: 4-chloro-6-vinyl-1H-pyrrolo[2,3-b]pyridine



To a solution of 4,6-dichloro-1H-pyrrolo[2,3-b]pyridine (20mg, 0.1 mmol), potassium vinyl trifluoroborate (13 mg, 0.1 mmol), 5 mg $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$ and CsF (45 mg, 0.3 mmol) in dioxane/ H_2O (5:1) 3 mL was stirred at 100°C for 1 hours. Then the mixture was partitioned between EtOAc and water, the organic was washed with water, brine and concentrated to give

the crude which was purified by column to give 14 mg of the product. ^1H NMR (CHLOROFORM- d) δ : 11.19 (br. s., 1H), 7.39 (br. s., 1H), 7.28 (s, 2H), 6.91 (dd, $J = 17.3, 10.9$ Hz, 1H), 6.62 (br. s., 1H), 6.21 (d, $J = 17.3$ Hz, 1H), 5.55 (d, $J = 10.9$ Hz, 1H). LC-MS : m/z 179.6 ($M+H$) $^+$

Building block 22: 2-vinyl-1,7-naphthyridin-5-yl trifluoromethanesulfonate



Step 1: To a suspension of 5-(4-methoxybenzyloxy)-1,7-naphthyridin-2-ol (180 mg, 0.64 mmol) in DMF (5 mL) was added POCl₃ (293 mg, 1.92 mmol). The mixture was heated at 45°C for 6h. After cooling to room temperature, the reaction mixture was poured into ice-water, neutralized with NaHCO₃, extracted with EtOAc (3 x 20mL). The organic layer washed with water (20mL) and brine (20mL). The solvent was removed and 150 mg crude product was obtained which was used in next step without further purification. LC-MS : m/z 300 ($M+H$) $^+$

Step 2: To a solution of 2-chloro-5-(4-methoxybenzyloxy)-1,7-naphthyridine (150 mg, 0.5 mmol) in EtOH (10mL) was added 1N HCl (2.5mL). Then the mixture was heated at 90°C for 2h. After cooling to room temperature, 190 mg of K₂CO₃ was added and followed 10 mL of methanol. The mixture was stirred vigorously for 1h at which time silica gel was added. The solvent was removed and the residue was purified by column chromatography (5%

methanol/dichloromethane) to give 70 mg of title compound (83%). LC-MS : m/z 180 ($M+H$) $^+$

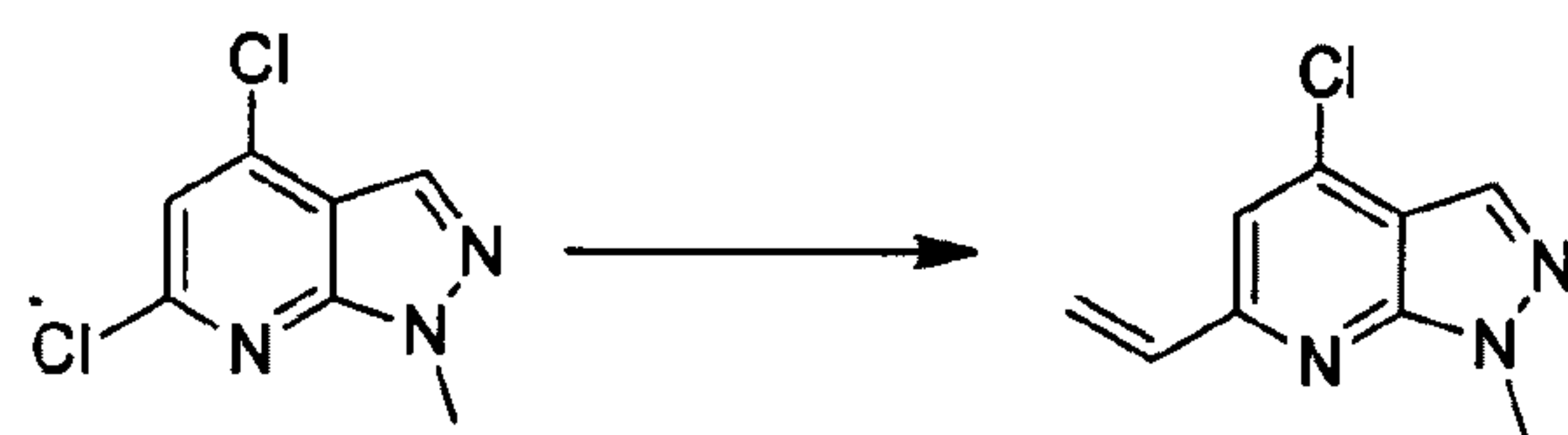
Step 3: A mixture of 2-chloro-1,7-naphthyridin-5-ol (70 mg, 0.39 mmol), Potassium vinyltrifluoroborate (104 mg, 0.78 mmol), Pd(dppf)Cl₂ (32 mg, 0.039 mmol) and CsF (119 mg, 0.78 mmol) in dioxane:H₂O=5:1 (5ml+1ml) was purged with N₂ for three times. Then the mixture was heated at 100°C for 2h. The solvent was removed and the residue was purified by

column chromatography (5% methanol/dichloromethane) to give 30 mg of title compound (45%).

LC-MS : m/z 173 ($M+H$)⁺

Step 4: To a solution of 2-vinyl-1,7-naphthyridin-5-ol (30 mg, 0.17 mmol) and Et₃N (35 mg, 0.34 mmol) in dichloromethane (3 mL) was added Tf₂O (59 mg, 0.21 mmol) at 0°C. Then the temperature was raised to room temperature and stirred for 2h. The solvent was removed and the residue was purified by prep. TLC (EtOAc/petroleum ether = 3/7) to give 10 mg of title compound (20%). LC-MS : m/z 305 ($M+H$)⁺

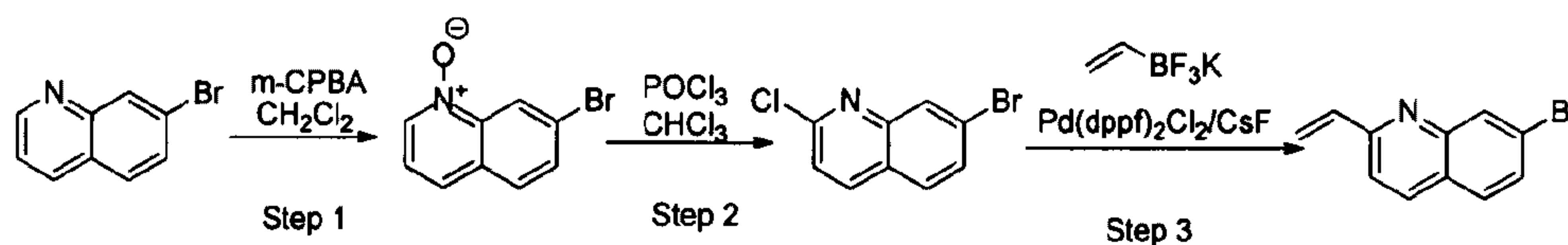
Building block 23: 4-chloro-1-methyl-6-vinyl-1H-pyrazolo[3,4-b]pyridine



WO2010/59788

A mixture of 4,6-dichloro-1-methyl-1H-pyrazolo[3,4-b]pyridine (0.8 g, 4.0 mmol), Potassium vinyltrifluoroborate (540 mg, 4.0 mmol), Pd(dppf)Cl₂ (98 mg, 0.12 mmol) and CsF (1.22 g, 8 mmol) in dioxane:H₂O=5:1 (10 mL + 2 mL) was purged with N₂ three times. Then the mixture was heated at 100°C for 2h. The solvent was removed and the residue was purified by column chromatography (30% EtOAc/petroleum ether) to give 500 mg of title compound (65%). ¹H NMR (CHLOROFORM-*d*) δ 8.03 (s, 1H), 7.24 (s, 1H), 6.89 (dd, *J* = 17.5, 10.7 Hz, 1H), 6.36 (d, *J* = 17.3 Hz, 1H), 5.64 (d, *J* = 10.9 Hz, 1H), 4.16 (s, 3H). LC-MS : m/z 193 ($M+H$)⁺

Building block 24: 7-bromo-2-vinylquinoline



Step 1: 7-bromoquinoline 1-oxide: to a solution of 7-bromoquinoline (1.04 g, 5 mmol) in 20 mL of DCM was added *m*-Chloroperbenzoic acid (1.01 g, 5 mmol) at room temperature. The reaction mixture was then stirred at room temperature overnight. After LC-MS showed the completion of reaction, the mixture was poured into water and extracted with methylene chloride.

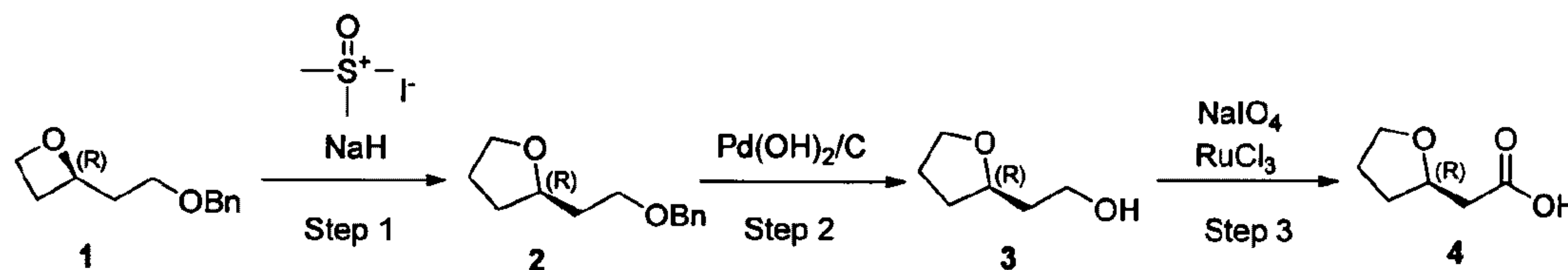
The combined organic layer was dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Column chromatography (hexane/ethyl acetate=3/1) afforded 1.0 g of title compound as a white solid.

LC-MS: m/z 225.1($\text{M}+\text{H}$)⁺

Step 2: 7-bromo-2-chloroquinoline: to a solution of 7-bromoquinoline 1-oxide (1.0 g, 4.5 mmol) in 20 mL of chloroform was added Phosphorus oxychloride (3.42 g, 22 mmol) at room temperature. The reaction mixture was then heated at reflux for 3 hours. After LC-MS showed the completion of reaction, the mixture was poured into water and extracted with methylene chloride. The combined organic layer was dried over anhy. Na_2SO_4 and concentrated *in vacuo*. Column chromatography (hexane/ethyl acetate=3/1) afforded 0.75 g of title compound as a white solid. LC-MS: m/z 244.1($\text{M}+\text{H}$)⁺

Step 3: 7-bromo-2-vinylquinoline: to a solution of 7-bromo-2-chloroquinoline (0.75 g, 3 mmol) in 1,4-dioxane (10 mL) was added Potassium vinyltrifluoroborate (0.42 g, 3 mmol), dichlorobis (triphenylphosphine) palladium (II) (143 mg) and Cesium fluoride (1.40 g, 9 mmol), and the mixture was stirred at 100 °C for 10 hours under nitrogen. The mixture was diluted with ethyl acetate and water. The organic layer was separated, washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate=4/1) afforded 0.42 g of title compound as a white solid. LC-MS: m/z 234.9($\text{M}+\text{H}$)⁺

Building block 25: (R)-2-(tetrahydrofuran-2-yl)acetic acid



Step 1: (R)-2-(2-(benzyloxy)ethyl)tetrahydrofuran: to a well stirred suspension of 1.28 g (52 mmol) of NaH in dry diglyme (15 mL) was added 6.86 g (31.2 mmol) of trimethylsulfoxonium iodide at room temperature. The mixture was gently heated to 120 °C, and compound 1 (Step 4 product in building block 6 scheme) (1 g, 5.2 mmol) in diglyme (3 mL) was added in one portion. The reaction mixture was stirred at 120° for 4 hours, cooled, carefully quenched with water, and extracted three times with n-hexane. The combined extracts were washed with water and brine

and dried over Na₂SO₄. Removal of solvent and purification by chromatography on silica gel gave the compound **2** (0.5 g, 46%). ¹H NMR (CHLOROFORM-d) δ 7.34 - 7.42 (m, 4H), 7.26 - 7.34 (m, 1H), 4.43 - 4.63 (m, 2H), 3.91 - 4.05 (m, 1H), 3.83 - 3.91 (m, 1H), 3.74 (td, J = 7.9, 6.5 Hz, 1H), 3.62 (t, J = 6.6 Hz, 2H), 1.96 - 2.05 (m, 1H), 1.73 - 1.95 (m, 4H), 1.52 (dd, J = 11.9, 8.7 Hz, 1H).

Step 2: (R)-2-(tetrahydrofuran-2-yl)ethanol: to a solution of compound **2** (0.3 g, 1.45 mmol) in MeOH (15 mL) was added 10% Pd(OH)₂/C (20 mg). The reaction mixture was purged with hydrogen and stirred under an atmosphere of hydrogen for 2 d. The black suspension was passed through a plug of celite eluting with MeOH, then the solution was concentrated to yield the desired product as colorless oil (0.15 g, 89%). ¹H NMR (CHLOROFORM-d, 400MHz): δ 4.00 - 4.08 (m, 1 H), 3.86 - 4.00 (m, 1 H), 3.66 - 3.86 (m, 3 H), 2.87 (br. s., 1 H), 1.98 - 2.10 (m, 1 H), 1.84 - 1.98 (m, 2 H), 1.70 - 1.84 (m, 2 H), 1.46 - 1.63 ppm (m, 1 H).

Step 3: (R)-2-(tetrahydrofuran-2-yl)acetic acid: to a mixture of compound **3** (0.15 g, 1.3 mmol), sodium periodate (0.72 G, 2.6 mmol), water (10 mL), acetonitrile (20 mL) and carbon tetrachloride (20 mL) was added ruthenium trichloride (29 mg, 10 mol%) at 0-5 °C. Afterwards, the resulting mixture was allowed to warm to rt and stirred at this temperature for 2 h. The precipitate was removed via filtration through a pad of celite and washed with diethylether (around 100 mL x 5). The combined organic phase was washed with brine (50 mL x 3) and then dried under reduced pressure to get the compound **4** (60 mg, contain about 8% of the byproduct). ¹H NMR (CHLOROFORM-d, 400MHz): δ 4.19 - 4.33 (m, 1 H), 3.89 - 4.06 (m, 1 H), 3.83 (td, J=7.8, 6.5 Hz, 1 H), 2.62 (dd, J=6.5, 1.5 Hz, 2 H), 2.07 - 2.23 (m, 1 H), 1.89 - 2.06 (m, 2 H), 1.54 - 1.72 (m, 1 H).

EXAMPLE 16: The following compounds were made following methods analogous to those for Compound 273.

(R)-5-(2-cyanophenyl)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (Compound 274; General procedure 1, Step H): ^1H NMR

(CHLOROFORM- d) δ 7.76 - 7.82 (m, 1H), 7.69 (td, J = 7.7, 1.4 Hz, 1H), 7.58 - 7.63 (m, 1H), 7.52 (td, J = 7.7, 1.1 Hz, 1H), 7.46 (d, J = 7.8 Hz, 1H), 4.56 - 4.79 (m, 1.5H), 4.44 (t, J = 10.3 Hz, 1.5H), 3.86 (d, J = 13.8 Hz, 0.5H), 3.70 - 3.79 (m, 2H), 3.51 - 3.65 (m, 0.5H), 3.34 - 3.49 (m, 3.5H), 3.03 - 3.24 (m, 2H), 2.87 - 3.00 (m, 0.5H), 2.53 - 2.82 (m, 2H), 2.05 - 2.29 (m, 1H), 1.63 - 1.77 (m, 1H), 1.26 (br. s., 1H), 0.93 - 1.23 (m, 7H), 0.87 - 0.92 (m, 1.5H), 0.84 (d, J = 6.8 Hz, 1.5H). LC-MS: m/z 458.2 ($M+H$) $^+$

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-methoxyphenyl)nicotinonitrile (Compound 275; General procedure 1, Step H): ^1H NMR

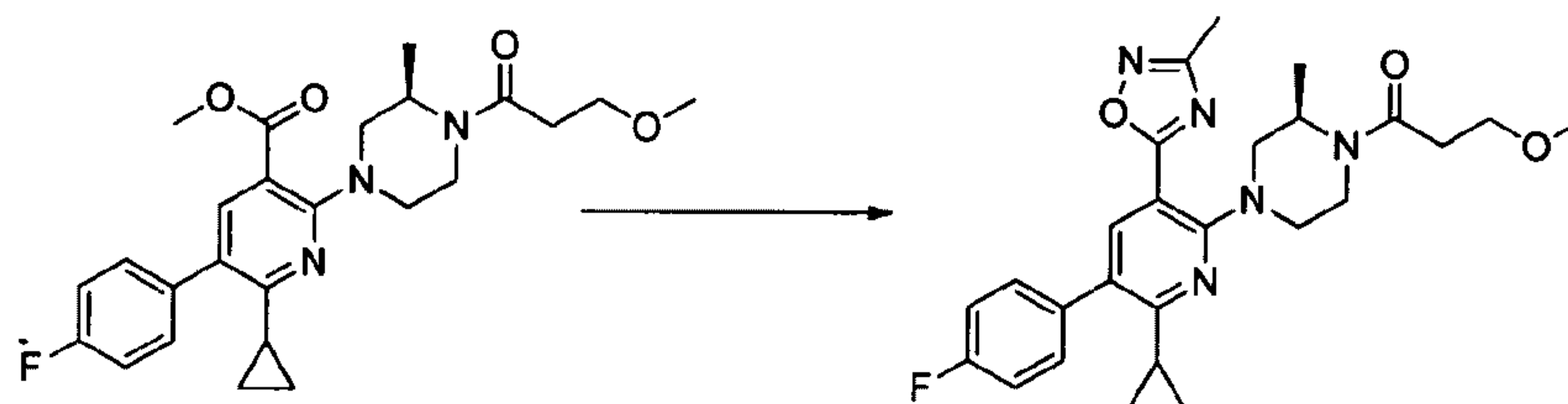
(CHLOROFORM- d) δ 7.58 (d, J = 2.5 Hz, 1H), 7.39 (td, J = 7.9, 1.8 Hz, 1H), 7.18 - 7.25 (m, 1H), 7.04 (td, J = 7.4, 1.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 4.69 (d, J = 12.8 Hz, 0.5H), 4.49 - 4.60 (m, 1H), 4.44 (d, J = 10.5 Hz, 0.5H), 4.25 - 4.38 (m, 1H), 3.79 - 3.89 (m, 4H), 3.68 - 3.78 (m, 2H), 3.51 - 3.63 (m, 0.5H), 3.34 - 3.42 (m, 3H), 2.90 - 3.16 (m, 2.5H), 2.53 - 2.82 (m, 2H), 2.09 - 2.36 (m, 1H), 1.75 - 1.88 (m, 1H), 1.02 - 1.18 (m, 5H), 0.79 - 0.96 (m, 5H). LC-MS: m/z 463.2 ($M+H$) $^+$

COMPOUND AGI-0007758/NB162-086 (General procedure 1, Step H)

(R)-6-cyclopropyl-2-(3-isopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(2-

(trifluoromethoxy)phenyl)nicotinonitrile (Compound 276; General procedure 1, Step H): ^1H NMR (CHLOROFORM- d) δ 7.54 (d, J = 2.0 Hz, 1H), 7.43 - 7.48 (m, 1H), 7.33 - 7.41 (m, 3H), 4.69 (d, J = 13.3 Hz, 0.5H), 4.60 (t, J = 13.3 Hz, 1H), 4.41 (dd, J = 16.8, 13.3 Hz, 1.5H), 3.85 (d, J = 13.3 Hz, 0.5H), 3.70 - 3.79 (m, 2H), 3.52 - 3.62 (m, 0.5H), 3.35 - 3.49 (m, 3.5H), 3.03 - 3.23 (m, 2H), 2.89 - 3.02 (m, 0.5H), 2.53 - 2.82 (m, 2H), 1.67 - 1.78 (m, 1H), 1.04 - 1.12 (m, 5H), 0.77 - 0.98 (m, 6H). LC-MS: m/z 517.2 ($M+H$) $^+$

(R)-1-(4-(6-cyclopropyl-5-(4-fluorophenyl)-3-(3-methyl-1,2,4-oxadiazol-5-yl)pyridin-2-yl)-2-methylpiperazin-1-yl)-3-methoxypropan-1-one (Compound 831)



To a solution of N'-hydroxyacetimidamide (221 mg, 2mmol) hydrochloride in 10 mL anhydrous THF was added NaH (48 mg, 2mmol). The reaction mixture was heated reflux for 0.5h and (R)-methyl 6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinate (455 mg, 1 mmol) was added to this solution. The reaction was continued reflux for 2h. The reaction was cooled down to RT and filtered. The filtrate was concentrated to dryness and 120 mg product was obtained by prep-TLC. ¹H NMR (CHLOROFORM-d) δ 7.99 (s, 1H), 7.33 - 7.49 (m, 2H), 7.05 - 7.23 (m, 2H), 4.85 (br. s., 0.5H), 4.42 (d, J = 13.1 Hz, 0.5H), 4.17 (br. s., 0.5H), 3.77 - 3.93 (m, 2H), 3.47 - 3.77 (m, 6H), 3.37 (s, 4H), 3.06 - 3.26 (m, 2H), 2.81 - 3.06 (m, 1H), 2.51 - 2.80 (m, 3H), 2.31 - 2.49 (m, 3H), 1.87 - 2.11 (m, 1H), 1.28 - 1.43 (m, 1.5H), 1.15 - 1.28 (m, 3.5H), 1.12 (br. s., 1H), 0.80 - 1.06 (m, 2H). **(R)-5-(3-cyanophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 283; General procedure 1, Step H):** ¹H NMR (CHLOROFORM-d) δ 7.66 - 7.71 (m, 2H), 7.62 - 7.65 (m, 1H), 7.55 - 7.60 (m, 2H), 4.90 (br. s., 0.5H), 4.53 (d, J = 12.8 Hz, 0.5H), 4.18 - 4.40 (m, 2.5H), 3.67 - 3.88 (m, 2.5H), 3.46 - 3.62 (m, 0.5H), 3.38 (s, 3H), 3.24 - 3.35 (m, 1H), 2.99 - 3.20 (m, 1.5H), 2.64 - 2.81 (m, 1H), 2.49 - 2.63 (m, 1H), 1.85 - 1.97 (m, 1H), 1.38 (d, J = 6.5 Hz, 1.5H), 1.27 (d, J = 6.5 Hz, 1.5H), 1.14 - 1.21 (m, 2H), 0.94 - 1.04 (m, 2H). LC-MS: m/z 430.2 (M+H)⁺

(R)-5-(3-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 285; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 7.57 - 7.60 (m, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.68 - 6.74 (m, 2H), 4.89 (br. s., 0.5H), 4.52 (d, J = 13.3 Hz, 0.5H), 4.09 - 4.31 (m, 2.5H), 3.67 - 3.81 (m, 2.5H), 3.47 - 3.60 (m, 0.5H), 3.37 (s, 3H), 3.18 - 3.29 (m, 1H), 2.95 - 3.16 (m, 1.5H), 2.63 - 2.78 (m, 1H), 2.52 - 2.61 (m, 1H), 2.09 - 2.17 (m, 1H), 1.38 (d, J = 6.5 Hz, 1.5H), 1.28 (d, J = 6.8 Hz, 1.5H), 1.06 - 1.16 (m, 2H), 0.88 - 0.99 (m, 2H). LC-MS: m/z 420.1 (M+H)⁺

(R)-6-cyclopropyl-5-(isoquinolin-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 286; General procedure 1, Step H): ^1H NMR

(CHLOROFORM- d) δ 9.34 (s, 1H), 8.53 (d, J = 6.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.68 - 7.75 (m, 1H), 7.61 - 7.68 (m, 2H), 7.43 (t, J = 5.6 Hz, 1H), 4.94 (br. s., 0.5H), 4.57 (d, J = 13.1 Hz, 0.5H), 4.18 - 4.47 (m, 2.5H), 3.69 - 3.86 (m, 2.5H), 3.54 - 3.67 (m, 0.5H), 3.37 - 3.44 (m, 3H), 3.34 (dd, J = 13.1, 6.3 Hz, 1H), 3.04 - 3.25 (m, 1.5H), 2.67 - 2.78 (m, 1H), 2.54 - 2.67 (m, 1H), 1.48 - 1.58 (m, 1H), 1.39 - 1.47 (m, 1.5H), 1.29 - 1.39 (m, 1.5H), 1.09 - 1.21 (m, 2H), 0.75 - 0.89 (m, 2H). LC-MS: m/z 456.1 ($M+H$) $^+$

(R)-6-cyclopropyl-5-(1H-indol-4-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 287; General procedure 1, Step I): ^1H NMR (CHLOROFORM-

d) δ 8.40 (br. s., 1H), 7.74 (s, 1H), 7.44 (d, J = 8.3 Hz, 1H), 7.24 - 7.29 (m, 1H), 7.02 - 7.10 (m, 1H), 6.37 - 6.45 (m, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J = 13.6 Hz, 0.5H), 4.17 - 4.39 (m, 2.5H), 3.71 - 3.86 (m, 2.5H), 3.51 - 3.65 (m, 0.5H), 3.35 - 3.44 (m, 3H), 3.20 - 3.32 (m, 1H), 2.98 - 3.17 (m, 1.5H), 2.66 - 2.81 (m, 1H), 2.54 - 2.64 (m, 1H), 1.94 - 2.04 (m, 1H), 1.40 - 1.46 (m, 1.5H), 1.32 (d, J = 6.5 Hz, 1.5H), 1.08 - 1.17 (m, 2H), 0.80 - 0.91 (m, 2H). LC-MS: m/z 444.2 ($M+H$) $^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(quinolin-5-yl)nicotinonitrile (Compound 288; General procedure 1, Step H): ^1H NMR

(CHLOROFORM- d) δ 8.97 (dd, J = 4.1, 1.6 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.94 - 8.05 (m, 1H), 7.82 (dd, J = 8.5, 7.0 Hz, 1H), 7.61 - 7.66 (m, 1H), 7.48 - 7.55 (m, 1H), 7.40 - 7.48 (m, 1H), 4.83 - 5.06 (m, 0.5H), 4.56 (d, J = 13.1 Hz, 0.5H), 4.15 - 4.43 (m, 2.5H), 3.69 - 3.91 (m, 2.5H), 3.57 (d, J = 10.5 Hz, 0.5H), 3.36 - 3.45 (m, 3H), 3.33 (dd, J = 13.1, 3.5 Hz, 1H), 3.01 - 3.26 (m, 1.5H), 2.65 - 2.82 (m, 1H), 2.52 - 2.64 (m, 1H), 1.48 - 1.56 (m, 1H), 1.39 - 1.47 (m, 1.5H), 1.29 - 1.38 (m, 1.5H), 1.07 - 1.18 (m, 2H), 0.74 - 0.91 (m, 2H). LC-MS: m/z 456.1 ($M+H$) $^+$

(R)-6-cyclopropyl-5-(1H-indol-6-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 289; General procedure 1, Step I): ^1H NMR (CHLOROFORM-

d) δ 8.41 (br. s., 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.66 (s, 1H), 7.39 (s, 1H), 7.27 - 7.30 (m, 1H), 7.13 (dd, J = 8.0, 1.5 Hz, 1H), 6.60 (t, J = 2.1 Hz, 1H), 4.91 (br. s., 0.5H), 4.53 (d, J = 13.6 Hz, 0.5H), 4.13 - 4.32 (m, 2.5H), 3.68 - 3.84 (m, 2.5H), 3.49 - 3.65 (m, 0.5H), 3.38 (s, 3H), 3.17 - 3.31 (m, 1H), 2.93 - 3.16 (m, 1.5H), 2.64 - 2.82 (m, 1H), 2.53 - 2.63 (m, 1H), 2.13 - 2.23 (m, 1H),

1.40 (d, J = 6.5 Hz, 1.5H), 1.30 (d, J = 6.8 Hz, 1.5H), 1.09 - 1.17 (m, 2H), 0.84 - 0.98 (m, 2H).

LC-MS: m/z 444.2 (M+H)⁺

(R)-6-cyclopropyl-5-(4-fluoronaphthalen-1-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 290; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 8.19 (d, J = 8.0 Hz, 1H), 7.50 - 7.65 (m, 4H), 7.30 - 7.37 (m, 1H), 7.22 (dd, J = 10.2, 7.9 Hz, 1H), 4.93 (br. s., 0.5H), 4.56 (d, J = 13.3 Hz, 0.5H), 4.15 - 4.42 (m, 2.5H), 3.69 - 3.90 (m, 2.5H), 3.50 - 3.68 (m, 0.5H), 3.36 - 3.43 (m, 3H), 3.24 - 3.34 (m, 1H), 3.00 - 3.23 (m, 1.5H), 2.65 - 2.85 (m, 1H), 2.55 - 2.64 (m, 1H), 1.54 - 1.61 (m, 1H), 1.40 - 1.48 (m, 1.5H), 1.33 (dd, J = 6.3, 3.5 Hz, 1.5H), 1.07 - 1.18 (m, 2H), 0.72 - 0.85 (m, 2H). LC-MS: m/z 473.1 (M+H)⁺

(R)-methyl 2-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetate (Compound 291; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.36 - 7.45 (m, 1H), 7.25 - 7.34 (m, 3H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.1 Hz, 0.5H), 4.26 (t, J = 12.5 Hz, 2.5H), 3.64 - 3.85 (m, 7H), 3.50 - 3.61 (m, 0.5H), 3.38 (s, 3H), 3.19 - 3.30 (m, 1H), 2.93 - 3.18 (m, 2H), 2.63 - 2.81 (m, 1H), 2.49 - 2.63 (m, 1H), 2.02 - 2.12 (m, 1H), 1.39 (d, J = 6.3 Hz, 1.5H), 1.28 (d, J = 6.5 Hz, 1.5H), 1.10 - 1.20 (m, 2H), 0.89 - 1.00 (m, 2H). LC-MS: m/z 477.1 (M+H)⁺

(R)-6-cyclopropyl-5-(1H-indazol-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 295; General procedure 2, Step M): ¹H NMR (CHLOROFORM-d) δ 8.14 (br. s., 1H), 7.75 (s, 1H), 7.65 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.42 (dd, J = 8.7, 1.4 Hz, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J = 13.3 Hz, 0.5H), 4.12 - 4.39 (m, 2.5H), 3.69 - 3.89 (m, 2.5H), 3.50 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.20 - 3.33 (m, 1H), 2.97 - 3.20 (m, 1.5H), 2.66 - 2.82 (m, 1H), 2.52 - 2.64 (m, 1H), 1.99 - 2.14 (m, 1H), 1.36 - 1.46 (m, 1.5H), 1.30 (d, J = 6.8 Hz, 1.5H), 1.13 - 1.21 (m, 2H), 0.90 - 0.99 (m, 2H). LC-MS: m/z 445.4 (M+H)⁺

(R)-4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)benzamide (Compound 296; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 7.84 - 7.96 (m, J = 8.5 Hz, 2H), 7.57 - 7.66 (m, 1H), 7.45 - 7.56 (m, 2H), 6.27 (br. s., 1H), 5.99 (br. s., 1H), 4.90 (br. s., 0.5H), 4.52 (d, J = 13.3 Hz, 0.5H), 4.14 - 4.38 (m, 2.5H), 3.70 - 3.87 (m, 2.5H), 3.47 - 3.62 (m, 0.5H), 3.33 - 3.43 (m, 3H), 3.27 (t, J = 10.3 Hz, 1H), 2.99 - 3.21 (m, 1.5H), 2.64 - 2.83 (m, 1H), 2.50 - 2.64 (m, 1H), 1.95 - 2.09 (m, 1H), 1.38 (d, J = 6.3 Hz,

1.5H), 1.25 - 1.31 (m, 1.5H), 1.13 - 1.21 (m, 2H), 0.92 - 1.02 (m, 2H). LC-MS: m/z 448.5 (M+H)⁺

(R)-6-cyclopropyl-5-(3-(2-hydroxyethyl)phenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 297; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 7.60 (s, 1H), 7.35 - 7.42 (m, 1H), 7.23 - 7.27 (m, 3H), 4.89 (br. s., 0.5H), 4.52 (d, J = 13.1 Hz, 0.5H), 4.14 - 4.31 (m, 2.5H), 3.91 (t, J = 6.7 Hz, 2H), 3.68 - 3.83 (m, 2.5H), 3.49 - 3.61 (m, 0.5H), 3.37 (s, 3H), 3.19 - 3.29 (m, 1H), 2.97 - 3.18 (m, 1.5H), 2.91 - 2.97 (m, 2H), 2.64 - 2.81 (m, 1H), 2.52 - 2.62 (m, 1H), 2.02 - 2.14 (m, 1H), 1.39 (d, J = 6.3 Hz, 1.5H), 1.27 - 1.32 (m, 1.5H), 1.08 - 1.19 (m, 2H), 0.89 - 1.02 (m, 2H). LC-MS: m/z 449.6 (M+H)⁺

(R)-3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)benzamide (Compound 305; General procedure 1, Step H): ¹H NMR (METHANOL-d₄) δ 7.96 (t, J = 1.5 Hz, 1H), 7.91 (dt, J = 7.7, 1.6 Hz, 1H), 7.81 (s, 1H), 7.62 - 7.67 (m, 1H), 7.56 - 7.62 (m, 1H), 4.82 (br. s., 0.5H), 4.38 - 4.48 (m, 1H), 4.16 - 4.29 (m, 2H), 3.97 (d, J = 13.6 Hz, 0.5H), 3.68 - 3.76 (m, 2H), 3.54 - 3.67 (m, 0.5H), 3.36 (s, 4H), 3.05 - 3.26 (m, 1.5H), 2.72 - 2.89 (m, 1H), 2.57 - 2.70 (m, 1H), 1.99 - 2.10 (m, 1H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.29 (d, J = 6.8 Hz, 1.5H), 1.20 (dq, J = 4.4, 3.1 Hz, 2H), 0.93 - 1.04 (m, 2H). LC-MS: m/z 448.3 (M+H)⁺

(R)-6-cyclopropyl-5-(3-(hydroxymethyl)phenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 306; General procedure 1, Step H): ¹H NMR (METHANOL-d₄) δ 7.71 (br. s., 1H), 7.37 - 7.48 (m, 3H), 7.32 (d, J = 7.5 Hz, 1H), 4.80 (br. s., 1H), 4.68 (s, 3H), 4.36 - 4.51 (m, 1H), 4.13 - 4.30 (m, 2H), 3.95 (d, J = 13.6 Hz, 0.5H), 3.67 - 3.78 (m, 2H), 3.50 - 3.65 (m, 0.5H), 3.27 - 3.35 (m, 2.5H), 2.99 - 3.20 (m, 1.5H), 2.70 - 2.84 (m, 1H), 2.61 - 2.67 (m, 1H), 2.06 - 2.13 (m, 1H), 1.40 (d, J = 6.5 Hz, 1.5H), 1.28 (d, J = 6.8 Hz, 1.5H), 1.12 - 1.24 (m, 2H), 0.96 (dd, J = 7.3, 3.5 Hz, 2H). LC-MS: m/z 435.3 (M+H)⁺

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-oxoindolin-6-yl)nicotinonitrile (Compound 313; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 8.40 (s, 1H), 7.53 - 7.64 (m, 1H), 7.29 (d, J = 7.8 Hz, 1H), 6.98 - 7.07 (m, 1H), 6.87 - 6.93 (m, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.4 Hz, 0.5H), 4.13 - 4.37 (m, 2.5H), 3.68 - 3.88 (m, 2.5H), 3.49 - 3.65 (m, 2.5H), 3.34 - 3.43 (m, 3H), 3.20 - 3.31 (m, 1H), 2.95 - 3.18 (m, 1.5H), 2.51 - 2.81 (m, 2H), 2.02 - 2.15 (m, 1H), 1.38 - 1.40 (m, 1.5H), 1.26 - 1.31 (m, 1.5H), 1.07 - 1.20 (m, 2H), 0.90 - 1.04 (m, 2H). LC-MS: m/z 460.2 (M+H)⁺

(R)-6'-amino-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,3'-bipyridine-5-carbonitrile (Compound 314; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 8.10 (d, J = 2.0 Hz, 1H), 7.54 (s, 1H), 7.44 - 7.50 (m, 1H), 6.55 - 6.64 (m, 1H), 4.89 (br. s., 0.5H), 4.72 (br. s., 2H), 4.52 (d, J = 13.3 Hz, 0.5H), 4.15 - 4.31 (m, 2.5H), 3.69 - 3.85 (m, 2.5H), 3.49 - 3.63 (m, 0.5H), 3.34 - 3.43 (m, 3H), 3.19 - 3.31 (m, 1H), 2.96 - 3.17 (m, 1.5H), 2.51 - 2.81 (m, 2H), 1.99 - 2.08 (m, 1H), 1.23 - 1.41 (m, 3H), 1.11 - 1.18 (m, 2H), 0.90 - 0.99 (m, 2H). LC-MS: m/z 421.4 (M+H)⁺

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(quinolin-4-yl)nicotinonitrile (Compound 315; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 8.99 (d, J = 4.5 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.78 (t, J = 7.5 Hz, 1H), 7.61 - 7.71 (m, 2H), 7.53 - 7.61 (m, 1H), 7.36 (d, J = 4.0 Hz, 1H), 4.93 (br. s., 0.5H), 4.56 (d, J = 12.5 Hz, 0.5H), 4.25 - 4.45 (m, 2.5H), 3.68 - 3.91 (m, 2.5H), 3.57 (d, J = 9.3 Hz, 0.5H), 3.29 - 3.45 (m, 4H), 3.01 - 3.27 (m, 1.5H), 2.65 - 2.84 (m, 1H), 2.51 - 2.65 (m, 1H), 1.54 (td, J = 8.2, 4.1 Hz, 1H), 1.42 (d, J = 5.5 Hz, 1.5H), 1.32 (t, J = 5.0 Hz, 1.5H), 1.05 - 1.21 (m, 2H), 0.74 - 0.92 (m, 2H). LC-MS: m/z 456.0 (M+H)⁺

(R)-6-cyclopropyl-5-(2,6-dimethoxyphenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 316; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 7.51 - 7.57 (m, 1H), 7.30 - 7.38 (m, 1H), 6.65 (d, J = 8.3 Hz, 2H), 4.90 (br. s., 0.5H), 4.52 (d, J = 13.6 Hz, 0.5H), 4.11 - 4.34 (m, 2.5H), 3.67 - 3.84 (m, 8.5H), 3.47 - 3.62 (m, 0.5H), 3.32 - 3.43 (m, 3H), 2.95 - 3.24 (m, 2.5H), 2.63 - 2.84 (m, 1H), 2.51 - 2.63 (m, 1H), 1.65 - 1.72 (m, 1H), 1.41 (d, J = 6.5 Hz, 1.5H), 1.31 (d, J = 6.8 Hz, 1.5H), 1.00 - 1.12 (m, 2H), 0.75 - 0.86 (m, 2H). LC-MS: m/z 465.2 (M+H)⁺

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-(2,2,2-trifluoroacetyl)-1H-indol-5-yl)nicotinonitrile (Compound 317; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 8.44 (s, 1H), 8.10 - 8.18 (m, 1H), 7.67 (s, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 8.3 Hz, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J = 12.8 Hz, 0.5H), 4.17 - 4.39 (m, 2.5H), 3.69 - 3.88 (m, 2.5H), 3.52 - 3.69 (m, 0.5H), 3.35 - 3.45 (m, 3H), 3.22 - 3.35 (m, 1H), 2.98 - 3.20 (m, 1.5H), 2.54 - 2.82 (m, 2H), 2.04 - 2.13 (m, 1H), 1.38 - 1.47 (m, 1.5H), 1.31 (d, J = 6.5 Hz, 1.5H), 1.14 - 1.19 (m, 2H), 0.90 - 0.97 (m, 2H). LC-MS: m/z 540.2 (M+H)⁺

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(quinolin-8-yl)nicotinonitrile (Compound 342; General procedure 1, Step H): ¹H NMR

(CHLOROFORM-d) δ 8.94 (dd, J = 4.1, 1.6 Hz, 1H), 8.23 (dd, J = 8.3, 1.8 Hz, 1H), 7.90 (dd, J = 8.2, 1.4 Hz, 1H), 7.73 (s, 1H), 7.66 - 7.71 (m, 1H), 7.59 - 7.66 (m, 1H), 7.45 (dd, J = 8.3, 4.3 Hz, 1H), 4.92 (br. s., 0.5H), 4.54 (d, J = 13.3 Hz, 0.5H), 4.13 - 4.38 (m, 2.5H), 3.68 - 3.87 (m, 2.5H), 3.50 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.24 (t, J = 12.8 Hz, 1H), 2.96 - 3.17 (m, 1.5H), 2.52 - 2.82 (m, 2H), 1.59 - 1.68 (m, 1H), 1.43 (d, J = 6.5 Hz, 1.5H), 1.33 (d, J = 6.5 Hz, 1.5H), 1.07 (br. s., 2H), 0.78 (br. s., 2H)

(R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetamide (Compound 284; General procedure 3, step N, method 1)

¹H NMR (CHLOROFORM-d) δ 7.64 (s, 1H), 7.58 (s, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 4.89 (br. s., 0.5H), 4.52 (d, J = 13.3 Hz, 0.5H), 4.11 - 4.36 (m, 2.5H), 3.67 - 3.86 (m, 2.5H), 3.54 (t, J = 10.9 Hz, 0.5H), 3.33 - 3.43 (m, 3H), 3.18 - 3.31 (m, 1H), 2.94 - 3.17 (m, 1.5H), 2.63 - 2.79 (m, 1H), 2.51 - 2.63 (m, 1H), 2.17 - 2.28 (m, 3H), 2.06 - 2.14 (m, 1H), 1.38 (d, J = 6.5 Hz, 1.5H), 1.27 (d, J = 7.0 Hz, 1.5H), 1.08 - 1.17 (m, 2H), 0.91 - 1.00 (m, 2H). LC-MS: m/z 462.2 (M+H)⁺

(R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acrylamide (Compound 343; General procedure 3, Step N, method 1): ¹H NMR (CHLOROFORM-d) δ 7.70 - 7.79 (m, 2H), 7.54 - 7.63 (m, 2H), 7.41 (t, J = 7.9 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 6.48 (dd, J = 16.8, 1.0 Hz, 1H), 6.31 (dd, J = 16.8, 10.0 Hz, 1H), 5.81 (dd, J = 10.2, 1.1 Hz, 1H), 4.91 (br. s., 1H), 4.54 (d, J = 13.1 Hz, 0.5H), 4.12 - 4.36 (m, 2.5H), 3.69 - 3.88 (m, 2.5H), 3.49 - 3.65 (m, 0.5H), 3.38 (s, 3H), 3.20 - 3.33 (m, 1H), 2.96 - 3.17 (m, 1.5H), 2.54 - 2.81 (m, 2H), 2.07 - 2.16 (m, 1H), 1.39 (d, J = 6.5 Hz, 1.5H), 1.25 - 1.35 (m, 1.5H), 1.15 (quin, J = 3.6 Hz, 2H), 0.89 - 1.02 (m, 2H). LC-MS: m/z 474.6 (M+H)⁺ (R,E)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)but-2-enamide (Compound 415; General procedure 3, Step N, method 2): ¹H

NMR (CHLOROFORM-d) δ 7.64 - 7.76 (m, 2H), 7.60 - 7.63 (m, 1H), 7.49 - 7.53 (m, 1H), 7.37 - 7.44 (m, 1H), 7.30 - 7.35 (m, 1H), 7.14 (d, J = 7.8 Hz, 1H), 6.95 - 7.10 (m, 1H), 5.99 (dd, J = 15.1, 1.8 Hz, 1H), 4.92 (s, 0.5H), 4.54 (d, J = 12.8 Hz, 0.5H), 4.20 - 4.32 (m, 2.5H), 3.76 (t, J = 6.3 Hz, 2H), 3.50 - 3.62 (m, 0.5H), 3.39 (s, 3H), 3.18 - 3.34 (m, 1.5H), 2.97 - 3.16 (m, 1.5H), 2.65

- 2.80 (m, 1H), 2.53 - 2.65 (m, 1H), 2.09 - 2.16 (m, 1H), 1.95 (dd, J = 6.8, 1.5 Hz, 3H), 1.40 (d, J = 6.3 Hz, 1H), 1.29 - 1.31 (m, 2H), 1.12 - 1.19 (m, 2H), 0.92 - 1.01 (m, 2H)

LC-MS: m/z 487.3 (M+H)⁺

(R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-2-oxopropanamide (Compound 416; General procedure 3, step N, method 2): ¹H NMR (CHLOROFORM-d) δ 7.38 - 7.66 (m, 4H), 7.32 (dd, J = 3.9, 1.9 Hz, 1H), 7.12 - 7.25 (m, 1H), 4.89 (s, 0.5H), 4.52 (d, J = 10.8 Hz, 0.5H), 4.22 - 4.34 (m, 2H), 4.10 - 4.22 (m, 0.5H), 3.66 - 3.85 (m, 2.5H), 3.55 (d, J = 3.5 Hz, 0.5H), 3.39 (d, J = 1.5 Hz, 3H), 3.20 - 3.31 (m, 1H), 3.10-3.14 (m, 1.5H), 2.97 - 3.09 (m, 1H), 2.66 - 2.80 (m, 1H), 2.53 - 2.64 (m, 1H), 1.97 - 2.07 (m, 1H), 1.55-1.58 (m, 3H), 1.35 - 1.42 (m, 2H), 1.10 - 1.17 (m, 1H), 1.05 - 1.10 (m, 1H), 0.73 - 0.96 (m, 4H). LC-MS: m/z 490.2 (M+H)⁺

(R)-2-chloro-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetamide (Compound 403; General procedure 3, Step N, method 1): ¹H NMR (CHLOROFORM-d) δ 8.34 (s, 1H), 7.66 - 7.75 (m, 1H), 7.62 (s, 1H), 7.50 - 7.55 (m, 1H), 7.42 - 7.48 (m, 1H), 7.22 (d, J = 7.8 Hz, 1H), 4.92 (s, 0.5H), 4.50-4.54 (m, 0.5H), 4.29 - 4.33 (m, 1H), 4.26 (m, 1H), 4.21-4.25 (m, 0.5H), 3.71 - 3.84 (m, 2.5H), 3.52-3.57 (m, 0.5H), 3.39 (s, 3H), 3.21 - 3.32 (m, 1H), 3.13 (d, J = 11.3 Hz, 1H), 3.05 (d, J = 12.3 Hz, 0.5H), 2.66 - 2.81 (m, 1H), 2.54 - 2.65 (m, 1H), 2.07 - 2.12 (m, 1H), 1.40 (d, J = 6.3 Hz, 1H), 1.28 - 1.31 (m, 2H), 1.14 - 1.19 (m, 2H), 0.94 - 1.00 (m, 2H). LC-MS: m/z 495.2 (M+H)⁺

(R)-1-chloro-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)methanesulfonamide (Compound 404; General procedure 3, Step N, method 1): ¹H NMR (CHLOROFORM-d) δ 7.61 (s, 1H), 7.44 - 7.52 (m, 1H), 7.36 - 7.41 (m, 1H), 7.29 - 7.36 (m, 2H), 7.11 (br. s., 1H), 4.92 (s, 1H), 4.45 - 4.63 (m, 2.5H), 4.18 - 4.40 (m, 2.5H), 3.66 - 3.89 (m, 2.5H), 3.50- 3.57 (m, 0.5H), 3.39 (s, 3H), 3.29 (t, J = 10.2 Hz, 1H), 2.99 - 3.20 (m, 1.5H), 2.65 - 2.83 (m, 1H), 2.52 - 2.64 (m, 1H), 1.99 - 2.06 (m, 1H), 1.40 (d, J = 6.3 Hz, 1H), 1.30 (s, 2H), 1.15 - 1.22 (m, 2H), 0.96 - 1.03 (m, 2H). LC-MS: m/z 531.2 (M+H)⁺

(R)-2-chloro-N-(3-(5-cyano-2-cyclopropyl-6-((R)-4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)propanamide (Compound 462; General procedure 3, Step N, method 2): ¹H NMR (CHLOROFORM-d) δ 8.54 (s, 1H), 7.67 - 7.73 (m, 1H), 7.60 (s, 1H), 7.49 - 7.57 (m, 1H), 7.38 - 7.45 (m, 1H), 7.14 - 7.22 (m, 1H), 4.90 (br. s.,

0.5H), 4.44 - 4.64 (m, 1.5H), 4.16 - 4.37 (m, 2.5H), 3.68 - 3.86 (m, 2.5H), 3.50 - 3.63 (m, 0.5H), 3.37 (s, 3H), 3.19 - 3.32 (m, 1H), 2.96 - 3.17 (m, 1.5H), 2.53 - 2.78 (m, 2H), 2.05 - 2.12 (m, 1H), 1.83 (d, J = 7.0 Hz, 3H), 1.39 (d, J = 6.5 Hz, 1.5H), 1.28 (dd, J = 6.9, 2.6 Hz, 1.5H), 1.10 - 1.19 (m, 2H), 0.90 - 1.02 (m, 2H). LC-MS: m/z 510.2 (M+H)⁺

(R)-N-(4-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)acetamide (Compound 412; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 7.55 - 7.67 (m, 3H), 7.31 - 7.44 (m, 3H), 4.91 (s, 0.5H), 4.54 (d, J = 13.6 Hz, 0.5H), 4.14 - 4.33 (m, 2.5H), 3.65 - 3.93 (m, 2.5H), 3.46 - 3.65 (m, 0.5H), 3.39 (s, 3H), 3.20 - 3.30 (m, 1H), 2.98 - 3.19 (m, 1.5H), 2.51 - 2.81 (m, 1H), 2.16 - 2.31 (m, 3H), 1.98 - 2.13 (m, 1H), 1.24 - 1.44 (m, 4H), 1.08 - 1.18 (m, 2H), 0.84 - 0.99 (m, 2H). LC-MS: m/z 462.6 (M+H)⁺

(R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)propionamide (Compound 424; General procedure 3, Step N, method 2): ¹H NMR (CHLOROFORM-d) δ 7.75 (s, 1H), 7.68 (s, 1H), 7.59 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.11 (d, J = 7.5 Hz, 1H), 4.89 (s, 0.5H), 4.52 (d, J = 13.3 Hz, 0.5H), 4.14 - 4.35 (m, 2.5H), 3.67 - 3.85 (m, 2.5H), 3.49 - 3.62 (m, 0.5H), 3.37 (s, 3H), 3.17 - 3.32 (m, 1H), 2.93 - 3.17 (m, 1.5H), 2.63 - 2.81 (m, 1H), 2.52 - 2.63 (m, 1H), 2.37 - 2.49 (m, 2H), 2.05 - 2.13 (m, 1H), 1.38 (d, J = 6.5 Hz, 1H), 1.22 - 1.31 (m, 5H), 1.14 (dt, J = 7.4, 3.6 Hz, 2H), 0.88 - 1.01 (m, 2H). LC-MS: m/z 476.3 (M+H)⁺

(R)-1-cyano-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)cyclopropanecarboxamide (Compound 425; General procedure 3, Step N, method 2): ¹H NMR (CHLOROFORM-d) δ 8.11 (s, 1H), 7.65 (s, 1H), 7.61 (s, 1H), 7.42 - 7.50 (m, 2H), 7.19 - 7.25 (m, 1H), 4.92 (s, 0.5H), 4.55 (d, J = 12.3 Hz, 0.5H), 4.17 - 4.39 (m, 2.5H), 3.71-3.76 (m, 2.5H), 3.55-3.58 (m, 0.5H), 3.36 - 3.46 (m, 3H), 3.21 - 3.33 (m, 1H), 3.14 (d, J = 13.3 Hz, 1.5H), 3.05 (d, J = 12.0 Hz, 1H), 2.63-3.75 (s, 1H), 2.61-3.63 (m, 1H), 2.02 - 2.12 (m, 1H), 1.81 - 1.91 (m, 2H), 1.66 (q, J = 4.5 Hz, 2H), 1.40 (d, J = 5.5 Hz, 1H), 1.25 - 1.33 (m, 2H), 1.12 - 1.20 (m, 2H), 0.92 - 1.01 (m, 2H). LC-MS: m/z 513.2 (M+H)⁺

Compound 427 (General procedure 3, Step N, method 1): ^1H NMR (CHLOROFORM- d) δ 7.62 (s, 1H), 7.47 - 7.56 (m, 1H), 7.35 - 7.44 (m, 1H), 7.18 - 7.25 (m, 2H), 6.42 (dd, J = 16.8, 2.0 Hz, 1H), 6.16 (dd, J = 16.6, 10.3 Hz, 1H), 5.57 (dd, J = 10.2, 1.6 Hz, 1H), 4.92 (d, J = 12.8 Hz, 0.5H), 4.55 (d, J = 12.8 Hz, 0.5H), 4.13 - 4.41 (m, 3H), 3.69 - 3.90 (m, 3H), 3.58 (d, J = 9.3 Hz, 1H), 3.39 (s, 3H), 3.42 (s, 3H), 3.29 (t, J = 9.5 Hz, 1H), 3.01 - 3.21 (m, 2H), 2.65 - 2.80 (m, 1H), 2.47 - 2.65 (m, 1H), 1.88 - 2.07 (m, 1H), 1.65 (br. s., 3H), 1.35 - 1.44 (m, 2H), 1.25 - 1.35 (m, 2H), 1.09 - 1.25 (m, 2H), 0.92 - 1.09 (m, 2H). LC-MS: m/z 488.2 ($M+H$) $^+$

(R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)propiolamide (Compound 428; General procedure 3, Step N, method 2): ^1H NMR (CHLOROFORM- d) δ 7.63 - 7.69 (m, 2H), 7.61 (s, 1H), 7.41 - 7.50 (m, 2H), 7.20 (d, J = 7.3 Hz, 1H), 4.92 (s, 0.5H), 4.54 (d, J = 11.8 Hz, 0.5H), 4.12 - 4.40 (m, 2.5H), 3.72 - 3.79 (m, 2.5H), 3.51-3.57 (m, 0.5H), 3.40 (s, 3H), 3.23 - 3.32 (m, 1H), 3.14 (d, J = 13.1 Hz, 1H), 3.05 (d, J = 11.0 Hz, 1H), 2.99 (s, 1H), 2.65 - 2.81 (m, 1H), 2.54 - 2.65 (m, 1H), 2.05 - 2.13 (m, 1H), 1.40 (d, J = 6.5 Hz, 1H), 1.14 - 1.19 (m, 2H), 0.95 - 1.01 (m, 2H), 0.88 - 0.93 (m, 2H). LC-MS: m/z 472.2 ($M+H$) $^+$

(R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)ethenesulfonamide (Compound 429; General procedure 3, Step N, method 1): To a solution of (R)-5-(3-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (20 mg, 0.048 mmol) and 2-chloroethanesulfonyl chloride (8.6 mg, 0.052 mmol) in 5 ml of DCM was added dropwise TEA (15 mg, 0.143 mmol) at 0 $^{\circ}\text{C}$, then the resulting mixture was allowed to warm to room temperature and stirred for 2 hours. The mixture was partitioned between EtOAc and water. The organic layer was dried over Na_2SO_4 and concentrated to give the crude which was purified by prep-TLC to give 15 mg of the product. ^1H NMR (CHLOROFORM- d) δ 7.55 - 7.61 (m, 1H), 7.37 - 7.46 (m, 1H), 7.15 - 7.26 (m, 3H), 6.70 (d, J = 12.8 Hz, 1H), 6.62 (dd, J = 16.4, 9.9 Hz, 1H), 6.34 (d, J = 16.3 Hz, 1H), 6.02 (d, J = 9.8 Hz, 1H), 4.92 (s, 0.5H), 4.54 (d, J = 13.3 Hz, 0.5H), 4.19 - 4.37 (m, 2.5H), 3.73 - 3.79 (m, 3H), 3.52 - 3.61 (m, 0.5H), 3.39 (s, 3H), 3.28 (t, J = 10.4 Hz, 1H), 3.02-3.14 (m, 1H), 2.65 - 2.80 (m, 1H), 2.55 - 2.64 (m, 1H), 1.98 - 2.07 (m, 1H), 1.27 (s, 3H), 1.14 - 1.19 (m, 2H), 0.95 - 1.01 (m, 2H).

(R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-2-fluoroacrylamide (Compound 431; General procedure 3, Step N, method 2): ^1H NMR (CHLOROFORM- d) δ 8.19 (d, J = 4.5 Hz, 1H), 7.75 (s, 1H), 7.61 (s, 1H), 7.57 (dd, J = 8.0, 1.3 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.16 - 7.23 (m, 1H), 5.84 (dd, J = 18.0 Hz, J = 3.3 Hz, 0.5H), 5.21 - 5.35 (m, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J = 13.1 Hz, 0.5H), 4.10 - 4.38 (m, 2.5H), 3.66 - 3.86 (m, 2.5H), 3.50 - 3.64 (m, 0.5H), 3.38 (s, 3H), 3.19 - 3.33 (m, 1H), 2.95 - 3.18 (m, 1.5H), 2.56 - 2.78 (m, 2H), 2.04 - 2.16 (m, 1H), 1.39 (d, J = 6.3 Hz, 1.5H), 1.28 (d, J = 6.8 Hz, 1.5H), 1.11 - 1.22 (m, 2H), 0.91 - 1.03 (m, 2H). LC-MS: m/z 492.7 ($M+H$) $^+$

(R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-2,2-difluoroacetamide (Compound 432; General procedure 3, Step N, method 2): ^1H NMR (CHLOROFORM- d) δ 8.79 (br. s., 1H), 7.77 (s, 1H), 7.55 - 7.65 (m, 2H), 7.44 (t, J = 7.9 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 6.05 (t, J = 56.0 Hz, 1H), 4.89 (br. s., 0.5H), 4.51 (d, J = 13.3 Hz, 0.5H), 4.08 - 4.37 (m, 2.5H), 3.66 - 3.88 (m, 2.5H), 3.49 - 3.63 (m, 0.5H), 3.36 (s, 3H), 2.96 - 3.25 (m, 2.5H), 2.81 (s, 6H), 2.50 - 2.79 (m, 2H), 2.03 - 2.13 (m, 1H), 1.32 - 1.45 (m, 1.5H), 1.27 (d, J = 6.8 Hz, 1.5H), 1.10 - 1.17 (m, 2H), 0.91 - 1.02 (m, 2H). LC-MS: m/z 498.8 ($M+H$) $^+$

(R)-5-(4-aminophenyl)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 383; General procedure 1, Step H): ^1H NMR (CHLOROFORM- d) δ 7.53 - 7.62 (m, 1H), 7.11 - 7.21 (m, 2H), 6.70 - 6.83 (m, 2H), 4.89 (br. s., 0.5H), 4.52 (d, J = 13.6 Hz, 0.5H), 4.04 - 4.28 (m, 2.5H), 3.64 - 3.88 (m, 4.5H), 3.47 - 3.64 (m, 0.5H), 3.30 - 3.43 (m, 3H), 3.14 - 3.27 (m, 1H), 2.92 - 3.14 (m, 1.5H), 2.50 - 2.79 (m, 2H), 2.08 - 2.15 (m, 1H), 1.34 - 1.43 (m, 1.5H), 1.28 - 1.30 (m, 1.5H), 1.06 - 1.15 (m, 2H), 0.84 - 0.95 (m, 2H). LC-MS: m/z 420.1 ($M+H$) $^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(2-oxoindolin-5-yl)nicotinonitrile (Compound 384; General procedure 1, Step H): ^1H NMR (CHLOROFORM- d) δ 8.22 (s, 1H), 7.50 - 7.64 (m, 1H), 7.21 - 7.26 (m, 2H), 6.85 - 7.03 (m, 1H), 4.90 (br. s., 0.5H), 4.53 (d, J = 13.6 Hz, 0.5H), 4.10 - 4.37 (m, 2.5H), 3.68 - 3.86 (m, 2.5H), 3.48 - 3.64 (m, 2.5H), 3.35 - 3.44 (m, 3H), 3.19 - 3.31 (m, 1H), 2.94 - 3.17 (m, 1.5H), 2.52 - 2.82 (m, 2H), 1.99 - 2.09 (m, 1H), 1.39 (d, J = 6.5 Hz, 1.5H), 1.28 (d, J = 6.8 Hz, 1.5H), 1.09 - 1.20 (m, 2H), 0.91 - 0.99 (m, 2H). LC-MS: m/z 460.5 ($M+H$) $^+$

(R)-6-cyclopropyl-5-(1H-indazol-6-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 385; General procedure 1, Step H): ^1H NMR

(CHLOROFORM- d) δ 8.14 (br. s., 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.66 (s, 1H), 7.50 (s, 1H), 7.16 - 7.24 (m, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J = 12.5 Hz, 0.5H), 4.16 - 4.39 (m, 2.5H), 3.69 - 3.85 (m, 2.5H), 3.50 - 3.65 (m, 0.5H), 3.38 (s, 3H), 3.20 - 3.32 (m, 1H), 2.98 - 3.14 (m, 1.5H), 2.52 - 2.82 (m, 2H), 2.04 - 2.13 (m, 1H), 1.28 - 1.43 (m, 3H), 0.91 - 0.98 (m, 2H), 0.81 - 0.89 (m, 2H). LC-MS: m/z 445.5 ($M+H$) $^+$

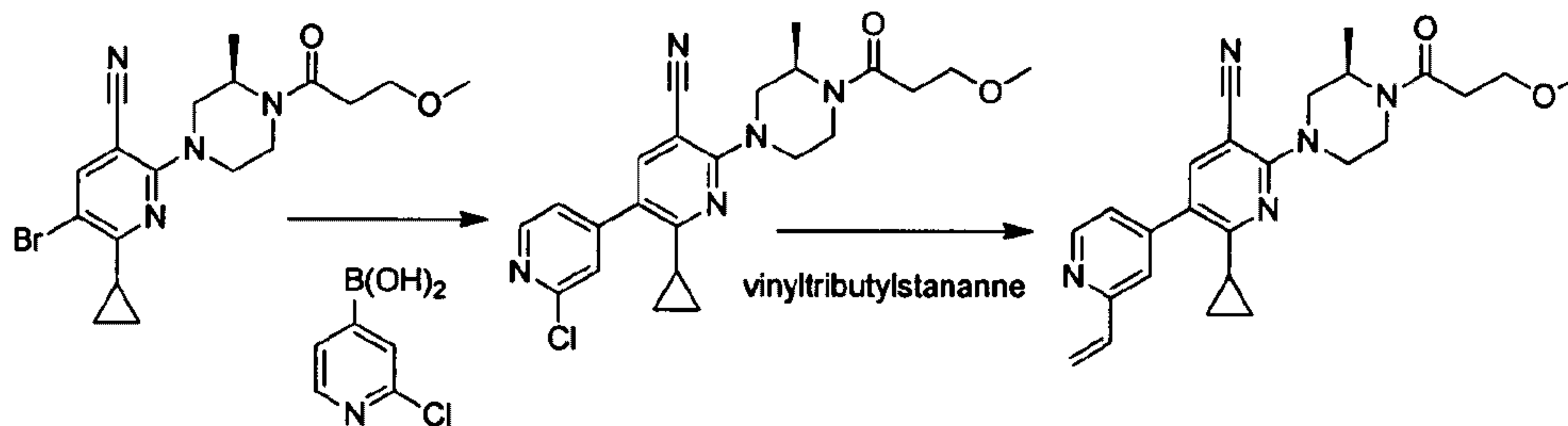
(R)-6-cyclopropyl-5-(isoquinolin-5-yl)-2-(3-methyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)nicotinonitrile (Compound 386; General procedure 2, Step M): ^1H NMR

(CHLOROFORM- d) δ 9.30 - 9.40 (m, 1H), 8.49 - 8.58 (m, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.67 - 7.75 (m, 1H), 7.62 - 7.67 (m, 2H), 7.36 - 7.45 (m, 1H), 4.95 (br. s., 0.5H), 4.58 - 4.61 (m, 0.5H), 4.27 - 4.49 (m, 2H), 4.14 (br. s., 0.5H), 3.59 - 3.73 (m, 1H), 3.11 - 3.39 (m, 4.5H), 1.45 - 1.55 (m, 2.5H), 1.37 (dd, J = 6.4, 4.4 Hz, 1.5H), 1.07 - 1.19 (m, 2H), 0.77 - 0.87 (m, 2H). LC-MS: m/z 480.1 ($M+H$) $^+$

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 387; General procedure 2, Step M): ^1H NMR

(CHLOROFORM- d) δ 9.40 (br. s., 1H), 8.56 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.72 - 7.78 (m, 1H), 7.64 - 7.71 (m, 2H), 7.46 (dd, J = 12.5, 5.8 Hz, 1H), 4.58 (dt, J = 13.1, 2.1 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.09 - 4.26 (m, 0.5H), 3.80 - 3.86 (m, 1.5H), 3.08 - 3.44 (m, 5H), 1.49 - 1.57 (m, 1H), 1.33 (br. s., 1H), 1.08 - 1.22 (m, 2H), 0.82 - 0.91 (m, 2H), 0.41 - 0.72 (m, 4H). LC-MS: m/z 506.7 ($M+H$) $^+$

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 390)



A mixture of 7-1 (410 mg, 1.01 mmol), 2-chloropyridin-4-ylboronic acid (237 mg, 0.95 mmol), K_2CO_3 (414 mg, 3.03 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (40 mg, 0.035 mmol) in DMF (2mL) was

stirred at 150°C in the microwave reactor for 1h. The resultant mixture was partitioned between EtOAc and water, the organic phase was washed with water, brine and concentrated and purified by prepTLC (PE:EA=1:1) to give 375 mg of (R)-2'-chloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4'-bipyridine-5-carbonitrile. ¹H NMR (CHLOROFORM-d) δ 8.34 - 8.61 (m, 1H), 7.60 (s, 1H), 7.39 (d, J = 1.0 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J = 11.8 Hz, 0.5H), 4.21 - 4.41 (m, 2.5H), 3.68 - 3.91 (m, 2.5H), 3.54 (d, J = 4.0 Hz, 1H), 3.25 - 3.45 (m, 4H), 2.95 - 3.25 (m, 1H), 2.63 - 2.92 (m, 1H), 2.42 - 2.63 (m, 1H), 1.87 - 2.07 (m, 1H), 1.36 (d, J = 6.5 Hz, 1.5H), 1.11 - 1.31 (m, 3.5H), 0.81 - 1.11 (m, 2H). LC-MS: m/z 440.1 (M+H)⁺

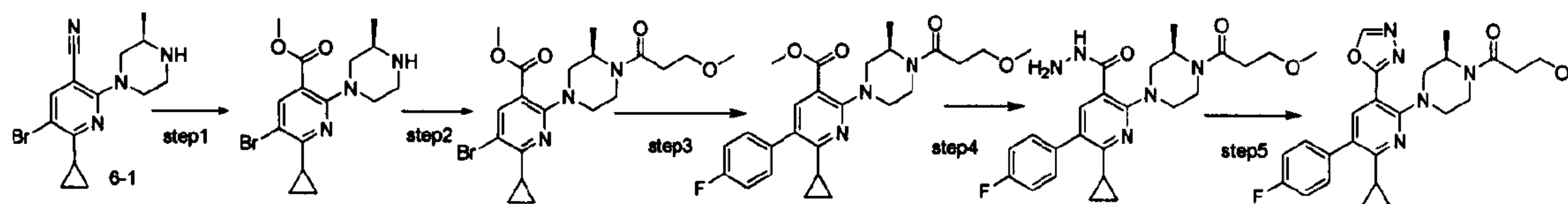
A mixture of (R)-2'-chloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4'-bipyridine-5-carbonitrile (40 mg, 0.09 mmol), vinyl tributyl stannane (30 mg, 0.09mmol), KOAc (10 mg) and Pd(PPh₃)₄ (5 mg) in DMF (2 mL) was stirred at 120°C in the microwave reactor for 20 min. The resulting mixture was concentrated and purified by prepTLC (PE: EA=1: 1) to give 25 mg of the title product. ¹H NMR (CHLOROFORM-d) δ 8.64 (d, J = 5.0 Hz, 1H), 7.63 (s, 1H), 7.31 - 7.45 (m, 1H), 7.22 (dd, J = 5.0, 1.8 Hz, 1H), 6.87 (dd, J = 17.6, 10.8 Hz, 1H), 6.27 (dd, J = 17.6, 1.0 Hz, 1H), 5.41 - 5.71 (m, 1H), 4.90 (m, 0.5H), 5.51 (m, 0.5H), 4.16 - 4.44 (m, 3H), 3.74 (t, J = 6.1 Hz, 3H), 3.38 (s, 4H), 3.31 (d, J = 4.0 Hz, 1H), 3.14 (br. s., 2H), 2.59 (t, J = 6.0 Hz, 2H), 1.86 - 2.06 (m, 1H), 1.38 (d, J = 6.3 Hz, 1.5H), 1.24 - 1.33 (m, 1.5H), 1.10 - 1.24 (m, 2H), 0.83 - 1.10 (m, 2H). LC-MS: m/z 432.6 (M+H)⁺

(R)-2'-chloro-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4'-bipyridine-5-carbonitrile (Compound 401): ¹H NMR (CHLOROFORM-d) δ 8.34 - 8.61 (m, 1H), 7.60 (s, 1H), 7.39 (d, J = 1.0 Hz, 1H), 4.90 (br. s., 0.5H), 4.52 (d, J = 11.8 Hz, 0.5H), 4.21 - 4.41 (m, 2.5H), 3.68 - 3.91 (m, 2.5H), 3.54 (d, J = 4.0 Hz, 1H), 3.25 - 3.45 (m, 4H), 2.95 - 3.25 (m, 1H), 2.63 - 2.92 (m, 1H), 2.42 - 2.63 (m, 1H), 1.87 - 2.07 (m, 1H), 1.36 (d, J = 6.5 Hz, 1.5H), 1.11 - 1.31 (m, 3.5H), 0.81 - 1.11 (m, 2H). LC-MS: m/z 440.1 (M+H)⁺

(R)-2-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl)nicotinonitrile (Compound 391; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 9.41 (s, 1H), 8.54 (d, J = 5.3 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.68 - 7.81 (m, 2H), 7.61 - 7.67 (m, 1H), 7.45 - 7.56 (m, 1H), 4.58 (d, J = 11.5 Hz, 1H), 4.46 (d, J = 13.1 Hz, 1H), 3.49 - 4.23 (m, 2.5H), 3.16 - 3.33 (m, 2.5H), 1.58 - 1.69 (m, 1H), 1.42 - 1.54 (m,

1H), 1.17 (t, J = 4.9 Hz, 2H), 1.00 - 1.10 (m, 3H), 0.76 - 0.87 (m, 4H), 0.69 (br. s., 1H), 0.41 - 0.62 (m, 3H); LC-MS: m/z 464.2 (M+H)

(R)-1-(4-(6-cyclopropyl-5-(4-fluorophenyl)-3-(1,3,4-oxadiazol-2-yl)pyridin-2-yl)-2-methylpiperazin-1-yl)-3-methoxypropan-1-one (Compound 392)



Step 1: (R)-5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinonitrile (2g, 6.3 mmol) was dissolved in MeOH (5 mL) and NaOH (20%wt aq, 10 mL) and the reaction solution was heated to reflux overnight. The resultant solution was concentrated and then dissolved in MeOH (10 mL), treated with SOCl₂ (0.1 ml) and then heated to reflux for 2 h. The resulting solution was concentrated, washed with brine and extracted with EA (50 mL). The organic phase was dried, concentrated and purified with flash column (EA : PE = 1 : 3) to give (R)-methyl 5-bromo-6-cyclopropyl-2-(3-methylpiperazin-1-yl)nicotinate as a white solid (804mg, 50% yield).

Step 2: Following the same procedure as General procedure 1, step F, method 1.

Step 3: Following the same procedure as General procedure 1, step H.

Step 4: (R)-methyl 6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotinate (500 mg, 1.1 mmol) and 2 mL hydrazine hydrate was dissolved in 10mL ethanol. The reaction mixture was heated reflux overnight and cooled down to rt. The mixture was filtered and the residue was washed with cold ethanol. 200 mg title compound was obtained without further purification.

Step 5: (R)-6-cyclopropyl-5-(4-fluorophenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl) nicotine-hydrazide (200 mg, 0.44 mmol) was dissolved in trimethoxymethane (25 mL). The reaction mixture was heated to reflux overnight. The rest of trimethoxymethane was removed under reduced pressure and purified by prep-TLC to give 50 mg of title compound. ¹H NMR (CHLOROFORM-d) δ 9.33 (s, 1H), 8.51 (d, J = 6.0 Hz, 1H), 8.10 (s, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.62 - 7.89 (m, 2H), 7.27 (s, 1H), 4.63 - 4.78 (m, 2H), 4.47 - 4.63 (m, 1H), 3.55 - 3.84 (m, 3H), 3.39 (s, 4H), 3.19 (dd, J = 13.3, 3.5 Hz, 1H), 2.91 - 3.12 (m, 2H), 2.66 - 2.88 (m, 3H), 2.44 - 2.66 (m, 2H), 1.28 - 1.43 (m, 1.5H), 1.15 - 1.28 (m, 3.5H), 1.12 (br. s., 1H), 0.80 - 1.06 (m, 2H); LC-MS: m/z 466.2 (M+H).

2-(4-(cyclopropanecarbonyl)-3-(trifluoromethyl)piperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl)nicotinonitrile (Compound 397; General procedure 4, Step R and S): ¹H NMR (CHLOROFORM-d) δ 9.35 (s, 1H), 8.54 (t, J = 6.4 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.60 - 7.76 (m, 3H), 7.35 - 7.49 (m, 1H), 5.39 (br. s., 0.5H), 4.28 - 4.86 (m, 3.5H), 3.70 - 3.97 (m, 1H), 3.44 (d, J = 14.3 Hz, 1H), 3.23 - 3.39 (m, 1H), 1.68 - 1.91 (m, 1H), 1.53 (td, J = 7.8, 3.5 Hz, 1H), 1.08 - 1.23 (m, 3H), 0.77 - 1.07 (m, 5H). LC-MS: m/z 492.2 (M+H)⁺

6-cyclopropyl-5-(isoquinolin-5-yl)-2-(4-(3-methoxypropanoyl)-3-(trifluoromethyl)piperazin-1-yl)nicotinonitrile (Compound 398; General procedure 4, Step R and S): ¹H NMR (CHLOROFORM-d) δ 9.35 (br. s., 1H), 8.55 (t, J = 6.0 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.60 - 7.80 (m, 3H), 7.42 (dd, J = 19.3, 5.5 Hz, 1H), 5.29 - 5.48 (m, 0.5H), 4.71 - 4.92 (m, 1.5H), 4.44 - 4.62 (m, 1H), 4.02 (d, J = 13.3 Hz, 0.5H), 3.63 - 3.86 (m, 2.5H), 3.33 - 3.51 (m, 3.5H), 3.19 - 3.32 (m, 2H), 2.75 - 2.94 (m, 1H), 2.52 - 2.75 (m, 1H), 2.06 (br. s., 1H), 1.52 (tq, J = 8.0, 4.1 Hz, 1H), 1.10 - 1.22 (m, 2H), 0.76 - 0.93 (m, 2H). LC-MS: m/z 510.4 (M+H)⁺

6-cyclopropyl-5-(isoquinolin-5-yl)-2-(3-(trifluoromethyl)-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)nicotinonitrile (Compound 399; General procedure 4, Step R and S): ¹H NMR (CHLOROFORM-d) δ 9.35 (s, 1H), 8.54 (t, J = 6.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.55 - 7.80 (m, 3H), 7.32 - 7.45 (m, 1H), 5.26 - 5.49 (m, 0.5H), 4.45 - 5.03 (m, 2.5H), 3.72 - 3.95 (m, 2H), 3.22 - 3.52 (m, 5H), 1.54 (tq, J = 8.0, 4.2 Hz, 1H), 1.10 - 1.22 (m, 2H), 0.78 - 0.94 (m, 3H). LC-MS: m/z 534.2 (M+H)⁺

(R)-6-cyclopropyl-2-(4-(3-hydroxypropanoyl)-3-methylpiperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 402; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 9.36 (br. s., 1H), 8.55 (d, J = 5.8 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.52 - 7.77 (m, 3H), 7.44 (t, J = 6.0 Hz, 1H), 4.93 (br. s., 0.5H), 4.25 - 4.48 (m, 2.5H), 4.21 (br. s., 0.5H), 3.95 (br. s., 2H), 3.66 - 3.86 (m, 1.5H), 3.56 - 3.66 (m, 1H), 3.28 - 3.47 (m, 1H), 2.99 - 3.28 (m, 2H), 2.49 - 2.77 (m, 1H), 1.40 - 1.57 (m, 3H), 1.11 - 1.40 (m, 2H), 0.75 - 1.04 (m, 2H); LC-MS: m/z 442.2 (M+H).

(R)-6-cyclopropyl-5-(3-(dimethylamino)phenyl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 413; General procedure 1, Step H): ¹H

NMR (CHLOROFORM-d) δ 7.61 - 7.69 (m, 1H), 7.29 - 7.34 (m, 1H), 6.65 - 6.83 (m, 3H), 4.91 (br. s., 0.5H), 4.54 (d, J = 13.3 Hz, 0.5H), 4.14 - 4.34 (m, 2.5H), 3.70 - 3.87 (m, 2.5H), 3.56 (t, J = 11.2 Hz, 0.5H), 3.34 - 3.46 (m, 3H), 3.00 - 3.28 (m, 8.5H), 2.54 - 2.83 (m, 2H), 2.14 - 2.23 (m, 1H), 1.29 - 1.43 (m, 3H), 1.07 - 1.20 (m, 2H), 0.84 - 1.01 (m, 2H). LC-MS: m/z 448.4 (M+H)⁺

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-

(methylamino)phenyl)nicotinonitrile (Compound 414; General procedure 1, Step H): ¹H

NMR (CHLOROFORM-d) δ 7.63 (s, 1H), 7.23 - 7.27 (m, 1H), 6.72 (d, J = 7.8 Hz, 1H), 6.62 - 6.68 (m, 1H), 6.56 - 6.62 (m, 1H), 4.91 (br. s., 0.5H), 4.54 (d, J = 13.6 Hz, 0.5H), 4.15 - 4.33 (m, 2.5H), 3.70 - 3.88 (m, 2.5H), 3.52 - 3.62 (m, 0.5H), 3.39 (s, 3H), 3.00 - 3.28 (m, 2.5H), 2.89 (s, 3H), 2.65 - 2.83 (m, 1H), 2.51 - 2.65 (m, 1H), 2.14 - 2.21 (m, 1H), 1.30 - 1.47 (m, 3H), 1.10 - 1.19 (m, 2H), 0.89 - 0.98 (m, 2H). LC-MS: m/z 434.5 (M+H)⁺

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-methoxypropanoyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 409; General procedure 1, Step H): ¹H NMR

(CHLOROFORM-d) δ 9.36 (br. s., 1H), 8.54 (d, J = 4.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.60 - 7.84 (m, 3H), 7.44 (dd, J = 12.3, 6.0 Hz, 1H), 4.71 - 4.73 (m, 0.5H), 4.56 (d, J = 11.8 Hz, 1H), 4.38 - 4.50 (m, 1H), 4.07 - 4.19 (m, 0.5H), 3.91 (d, J = 11.0 Hz, 0.5H), 3.69 - 3.83 (m, 3H), 3.51 (s, 3H), 3.20 - 3.29 (m, 1.5H), 3.13 (br. s., 1H), 2.61 - 2.70 (m, 2H), 1.52 (ddd, J = 12.0, 7.9, 4.6 Hz, 1H), 1.40 (br. s., 1H), 1.12 - 1.20 (m, 2H), 0.80 - 0.90 (m, 2H), 0.48 - 0.77 (m, 4H). LC-MS: m/z 482.6 (M+H)⁺

(R)-6-cyclopropyl-2-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-5-(isoquinolin-5-yl)nicotinonitrile (Compound 419; General procedure 1, Step H): ¹H NMR

(CHLOROFORM-d) δ 9.40 (br. s., 1H), 8.48 - 8.69 (m, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.63 - 7.86 (m, 3H), 7.44 - 7.55 (m, 1H), 4.70 - 4.73 (m, 0.5H), 4.57 (dd, J = 13.1, 2.0 Hz, 1H), 4.41 - 4.52 (m, 1H), 4.13 (d, J = 7.8 Hz, 0.5H), 3.94 (br. s., 2H), 3.69 - 3.82 (m, 1H), 3.13 - 3.26 (m, 3H), 2.50 - 2.71 (m, 2H), 1.48 - 1.57 (m, 1H), 1.39 - 1.48 (m, 1H), 1.12 - 1.21 (m, 2H), 0.86 - 0.91 (m, 2H), 0.42 - 0.69 (m, 4H). LC-MS: m/z 468.5 (M+H)⁺

(R)-5-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)isoquinoline 2-oxide (Compound 420): ¹H NMR (CHLOROFORM-d) δ 8.88 (br. s., 1H), 8.15 (d, J = 6.5 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.63 (s, 1H), 7.52 - 7.58 (m, 1H), 7.44 - 7.52 (m, 1H), 4.94 (br. s., 0.5H), 4.55 - 4.59 (m, 0.5H), 4.21 - 4.44 (m,

2.5H), 3.57 - 3.86 (m, 3H), 3.34 - 3.40 (m, 4H), 3.19 - 3.22 (m, 1.5H), 2.58 - 2.86 (m, 2H), 1.47 - 1.55 (m, 1H), 1.30 - 1.38 (m, 3H), 1.09 - 1.21 (m, 2H), 0.78 - 0.95 (m, 2H). LC-MS: m/z 472.4 (M+H)⁺

6-cyclopropyl-5-(isoquinolin-5-yl)-2-(4-(3-methoxypropanoyl)piperazin-1-yl)nicotinonitrile (Compound 421; General procedure 1, Step H): ¹H NMR (CHLOROFORM-d) δ 9.35 (br. s., 1H), 8.53 (d, J = 5.0 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.68 - 7.75 (m, 1H), 7.60 - 7.67 (m, 2H), 7.42 (d, J = 5.8 Hz, 1H), 3.39 - 3.85 (m, 10H), 3.38 (s, 3H), 2.63 - 2.75 (m, 2H), 1.46 - 1.55 (m, 1H), 1.08 - 1.18 (m, 2H), 0.75 - 0.85 (m, 2H). LC-MS: m/z 442.5 (M+H)⁺

2-(4-(cyclopropanecarbonyl)-3-(difluoromethyl)piperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl)nicotinonitrile (Compound 422; General procedure 4, Step R and S): ¹H NMR (CHLOROFORM-d) δ 9.37 (br. s., 1H), 8.56 (br. s., 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.60 - 7.79 (m, 3H), 7.43 (d, J = 10.3 Hz, 1H), 6.09 (br. s., 1H), 4.97 - 5.45 (m, 4H), 3.12 - 3.89 (m, 3H), 1.98 - 2.08 (m, 1H), 1.80 - 1.87 (m, 1H), 1.00 - 1.21 (m, 4H), 0.83 - 0.92 (m, 4H). LC-MS: m/z 474.5 (M+H)⁺

2-(4-(cyclopropanecarbonyl)-3-(2,2,2-trifluoroethyl)piperazin-1-yl)-6-cyclopropyl-5-(isoquinolin-5-yl)nicotinonitrile (Compound 423; General procedure 4, Step R and S): ¹H NMR (CHLOROFORM-d) δ 9.36 (s, 1H), 8.55 (dd, J = 5.8, 3.5 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.59 - 7.81 (m, 3H), 7.33 - 7.50 (m, 1H), 5.24 (br. s., 0.5H), 4.34 (d, J = 13.1 Hz, 1H), 4.26 - 4.50 (m, 2.5H), 3.69 (br. s., 0.5H), 3.20 - 3.45 (m, 2H), 3.13 (br. s., 0.51H), , 2.58 - 2.75 (m, 2H), 1.77 (br. s., 1H), 1.47 - 1.61 (m, 1H), 1.09 - 1.24 (m, 4H), 0.77 - 0.93 (m, 4H). LC-MS: m/z 506.5 (M+H)⁺

(R)-2-cyclopropyl-2'-ethyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-3,4'-bipyridine-5-carbonitrile (Compound 426)

Compound 390 (18 mg) in EtOH was treated with Pd/C and hydrogenated at room temperature and normal pressure to give the title compound as a white solid. ¹H NMR (CHLOROFORM-d) δ 8.63 (d, J = 4.8 Hz, 1H), 7.63 (s, 1H), 7.23 (d, J = 4.5 Hz, 2H), 4.92 (br. s., 1H), 4.55 (d, J = 12.8 Hz, 1H), 4.14 - 4.43 (m, 3H), 3.64 - 3.89 (m, 3H), 3.57 (br. s., 1H), 3.40 (s, 3H), 3.32 (d, J = 11.8 Hz, 1H), 3.14 (d, J = 14.3 Hz, 1H), 2.94 (q, J = 7.4 Hz, 2H), 2.65 - 2.83 (m, 1H), 2.39 - 2.65 (m, 1H), 2.03 (td, J = 8.0, 3.9 Hz, 2H), 1.25 - 1.42 (m, 8H), 1.11 - 1.25 (m, 3H), 1.01 (dd, J = 7.8, 3.0 Hz, 2H). LC-MS: m/z 434.2 (M+H)⁺

Compound 430 (General procedure 1, Step I): ^1H NMR (CHLOROFORM- d) δ 8.41 (dd, J = 7.9, 1.4 Hz, 1H), 8.14 (s, 1H), 7.72 - 7.84 (m, 1H), 7.57 - 7.71 (m, 2H), 4.93 (d, J = 13.3 Hz, 0.5H), 4.55 (d, J = 13.3 Hz, 0.5H), 4.14 - 4.43 (m, 3H), 3.69 - 3.90 (m, 3H), 3.53 - 3.68 (m, 1H), 3.34 - 3.46 (m, 3H), 3.27 (t, J = 11.2 Hz, 1H), 2.97 - 3.22 (m, 2H), 2.54 - 2.84 (m, 2H), 1.55 - 1.80 (m, 2H), 1.43 (d, J = 6.5 Hz, 2H), 1.18 - 1.38 (m, 3H), 1.09 (br. s., 1H), 0.70 - 0.99 (m, 2H). LC-MS: m/z 473.2 ($M+H$) $^+$

(R)-6-cyclopropyl-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-5-(3-methylisoquinolin-5-yl)nicotinonitrile (Compound 433): ^1H NMR (CHLOROFORM- d) δ 9.23 (s, 1H), 7.93 - 8.03 (m, 1H), 7.50 - 7.66 (m, 3H), 7.21 (d, J = 6.0 Hz, 1H), 4.92 (br. s., 0.5H), 4.55 (d, J = 12.8 Hz, 0.5H), 4.19 - 4.42 (m, 2.5H), 3.83 (d, J = 12.3 Hz, 0.5H), 3.65 - 3.78 (m, 2H), 3.56 (d, J = 16.8 Hz, 0.5H), 3.37 (s, 3H), 3.31 (d, J = 13.1 Hz, 1H), 2.98 - 3.25 (m, 1.5H), 2.68 - 2.84 (m, 1H), 2.53 - 2.68 (m, 5H), 1.47 - 1.57 (m, 1H), 1.43 (d, J = 6.3 Hz, 1.5H), 1.29 - 1.36 (m, 1.5H), 1.13 (dd, J = 6.5, 4.0 Hz, 2H), 0.76 - 0.84 (m, 2H). LC-MS: m/z 470.2 ($M+H$) $^+$

(R)-6-cyclopropyl-5-(1-methoxyisoquinolin-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 434): ^1H NMR (CHLOROFORM- d) δ 8.32 (dd, J = 7.5, 1.3 Hz, 1H), 7.98 (d, J = 6.0 Hz, 1H), 7.52 - 7.65 (m, 3H), 6.94 (t, J = 5.9 Hz, 1H), 4.85 (br. s., 0.5H), 4.55 (d, J = 12.8 Hz, 0.5H), 4.20 - 4.40 (m, 2.5H), 4.15 (s, 3H), 3.66 - 3.89 (m, 3H), 3.38 (s, 3H), 3.31 (d, J = 8.3 Hz, 1H), 3.17 (d, J = 13.3 Hz, 1.5H), 2.65 - 2.84 (m, 1H), 2.51 - 2.65 (m, 1H), 1.48 - 1.60 (m, 1H), 1.42 (m, 1.5H), 1.29 - 1.36 (m, 1.5H), 1.03 - 1.19 (m, 2H), 0.81 (dd, J = 8.0, 3.0 Hz, 2H). LC-MS: m/z 486.2 ($M+H$) $^+$

(1R,2R)-ethyl 2-((R)-4-(3-cyano-6-cyclopropyl-5-(isoquinolin-5-yl)pyridin-2-yl)-2-methylpiperazine-1-carbonyl)cyclopropanecarboxylate (Compound 435): ^1H NMR (CHLOROFORM- d) δ 9.34 (s, 1H), 8.53 (d, J = 5.8 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.62 - 7.80 (m, 3H), 7.42 (t, J = 5.9 Hz, 1H), 4.87 (br. s., 0.5H), 4.38 - 4.65 (m, 1.5H), 4.33 (d, J = 12.0 Hz, 2H), 4.19 (q, J = 7.0 Hz, 2H), 3.62 - 3.85 (m, 0.5H), 3.46 (d, J = 13.1 Hz, 0.5H), 3.10 - 3.40 (m, 2H), 2.36 (br. s., 1H), 2.17 - 2.31 (m, 1H), 2.09 (br. s., 1H), 1.38 - 1.45 (m, 2H), 1.22 - 1.37 (m, 6H), 1.03 - 1.22 (m, 2H), 0.69 - 0.94 (m, 2H). LC-MS: m/z 461.2 ($M+H$) $^+$

(R)-5-(5-cyano-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropylpyridin-3-yl)isoquinoline 2-oxide (Compound 439): ^1H NMR (CHLOROFORM- d) δ 8.87 (br. s., 1H), 8.06 - 8.26 (m, 1H), 7.70 - 7.83 (m, 2H), 7.61 - 7.69 (m, 1H), 7.54 (br. s., 2H),

4.59 (d, $J = 7.0$ Hz, 1H), 4.47 (d, $J = 12.5$ Hz, 1H), 3.51 - 4.30 (m, 3H), 3.32 (br. s., 1H), 3.17 (br. s., 1H), 1.96 - 2.10 (m, 1H), 1.75 (br. s., 1H), 1.43 - 1.54 (m, 1H), 1.14 - 1.23 (m, 2H), 1.00 - 1.12 (m, 2H), 0.81 - 0.94 (m, 4H), 0.38 - 0.73 (m, 4H). LC-MS: m/z 480.2 ($M+H$)⁺

(R)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-N-(vinylsulfonyl)ethanesulfonamide (Compound 440; General procedure 3, Step N, method 1): ¹H NMR (CHLOROFORM-*d*) δ 7.60 - 7.64 (m, 1H), 7.50 - 7.56 (m, 2H), 7.29 - 7.37 (m, 3H), 7.01 - 7.16 (m, 2H), 6.26 - 6.40 (m, 2H), 6.11 - 6.25 (m, 2H), 4.92 (s, 0.5H), 4.54 (d, $J = 13.3$ Hz, 0.5H), 4.19 - 4.37 (m, 2.5H), 3.73 - 3.79 (m, 3H), 3.52 - 3.61 (m, 0.5H), 3.39 (s, 3H), 3.28 (t, $J = 10.4$ Hz, 1H), 3.02-3.14 (m, 1H), 2.65 - 2.80 (m, 1H), 2.55 - 2.64 (m, 1H), 1.98 - 2.07 (m, 1H), 1.27 (s, 3H), 1.14 - 1.19 (m, 2H), 0.95 - 1.01 (m, 2H). LC-MS: m/z 600.2 ($M+H$)⁺

(R,E)-N-(3-(5-cyano-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)pyridin-3-yl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 441; General procedure 3, Step N, method 2): ¹H NMR (CHLOROFORM-*d*) δ 9.22 (s, 1H), 7.68 (s, 1H), 7.53 - 7.60 (m, 1H), 7.41 - 7.53 (m, 1H), 7.31 (s, 1H), 7.08 (d, $J = 7.3$ Hz, 1H), 6.86 (s, 1H), 6.61 (d, $J = 15.3$ Hz, 1H), 4.83 (s, 0.5H), 4.46 (d, $J = 11.0$ Hz, 0.5H), 4.22 (d, $J = 9.8$ Hz, 2.5H), 3.90 (s, 1.5H), 3.67 - 3.81 (m, 2.5H), 3.52 (s, 0.5H), 3.28 - 3.41 (m, 3H), 3.24 (s, 1H), 3.04 - 3.15 (m, 1H), 2.94 - 3.04 (m, 1H), 2.88 (s, 2H), 2.82 (s, 6H), 2.57 (d, $J = 15.8$ Hz, 1H), 1.97 - 2.08 (m, 1H), 1.33 - 1.40 (m, 2H), 1.18 - 1.30 (m, 2H), 1.02 - 1.15 (m, 2H), 0.89 (s, 2H). LC-MS: m/z 531.3 ($M+H$)⁺

(R)-6-cyclopropyl-5-(2-hydroxyquinolin-5-yl)-2-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)nicotinonitrile (Compound 442): ¹H NMR (CHLOROFORM-*d*) δ 7.88 (d, $J = 9.5$ Hz, 1H), 7.63 - 7.70 (m, 1H), 7.43 - 7.63 (m, 3H), 6.80 (d, $J = 9.5$ Hz, 1H), 4.92 (br. s., 0.5H), 4.57 (d, $J = 13.1$ Hz, 0.5H), 4.15 - 4.45 (m, 3H), 3.66 - 3.87 (m, 2H), 3.40 (s, 2H), 3.29 (t, $J = 9.7$ Hz, 1H), 3.11 - 3.22 (m, 1H), 2.66 - 2.88 (m, 1H), 2.48 - 2.66 (m, 1H), 1.96 - 2.10 (m, 1H), 1.36 - 1.56 (m, 1.5H), 1.08 - 1.36 (m, 3.5H), 0.97 (dd, $J = 7.8, 3.0$ Hz, 2H). LC-MS: m/z 472.3 ($M+H$)⁺

(R)-6-(4-(cyclopropanecarbonyl)-3-methylpiperazin-1-yl)-2-cyclopropyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 443; General procedure 5, Step W): ¹H NMR

(CHLOROFORM-d) δ 8.66 (d, $J = 4.3$ Hz, 1H), 7.59 - 7.67 (m, 1H), 7.35 - 7.45 (m, 1H), 7.24 (d, $J = 4.3$ Hz, 1H), 6.89 (dd, $J = 17.3, 10.8$ Hz, 1H), 6.29 (d, $J = 17.3$ Hz, 1H), 5.58 (d, $J = 10.8$ Hz, 1H), 4.87 (br. s., 1H), 4.56 (br. s., 1H), 4.30 (d, $J = 13.3$ Hz, 1H), 4.13 (br. s., 1H), 3.58 - 3.88 (m, 1H), 3.33 (d, $J = 10.0$ Hz, 1H), 3.20 (br. s., 2H), 1.91 - 2.09 (m, 1H), 1.38 - 1.51 (m, 1.5H), 1.11 - 1.38 (m, 2.5H), 0.87 - 1.08 (m, 6H), 0.79 - 0.87 (m, 2H). LC-MS: m/z 414.4 (M+H)⁺

(R)-2-cyclopropyl-6-(3-methyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 444; General procedure 5, Step W): ¹H NMR

(CHLOROFORM-d) δ 7.59 - 7.69 (m, 1H), 7.34 - 7.43 (m, 1H), 7.15 - 7.27 (m, 1H), 6.89 (dd, $J = 17.6, 10.8$ Hz, 1H), 6.23 - 6.37 (m, 1H), 5.58 (d, $J = 11.5$ Hz, 1H), 4.94 (br. s., 1H), 4.20 - 4.48 (m, 2H), 3.51 - 3.79 (m, 1H), 3.37 (d, $J = 5.5$ Hz, 1H), 3.05 - 3.34 (m, 4H), 1.87 - 2.07 (m, 1H), 1.42 - 1.51 (m, 2H), 1.13 - 1.42 (m, 3H), 0.95 - 1.08 (m, 2H). LC-MS: m/z 456.8 (M+H)⁺

(R)-6-(4-(cyclopropanecarbonyl)-3-cyclopropylpiperazin-1-yl)-2-cyclopropyl-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 485; General procedure 5, Step W): ¹H NMR

(CHLOROFORM-d) δ 8.77 (br. s., 1H), 7.96 (br. s., 1H), 7.80 - 7.92 (m, 2H), 7.12 - 7.27 (m, 1H), 6.82 (d, $J = 17.6$ Hz, 1H), 6.06 (d, $J = 10.8$ Hz, 1H), 4.67 (d, $J = 12.3$ Hz, 1H), 4.54 (d, $J = 11.5$ Hz, 2H), 4.24 (br. s., 1H), 3.67 (br. s., 1H), 3.33 (br. s., 1H), 3.18 (br. s., 1H), 1.93 (br. s., 1H), 1.67 (br. s., 1H), 1.25 (br. s., 2H), 1.04 - 1.23 (m, 3H), 0.89 - 1.04 (m, 3H), 0.47 (d, $J = 4.8$ Hz, 2H), 0.39 (br. s., 2H). LC-MS: m/z 440.2 (M+H)⁺

Compound 527 (General procedure 5, Step W): ¹H NMR (CHLOROFORM-d) δ 8.65 (d, $J = 4.7$ Hz, 1H), 7.65 (s, 1H), 7.38 (s, 1H), 7.23 (d, $J = 4.1$ Hz, 1H), 6.87 (dd, $J = 17.5, 10.7$ Hz, 1H), 6.28 (d, $J = 17.6$ Hz, 1H), 5.56 (d, $J = 10.9$ Hz, 1H), 4.55 (d, $J = 13.2$ Hz, 1H), 4.43 (d, $J = 12.6$ Hz, 1H), 4.03 - 4.16 (m, 1H), 3.91 (br. s., 2H), 3.65 - 3.82 (m, 1H), 3.40 - 3.53 (m, 1H), 3.02 - 3.32 (m, 3H), 2.49 - 2.69 (m, 2H), 1.98 - 2.10 (m, 1H), 1.13 - 1.38 (m, 3H), 1.01 (dd, $J = 7.5, 3.4$ Hz, 2H), 0.63 (br. s., 1H), 0.55 (br. s., 1H), 0.32 - 0.51 (m, 2H). LC-MS: m/z 444.3 (M+H)⁺

(R)-2-cyclopropyl-6-(3-cyclopropyl-4-(3,3,3-trifluoropropanoyl)piperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 498; General procedure 5, Step W): ¹H NMR (CHLOROFORM-d) δ 8.54 - 8.72 (m, 1H), 7.57 - 7.74 (m, 1H), 7.38 (d, $J = 1.0$ Hz, 1H), 7.23 (dd, $J = 5.1, 1.6$ Hz, 1H), 6.88 (dd, $J = 17.3, 10.8$ Hz, 1H), 6.28 (dd, $J = 17.4, 1.1$ Hz, 1H), 5.48 - 5.63 (m, 1H), 4.56 (dd, $J = 13.2, 1.9$ Hz, 1H), 4.45 (d, $J = 13.1$ Hz, 1H), 4.11 (br. s., 1H), 3.65 - 3.88 (m, 2H), 3.32 (q, $J = 9.6$ Hz, 2H), 3.20 (d, $J = 12.0$ Hz, 1H), 2.98 - 3.15 (m, 1H), 2.04 (tt, J

= 8.0, 4.7 Hz, 1H), 1.30 - 1.39 (m, 1H), 1.14 - 1.25 (m, 2H), 0.96 - 1.07 (m, 2H), 0.65 (br. s., 1H), 0.56 (br. s., 1H), 0.41 - 0.54 (m, 2H). LC-MS: m/z 482.5 (M+H)⁺

(R)-2-cyclopropyl-6-(4-(3-methoxypropanoyl)-3-methylpiperazin-1-yl)-2'-vinyl-3,4'-bipyridine-5-carbonitrile (Compound 500; General procedure 5, Step W): ¹H NMR (CHLOROFORM-d) δ 8.66 (d, J = 5.0 Hz, 1H), 7.60 - 7.71 (m, 1H), 7.41 (s, 1H), 7.26 (dd, J = 5.0, 1.3 Hz, 1H), 6.90 (dd, J = 17.4, 10.9 Hz, 1H), 6.31 (d, J = 17.1 Hz, 1H), 5.60 (d, J = 11.0 Hz, 1H), 4.72 - 4.99 (m, 0.5H), 4.54 (d, J = 13.1 Hz, 0.5H), 4.22 - 4.49 (m, 2H), 3.74 (d, J = 13.6 Hz, 1H), 3.56 (br. s., 1H), 3.40 (br. s., 1H), 3.32 (td, J = 8.6, 3.9 Hz, 1H), 2.95 - 3.25 (m, 2H), 2.68 (br. s., 1H), 2.44 - 2.65 (m, 2H), 2.00 - 2.19 (m, 1H), 1.16 - 1.45 (m, 3H), 0.95 - 1.12 (m, 3H), 0.90 (t, J = 6.8 Hz, 1H). LC-MS: m/z 418.6 (M+H)⁺

(R)-2-cyclopropyl-6-(4-(4,4-dimethoxybutanoyl)-3-methylpiperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile (Compound 606; General procedure 5, Step W): ¹H NMR (CHLOROFORM-d) δ 8.64 (d, J = 5.0 Hz, 1H), 7.63 (s, 1H), 7.38 (s, 1H), 7.23 (dd, J = 5.0, 1.5 Hz, 1H), 6.81 - 6.93 (m, 1H), 6.28 (d, J = 11.0 Hz, 1H), 5.56 (d, J = 11.0 Hz, 1H), 4.88 (s, 0.5H), 4.24 - 4.53 (m, 1.5H), 4.24 - 4.36 (m, 2.5H), 3.78 (d, 0.5H), 3.54 (t, 0.5H), 3.27 - 3.37 (m, 4H), 3.02 - 3.18 (m, 1.5H), 2.35 - 2.56 (m, 2H), 1.92 - 2.06 (m, 4H), 1.38 (d, 1.5H), 1.28 (d, 1.5 H), 1.18 - 1.21 (m, 2H), 0.99 - 1.02 (m, 2H). LC-MS: m/z 476.2 (M+H)⁺

(R)-2-cyclopropyl-6-(3-methyl-4-(4-oxobutanoyl)piperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile (Compound 607), which was obtained as the by-product of Compound 606.

¹H NMR (CHLOROFORM-d) δ 9.90 (s, 1H), 8.65 (d, J = 5.0 Hz, 1H), 7.64 (s, 1H), 7.38 (s, 1H), 7.24 (d, J = 5.0 Hz, 1H), 6.88 (q, 1H), 6.28 (d, 1H), 5.56 (d, 1H), 4.85 (br. s., 0.5H), 4.48 (d, J = 12.8 Hz, 0.5H), 4.25 - 4.37 (m, 2.5H), 3.80 (br. s., 0.5H), 3.60 (br. s., 0.5H), 3.03 - 3.38 (m, 3H), 2.62-2.89 (m, 4.5H), 2.03 (m, 1H), 1.42 (d, 1.5H), 1.28 (d, 1.5H), 1.18 - 1.21 (m, 2H), 0.99 - 1.10 (m, 2H). LC-MS: m/z 430.2 (M+H)⁺

(S)-2-cyclopropyl-6-(3-cyclopropyl-4-(3-hydroxypropanoyl)piperazin-1-yl)-2'-vinyl-[3,4'-bipyridine]-5-carbonitrile (Compound 587; General procedure 5, Step W): ¹H NMR (CHLOROFORM-d) δ 8.66 (d, J = 5.0 Hz, 1H), 7.62 - 7.73 (m, 1H), 7.39 (s, 1H), 7.24 (dd, J = 5.0, 1.5 Hz, 1H), 6.88 (dd, J = 17.6, 10.8 Hz, 1H), 6.29 (d, J = 17.3 Hz, 1H), 5.57 (d, J = 10.8 Hz, 1H), 4.56 (d, J = 13.1 Hz, 1H), 4.43 (d, J = 11.3 Hz, 1.5H), 4.09 (d, J = 8.8 Hz, 0.5H), 3.93 (d, J = 5.0 Hz, 2H), 3.75 - 3.82 (m, 1.5H), 3.43 (br. s., 1H), 3.16 - 3.32 (m, 1.5H), 3.02 - 3.16 (m, 1H),

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

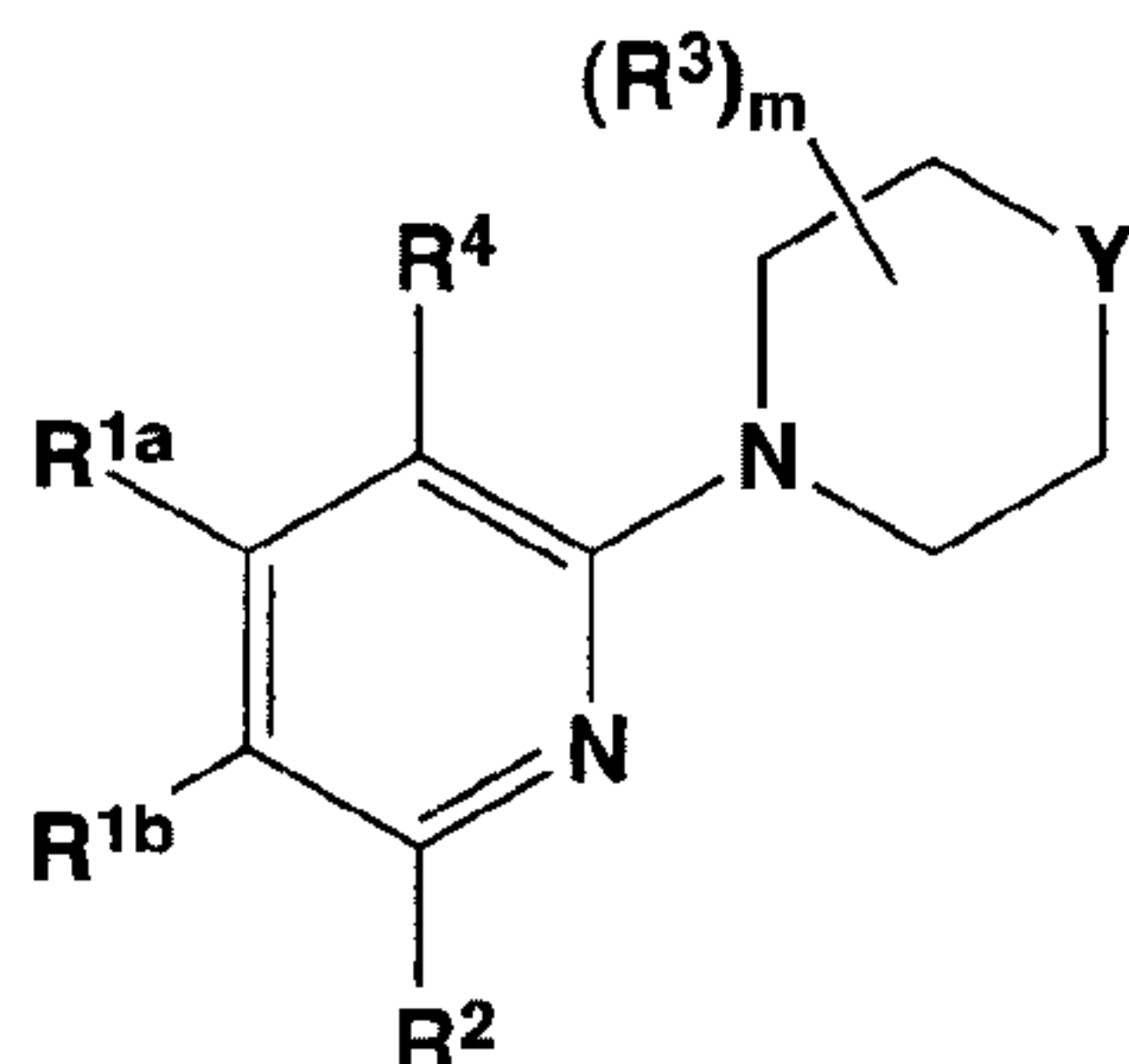
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

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Claims

1. A compound of Structural Formula (I):



(I) or a pharmaceutically acceptable salt thereof, wherein:

Y is -N(R⁵)-, -N(R⁵)-CH₂-, -CH₂-N(R⁵)- or -CH(R⁵)-;

R^{1a} is hydrogen, -C₁-C₄ alkyl, -N(R⁷)(C₁-C₄ alkylene)-N(R⁷)(C₁-C₄ alkyl), aryl, heterocyclyl, -C(O)N(R⁷)-aryl, -N(R⁷)C(O)-aryl, -(C₁-C₄ alkylene)-aryl, -(C₁-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-aryl, -O-(C₀-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-heterocyclyl, -O-(C₀-C₄ alkylene)-carbocyclyl, -N(R⁷)-aryl, -N(R⁷)-heteroaryl, -N(R⁹)-aryl, -N(R⁹)-heteroaryl, -O-(C₁-C₄ alkylene)-N(R⁷)C(O)O-(C₁-C₄ alkylene)-aryl, or -N(R⁹)-C(O)-(C₂-C₄ alkenyl);

R^{1b} is hydrogen, -C₁-C₄ alkyl, -N(R⁷)(C₁-C₄ alkylene)-N(R⁷)(C₁-C₄ alkyl), aryl, heteroaryl, heterocyclyl, -C(O)N(R⁷)-aryl, -N(R⁷)C(O)-aryl, -(C₁-C₄ alkylene)-aryl, -(C₁-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-aryl, -O-(C₀-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-heterocyclyl, -O-(C₀-C₄ alkylene)-carbocyclyl, -N(R⁷)-aryl, -N(R⁷)-heteroaryl, -N(R⁹)-aryl, -N(R⁹)-heteroaryl, -O-(C₁-C₄ alkylene)-N(R⁷)C(O)O-(C₁-C₄ alkylene)-aryl, or -N(R⁹)-C(O)-(C₂-C₄ alkenyl):

wherein:

at least one of R^{1a} and R^{1b} is not hydrogen or methyl;

any alkylene moiety present in R^{1a} or R^{1b} is optionally substituted with OH or F;

each R⁷ is independently selected from the group consisting of hydrogen and C₁-C₄ alkyl; and

any aryl, heteroaryl, or heterocyclyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from the group consisting of -G-L-M, halo, -NO₂, C₁-C₆ alkyl, -C≡N, =O, -CF₃ and -OCF₃;

G is a bond or a bivalent C₁-C₆ saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon

chain are independently replaced by $\text{-NR}^8\text{-}$, -O- , -C(O)- , -OC(O)- , -C(O)O- , -S- , -SO- , $\text{-SO}_2\text{-}$, -C(=S)- , $\text{-C(=NR}^8\text{)-}$, -N=N- , or $\text{-C(=N}_2\text{)-}$;

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, $\text{-NR}^8\text{-}$, $\text{-N(R}^8\text{)C(O)-}$, $\text{-C(O)N(R}^8\text{)-}$, $\text{-N(R}^8\text{)SO}_2\text{-}$, $\text{SO}_2\text{N(R}^8\text{)-}$, -O- , -C(O)- , -OC(O)- , -C(O)O- , -S- , -SO- , $\text{-SO}_2\text{-}$, -C(=S)- , $\text{-C(=NR}^8\text{)-}$, -N=N- , or $\text{-C(=N}_2\text{)-}$;

M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms which are independently nitrogen, oxygen, and sulfur, and wherein said ring is substituted with 1-4 groups which are independently -D-E, oxo, NO_2 , halogen, CN, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, and $\text{C}_2\text{-C}_6$ alkynyl;

D is a covalent bond or a bivalent $\text{C}_1\text{-C}_6$ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of D are optionally and independently replaced by $\text{-NR}^8\text{-}$, -S- , -O- , -C(O)- , -SO- , or $\text{-SO}_2\text{-}$;

E is hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, or $\text{C}_2\text{-C}_6$ alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

each R^8 is independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_2\text{-C}_6$ alkynyl, $\text{-C}_1\text{-C}_6$ alkoxy, $\text{-S(O)}_2\text{-C}_2\text{-C}_4$ alkenyl, or an optionally substituted group which is phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms independently nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms which are independently nitrogen, oxygen, or sulfur;

R^2 is phenyl, a 3-7 membered cycloalkyl, $\text{C}_2\text{-C}_4$ alkyl, or CF_3 , wherein the phenyl or cycloalkyl is optionally substituted with a substituent selected from methyl or fluoro;

each R^3 is independently halo, $\text{-(C}_1\text{-C}_4\text{ alkylene)-O-(C}_1\text{-C}_4\text{ alkyl)-}$, $\text{C}_1\text{-C}_4$ fluoroalkyl, $\text{-C(O)-O-(C}_1\text{-C}_4\text{ alkyl)-}$, -phenyl, -heteroaryl, $\text{C}_3\text{-C}_7$ cycloalkyl, $\text{-CH}_2\text{-N(C}_1\text{-C}_4\text{ alkyl)}_2$, $\text{C(O)-N-(C}_1\text{-C}_4\text{ alkyl)}_2$, $\text{-C(O)-NH-(C}_1\text{-C}_4\text{ alkyl)-}$, $\text{-C}_1\text{-C}_4$ alkyl optionally substituted with one or more halo or -OH, or two R^3 s are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or fused phenyl is optionally substituted with 1 to 2 methyl;

R^4 is selected from the group consisting of hydrogen, -CN, halo, $\text{C}_1\text{-C}_4$ alkoxy, $\text{-CH}_2\text{NH(C}_1\text{-C}_4\text{ alkyl)-}$, $\text{C}_2\text{-C}_4$ alkenyl, $\text{C}_2\text{-C}_4$ alkynyl, $\text{-(C}_1\text{-C}_4\text{ alkyl)-O-(C}_1\text{-C}_4\text{ alkyl)-}$,

C₁-C₄ fluoroalkyl, C(O)-N-(C₁-C₄ alkyl)₂, -C(O)-NH-(C₁-C₄ alkyl), -C(O)-O-(C₁-C₄ alkyl), -C(O)-OH, -S(O)₂-(C₁-C₄ alkyl), and a 5-membered heteroaryl;

R⁵ is -C(O)-(C₁-C₅ alkyl), -C(O)-(C₂-C₆ alkenyl), -C(O)-(C₀-C₂ alkylene)-Q, -C(O)-(C₂-C₄ alkenylene)-Q, -C(O)-(C₀-C₂ alkylene)-N(R⁶)-(C₀-C₂ alkylene)-Q, -C(O)-O-(C₀-C₂ alkylene)-Q, -C(O)-(C₁-C₂ alkylene)-O-(C₀-C₂ alkylene)-Q, -C(O)-C(O)-Q, -S(O)₂-Q, -C(O)-(C₁-C₄ alkylene)-O-C(O)-(C₁-C₄ alkyl), -C(O)-(C₁-C₄ alkylene)-C(O)-O-(C₁-C₄ alkyl), -C(O)-N(R⁶)-(C₁-C₄ alkylene)-O-C(O)-(C₁-C₄ alkyl), -C(O)-N(R⁶)-(C₁-C₄ alkylene)-C(O)-O-(C₁-C₄ alkyl), -C(O)-(C₀-C₂ alkylene)-N(R⁶)-(C₁-C₆ alkyl), -C(O)-(C₀-C₂ alkylene)-N(R⁶)-(C₂-C₆ alkynyl), -C(O)-(C₀-C₂ alkylene)-N(R⁶)-(C₂-C₆ alkenyl), -C(O)-(C₀-C₂ alkylene)-N(R⁶)-(C₀-C₂ alkylene)-O-(C₁-C₄ alkyl), -C(O)-(C₁-C₂ alkylene)-O-(C₁-C₄ alkyl), -C(O)-(C₁-C₂ alkylene)-C(O)C(O)N(R)(C₁-C₄ alkyl), -C(O)-O-(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(C₀-C₄ alkylene)-O-C(O)-(C₁-C₄ alkyl), -(C₀-C₄ alkylene)-C(O)-O-(C₁-C₄ alkyl), -(C₀-C₄ alkylene)-O-(C₁-C₄ alkyl), -C(O)-(C₁-C₂ alkylene)-S(O)₀₋₂-(C₁-C₄ alkyl), -S(O)₂-(C₁-C₄ alkyl), -C(O)-(C₁-C₄ alkylene)-C(O)C(O)N(R⁶)(C₁-C₆ alkyl), -C(O)-(C₁-C₄ alkylene)-N(R⁶)S(O)₂-(C₁-C₆ alkyl), or -C(O)-(C₁-C₄ alkylene)-N(R⁶)S(O)₂Q, wherein:

any alkylene moiety present in R⁵ is optionally substituted with OCH₃, OH or F;

any terminal methyl moiety present in R⁵ is optionally replaced with -CH₂OH, CF₃, -CH₂F, -CH₂Cl, C(O)CH₃, C(O)CF₃, CN, -OCH₃, -C(O)H, -OP(O)(OH)₂, -OP(O)(C₁-C₄ alkoxy)₂ or CO₂H;

each R⁶ is independently selected from the group consisting of hydrogen and methyl;

Q is selected from the group consisting of aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3 substituents independently selected from C₁-C₄ alkyl optionally substituted with OH, C₁-C₄ alkoxy, -C(O)O-(C₁-C₄ alkyl), -(C₁-C₄ alkylene)-(C₁-C₄ alkoxy), -CN, -OH, fluoro, chloro, and bromo;

R⁹ is selected from the group consisting of aryl and heteroaryl, wherein each aryl or heteroaryl is optionally substituted with one or more substituents selected from -G-L-M, halo, C₁-C₆ alkyl, -C≡N, =O, -CF₃ and -OCF₃; and

m is 0, 1, 2 or 3.

2. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein:

Y is -N(R⁵)- or -CH(R⁵)-;

R^{1a} is hydrogen, -C₁-C₄ alkyl, -N(R⁷)(C₁-C₄ alkylene)-N(R⁷)(C₁-C₄ alkyl), aryl, heterocyclyl, -C(O)N(R⁷)-aryl, -N(R⁷)C(O)-aryl, -(C₁-C₄ alkylene)-aryl, -(C₁-C₄ alkylene)-heteroaryl, -O-(C₁-C₄ alkylene)-aryl, -O-(C₁-C₄ alkylene)-heteroaryl, -O-(C₁-C₄ alkylene)-heterocyclyl, -N(R⁷)-aryl, or -N(R⁷)-heteroaryl,

R^{1b} is hydrogen, -C₁-C₄ alkyl, -N(R⁷)(C₁-C₄ alkylene)-N(R⁷)(C₁-C₄ alkyl), aryl, heteroaryl, heterocyclyl, -C(O)N(R⁷)-aryl, -N(R⁷)C(O)-aryl, -(C₁-C₄ alkylene)-aryl, -(C₁-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-aryl, -O-(C₀-C₄ alkylene)-heteroaryl, -O-(C₀-C₄ alkylene)-heterocyclyl, -O-(C₀-C₄ alkylene)-carbocyclyl, -N(R⁷)-aryl, -N(R⁷)-heteroaryl, -N(R⁹)-aryl, -N(R⁹)-heteroaryl, -O-(C₁-C₄ alkylene)-N(R⁷)C(O)O-(C₁-C₄ alkylene)-aryl, or -N(R⁹)-C(O)-(C₂-C₄ alkenyl):

wherein:

at least one of R^{1a} and R^{1b} is not hydrogen or methyl;

any alkylene moiety present in R^{1a} or R^{1b} is optionally substituted with OH or F;

each R⁷ is independently selected from the group consisting of hydrogen and C₁-C₄ alkyl; and

any aryl, heteroaryl, or heterocyclyl of R^{1a} or R^{1b} is optionally substituted with one or more substituents selected from the group consisting of -G-L-M, halo, C₁-C₆ alkyl, -C≡N, =O, -CF₃ and -OCF₃;

G is a bond or a bivalent C₁-C₆ saturated or unsaturated, straight or branched hydrocarbon chain wherein optionally one, two or three methylene units of the hydrocarbon chain are independently replaced by -NR⁸-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO₂-, -C(=S)-, -C(=NR⁸)-, -N=N-, or -C(=N₂)-;

L is a covalent bond or a bivalent C₁₋₈ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, -NR⁸-, -N(R⁸)C(O)-, -C(O)N(R⁸)-, -N(R⁸)SO₂-, SO₂N(R⁸)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO₂-, -C(=S)-, -C(=NR⁸)-, -N=N-, or -C(=N₂)-;

M is E, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aromatic ring having 0-3 heteroatoms which are independently nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups which are independently -D-E, oxo, NO₂, halogen, CN, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl;

D is a covalent bond or a bivalent C₁-C₆ saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of D are optionally and independently replaced by-NR⁸-, -S-, -O-, -C(O)-, -SO-, or-SO₂-;

E is hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, or C₂-C₆ alkynyl, wherein said alkyl, alkenyl or alkynyl is optionally substituted with oxo, halogen, or CN; and

each R⁸ is independently hydrogen, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, or an optionally substituted group which is phenyl, a 4-7 membered heterocyclyl having 1-2 heteroatoms which are independently nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms which are independently nitrogen, oxygen, or sulfur;

R² is selected from the group consisting of phenyl, a 3-7 membered cycloalkyl, and C₂-C₄ alkyl, wherein the phenyl or cycloalkyl is optionally substituted with a methyl or fluoro;

each R³ is independently selected from the group consisting of -C₁-C₄ alkyl, -(C₁-C₄ alkyl)-O-(C₁-C₄ alkyl), -C₁-C₄ fluoroalkyl, -C(O)-O-(C₁-C₄ alkyl), -phenyl, -heteroaryl, C₃-C₇ cycloalkyl, -CH₂-N(C₁-C₄ alkyl)₂, C(O)-N-(C₁-C₄ alkyl)₂, and -C(O)-NH-(C₁-C₄ alkyl),

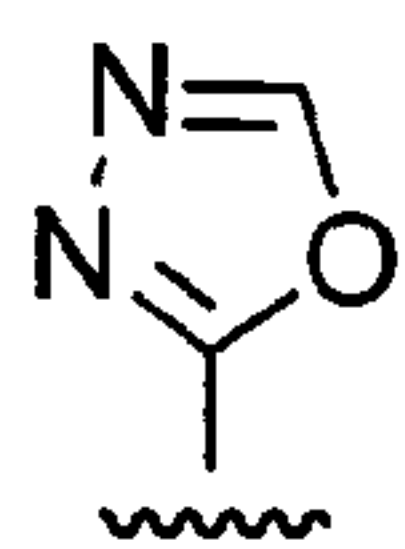
or two R³s are taken together to form a 3-8 saturated ring or a fused phenyl wherein said saturated ring or fused phenyl is optionally substituted with 1 to 2 methyl groups;

R⁴ is selected from the group consisting of hydrogen, -CN, halo, C₁-C₄ alkoxy, -CH₂NH(C₁-C₄ alkyl), C₂-C₄ alkenyl, C₂-C₄ alkynyl, -(C₁-C₄ alkyl)-O-(C₁-C₄ alkyl), C₁-C₄ fluoroalkyl, C(O)-N-(C₁-C₄ alkyl)₂, -C(O)-NH-(C₁-C₄ alkyl), -C(O)-O-(C₁-C₄ alkyl), -C(O)-OH, -S(O)₂-(C₁-C₄ alkyl), and a 5-membered heteroaryl;

R⁵ is selected from the group consisting of: -C(O)-(C₁-C₄alkyl), -C(O)-(CH₂)₀₋₂-Q, -C(O)-(CH₂)₀₋₂-N(R⁶)-(CH₂)₀₋₂-Q, -C(O)-O-(CH₂)₁₋₂-Q, -C(O)-(CH₂)₁₋₂-O-(CH₂)₀₋₂-Q, -C(O)-C(O)-Q, -S(O)₂-Q, -C(O)-(C₁-C₄ alkylene)-O-C(O)-(C₁-C₄ alkyl), -C(O)-(C₁-C₄ alkylene)-C(O)-O-(C₁-C₄ alkyl), -C(O)-N(R⁶)-(C₁-C₄ alkylene)-O-C(O)-(C₁-C₄ alkyl), -C(O)-N(R⁶)-(C₁-C₄ alkylene)-C(O)-O-(C₁-C₄ alkyl), -C(O)-(CH₂)₀₋₂-N(R⁶)-(C₁-C₆ alkyl), -C(O)-(CH₂)₀₋₂-N(R⁶)-(C₂-C₆ alkynyl), -C(O)-(CH₂)₀₋₂-N(R⁶)-(C₂-C₆ alkenyl), -C(O)-(CH₂)₀₋₂-N(R⁶)-(CH₂)₀₋₂-O-(C₁-C₄ alkyl), -C(O)-(CH₂)₁₋₂-O-(C₁-C₄ alkyl), -C(O)-O-(C₁-C₄ alkylene)-O-(C₁-C₄ alkyl), -(CH₂)₀₋₄-O-C(O)-(C₁-C₄ alkyl), -(CH₂)₀₋₄-C(O)-O-(C₁-C₄ alkyl), -(CH₂)₀₋₄-O-(C₁-C₄ alkyl), -C(O)-(CH₂)₁₋₂-S-(C₁-C₄ alkyl), -S(O)₂-(C₁-C₄ alkyl), -C(O)-(C₁-C₄ alkylene)-C(O)C(O)N(R⁶) (C₁-C₆ alkyl), -C(O)-(C₁-C₄ alkylene)-N(R⁶)S(O)₂-(C₁-C₆ alkyl), and -C(O)-(C₁-C₄ alkylene)-N(R⁶)S(O)₂Q, wherein:

any alkylene moiety present in R^5 is optionally substituted with OH or F;
any terminal methyl moiety present in R^5 is optionally replaced with $-CH_2OH$, CF_3 , $-CH_2F$, $-CH_2Cl$, $C(O)CH_3$, or $C(O)CF_3$;
each R^6 is independently selected from the group consisting of hydrogen and methyl;
Q is selected from the group consisting of aryl, heteroaryl, carbocyclyl and heterocyclyl, wherein Q is optionally substituted with up to 3 substituents independently selected from C_1 - C_4 alkyl, C_1 - C_4 alkoxy, $-CN$, fluoro, chloro, and bromo; and
m is 0, 1, 2 or 3.

3. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^4 is selected from $-CN$ and $C(O)-O-C_1-C_4$ alkyl.
4. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^4 is



5. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein Y is $-N(R^5)-$.

6. The compound of claim 5 or a pharmaceutically acceptable salt thereof, wherein R^5 is $-C(O)-(C_1-C_2$ alkylene)- $O-(C_1-C_2$ alkyl) $C(O)-Q$, $-C(O)-(C_1-C_5$ alkyl), $-C(O)-(C_1-C_2$ alkylene)- Q , $-C(O)-(C_2-C_4$ alkenyl), or $-C(O)-(C_2-C_4$ alkenylene)- Q ; wherein: any alkylene moiety present in R^5 is optionally substituted with OH; any terminal methyl moiety present in R^5 is optionally replaced with CF_3 , OCH_3 , $-C(O)H$, $OP(O)(C_1-C_4$ alkoxy) $_2$, or $-OP(O)(OH)_2$ (or a salt of $-OP(O)(OH)_2$).

7. The compound of claim 6 or a pharmaceutically acceptable salt thereof, wherein Q is cyclopropyl, cyclobutyl, oxetanyl, furanyl, azetidinonyl, pyrrolidinonyl, tetrahydrofuranyl, dihydrofuranonyl, or cyclopentyl, wherein each member of Q is optionally substituted with one substituent independently selected from the group consisting of C_1 - C_4 alkyl optionally substituted with OH, C_1 - C_4 alkoxy, $-(C_1-C_4$ alkylene)- $(C_1-C_4$ alkoxy), and $-OH$.

8. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^{1a} is H and R^{1b} is aryl, heteroaryl, heterocyclyl, $-(C_1-C_4$ alkylene)-aryl, $-(C_1-C_4$ alkylene)-heteroaryl, $-O-(C_0-C_4$ alkylene)-aryl, $-O-(C_0-C_4$ alkylene)-heteroaryl, $-N(R^7)-$

aryl, -N(R⁷)heteroaryl, -N(R⁹)-aryl, or -N(R⁹)-heteroaryl; wherein said aryl or heteroaryl is substituted with -G-L-M, CH₃, or CN.

9. The compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein any aryl in R^{1b} is phenyl.

10. The compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein any heteroaryl associated in R^{1b} is pyridyl, pyrimidinyl, naphthyridinyl, quinolyl, isoquinolyl, isoxazolyl, benzoxazolyl, imidazopyrazinyl, benzothiazolyl, benzimidazolyl, pyrrollopyridinyl, pyrazolopyridinyl, indolyl, indazolyl, imidazopyridinyl, quinoxalinyl, quinazolinyl, pyridazinyl or pyrazolyl.

11. The compound of claim 8 or a pharmaceutically acceptable salt thereof, wherein any heterocyclyl in R^{1b} is benzodioxole, pyridazinone, benzoxazolone, indolinone, N-methylindolinone, piperazinyl, N-methylisoquinolinone, tetrahydropyridinyl, dihydropyrrolyl, pyridyl, pyrimidinyl, naphthyridinyl, quinolyl, isoquinolyl, isoxazolyl, benzoxazolyl, imidazopyrazinyl, benzothiazolyl, benzimidazolyl, pyrrollopyridinyl, pyrazolopyridinyl, indolyl, indazolyl, imidazopyridinyl, quinoxalinyl, quinazolinyl, pyridazinyl, pyrazolyl, benzodioxole, pyridazinone, benzoxazolone, indolinone, N-methylindolinone, piperazinyl, N-methylisoquinolinone, tetrahydropyridinyl, or dihydropyrrolyl.

12. The compound of any one of claims 9-11 or a pharmaceutically acceptable salt thereof, wherein any aryl, heteroaryl or heterocyclyl in R^{1b} is substituted with -G-L-M, -CF₃, -OCF₃, halo, CH₃, or CN.

13. The compound of claim 1 or a pharmaceutically acceptable salt thereof, wherein R^{1a} is methyl and R^{1b} is aryl, heteroaryl, heterocyclyl, -O-(C₀-C₄ alkylene)-aryl, or -O-(C₀-C₄ alkylene)-heteroaryl.

14. The compound of claim 13 or a pharmaceutically acceptable salt thereof, wherein R^{1a} is methyl and R^{1b} is aryl, heteroaryl, heterocyclyl, -O-(CH₂)-aryl, -O-CH(CH₃)-aryl, -O-(CH₂)-heteroaryl or -O-CH(CH₃)-heteroaryl.

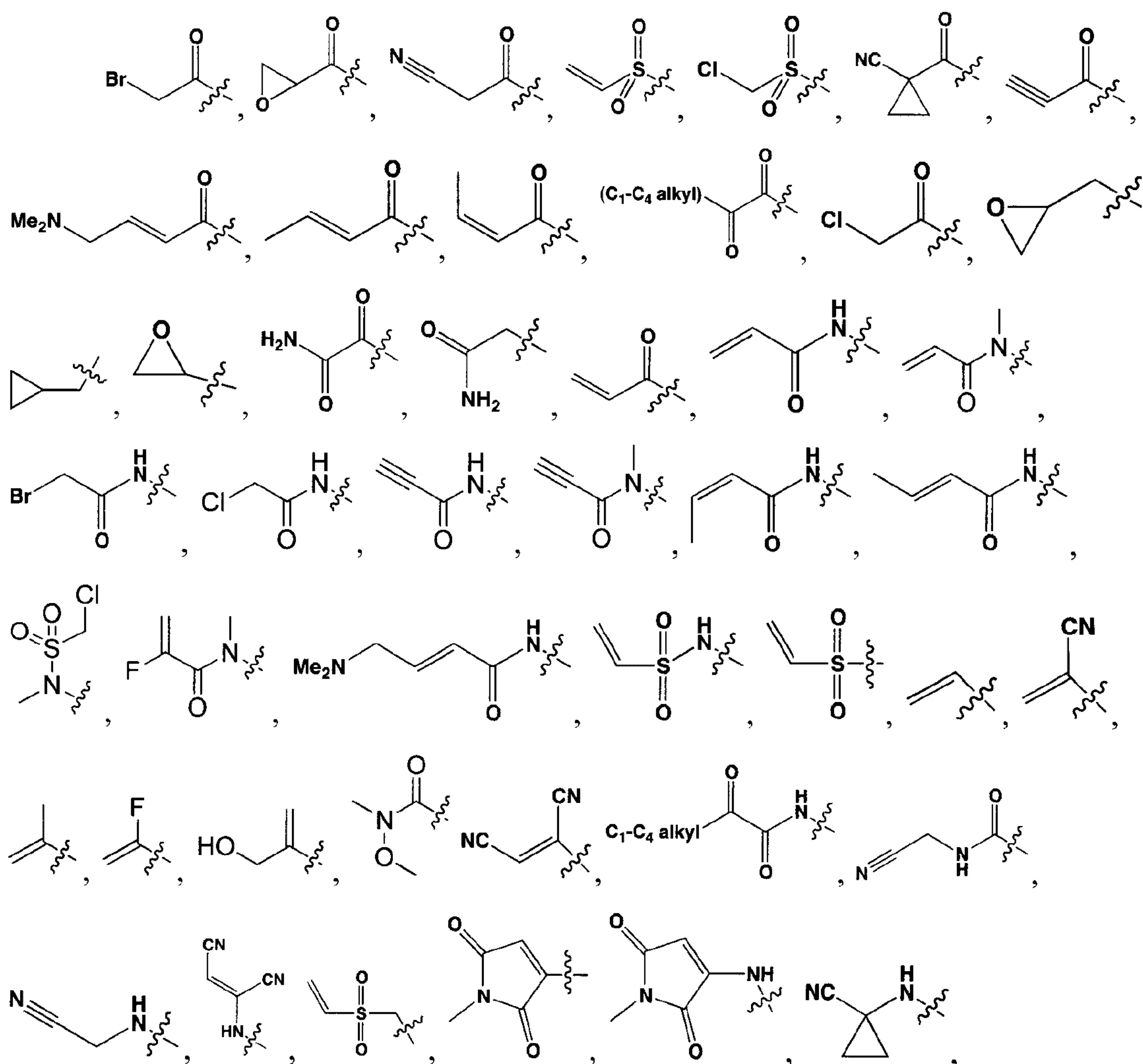
15. The compound of any one of claims 13-14 or a pharmaceutically acceptable salt thereof, wherein any aryl associated in R^{1b} is phenyl or naphthyl.

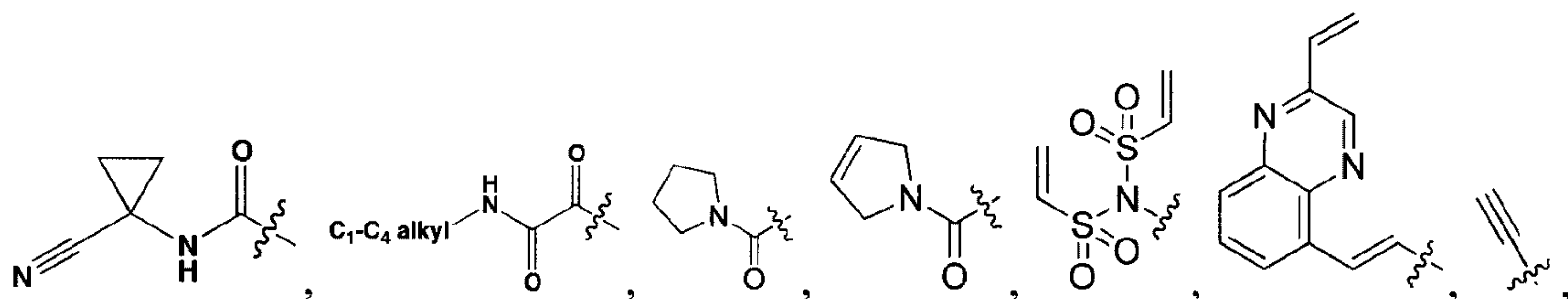
16. The compound of any one of claims 13-14 or a pharmaceutically acceptable salt thereof, wherein any heteroaryl in R^{1b} is quinolinyl, pyrazolyl, isoquinolinyl, pyridyl, pyrimidinyl, indolyl, or pyrazolyl.

17. The compound of any one of claims 13-14 or a pharmaceutically acceptable salt thereof wherein any heterocyclyl in R^{1b} is tetrahydropyridinyl.

18. The compound of any one of claims 13-17 or a pharmaceutically acceptable salt thereof, wherein any aryl, heteroaryl or heterocyclyl in R^{1b} is substituted with -G-L-M, halo, CH₃, or CN.

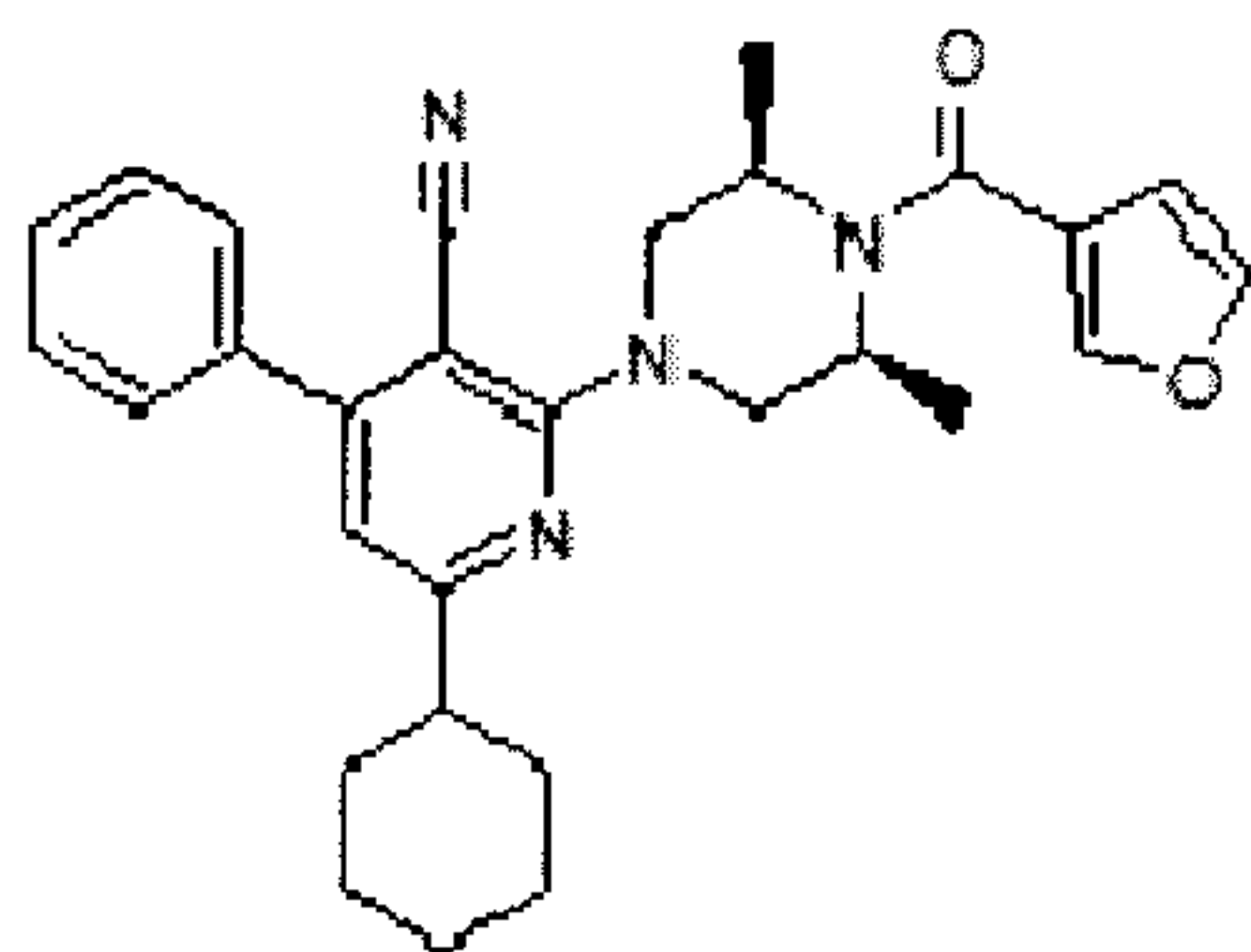
19. The compound of any one of claims 8-18 or a pharmaceutically acceptable salt thereof, wherein -G-L-M is selected from:



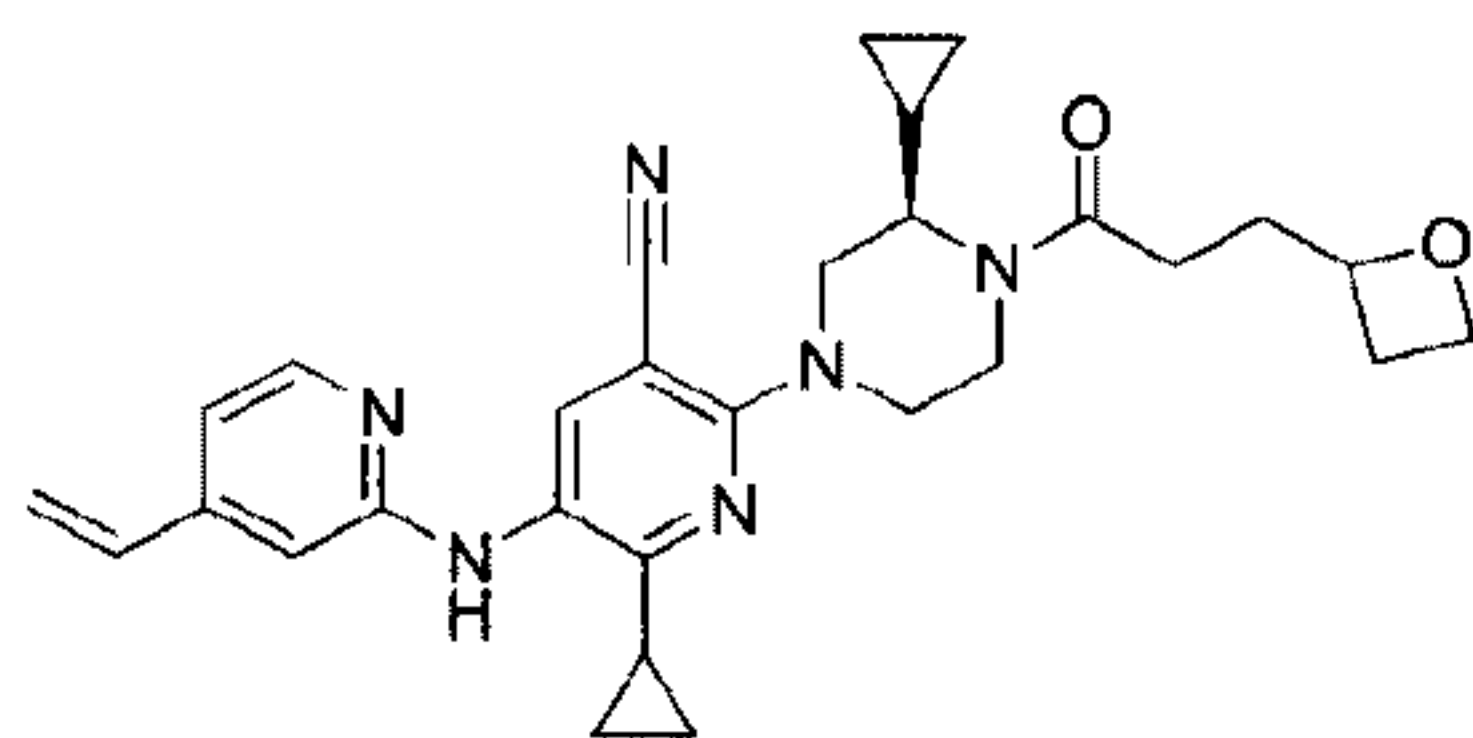


C₁-C₄ alkyl, C₂-C₄ alkenyl, C₁-C₄ alkoxy, tetrazolyl, morpholino, piperazinyl, pyrrolidinone, pyrazolyl, benzyl, -(CH₂)₁₋₄-SH, -(CH₂)₁₋₄-NH₂, -NH₂, -(CH₂)₁₋₄-OH, -N(H)C(O)OCH(CH₃)₃, -(CH₂)₁₋₄-OCH₃, -NH-(CH₂)₁₋₄-OH, -C(O)-(C₁-C₄ alkyl), -C(O)-(C₁-C₄ alkenyl), -O-(CH₂)₁₋₄-C(O)-O-(C₁-C₄ alkyl), -C(O)NH₂, -(CH₂)₁₋₄C(O)CH₃, -N(CH₃)(CH₃), -NHC(O)(C₂-C₄ alkenyl), -NHC(O)(C₂-C₄ alkyl), -SO₂(CH₂)₁₋₄, -(CH₂)₁₋₄-NHSO₂Me, -NHSO₂(CH₂)₁₋₄, -O-SO₂CF₃, -SO₂NH-(C₁-C₄ alkyl), --SO₂NH-(C₂-C₄ alkenyl), SO₂-NH₂ and -NHSO₂Me.

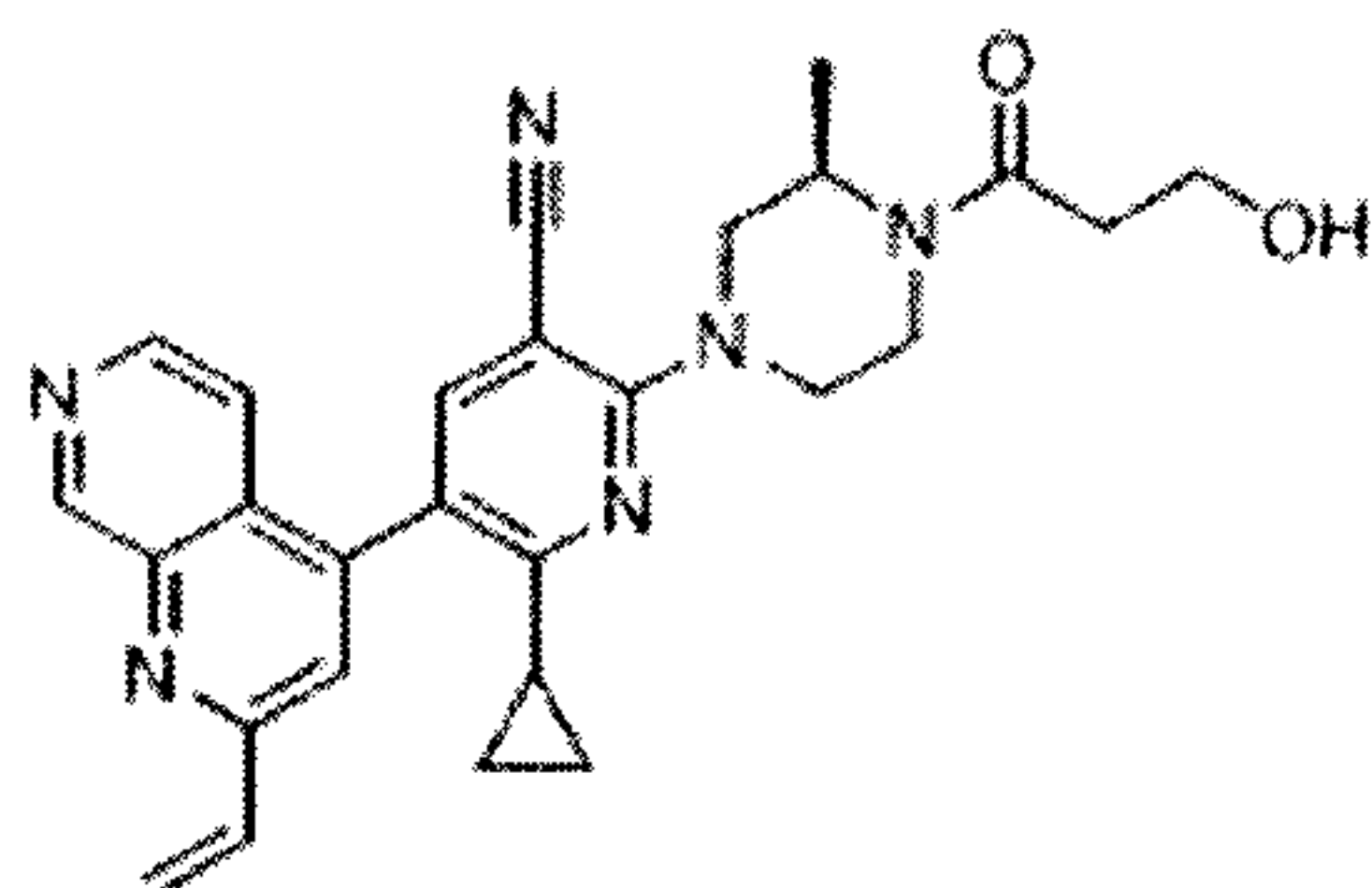
20. The compound according to claim 1 or a pharmaceutically acceptable salt thereof which is:



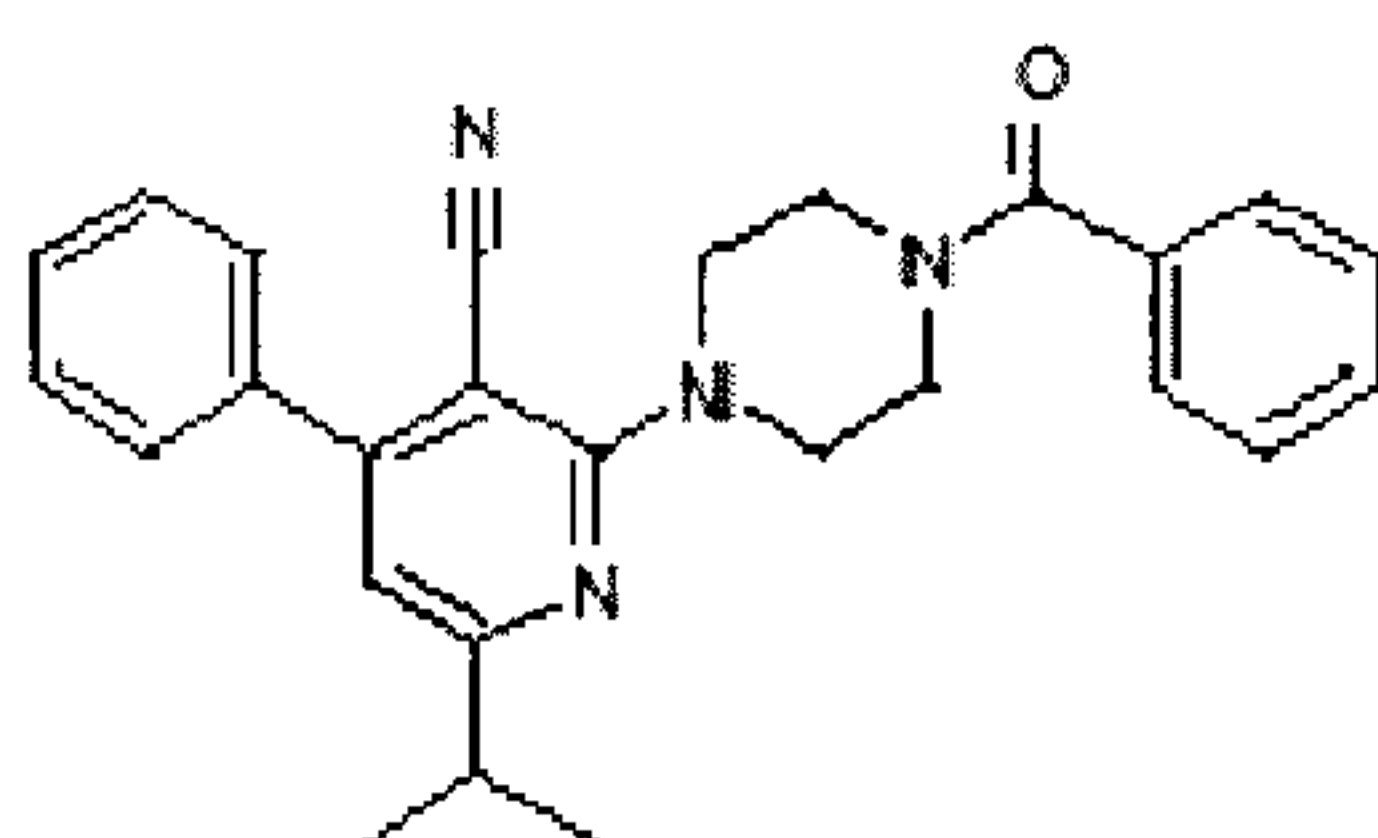
21. The compound according to claim 1 or a pharmaceutically acceptable salt thereof which is:



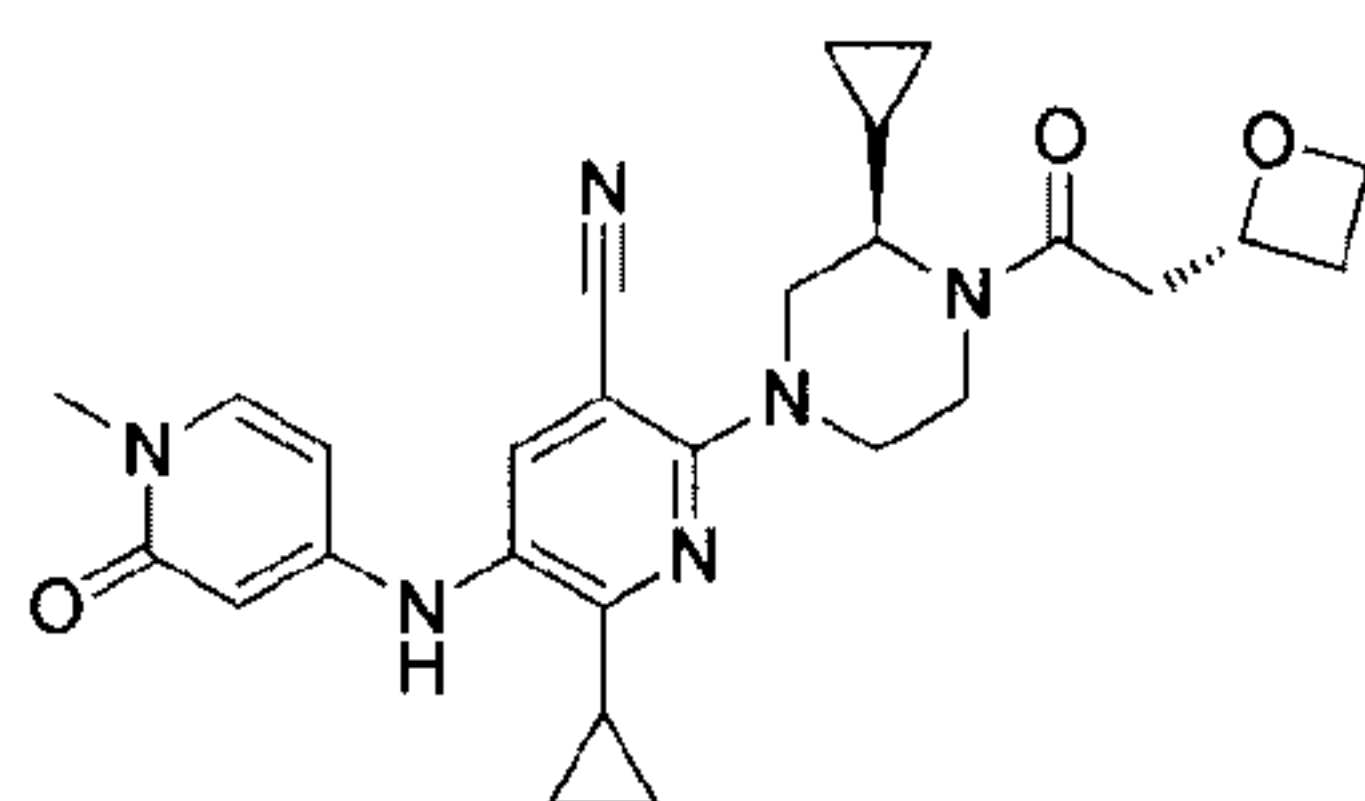
22. The compound according to claim 1 or a pharmaceutically acceptable salt thereof which is:



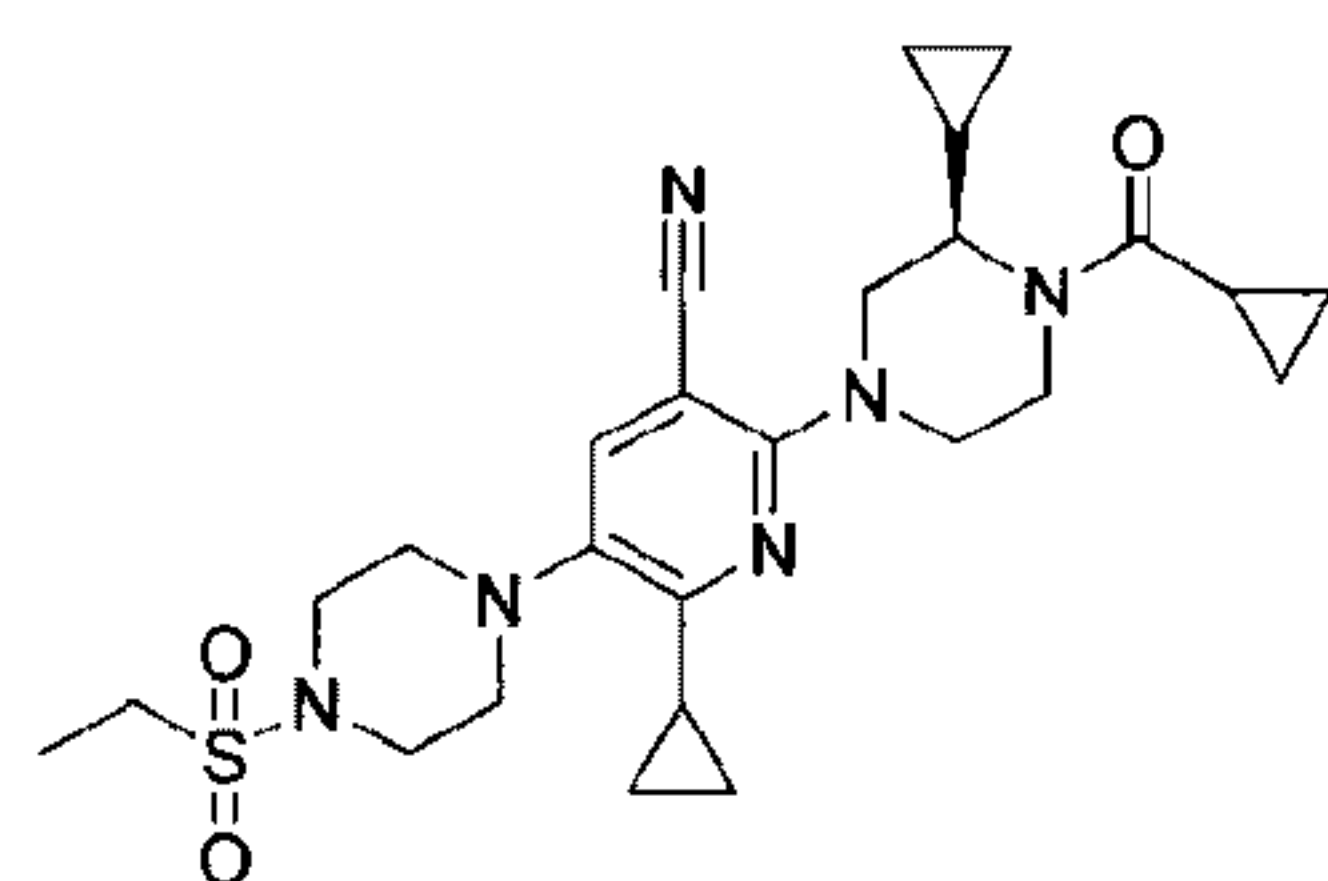
23. The compound according to claim 1 or a pharmaceutically acceptable salt thereof which is:



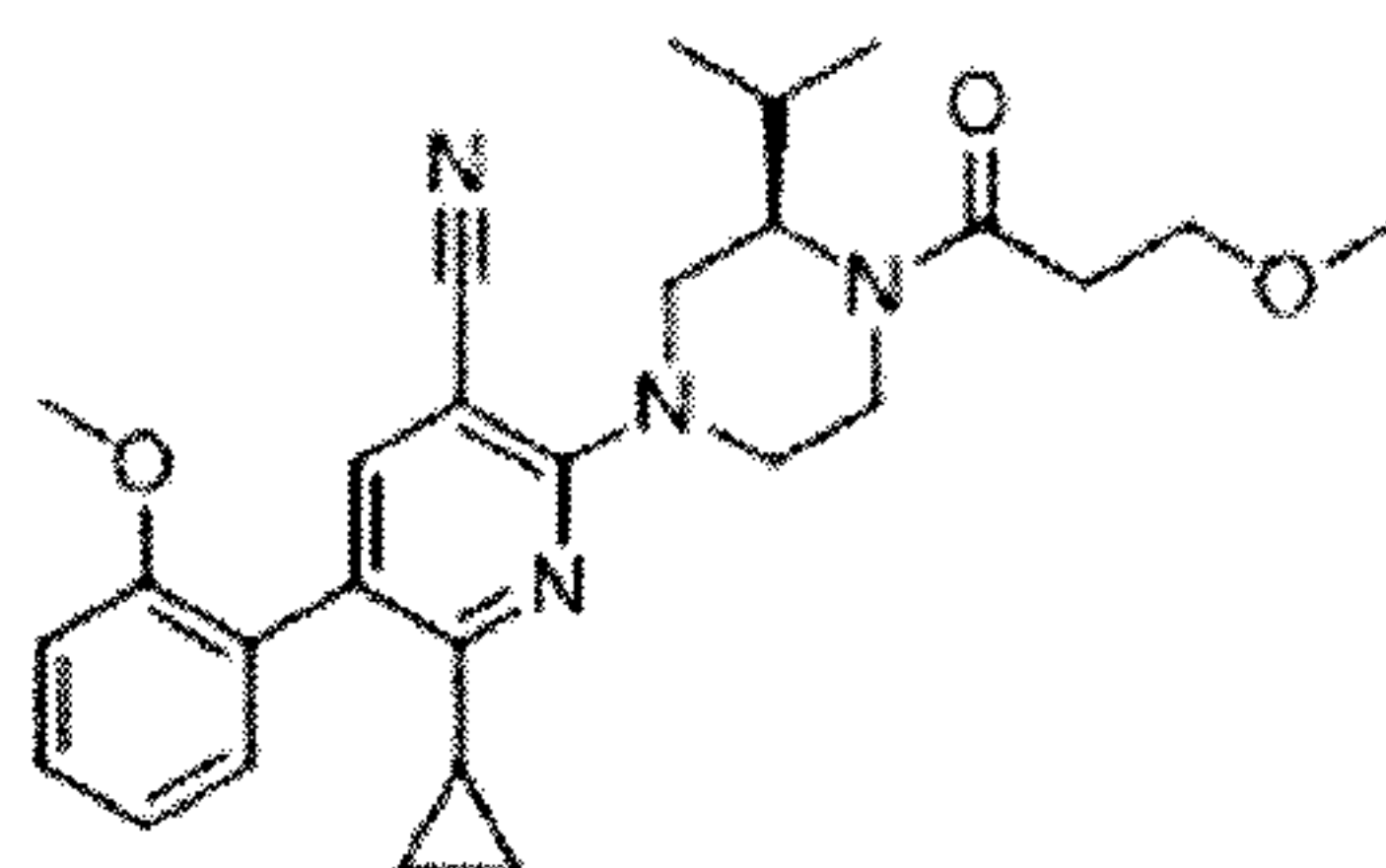
24. The compound according to claim 1 or a pharmaceutically acceptable salt thereof which is:



25. The compound according to claim 1 or a pharmaceutically acceptable salt thereof which is:



26. The compound according to claim 1 or a pharmaceutically acceptable salt thereof which is:



27. A pharmaceutical composition comprising a compound of claim 1 or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

28. The pharmaceutical composition of claim 27, further comprising a second therapeutic agent.

29. Use of the composition of claim 27 for treating a cancer characterized by the presence of an IDH1 mutation, wherein the IDH1 mutation results in a new ability of the enzyme to catalyze the reduction of α -ketoglutarate to R(-)-2-hydroxyglutarate in a patient.

30. The use of claim 29, wherein the IDH1 mutation is an IDH1 R132H or IDH1 R132C mutation.

31. The use of claim 30, wherein the cancer is selected from the group consisting of glioma (glioblastoma), acute myelogenous leukemia, sarcoma, melanoma, non-small cell lung cancer, cholangiocarcinomas, chondrosarcoma, myelodysplastic syndromes (MDS), myeloproliferative neoplasm (MPN), and colon cancer.

32. The use of any one of claims 29-31 wherein the composition is for administration with a second therapeutic agent to the patient.

