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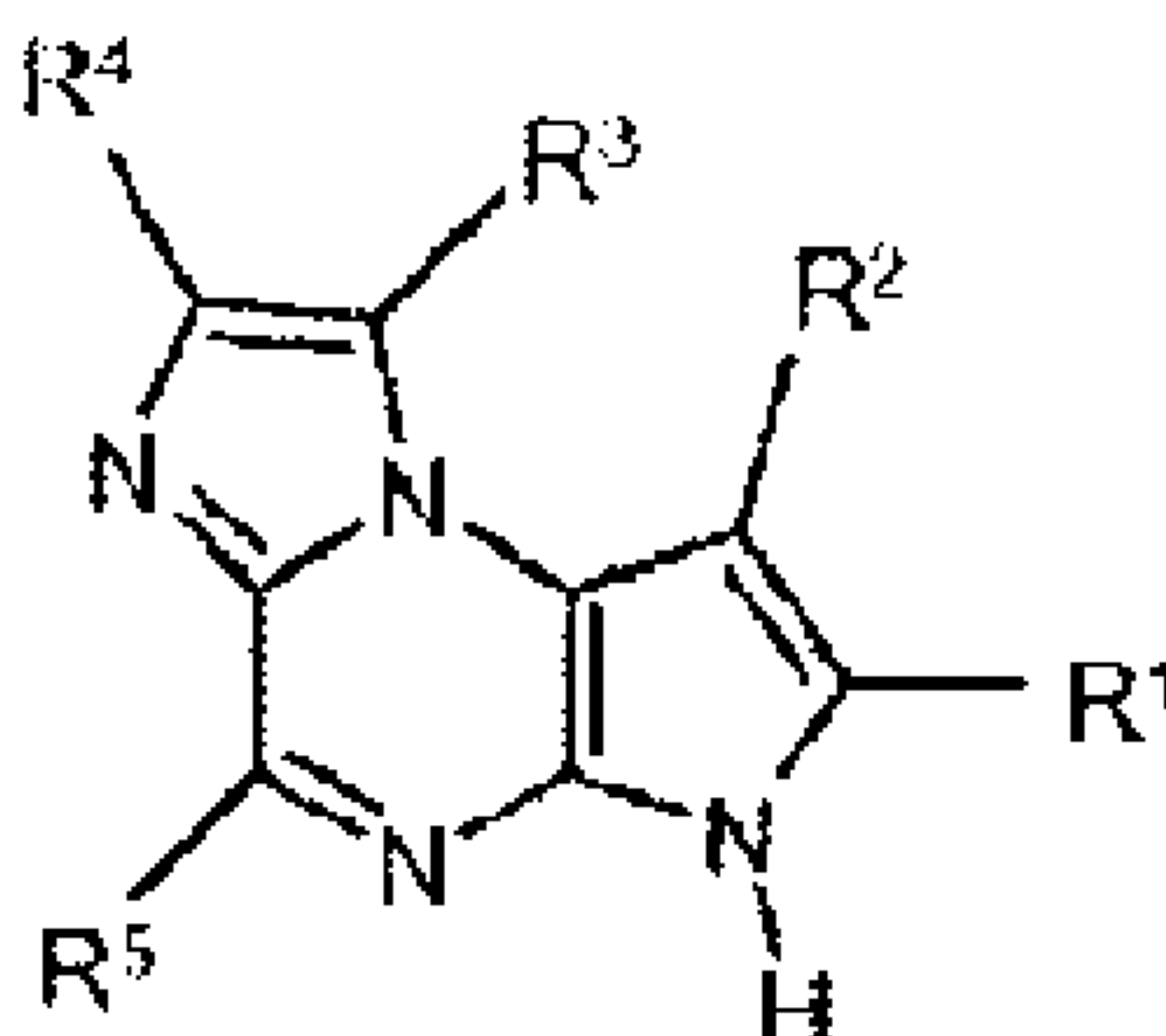
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(54) **Titre : COMPOSES TRICYCLIQUES NOVATEURS COMME INHIBITEURS DE LA PROTEINE KINASE**
(54) **Title: NOVEL TRICYCLIC COMPOUNDS AS PROTEIN KINASE INHIBITORS**



Formula (Ic)

(57) **Abrégé/Abstract:**

The invention provides compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, pro-drugs, biologically active metabolites, stereoisomers and isomers thereof wherein the variable are defined herein. The compounds of the invention are useful for treating immunological and oncological conditions.

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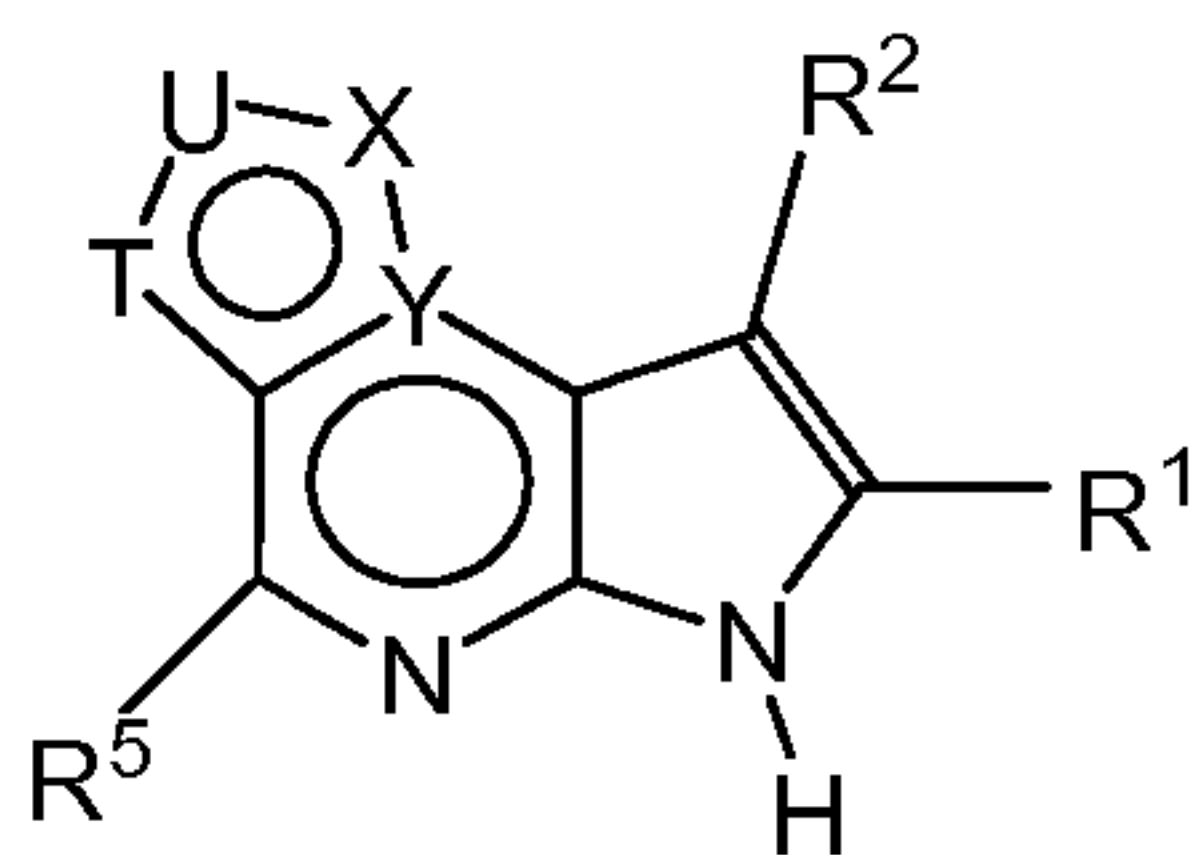
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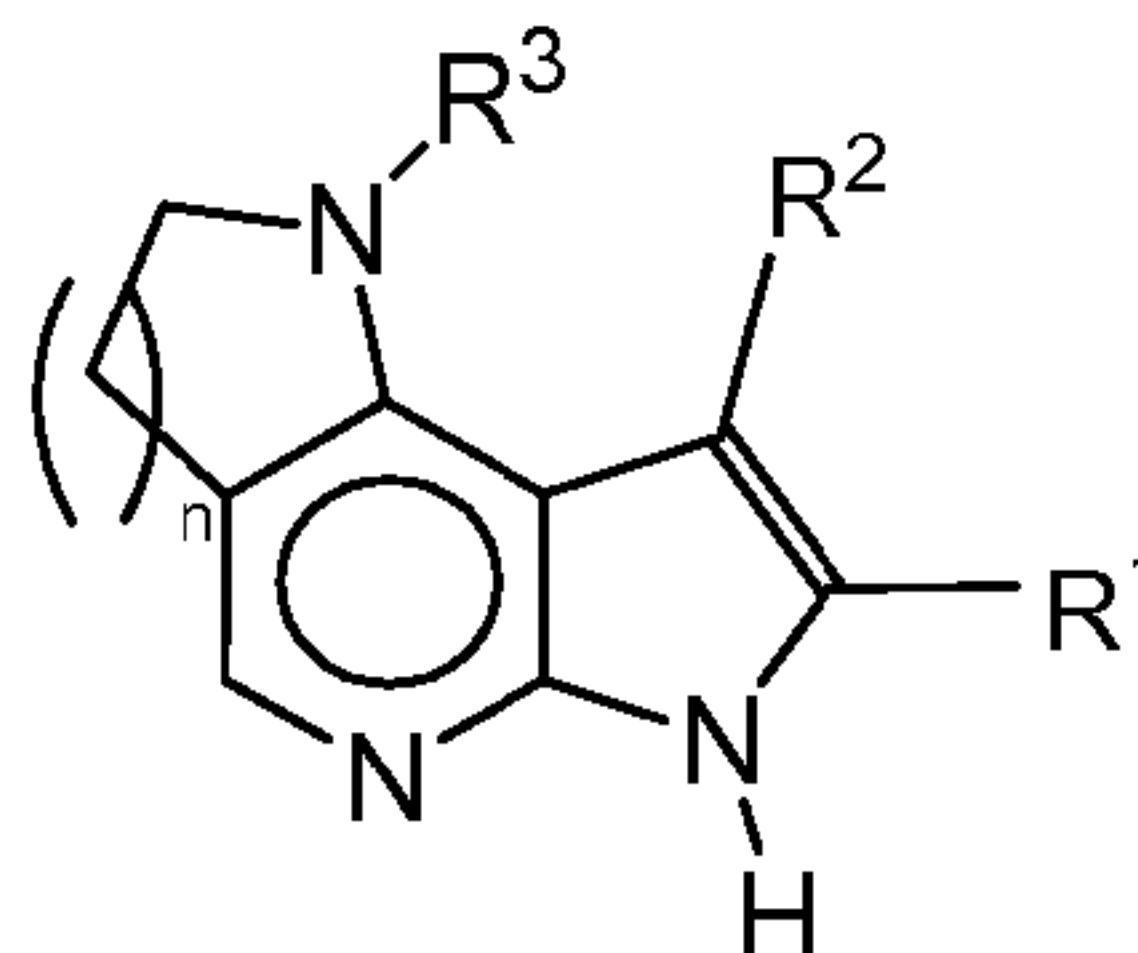
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(54) Title: NOVEL TRICYCLIC COMPOUNDS



Formula (I)



Formula (II)

(57) Abstract: The invention provides compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, pro-drugs, biologically active metabolites, stereoisomers and isomers thereof wherein the variable are defined herein. The compounds of the invention are useful for treating immunological and oncological conditions.

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DEMANDES OU BREVETS VOLUMINEUX

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CECI EST LE TOME __1__ DE __3__

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JUMBO APPLICATIONS / PATENTS

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

THIS IS VOLUME __1__ OF __3__

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

WO 2011/068881

PCT/US2010/058572

Novel tricyclic compounds as protein kinase inhibitors

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application Serial No. 61/265,563 filed on December 1, 2009, and U.S. Provisional Application Serial No. 61/364,116 filed July 14, 2010 .

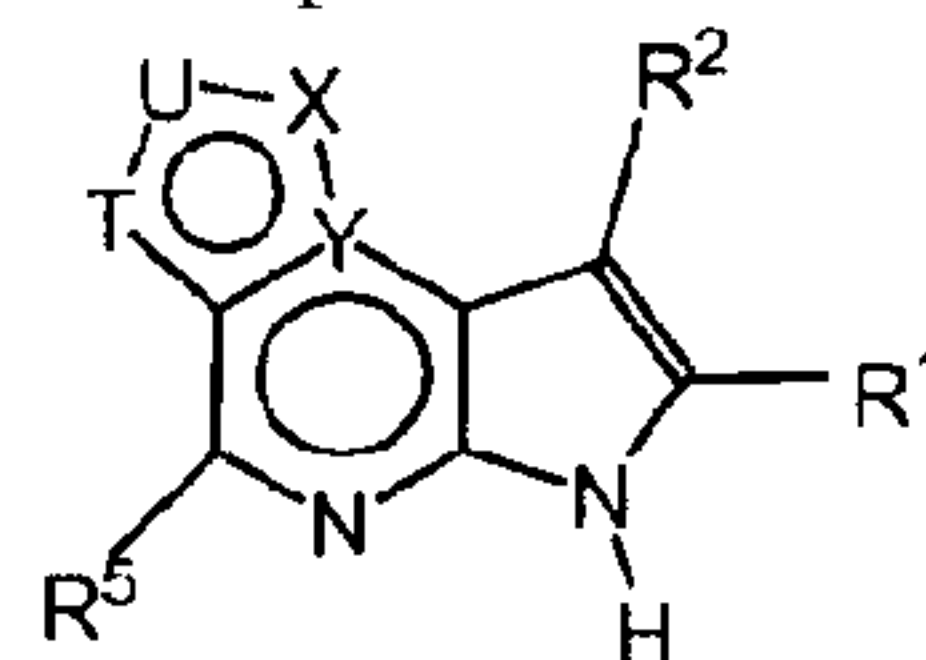
BACKGROUND OF THE INVENTION

The invention provides a novel class of compounds, pharmaceutical compositions comprising such compounds and methods of using such compounds to treat or prevent diseases or disorders associated with abnormal or deregulated kinase activity, particularly diseases or disorders that involve abnormal activation of the Jak1, Jak2, Jak3, Tyk2, KDR, Flt-3, CDK2, CDK4, TANK, Trk, FAK, Abl, Bcr-Abl, cMet, b-RAF, FGFR3, c-kit, PDGF-R, Syk, BTK, CSF1R, PKC kinases or Aurora kinases.

The protein kinases represent a large family of proteins that play a central role in the regulation of a wide variety of cellular processes and maintenance of cellular function. A partial, non-limiting, list of these kinases include: non-receptor tyrosine kinases such as the Janus kinase family (Jak1, Jak2, Jak3 and Tyk2); the fusion kinases, such as BCR-Abl, focal adhesion kinase (FAK), Fes, Lck and Syk; receptor tyrosine kinases such as platelet-derived growth factor receptor kinase (PDGF-R), the receptor kinase for stem cell factor, c-kit, the hepatocyte growth factor receptor, c-Met, and the fibroblast growth factor receptor, FGFR3; and serine/threonine kinases such as b-RAF, mitogen-activated protein kinases (e.g., MKK6) and SAPK2 β . Aberrant kinase activity has been observed in many disease states including benign and malignant proliferative disorders as well as diseases resulting from inappropriate activation of the immune and nervous systems. The novel compounds of this invention inhibit the activity of one or more protein kinases and are, therefore, expected to be useful in the treatment of kinase-mediated diseases.

SUMMARY OF THE INVENTION

In a first embodiment the invention provides a compound of Formula (I)



Formula (I)

pharmaceutically acceptable salts, pro-drugs, biologically active metabolites, stereoisomers and isomers thereof wherein

T is N, U is N, X is CR³ and Y is N; or

T is CR⁶, U is N, X is CR³ and Y is N; or

T is N, U is CR⁴, X is CR³ and Y is N; or

T is CR⁶, U is CR⁴, X is CR³ and Y is N; or

T is CR⁶, U is N, X is NR³ and Y is C; or

T is O, U is N, X is CR³ and Y is C; or

T is NR⁶, U is N, X is CR³ and Y is C; or

T is CR⁶, U is CR⁴, X is NR³ and Y is C; or

T is S, U is N, X is CR³ and Y is C; or

T is N, U is CR⁴, X is NR³ and Y is C; or

T is N, U is N, X is NR³ and Y is C;

R¹, R² and R⁵ are each independently hydrogen, deuterium, -N(R^a)(R^b), halogen, -OR^a, -SR^a, -S(O)R^a, -S(O)₂R^a, -NO₂, -C(O)OR^a, -CN, -C(O)N(R^a)(R^b), -N(R^a)C(O)(R^b), -C(O)R^a, -C(OH)R^aR^b, -N(R^a)S(O)₂-R^b, -S(O)₂N(R^a)(R^b), -CF₃, -OCF₃, optionally substituted (C₁-C₆)alkyl, optionally substituted (C₂-C₆)alkenyl, optionally substituted (C₂-C₆)alkynyl, optionally substituted (C₃-C₁₀)cycloalkyl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₁-C₁₀)heterocyclyl, or optionally substituted (C₆-C₁₀)aryl;

wherein in a moiety containing -N(R^a)(R^b), the nitrogen, R^a and R^b may form a ring such that -N(R^a)(R^b) represents an optionally substituted (C₂-C₁₀)heterocyclyl or optionally substituted (C₁-C₁₀)heteroaryl linked through a nitrogen;

R³ is hydrogen, an optionally substituted bridged (C₅-C₁₂)cycloalkyl, optionally substituted bridged (C₂-C₁₀)heterocyclyl, optionally substituted (C₁-C₈)alkyl, optionally substituted (C₃-C₁₀)cycloalkyl, optionally substituted (C₃-C₈)cycloalkenyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₂-C₁₀)heterocyclyl; or

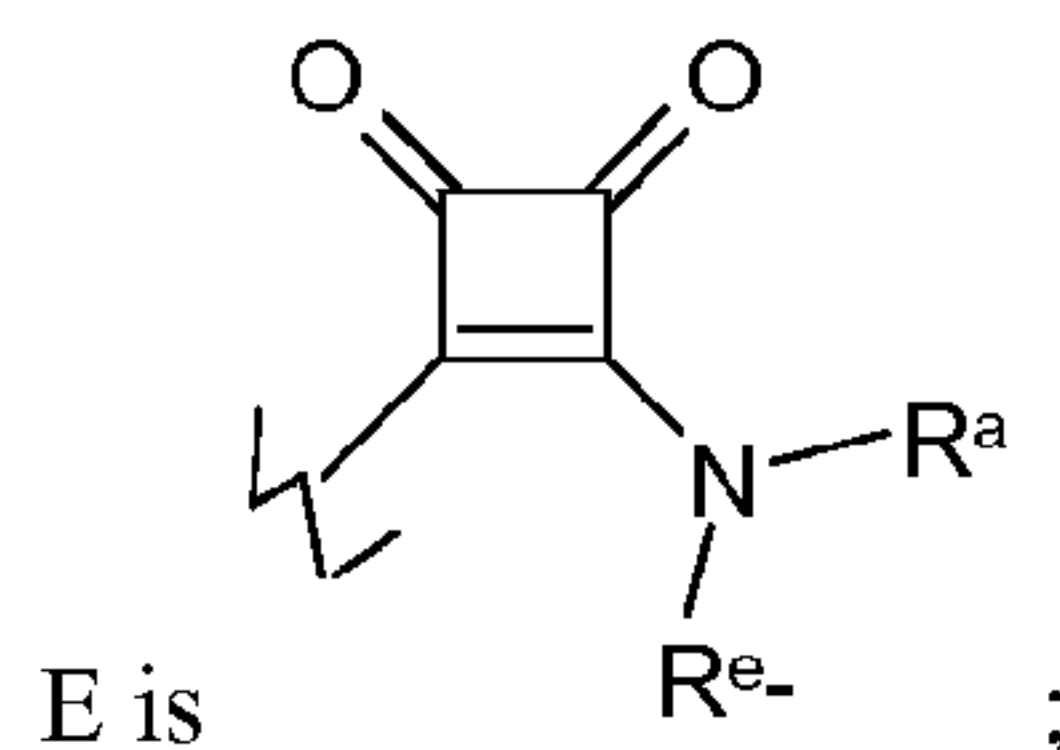
R³ is -A-D-E-G, wherein:

A is a bond, -C(O)-, optionally substituted (C₁-C₆)alkylene, optionally substituted (C₂-C₆)alkenylene, optionally substituted (C₂-C₆)alkynylene, optionally substituted (C₃-C₁₂)cycloalkylene, optionally substituted (C₂-C₆)heterocyclylene, -C(O)N(R^a)-R^e-, -N(R^a)C(O)-R^e-, -O-R^e-, -N(R^a)-R^e-, -S-R^e-, -S(O)₂-R^e-, -S(O)R^e-, -C(O-R^a)(R^b)-R^e-, -S(O)₂N(R^a)-R^e-, -N(R^a)S(O)₂-R^e- or -N(R^a)C(O)N(R^b)-R^e-;

D is an optionally substituted (C₁-C₈)alkylene, optionally substituted bridged (C₅-C₁₂)cycloalkylene, optionally substituted (C₃-C₁₀)cycloalkylene, optionally substituted bridged (C₅-C₁₀)cycloalkenylene, optionally substituted (C₃-C₁₀)cycloalkenylene, optionally substituted

(C₆-C₁₀)arylene, optionally substituted (C₁-C₁₀)heteroarylene, optionally substituted bridged (C₂-C₁₀)heterocyclylene or an optionally substituted (C₂-C₁₀)heterocyclylene;

E is a bond, -R^e-, -R^e-C(=NCN)-R^e-, -R^e-C(O)-R^e-, -R^e-C(O)C(O)-R^e-, -R^e-C(O)O-R^e-, -R^c-C(O)C(O)N(R^a)-R^c-, -R^c-N(R^a)-C(O)C(O)-R^c-, -R^c-O-R^c-, -R^c-S(O)₂-R^c-, -R^c-S(O)-R^c-, -R^c-S-R^e-, -R^e-N(R^a)-R^e-, =N-R^e-, -R^e-N(R^a)C(O)-R^e-, -R^eC(O)N(R^a)R^e-, -R^e-OC(O)N(R^a)-R^e-, -R^e-N(R^a)C(O)OR^c-, -R^c-OC(O)-R^c-, -R^c-OC(O)-O-R^c-, -R^c-N(R^a)C(O)N(R^b)-R^c-, -R^c-N(R^a)S(O)₂-R^c-, -R^e-S(O)₂N(R^a)-R^e-, or -R^e-N(R^a)S(O)₂N(R^a)-R^e-; or



where in all cases, E is linked to either a carbon or a nitrogen atom in D;

G is hydrogen, deuterium, -N(R^a)(R^b), halogen, -OR^a, -SR^a, -S(O)R^a, -S(O)₂R^a, -NO₂, -C(O)OR^a, -CN, -C(O)N(R^a)(R^b), -N(R^a)C(O)R^b, -N(R^a)C(O)OR^b, -OC(O)N(R^a), -N(R^a)C(O)N(R^b)₂, -C(O-R^a)(R^b)₂, -C(O)R^a, -CF₃, -OCF₃, -N(R^a)S(O)₂R^b, -S(O)₂N(R^a)(R^b), -S(O)₂N(R^a)C(O)R^b, an optionally substituted -(C₁-C₆)alkyl, an optionally substituted -(C₂-C₆)alkenyl, an optionally substituted -(C₂-C₆)alkynyl, an optionally substituted -(C₃-C₁₀)cycloalkyl, an optionally substituted -(C₁-C₁₀)heteroaryl, an optionally substituted -(C₁-C₁₀)heterocyclyl, an optionally substituted -(C₆-C₁₀)aryl;

wherein in a moiety containing -N(R^a)(R^b), the nitrogen, R^a and R^b may form a ring such that -N(R^a)(R^b) represents an optionally substituted (C₂-C₁₀)heterocyclyl or an optionally substituted (C₁-C₁₀) heteroaryl linked through a nitrogen;

R⁴ and R⁶ are each independently a hydrogen, halogen, deuterium, CF₃, CHF₂, CH₂F, CH₂CF₃, C(O)OH, C(O)OCH₃, CN, an optionally substituted bridged (C₅-C₁₂)cycloalkyl group, optionally substituted bridged (C₂-C₁₀)heterocyclyl group, optionally substituted (C₁-C₈)alkyl, optionally substituted (C₃-C₁₀)cycloalkyl, optionally substituted (C₃-C₈)cycloalkenyl, optionally substituted (C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₂-C₁₀)heterocyclyl or -J-L-M-Q;

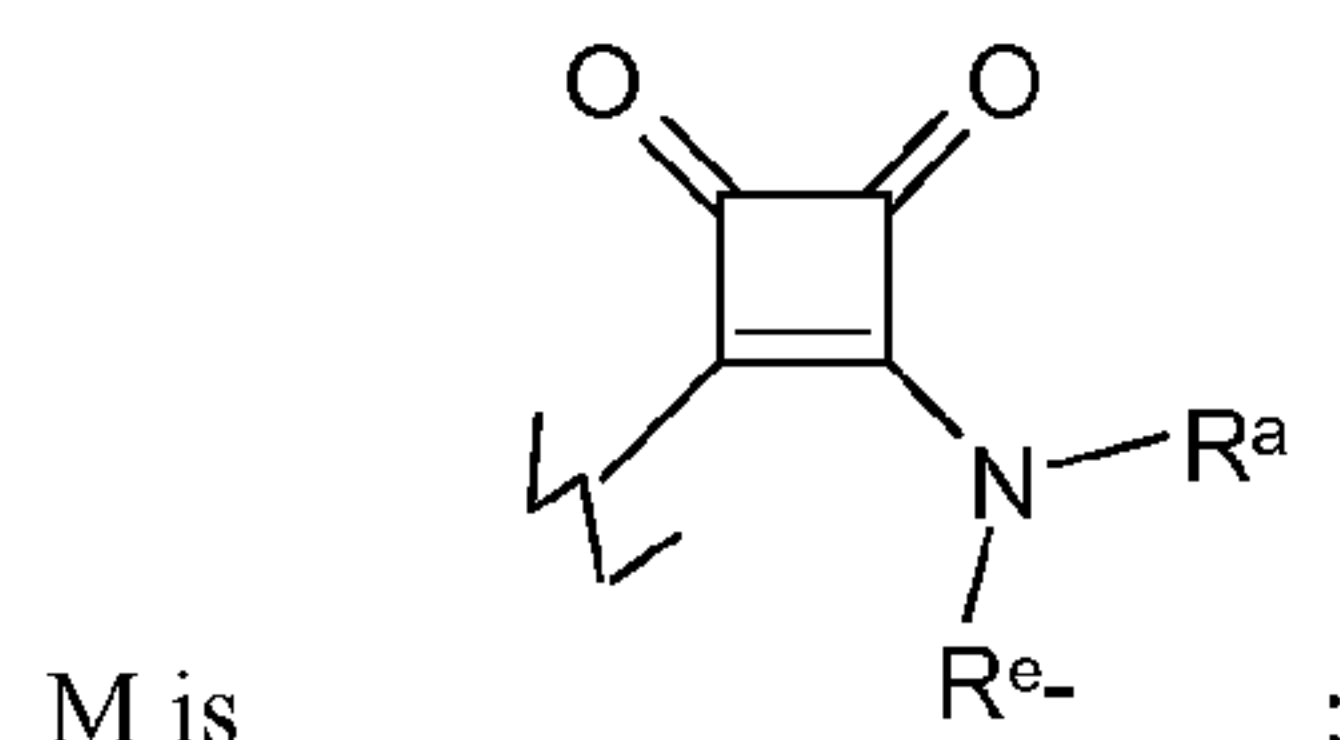
wherein:

J is a bond, -C(O)-, optionally substituted (C₁-C₆)alkylene, optionally substituted (C₂-C₆)alkenylene, optionally substituted (C₂-C₆)alkynylene, optionally substituted (C₃-C₁₂)cycloalkylene, optionally substituted (C₂-C₆)heterocyclylene, -C(O)N(R^a)-R^e-, -N(R^a)C(O)-R^e-, -O-R^e-, -N(R^a)-R^e-, -S-R^e-, -S(O)₂-R^e-, -S(O)R^e-, -C(O-R^a)(R^b)-R^e-, -S(O)₂N(R^a)-R^e-, -N(R^a)S(O)₂-R^e- or -N(R^a)C(O)N(R^b)-R^e-;

L is a bond, an optionally substituted (C₁-C₈)alkylene, optionally substituted bridged (C₅-C₁₂)cycloalkylene, optionally substituted (C₃-C₁₀)cycloalkylene, optionally substituted bridged

(C₅-C₁₀)cycloalkenylene, optionally substituted (C₃-C₁₀)cycloalkenylene, optionally substituted (C₆-C₁₀)arylene, optionally substituted (C₁-C₁₀)heteroarylene, optionally substituted bridged (C₂-C₁₀)heterocyclylene or an optionally substituted (C₂-C₁₀)heterocyclylene;

M is a bond, -R^c-, -R^c-C(O)-R^c-, -R^c-C(O)C(O)-R^c-, -R^c-C(O)O-R^c-, -R^c-OC(O)-R^c-, -R^c-C(O)C(O)N(R^a)-R^c-, -R^c-N(R^a)-C(O)C(O)-R^c-, -R^c-O-R^c-, -R^c-S(O)₂-R^c-, -R^c-S(O)-R^c-, -R^c-S-R^c-, -R^c-N(R^a)-R^c-, -R^c-N(R^a)C(O)-R^c-, -R^c-C(O)N(R^a)R^c-, -R^c-OC(O)N(R^a)-R^c-, -R^c-N(R^a)C(O)OR^c-, -R^c-N(R^a)C(O)N(R^b)-R^c-, -R^c-N(R^a)S(O)₂-R^c-, or -R^c-S(O)₂N(R^a)-R^c-; or



where in all cases, M is linked to either a carbon or a nitrogen atom in L;

Q is hydrogen, deuterium, -N(R^a)(R^b), halogen, -OR^a, -SR^a, -S(O)R^a, -S(O)₂R^a, -NO₂, -C(O)OR^a, -CN, -C(O)N(R^a)(R^b), -N(R^a)C(O)R^b, -N(R^a)C(O)OR^b, -N(R^a)C(O)N(R^b)₂, -C(O-R^a)(R^b)₂, -C(O)R^a, -CF₃, -OCF₃, -N(R^a)S(O)₂R^b, -S(O)₂N(R^a)(R^b), -S(O)₂N(R^a)C(O)R^b, an optionally substituted (C₁-C₆)alkyl, an optionally substituted (C₂-C₆)alkenyl, an optionally substituted (C₂-C₆)alkynyl, an optionally substituted (C₃-C₁₀)cycloalkyl, an optionally substituted (C₁-C₁₀)heteroaryl, an optionally substituted (C₁-C₁₀) heterocyclyl, an optionally substituted (C₆-C₁₀)aryl,;

wherein in a moiety containing -N(R^a)(R^b), the nitrogen, R^a and R^b may form a ring such that -N(R^a)(R^b) represents an optionally substituted (C₂-C₁₀)heterocyclyl or an optionally substituted (C₁-C₁₀) heteroaryl linked through a nitrogen;

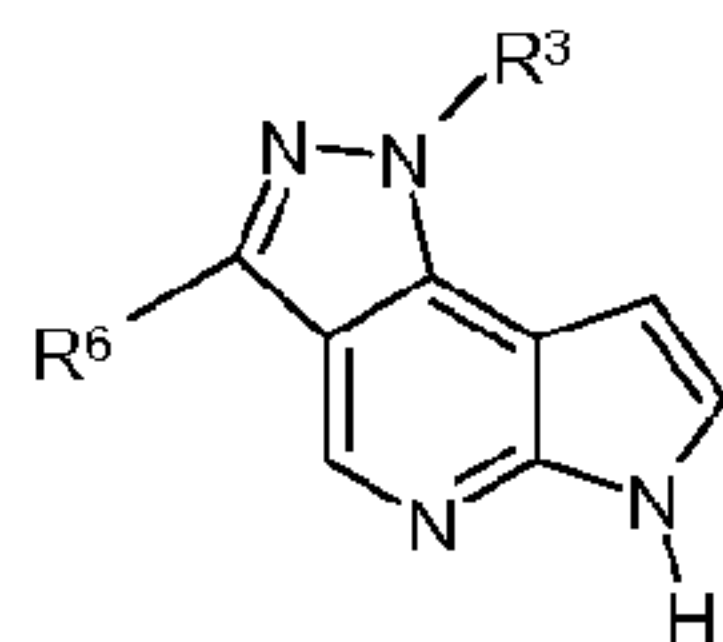
R^a and R^b are each independently hydrogen, deuterium, CN, an optionally substituted (C₁-C₁₀)alkyl, an optionally substituted (C₂-C₁₀)alkenyl, an optionally substituted (C₂-C₁₀)alkynyl, an optionally substituted (C₁-C₁₀)alkyl-O-(C₁-C₁₀)alkyl, an optionally substituted (C₃-C₁₀)cycloalkyl, an optionally substituted (C₆-C₁₀)aryl, an optionally substituted (C₁-C₁₀)heteroaryl, an optionally substituted (C₁-C₁₀)heterocyclyl, an optionally substituted -(C₁-C₆)alkylene-(C₃-C₁₀)cycloalkyl, an optionally substituted -(C₁-C₆)alkylene-(C₆-C₁₀)aryl, an optionally substituted -(C₁-C₆)alkylene-(C₁-C₁₀)heteroaryl, or an optionally substituted -(C₁-C₆)alkylene-(C₁-C₁₀)heterocyclyl; and

R^c for each occurrence is independently a bond, an optionally substituted (C₁-C₁₀)alkylene, an optionally substituted (C₂-C₁₀)alkenylene, an optionally substituted (C₂-C₁₀)alkynylene, an optionally substituted -(C₁-C₁₀)alkylene-O-(C₁-C₁₀)alkylene group, an optionally substituted (C₃-C₁₀)cycloalkylene, an optionally substituted (C₆-C₁₀)arylene, an optionally substituted (C₁-C₁₀)heteroarylene, or an optionally substituted (C₁-C₁₀)heterocyclylene;

provided that when T is N, U is CR⁴, X is NR³ and Y is C, R⁴ is not OH;

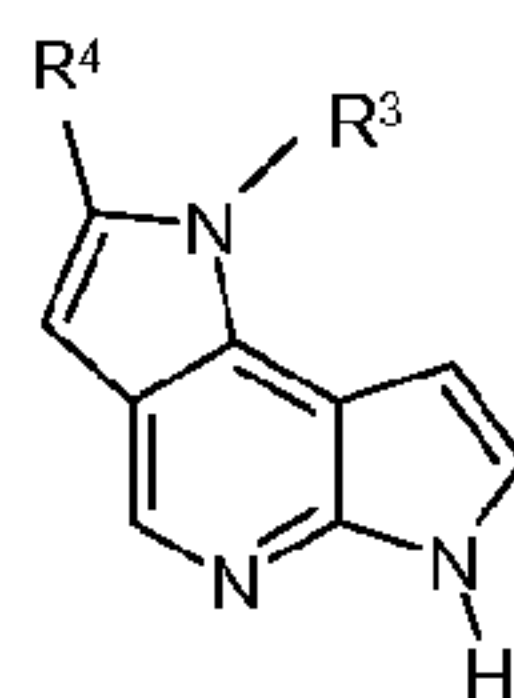
provided that when T is N, U is CR⁴, X is NR³ and Y is C, R¹ is H;

provided that when the compound is



R^3 is defined as above and R^6 is not linked to the pyrazole ring by a nitrogen or oxygen atom; and

provided that when the compound is



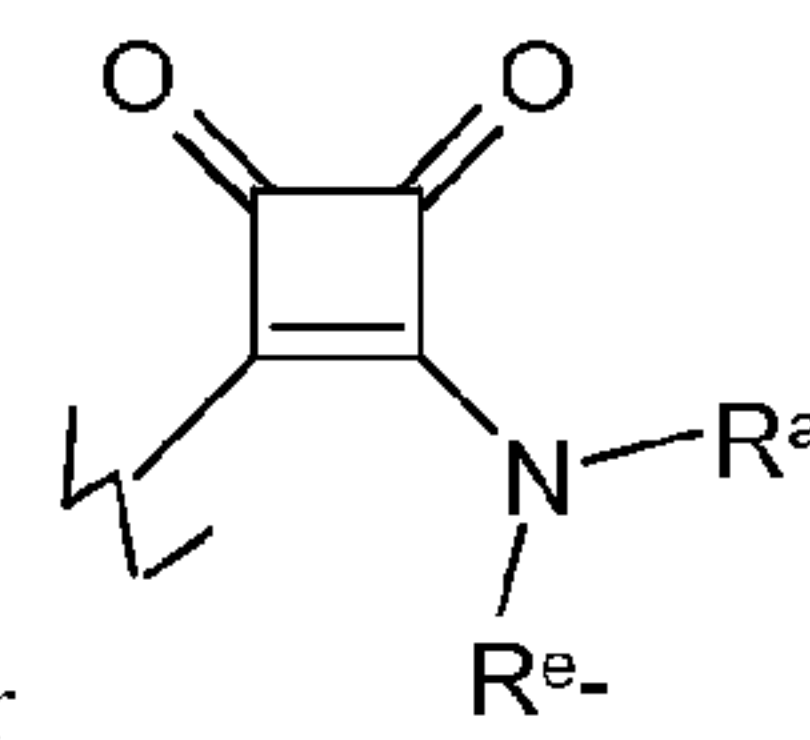
when R^3 is H, CH_3 or $-C(O)OH$ then R^4 is not H, $-C(O)OCH_2CH_3$, $-C(O)NH$ -optionally substituted phenyl, $-NHC(O)$ -optionally substituted phenyl or $-S(O)_2$ -phenyl.

In a second embodiment the invention provides a compound according to the first embodiment wherein R^3 is -A-D-E-G and A is a bond, optionally substituted (C_1 - C_6)alkylene, optionally substituted (C_3 - C_{12})cycloalkylene or optionally substituted (C_2 - C_6)heterocyclylene.

In a third embodiment the invention provides a compound according to the any of the foregoing embodiments wherein R^3 is -A-D-E-G and D is an optionally substituted (C_1 - C_8)alkylene, optionally substituted (C_3 - C_{10})cycloalkylene, optionally substituted bridged (C_5 - C_{10})cycloalkenylene, optionally substituted (C_3 - C_{10})bridged heterocyclylene or optionally substituted (C_2 - C_{10})heterocyclylene.

In a fourth embodiment the invention provides a compound according to the any of the foregoing embodiments 3 wherein D is optionally substituted (C_1 - C_6)alkylene, optionally substituted (C_3 - C_6)cycloalkylene, optionally substituted bicyclo[2.2.2]octany-1-yl, optionally substituted 2,5-diazabicyclo[2.2.1]heptane, optionally substituted 2,6-diazabicyclo[3.2.1]octane, optionally substituted octahydropyrrolo[3,4-*c*]pyrrole, optionally substituted octahydropyrrolo[3,2-*b*]pyridine, optionally substituted 1,4-diazepane, optionally substituted cubane, optionally substituted 1,4-dioxane-spiro[4.4]nonane, optionally substituted 2,5-diazaspiro[3.5]nonane, optionally substituted piperidine, optionally substituted piperazine, optionally substituted pyrrolidine, optionally substituted tetrahydrofuran or optionally substituted tetrahydropyran.

In a fifth embodiment the invention provides a compound according to the any of the foregoing embodiments wherein R^3 is -A-D-E-G and E is a bond, $-R^e$ -, $-R^e-C(O)-R^e$ -, $-R^e-O-R^e$ -, $-R^e-S(O)_2-R^e$ -, $-R^e-N(R^a)-R^e$ -, $=N-R^e$ -, $-R^e-N(R^a)C(O)-R^e$ -, $-R^e-N(R^a)C(O)O-R^e$ -, $-R^e-N(R^a)C(O)N(R^b)-R^e$ -, $-R^eC(O)N(R^a)R^e$ -, $-R^e-N(R^a)S(O)_2-R^e$ -, $-R^e-S(O)_2N(R^a)-R^e$ -, $-R^e$ -



$N(R^a)S(O)_2N(R^a)-R^e$, $-R^e-OC(O)N(R^a)-R^e$, $-R^e-C(O)O-R^e$, $-R^e-OC(O)-R^e$; or

wherein

R^a for each occurrence is independently hydrogen, CN, an optionally substituted (C_1-C_{10}) alkyl or an optionally substituted $-(C_1-C_6)$ alkylene- (C_3-C_{10}) cycloalkyl; and

R^e for each occurrence is independently a bond, an optionally substituted (C_1-C_{10}) alkylene, an optionally substituted (C_3-C_{10}) cycloalkylene, an optionally substituted (C_6-C_{10}) arylene, an optionally substituted (C_1-C_{10}) heteroarylene, or an optionally substituted (C_1-C_{10}) heterocyclylene.

In a sixth embodiment the invention provides a compound according to the any of the foregoing embodiments wherein R^3 is $-A-D-E-G$ and G is hydrogen, deuterium, $-N(R^a)(R^b)$, halogen, $-OR^a$, $-S(O)_2R^a$, $-CN$, $-C(O)N(R^a)(R^b)$, $-N(R^a)C(O)R^b$, $-CF_3$, $-S(O)_2N(R^a)(R^b)$, an optionally substituted $-(C_1-C_6)$ alkyl, an optionally substituted $-(C_3-C_{10})$ cycloalkyl, an optionally substituted $-(C_1-C_{10})$ heteroaryl, an optionally substituted $-(C_1-C_{10})$ heterocyclyl, or an optionally substituted $-(C_6-C_{10})$ aryl;

wherein in a moiety containing $-N(R^a)(R^b)$, the nitrogen, R^a and R^b may form a ring such that $-N(R^a)(R^b)$ represents an optionally substituted (C_2-C_{10}) heterocyclyl or an optionally substituted (C_1-C_{10}) heteroaryl linked through a nitrogen;

R^a is independently hydrogen, CN, an optionally substituted (C_1-C_{10}) alkyl, an optionally substituted (C_3-C_{10}) cycloalkyl, or an optionally substituted (C_6-C_{10}) aryl.

In a seventh embodiment the invention provides a compound according to the any of the foregoing embodiments wherein G is hydrogen, deuterium, $-N(R^a)(R^b)$, halogen, $-OR^a$, $-S(O)_2R^a$, $-CN$, $-C(O)N(R^a)(R^b)$, $-N(R^a)C(O)R^b$, $-CF_3$, $-S(O)_2N(R^a)(R^b)$, an optionally substituted $-(C_1-C_4)$ alkyl, an optionally substituted $-(C_3-C_6)$ cycloalkyl, optionally substituted azepanyl, optionally substituted azetidiny, optionally substituted benzo[d]isoxazolyl, optionally substituted 4,5-dihydroisoxazolyl, optionally substituted isothiazolidiny, optionally substituted isothiazolyl, optionally substituted isoxazolyl, optionally substituted morpholiny, optionally substituted oxadiazolyl, optionally substituted oxazolyl, optionally substituted oxetanyl, optionally substituted phenyl, optionally substituted piperaziny, optionally substituted piperidiny, optionally substituted pyraziny, optionally substituted pyrazolyl, optionally substituted pyridaziny, optionally substituted pyridiny, optionally substituted pyrimidiny, optionally substituted pyrrolidiny, optionally substituted pyrrolyl, optionally substituted tetrahydrofuranyl, optionally substituted tetrahydropyranyl, optionally substituted tetrahydrothiopyranyl, optionally substituted

thienyl, optionally substituted thiomorpholinyl, optionally substituted 1,1-dioxo-thiomorpholinyl, optionally substituted thiazolyl or optionally substituted triazolyl.

In eighth embodiment the invention provides a compound according to the any of the foregoing embodiments wherein R^3 is hydrogen, optionally substituted (C_1 - C_8)alkyl, optionally substituted (C_3 - C_{10})cycloalkyl, or optionally substituted (C_2 - C_{10})heterocyclyl.

In a ninth embodiment the invention provides a compound according to the any of the foregoing embodiments wherein R^6 is $-J-L-M-Q$ and J is a bond, optionally substituted (C_1 - C_6)alkylene, or an optionally substituted (C_2 - C_6)alkenylene.

In a tenth embodiment the invention provides a compound according to the any of the foregoing embodiments wherein R^6 is $-J-L-M-Q$ and L is a bond, or an optionally substituted (C_1 - C_8)alkylene.

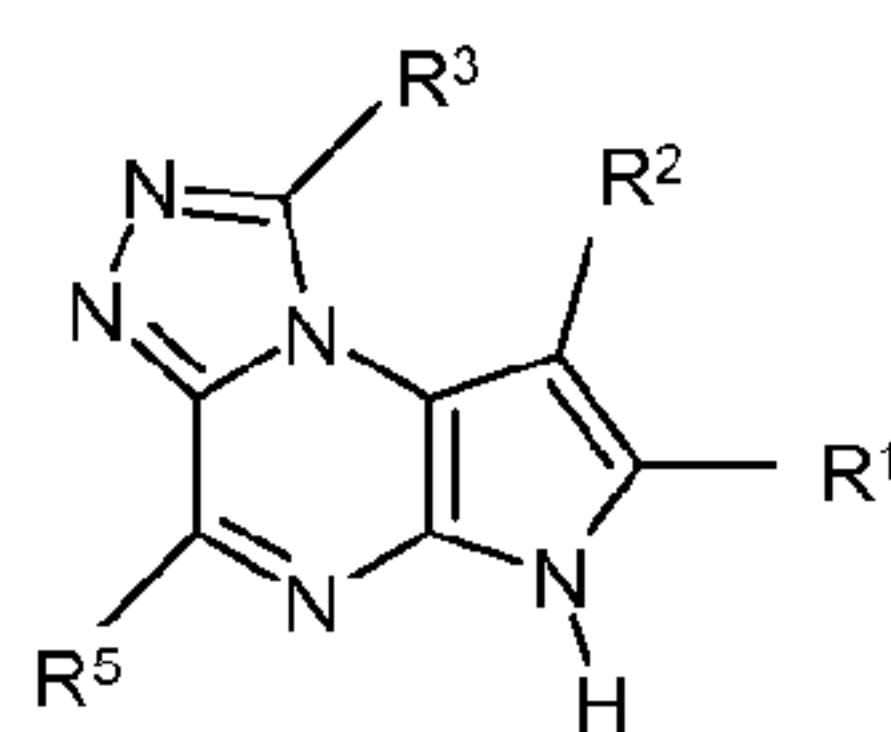
In an eleventh embodiment the invention provides a compound according to the any of the foregoing embodiments wherein R^6 is $-J-L-M-Q$ and M is a bond, $-R^e$ -, $-R^e-C(O)-R^e$ -, $-R^e-O-R^e$ -, $-R^e-S(O)_2-R^e$ -, $-R^e-S(O)-R^e$ -, $-R^e-S-R^e$ -, $-R^e-N(R^a)-R^e$ -, $-R^e-N(R^a)C(O)-R^e$ -, $-R^e-C(O)N(R^a)R^e$ -, $-R^e-N(R^a)C(O)N(R^b)-R^e$ -, $-R^e-N(R^a)S(O)_2-R^e$ -, or $-R^e-S(O)_2N(R^a)-R^e$ -, where in all cases, M is linked to either a carbon or a nitrogen atom in L.

In a twelfth embodiment the invention provides a compound according to the any of the foregoing embodiments wherein R^6 is $-J-L-M-Q$ and Q is hydrogen, deuterium, $-N(R^a)(R^b)$, halogen, $-OR^a$, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$, $-NO_2$, $-C(O)OR^a$, $-CN$, $-C(O)N(R^a)(R^b)$, $-N(R^a)C(O)R^b$, $-N(R^a)C(O)OR^b$, $-N(R^a)C(O)N(R^b)_2$, $-C(O-R^a)(R^b)_2$, $-C(O)R^a$, $-CF_3$, $-OCF_3$, $-N(R^a)S(O)_2R^b$, $-S(O)_2N(R^a)(R^b)$, $-S(O)_2N(R^a)C(O)R^b$, an optionally substituted (C_1 - C_6)alkyl, an optionally substituted (C_3 - C_{10})cycloalkyl, an optionally substituted (C_1 - C_{10})heteroaryl, an optionally substituted (C_1 - C_{10}) heterocyclyl, an optionally substituted (C_6 - C_{10})aryl;

wherein in a moiety containing $-N(R^a)(R^b)$, the nitrogen, R^a and R^b may form a ring such that $-N(R^a)(R^b)$ represents an optionally substituted (C_2 - C_{10})heterocyclyl or an optionally substituted (C_1 - C_{10}) heteroaryl linked through a nitrogen;

R^a and R^b are each independently hydrogen, deuterium, an optionally substituted (C_1 - C_6)alkyl, an optionally substituted (C_2 - C_{10})alkenyl, an optionally substituted (C_3 - C_6)cycloalkyl, an optionally substituted (C_6 - C_{10})aryl, an optionally substituted (C_1 - C_{10})heteroaryl, or an optionally substituted (C_1 - C_{10})heterocyclyl.

In a thirteenth embodiment the invention provides a compound according to the any of the foregoing embodiments wherein T is N, U is N, X is CR^3 and Y is N and forms a compound of Formula (Ia)



Formula (Ia)

In a fourteenth embodiment the invention provides a compound according to the thirteenth embodiment wherein in the compound is

N-(1-((6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)methyl)cyclobutyl)cyclopropanesulfonamide;

N-(1-((6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)methyl)cyclobutyl)-2-cyanoacetamide;

(*S*)-1-((1-(cyclopropylsulfonyl)pyrrolidin-3-yl)methyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

N-((1*S*,3*R*,4*R*)-4-ethyl-3-fluoro-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*R*,3*S*,4*S*)-4-ethyl-3-fluoro-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*R*,3*R*,4*S*)-4-ethyl-3-fluoro-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*S*,4*R*)-4-ethyl-3-fluoro-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

(1*S*,3*R*)-1-[3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-isothiazolidin-2-yl-1,1-dioxide]cyclopentane;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-*N*-methylcyclopropanesulfonamide;

1-((1*S*,2*R*,4*S*)-2-ethyl-4-(4-methoxybenzyloxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

(*S*)-5-(3-((6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)methyl)pyrrolidin-1-yl)pyrazine-2-carbonitrile;

N-(cyclopropylmethyl)-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-(4-cyanophenyl)acetamide;

N-((1*S*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanecarboxamide;

N-((1*S*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-cyclopropylacetamide;

N-((1*S*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-4-cyanobenzamide;

N,N-diethyl-1-(3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methanesulfonamide;

1-((1*S*,2*S*,4*R*)-4-((azetidin-1-ylsulfonyl)methyl)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*R*,2*R*,4*S*)-4-((azetidin-1-ylsulfonyl)methyl)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*R*,2*S*,4*R*)-4-((azetidin-1-ylsulfonyl)methyl)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*S*)-4-((azetidin-1-ylsulfonyl)methyl)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(7-methyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-*N*-(2-hydroxyethyl)cyclopropanesulfonamide;

5-((1*R*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)pyrazine-2-carbonitrile

N-((1*R*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-4-methylaniline;

1-((1*R*,3*S*)-3-(1*H*-pyrrol-1-yl)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-1*H*-pyrrole-3-carbonitrile;

N-((1*R*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)aniline;

N-((1-((6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)methyl)cyclobutyl)methyl)-2-cyanoacetamide;

N-((1*R*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-4-fluoroaniline;

N-((1*R*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-4-chloroaniline;

N-((1*R*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-3,4-dichloroaniline;

N-((1*R*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-4-methoxyaniline;

N-((1*R*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-4-methoxy-*N*-(4-methoxyphenyl)aniline;

3-((3*R*,4*R*)-4-methyl-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)piperidin-1-yl)-3-oxopropanenitrile;

1-methyl-*N*-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-1*H*-pyrazole-4-sulfonamide;

3-((1*R*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)benzonitrile;

N-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)aniline;

4-((1*S*,2*R*,4*S*)-4-(benzyloxy)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

4-((1*R*,2*S*,4*R*)-4-(benzyloxy)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

5-methyl-*N*-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)isoxazole-4-sulfonamide;

N-(4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclobutanesulfonamide;

6-((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)nicotinonitrile;

N-(4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)pyrrolidine-1-carboxamide;

4-((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)benzonitrile;

4-((1*S*,3*S*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)benzonitrile;

4-methyl-*N*-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)aniline;

4-chloro-*N*-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)aniline;

3-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)benzonitrile;

4-fluoro-*N*-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)aniline;

N-((1*S*,3*S*,4*R*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)aniline;

N-((1*R*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)aniline;

5-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)pyrazine-2-carbonitrile;

6-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)nicotinonitrile;

6-((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)nicotinonitrile;

6-((1*S*,3*S*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)nicotinonitrile;

1-((1*S*,2*S*,4*R*)-2-ethyl-4-(4-methoxybenzyloxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*R*,2*R*,4*S*)-2-ethyl-4-(4-methoxybenzyloxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-3,3,3-trifluoropropane-1-sulfonamide;

5-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)pyrazine-2-carbonitrile;

6-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)nicotinonitrile;

2-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)thiazole-5-carbonitrile;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)azetidine-1-sulfonamide;

N-((1*R*,3*R*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*S*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

3-cyano-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)azetidine-1-sulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-3,3-difluoroazetidine-1-sulfonamide;

5-((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)pyrazine-2-carbonitrile;

5-((1*S*,3*S*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)pyrazine-2-carbonitrile;

6-((1*S*,3*S*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)nicotinonitrile;

6-((1*R*,3*R*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)nicotinonitrile;

2-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)thiazole-5-carbonitrile;

5-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)pyrazine-2-carbonitrile;

5-((1*R*,3*S*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)pyrazine-2-carbonitrile;

N-(4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)pyrrolidine-1-sulfonamide;

5-(((1*S*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methylamino)pyrazine-2-carbonitrile;

(*S*)-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-(trifluoromethyl)pyrrolidine-1-sulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-3,3-difluoropyrrolidine-1-sulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-4,4-difluoropiperidine-1-sulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-1-methylcyclopropane-1-sulfonamide;

N-(4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)-1-methylcyclopropane-1-sulfonamide;

N-(4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)azetidine-1-sulfonamide;

6-((1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)nicotinonitrile;

N-((1*S*,3*R*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopentanesulfonamide;

5-(((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methoxy)pyrazine-2-carboxamide;

((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methanol;

((1*R*,3*S*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methanol;

5-(((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methoxy)pyrazine-2-carbonitrile;

5-(((1*R*,3*S*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methoxy)pyrazine-2-carbonitrile;

N-(4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)-3,3-difluoroazetidine-1-sulfonamide;

N-(3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)aniline;

1-((1*S*,2*R*,4*R*)-2-ethyl-4-(5-(trifluoromethyl)pyridin-2-yloxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*R*,2*S*,4*S*)-2-ethyl-4-(5-(trifluoromethyl)pyridin-2-yloxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

5-((1*R*,3*S*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)pyrazine-2-carbonitrile;

5-((1*S*,3*R*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)pyrazine-2-carbonitrile;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2,2,2-trifluoroethanesulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-4-methylpiperazine-1-sulfonamide;

4-((1*S*,3*S*,4*R*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)benzonitrile;

4-((1*R*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)benzonitrile;

3-(((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)methyl)benzonitrile;

3-(((1*S*,3*S*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)methyl)benzonitrile;

4-(((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)methyl)benzonitrile;

4-(((1*S*,3*S*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)methyl)benzonitrile;

1-ethyl-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropane-1-sulfonamide;

N-(((1*R*,3*S*,4*R*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methyl)cyclopropanesulfonamide;

N-(((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methyl)cyclopropanesulfonamide;

4-((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)-2-fluorobenzonitrile;

4-((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)-3-fluorobenzonitrile;

3-((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyloxy)benzonitrile;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-morpholinoethanesulfonamide;

1-butyl-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropane-1-sulfonamide;

2-(3,3-difluoropyrrolidin-1-yl)-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)ethanesulfonamide;

2-(((1*S*,3*R*)-3-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)methylamino)isonicotinonitrile;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-methylpropane-2-sulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanesulfonamide;

2-(4,4-difluoropiperidin-1-yl)-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)ethanesulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-(2*H*-1,2,3-triazol-2-yl)ethanesulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-(1*H*-1,2,3-triazol-1-yl)ethanesulfonamide;

(1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanol;

1-((1*S*,2*R*,4*R*)-2-ethyl-4-(3,3,3-trifluoropropoxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(8-iodo-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

(1*S*,3*R*,4*S*)-*N*-(2-(3,3-difluoropyrrolidin-1-ylsulfonyl)ethyl)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine;

N-cyano-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)cyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(8-methyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-*N*-(hydroxymethyl)cyclopropanesulfonamide;

N-((1*S*,3*S*,4*R*)-3-(8-cyano-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-4-ethylcyclopentyl)cyclopropanesulfonamide;

1-((1*S*,2*R*,4*S*)-4-(cyclopropylmethoxy)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*S*)-4-(cyclopropylmethoxy)-2-methylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*S*)-2-ethyl-4-(2,2,2-trifluoroethylsulfonyl)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*S*)-2-ethyl-4-(tetrahydro-2*H*-pyran-4-yloxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*S*)-2-ethyl-4-((tetrahydro-2*H*-pyran-4-yl)methoxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*R*,2*R*,4*S*)-2-ethyl-4-((tetrahydro-2*H*-pyran-4-yl)methoxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*R*)-4-(cyclopropylmethoxy)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*R*)-2-ethyl-4-(tetrahydro-2*H*-pyran-4-yloxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

2-(4-cyano-1*H*-pyrazol-1-yl)-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)ethanesulfonamide;

1-((1*S*,2*R*,4*S*)-2-ethyl-4-(2-(tetrahydro-2*H*-pyran-4-yl)ethoxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*R*,2*R*,4*S*)-2-ethyl-4-(2-(tetrahydro-2*H*-pyran-4-yl)ethoxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*R*)-2-ethyl-4-((tetrahydro-2*H*-pyran-4-yl)methoxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*S*)-2-ethyl-4-(2-methoxyethoxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*R*,2*R*,4*S*)-2-ethyl-4-(2-methoxyethoxy)cyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*R*)-2-ethyl-4-isopropoxycyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

N-((3*R*,5*R*)-1-ethyl-5-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide;

(3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanone;

1-((7*S*,8*R*)-8-ethyl-1,4-dioxaspiro[4.4]nonan-7-yl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

(1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-*N*-(2,2,2-trifluoroethyl)cyclopentanamine;

(3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanone O-cyclopropylmethyl oxime;

(3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanone O-2-(methylsulfonyl)ethyl oxime;

(3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanone O-cyclobutylmethyl oxime;

1-((1*S*,2*R*,4*R*)-4-(4,4-dimethylcyclohexyloxy)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-methoxyethanesulfonamide;

N-((3*R*,5*R*)-1-acetyl-5-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide;

1-((3*S*,4*R*)-1-(cyclopropylmethylsulfonyl)-4-ethylpyrrolidin-3-yl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

2-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)acetic acid;

N-cyclopropyl-2-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)acetamide;

3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanone O-tetrahydro-2*H*-pyran-4-yl oxime;

1-((1*S*,2*R*,4*S*)-4-(3,3-difluoroazetidin-1-yl)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

1-((1*S*,2*R*,4*S*)-4-(3,3-difluoropyrrolidin-1-yl)-2-ethylcyclopentyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine;

Dimethyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

{3-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentylamino]-oxetan-3-yl}-acetonitrile;

Cyclopropanesulfonic acid cyanomethyl-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-amide;

1-[(3*R*,4*S*)-4-Ethyl-1-(2-morpholin-4-yl-ethyl)-pyrrolidin-3-yl]-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

Cyclopropanesulfonic acid [(3*R*,5*R*)-1-(2,2-difluoro-ethyl)-5-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-3-yl]-amide;

1-[(3*R*,4*S*)-4-Ethyl-1-(3,3,3-trifluoro-propane-1-sulfonyl)-pyrrolidin-3-yl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

3-[(1*R*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyloxy]-propionitrile;

1-[(3*R*,4*S*)-4-Ethyl-1-(3,3,3-trifluoro-propyl)-pyrrolidin-3-yl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

2-Cyclopropyl-1-[(3*S*,4*R*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-ethanone;

1-[(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-2-(tetrahydro-pyran-4-yl)-ethanone;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid cyclopropylmethyl-amide;

Cyclopropanesulfonic acid [(3*R*,5*R*)-1-ethyl-5-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-3-yl]-methyl-amide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (tetrahydro-pyran-4-ylmethyl)-amide;

3,3-Difluoro-cyclobutanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-amide;

Cyclopropanesulfonic acid [(1*S*,4*S*)-3,3-dimethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-amide;

Cyclopropanesulfonic acid [(1*R*,4*R*)-3,3-dimethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-amide;

1-[(1*S*,2*R*,4*R*)-4-(4,4-Difluoro-cyclohexyloxy)-2-ethyl-cyclopentyl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

1-[(1*R*,2*R*,4*R*)-4-(4,4-Difluoro-cyclohexyloxy)-2-ethyl-cyclopentyl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

6-[(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-nicotinonitrile;

1-[(3*R*,4*S*)-1-(3,3-Difluoro-cyclobutanesulfonyl)-4-ethyl-pyrrolidin-3-yl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-bis-(4,4,4-trifluoro-butyl)-amine;

1-[(1*S*,2*R*,4*R*)-2-Ethyl-4-(4-trifluoromethyl-cyclohexyloxy)-cyclopentyl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

4-[(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-ylmethyl]-benzonitrile;

3-[(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-3-oxo-propionitrile;

1-[(1*S*,2*R*,4*R*)-2-Ethyl-4-(4-trifluoromethyl-cyclohexyloxy)-cyclopentyl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

1-[(1*R*,2*R*,4*R*)-2-Ethyl-4-(4-trifluoromethyl-cyclohexyloxy)-cyclopentyl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

1-[(1*R*,2*R*,4*R*)-2-Ethyl-4-(4-trifluoromethyl-cyclohexyloxy)-cyclopentyl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

{3-[(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-oxetan-3-yl}-acetonitrile;

3-[(1*S*,3*R*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyloxy]-propionitrile;

3-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyloxy]-propionitrile;

Cyclopropanesulfonic acid (2-cyano-ethyl)-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-amide;

4-[(1*R*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyloxy]-cyclohexanecarbonitrile;

4-[(1*R*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyloxy]-cyclohexanecarbonitrile;

1-((3*R*,4*S*)-1-Cyclopropanesulfonyl-4-ethyl-pyrrolidin-3-yl)-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

N-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-N-(4,4,4-trifluoro-butyl)-acetamide;

Cyclopropyl-carbamic acid (1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

3,3-Difluoro-azetidine-1-carboxylic acid (1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

Cyanomethyl-carbamic acid (1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

N-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-N-(tetrahydro-pyran-4-ylmethyl)-acetamide;

3-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-1,1-dimethyl-urea;

Dimethyl-carbamic acid (1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(1*S*,3*R*,4*S*)-3-Ethyl-1-(morpholine-4-sulfonylmethyl)-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentanol;

(1*R*,3*R*,4*R*)-3-Ethyl-1-(morpholine-4-sulfonylmethyl)-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentanol;

(1*S*,3*R*,4*R*)-3-Ethyl-1-(morpholine-4-sulfonylmethyl)-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentanol;

N-Cyclopropylmethyl-*N*-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-acetamide;

1-[(1*S*,3*R*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-2-methyl-propan-2-ol;

1-[(1*R*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-2-methyl-propan-2-ol;

1-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-2-methyl-propan-2-ol;

1-[(1*R*,2*R*,4*S*)-4-(3-Cyclopropyl-[1,2,4]oxadiazol-5-ylmethyl)-2-ethyl-cyclopentyl]-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl;

1-[(1*S*,2*R*,4*S*)-4-(3-Cyclopropyl-[1,2,4]oxadiazol-5-ylmethyl)-2-ethyl-cyclopentyl]-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl;

1-[(1*S*,2*R*,4*R*)-4-(3-Cyclopropyl-[1,2,4]oxadiazol-5-ylmethyl)-2-ethyl-cyclopentyl]-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl;

1-[(1*S*,2*R*,4*R*)-2-Ethyl-4-(5-methyl-isoxazol-3-ylmethoxy)-cyclopentyl]-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl;

Oxetan-3-yl-carbamic acid (1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

Cyclobutyl-carbamic acid (1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

Cyclopropanesulfonic acid [(1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

{3-[(1*R*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentylamino]-oxetan-3-yl}-acetonitrile;

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-carbamic acid isopropyl ester;

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-oxetan-3-yl-amine;

1-((3*R*,4*S*)-1-Benzyl-4-isopropyl-pyrrolidin-3-yl)-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl;

3-Fluoro-propane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-(3-methyl-oxetan-3-yl)-amine;

1-[(1*S*,2*R*,4*R*)-2-Ethyl-4-(2-morpholin-4-yl-ethoxy)-cyclopentyl]-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl;

Carbamoylmethyl-carbamic acid (1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

4-Hydroxy-piperidine-1-carboxylic acid (1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

(2,2,2-Trifluoro-ethyl)-carbamic acid (1*R*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

Cyclopropylmethyl-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-oxetan-3-yl-amine;

Pentane-2-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

3-Phenyl-propane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

4,4,4-Trifluoro-butane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

2-Ethyl-cyclopropanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

2-Methyl-propane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

2-Phenyl-ethanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

C-Cyclohexyl-N-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-methanesulfonamide;

Butane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

Propane-2-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

N-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-C-phenyl-methanesulfonamide;

Propane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

3-Methyl-butane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

N-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-C,C-difluoro-methanesulfonamide;

4-Cyano-butane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

2-Ethoxy-ethanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

N-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-C-(tetrahydro-furan-2-yl)-methanesulfonamide;

Tetrahydro-pyran-4-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

3-Cyano-propane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

N-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-C-(5-methyl-isoxazol-3-yl)-methanesulfonamide;

N-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-C-(tetrahydro-pyran-2-yl)-methanesulfonamide;

2-Pyridin-2-yl-ethanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-amide;

C-(2,2-Dichloro-cyclopropyl)-N-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl]-methanesulfonamide;

(3*S*,4*R*)-3-Isopropyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid cyclobutylamide;

(1*S*,3*R*,4*S*)-3-Ethyl-1-methyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentanol;

Carbonic acid (1*S*,3*R*,4*S*)-3-ethyl-4-[6-(toluene-4-sulfonyl)-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl]-cyclopentyl ester 4-nitro-phenyl ester;

Cyclobutyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

4-Hydroxy-piperidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

3-(Cyclopropylmethyl-amino)-4-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentylamino]-cyclobut-3-ene-1,2-dione;

3-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentylamino]-4-(oxetan-3-ylamino)-cyclobut-3-ene-1,2-dione;

3-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentylamino]-4-(3,3,3-trifluoro-propylamino)-cyclobut-3-ene-1,2-dione;

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-methyl-oxetan-3-yl-amine;

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-(3-methyl-oxetan-3-ylmethyl)-amine;

3-Cyclopropylamino-4-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentylamino]-cyclobut-3-ene-1,2-dione;

Cyanomethyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

Cyclopropyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(2,2,2-Trifluoro-ethyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

3,3-Difluoro-azetidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

4-Cyano-piperidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (1-cyano-cyclopropyl)-amide;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (1-cyano-cyclopropyl)-amide;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid cyclobutylamide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid cyclobutylamide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (3-methyl-isothiazol-5-yl)-amide;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (3-methyl-isothiazol-5-yl)-amide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid cyanomethyl-amide;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid cyanomethyl-amide;

(2-Cyclopropyl-ethyl)-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-oxetan-3-yl-amine;

Cyclopropylmethyl-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-(3-methyl-oxetan-3-yl)-amine;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (oxazol-4-ylmethyl)-amide;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (oxazol-4-ylmethyl)-amide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (2,2,2-trifluoro-ethyl)-amide;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (2,2,2-trifluoro-ethyl)-amide;

(2-Cyclopropyl-ethyl)-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-(3-methyl-oxetan-3-yl)-amine;

3-Cyano-azetidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

Benzyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

Oxetan-3-yl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(1-Cyano-cyclopropyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(3-Methyl-oxetan-3-yl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(*R*)-3-Hydroxy-pyrrolidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(*S*)-3-Hydroxy-pyrrolidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

4-Fluoro-piperidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(2,2-Difluoro-ethyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(3,3-Difluoro-azetidin-1-yl)-[(3*S*,4*R*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-methanone;

1-[(1*S*,2*R*,4*R*)-2-Ethyl-4-(pyrazol-1-yloxy)-cyclopentyl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

(3,3-Difluoro-azetidin-1-yl)-[(3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-methanone;

{2-[(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-4,5-dihydro-oxazol-4-yl}-methanol;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid oxetan-3-ylamide;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid oxetan-3-ylamide;

3-Fluoro-azetidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(1-Methyl-cyclobutyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(1-Hydroxy-cyclopropylmethyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

Methyl-oxetan-3-yl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(3-Methyl-oxetan-3-ylmethyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

Phenyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

[(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-((*R*)-3-hydroxy-pyrrolidin-1-yl)-methanone;

[(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-((*R*)-3-hydroxy-pyrrolidin-1-yl)-methanone;

(1*R*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentanecarbonitrile;

[(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-((*S*)-3-hydroxy-pyrrolidin-1-yl)-methanone;

[(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidin-1-yl]-((*S*)-3-hydroxy-pyrrolidin-1-yl)-methanone;

tert-Butyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(2,2-Dimethyl-propyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(2-Methoxy-ethyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(3,5-Bis-trifluoromethyl-benzyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl ester;

(2-Dimethylamino-ethyl)-methyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

(3-Dimethylamino-propyl)-methyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

Benzyl-isopropyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

(*R*)-3-Hydroxy-piperidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

4-Methyl-piperazine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

4-Acetyl-piperazine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

4-(2-Fluoro-phenyl)-piperazine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

Pyridin-2-ylmethyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

Pyridin-3-ylmethyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

Pyridin-4-ylmethyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

Isobutyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

[(*S*)-1-(Tetrahydro-furan-2-yl)methyl]-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

[(*R*)-1-(Tetrahydro-furan-2-yl)methyl]-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

(2-Cyano-ethyl)-cyclopropyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

Diisobutyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

Azetidine-1-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

(2-Methoxy-ethyl)-methyl-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

Morpholine-4-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

Thiomorpholine-4-carboxylic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester;

(2-Dimethylamino-ethyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

(3-Dimethylamino-propyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

(2-Pyrrolidin-1-yl-ethyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

(3-Pyrrolidin-1-yl-propyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

(2-Piperidin-1-yl-ethyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

(3-Piperidin-1-yl-propyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

(2-Morpholin-4-yl-ethyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

(3-Morpholin-4-yl-propyl)-carbamic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-cyclopentyl ester; compound with trifluoro-acetic acid;

1-[(1*S*,2*R*,4*S*)-4-(2,2-Difluoro-ethoxy)-2-ethyl-cyclopentyl]-6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl;

1-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-
cyclopentyloxy]-2-methyl-propan-2-ol;

(2-Cyclopropyl-ethyl)-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-
a]pyrazin-1-yl)-cyclopentyl]-(2,2,2-trifluoro-ethyl)-amine;

Cyclopropylmethyl-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-
a]pyrazin-1-yl)-cyclopentyl]-(2,2,2-trifluoro-ethyl)-amine;

Cyclopropylmethyl-[(1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-
a]pyrazin-1-yl)-cyclopentyl]-(2,2,2-trifluoro-ethyl)-amine;

1-((7*S*,8*R*)-8-Ethyl-1,4-dioxo-spiro[4.4]non-7-yl)-6-(toluene-4-sulfonyl)-6H-pyrrolo[2,3-
e][1,2,4]triazolo[4,3-a]pyrazin-1-yl;

1-[(1*R*,3*R*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-
cyclopentyl]-2-methyl-propan-2-ol;

Acetic acid (1*S*,3*R*,4*S*)-3-ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-
cyclopentyl ester;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)-pyrrolidine-1-
sulfonic acid cyclopropylmethyl-amide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-sulfonic acid cyclopropylmethyl-amide;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (2-cyclopropyl-ethyl)-amide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-carboxylic acid (2-cyclopropyl-ethyl)-amide;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-sulfonic acid oxetan-3-ylamide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-sulfonic acid oxetan-3-ylamide;

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-oxetan-3-yl-(4,4,4-trifluoro-butyl)-amine;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentanesulfonic acid cyclopropylamide;

2-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*c*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-ethanol;

2-[(1*R*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-ethanol;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-sulfonic acid cyclobutylamide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-sulfonic acid cyclobutylamide;

1-[(1*S*,2*R*,4*S*)-2-Ethyl-4-(3-methoxymethyl-[1,2,4]oxadiazol-5-ylmethyl)-cyclopentyl]-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

(3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-sulfonic acid amide;

(3*S*,4*R*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-sulfonic acid amide;

4-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-butyronitrile;

4-[(1*R*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-butyronitrile;

[(1*R*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-acetonitrile;

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-acetonitrile;

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-(5-methyl-isoxazol-3-ylmethyl)-oxetan-3-yl-amine;

{5-[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentylmethyl]-[1,2,4]oxadiazol-3-yl}-methanol;

1-[(1*S*,2*R*,4*S*)-4-(3-Cyclopropyl-pyrazol-1-yl)-2-ethyl-cyclopentyl]-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

1-[(1*S*,2*R*,4*S*)-4-(5-Cyclopropyl-pyrazol-1-yl)-2-ethyl-cyclopentyl]-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

(3*S*,4*R*)-3-Ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-sulfonic acid (2,2,2-trifluoro-ethyl)-amide;

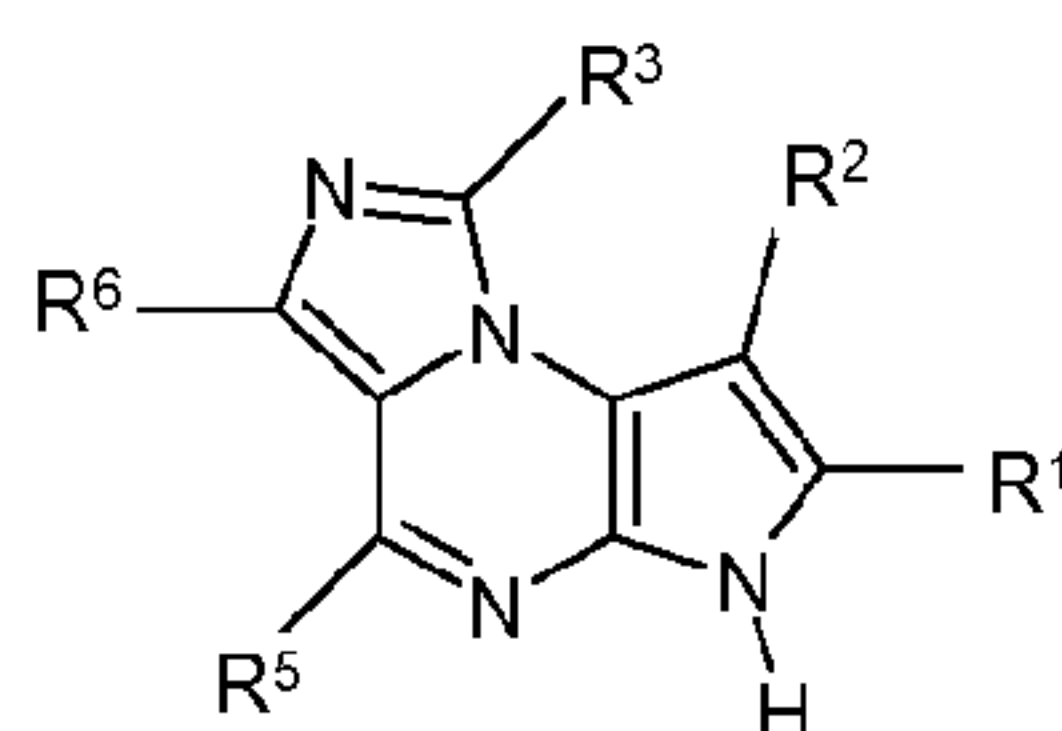
(3*R*,4*S*)-3-Ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-pyrrolidine-1-sulfonic acid (2,2,2-trifluoro-ethyl)-amide;

1-[(1*S*,2*R*,4*S*)-4-(3-Cyclopropyl-[1,2,4]triazol-1-yl)-2-ethyl-cyclopentyl]-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl;

1-[(1*S*,2*R*,4*S*)-4-(5-Cyclopropyl-[1,2,4]triazol-1-yl)-2-ethyl-cyclopentyl]-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl; or

[(1*S*,3*R*,4*S*)-3-Ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-cyclopentyl]-oxetan-3-yl-(3,3,3-trifluoro-propyl)-amine.

In a fifteenth embodiment the invention provides a compound according to the first through twelfth embodiments wherein T is CR⁶, U is N, X is CR³ and Y is N and forms a compound of Formula (Ib)



Formula (Ib)

In a sixteenth embodiment the invention provides a compound according to the fifteenth embodiment wherein the compound is

((*cis*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(2,4-difluorophenyl)methanone;

((*cis*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(4-(trifluoromethyl)phenyl)methanone;

((*cis*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(pyridin-3-yl)methanone;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(3-(trifluoromethyl)phenyl)methanone;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(pyrazin-2-yl)methanone;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(pyrimidin-5-yl)methanone;

1-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-cyclopropylethanone;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(phenyl)methanone;

1-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-cyclobutylethanone;

1-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-3-cyclobutylpropan-1-one;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(1*H*-pyrazol-4-yl)methanone;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(1*H*-pyrazol-3-yl)methanone;

1-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)propan-1-one;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(3-(3-hydroxypropyl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

1-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carbonyl)cyclopropanecarbonitrile;

3-((3*S*,4*S*)-4-ethyl-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)-3-oxopropanenitrile;

3-((3*R*,4*R*)-4-ethyl-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)-3-oxopropanenitrile;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(3-(hydroxymethyl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(3-(2-hydroxyethyl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(1-methyl-1*H*-pyrazol-4-yl)methanone;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(pyridin-4-yl)methanone;

1-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-(3-methylisoxazol-5-yl)ethanone;

1-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-(2,4-difluorophenyl)ethanone;

6-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)pyridazine-3-carbonitrile;

5-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)pyrazine-2-carbonitrile;

2-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)thiazole-5-carbonitrile;

6-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)nicotinonitrile;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(pyrrolidin-1-yl)methanone;

1-((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carbonyl)azetidine-3-carbonitrile;

(cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-*N,N*,4-trimethylpiperidine-1-carboxamide;

1-((cis)-1-(cyclopropylsulfonyl)-4-methylpiperidin-3-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

(cis)-*N*-(cyanomethyl)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carboxamide;

((cis)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(isoxazol-5-yl)methanone;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-3,3,3-trifluoropropan-1-one;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-3-hydroxy-3-methylbutan-1-one;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-methoxyethanone;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-3-methoxypropan-1-one;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)pent-4-yn-1-one;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-(4-chlorophenyl)ethanone;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-(3-chlorophenyl)ethanone;

4-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carbonyl)benzonitrile;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-3-(3-chloroisoxazol-5-yl)propan-1-one;

3-(2-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-oxoethyl)benzonitrile;

4-(2-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-oxoethyl)benzonitrile;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-(1*H*-pyrrol-2-yl)ethanone;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-(pyrazin-2-yl)ethanone;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-(tetrahydro-2*H*-pyran-4-yl)ethanone;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-2-(pyrimidin-2-yl)ethanone;

5-((1*S*,3*S*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentylamino)pyrazine-2-carbonitrile;

N-(4-(3-allyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide;

N-(1-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide;

N-(4-(3-propyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide;

2-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)thiazole-5-carbonitrile;

N-(4-(3-(2,3-dihydroxypropyl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carbonyl)pyrrolidine-3-carbonitrile;

(3*R*,4*R*)-*N*-(4-(cyanomethyl)phenyl)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carboxamide;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(morpholino)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(4-methylpiperazin-1-yl)methanone;
 ((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(piperidin-1-yl)methanone;
 (3*R*,4*R*)-*N*-(2,4-difluorophenyl)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carboxamide;
 (3*R*,4*R*)-*N*-(3-cyanophenyl)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carboxamide;
 (*R*)-1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carbonyl)pyrrolidine-2-carbonitrile;
 (*S*)-1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carbonyl)pyrrolidine-2-carbonitrile;
 ((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)((*R*)-2-(trifluoromethyl)pyrrolidin-1-yl)methanone;
 ((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)((*S*)-2-(trifluoromethyl)pyrrolidin-1-yl)methanone;
 ((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(3,3-difluoroazetidin-1-yl)methanone;
 2-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)benzo[d]oxazole;
N-((1*S*,3*R*,4*S*)-3-ethyl-4-(3-(2-(methylsulfonyl)ethyl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide;
 ((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(azetidin-1-yl)methanone;
 (3*R*,4*R*)-*N*-(4-cyanophenyl)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carboxamide;
 ((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)((*R*)-3-fluoropyrrolidin-1-yl)methanone;
 ((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(3,3-difluoropyrrolidin-1-yl)methanone;
 1-((3*R*,4*R*)-4-methyl-1-(pyrrolidin-1-ylsulfonyl)piperidin-3-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;
 (*R*)-*N*-(1-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide;
 (*S*)-*N*-(1-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide;

3-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-(trifluoromethyl)piperidin-1-yl)-3-oxopropanenitrile;

3-((3*S*,4*S*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-(trifluoromethyl)piperidin-1-yl)-3-oxopropanenitrile;

N-(3-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-3-oxopropyl)acetamide;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(tetrahydrofuran-2-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(tetrahydrofuran-3-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(3-methoxycyclohexyl)methanone;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-3-hydroxypropan-1-one;

1-((3*R*,4*R*)-1-benzyl-4-methylpiperidin-3-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-4,4,4-trifluorobutan-1-one;

((3*R*,4*R*)-3-(6*II*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(tetrahydro-2*H*-pyran-4-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(tetrahydro-2*H*-pyran-3-yl)methanone;

4-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-4-oxobutanenitrile;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(tetrahydro-2*H*-pyran-2-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)((*R*)-2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(3-methylpyrrolidin-1-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(3-fluoroazetidin-1-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)((*S*)-3-fluoropyrrolidin-1-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)((*R*)-2-methylpyrrolidin-1-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)((*R*)-morpholin-3-yl)methanone;

1-((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)-3-(methylsulfonyl)propan-1-one;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(1,4-dioxan-2-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(tetrahydrothiophen-3-yl-1,1-dioxide)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(3,3-difluorocyclobutyl)methanone;

N-((1*S*,3*R*,4*S*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentyl)aniline;

N-((1*R*,3*S*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentyl)aniline;

3-bromo-1-cyclohexyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

(*R*)-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)(3,3-difluoroazetidin-1-yl)methanone;

(*R*)-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)(3,3-difluoropyrrolidin-1-yl)methanone;

(*R*)-(3-(6*II*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)(4,4-difluoropiperidin-1-yl)methanone;

(*R*)-1-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidine-1-carbonyl)azetidine-3-carbonitrile;

(3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methyl-*N*-(pyrimidin-2-yl)piperidine-1-carboxamide;

(3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methyl-*N*-(pyridin-2-yl)piperidine-1-carboxamide;

(3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methyl-*N*-(pyrimidin-4-yl)piperidine-1-carboxamide;

(3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methyl-*N*-(pyrazin-2-yl)piperidine-1-carboxamide;

1-cyclohexyl-3-phenyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

N-((3*S*,5*R*)-1-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-5-methylpyrrolidin-3-yl)cyclopropanesulfonamide;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(1-methylpyrrolidin-3-yl)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(1-methylpiperidin-4-yl)methanone;

(3*R*,4*R*)-phenyl 3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carboxylate;

((*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)((*R*)-2-(trifluoromethyl)pyrrolidin-1-yl)methanone;

(*R*)-1-(1-(pyrrolidin-1-ylsulfonyl)piperidin-3-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

(*R*)-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)(pyrrolidin-1-yl)methanone;

3-(1-cyclohexyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-3-yl)propanoic acid;

(*S*)-1-((*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidine-1-carbonyl)pyrrolidine-3-carbonitrile;

(*R*)-cyclopentyl 3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidine-1-carboxylate;

(*E*)-*N*-(((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(pyrrolidin-1-yl)methylene)cyanamide;

4-((1*R*,3*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentylamino)benzonitrile;

(*R*)-(3-(6*II*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)(3,3-difluorocyclobutyl)methanone;

5-((1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentylamino)pyrazine-2-carbonitrile;

N-((1*S*,3*S*,4*R*)-3-(3-bromo-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-ethylcyclopentyl)cyclopropanesulfonamide;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(4,4-difluorocyclohexyl)methanone;

(*R*)-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-1-yl)(3,3-dimethylpyrrolidin-1-yl)methanone;

(*R*)-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)(3,3-difluoropiperidin-1-yl)methanone;

(*R*)-1-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidine-1-carbonyl)piperidine-4-carbonitrile;

(*R*)-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)(thiomorpholino-1,1-dioxide)methanone;

((3*R*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidin-1-yl)(azepan-1-yl)methanone;

(*R*)-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)(4,4-dimethylpiperidin-1-yl)methanone;

(*R*)-(3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-1-yl)(4-chloropiperidin-1-yl)methanone;

5-(((1*S*,3*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyl)methylamino)pyrazine-2-carbonitrile;

5-(((1*S*,3*S*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyl)methylamino)pyrazine-2-carbonitrile;

1-((*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidine-1-carbonyl)piperidine-3-carbonitrile;

N-((3*S*,5*R*)-5-ethyl-1-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide;

1-(3,3-difluorocyclobutyl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

N-(1-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide;

(*E*)-3-(1-cyclohexyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-3-yl)acrylic acid;

N-((1*S*,3*S*,4*R*)-3-(3-chloro-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-ethylcyclopentyl)cyclopropanesulfonamide;

4-(((*cis*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclobutoxy)methyl)benzonitrile;

5-((3*S*,5*R*)-5-ethyl-1-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-3-ylamino)pyrazine-2-carbonitrile;

N-((3*S*,5*R*)-5-ethyl-1-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-3-yl)-3,3,3-trifluoropropane-1-sulfonamide;

4-((1*R*,3*R*,4*S*)-3-ethyl-4-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyloxy)benzonitrile;

N-((1*S*,3*S*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentyl)-1-methylcyclopropane-1-sulfonamide;

1-((1*S*,4*S*)-5-(3,3,3-trifluoropropylsulfonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

N-((1*S*,3*S*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentyl)-3,3-difluoroazetidine-1-sulfonamide;

N-((1*S*,3*S*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentyl)-3,3,3-trifluoropropane-1-sulfonamide;

N-((1*S*,3*S*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentyl)-3,3-difluoropyrrolidine-1-sulfonamide;

(*S*)-*N*-((1*S*,3*S*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentyl)-2-(trifluoromethyl)pyrrolidine-1-sulfonamide;

N-(((1*S*,3*S*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyl)methyl)cyclopropanesulfonamide;

N-(((1*S*,3*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyl)methyl)-3,3,3-trifluoropropane-1-sulfonamide;

N-(((1*S*,3*S*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cyclopentyl)methyl)-3,3,3-trifluoropropane-1-sulfonamide;

N-((1*S*,3*S*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentyl)-1-ethylcyclopropane-1-sulfonamide;

1-((3*aR*,6*aS*)-5-(3,3,3-trifluoropropylsulfonyl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

1-(6-fluoro-4-(3,3,3-trifluoropropylsulfonyl)-1,4-diazepan-1-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

4-([4-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)cubanyl]methoxy)benzonitrile;

N-((3*R*,4*S*)-4-methyl-1-(3,3,3-trifluoropropylsulfonyl)piperidin-3-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-amine;

1-(2-(3,3,3-trifluoropropylsulfonyl)-2,5-diazaspiro[3.5]nonan-5-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

1-((3*aS*,7*aR*)-4-(3,3,3-trifluoropropylsulfonyl)octahydro-1*H*-pyrrolo[3,2-*b*]pyridin-1-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

1-(7-methyl-4-(3,3,3-trifluoropropylsulfonyl)-1,4-diazepan-1-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

1-(5-(3,3,3-trifluoropropylsulfonyl)-2,5-diazaspiro[3.5]nonan-2-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

N-(1-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidin-3-yl)-3,3,3-trifluoropropane-1-sulfonamide;

1-((1*R*,5*S*)-2-(3,3,3-trifluoropropylsulfonyl)-2,6-diazabicyclo[3.2.1]octan-6-yl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

1-cyclohexyl-3-(4-(methylsulfonyl)phenyl)-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazine;

N-(4-(1-cyclohexyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-3-yl)phenyl)methanesulfonamide;

N-((1*S*,3*S*,4*R*)-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylcyclopentyl)-3-chlorobenzenesulfonamide;

Cyclopropanesulfonic acid [(1*S*,3*R*,4*R*)-3-ethyl-4-(3-trifluoromethyl-6*H*-2,5,6,8b-tetraaza-as-indacen-1-yl)-cyclopentyl]-amide;

Cyclopropanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(3-trifluoromethyl-6*H*-2,5,6,8b-tetraaza-as-indacen-1-yl)-cyclopentyl]-amide;

1-((1*S*,2*R*,4*S*)-4-Cyclopropanesulfonylamino-2-ethyl-cyclopentyl)-6*H*-2,5,6,8*b*-tetraaza-as-indacene-3-carboxylic acid;

1-((1*R*,2*R*,4*S*)-4-Cyclopropanesulfonylamino-2-ethyl-cyclopentyl)-6*H*-2,5,6,8*b*-tetraaza-as-indacene-3-carboxylic acid;

Cyclopropanesulfonic acid [(1*S*,3*R*,4*S*)-3-methyl-4-(3-trifluoromethyl-6*H*-2,5,6,8*b*-tetraaza-as-indacen-1-yl)-cyclopentyl]-amide;

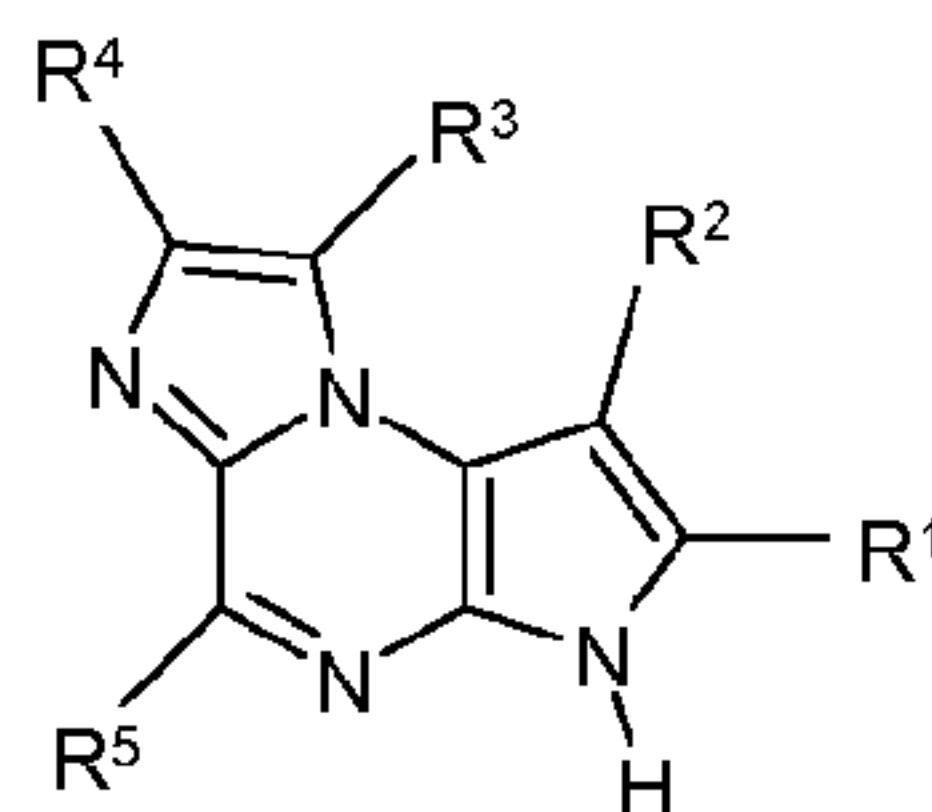
1-[(1*R*,3*R*,4*S*)-3-Ethyl-4-(3-trifluoromethyl-6*H*-2,5,6,8*b*-tetraaza-as-indacen-1-yl)-cyclopentyl]-2-methyl-propan-2-ol;

Cyclopropanesulfonic acid {(1*S*,3*R*,4*S*)-3-ethyl-4-[3-(2,2,2-trifluoro-ethyl)-6*H*-2,5,6,8*b*-tetraaza-as-indacen-1-yl]-cyclopentyl}-amide;

[(1*R*,3*R*,4*S*)-3-Ethyl-4-(3-trifluoromethyl-6*H*-2,5,6,8*b*-tetraaza-as-indacen-1-yl)-cyclopentyl]-acetic acid ethyl ester or

1-[(1*S*,2*R*,4*R*)-2-Ethyl-4-(3-methoxymethyl-[1,2,4]oxadiazol-5-ylmethyl)-cyclopentyl]-3-trifluoromethyl-6*H*-2,5,6,8*b*-tetraaza-as-indacene.

In a seventeenth embodiment the invention provides a compound according to the first through twelfth embodiments wherein T is N, U is CR⁴, X is CR³ and Y is N and forms a compound of Formula (Ic)



Formula (Ic)

In an eighteenth embodiment the invention provides a compound according to the seventeenth embodiment wherein the compound is

3-((3*S*,4*S*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylpiperidin-1-yl)-3-oxopropanenitrile;

5-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)pyrazine-2-carbonitrile;

(*S*)-1-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidine-1-carbonyl)cyclopropanecarbonitrile;

N-((1*S*,3*R*,4*R*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*R*,3*S*,4*S*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)cyclopropanesulfonamide;

(S)-6-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)nicotinonitrile;
 (R)-6-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)nicotinonitrile;
 (S)-2-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)thiazole-5-carbonitrile;
 (R)-2-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)thiazole-5-carbonitrile;
 (R)-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)(3,3-difluoroazetidin-1-yl)methanone;
 (S)-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)(3,3-difluoroazetidin-1-yl)methanone;
 5-((1*R*,3*S*,4*S*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentylamino)pyrazine-2-carbonitrile;
 5-((1*S*,3*R*,4*R*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentylamino)pyrazine-2-carbonitrile;
 5-((1*R*,3*R*,4*S*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentylamino)pyrazine-2-carbonitrile;
 5-((1*S*,3*S*,4*R*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentylamino)pyrazine-2-carbonitrile;
N-(4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide;
 (R)-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)(3,3-difluorocyclobutyl)methanone;
 (R)-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)(3,3-difluoropyrrolidin-1-yl)methanone;
 (R)-(3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)(4,4-difluoropiperidin-1-yl)methanone;
N-((1*S*,3*S*,4*R*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentyl)-3,3,3-trifluoropropane-1-sulfonamide;
N-((1*R*,3*R*,4*S*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentyl)-3,3,3-trifluoropropane-1-sulfonamide;
N-((1*R*,3*S*,4*S*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentyl)-3,3,3-trifluoropropane-1-sulfonamide;
N-((1*S*,3*R*,4*R*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentyl)-3,3,3-trifluoropropane-1-sulfonamide;
 ((*R*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)piperidin-1-yl)((*R*)-2-(trifluoromethyl)pyrrolidin-1-yl)methanone;

N-((3*S*,5*R*)-5-ethyl-1-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)pyrrolidin-3-yl)cyclopropanesulfonamide;
 1-cyclohexyl-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine;
N-((3*S*,5*R*)-5-ethyl-1-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)pyrrolidin-3-yl)-3,3,3-trifluoropropane-1-sulfonamide;
 3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentanamine;
N-((1*R*,3*S*,4*R*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)-3,3,3-trifluoropropane-1-sulfonamide;
N-((1*S*,3*R*,4*S*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)-3,3,3-trifluoropropane-1-sulfonamide;
N-((1*S*,3*S*,4*R*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentyl)cyclopropanesulfonamide;
N-((1*S*,3*R*,4*S*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)cyclopropanesulfonamide;
N-((1*S*,3*R*,4*S*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)-3,3-difluoroazetidine-1-sulfonamide;
 3-chloro-*N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)-4-fluorobenzenesulfonamide;
N-((1*S*,3*S*,4*R*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentyl)-3,3-difluoroazetidine-1-sulfonamide;
N-(((1*S*,3*R*,4*S*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)methyl)-3,3,3-trifluoropropane-1-sulfonamide;
N-(((1*R*,3*S*,4*R*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)methyl)-3,3,3-trifluoropropane-1-sulfonamide;
N-(((1*S*,3*S*,4*R*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)methyl)-3,3,3-trifluoropropane-1-sulfonamide;
N-(((1*R*,3*R*,4*S*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentyl)methyl)-3,3,3-trifluoropropane-1-sulfonamide;
N-((1*S*,3*S*,4*R*)-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentyl)morpholine-4-sulfonamide;
 3,3,3-Trifluoro-propane-1-sulfonic acid [(2*S*,4*S*,5*R*)-4-methyl-5-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-tetrahydro-furan-2-ylmethyl]-amide;
 3,3,3-Trifluoro-propane-1-sulfonic acid [(2*R*,4*R*,5*S*)-4-methyl-5-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-tetrahydro-furan-2-ylmethyl]-amide;
 3,3,3-Trifluoro-propane-1-sulfonic acid methyl-[(1*S*,3*R*,4*S*)-3-methyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-amide;

Azetidine-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-methyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-amide;

{3-[(1*S*,3*R*,4*S*)-3-Methyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentylamino]-oxetan-3-yl}-acetonitrile;

3,3-Difluoro-cyclobutanesulfonic acid [(1*S*,3*R*,4*S*)-3-methyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-amide;

8-[(1*S*,2*R*,4*S*)-2-Methyl-4-(tetrahydro-pyran-4-yloxy)-cyclopentyl]-3*H*-3,4,6,8a-tetraaza-as-indacene;

8-[(1*R*,2*R*)-2-Methyl-4-(tetrahydro-pyran-4-yloxy)-cyclopentyl]-3*H*-3,4,6,8a-tetraaza-as-indacene;

3-Fluoro-azetidine-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-methyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-amide;

3-Fluoro-propane-1-sulfonic acid [(1*S*,3*R*,4*S*)-3-methyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-amide;

Cyclopropanesulfonic acid [(1*S*,3*R*,4*S*)-3-methyl-4-(7-methyl-3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-amide;

Cyclopropanesulfonic acid [(1*R*,3*S*,4*R*)-3-methyl-4-(7-methyl-3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-amide;

2-Cyano-N-[(1*S*,3*R*,4*S*)-3-methyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-acetamide;

8-[(1*S*,2*R*,4*R*)-2-Methyl-4-(tetrahydro-pyran-4-yloxy)-cyclopentyl]-3*H*-3,4,6,8a-tetraaza-as-indacene;

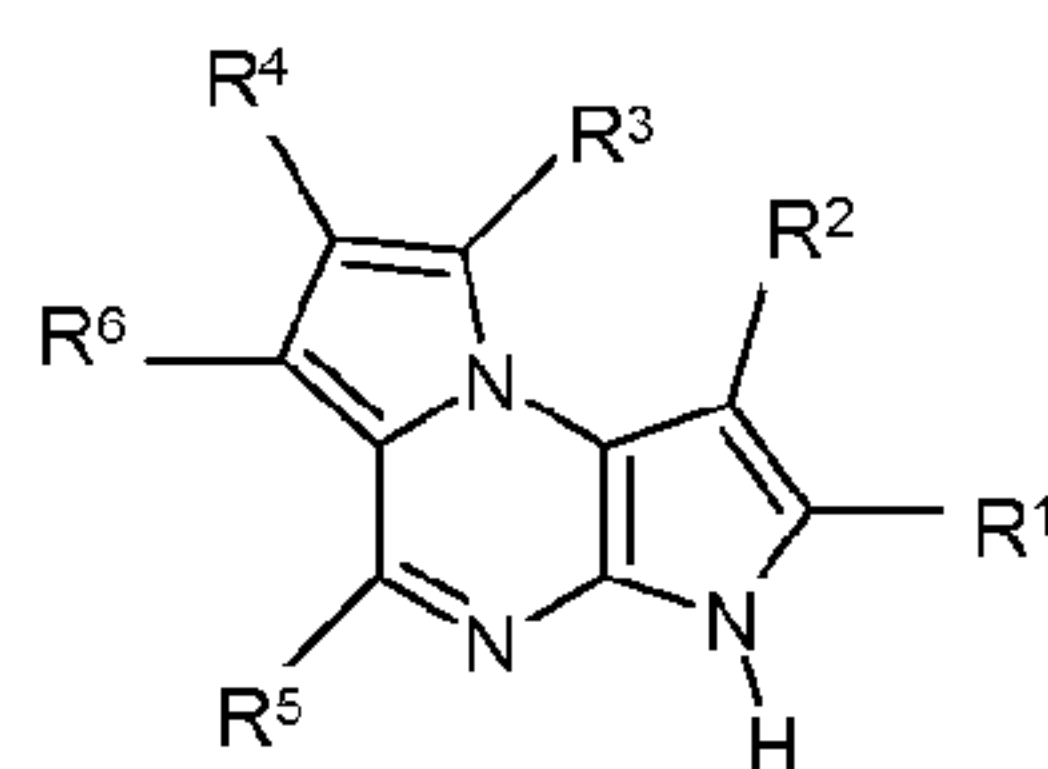
(2-Cyclopropyl-ethyl)-[(1*S*,3*R*,4*S*)-3-methyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-oxetan-3-yl-amine;

Cyclopropylmethyl-[(1*S*,3*R*,4*S*)-3-methyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-cyclopentyl]-oxetan-3-yl-amine;

(3*R*,4*S*)-3-Ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-pyrrolidine-1-carboxylic acid (2,2,2-trifluoro-ethyl)-amide; or

(3*S*,4*R*)-3-Ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-pyrrolidine-1-carboxylic acid (2,2,2-trifluoro-ethyl)-amide.

In a nineteenth embodiment the invention provides a compound according to the first through twelfth embodiments wherein T is CR⁶, U is CR⁴, X is CR³ and Y is N and forms a compound of Formula (Id)

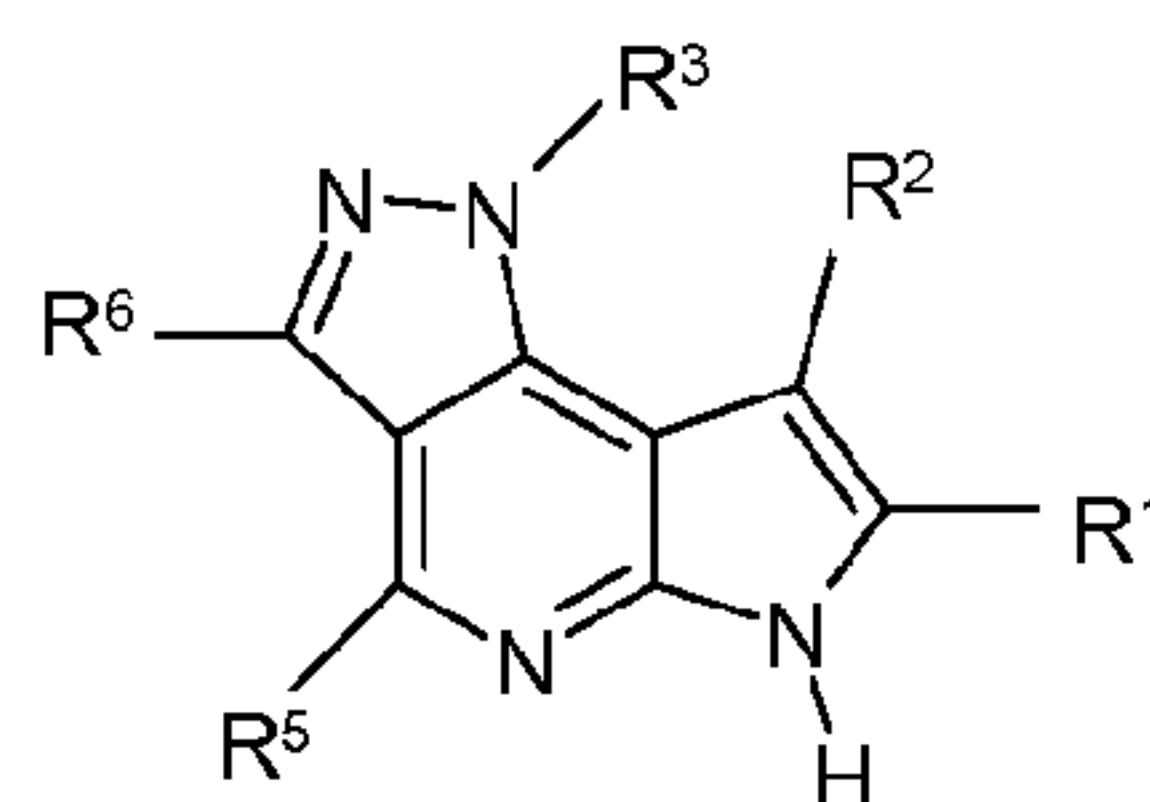


Formula (Id)

In a twentieth embodiment the invention provides a compound according to the nineteenth embodiment wherein the compound is

N-(4-(3*H*-dipyrrolo[1,2-*a*:2',3'-*e*]pyrazin-8-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide.

In a twenty-first embodiment the invention provides a compound according to the first through twelfth embodiments wherein T is CR⁶, U is N, X is NR³ and Y is C and forms a compound of Formula (Ie)



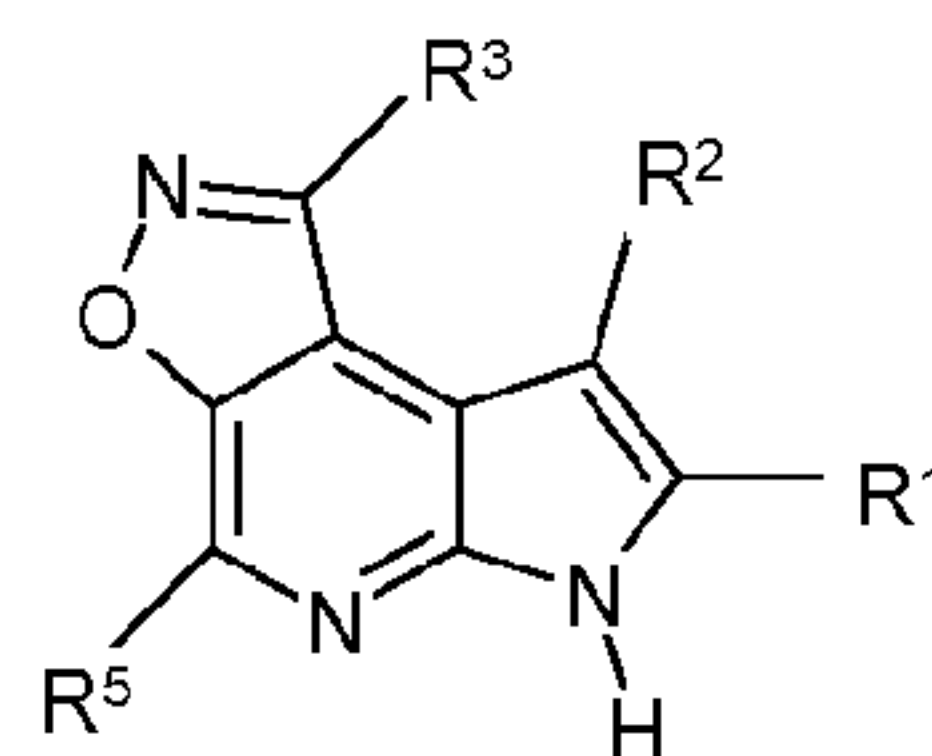
Formula (Ie)

In a twenty-second embodiment the invention provides a compound according to the twenty-first embodiment wherein the compound is

(*R*)-1-(3-(pyrazolo[3,4-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)piperidine-1-carbonyl)cyclopropanecarbonitrile; or

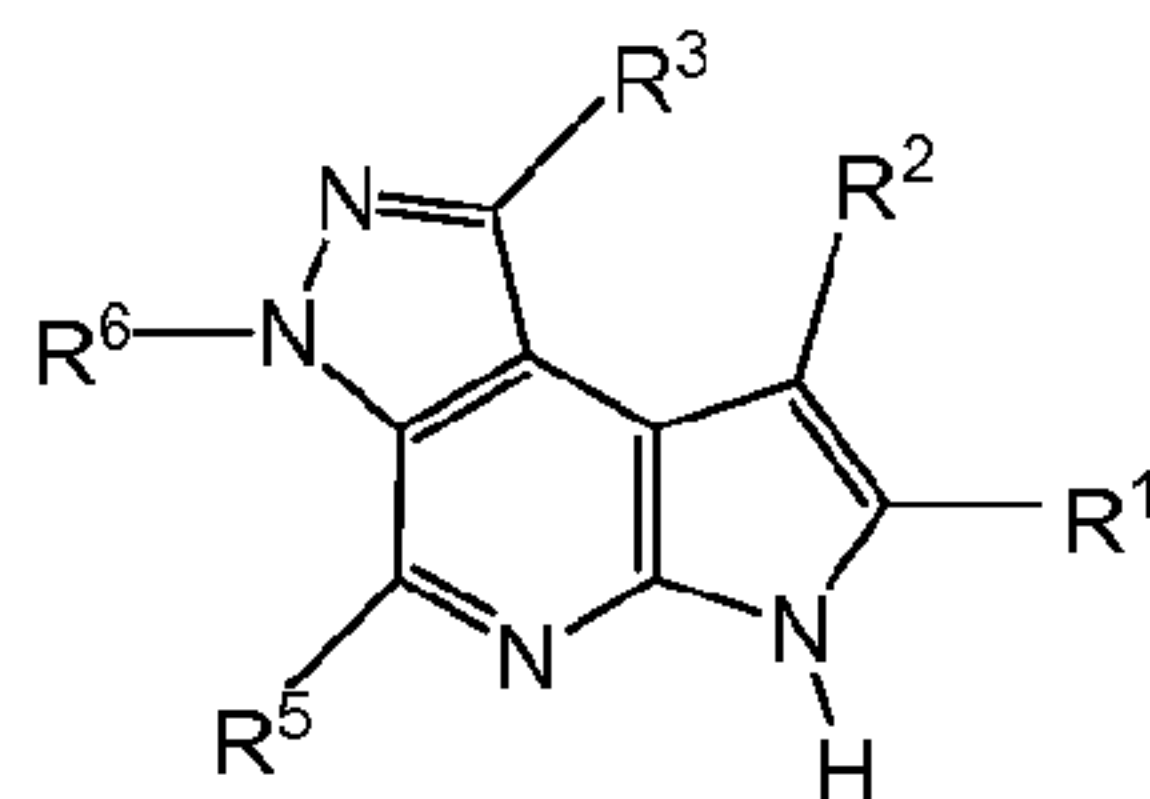
(*S*)-1-(3-(pyrazolo[3,4-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)piperidine-1-carbonyl)cyclopropanecarbonitrile.

In a twenty-third embodiment the invention provides a compound according to the first through twelfth embodiments wherein T is O, U is N, X is CR³ and Y is C and forms a compound of Formula (If)



Formula (If)

In a twenty-fourth embodiment the invention provides a compound according to the first through twelfth embodiments wherein T is NR^6 , U is N, X is CR^3 and Y is C and forms a compound of Formula (Ig)



Formula (Ig)

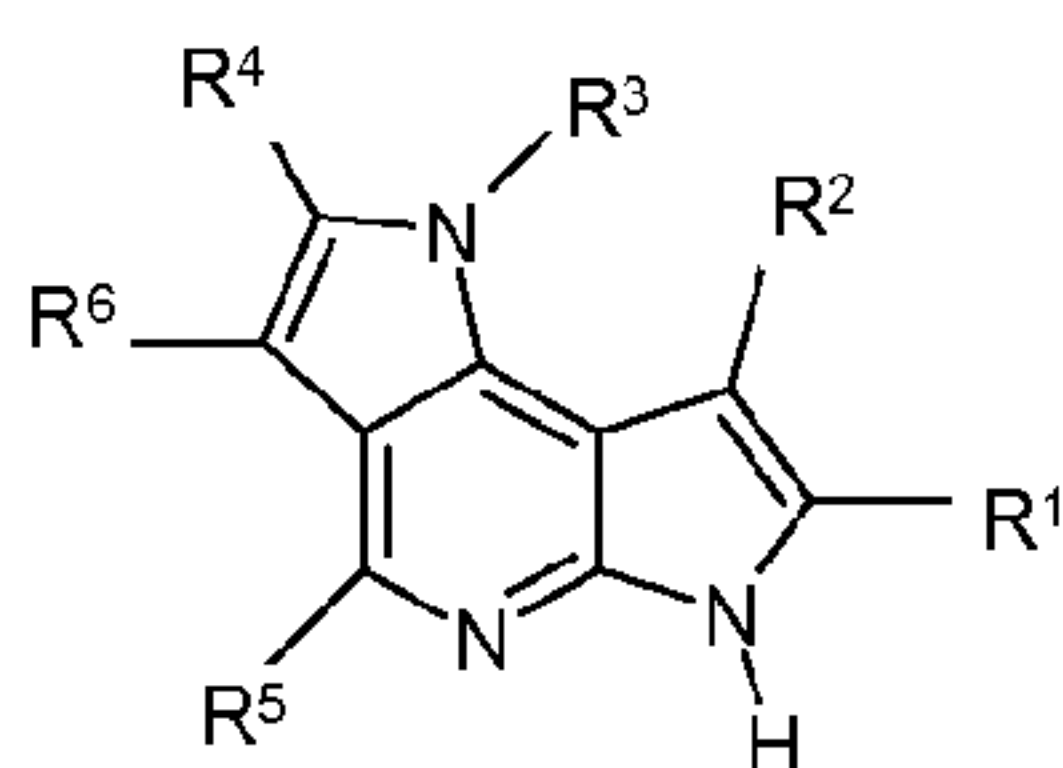
In a twenty-fifth embodiment the invention provides a compound according to the twenty-fourth embodiment wherein the compound is

1-((1*R*,2*R*,4*S*)-2-ethyl-4-(4-methoxybenzyloxy)cyclopentyl)-3,6-dihydropyrazolo[4,3-*d*]pyrrolo[2,3-*b*]pyridine;

1-((1*S*,2*S*,4*R*)-2-ethyl-4-(4-methoxybenzyloxy)cyclopentyl)-3,6-dihydropyrazolo[4,3-*d*]pyrrolo[2,3-*b*]pyridine; or

N-(4-(3,6-dihydropyrazolo[4,3-*d*]pyrrolo[2,3-*b*]pyridin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide.

In a twenty-sixth embodiment the invention provides a compound according to the first through twelfth embodiments wherein T is CR^6 , U is CR^4 , X is NR^3 and Y is C and forms a compound of Formula (Ih)



Formula (Ih)

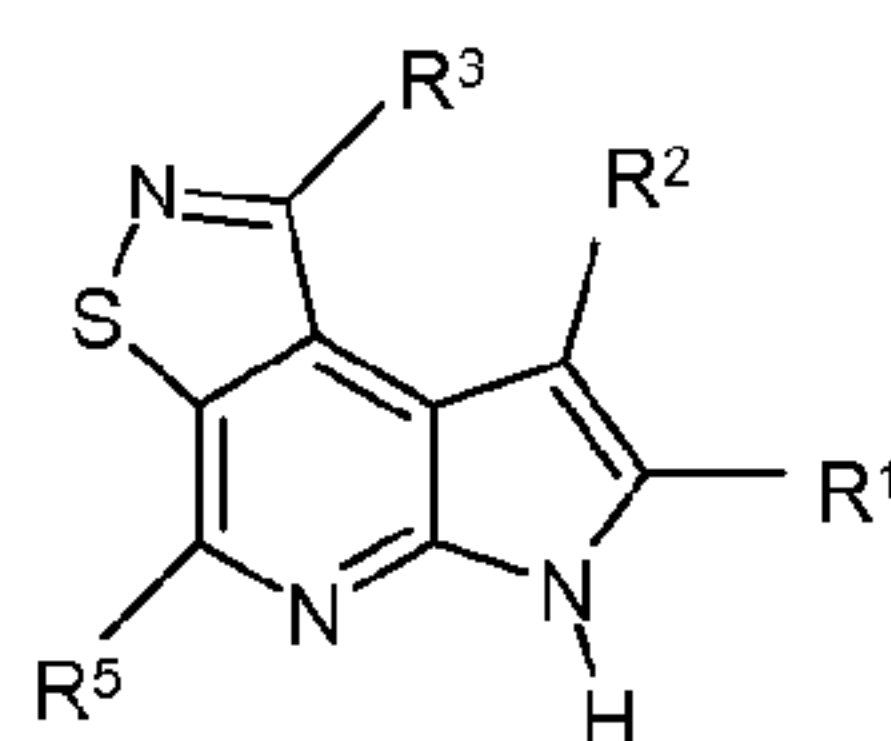
In a twenty-seventh embodiment the invention provides a compound according to the twenty-sixth embodiment wherein the compound is

1-cyclohexyl-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine;

1-cyclohexyl-2-methyl-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine; or

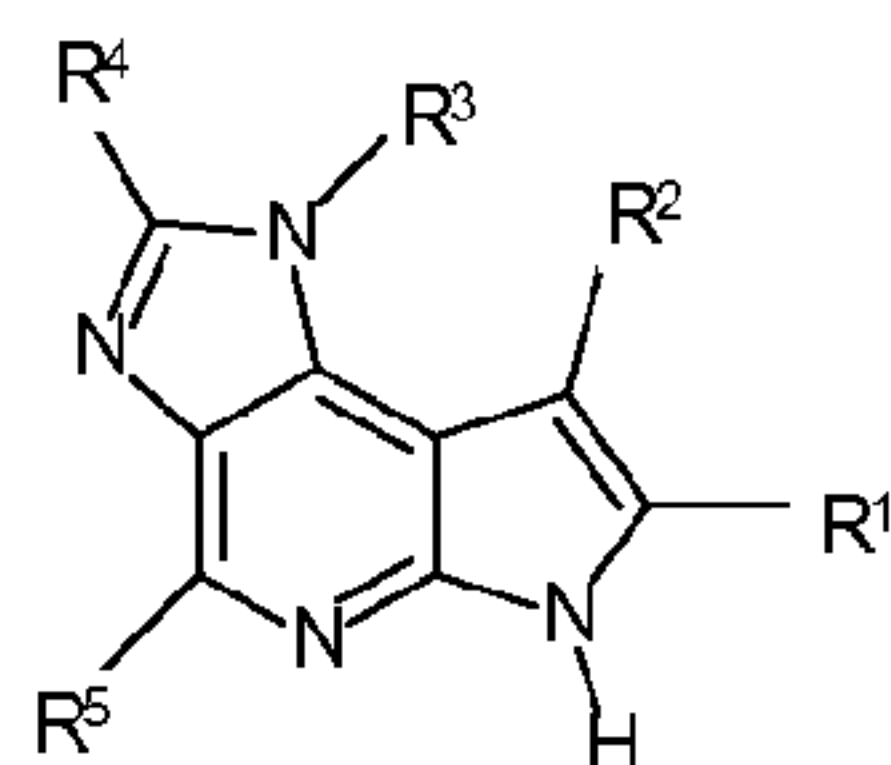
1-cyclohexyl-2-(trifluoromethyl)-1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine.

In a twenty-eighth embodiment the invention provides a compound according to the first through twelfth embodiments wherein T is S, U is N, X is CR^3 and Y is C and forms a compound of Formula (Ii)



Formula (Ii)

In a twenty-ninth embodiment the invention provides a compound according to the first through twelfth embodiments wherein T is N, U is CR⁴, X is NR³ and Y is C and forms a compound of formula (Ij)



Formula (Ij)

In a thirtieth embodiment the invention provides a compound according to the twenty-ninth embodiment wherein the compound is

N-((1*S*,3*R*,4*S*)-3-ethyl-4-(imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)cyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*S*,4*R*)-3-(imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)-4-methylcyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*S*,4*R*)-3-(2-cyclopropylimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)-4-methylcyclopentyl)cyclopropanesulfonamide;

N-((1*S*,3*R*,4*S*)-3-methyl-4-(2-methylimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)cyclopentyl)cyclopropanesulfonamide;

Cyclopropanesulfonic acid [(1*S*,3*R*,4*S*)-3-methyl-4-(2-trifluoromethyl-imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)-cyclopentyl]-amide;

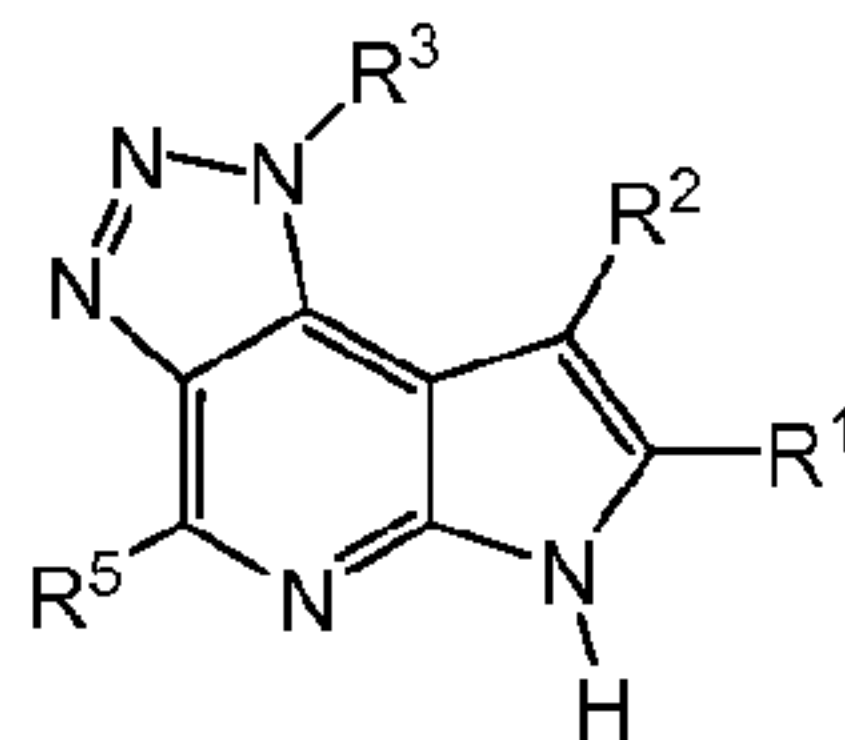
Cyclopropanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(2-trifluoromethyl-imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)-cyclopentyl]-amide;

Cyclopropanesulfonic acid [(1*S*,3*S*,4*R*)-3-(2-difluoromethyl-imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)-4-ethyl-cyclopentyl]-amide;

Cyclopropanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(2-methyl-imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)-cyclopentyl]-amide;

Cyclopropanesulfonic acid [(1*S*,3*S*,4*R*)-3-(2-amino- imidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1(6*H*)-yl)-4-ethyl-cyclopentyl]-amide.

according to the first through twelfth embodiments wherein X is N, U is N, X is NR^3 and Y is C and forms a compound of Formula (Ik)

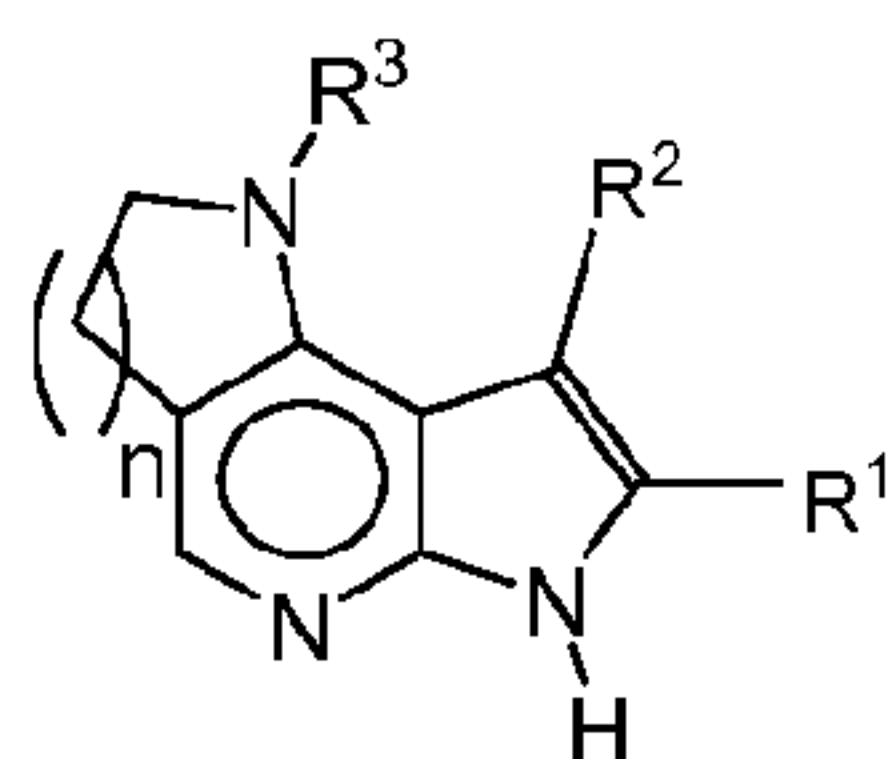


Formula (Ik)

In a thirty-second embodiment the invention provides a compound according to the thirty-first embodiment wherein the compound is

Cyclopropanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-[1,2,3]triazolo[4,5-*d*]pyrrolo[2,3-*b*]pyridin-1-yl)-cyclopentyl]-amide.

In a thirty-third embodiment the invention provides a compound of Formula (II) wherein the compound is



Formula (II)

pharmaceutically acceptable salts, pro-drugs, biologically active metabolites, stereoisomers and isomers thereof wherein

R^1 , and R^2 are independently hydrogen, deuterium, $-\text{N}(\text{R}^a)(\text{R}^b)$, halogen, $-\text{OR}^a$, $-\text{SR}^a$, $-\text{S}(\text{O})\text{R}^a$, $-\text{S}(\text{O})_2\text{R}^a$, $-\text{NO}_2$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{CN}$, $-\text{C}(\text{O})\text{N}(\text{R}^a)(\text{R}^b)$, $-\text{N}(\text{R}^a)\text{C}(\text{O})(\text{R}^b)$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{OH})\text{R}^a\text{R}^b$, $-\text{N}(\text{R}^a)\text{S}(\text{O})_2-\text{R}^b$, $-\text{S}(\text{O})_2\text{N}(\text{R}^a)(\text{R}^b)$, $-\text{CF}_3$, $-\text{OCF}_3$, optionally substituted (C_1 - C_6)alkyl, optionally substituted (C_2 - C_6)alkenyl, optionally substituted (C_2 - C_6)alkynyl, optionally substituted (C_3 - C_{10})cycloalkyl, optionally substituted (C_1 - C_{10})heteroaryl, optionally substituted (C_1 - C_{10})heterocyclyl, or optionally substituted (C_6 - C_{10})aryl;

wherein in a moiety containing $-\text{N}(\text{R}^a)(\text{R}^b)$, the nitrogen, R^a and R^b may form a ring such that $-\text{N}(\text{R}^a)(\text{R}^b)$ represents an optionally substituted (C_2 - C_{10})heterocyclyl or optionally substituted (C_1 - C_{10})heteroaryl linked through a nitrogen;

R^3 is hydrogen, an optionally substituted bridged (C_5 - C_{12})cycloalkyl, optionally substituted bridged (C_2 - C_{10})heterocyclyl, optionally substituted (C_1 - C_8)alkyl, optionally substituted (C_3 - C_{10})cycloalkyl, optionally substituted (C_3 - C_8)cycloalkenyl, optionally substituted

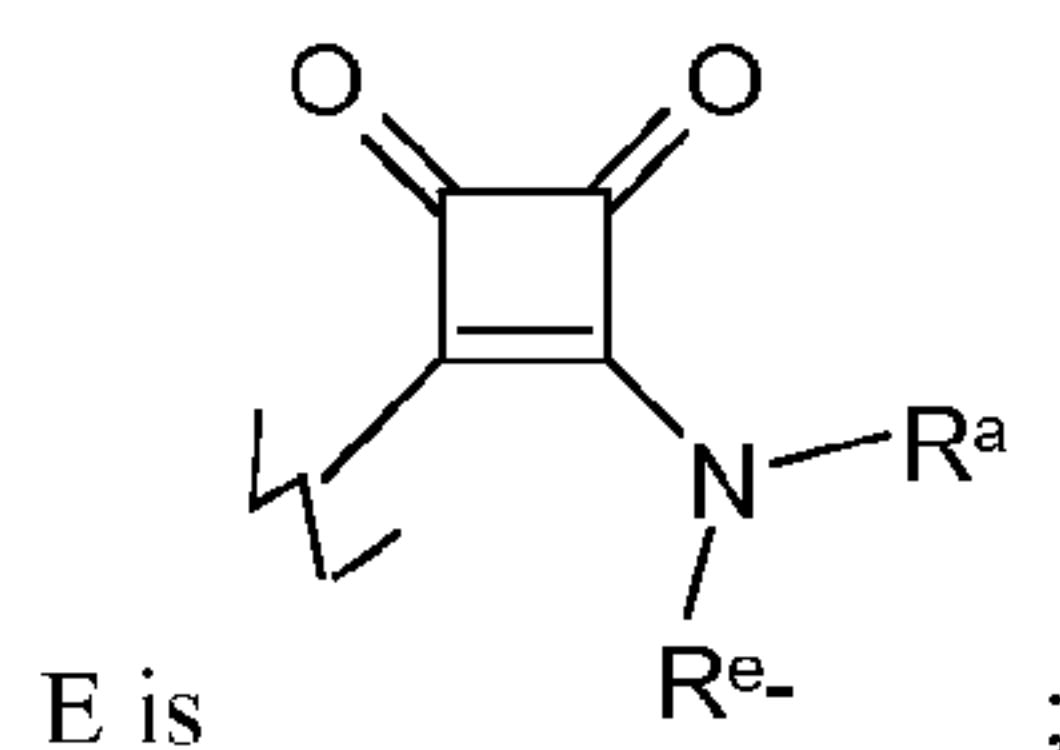
(C₆-C₁₀)aryl, optionally substituted (C₁-C₁₀)heteroaryl, optionally substituted (C₂-C₁₀)heterocyclyl; or

R³ is -A-D-E-G, wherein:

A is a bond, -C(O)-, optionally substituted (C₁-C₆)alkylene, optionally substituted (C₂-C₆)alkenylene, optionally substituted (C₂-C₆)alkynylene, optionally substituted (C₃-C₁₂)cycloalkylene, optionally substituted (C₂-C₆)heterocyclylene, -C(O)N(R^a)-R^e-, -N(R^a)C(O)-R^e-, -O-R^e-, -N(R^a)-R^e-, -S-R^e-, -S(O)₂-R^e-, -S(O)R^e-, -C(O-R^a)(R^b)-R^e-, -S(O)₂N(R^a)-R^e-, -N(R^a)S(O)₂-R^e- or -N(R^a)C(O)N(R^b)-R^e-;

D is an optionally substituted (C₁-C₈)alkylene, optionally substituted bridged (C₅-C₁₂)cycloalkylene, optionally substituted (C₃-C₁₀)cycloalkylene, optionally substituted bridged (C₅-C₁₀)cycloalkenylene, optionally substituted (C₃-C₁₀)cycloalkenylene, optionally substituted (C₆-C₁₀)arylene, optionally substituted (C₁-C₁₀)heteroarylene, optionally substituted bridged (C₂-C₁₀)heterocyclylene or an optionally substituted (C₂-C₁₀)heterocyclylene;

E is a bond, -R^e-, -R^e-C(=NCN)-R^e-, -R^e-C(O)-R^e-, -R^e-C(O)C(O)-R^e-, -R^e-C(O)O-R^e-, -R^e-C(O)C(O)N(R^a)-R^e-, -R^e-N(R^a)-C(O)C(O)-R^e-, -R^e-O-R^e-, -R^e-S(O)₂-R^e-, -R^e-S(O)-R^e-, -R^e-S-R^e-, -R^e-N(R^a)-R^e-, =N-R^e-, -R^e-N(R^a)C(O)-R^e-, -R^eC(O)N(R^a)R^e-, -R^e-OC(O)N(R^a)-R^e-, -R^e-N(R^a)C(O)OR^e-, -R^e-OC(O)-R^e-, -R^e-OC(O)-O-R^e-, -R^e-N(R^a)C(O)N(R^b)-R^e-, -R^e-N(R^a)S(O)₂-R^e-, -R^e-S(O)₂N(R^a)-R^e-, or -R^e-N(R^a)S(O)₂N(R^a)-R^e-; or



where in all cases, E is linked to either a carbon or a nitrogen atom in D;

G is hydrogen, deuterium, -N(R^a)(R^b), halogen, -OR^a, -SR^a, -S(O)R^a, -S(O)₂R^a, -NO₂, -C(O)OR^a, -CN, -C(O)N(R^a)(R^b), -N(R^a)C(O)R^b, -N(R^a)C(O)OR^b, -OC(O)N(R^a), -N(R^a)C(O)N(R^b)₂, -C(O-R^a)(R^b)₂, -C(O)R^a, -CF₃, -OCF₃, -N(R^a)S(O)₂R^b, -S(O)₂N(R^a)(R^b), -S(O)₂N(R^a)C(O)R^b, an optionally substituted -(C₁-C₆)alkyl, an optionally substituted -(C₂-C₆)alkenyl, an optionally substituted -(C₂-C₆)alkynyl, an optionally substituted -(C₃-C₁₀)cycloalkyl, an optionally substituted -(C₁-C₁₀)heteroaryl, an optionally substituted -(C₁-C₁₀)heterocyclyl, an optionally substituted -(C₆-C₁₀)aryl;

wherein in a moiety containing -N(R^a)(R^b), the nitrogen, R^a and R^b may form a ring such that -N(R^a)(R^b) represents an optionally substituted (C₂-C₁₀)heterocyclyl or an optionally substituted (C₁-C₁₀) heteroaryl linked through a nitrogen;

R^a and R^b are each independently hydrogen, deuterium, CN, an optionally substituted (C₁-C₁₀)alkyl, an optionally substituted (C₂-C₁₀)alkenyl, an optionally substituted (C₂-C₁₀)alkynyl, an optionally substituted (C₁-C₁₀)alkyl-O-(C₁-C₁₀)alkyl, an optionally substituted (C₃-C₁₀)cycloalkyl,

an optionally substituted (C₆-C₁₀)aryl, an optionally substituted (C₁-C₁₀)heteroaryl, an optionally substituted (C₁-C₁₀)heterocyclyl, an optionally substituted -(C₁-C₆)alkylene-(C₃-C₁₀)cycloalkyl, an optionally substituted -(C₁-C₆)alkylene-(C₆-C₁₀)aryl, an optionally substituted -(C₁-C₆)alkylene-(C₁-C₁₀)heteroaryl, or an optionally substituted -(C₁-C₆)alkylene-(C₁-C₁₀)heterocyclyl; and

R^e for each occurrence is independently a bond, an optionally substituted (C₁-C₁₀)alkylene, an optionally substituted (C₂-C₁₀)alkenylene, an optionally substituted (C₂-C₁₀)alkynylene, an optionally substituted -(C₁-C₁₀)alkylene-O-(C₁-C₁₀)alkylene group, an optionally substituted (C₃-C₁₀)cycloalkylene, an optionally substituted (C₆-C₁₀)arylene, an optionally substituted (C₁-C₁₀)heteroarylene, or an optionally substituted (C₁-C₁₀)heterocyclylene.

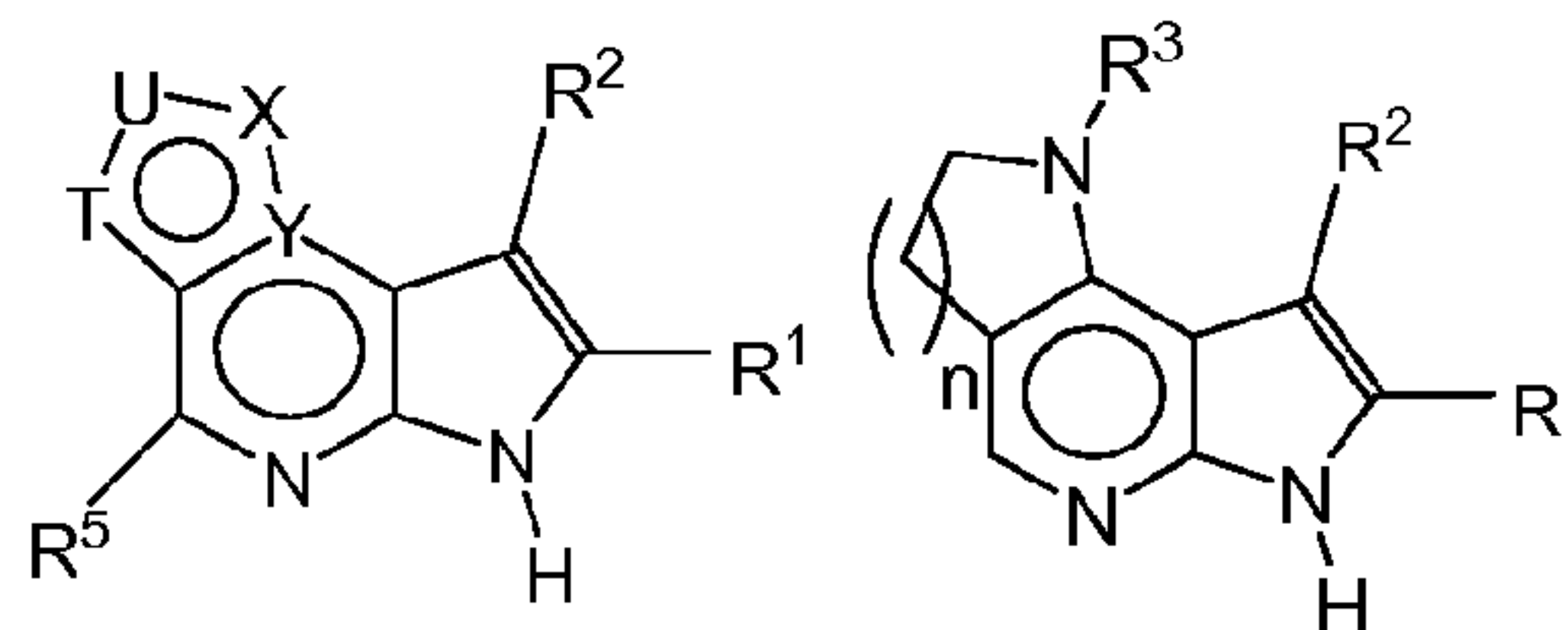
In a thirty-fourth embodiment the invention provides a compound according to the thirty-third embodiment wherein the compound is

1-Cyclohexyl-2,3,4,7-tetrahydro-1*H*-pyrrolo[2,3-*h*][1,6]naphthyridine;

Cyclopropanesulfonic acid [(1*S*,3*R*,4*S*)-3-ethyl-4-(3,6,7,8-tetrahydro-3,4,9-triazacyclopenta[*a*]naphthalen-9-yl)-cyclopentyl]-amide; or

Cyclopropanesulfonic acid [(1*S*,3*S*,4*R*)-3-(3,6-dihydro-2*H*-dipyrrolo[2,3-*b*;2',3'-*d*]pyridin-1-yl)-4-ethyl-cyclopentyl]-amide.

In a thirty-fifth embodiment the invention provides a pharmaceutical composition comprising a compound of Formula (I) or Formula (II) as defined in any of the foregoing embodiments



Formula (I)

Formula (II)

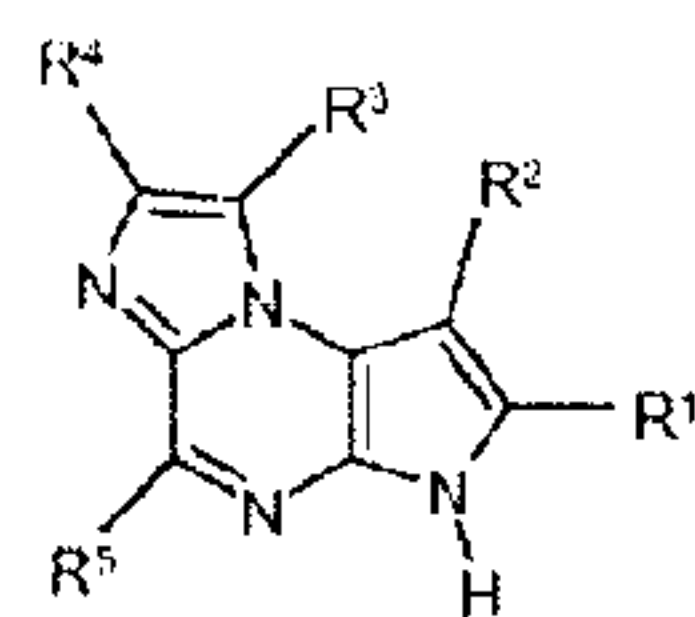
a pharmaceutically acceptable carrier and excipient and a second therapeutic agent selected from the group consisting of cytokine suppressive anti-inflammatory drugs, antibodies to or antagonists of other human cytokines or growth factors, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-12, IL-15, IL-16, IL-21, IL-23, interferons, EMAP-II, GM-CSF, FGF, PDGF, CTLA or their ligands including CD154, HUMIRATM, REMICADETM, SIMPONITM (golimumab), CIMZIATM, ACTEMRATM, CDP 571, soluble p55 or p75 TNF receptors, ENBRELETM, Lenercept, TNF α converting enzyme inhibitors, IL-1 inhibitors, Interleukin 11, IL-18 antagonists, IL-12 antagonists, IL-12 antibodies, soluble IL-12 receptors, IL-12 binding proteins, non-depleting anti-CD4 inhibitors FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, ibuprofen, corticosteroids, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, IL-1 β converting enzyme inhibitors, T-cell signalling

kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, 6-mercaptopurines, derivatives p75TNFRIgG, sIL-1RI, sIL-1RII, sIL-6R, celecoxib, hydroxychloroquine sulfate, rofecoxib, infliximab, naproxen, valdecoxib, sulfasalazine, meloxicam, acetate, gold sodium thiomalate, aspirin, triamcinolone acetonide, propoxyphene napsylate/apap, folate, nabumetone, diclofenac, piroxicam, etodolac, diclofenac sodium, oxaprozin, oxycodone HCl, hydrocodone bitartrate/apap, diclofenac sodium/misoprostol, fentanyl, anakinra, tramadol HCl, salsalate, sulindac, cyanocobalamin/fa/pyridoxine, acetaminophen, alendronate sodium, morphine sulfate, lidocaine hydrochloride, indomethacin, glucosamine sulf/chondroitin, amitriptyline HCl, sulfadiazine, oxycodone HCl/acetaminophen, olopatadine HCl misoprostol, naproxen sodium, omeprazole, cyclophosphamide, rituximab, IL-1 TRAP, MRA, CTLA4-IG, IL-18 BP, anti-IL-12, anti-IL15, VX-740, Roflumilast, IC-485, CDC-801, S1P1 agonists, FTY720, PKC family inhibitors, Ruboxistaurin, AEB-071, Mesopram, methotrexate, leflunomide, corticosteroids, budenoside, dexamethasone, sulfasalazine, 5-aminosalicylic acid, olsalazine, IL-1 β converting enzyme inhibitors, IL-1ra, T cell signaling inhibitors, tyrosine kinase inhibitors, 6-mercaptopurines, IL-11, mesalamine, prednisone, azathioprine, mercaptopurine, infliximab, methylprednisolone sodium succinate, diphenoxylate/atrop sulfate, loperamide hydrochloride, omeprazole, folate, ciprofloxacin/dextrose-water, hydrocodone, bitartrate/apap, tetracycline hydrochloride, fluocinonide, metronidazole, thimerosal/boric acid, cholestyramine/sucrose, ciprofloxacin hydrochloride, hyoscyamine sulfate, meperidine hydrochloride, midazolam hydrochloride, oxycodone HCl/acetaminophen, promethazine hydrochloride, sodium phosphate, sulfamethoxazole/trimethoprim, polycarbophil, propoxyphene napsylate, hydrocortisone, multivitamins, balsalazide disodium, codeine phosphate/apap, colesevelam HCl, cyanocobalamin, folic acid, levofloxacin, natalizumab, interferon-gamma, methylprednisolone, azathioprine, cyclophosphamide, cyclosporine, methotrexate, 4-aminopyridine, tizanidine, interferon- β 1a, AVONEX[®], interferon- β 1b, BETASERON[®], interferon α -n3, interferon- α , interferon β 1A-IF, Peginterferon α 2b, Copolymer 1, COPAXONE[®], hyperbaric oxygen, intravenous immunoglobulin, cladribine, cyclosporine, FK506, mycophenolate mofetil, leflunomide, NSAIDs, corticosteroids, prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, antiinflammatory cytokines, interferon- β , IFN β 1a, IFN β 1b, copaxone, corticosteroids, caspase inhibitors, inhibitors of caspase-1, antibodies to CD40 ligand and CD80, alemtuzumab, dronabinol, daclizumab, mitoxantrone, xaliproden hydrochloride, fampridine, glatiramer acetate, natalizumab, sinnabidol, α -immunokine NNSO3, ABR-215062, AnergiX.MS, chemokine receptor antagonists, BBR-2778, calagualine, CPI-1189, liposome encapsulated mitoxantrone, THC.CBD, cannabinoid agonists, MBP-8298, mesopram, MNA-715, anti-IL-6 receptor antibody, neurovax, pirfenidone allotrap 1258 (RDP-1258), sTNF-R1, talampanel, teriflunomide, TGF-beta2, tiplimotide, VLA-4 antagonists, interferon gamma

antagonists, IL-4 agonists, diclofenac, misoprostol, naproxen, meloxicam, indomethacin, diclofenac, methotrexate, azathioprine, minocyclin, prednisone, etanercept, rofecoxib, sulfasalazine, naproxen, leflunomide, methylprednisolone acetate, indomethacin, hydroxychloroquine sulfate, prednisone, sulindac, betamethasone diprop augmented, infliximab, methotrexate, folate, triamecinolone acetonide, diclofenac, dimethylsulfoxide, piroxicam, diclofenac sodium, ketoprofen, meloxicam, methylprednisolone, nabumetone, tolmetin sodium, calcipotriene, cyclosporine, diclofenac sodium/misoprostol, fluocinonide, glucosamine sulfate, gold sodium thiomalate, hydrocodone bitartrate/apap, risedronate sodium, sulfadiazine, thioguanine, valdecoxib, alefacept, and efalizumab, diclofenac, naproxen, ibuprofen, piroxicam, indomethacin, COX2 inhibitors, rofecoxib, valdecoxib, hydroxychloroquine, steroids, prednisolone, budenoside, dexamethasone, cytotoxics, azathioprine, cyclophosphamide, mycophenolate mofetil, inhibitors of PDE4, purine synthesis inhibitor, sulfasalazine, 5-aminosalicylic acid, olsalazine, Imuran[®], CTLA-4-IgG, anti-B7 family antibodies, anti-PD-1 family antibodies, anti-cytokine antibodies, fonotolizumab, anti-IFNg antibody, anti-receptor receptor antibodies, anti-IL-6 receptor antibody, antibodies to B-cell surface molecules, LJP 394, Rituximab, anti-CD20 antibody and lymphostat-B.

This invention relates to:

<1> A compound of formula Ic:



Formula (Ic)

or a pharmaceutically-acceptable salt thereof, wherein:

R¹, R², R⁴ and R⁵ are each hydrogen;

R³ is A-D-E-G, wherein A is a bond; D is an optionally substituted (C₂-C₁₀)heterocyclylene; E is a bond, R^e C(O)N(R^a)R^e-, -C(O)NHR^e-, or -R^e-N(R^a)C(O)-R^e-, and G is -CF₃ or -C(O)N(R^a)(R^b);

R^e for each occurrence is independently a bond or an optionally substituted (C₁-C₁₀)alkylene; and

R^a and R^b are each hydrogen or an optionally substituted (C₁-C₁₀)alkyl;

wherein E is linked to either a carbon or a nitrogen atom in D; and, when G contains -N(R^a)(R^b), the nitrogen, R^a, and R^b may form a ring, such that -N(R^a)(R^b) represents an

optionally substituted (C₂-C₁₀)heterocyclyl linked through a nitrogen.

<2> The compound of <1>, wherein:

G is -C(O)N(R^a)(R^b); and

R^a is hydrogen; and R^b is an optionally substituted (C₁-C₁₀)alkyl.

<3> The compound of <2>, wherein R^b is substituted by halogen or -CF₃.

<4> The compound of <1>, wherein:

D is an optionally substituted (C₂-C₁₀)heterocyclylene; E is -R^e C(O)N(R^a)R^e-; and G is -CF₃;

R^e for each occurrence is independently a bond or an optionally substituted (C₁-C₁₀)alkylene; and

R^a is hydrogen.

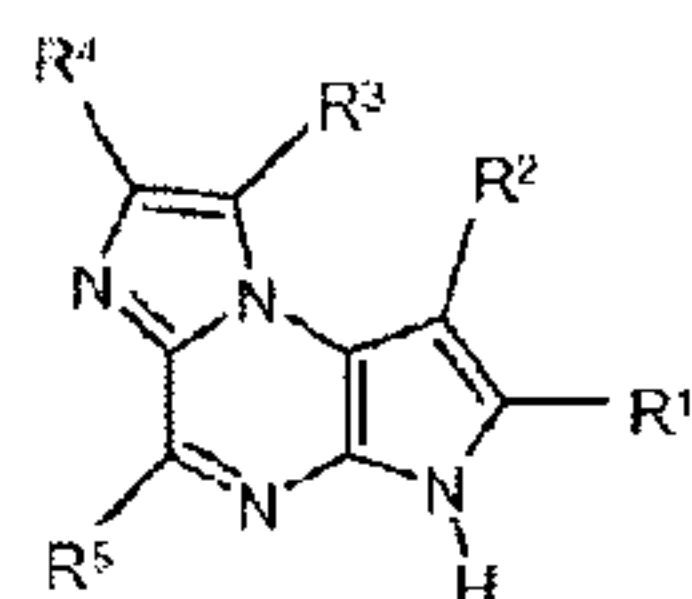
<5> The compound of <4>, wherein E is -R^e C(O)N(R^a)R^e-.

<6> The compound of any one of <1>-<5>, wherein D is a saturated heterocyclylene.

<7> The compound of <6>, wherein D is optionally substituted pyrrolidinylene.

<8> The compound of <7>, wherein D is ethyl-substituted pyrrolidinylene.

<9> A compound of formula I(c):

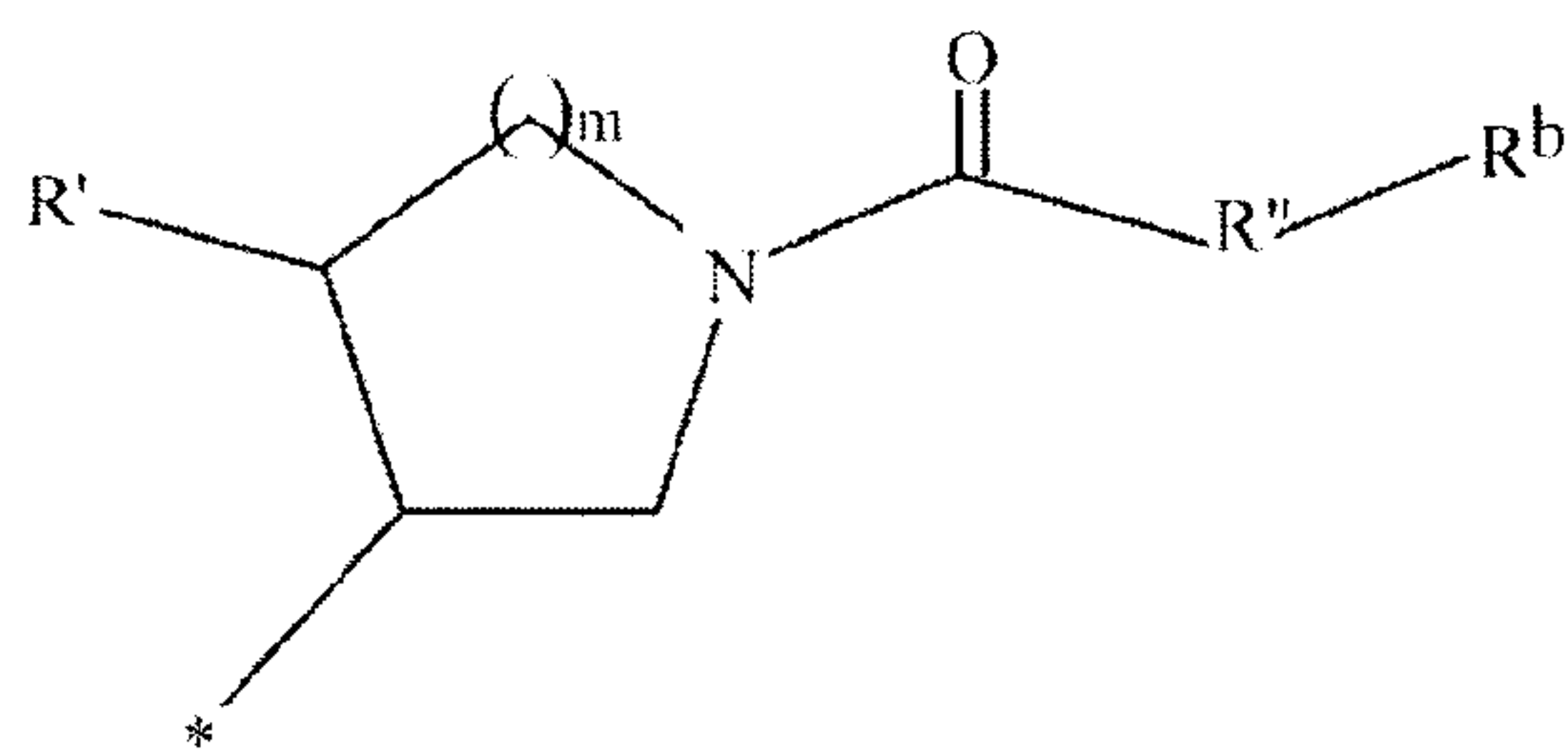


Formula I(c)

or a pharmaceutically-acceptable salt thereof, wherein:

R¹, R², R⁴ and R⁵ are each independently hydrogen; and

R³ is:



in which:

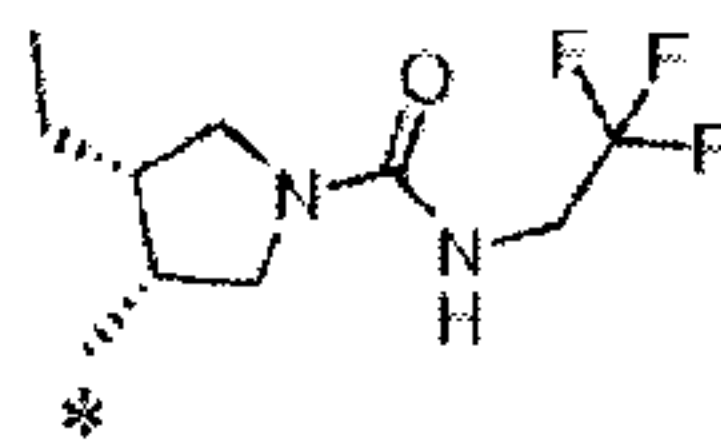
m is 0 or 1; R' is methyl or ethyl; R'' is a bond or -N(R^a)-; R^a is hydrogen, or (C₁-C₃)alkyl; and R^b is an optionally substituted (C₁-C₃)alkyl,

wherein a line marked with an asterisk represents a bond that links R³ to a tricyclic moiety of formula I(c).

<10> The compound of <9>, wherein R'' is -NH-.

<11>. The compound of <9>, wherein R^b is substituted by -CF₃.

<12> The compound of <1>, wherein R³ is



wherein a line marked with an asterisk represents a bond that links R³ to the tricyclic moiety of formula Ic.

<13> The compound of <1>, wherein:

D is methyl-substituted pyrrolidinylenc;

E is a bond;

G is -C(O)NH(R^b); and

R^b is an optionally substituted (C₁-C₁₀)alkyl;

wherein G is linked to the nitrogen atom of D, and R^b is substituted by -CF₃.

<14> The compound of <13>, wherein R^b is methyl and wherein R^b is substituted by -F, -Cl, -CN, or -CF₃.

<15> The compound of <1>, wherein:

D is ethyl-substituted pyrrolidine;

E is $-\text{C}(\text{O})\text{NHR}^e$;

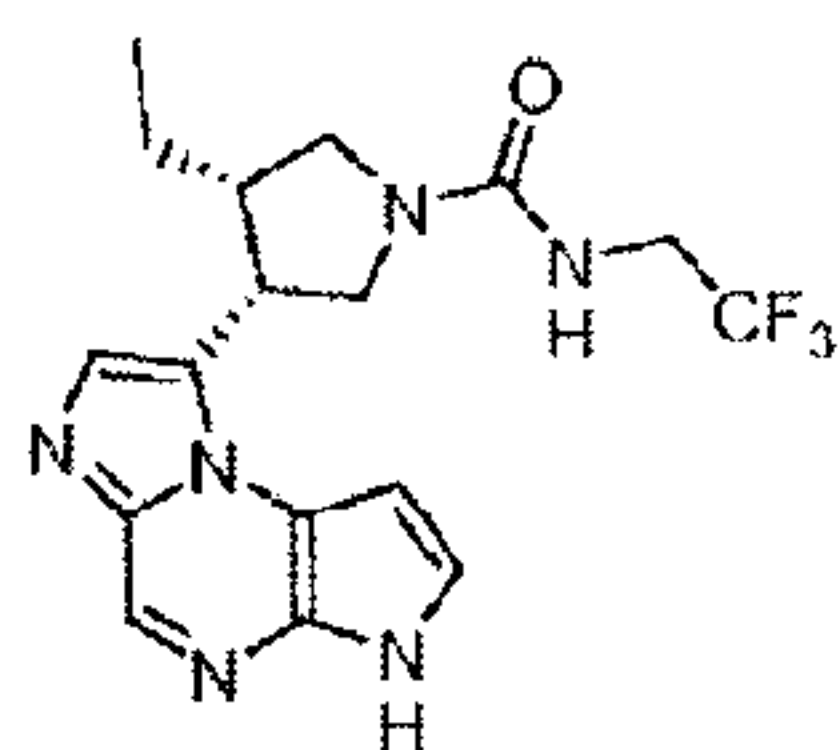
G is $-\text{CF}_3$; and

R^e is an optionally substituted (C_1 - C_{10})alkylene,

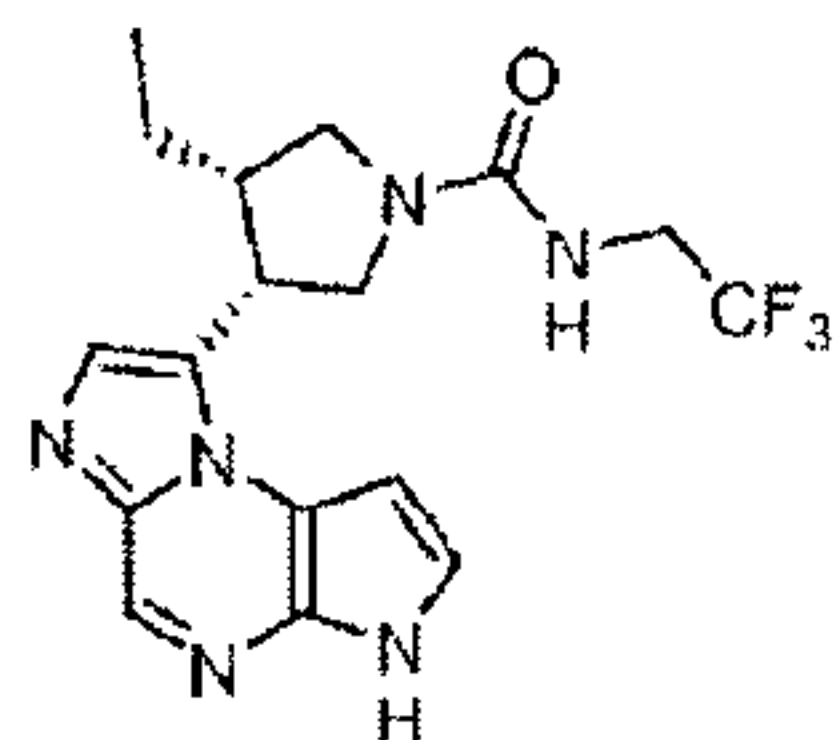
wherein E is linked to the nitrogen atom of D.

<16> The compound of <15>, wherein R^e is a methylene, ethylene, propylene, cyclopropylene, cyclobutylene, cyclopentylene, or phenylene.

<17> A compound represented by the following formula:



<18> A pharmaceutically acceptable salt of a compound represented by the following formula:



<19> A pharmaceutical composition comprising the compound of <17> or the pharmaceutically acceptable salt of the compound of <18>, and a pharmaceutically acceptable carrier or excipient.

DETAILED DESCRIPTION OF THE INVENTION

Protein kinases are a broad and diverse class, of over 500 enzymes, that include oncogenes, growth factors receptors, signal transduction intermediates, apoptosis related kinases and cyclin dependent kinases. They are responsible for the transfer of a phosphate group to specific tyrosine, serine or threonine amino acid residues, and are broadly classified as tyrosine and serine/threonine kinases as a result of their substrate specificity.

The Jak family kinases (Jak1, Jak2, Jak3 and Tyk2) are cytoplasmic tyrosine kinases that associate with membrane bound cytokine receptors. Cytokine binding to their receptor initiates Jak kinase activation via trans and autophosphorylation processes. The activated Jak kinases phosphorylate residues on the cytokine receptors creating phosphotyrosine binding sites for SH2 domain containing proteins such as Signal Transduction Activators of Transcript (STAT) factors and other signal regulators transduction such as suppressor of cytokine signaling (SOCS) proteins and SH2 domain-containing inositol 5'- phosphatases (SHIP). Activation of STAT factors via this process leads to their dimerization, nuclear translocation and new mRNA transcription resulting in expression of immunocyte proliferation and survival factors as well as additional cytokines, chemokines and molecules that facilitate cellular trafficking (see *Journal of Immunology*, 2007, 178, p. 2623). Jak kinases transduce signals for many different cytokine families and hence potentially play roles in diseases with widely different pathologies including but not limited to the following examples. Both Jak1 and Jak3 control signaling of the so-called common gamma chain cytokines (IL2, IL4, IL7, IL9, IL15 and IL21), hence simultaneous inhibition of either Jak1 or

Jak3 could be predicted to impact Th1 mediated diseases such as rheumatoid arthritis via blockade of IL2, IL7 and IL15 signaling. On the other hand, IL2 signaling has recently been shown to be essential for development and homeostasis of T-regulatory cells (Malek TR *et al.*, *Immunity*, **2002**, 17(2), p.167-78). Thus, based on genetic data, blockade of IL2 signaling alone is predicted to result in autoimmunity (Yamanouchi J *et al.*, *Nat Genet.*, **2007**, 39(3), p.329-37, and Willerford DM *et al.*, *Immunity*, **1995**, 3(4), p.521-30). Th2 mediated diseases such as asthma or atopic dermatitis via IL4 and IL9 signaling blockade. Jak1 and Tyk2 mediate signaling of IL13 (see *Int. Immunity*, 2000, 12, p. 1499). Hence, blockade of these may also be predicted to have a therapeutic effect in asthma. These two kinases are also thought to mediate Type I interferon signaling; their blockade could therefore be predicted to reduce the severity of systemic lupus erythematosus (SLE). Tyk2 and Jak2 mediate signaling of IL12 and IL23. In fact, blockade of these cytokines using monoclonal antibodies has been effective in treating psoriasis. Therefore blockade of this pathway using inhibitors of these kinases could be predicted to be effective in psoriasis as well. In summary, this invention describes small-molecule compounds that inhibit, regulate and/or modulate Jak family kinase activity that is pivotal to several mechanisms thought critical to the progression of autoimmune diseases including, but not limited to, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), Crohn's disease, psoriasis and asthma.

Several pathologically significant cytokines signal via Jak1 alone (Guschin D, *et al.*, *EMBO J.* 1995 Apr 3;14(7):1421-9; Parganas E, *et al.*, *Cell.* 1998 May 1;93(3):385-95; Rodig S.J., *et al.*, *Cell.* 1998 May 1; 93(3):373-83). Blockade of one of these, IL6, using an IL6R neutralizing antibody, has been shown to significantly improve disease scores in human rheumatoid arthritis patients (Nishimoto N. *et al.*, *Ann Rheum Dis.*, 2007, 66(9), p.1162-7). Similarly, blockade of GCSF signaling, which is also mediated by Jak1 alone, using neutralizing monoclonal antibodies or target gene deletion protects mice from experimental arthritis (Lawlor K.E. *et al.*, *Proc Natl Acad Sci U.S.A.*, 2004, 101(31), p.11398-403). Accordingly, the identification of small-molecule compounds that inhibit, regulate and/or modulate the signal transduction of kinases, such as Jak1, is a desirable means to prevent or treat autoimmune diseases or other diseases related to aberrant Jak1 function.

Jak2 is also activated in a wide variety of human cancers such as prostate, colon, ovarian and breast cancers, melanoma, leukemia and other haematopoietic malignancies. In addition, somatic point mutation of the Jak2 gene has been identified to be highly associated with classic myeloproliferative disorders (MPD) and infrequently in other myeloid disorders. Constitutive activation of Jak2 activity is also caused by chromosomal translocation in hematopoietic malignancies. It has also been shown that inhibition of the Jak/STAT pathway, and in particular inhibition of Jak2 activity, results in anti-proliferative and pro-apoptotic effects largely due to inhibition of phosphorylation of STAT. Furthermore, pharmacological modulation or inhibition

of Jak2 activity could effectively block tumor growth and induce apoptosis by reducing the STAT phosphorylation in cell culture and human tumor xenografts *in vivo*. Accordingly, the identification of small-molecule compounds that inhibit, regulate and/or modulate the signal transduction of kinases, particularly Jak2, is desirable as a means to treat or prevent diseases and conditions associated with cancers.

Jak kinases also transmit signals regulating essential physiological processes whose inhibition could be undesirable. For example Jak2 mediates the signaling of Erythropoietin (Epo) and Granulocyte/Monocyte-Colony Stimulating Factor (GM-CSF). Individuals with genetic, congenital or acquired defects in these signaling pathways can develop potentially life-threatening complications such as anemia and neutrophil dysfunction. Accordingly, one non-limiting aspect of this invention also relates to a method to identify compounds that may have a favorable safety profile as a result of them selectively avoiding inhibition of Jak2.

The protein kinase C family is a group of serine/threonine kinases that comprises twelve related isoenzymes. Its members are encoded by different genes and are sub-classified according to their requirements for activation. The classical enzymes (cPKC) require diacylglycerol (DAG), phosphatidylserine (PS) and calcium for activation. The novel PKC's (nPKC) require DAG and PS but are calcium independent. The atypical PKC's (aPKC) do not require calcium or DAG.

PKCtheta is a member of the nPKC sub-family (Baier, G., *et al.*, *J. Biol. Chem.*, 1993, 268, 4997). It has a restricted expression pattern, found predominantly in T cells and skeletal muscle (Mischak, H. *et al.*, *FEBS Lett.*, 1993, 326, p. 51), with some expression reported in mast cells (Liu, Y. *et al.*, *J. Leukoc. Biol.*, 2001, 69, p. 831) and endothelial cells (Mattila, P. *et al.*, *Life Sci.*, 1994, 55, p. 1253).

Upon T cell activation, a supramolecular activation complex (SMAC) forms at the site of contact between the T cell and the antigen presenting cell (APC). PKCtheta is the only PKC isoform found to localize at the SMAC (Monks, C. *et al.*, *Nature*, 1997, 385, 83), placing it in proximity with other signaling enzymes that mediate T cell activation processes.

In another study (Baier-Bitterlich, G. *et al.*, *Mol. Cell. Biol.*, 1996, 16, 842) the role of PKCtheta in the activation of AP-1, a transcription factor important in the activation of the IL-2 gene, was confirmed. In unstimulated T cells, constitutively active PKCtheta stimulated AP-1 activity while in cells with dominant negative PKCtheta, AP-1 activity was not induced upon activation by PMA.

Other studies showed that PKCtheta, via activation of I κ B kinase beta, mediates activation of NF- κ B induced by T cell receptor/CD28 co-stimulation (N. Coudronniere *et al.*, *Proc. Nat. Acad. Sci. U.S.A.*, 2000, 97, p. 3394; and Lin, X. *et al.*, *Mol. Cell. Biol.*, 2000, 20, p. 2933).

Proliferation of peripheral T cells from PKC θ knockout mice, in response to T cell receptor (TCR)/CD28 stimulation was greatly diminished compared to T cells from wild type mice. In addition, the amount of IL-2 released from the T cells was also greatly reduced (Sun, Z. *et al.*, *Nature*, 2000, 404, p. 402). It has also been shown that PKC θ -deficient mice show impaired pulmonary inflammation and airway hyperresponsiveness (AHR) in a Th2-dependent murine asthma model, with no defects in viral clearance and Th1-dependent cytotoxic T cell function (Berg-Brown, N.N. *et al.*, *J. Exp. Med.*, 2004, 199, p. 743; Marsland, B.J. *et al.*, *J. Exp. Med.*, 2004, 200, p. 181). The impaired Th2 cell response results in reduced levels of IL-4 and immunoglobulin E (IgE), contributing to the AHR and inflammatory pathophysiology. Otherwise, the PKC θ knockout mice seemed normal and fertile.

Evidence also exists that PKC θ participates in the IgE receptor (Fc ϵ RI)-mediated response of mast cells (Liu, Y. *et al.*, *J. Leukoc. Biol.*, 2001, 69, p. 831). In human-cultured mast cells (HCMC), it has been demonstrated that PKC kinase activity rapidly localizes to the membrane following Fc ϵ RI cross-linking (Kimata, M. *et al.*, *Biochem. Biophys. Res. Commun.*, 1999, 257(3), p. 895). A recent study examining *in vitro* activity of bone marrow mast cells (BMMC) derived from wild-type and PKC θ -deficient mice shows that upon Fc ϵ RI cross linking, BMMCs from PKC θ -deficient mice reduced levels of IL-6, tumor necrosis factor- α (TNF α) and IL-13 in comparison with BMMCs from wild-type mice, suggesting a potential role for PKC θ in mast cell cytokine production in addition to T cell activation (Ciarletta, A.B. *et al.*, poster presentation at the 2005 American Thoracic Society International Conference).

The studies cited above and others studies confirm the critical role of PKC θ in T cells activation and in mast cell (MC) signaling. Thus an inhibitor of PKC θ would be of therapeutic benefit in treating immunological disorders and other diseases mediated by the inappropriate activation of T cells and MC signaling.

Many of the kinases, whether a receptor or non-receptor tyrosine kinase or a S/T kinase have been found to be involved in cellular signaling pathways involved in numerous pathogenic conditions, including immunomodulation, inflammation, or proliferative disorders such as cancer.

Many autoimmune diseases and disease associated with chronic inflammation, as well as acute responses, have been linked to excessive or unregulated production or activity of one or more cytokines.

The compounds of the invention are also useful in the treatment of cardiovascular disorders, such as acute myocardial infarction, acute coronary syndrome, chronic heart failure, myocardial infarction, atherosclerosis, viral myocarditis, cardiac allograft rejection, and sepsis-associated cardiac dysfunction. Furthermore, the compounds of the present invention are also useful for the treatment of central nervous system disorders such as meningococcal meningitis, Alzheimer's disease and Parkinson's disease.

The compounds of the invention are also useful in the treatment of an ocular condition, a cancer, a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, hypersensitivity reactions, hyperkinetic movement disorders, hypersensitivity pneumonitis, hypertension, hypokinetic movement disorders, aortic and peripheral aneurysms, hypothalamic-pituitary-adrenal axis evaluation, aortic dissection, arterial hypertension, arteriosclerosis, arteriovenous fistula, ataxia, spinocerebellar degenerations, streptococcal myositis, structural lesions of the cerebellum, Subacute sclerosing panencephalitis, Syncope, syphilis of the cardiovascular system, systemic anaphalaxis, systemic inflammatory response syndrome, systemic onset juvenile rheumatoid arthritis, T-cell or FAB ALL, Telangiectasia, thromboangitis obliterans, transplants, trauma/hemorrhage, type III hypersensitivity reactions, type IV hypersensitivity, unstable angina, uremia, urosepsis, urticaria, valvular heart diseases, varicose veins, vasculitis, venous diseases, venous thrombosis, ventricular fibrillation, viral and fungal infections, viral encephalitis/aseptic meningitis, viral-associated hemaphagocytic syndrome, Wernicke-Korsakoff syndrome, Wilson's disease, xenograft rejection of any organ or tissue, heart transplant rejection, hemochromatosis, hemodialysis, hemolytic uremic syndrome/thrombolytic thrombocytopenic purpura, hemorrhage, idiopathic pulmonary fibrosis, antibody mediated cytotoxicity, Asthenia, infantile spinal muscular atrophy, inflammation of the aorta, influenza A, ionizing radiation exposure, iridocyclitis/uveitis/optic neuritis, juvenile spinal muscular atrophy, lymphoma, myeloma, leukaemia, malignant ascites, hematopoietic cancers, a diabetic condition such as insulin-dependent diabetes mellitus glaucoma, diabetic retinopathy or microangiopathy, sickle cell anaemia, chronic inflammation, glomerulonephritis, graft rejection, Lyme disease, von Hippel Lindau disease, pemphigoid, Paget's disease, fibrosis, sarcoidosis, cirrhosis, thyroiditis, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic occlusive pulmonary disease, asthma or edema following burns, trauma, radiation, stroke, hypoxia, ischemia, ovarian hyperstimulation syndrome, post perfusion syndrome, post pump syndrome, post-MI cardiomyopathy syndrome, preeclampsia, menometrorrhagia, endometriosis, pulmonary hypertension, infantile hemangioma, or infection by Herpes simplex, Herpes Zoster, human immunodeficiency virus, parapoxvirus, protozoa or toxoplasmosis, progressive supranuclear palsy, primary pulmonary hypertension, radiation therapy, Raynaud's phenomenon, Raynaud's disease, Refsum's disease, regular narrow QRS tachycardia, renovascular hypertension, restrictive cardiomyopathy, sarcoma, senile chorea, senile dementia of Lewy body type, shock, skin allograft, skin changes syndrome, ocular or macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser treatment complications, conjunctivitis, Stargardt's disease, Eales disease, retinopathy, macular degeneration, restenosis, ischemia/reperfusion injury, ischemic stroke, vascular occlusion, carotid obstructive disease, ulcerative colitis, inflammatory bowel disease, diabetes, diabetes mellitus, insulin dependent

diabetes mellitus, allergic diseases, dermatitis scleroderma, graft versus host disease, organ transplant rejection (including but not limited to bone marrow and solid organ rejection), acute or chronic immune disease associated with organ transplantation, sarcoidosis, disseminated intravascular coagulation, Kawasaki's disease, nephrotic syndrome, chronic fatigue syndrome, Wegener's granulomatosis, Henoch-Schoenlein purpura, microscopic vasculitis of the kidneys, chronic active hepatitis, septic shock, toxic shock syndrome, sepsis syndrome, cachexia, infectious diseases, parasitic diseases, acquired immunodeficiency syndrome, acute transverse myelitis, Huntington's chorea, stroke, primary biliary cirrhosis, hemolytic anemia, malignancies, Addison's disease, idiopathic Addison's disease, sporadic, polyglandular deficiency type I and polyglandular deficiency type II, Schmidt's syndrome, adult (acute) respiratory distress syndrome, alopecia, alopecia areata, seronegative arthropathy, arthropathy, Reiter's disease, psoriatic arthropathy, ulcerative colitic arthropathy, enteropathic synovitis, chlamydia, yersinia and salmonella associated arthropathy, atheromatous disease/arteriosclerosis, atopic allergy, autoimmune bullous disease, pemphigus vulgaris, pemphigus foliaceus, pemphigoid, linear IgA disease, autoimmune haemolytic anaemia, Coombs positive haemolytic anaemia, acquired pernicious anaemia, juvenile pernicious anaemia, peripheral vascular disorders, peritonitis, pernicious anemia, myalgic encephalitis/Royal Free Disease, chronic mucocutaneous candidiasis, giant cell arteritis, primary sclerosing hepatitis, cryptogenic autoimmune hepatitis, Acquired Immunodeficiency Disease Syndrome, Acquired Immunodeficiency Related Diseases, Hepatitis A, Hepatitis B, Hepatitis C, His bundle arrhythmias, HIV infection/HIV neuropathy, common varied immunodeficiency (common variable hypogammaglobulinaemia), dilated cardiomyopathy, female infertility, ovarian failure, premature ovarian failure, fibrotic lung disease, chronic wound healing, cryptogenic fibrosing alveolitis, post-inflammatory interstitial lung disease, interstitial pneumonitis, pneumocystis carinii pneumonia, pneumonia, connective tissue disease associated interstitial lung disease, mixed connective tissue disease, associated lung disease, systemic sclerosis associated interstitial lung disease, rheumatoid arthritis associated interstitial lung disease, systemic lupus erythematosus associated lung disease, dermatomyositis/polymyositis associated lung disease, Sjögren's disease associated lung disease, ankylosing spondylitis associated lung disease, vasculitic diffuse lung disease, haemosiderosis associated lung disease, drug-induced interstitial lung disease, radiation fibrosis, bronchiolitis obliterans, chronic eosinophilic pneumonia, lymphocytic infiltrative lung disease, postinfectious interstitial lung disease, gouty arthritis, autoimmune hepatitis, type-1 autoimmune hepatitis (classical autoimmune or lupoid hepatitis), type-2 autoimmune hepatitis (anti-LKM antibody hepatitis), autoimmune mediated hypoglycaemia, type B insulin resistance with acanthosis nigricans, hypoparathyroidism, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, osteoarthritis, primary sclerosing cholangitis, psoriasis type 1, psoriasis type 2, idiopathic leucopaenia, autoimmune neutropaenia,

renal disease NOS, glomerulonephritides, microscopic vasculitis of the kidneys, Lyme disease, discoid lupus erythematosus, male infertility idiopathic or NOS, sperm autoimmunity, multiple sclerosis (all subtypes), sympathetic ophthalmia, pulmonary hypertension secondary to connective tissue disease, acute and chronic pain (different forms of pain), Goodpasture's syndrome, pulmonary manifestation of polyarteritis nodosa, acute rheumatic fever, rheumatoid spondylitis, Still's disease, systemic sclerosis, Sjögren's syndrome, Takayasu's disease/arteritis, autoimmune thrombocytopaenia, toxicity, transplants, and diseases involving inappropriate vascularization for example diabetic retinopathy, retinopathy of prematurity, choroidal neovascularization due to age-related macular degeneration, and infantile hemangiomas in human beings. In addition, such compounds may be useful in the treatment of disorders such as ascites, effusions, and exudates, including for example macular edema, cerebral edema, acute lung injury, adult respiratory distress syndrome (ARDS), proliferative disorders such as restenosis, fibrotic disorders such as hepatic cirrhosis and atherosclerosis, mesangial cell proliferative disorders such as diabetic nephropathy, malignant nephrosclerosis, thrombotic microangiopathy syndromes, and glomerulopathies, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, ischemia/reperfusion injury, peptic ulcer Helicobacter related diseases, virally-induced angiogenic disorders, preeclampsia, menometrorrhagia, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy, retinopathy of prematurity, or age-related macular degeneration. In addition, these compounds can be used as active agents against hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome) and polycystic kidney disease since such diseases require a proliferation of blood vessel cells for growth and/or metastasis.

Compounds of Formula (I) or Formula (II) of the invention can be used alone or in combination with an additional agent, e.g., a therapeutic agent, said additional agent being selected by the skilled artisan for its intended purpose. For example, the additional agent can be a therapeutic agent art-recognized as being useful to treat the disease or condition being treated by the compound of the present invention. The additional agent also can be an agent that imparts a beneficial attribute to the therapeutic composition e.g., an agent that affects the viscosity of the composition.

It should further be understood that the combinations which are to be included within this invention are those combinations useful for their intended purpose. The agents set forth below are illustrative for purposes and not intended to be limited. The combinations, which are part of this invention, can be the compounds of the present invention and at least one additional agent selected from the lists below. The combination can also include more than one additional agent, e.g., two or three additional agents if the combination is such that the formed composition can perform its intended function.

Preferred combinations are non-steroidal anti-inflammatory drug(s) also referred to as NSAIDS which include drugs like ibuprofen. Other preferred combinations are corticosteroids including prednisolone; the well known side-effects of steroid use can be reduced or even eliminated by tapering the steroid dose required when treating patients in combination with the compounds of this invention. Non-limiting examples of therapeutic agents for rheumatoid arthritis with which a compound of Formula (I) or Formula (II) of the invention can be combined include the following: cytokine suppressive anti-inflammatory drug(s) (CSAIDs); antibodies to or antagonists of other human cytokines or growth factors, for example, TNF, LT, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-12, IL-15, IL-16, IL-21, IL-23, interferons, EMAP-II, GM-CSF, FGF, and PDGF. Compounds of the invention can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD80 (B7.1), CD86 (B7.2), CD90, CTLA or their ligands including CD154 (gp39 or CD40L).

Preferred combinations of therapeutic agents may interfere at different points in the autoimmune and subsequent inflammatory cascade; preferred examples include TNF antagonists like chimeric, humanized or human TNF antibodies, D2E7 (U.S. Patent 6,090,382, HUMIRATM), CA2 (REMICADETM), SIMPONITM (golimumab), CIMZIATM, ACTEMRATM, CDP 571, and soluble p55 or p75 TNF receptors, derivatives, thereof, (p75TNFR1gG (ENBRELTM) or p55TNFR1gG (Lenercept), and also TNF α converting enzyme (TACE) inhibitors; similarly IL-1 inhibitors (Interleukin-1-converting enzyme inhibitors, IL-1RA etc.) may be effective for the same reason. Other preferred combinations include Interleukin 11. Yet other preferred combinations are the other key players of the autoimmune response which may act parallel to, dependent on or in concert with IL-18 function; especially preferred are IL-12 antagonists including IL-12 antibodies or soluble IL-12 receptors, or IL-12 binding proteins. It has been shown that IL-12 and IL-18 have overlapping but distinct functions and a combination of antagonists to both may be most effective. Yet another preferred combination is non-depleting anti-CD4 inhibitors. Yet other preferred combinations include antagonists of the co-stimulatory pathway CD80 (B7.1) or CD86 (B7.2) including antibodies, soluble receptors or antagonistic ligands.

A compound of Formula (I) or Formula (II) of the invention may also be combined with agents, such as methotrexate, 6-mercaptopurine, azathioprine sulphasalazine, mesalazine, olsalazine chloroquine/ hydroxychloroquine, pencillamine, aurothiomalate (intramuscular and oral), azathioprine, cochlincine, corticosteroids (oral, inhaled and local injection), beta-2 adrenoreceptor agonists (salbutamol, terbutaline, salmeteral), xanthines (theophylline, aminophylline), cromoglycate, nedocromil, ketotifen, ipratropium and oxitropium, cyclosporin, FK506, rapamycin, mycophenolate mofetil, leflunomide, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with

signalling by proinflammatory cytokines such as $\text{TNF}\alpha$ or IL-1 (e.g., NIK, IKK, p38 or MAP kinase inhibitors), IL-1 β converting enzyme inhibitors, T-cell signalling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof (e.g. soluble p55 or p75 TNF receptors and the derivatives p75TNFRlgG (EnbrelTM) and p55TNFRlgG (Lenercept), sIL-1RI, sIL-1RII, sIL-6R), antiinflammatory cytokines (e.g. IL-4, IL-10, IL-11, IL-13 and TGF β), celecoxib, folic acid, hydroxychloroquine sulfate, rofecoxib, etanercept, infliximab, naproxen, valdecoxib, sulfasalazine, methylprednisolone, meloxicam, methylprednisolone acetate, gold sodium thiomalate, aspirin, triamcinolone acetonide, propoxyphene napsylate/apap, folate, nabumetone, diclofenac, piroxicam, etodolac, diclofenac sodium, oxaprozin, oxycodone HCl, hydrocodone bitartrate/apap, diclofenac sodium/misoprostol, fentanyl, anakinra, tramadol HCl, salsalate, sulindac, cyanocobalamin/fa/pyridoxine, acetaminophen, alendronate sodium, prednisolone, morphine sulfate, lidocaine hydrochloride, indomethacin, glucosamine sulf/chondroitin, amitriptyline HCl, sulfadiazine, oxycodone HCl/acetaminophen, olopatadine HCl misoprostol, naproxen sodium, omeprazole, cyclophosphamide, rituximab, IL-1 TRAP, MRA, CTLA4-IG, IL-18 BP, anti-IL-12, Anti-IL15, BIRB-796, SCIO-469, VX-702, AMG-548, VX-740, Roflumilast, IC-485, CDC-801, S1P1 agonists (such as FTY720), PKC family inhibitors (such as Ruboxistaurin or AEB-071) and Mesopram. Preferred combinations include methotrexate or leflunomide and in moderate or severe rheumatoid arthritis cases, cyclosporine and anti-TNF antibodies as noted above.

Non-limiting examples of therapeutic agents for inflammatory bowel disease with which a compound of Formula (I) or Formula (II) of the invention can be combined include the following: budenoside; epidermal growth factor; corticosteroids; cyclosporin, sulfasalazine; aminosalicylates; 6-mercaptopurine; azathioprine; metronidazole; lipoxygenase inhibitors; mesalamine; olsalazine; balsalazide; antioxidants; thromboxane inhibitors; IL-1 receptor antagonists; anti-IL-1 β monoclonal antibodies; anti-IL-6 monoclonal antibodies; growth factors; elastase inhibitors; pyridinyl-imidazole compounds; antibodies to or antagonists of other human cytokines or growth factors, for example, TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-15, IL-16, IL-23, EMAP-II, GM-CSF, FGF, and PDGF; cell surface molecules such as CD2, CD3, CD4, CD8, CD25, CD28, CD30, CD40, CD45, CD69, CD90 or their ligands; methotrexate; cyclosporine; FK506; rapamycin; mycophenolate mofetil; leflunomide; NSAIDs, for example, ibuprofen; corticosteroids such as prednisolone; phosphodiesterase inhibitors; adenosine agonists; antithrombotic agents; complement inhibitors; adrenergic agents; agents which interfere with signalling by proinflammatory cytokines such as $\text{TNF}\alpha$ or IL-1 (e.g. NIK, IKK, or MAP kinase inhibitors); IL-1 β converting enzyme inhibitors; $\text{TNF}\alpha$ converting enzyme inhibitors; T-cell signalling inhibitors such as kinase inhibitors; metalloproteinase inhibitors; sulfasalazine;

azathioprine; 6-mercaptopurines; angiotensin converting enzyme inhibitors; soluble cytokine receptors and derivatives thereof (e.g. soluble p55 or p75 TNF receptors, sIL-1RI, sIL-1RII, sIL-6R) and antiinflammatory cytokines (e.g. IL-4, IL-10, IL-11, IL-13 and TGF β). Preferred examples of therapeutic agents for Crohn's disease with which a compound of Formula (I) or Formula (II) can be combined include the following: TNF antagonists, for example, anti-TNF antibodies, D2E7 (U.S. Patent 6,090,382, HUMIRATM), CA2 (REMICADETM), CDP 571, TNFR-Ig constructs, (p75TNFRIgG (ENBRELETM) and p55TNFRIgG (LENERCEPTTM) inhibitors and PDE4 inhibitors. A compound of Formula (I) or Formula (II) can be combined with corticosteroids, for example, budenoside and dexamethasone; sulfasalazine, 5-aminosalicylic acid; olsalazine; and agents which interfere with synthesis or action of proinflammatory cytokines such as IL-1, for example, IL-1 β converting enzyme inhibitors and IL-1ra; T cell signaling inhibitors, for example, tyrosine kinase inhibitors; 6-mercaptopurine; IL-11; mesalamine; prednisone; azathioprine; mercaptopurine; infliximab; methylprednisolone sodium succinate; diphenoxylate/atrop sulfate; loperamide hydrochloride; methotrexate; omeprazole; folate; ciprofloxacin/dextrose-water; hydrocodone bitartrate/apap; tetracycline hydrochloride; fluocinonide; metronidazole; thimerosal/boric acid; cholestyramine/sucrose; ciprofloxacin hydrochloride; hyoscyamine sulfate; meperidine hydrochloride; midazolam hydrochloride; oxycodone HCl/acetaminophen; promethazine hydrochloride; sodium phosphate; sulfamethoxazole/trimethoprim; celecoxib; polycarbophil; propoxyphene napsylate; hydrocortisone; multivitamins; balsalazide disodium; codeine phosphate/apap; colesevelam HCl; cyanocobalamin; folic acid; levofloxacin; methylprednisolone; natalizumab and interferon-gamma.

Non-limiting examples of therapeutic agents for multiple sclerosis with which a compound of Formula (I) or Formula (II) can be combined include the following: corticosteroids; prednisolone; methylprednisolone; azathioprine; cyclophosphamide; cyclosporine; methotrexate; 4-aminopyridine; tizanidine; interferon- β 1a (AVONEX®; Biogen); interferon- β 1b (BETASERON®; Chiron/Berlex); interferon α -n3 (Interferon Sciences/Fujimoto), interferon- α (Alfa Wassermann/J&J), interferon β 1A-IF (Serono/Inhale Therapeutics), Peginterferon α 2b (Enzon/Schering-Plough), Copolymer 1 (Cop-1; COPAXONE®; Teva Pharmaceutical Industries, Inc.); hyperbaric oxygen; intravenous immunoglobulin; cladribine; antibodies to or antagonists of other human cytokines or growth factors and their receptors, for example, TNF, LT, IL-1, IL-2, IL-6, IL-7, IL-8, IL-12, IL-23, IL-15, IL-16, EMAP-II, GM-CSF, FGF, and PDGF. A compound of Formula (I) or Formula (II) can be combined with antibodies to cell surface molecules such as CD2, CD3, CD4, CD8, CD19, CD20, CD25, CD28, CD30, CD40, CD45, CD69, CD80, CD86, CD90 or their ligands. A compound of Formula (I) or Formula (II) may also be combined with agents such as methotrexate, cyclosporine, FK506, rapamycin, mycophenolate mofetil,

leflunomide, an S1P1 agonist, NSAIDs, for example, ibuprofen, corticosteroids such as prednisolone, phosphodiesterase inhibitors, adenosine agonists, antithrombotic agents, complement inhibitors, adrenergic agents, agents which interfere with signalling by proinflammatory cytokines such as TNF α or IL-1 (e.g., NIK, IKK, p38 or MAP kinase inhibitors), IL-1 β converting enzyme inhibitors, TACE inhibitors, T-cell signaling inhibitors such as kinase inhibitors, metalloproteinase inhibitors, sulfasalazine, azathioprine, 6-mercaptopurines, angiotensin converting enzyme inhibitors, soluble cytokine receptors and derivatives thereof (e.g. soluble p55 or p75 TNF receptors, sIL-1RI, sIL-1RII, sIL-6R) and antiinflammatory cytokines (e.g. IL-4, IL-10, IL-13 and TGF β).

Preferred examples of therapeutic agents for multiple sclerosis in which a compound of Formula (I) or Formula (II) can be combined to include interferon- β , for example, IFN β 1a and IFN β 1b; copaxone, corticosteroids, caspase inhibitors, for example inhibitors of caspase-1, IL-1 inhibitors, TNF inhibitors, and antibodies to CD40 ligand and CD80.

A compound of Formula (I) or Formula (II) may also be combined with agents, such as alemtuzumab, dronabinol, daclizumab, mitoxantrone, xaliproden hydrochloride, fampridine, glatiramer acetate, natalizumab, sinnabidol, α -immunokine NNSO3, ABR-215062, Anergix.MS, chemokine receptor antagonists, BBR-2778, calagualine, CPI-1189, LEM (liposome encapsulated mitoxantrone), THC.CBD (cannabinoid agonist), MBP-8298, mesopram (PDE4 inhibitor), MNA-715, anti-IL-6 receptor antibody, neurovax, pirfenidone allopurinol 1258 (RDP-1258), sTNF-R1, talampanel, teriflunomide, TGF-beta2, tiplimotide, VLA-4 antagonists (for example, TR-14035, VLA4 Ultrahaler, Antegran-ELAN/Biogen), interferon gamma antagonists and IL-4 agonists.

Non-limiting examples of therapeutic agents for ankylosing spondylitis with which a compound of Formula (I) or Formula (II) can be combined include the following: ibuprofen, diclofenac, misoprostol, naproxen, meloxicam, indomethacin, diclofenac, celecoxib, rofecoxib, sulfasalazine, methotrexate, azathioprine, minocyclin, prednisone, and anti-TNF antibodies, D2E7 (U.S. Patent 6,090,382; HUMIRATM), CA2 (REMICADETM), CDP 571, TNFR-Ig constructs, (p75TNFR-IgG (ENBRELTM) and p55TNFR-IgG (LENERCEPTTM).

Non-limiting examples of therapeutic agents for asthma with which a compound of Formula (I) or Formula (II) can be combined include the following: albuterol, salmeterol/fluticasone, montelukast sodium, fluticasone propionate, budesonide, prednisone, salmeterol xinafoate, levalbuterol HCl, albuterol sulfate/ipratropium, prednisolone sodium phosphate, triamcinolone acetonide, beclomethasone dipropionate, ipratropium bromide, azithromycin, pirbuterol acetate, prednisolone, theophylline anhydrous, methylprednisolone sodium succinate, clarithromycin, zafirlukast, formoterol fumarate, influenza virus vaccine, amoxicillin trihydrate, flunisolide, allergy injection, cromolyn sodium, fexofenadine hydrochloride, flunisolide/menthol, amoxicillin/clavulanate, levofloxacin, inhaler assist device,

guaifenesin, dexamethasone sodium phosphate, moxifloxacin HCl, doxycycline hyclate, guaifenesin/d-methorphan, p-ephedrine/cod/chlorphenir, gatifloxacin, cetirizine hydrochloride, mometasone furoate, salmeterol xinafoate, benzonatate, cephalexin, pe/hydrocodone/chlorphenir, cetirizine HCl/pseudoephed, phenylephrine/cod/promethazine, codeine/promethazine, cefprozil, dexamethasone, guaifenesin/pseudoephedrine, chlorpheniramine/hydrocodone, nedocromil sodium, terbutaline sulfate, epinephrine, methylprednisolone, anti-IL-13 antibody, and metaproterenol sulfate.

Non-limiting examples of therapeutic agents for COPD with which a compound of Formula (I) or Formula (II) can be combined include the following: albuterol sulfate/ipratropium, ipratropium bromide, salmeterol/fluticasone, albuterol, salmeterol xinafoate, fluticasone propionate, prednisone, theophylline anhydrous, methylprednisolone sodium succinate, montelukast sodium, budesonide, formoterol fumarate, triamcinolone acetonide, levofloxacin, guaifenesin, azithromycin, beclomethasone dipropionate, levalbuterol HCl, flunisolide, ceftriaxone sodium, amoxicillin trihydrate, gatifloxacin, zafirlukast, amoxicillin/clavulanate, flunisolide/menthol, chlorpheniramine/hydrocodone, metaproterenol sulfate, methylprednisolone, mometasone furoate, p-ephedrine/cod/chlorphenir, pirbuterol acetate, p-ephedrine/loratadine, terbutaline sulfate, tiotropium bromide, (R,R)-formoterol, TgAAT, cilomilast and roflumilast.

Non-limiting examples of therapeutic agents for HCV with which a compound of Formula (I) or Formula (II) can be combined include the following: Interferon- α -2 α , Interferon- α -2 β , Interferon- α con1, Interferon- α -n1, pegylated interferon- α -2 α , pegylated interferon- α -2 β , ribavirin, peginterferon α -2b + ribavirin, ursodeoxycholic acid, glycyrrhizic acid, thymalfasin, Maxamine, VX-497 and any compounds that are used to treat HCV through intervention with the following targets: HCV polymerase, HCV protease, HCV helicase, and HCV IRES (internal ribosome entry site).

Non-limiting examples of therapeutic agents for Idiopathic Pulmonary Fibrosis with which a compound of Formula (I) or Formula (II) can be combined include the following: prednisone, azathioprine, albuterol, colchicine, albuterol sulfate, digoxin, gamma interferon, methylprednisolone sodium succinate, lorazepam, furosemide, lisinopril, nitroglycerin, spironolactone, cyclophosphamide, ipratropium bromide, actinomycin d, alteplase, fluticasone propionate, levofloxacin, metaproterenol sulfate, morphine sulfate, oxycodone HCl, potassium chloride, triamcinolone acetonide, tacrolimus anhydrous, calcium, interferon- α , methotrexate, mycophenolate mofetil and interferon- γ -1 β .

Non-limiting examples of therapeutic agents for myocardial infarction with which a compound of Formula (I) or Formula (II) can be combined include the following: aspirin, nitroglycerin, metoprolol tartrate, enoxaparin sodium, heparin sodium, clopidogrel bisulfate, carvedilol, atenolol, morphine sulfate, metoprolol succinate, warfarin sodium, lisinopril,

isosorbide mononitrate, digoxin, furosemide, simvastatin, ramipril, tenecteplase, enalapril maleate, torsemide, retavase, losartan potassium, quinapril hydrochloride/magnesium carbonate, bumetanide, alteplase, enalaprilat, amiodarone hydrochloride, tirofiban HCl m-hydrate, diltiazem hydrochloride, captopril, irbesartan, valsartan, propranolol hydrochloride, fosinopril sodium, lidocaine hydrochloride, eptifibatide, cefazolin sodium, atropine sulfate, aminocaproic acid, spironolactone, interferon, sotalol hydrochloride, potassium chloride, docusate sodium, dobutamine HCl, alprazolam, pravastatin sodium, atorvastatin calcium, midazolam hydrochloride, meperidine hydrochloride, isosorbide dinitrate, epinephrine, dopamine hydrochloride, bivalirudin, rosuvastatin, ezetimibe/simvastatin, avasimibe, and cariporide.

Non-limiting examples of therapeutic agents for psoriasis with which a compound of Formula (I) or Formula (II) can be combined include the following: calcipotriene, clobetasol propionate, triamcinolone acetonide, halobetasol propionate, tazarotene, methotrexate, fluocinonide, betamethasone diprop augmented, fluocinolone acetonide, acitretin, tar shampoo, betamethasone valerate, mometasone furoate, ketoconazole, pramoxine/fluocinolone, hydrocortisone valerate, flurandrenolide, urca, betamethasone, clobetasol propionate/emoll, fluticasone propionate, azithromycin, hydrocortisone, moisturizing formula, folic acid, desonide, pimecrolimus, coal tar, diflorasone diacetate, etanercept folate, lactic acid, methoxsalen, hc/bismuth subgal/znox/resor, methylprednisolone acetate, prednisone, sunscreen, halcinonide, salicylic acid, anthralin, clocortolone pivalate, coal extract, coal tar/salicylic acid, coal tar/salicylic acid/sulfur, desoximetasone, diazepam, emollient, fluocinonide/emollient, mineral oil/castor oil/na lact, mineral oil/peanut oil, petroleum/isopropyl myristate, psoralen, salicylic acid, soap/tribromsalan, thimerosal/boric acid, celecoxib, infliximab, cyclosporine, alefacept, efalizumab, tacrolimus, pimecrolimus, PUVA, UVB, sulfasalazine, ABT-874 and ustekinumab.

Non-limiting examples of therapeutic agents for psoriatic arthritis with which a compound of Formula (I) or Formula (II) can be combined include the following: methotrexate, etanercept, rofecoxib, celecoxib, folic acid, sulfasalazine, naproxen, leflunomide, methylprednisolone acetate, indomethacin, hydroxychloroquine sulfate, prednisone, sulindac, betamethasone diprop augmented, infliximab, methotrexate, folate, triamcinolone acetonide, diclofenac, dimethylsulfoxide, piroxicam, diclofenac sodium, ketoprofen, meloxicam, methylprednisolone, nabumetone, tolmetin sodium, calcipotriene, cyclosporine, diclofenac sodium/misoprostol, fluocinonide, glucosamine sulfate, gold sodium thiomalate, hydrocodone bitartrate/apap, ibuprofen, risedronate sodium, sulfadiazine, thioguanine, valdecoxib, alefacept, D2E7 (U.S. Patent 6,090,382, HUMIRATM), and efalizumab.

Non-limiting examples of therapeutic agents for restenosis with which a compound of Formula (I) or Formula (II) can be combined include the following: sirolimus, paclitaxel, everolimus, tacrolimus, ABT-578, and acetaminophen.

Non-limiting examples of therapeutic agents for sciatica with which a compound of Formula (I) or Formula (II) can be combined include the following: hydrocodone bitartrate/apap, rofecoxib, cyclobenzaprine HCl, methylprednisolone, naproxen, ibuprofen, oxycodone HCl/acetaminophen, celecoxib, valdecoxib, methylprednisolone acetate, prednisone, codeine phosphate/apap, tramadol hcl/acetaminophen, metaxalone, meloxicam, methocarbamol, lidocaine hydrochloride, diclofenac sodium, gabapentin, dexamethasone, carisoprodol, ketorolac tromethamine, indomethacin, acetaminophen, diazepam, nabumetone, oxycodone HCl, tizanidine HCl, diclofenac sodium/misoprostol, propoxyphene n-pap, asa/oxycod/oxycodone ter, ibuprofen/hydrocodone bit, tramadol HCl, etodolac, propoxyphene HCl, amitriptyline HCl, carisoprodol/codeine phos/asa, morphine sulfate, multivitamins, naproxen sodium, orphenadrine citrate, and temazepam.

Preferred examples of therapeutic agents for SLE (Lupus) with which a compound of Formula (I) or Formula (II) can be combined include the following: NSAIDS, for example, diclofenac, naproxen, ibuprofen, piroxicam, indomethacin; COX2 inhibitors, for example, celecoxib, rofecoxib, valdecoxib; anti-malarials, for example, hydroxychloroquine; steroids, for example, prednisone, prednisolone, budenoside, dexamethasone; cytotoxics, for example, azathioprine, cyclophosphamide, mycophenolate mofetil, methotrexate; inhibitors of PDE4 or purine synthesis inhibitor, for example Cellcept®. A compound of Formula (I) or Formula (II) may also be combined with agents such as sulfasalazine, 5-aminosalicylic acid, olsalazine, Imuran® and agents which interfere with synthesis, production or action of proinflammatory cytokines such as IL-1, for example, caspase inhibitors like IL-1 β converting enzyme inhibitors and IL-1ra. A compound of Formula (I) or Formula (II) may also be used with T cell signaling inhibitors, for example, tyrosine kinase inhibitors; or molecules that target T cell activation molecules, for example, CTLA-4-IgG or anti-B7 family antibodies, anti-PD-1 family antibodies. A compound of Formula (I) or Formula (II) can be combined with IL-11 or anti-cytokine antibodies, for example, fonotolizumab (anti-IFN γ antibody), or anti-receptor antibodies, for example, anti-IL-6 receptor antibody and antibodies to B-cell surface molecules. A compound of Formula (I) or Formula (II) may also be used with LJP 394 (abetimus), agents that deplete or inactivate B-cells, for example, Rituximab (anti-CD20 antibody), lymphostat-B (anti-BlyS antibody), TNF antagonists, for example, anti-TNF antibodies, D2E7 (U.S. Patent 6,090,382; HUMIRA™), CA2 (REMICADE™), CDP 571, TNFR-Ig constructs, (p75TNFR-IgG (ENBREL™) and p55TNFR-IgG (LENERCEPT™).

In this invention, the following definitions are applicable:

A “therapeutically effective amount” is an amount of a compound of Formula (I) or Formula (II) or a combination of two or more such compounds, which inhibits, totally or partially, the progression of the condition or alleviates, at least partially, one or more symptoms of the condition. A therapeutically effective amount can also be an amount which is prophylactically

effective. The amount which is therapeutically effective will depend upon the patient's size and gender, the condition to be treated, the severity of the condition and the result sought. For a given patient, a therapeutically effective amount can be determined by methods known to those of skill in the art.

"Pharmaceutically acceptable salts" refers to those salts which retain the biological effectiveness and properties of the free bases and which are obtained by reaction with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid or organic acids such as sulfonic acid, carboxylic acid, organic phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, citric acid, fumaric acid, maleic acid, succinic acid, benzoic acid, salicylic acid, lactic acid, tartaric acid (e.g. (+) or (-)-tartaric acid or mixtures thereof), amino acids (e.g. (+) or (-)-amino acids or mixtures thereof), and the like. These salts can be prepared by methods known to those skilled in the art.

Certain compounds of Formula (I) or Formula (II) which have acidic substituents may exist as salts with pharmaceutically acceptable bases. The present invention includes such salts. Examples of such salts include sodium salts, potassium salts, lysine salts and arginine salts. These salts may be prepared by methods known to those skilled in the art.

Certain compounds of Formula (I) or Formula (II) and their salts may exist in more than one crystal form and the present invention includes each crystal form and mixtures thereof.

Certain compounds of Formula (I) or Formula (II) and their salts may also exist in the form of solvates, for example hydrates, and the present invention includes each solvate and mixtures thereof.

Certain compounds of Formula (I) or Formula (II) may contain one or more chiral centers, and exist in different optically active forms. When compounds of Formula (I) or Formula (II) contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures. The enantiomers may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of Formula (I) or Formula (II) contains more than one chiral center, it may exist in diastereoisomeric forms. The diastereoisomeric compounds may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers may be separated as described above. The present invention includes each diastereoisomer of compounds of Formula (I) or Formula (II), and mixtures thereof.

Certain compounds of Formula (I) or Formula (II) may exist in different tautomeric forms or as different geometric isomers, and the present invention includes each tautomer and/or geometric isomer of compounds of Formula (I) or Formula (II) and mixtures thereof.

Certain compounds of Formula (I) or Formula (II) may exist in different stable conformational forms which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of Formula (I) or Formula (II) and mixtures thereof.

Certain compounds of Formula (I) or Formula (II) may exist in zwitterionic form and the present invention includes each zwitterionic form of compounds of Formula (I) or Formula (II) and mixtures thereof.

As used herein the term "pro-drug" refers to an agent which is converted into the parent drug *in vivo* by some physiological chemical process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form). Pro-drugs are often useful because, in some situations, they may be easier to administer than the parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The pro-drug may also have improved solubility in pharmacological compositions over the parent drug. An example, without limitation, of a pro-drug would be a compound of the present invention wherein it is administered as an ester (the "pro-drug") to facilitate transmittal across a cell membrane where water solubility is not beneficial, but then it is metabolically hydrolyzed to the carboxylic acid once inside the cell where water solubility is beneficial.

Pro-drugs have many useful properties. For example, a pro-drug may be more water soluble than the ultimate drug, thereby facilitating intravenous administration of the drug. A pro-drug may also have a higher level of oral bioavailability than the ultimate drug. After administration, the prodrug is enzymatically or chemically cleaved to deliver the ultimate drug in the blood or tissue.

Exemplary pro-drugs upon cleavage release the corresponding free acid, and such hydrolyzable ester-forming residues of the compounds of this invention include but are not limited to carboxylic acid substituents wherein the free hydrogen is replaced by (C₁-C₄)alkyl, (C₁-C₁₂)alkanoyloxymethyl, (C₄-C₉)1-(alkanoyloxy)ethyl, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl

having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C₁-C₂)alkylamino(C₂-C₃)alkyl (such as β -dimethylaminoethyl), carbamoyl-(C₁-C₂)alkyl, N,N-di(C₁-C₂)-alkylcarbamoyl-(C₁-C₂)alkyl and piperidino-, pyrrolidino- or morpholino(C₂-C₃)alkyl.

Other exemplary pro-drugs release an alcohol of Formula (I) or Formula (II) wherein the free hydrogen of the hydroxyl substituent (e.g., R group contains hydroxyl) is replaced by (C₁-C₆)alkanoyloxymethyl, 1-((C₁-C₆)alkanoyloxy)ethyl, 1-methyl-1-((C₁-C₆)alkanoyloxy)ethyl, (C₁-C₁₂)alkoxycarbonyloxymethyl, N-(C₁-C₆)alkoxycarbonylamino-methyl, succinoyl, (C₁-C₆)alkanoyl, α -amino(C₁-C₄)alkanoyl, arylactyl and α -aminoacyl, or α -aminoacyl- α -aminoacyl wherein said α -aminoacyl moieties are independently any of the naturally occurring L-amino acids found in proteins, P(O)(OH)₂, -P(O)(O(C₁-C₆)alkyl)₂ or glycosyl (the radical resulting from detachment of the hydroxyl of the hemiacetal of a carbohydrate).

As used herein, the term "bridged (C₅-C₁₂) cycloalkyl group" means a saturated or unsaturated, bicyclic or polycyclic bridged hydrocarbon group having two or three C₃-C₁₀ cycloalkyl rings. Non bridged cycloalkyls are excluded. Bridged cyclic hydrocarbon may include, such as bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[4.3.1]decyl, bicyclo[3.3.1]nonyl, bornyl, bornenyl, norbornyl, norbornenyl, 6,6-dimethylbicyclo [3.1.1]heptyl, tricyclobutyl, and adamantyl.

As used herein the term "bridged (C₂-C₁₀) heterocyclyl" means bicyclic or polycyclic aza-bridged hydrocarbon groups and may include azanorbornyl, quinuclidinyl, isoquinuclidinyl, tropanyl, azabicyclo[3.2.1]octanyl, azabicyclo[2.2.1]heptanyl, 2-azabicyclo[3.2.1]octanyl, azabicyclo[3.2.1]octanyl, azabicyclo[3.2.2]nonanyl, azabicyclo[3.3.0]nonanyl, and azabicyclo [3.3.1]nonanyl.

The term "heterocyclic", "heterocyclyl" or "heterocyclylene", as used herein, include non-aromatic, ring systems, including, but not limited to, monocyclic, bicyclic, tricyclic and spirocyclic rings, which can be completely saturated or which can contain one or more units of unsaturation, for the avoidance of doubt, the degree of unsaturation does not result in an aromatic ring system) and have 5 to 12 atoms including at least one heteroatom, such as nitrogen, oxygen, or sulfur. For purposes of exemplification, which should not be construed as limiting the scope of this invention, the following are examples of heterocyclic rings: azepinyl, azetidiny, indolinyl, isoindolinyl, morpholinyl, piperazinyl, piperidinyl, pyrrolidinyl, quinuclidinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrofuranyl, tetrahydroindolyl, thiomorpholinyl and tropanyl.

The term "heteroaryl" or "heteroarylene" as used herein, include aromatic ring systems, including, but not limited to, monocyclic, bicyclic and tricyclic rings, and have 5 to 12 atoms including at least one heteroatom, such as nitrogen, oxygen, or sulfur. For purposes of

exemplification, which should not be construed as limiting the scope of this invention: azaindolyl, benzo(b)thienyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, furanyl, imidazolyl, imidazopyridinyl, indolyl, indazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-d]pyrimidinyl, quinoliny, quinazoliny, triazolyl, thiazolyl, thiophenyl, tetrazolyl, thiadiazolyl, or thienyl.

An “heterocycloalkyl” group, as used herein, is a heterocyclic group that is linked to a compound by an aliphatic group having from one to about eight carbon atoms. For example, a heterocycloalkyl group is a morpholinomethyl group.

As used herein, “alkyl”, “alkylene” or notations such as “(C₁-C₈)” include straight chained or branched hydrocarbons which are completely saturated. Examples of alkyls are methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl and isomers thereof. As used herein, “alkenyl”, “alkenylene”, “alkynylene” and “alkynyl” means C₂-C₈ and includes straight chained or branched hydrocarbons which contain one or more units of unsaturation, one or more double bonds for alkenyl and one or more triple bonds for alkynyl.

As used herein, “aromatic” groups (or “aryl” or “arylene” groups) include aromatic carbocyclic ring systems (e.g. phenyl) and fused polycyclic aromatic ring systems (e.g. naphthyl, biphenyl and 1,2,3,4-tetrahydronaphthyl).

As used herein, “cycloalkyl” or “cycloalkylene” means C₃-C₁₂ monocyclic or multicyclic (e.g., bicyclic, tricyclic, spirocyclic, etc.) hydrocarbons that is completely saturated or has one or more unsaturated bonds but does not amount to an aromatic group. Examples of a cycloalkyl group are cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl and cyclohexenyl.

As used herein, many moieties or substituents are termed as being either “substituted” or “optionally substituted”. When a moiety is modified by one of these terms, unless otherwise noted, it denotes that any portion of the moiety that is known to one skilled in the art as being available for substitution can be substituted, which includes one or more substituents, where if more than one substituent then each substituent is independently selected. Such means for substitution are well-known in the art and/or taught by the instant disclosure. For purposes of exemplification, which should not be construed as limiting the scope of this invention, some examples of groups that are substituents are: (C₁-C₈)alkyl groups, (C₂-C₈)alkenyl groups, (C₂-C₈)alkynyl groups, (C₃-C₁₀)cycloalkyl groups, halogen (F, Cl, Br or I), halogenated (C₁-C₈)alkyl groups (for example but not limited to -CF₃), -O-(C₁-C₈)alkyl groups, -OH, -S-(C₁-C₈)alkyl groups, -SH, -NH(C₁-C₈)alkyl groups, -N((C₁-C₈)alkyl)₂ groups, -NH₂, -C(O)NH₂, -C(O)NH(C₁-C₈)alkyl groups, -C(O)N((C₁-C₈)alkyl)₂, -NHC(O)H, -NHC(O) (C₁-C₈)alkyl groups, -NHC(O) (C₃-C₈)cycloalkyl groups, -N((C₁-C₈)alkyl)C(O)H, -N((C₁-C₈)alkyl)C(O)(C₁-C₈)alkyl groups, -NHC(O)NH₂, -NHC(O)NH(C₁-C₈)alkyl groups, -N((C₁-C₈)alkyl)C(O)NH₂ groups, -NHC(O)N((C₁-C₈)alkyl)₂ groups, -N((C₁-C₈)alkyl)C(O)N((C₁-C₈)alkyl)₂ groups, -N((C₁-

C₈)alkyl)C(O)NH((C₁-C₈)alkyl), -C(O)H, -C(O)(C₁-C₈)alkyl groups, -CN, -NO₂, -S(O)(C₁-C₈)alkyl groups, -S(O)₂(C₁-C₈)alkyl groups, -S(O)₂N((C₁-C₈)alkyl)₂ groups, -S(O)₂NH(C₁-C₈)alkyl groups, -S(O)₂NH(C₃-C₈)cycloalkyl groups, -S(O)₂NH₂ groups, -NHS(O)₂(C₁-C₈)alkyl groups, -N((C₁-C₈)alkyl)S(O)₂(C₁-C₈)alkyl groups, -(C₁-C₈)alkyl-O-(C₁-C₈)alkyl groups, -O-(C₁-C₈)alkyl-O-(C₁-C₈)alkyl groups, -C(O)OH, -C(O)O(C₁-C₈)alkyl groups, NHOH, NHO(C₁-C₈)alkyl groups, -O-halogenated (C₁-C₈)alkyl groups (for example but not limited to -OCF₃), -S(O)₂-halogenated (C₁-C₈)alkyl groups (for example but not limited to -S(O)₂CF₃), -S-halogenated (C₁-C₈)alkyl groups (for example but not limited to -SCF₃), -(C₁-C₆) heterocycle (for example but not limited to pyrrolidine, tetrahydrofuran, pyran or morpholine), -(C₁-C₆) heteroaryl (for example but not limited to tetrazole, imidazole, furan, pyrazine or pyrazole), -phenyl, -NHC(O)O-(C₁-C₆)alkyl groups, -N((C₁-C₆)alkyl)C(O)O-(C₁-C₆)alkyl groups, -C(=NH)-(C₁-C₆)alkyl groups, -C(=NOH)-(C₁-C₆)alkyl groups, or -C(=N-O-(C₁-C₆)alkyl)-(C₁-C₆)alkyl groups.

“” in Formula (I) represents an aromatic ring.

One or more compounds of this invention can be administered to a human patient by themselves or in pharmaceutical compositions where they are mixed with biologically suitable carriers or excipient(s) at doses to treat or ameliorate a disease or condition as described herein. Mixtures of these compounds can also be administered to the patient as a simple mixture or in suitable formulated pharmaceutical compositions. A therapeutically effective dose refers to that amount of the compound or compounds sufficient to result in the prevention or attenuation of a disease or condition as described herein. Techniques for formulation and administration of the compounds of the instant application may be found in references well known to one of ordinary skill in the art, such as "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, latest edition.

Suitable routes of administration may, for example, include oral, eyedrop, rectal, transmucosal, topical, or intestinal administration; parenteral delivery, including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraventricular, intravenous, intraperitoneal, intranasal, or intraocular injections.

Alternatively, one may administer the compound in a local rather than a systemic manner, for example, via injection of the compound directly into an edematous site, often in a depot or sustained release formulation.

Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with endothelial cell-specific antibody.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

Pharmaceutical compositions for use in accordance with the present invention thus may be formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

For injection, the agents of the invention may be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration.

For buccal administration, the compositions may take the form of tablets or lozenges formulated in conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds can be formulated for parenteral administration by injection, e.g. bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly or by intramuscular injection). Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

An example of a pharmaceutical carrier for the hydrophobic compounds of the invention is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be the VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent

system (VPD:5W) consists of VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are well known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials have been established and are well known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few hours up to over several days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include but are not limited to calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Many of the compounds of the invention may be provided as salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms.

Pharmaceutical compositions suitable for use in the present invention include compositions wherein the active ingredients are contained in an effective amount to achieve its intended purpose. More specifically, a therapeutically effective amount means an amount effective to prevent development of or to alleviate the existing symptoms of the subject being treated. Determination of the effective amounts is well within the capability of those skilled in the art.

For any compound used in a method of the present invention, the therapeutically effective dose can be estimated initially from cellular assays. For example, a dose can be formulated in cellular and animal models to achieve a circulating concentration range that includes the IC_{50} as determined in cellular assays (i.e., the concentration of the test compound which achieves a half-

maximal inhibition of a given protein kinase activity). In some cases it is appropriate to determine the IC_{50} in the presence of 3 to 5% serum albumin since such a determination approximates the binding effects of plasma protein on the compound. Such information can be used to more accurately determine useful doses in humans. Further, the most preferred compounds for systemic administration effectively inhibit protein kinase signaling in intact cells at levels that are safely achievable in plasma.

A therapeutically effective dose refers to that amount of the compound that results in amelioration of symptoms in a patient. Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the maximum tolerated dose (MTD) and the ED_{50} (effective dose for 50% maximal response). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio between MTD and ED_{50} . Compounds which exhibit high therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. The exact formulation, route of administration and dosage can be chosen by the individual physician in view of the patient's condition (see e.g. Fingl *et al.*, 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). In the treatment of crises, the administration of an acute bolus or an infusion approaching the MTD may be required to obtain a rapid response.

Dosage amount and interval may be adjusted individually to provide plasma levels of the active moiety which are sufficient to maintain the kinase modulating effects, or minimal effective concentration (MEC). The MEC will vary for each compound but can be estimated from *in vitro* data; e.g. the concentration necessary to achieve 50-90% inhibition of protein kinase using the assays described herein. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. However, HPLC assays or bioassays can be used to determine plasma concentrations.

Dosage intervals can also be determined using the MEC value. Compounds should be administered using a regimen which maintains plasma levels above the MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90% until the desired amelioration of symptoms is achieved. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

The amount of composition administered will, of course, be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and the judgment of the prescribing physician.

The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labelled for treatment of an indicated condition.

In some formulations it may be beneficial to use the compounds of the present invention in the form of particles of very small size, for example as obtained by fluid energy milling.

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of one of the following Examples.

a) Capsules

In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose can be de-aggregated and blended. The mixture can be filled into hard gelatin capsules, each capsule containing a unit dose or part of a unit dose of active compound.

b) Tablets

Tablets can be prepared, for example, from the following ingredients.

Parts by weight

Active compound	10
Lactose	190
Maize starch	22
Polyvinylpyrrolidone	10
Magnesium stearate	3

The active compound, the lactose and some of the starch can be de-aggregated, blended and the resulting mixture can be granulated with a solution of the polyvinylpyrrolidone in ethanol. The dry granulate can be blended with the magnesium stearate and the rest of the starch. The mixture is then compressed in a tableting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

c) Enteric coated tablets

Tablets can be prepared by the method described in (b) above. The tablets can be enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories

In the preparation of suppositories, for example, 100 parts by weight of active compound can be incorporated in 1300 parts by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients. For example, the compounds of this invention can be administered in combination with another therapeutic agent that is known to treat a disease or condition described herein. For example, with one or more additional pharmaceutical agents that inhibit or prevent the production of VEGF or angiopoietins, attenuate intracellular responses to VEGF or angiopoietins, block intracellular signal transduction, inhibit vascular hyperpermeability, reduce inflammation, or inhibit or prevent the formation of edema or neovascularization. The compounds of the invention can be administered prior to, subsequent to or simultaneously with the additional pharmaceutical agent, whichever course of administration is appropriate. The additional pharmaceutical agents include, but are not limited to, anti-edemic steroids, NSAIDS, ras inhibitors, anti-TNF agents, anti-IL1 agents, antihistamines, PAF-antagonists, COX-1 inhibitors, COX-2 inhibitors, NO synthase inhibitors, Akt/PTB inhibitors, IGF-1R inhibitors, PKC inhibitors, PI3 kinase inhibitors, calcineurin inhibitors and immunosuppressants. The compounds of the invention and the additional pharmaceutical agents act either additively or synergistically. Thus, the administration of such a combination of substances that inhibit angiogenesis, vascular hyperpermeability and/or inhibit the formation of edema can provide greater relief from the deleterious effects of a hyperproliferative disorder, angiogenesis, vascular hyperpermeability or edema than the administration of either substance alone. In the treatment of malignant disorders combinations with antiproliferative or cytotoxic chemotherapies or radiation are included in the scope of the present invention.

The present invention also comprises the use of a compound of Formula (I) or Formula (II) as a medicament.

A further aspect of the present invention provides the use of a compound of Formula (I) or Formula (II) or a salt thereof in the manufacture of a medicament for treating vascular hyperpermeability, angiogenesis-dependent disorders, proliferative diseases and/or disorders of the immune system in mammals, particularly human beings.

The present invention also provides a method of treating vascular hyperpermeability, inappropriate neovascularization, proliferative diseases and/or disorders of the immune system which comprises the administration of a therapeutically effective amount of a compound of Formula (I) or Formula (II) to a mammal, particularly a human being, in need thereof.

ABBREVIATIONS

aa	Amino acids
Ac ₂ O	Acetic anhydride
AcOH	Glacial acetic acid
ATP	Adenosine triphosphate
b.p.	Boiling point
BArF	<i>tetrakis</i> -[3,5-bis(trifluoromethyl)phenyl]borate
Bn	Benzyl
Boc	<i>t</i> -Butoxycarbonyl
BOP-Cl	Bis(2-oxo-3-oxazolidinyl)phosphonic chloride
BSA	Bovine serum albumin
BuOH	Butanol
CAN	Ceric ammonium nitrate
Cbz	Carboxybenzyl
CDI	1,1'-Carbonyldiimidazole
COD	1,5-Cyclooctadiene
concd	Concentrated
CT	Computed tomography
cym	<i>p</i> -cymene (4-isopropyltoluene)
CyPFt-Bu	1-Dicyclohexylphosphino-2-di- <i>tert</i> -butylphosphinoethylferrocene
d	Doublet
DAST	Diethylaminosulfur trifluoride
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane (methylene chloride)
dd	Doublet of doublets
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIAD	Diisopropyl azodicarboxylate
DIEA	<i>N,N</i> -Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	<i>N,N</i> -Dimethylaminopyridine
DME	1,2-Dimethoxyethane
DMEM	Dulbecco's Modified Eagle Medium

DMF	<i>N,N</i> -Dimethylformamide
DMS	Dimethylsulfide
DMSO	Dimethyl sulfoxide
DNP-HSA	Dinitrophenyl-human serum albumin
DPPA	Diphenyl phosphorazidate
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diastereomeric ratio
DTT	Dithiothreitol
EDC•HCl	<i>N</i> -(3-Dimethylaminopropyl)- <i>N</i> '-ethylcarbodiimide hydrochloride
EDTA	Ethylene diamine tetraacetic acid
EGTA	Ethylene glycol tetraacetic acid
equiv	Equivalent(s)
er	Enantiomeric ratio
Et ₂ NH	Diethylamine
EtOAc	Ethyl acetate
Et ₂ O	Diethyl ether
EtOH	Ethanol
FBS	Fetal bovine serum
FLAG	DYKDDDDK peptide sequence
g	Gram(s)
GST	Glutathione S-transferase
h	Hour(s)
H ₂ SO ₄	Sulfuric acid
HATU	<i>O</i> -(7-Azabenzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HEPES	<i>N</i> -2-Hydroxyethylpiperazine- <i>N'</i> -2-ethanesulfonic acid
HOBt	Hydroxybenzotriazole
HPLC	High-pressure liquid chromatography
Hz	Hertz
IBCF	Isobutylchloroformate
i.d.	Intradermal
IFA	Incomplete Freund's Adjuvant
IPA	Isopropyl alcohol
KHMDS	Potassium hexamethyldisilazane
LAH	Lithium aluminum hydride
LC	Liquid chromatography
LDA	Lithium diisopropylamide

LHMDS	Lithium bis(trimethylsilyl)amide
LiBH ₄	Lithium borohydride
LiOH	Lithium hydroxide
m	Multiplet
M	Molar
<i>m</i> -CPBA	<i>meta</i> -Chloroperbenzoic acid
MeCN	Acetonitrile
MeOH	Methyl alcohol
min	Minute(s)
mL	Milliliter(s)
mmHg	Millimeters of mercury
mmol	Millimole
MOPS	3-(<i>N</i> -morpholino)-propanesulfonic acid
MOPSO	3-(<i>N</i> -morpholino)-2-hydroxypropanesulfonic acid
MS	Mass spectrometry
MTBE	Methyl <i>tert</i> -butyl ether
<i>n</i> -	Normal (nonbranched)
<i>n</i> -BuLi	<i>n</i> -Butyl lithium
N	Normal
NaHMDS	Sodium bis(trimethylsilyl)amide
NaOAc	Sodium acetate
Na(OAc) ₃ BH	Sodium triacetoxyborohydride
NaOt-Bu	Sodium <i>tert</i> -butoxide
NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
ND	Not determined
NH ₄ OAc	Ammonium acetate
NIS	<i>N</i> -Iodosuccinimide
NMM	<i>N</i> -Methylmorpholine
NMP	<i>N</i> -Methylpyrrolidinone
NMR	Nuclear magnetic resonance
OD	Optical density
or	Optical rotation
OVA	Ovalbumin
<i>p</i> -	Para
PBS	Phosphate buffered saline
PFPA	2,2,3,3,3-Pentafluoropropanoic Anhydride

pH	$-\log[\text{H}^+]$
PMB	<i>p</i> -Methoxybenzyl
pNAG	Nitrophenyl- <i>N</i> -acetyl- β -D-glucosaminide
P(<i>n</i> -Bu) ₃	<i>tri-n</i> -Butyl phosphine
POCl ₃	Phosphorus oxychloride
PPh ₃	Triphenylphosphine
ppm	Parts per million
PrOH	Propanol
psi	Pounds per square inch
rcf	Relative centrifugal force
RP-HPLC	Reverse-phase high-pressure liquid chromatography
R _t	Retention time
rt	Room temperature
s	Singlet
SEM	2-(Trimethylsilyl)ethoxymethyl
SEM-Cl	2-(Trimethylsilyl)ethoxymethyl chloride
SFC	Supercritical Fluid Chromatography
SLM	Standard liters per minute
t	Triplet
<i>t</i> -	Tertiary
TBDMS	<i>tert</i> -Butyldimethylsilyl
TBDMSCl	<i>tert</i> -Butyldimethylsilyl chloride
TBAB	Tetra- <i>n</i> -butylammonium bromide
TBAF	Tetra- <i>n</i> -butylammonium fluoride
TBAI	Tetra- <i>n</i> -butylammonium iodide
TEA	Triethylamine
<i>tert</i> -	Tertiary
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TMA	Trimethyl aluminium
TMAD	<i>N,N,N',N'</i> -Tetramethylazodicarbonamide or 1,1'-azobis(<i>N,N</i> -dimethylformamide) or diamide [Sigma [®]]
TMOF	Trimethyl orthoformate
TMS	Trimethylsilyl

TPP	2,4,6-Tripropyl-[1,3,5,2,4,6]trioxatriphosphinane 2,4,6-trioxide
TsCl	<i>para</i> -Toluenesulfonyl chloride
TsOH	<i>para</i> -Toluenesulfonic acid
USP	United States Pharmacopeia
UV	Ultraviolet
wt%	Weight percent
w/v	Weight/volume

ASSAYS

***In vitro* Jak1 kinase activity measured by time-resolved fluorescence resonance energy transfer (trFRET)**

Varying concentrations of inhibitor were added to to an assay well containing: Jak1 enzyme (aa 845-1142; expressed in SF9 cells as a GST fusion and purified by glutathione affinity chromatography; 4 nM), peptide substrate (biotin-TYR2, Sequence: Biotin-(Ahx)-AEEYFFLFA-amide; 2 μ M), MOPSO pH 6.5 (50 mM), MgCl₂ (10 mM), MnCl₂ (2 mM), DTT (2.5 mM), BSA (0.01% w/v), Na₃VO₄ (0.1 mM) and ATP (0.001 mM). After about 60 min incubation at rt, the reaction was quenched by addition of EDTA (final concentration: 100 mM) and developed by addition of revelation reagents (final approximate concentrations: 30 mM HEPES pH 7.0, 0.06% BSA, 0.006% Tween-20, 0.24 M KF, 80 ng/mL PT66K (europium labeled anti-phosphotyrosine antibody cat #61T66KLB Cisbio, Bedford, MA) and 3.12 μ g/mL SAXL (Phycolink streptavidin-allophycocyanin acceptor, cat #PJ52S, Prozyme, San Leandro, CA). The developed reaction was incubated in the dark either at about 4 °C for about 14 h or for about 60 min at rt, then read via a time-resolved fluorescence detector (Rubystar, BMG) using a 337 nm laser for excitation and emission wavelength of 665 nm. Within the linear range of the assay, the observed signal at 665 nm is directly related to phosphorylated product and used to calculate the IC₅₀ values.

***In vitro* Jak3 kinase activity measured by time-resolved fluorescence resonance energy transfer (trFRET)**

Varying concentrations of inhibitor were added to to an assay well containing: Jak3 enzyme (aa 811-1103; expressed in SF9 cells as a GST fusion and purified by glutathione affinity chromatography; 3 nM), peptide substrate (biotin-TYR2, Sequence: Biotin-(Ahx)-AEEYFFLFA-amide; 2 μ M), MOPSO pH 6.5 (50 mM), MgCl₂ (10 mM), MnCl₂ (2 mM), DTT (2.5 mM), BSA (0.01% w/v), Na₃VO₄ (0.1 mM) and ATP (0.001 mM). After about 60 min incubation at rt, the reaction was quenched by addition of EDTA (final concentration: 100 mM) and developed by addition of revelation reagents (final approximate concentrations: 30 mM HEPES pH 7.0, 0.06% BSA, 0.006% Tween-20, 0.24 M KF, 80 ng/mL PT66K (europium labeled

anti-phosphotyrosine antibody cat #61T66KLB Cisbio, Bedford, MA) and 0.8 $\mu\text{g/mL}$ SAXL (Phycolink streptavidin-allophycocyanin acceptor, cat #PJ52S, Prozyme, San Leandro, CA). The developed reaction was incubated in the dark either at about 4 °C for about 14 h or for about 60 min at rt, then read via a time-resolved fluorescence detector (Rubystar, BMG) using a 337 nm laser for excitation and emission wavelength of 665 nm. Within the linear range of the assay, the observed signal at 665 nm is directly related to phosphorylated product and used to calculate the IC_{50} values.

***In vitro* Syk kinase activity measured by time-resolved fluorescence resonance energy transfer (trFRET)**

0.3 nM Syk catalytic domain (aa356-635, purified in-house at the Abbott Bioresearch Center) was mixed with 0.1 μM peptide substrate (biotin-TYR1, Sequence: Biotin-(Ahx)-GAEEEIYAAFFA-COOH) at varying concentrations of inhibitor in reaction buffer: 50 mM MOPSO pH 6.5, 10 mM MgCl_2 , 2 mM MnCl_2 , 2.5 mM DTT, 0.01% BSA, 0.1 mM Na_3VO_4 and 0.001 mM ATP. After about 60 min incubation at rt, the reaction was quenched by addition of EDTA (final concentration: 100 mM) and developed by addition of revelation reagents (final approximate concentrations: 30 mM HEPES pH 7.0, 0.06% BSA, 0.006% Tween-20, 0.24 M KF, 90 ng/mL PT66K (europium labeled anti-phosphotyrosine antibody cat #61T66KLB Cisbio, Bedford, MA) and 0.6 $\mu\text{g/mL}$ SAXL (Phycolink streptavidin-allophycocyanin acceptor, cat #PJ52S, Prozyme, San Leandro, CA). The developed reaction was incubated in the dark either at about 4 °C for about 14h or for about 60 min at rt, then read via a time-resolved fluorescence detector (Rubystar, BMG) using a 337 nm laser for excitation and emission wavelength of 665 nm. Within the linear range of the assay, the observed signal at 665 nm is directly related to phosphorylated product and used to calculate the IC_{50} values.

Other *in vitro* kinase assays measured by time-resolved fluorescence resonance energy transfer (trFRET)

Other kinase assays were performed using a similar protocol. Additional purified enzymes Tyk2 (aa 880-1185 with an N-terminal histidine-tag and C-terminal FLAG tag; purified in-house by immobilized metal ion affinity chromatography), RET (aa 711-1072 with an N-terminal histidine-tag; purified by immobilized metal ion affinity chromatography), Syk (aa356-635 with a C-terminal histidine tag; purified by immobilized metal ion affinity chromatography), and KDR (aa 792-1354 with an N-terminal histidine-tag; purified in-house by immobilized metal ion affinity and ion-exchange chromatography) were expressed in SF9 cells and Aurora 1/B (aa 1-344 with a N-terminal histidine-tag and purified by immobilized metal ion affinity chromatography) was expressed in *E. coli*. Other enzymes used are available from commercial

sources. Enzymes were mixed with biotinylated substrates at varying concentrations of inhibitor in different reaction buffers (see **Table A**). After about 60 min incubation at rt, the reaction was quenched by addition of EDTA and developed by addition of revelation reagents (final approximate concentrations: 30 mM HEPES pH 7.0, 0.06% BSA, 0.006% Tween-20, 0.24 M KF, varying amounts of donor europium labeled antibodies and acceptor streptavidin labeled allophycocyanin (SAXL)). The developed reactions were incubated in the dark either at about 4 °C for about 14 h or for about 60 min at rt, then read in a time-resolved fluorescence detector (Rubystar, BMG Labtech) as described above.

Table A. Specific conditions (per 40 μ L enzyme reaction) for the various enzymes are detailed below:

Enzyme	Construct	Substrate	Assay Buffer	Enzyme Conc. (ng/well)	Substrate Conc.	ATP Conc. (mM)	DMSO Conc. (%)	Reaction Time (min)	Detection condition
Jak1	aa 845-1142	Biotin-TYR2	MOPSO	5	2 μ M	0.001	5	60	8 ng/well PT66K, 0.39 μ g/well SAXL
Jak2	Millipore cat# 14-640	Biotin-TYR1	MOPSO	2.5	2 μ M	0.001	5	60	8 ng/well PT66K, 0.078 μ g/well SAXL
Jak3	aa 811-1103	Biotin-TYR2	MOPSO	4.5	2 μ M	0.001	5	60	8 ng/well PT66K, 0.078 μ g/well SAXL
Tyk2	aa880-1185	Biotin-TYR1	MOPSO	9	2 μ M	0.001	5	60	8 ng/well PT66K, 0.078 μ g/well SAXL

Enzyme	Construct	Substrate	Assay Buffer	Enzyme Conc. (ng/well)	Substrate Conc.	ATP Conc. (mM)	DMSO Conc. (%)	Reaction Time (min)	Detection condition
Aurora 1/B	aa1-344	KinEAS E S2	MOPS	20	0.5 μ M	0.1	5	60	15 ng/well Eu-STK-Ab, 0.34 μ g/well SAXL
KDR	aa789-1354	Biotin-TYR2	HEPES	10	2 μ M	0.1	5	60	8 ng/well PT66K, 0.078 μ g/well SAXL
JNK1	Millipore cat# 14-327	Biotin-ATF2-pep	MOPS	10	1 μ M	0.01	5	60	2.58 ng/well Anti-pATF2-Eu, 0.6 μ g/well SAXL
JNK2	Millipore cat# 14-329	Biotin-ATF2-pep	MOPS	5	0.5 μ M	0.01	5	60	2.58 ng/well Anti-pATF2-Eu, 0.6 μ g/well SAXL
RET	aa711-1072	Biotin-poly GluTyr	HEPES	4	10 ng/well	0.01	5	60	8 ng/well PT66K, 0.078 μ g/well SAXL

Enzyme	Construct	Substrate	Assay Buffer	Enzyme Conc. (ng/well)	Substrate Conc.	ATP Conc. (mM)	DMSO Conc. (%)	Reaction Time (min)	Detection condition
P70 S6 Kinase	Millipore cat # 14-486	KinEAS E S3	MOPS	0.5	0.25 μ M	0.01	5	60	15 ng/well Eu-STK-Ab, 0.34 μ g/well SAXL
PKN2	Invitrogen cat # PV3879	KinEAS E S3	MOPS	0.7	0.5 μ M	0.001	5	60	15 ng/well Eu-STK-Ab, 0.34 μ g/well SAXL
Syk	aa356-635	Biotin-TYR1	MOPSO	0.4	0.1 μ M	0.001	5	60	6.8 ng/well PT66K, 0.045 μ g/well SAXL
CDK2/Cyclin A	Millipore cat # 14-448	Biotin-MBP	MOPS	50	2 μ M	0.1	5	60	15 ng/well Anti-pMBP-Eu; 0.34 μ g/well SAXL

Reaction Buffers:

MOPSO buffer contains: 50 mM MOPSO pH 6.5, 10 mM MgCl_2 , 2 mM MnCl_2 , 2.5 mM DTT, 0.01% BSA, and 0.1 mM Na_3VO_4

HEPES buffer contains: 50 mM HEPES pH 7.1, 2.5 mM DTT, 10 mM MgCl_2 , 2 mM MnCl_2 , 0.01% BSA, and 0.1 mM Na_3VO_4

MOPS buffer contains: 20 mM MOPS pH 7.2, 10 mM MgCl₂, 5 mM EGTA, 5 mM Beta-phosphoglycerol, 1 mM Na₃VO₄, 0.01% Triton-X-100 and 1 mM DTT

Substrates:

Biotin-ATF2-peptide sequence: Biotin-(Ahx)-AGAGDQTPTPTRFLKRPR-amide

Biotin-TYR1-peptide sequence: Biotin-(Ahx)-GAEEEIYAAFFA-COOH

Biotin-TYR2-peptide sequence: Biotin-(Ahx)-AEEYFFLFA-amide

Biotin-MBP-peptide sequence: Biotin-(Ahx)-VHFFKNIVTPRTPPPSQGKGAEGQR-amide

Biotin-polyGluTyr peptide was purchased from Cisbio (cat #61GT0BLA, Bedford, MA)

KinEASE S2 and S3 peptides were purchased from Cisbio (cat #62ST0PEB, Bedford, MA)

Detection Reagents:

Anti-pATF2-Eu was custom-labeled by Cisbio (Bedford, MA)

Anti-pMBP-Eu was custom-labeled by Cisbio (Bedford, MA)

PT66K was purchased from Cisbio (cat #61T66KLB, Bedford, MA)

SAXL was purchased from Prozyme (cat #PJ25S, San Leandro, CA)

Human T-Blasts IL-2 pSTAT5 Cellular Assay

Materials:

Phytohemagglutinin T-blasts were prepared from Leukopacks purchased from Biological Specialty Corporation, Colmar, PA 18915, and cryopreserved in 5% DMSO/media prior to assay.

For this assay the cells were thawed in assay medium with the following composition: RPMI 1640 medium (Gibco 11875093) with 2 mM L-glutamine (Gibco 25030-081), 10 mM HEPES (Gibco 15630-080), 100 µg/mL Pen/Strep (Gibco 15140-122), and 10% heat inactivated FBS (Gibco 10438026). Other materials used in the assay: DMSO (Sigma D2650), 96-well dilution plates (polypropylene) (Corning 3365), 96-well assay plates (white, ½ area, 96 well) (Corning 3642), D-PBS (Gibco 14040133), IL-2 (R&D 202-IL-10 (10µg)), Alphascreen pSTAT5 kit (Perkin Elmer TGRS5S10K) and Alphascreen protein A kit (Perkin Elmer 6760617M)

Methods:

T-Blasts were thawed and cultured for about 24 h without IL-2 prior to assay. Test compounds or controls are dissolved and serially diluted in 100% DMSO. DMSO stocks are subsequently diluted 1:50 in cell culture media to create the 4x compound stocks (containing 2% DMSO). Using a Corning white 96 well, ½ area plate, cells are plated at 2x10⁵/10 µl/well in 10 µL media followed by addition of 5 µL of 4x test compound in duplicate. Cells are incubated with compound for about 0.5 h at about 37 °C. Next, 5 µL of IL-2 stock is added at 20 ng/mL final concentration. IL-2 is stored as a 4 µg/mL stock solution, as specified by the manufacturer, at about -20 °C in aliquots and diluted 1:50 with assay media (to 80 ng/mL) just prior to use. The contents of the wells are mixed by carefully tapping sides of plate(s) several times followed by

incubation at about 37 °C for about 15 min. The assay is terminated by adding 5 µL of 5x AlphaScreen lysis buffer and shaking on an orbital shaker for about 10 min at rt. Alphascreen acceptor bead mix is reconstituted following Perkin Elmer's protocol. 30 µL/well of reconstituted Alphascreen acceptor bead mix was added, covered with foil then shaken on orbital shaker for about 2 min on high then about 2 h on low. Donor bead mix is reconstituted following Perkin Elmer's AlphaScreen protocol; 12 µL/well are added, covered with foil then shaken for about 2 min on high, and about 2 h on low. Plates are read on an EnVision reader following Perkin Elmer's AlphaScreen protocol instructions.

TF-1 IL-6 pSTAT3 Cellular Assay

Materials:

TF-1 cells (ATCC #CRL-2003). Culture medium: DMEM medium (Gibco 11960-044) with 2 mM L-glutamine (Gibco 25030-081), 10 mM HEPES (Gibco 15630-080), 100 µg/mL Pen/Strep (Gibco 15140-122), 1.5g/L sodium bicarbonate (Gibco 25080-094), 1 mM sodium pyruvate (Gibco 11360-070), 10% heat inactivated FBS (Gibco 10437-028), and 2 ng/mL GM-CSF (R&D 215-GM-010). Other materials used in this assay: DMSO (Sigma D2650), 96-well dilution plates (polypropylene) (Corning 3365), 96-well assay plates (white, ½ area, 96 well) (Corning 3642), D-PBS (Gibco 14040133), IL-6 (R&D 206-IL/CF-050 (50 µg)), Alphascreen pSTAT3 kit (Perkin Elmer TGRS3S10K) and Alphascreen protein A kit (Perkin Elmer 6760617M).

Methods:

Prior to the assay, cells are cultured for about 18 h in the culture medium without GM-CSF. Test compounds or controls are dissolved and serially diluted in 100% DMSO. DMSO stocks are subsequently diluted 1:50 in cell culture media to create the 4x compound stocks (containing 2% DMSO). Using a Corning white 96 well, ½ area plate, cells are plated at 2×10^4 /10 µL/well in 10 µL media followed by addition of 5 µL of the 4x test compound stock in duplicate. Cells are incubated with compound for about 0.5 h at about 37 °C followed by addition of 5 µL of 400 ng/mL IL-6. IL-6 is stored in 10 µg/mL aliquots using endotoxin free D-PBS (0.1% BSA) at about -20 °C. Prior to assay IL-6 is diluted to 400 ng/mL in culture media and applied (5 µL/well) to all wells, except to negative control wells where 5 µL/well of media is added. The contents of the wells are mixed carefully by tapping the side of the plate several times. Plates are incubated at about 37 °C for about 30 min. Cells are lysed by adding 5 µL of 5X AlphaScreen cell lysis buffer to all wells, shaken for about 10 min at rt then assayed. Alternatively, assay plates may be frozen at about -80 °C and thawed later at rt. Using the pSTAT3 SureFire Assay kit (Perkin Elmer #TGRS3S10K) acceptor bead mix is reconstituted following Perkin Elmer's AlphaScreen protocol instructions. 30 µL are added per well then the plate is covered with foil and shaken on an orbital shaker for about 2 min on high, then about 2 h on low at rt. Donor bead mix is

reconstituted following Perkin Elmer's AlphaScreen protocol instructions. 12 μ L are added per well, then covered with foil and shaken on orbital shaker for about 2 min on high, then about 2 h on low at about 37 °C. Plates are read on an EnVision reader following Perkin Elmer's AlphaScreen protocol instructions at rt.

UT7/EPO pSTAT5 Cellular Assay

Materials:

UT7/EPO cells are passaged with erythropoietin (EPO), split twice per week and fresh culture medium is thawed and added at time of split. Culture Medium: DMEM medium (Gibco 11960-044) with 2 mM L-glutamine (Gibco 25030-081), 10 mM HEPES (Gibco 15630-080), 100 U/mL Pen/Strep (Gibco 15140-122), 10% heat inactivated FBS (Gibco 10437-028), EPO (5 μ L/mL = 7.1 μ L of a 7 μ g/mL stock per mL of medium). Assay media: DMEM, 2 mM L-glutamine, 5% FBS, 10 mM HEPES. Other materials used in the assay: DMSO (Sigma D2650), 96-well dilution plates (polypropylene) (Corning 3365), 96-well assay plates (white, $\frac{1}{2}$ area, 96 well) (Corning 3642), D-PBS (Gibco 14040133), IL-2 (R&D 202-IL-10 (10 μ g)), Alphascreen pSTAT5 kit (Perkin Elmer TGRS5S10K) and Alphascreen protein A kit (Perkin Elmer 6760617M).

Methods:

Culture cells for about 16 h without EPO prior to running assay. Test compounds or controls are dissolved and serially diluted in 100% DMSO. DMSO stocks are subsequently diluted 1:50 in cell culture media to create the 4x compound stocks (containing 2% DMSO). Using a Corning white 96 well, $\frac{1}{2}$ area plate, cells are plated at 2×10^5 /10 μ L/well in 10 μ L media followed by addition of 5 μ L of 4x test compound stock in duplicate. Cells are incubated with compound for about 0.5 h at about 37 °C. After incubation, 5 μ L of EPO is added to afford a final concentration of 1 nM EPO. The contents of the wells are mixed by carefully tapping sides of the plate several times followed by incubation at about 37 °C for about 20 min. 5 μ L of 5x AlphaScreen lysis buffer are added followed by shaking on an orbital shaker for about 10 min at rt. 30 μ L/well of acceptor beads are added after reconstitution following Perkin Elmer's AlphaScreen protocol, covered with foil and shaken on orbital shaker for about 2 min on high, then about 2 h on low. Donor beads are reconstituted following Perkin Elmer's AlphaScreen protocol instructions followed by addition of 12 μ L/well, covered with foil and shaken on an orbital shaker for about 2 min on high, about 2 h on low. Plates are read on an EnVision reader following Perkin Elmer's AlphaScreen protocol instructions.

Antigen-Induced Degranulation of RBL-2H3 Cells:

RBL-2H3 cells are maintained in T75 flasks at about 37 °C and 5% CO₂, and passaged every 3-4 days. To harvest cells, 20 mL of PBS is used to rinse the flask once, and then 3 mL of Trypsin-EDTA is added and incubated at about 37 °C for about 2 min. Cells are transferred to a tube with 20 mL medium, spun down at 1000 RPM at rt for about 5 min and resuspended at 1×10^6 cells/mL. Cells are sensitized by adding DNP-specific mouse IgE to a final concentration of 0.1 µg/mL. 50 µL of cells are added to each well of a 96 well flat bottom plate (50×10^3 cells/well) and incubated overnight at about 37 °C in 5% CO₂. The next day, compounds are prepared in 100% DMSO at 10 mM. Each compound is then serially diluted 1:4 six times in 100% DMSO. Each compound dilution is then diluted 1:20 and then 1:25, both dilutions in Tyrode's buffer. Media is aspirated from the cell plates and the cells are rinsed twice with 100 µL of Tyrode's buffer (prewarmed to about 37 °C). 50 µL of compounds diluted in Tyrode's buffer are added to each well and the plates are incubated for about 15 min at about 37 °C in 5% CO₂. 50 µL of 0.2 µg/mL DNP-HSA in Tyrode's buffer is then added to each well and the plates are incubated for about 30 min at about 37 °C in 5% CO₂. The final concentration of the various components in the incubation mix are 0.002 – 10 µM compounds, 0.1% DMSO, and 0.1 µg/mL DNP-HSA. As one control, 0.2% DMSO (no compound) in Tyrode's buffer is added to a set of wells to determine maximum stimulated release. As a second control, Tyrode's buffer without DNP-HSA is added to a set of wells with containing 0.2% DMSO without compounds to determine unstimulated release. Each condition (compounds and controls) is set up in triplicate wells. At the end of the 30 min incubation, 50 µL of supernate is transferred to a new 96 well plate. The remaining supernate in the cell plates is aspirated and replaced with 50 µL of 0.1% Triton X-100 in Tyrode's buffer to lyse the cells. 50 µL of freshly prepared 1.8 mM 4-Nitrophenyl N-acetyl-β-D-glucosaminide (pNAG) is then added to each well of supernate and cell lysate and the plates are incubated for about 60 min at about 37 °C in 5% CO₂. 100 µL of 7.5 mg/mL sodium bicarbonate is added to each well to stop the reaction. The plates are then read at 405 nm on a Molecular Devices SpectraMax 250 plate reader.

Calculation of results

- 1) The plate background OD₄₀₅ obtained from wells containing Tyrode's buffer and pNAG (no supernate or lysate) is subtracted from the OD₄₀₅ reading for each well containing supernate or lysate.
- 2) The release for each well is expressed as the percentage of the total release for that well, where the total release is twice the release in the supernate plus the release in the cell lysate. This calculation corrects for variable cell number in each well.
- 3) The maximum response is the mean response of wells containing DNP-HSA but no compound.

- 4) The minimum response is the mean response of wells containing no DNP-HSA and no compound.
- 5) The response in each compound well is calculated as a percentage of the maximum response (expressed as % control) where the maximum response is 100% and the minimum response is 0%.
- 6) A dose response curve is generated for each compound and the IC₅₀ of the curve is calculated using Prism GraphPad software and nonlinear least squares regression analysis.

Acute *in vivo* measurement of JAK inhibition by compounds is measured using the:

Concanavalin A (Con A)-induced cytokine production in Lewis Rats

The test compound is formulated in an inert vehicle (for example but not limited to 0.5% hydroxypropylmethyl cellulose (Sigma, cat # H3785)/0.02% Tween 80 (Sigma, cat # 4780) in water) at the desired concentration to achieve doses in the range of 0.01- 100 mg/kg. Six-week-old male Lewis rats (125g-150g) (Charles River Laboratories) are dosed with the compound orally, at time zero (0 min). After about 30 min the rats are injected intravenously (i.v.) with 10 mg/kg Concanavalin A (Con A, AmershamBioscience, cat #17-0450-01) dissolved in PBS (Invitrogen, cat # 14190). About 4 h later, the rats are cardiac bled and their plasma is analyzed for levels of IL-2 (ELISA kit: R&D Systems cat #R2000) and IFN- γ (ELISA kit: R&D Systems cat #RIF00).

Acute *in vivo* measurement of Fc γ receptor signaling inhibition of the compounds is measured using the:

Reverse Passive Arthus Model

On day 0, OVA was made up at a concentration of 17.5mg/mL, in PBS by rocking gently until a solution was formed. 2% Evans Blue solution (Sigma Aldrich, cat # E2129) was then added to double the volume for a final concentration of 8.75 mg/mL of OVA and 1% Evans Blue dye. Anti-OVA antibody (Abazyme), stock concentration 10 mg/mL, was thawed and a 400 μ g/100 μ L solution was made with PBS. Compounds were made up by adding the vehicle, 0.5% HPMC with 0.02% Tween80, and vortexing for about 15 seconds followed by homogenizing for a minimum of about 2 min at 28,000 rpm until there was a fine particulate suspension with no clumps of compound. Rats were weighed and dosed with compound at a pre-determined t-max based on pharmacokinetic studies. Animals were then placed under general anesthesia with a 5% isoflourane and oxygen mixture and shaved. Using a 1/2 mL insulin syringe two sites were injected i.d., 1 site with 100 μ L of 400 μ g/100 μ L of anti-OVA antibody, and 1 site with 100 μ L of sterile PBS. Each site was then circled with permanent marker for explant later. Right after i.d. injections animals were injected with 200 μ L of the OVA (10mg/kg)/ Evans Blue mixture i.v., using a 1/2 mL insulin syringe. About four hours post injection animals were euthanized, bled via

cardiac puncture and blood was collected using a plasma separating tube. Blood samples were stored on ice until centrifugation (within about 2 h of collection). Each injection site was removed with a disposable biopsy punch (Acuderm Acu-Punch Disposable 12mm), cut into four pieces and placed in a pre-labeled 2 mL eppendorf tube. One mL of DMF was added to each biopsy tube and placed in a heat block for about 24 h at about 50 °C. About 24 h after incubation 100 µL of each sample was added to a 96 well flat bottom plate. The samples were read at 620 nm on a plate reader using the Softmax software in order to measure the levels of Evan's Blue dye. Background was removed by subtracting the OD from the PBS injected site from the OD of the anti-OVA injected site for each individual animal. Plasma samples were spun down in a microcentrifuge for about 5 min at 16.1 rcf. 200 µL of plasma was placed in a 1.7 mL eppendorf tube for drug level measurement and tubes were stored at -80 °C until evaluation.

Chronic *in vivo* effects of the compounds on an arthritis disease model is measured using the:

Adjuvant Induced Arthritis (AIA) in a Lewis Rat

Female Lewis rats, (6 weeks of age, 125g-150g in weight from Charles River Laboratories) are immunized intradermally (i.d.) in the right hind-footpad with 100 µL of a suspension of mineral oil (Sigma, cat # M5905) and containing 200 µg *M. tuberculosis*, H37RA (Difco, cat # 231141). The inflammation appears in the contra-lateral (left) hind paw seven days after the initial immunization. Seven days post immunization, the compound is formulated in an inert vehicle (for example but not limited to 0.5% hydroxypropylmethyl cellulose (Sigma, cat #H3785)/0.02% Tween 80 (Sigma, cat # 4780) in water) and dosed orally once or twice a day for at least 10 days. Baseline paw volume is taken on day 0 using a water displacement plethysmograph (Vgo Basile North America Inc. PA 19473, Model # 7140). Rats are lightly anesthetized with an inhalant anesthetic (isoflurane) and the contra-lateral (left) hind paw is dipped into the plethysmograph and the paw volume is recorded. The rats are scored every other day up to day 17 after immunization. On day 17 after immunization, all rats are exsanguinated by cardiac puncture under isoflurane anesthesia, and the left hind paw is collected to assess the impact on bone erosion using micro-CT scans (SCANCO Medical, Southeastern, PA, Model # µCT 40) at a voxel size of 18 µm, a threshold of 400, sigma-gauss 0.8, support-gauss 1.0. Bone volume and density is determined for a 360 µm (200 slice) vertical section encompassing the tarsal section of the paw. The 360 µm section is analyzed from the base of the metatarsals to the top of the tibia, with the lower reference point fixed at the tibiotalar junction. Drug exposure is determined in the plasma using LC/MS.

or the:

Collagen Induced Arthritis (CIA) in a Lewis Rat

On day -1 Collagen Type II (CII), soluble from bovine nasal septum (Elastin Products, Cat #CN276) was weighed out for a dose of 600 µg/rat, 0.01M acetic acid (150 µL HOAc USP grade. J.T.Baker, order# 9522-03, and 250 mL Milli Q Water) was added for a concentration of 4

mg/mL. The vial was covered with aluminum foil and placed on a rocker at about 4 °C overnight. On day 0 collagen stock solution was diluted 1:1 with Incomplete Freund's adjuvant (IFA) (Difco labs, cat #263910) using a glass Hamilton luer lock syringe (SGE Syringe Perfection VWR cat # 007230), final concentration 2 mg/mL. Female Lewis rats (Charles River Laboratories) acclimated for 7 days at the time of immunization weighing approximately 150 g were anesthetized in an anesthesia chamber using isoflurane (5%) and oxygen. Once the rats were completely anesthetized, they were transferred to a nose cone to maintain anesthesia during the injections. Rats were shaved at the base of the tail, 300 µL of collagen was injected i.d. on the rump of the rat, n=9 per group. 100 µL at three sites with a 500 µL luer lock syringe and a 27 g needle. IFA control rats are injected in the same manner (n=6). The IFA is a 1:1 emulsion with the 0.01M acetic acid. Boost was done on day 6 of the study. Shaving was not done on this day and injections were done in the same manner as the immunization. The inflammation appears in both hind paws 10 days after the initial immunization. 10 days post immunization, the compound was formulated in an inert vehicle (for example but not limited to 0.5% hydroxypropylmethyl cellulose (Sigma, cat # H3785)/0.02% Tween 80 (Sigma, cat # 4780) in water) and dosed orally once or twice a day for at least 9 days. Baseline paw volume was taken on day 7 using a water displacement plethysmograph (Vgo Basile North America Inc. PA 19473, Model # 7140). Rats were lightly anesthetized with an inhalant anesthetic (isoflurane) and both hind paws were dipped into the plethysmograph and the paw volume was recorded. The rats were scored 2 to 3 times a week up to day 18 after immunization. On day 18 after immunization, all rats were exsanguinated by cardiac puncture under isoflurane anesthesia, and the hind paws were collected to assess the impact on bone erosion using micro-CT scans (SCANCO Medical, Southeastern, PA, Model # µCT 40) at a voxel size of 18 µm, a threshold of 400, sigma-gauss 0.8, support-gauss 1.0. Bone volume and density was determined for a 360 µm (200 slice) vertical section encompassing the tarsal section of the paw. The 360 µm section was analyzed from the base of the metatarsals to the top of the tibia, with the lower reference point fixed at the tibiotalar junction. Drug exposure was determined from plasma using LC/MS.

Chronic *in vivo* effects of the compounds on an asthma disease model is measured using the:

OVA induced rat asthma model

Female Brown Norway rats (7-9 weeks of age) were sensitized on day 0 and 7 with 40 µg ovalbumin (OVA) (Sigma-Aldrich, St. Louis, MO) in a 20mg/ml solution of Alum Inject (Pierce, Rockford, IL). The rats were subsequently challenged intratracheally on day 19 and 20 with 1.5 µg OVA in 50 µL PBS. Dosing of inhibitor began on day 18 and continues through day 22. On day 22, 48 h after the second challenge, rats were subjected to an anesthetized and restrained pulmonary function test. Airway hyperresponsiveness (AHR) was assessed using whole body

plethysmography. Briefly, a surgical plane of anesthesia was induced with an intraperitoneal injection of 60mg/kg ketamine and 5 mg/kg xylazine (Henry Schein, Inc., Melville, NY). A tracheal cannula was surgically inserted between the 3rd and 4th tracheal rings. Spontaneous breathing was prevented by jugular vein injection of 0.12 mg/kg pancuronium bromide (Sigma-Aldrich, St Louis, MO). Animals were placed in a whole body plethysmograph (Buxco Electronics, Inc., Wilmington, NC) and mechanically ventilated with 0.2 mL room air at 150 breaths per minute with a volume controlled ventilator (Harvard Apparatus, Framingham, MA). Pressure in the lung and flow within the plethysmograph were measured using transducers and lung resistance was calculated as pressure/flow using Biosystem Xa software (Buxco Electronics). Airway resistance was measured at baseline and following challenge with 3, 10, and 30 mg/mL methacholine (Sigma Aldrich, St. Louis, MO) delivered with an inline ultrasonic nebulizer. Upon completion of pulmonary function testing, the lungs were lavaged 3 times with 1 mL sterile PBS. The volume from the first wash was centrifuged at 2000 rpm for 5 min, and the supernatant is stored for subsequent analysis. The volume of washes 2 through 3 are added to the pellet derived from the first wash and subsequently processed for evaluation of cellular infiltrate by flow cytometry. Plasma was collected from blood drawn from the vena cava and was used for evaluation of drug concentrations.

The following examples are for illustrative purposes and are not to be construed as limiting the scope of the present invention.

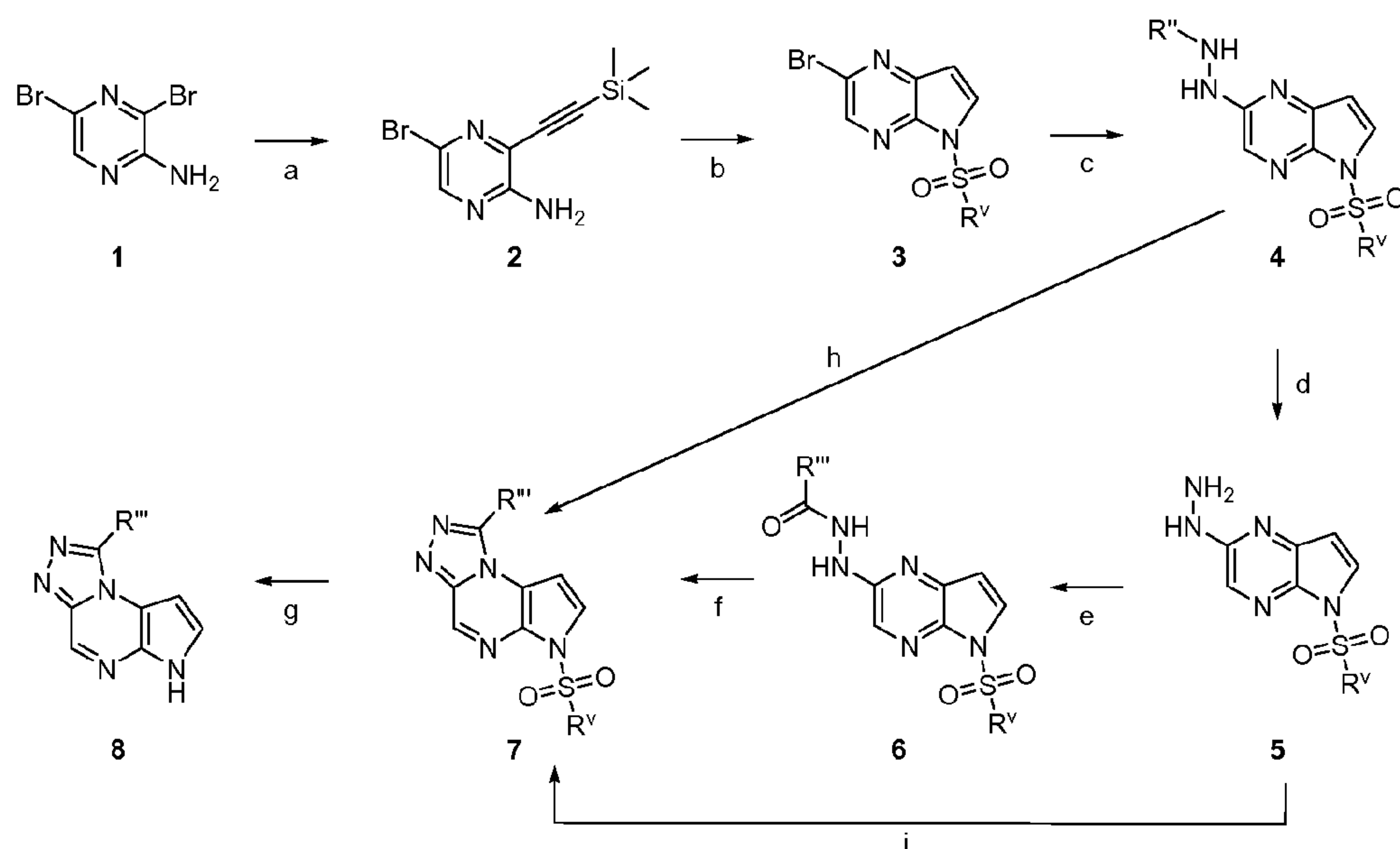
GENERAL SYNTHETIC SCHEMES

Compounds of the invention may be prepared using the synthetic transformations illustrated in Schemes I- XXVIII. Starting materials are commercially available, may be prepared by the procedures described herein, by literature procedures, or by procedures that would be well known to one skilled in the art of organic chemistry. Methods for preparing pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine compounds of the invention are illustrated in Scheme I. In Scheme I, step a, commercially available 3,5-dibromopyrazin-2-amine **1** is reacted with a (trimethylsilyl)acetylene via a Sonogashira cross coupling using methods known to one skilled in the art (for example Example #1 or WO2006058120A1) to give alkyne **2**. Alkyne **2** can be cyclized (Scheme I, step b) to provide protected pyrrolo[2,3-*b*]pyrazine **3** using methods known to one skilled in the art (for example Example #1 or WO2006058120A1). In Scheme I, step c, a substituted hydrazine is introduced by reaction with pyrrolopyrazines **3** under Buchwald-Hartwig amination conditions (for example Example #1 or *Advanced Synthesis & Catalysis* **2004**, 346, 1599-1626) to give pyrrolopyrazines **4**. If R" is such that pyrrolopyrazines **4** contain a hydrazide

(R"= -C(O)R'''), the material may be directly cyclized to pyrrolotriazolopyrazines **7** (Scheme I, step h) using conditions such as those described in General Procedures **B** or **ZZZZ** or by methods known to one skilled in the art (for example *Bioorganic & Medicinal Chemistry Letters* **2007**, 17(12), 3373-3377 or *Journal of Medicinal Chemistry* **1990**, 33(9), 2326-2334). If R" is a protecting group, deprotection of compounds **4** (Scheme I, step d) to yield hydrazinylpyrrolopyrazines **5** can be performed using conditions such as those described in General Procedures **E**, **E.1**, **F**, **F.1**, **Y** or **BB**; or Greene, T.W. and Wuts, P.G.M. "Protective Groups in Organic Synthesis, 3rd Edition", 1999, Wiley-Interscience. For example, a protecting group such as a *t*-butoxycarbonyl (Boc) group can be removed with acid using conditions such as those described in Example #1, General Procedures **E** and **E.1**, or by methods known to one skilled in the art (for example, the books from Larock, R.C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd edition", 1999, Wiley-VCH or Greene, T.W. and Wuts, P.G.M. referenced above). The formation of hydrazides **6** from hydrazinylpyrrolopyrazines **5** (Scheme I, step e) may be accomplished by a variety of methods known to one skilled in the art including *in situ* conditions such as those described in Example #1, General Procedure **A**, or standard peptide coupling methods such as those found in Larock, R.C. referenced above. The hydrazides **6** may be cyclized to pyrrolotriazolopyrazines **7** using conditions such as those described in Example #1, General Procedures **B**, **OO**, **OO.1**, or **ZZZZ**, or by methods known to one skilled in the art (for example, *Bioorganic & Medicinal Chemistry Letters* **2007**, 17(12), 3373-3377 or *Journal of Medicinal Chemistry* **1990**, 33(9), 2326-34). Further functionalization of hydrazides **6** or pyrrolotriazolopyrazines **7** can be performed, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, formation of amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared from pyrrolotriazolopyrazines **7** containing a primary or secondary amine (for example General Procedures **G**, **H**, **I**, **J**, **J.1**, **XXX**, **EEEE**, **K**, **K.1**, **L**, **DD**, **QQ**, **RR**, **YY**, **ZZ** followed by **AAA**, **CCC**, **YYY**, **X**, **X.1**, **TTTT**, or **EEEEEE**). Also, deprotection of hydrazides **6** or pyrrolotriazolopyrazines **7** containing a protected primary or secondary amine can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above or in General Procedures **E**, **E.1**, **F**, **F.1**, or **BB**. For example, for R''' containing a protecting group such as a benzyloxycarbonyl (Cbz) group, the protecting group can be removed to yield the unprotected amine (for example General Procedures **F**, **F.1**, and **DDDDD**) and the deprotected compounds **7** may then be reacted further as described above. In some cases, additional reactions may also occur without isolation of initial pyrrolotriazolopyrazines **7** as seen in General Procedure **C**. Alternatively, hydrazinylpyrrolopyrazines **5** may be directly cyclized to pyrrolotriazolopyrazines **7** (Scheme I, step i) using conditions such as those described in General Procedure **BBBBB**. Removal of the sulfonamide protecting group of pyrrolotriazolopyrazines **7**

may be accomplished using conditions such as those described in Example #1, General Procedures **D**, **XXX**, **AAAA**, **BBBB**, or **CCCC** or by methods known to one skilled in the art (for example, the books from Larock, R.C. or Greene, T.W. and Wuts, P.G.M. referenced above) to give pyrrolotriazolopyrazines **8** (Scheme I, step g). Further functionalization of the R^{'''} group in pyrrolotriazolopyrazines **8** can be performed, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared from pyrrolotriazolopyrazines **8** with an R^{'''} containing a primary or secondary amine (for example Examples #8-9 or General Procedures **G**, **H**, **I**, **J**, **J.1**, **XXX**, **EEEE**, **K**, **K.1**, **L**, **DD**, **QQ**, **RR**, **YY**, **ZZ** followed by **AAA**, **CCC**, **YYY**, **X**, **X.1**, **TTTT**, or **EEEE**). Also, deprotection of the R^{'''} group in pyrrolotriazolopyrazines **8** to yield an unprotected compound can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above or in General Procedures **E**, **E.1**, **F**, **F.1**, **Y**, or **BB**. For example, a protecting group such as a benzyloxycarbonyl (Cbz) group can be removed from a protected amine to yield the unprotected amine (for example General Procedures **F**, **F.1**, and **DDDDD**) and the deprotected compounds **8** may then be reacted further as described above.

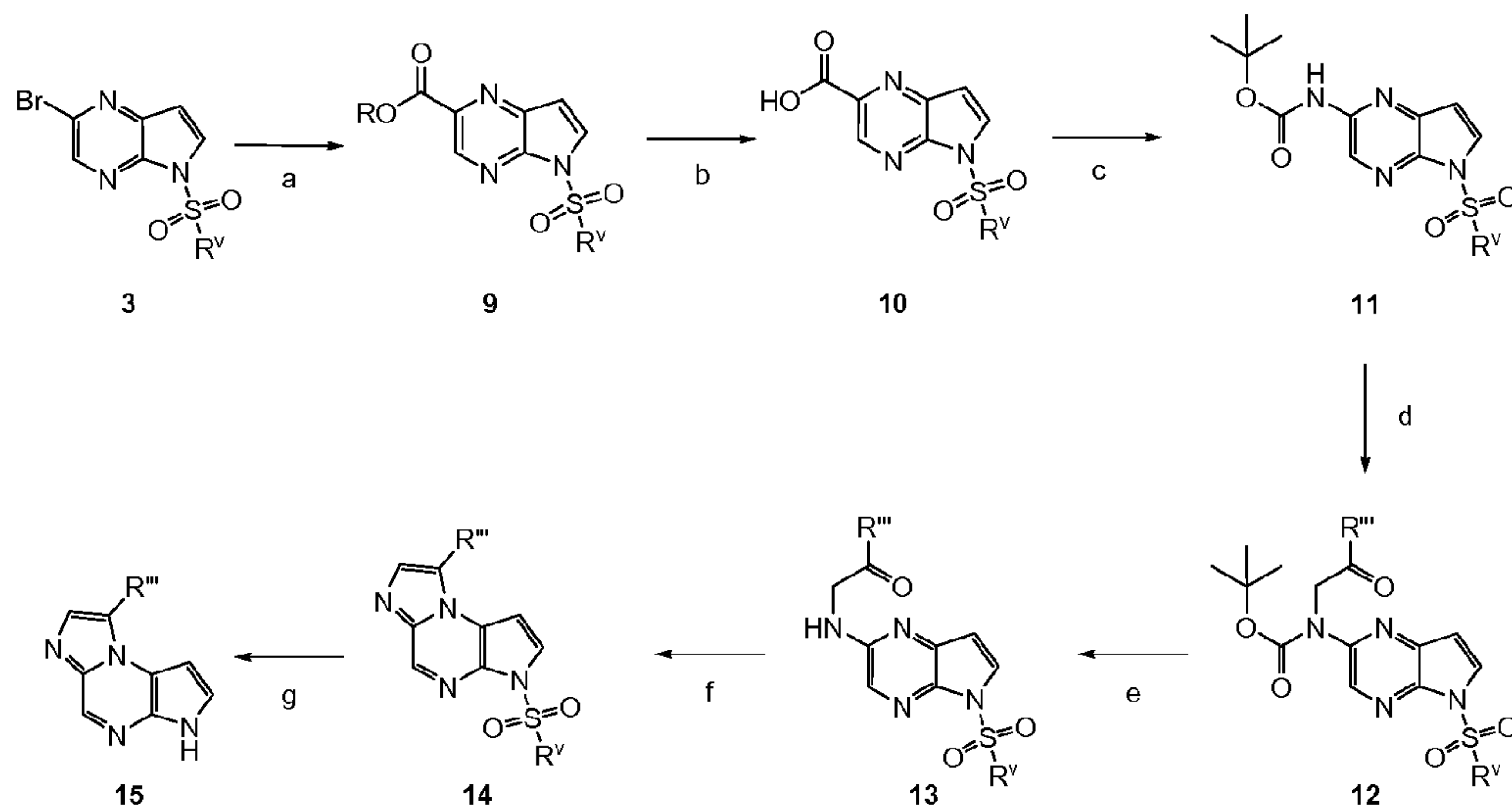
Scheme I



Methods for preparing imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazines compounds of the invention are illustrated in Scheme II. In step a, Pd-mediated carbonylation of pyrrolopyrazines **3** gives esters **9** using methods known to one skilled in the art such as those described in Example #3; U.S. Pat. Appl. Publ., US 2007293509; or U.S. Pat. Appl. Publ., US 2008248537. Hydrolysis of

esters **9** gives acids **10** (Scheme II, step b) using well known conditions such as those described in Example #3 or General Procedure **Z**. A Curtius rearrangement is used to prepare carbamates **11** as shown in Scheme II, step c using conditions such as those described in Example #3 or referenced in Li, J.J. "Name Reactions. A Collection of Detailed Reaction Mechanisms, 2nd edition", 2003, Springer: New York. Alkylation of pyrrolopyrazin-2-ylcarbamates **11** with appropriately substituted 2-halomethyl ketones (which may be prepared via procedures such as those described in General Procedures **R** and **LLLL**; *Tetrahedron Letters*, **1992**, (33), 309-312) by methods known to one skilled in the art (for example General Procedures **S** or **S.1**; *Tetrahedron Letters*, **2006**, 47(34), 6113-6115; or *Journal of Medicinal Chemistry*, **2005**, 48(14), 4535-4546) yields pyrrolopyrazines **12** (Scheme II, step d). The deprotection of pyrrolopyrazines **12** to pyrrolopyrazines **13** (Scheme II, step e) is accomplished using conditions such as those described in General Procedures **E** and **E.1**, or in Greene, T.W. and Wuts, P.G.M. referenced above. As shown in Scheme II, step f, cyclization of pyrrolopyrazines **13** to imidazopyrrolopyrazines **14** can be accomplished by methods known to one skilled in the art (for example, General Procedures **T** or **KKKK**; Example #3, *European Journal of Medicinal Chemistry*, **2001**, 36(3), 255-264; or *Bioorganic and Medicinal Chemistry Letters*, **2007**, 17(5), 1233-1237). Further functionalization of the R''' group in imidazopyrrolopyrazines **14** can be performed, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared from imidazopyrrolopyrazines **14** with an R''' group containing a primary or secondary amine (for example, Example #3, Example #7, or General Procedures **G**, **H**, **I**, **J**, **J.1**, **XXX**, **EEEE**, **K**, **K.1**, **L**, **DD**, **QQ**, **RR**, **YY**, **ZZ** followed by **AAA**, **CCC**, **YYY**, **X**, **X.1**, **TTTT**, or **EEEEEE**). Also, deprotection of the R''' group in imidazopyrrolopyrazines **14** to yield deprotected compounds **14** can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above or in General Procedures **E**, **E.1**, **F**, **F.1**, **Y**, or **BB** and the deprotected compounds **14** may then be reacted further as described above. Removal of the sulfonamide protecting group of imidazopyrrolopyrazines **14** may be accomplished using conditions such as those described in Example #3, General Procedures **D**, **XXX**, **AAAA**, **BBBB**, or **CCCC** or by methods known to one skilled in the art (for example, the books from Larock, R.C. or Greene, T.W. and Wuts, P.G.M. referenced above) to give imidazopyrrolopyrazines **15** (Scheme II, step g).

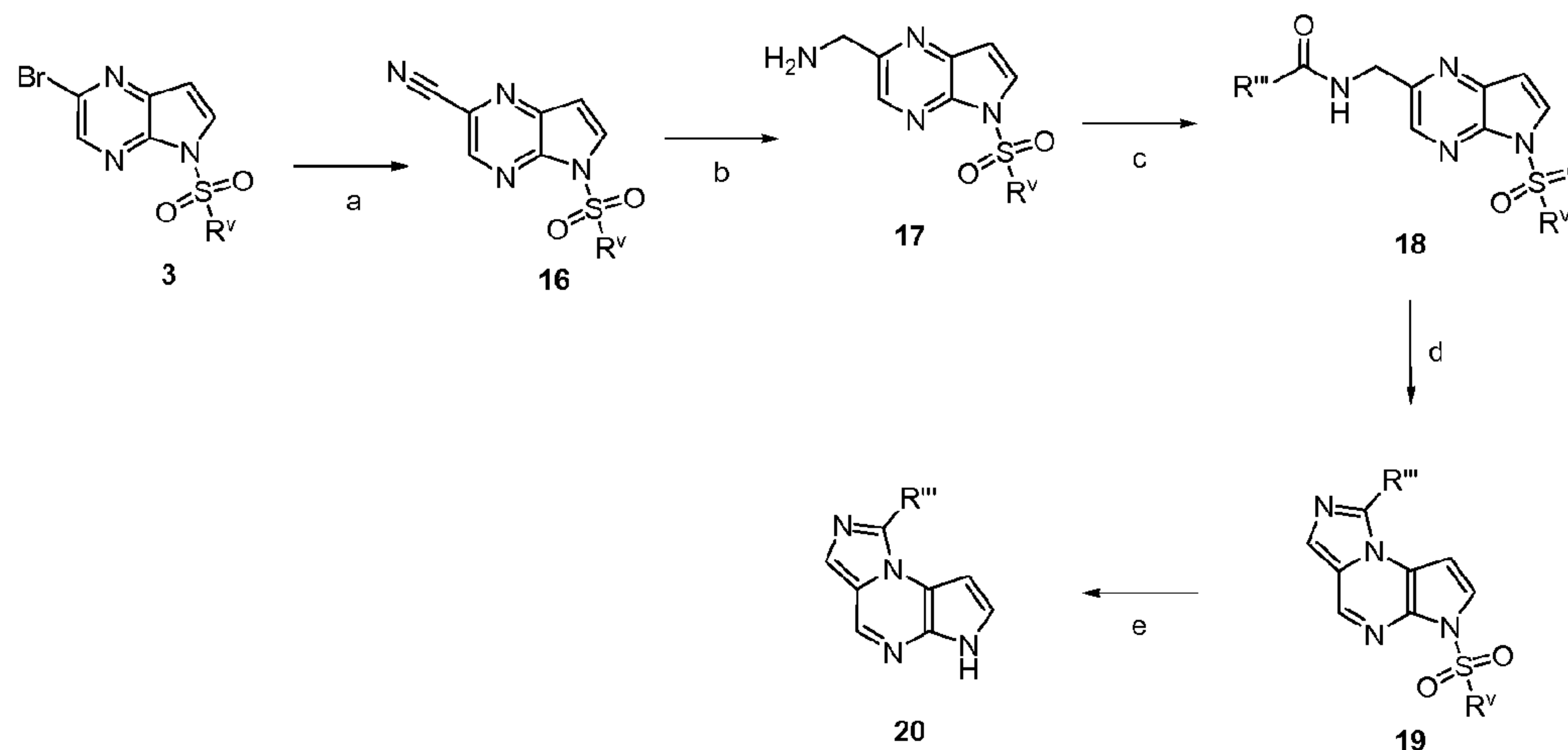
Scheme II



Methods for preparing imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines compounds of the invention are illustrated in Scheme III. In step a, Pd-mediated cyanation of bromides **3** gives the corresponding nitriles **16** (for example Example #5 or *Tetrahedron Letters* **1999**, 40(47), 8193-8195). Subsequent reduction of nitriles **16** gives amines **17** (Scheme III, step b) using methods known to one skilled in the art (for example Example #5 or *Journal of Medicinal Chemistry* **2003**, 46(4), 461-473). The coupling of amines **17** with acids provides amides **18** (Scheme III, step c) using well known conditions such as those given in Example #5 or General Procedure **H**. As shown in Scheme III, step d, the cyclization of amides **18** can be accomplished by conversion to the thioamide followed by treatment with an activating agent (such as a mercury salt, a silver salt or a copper salt) providing the imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines **19** (for example Example #5 or General Procedure **Q**). Alternatively, if R^{'''} contains a nitrogen such that the compounds **18** are ureas instead of amides, then cyclization to imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines **19** may be accomplished using POCl₃ as described in General Procedure **OO** or **OO.1**. Deprotection of the sulfonamide of compounds **19** to yield imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines **20** (Scheme III, step e) can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. "Protective Groups in Organic Synthesis, 3rd Edition", 1999, Wiley-Interscience, General Procedures **D**, **XXX**, **AAAA**, **BBBB**, or **CCCC**, or Example #5. Further functionalization of the R^{'''} group in imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines **19** or imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines **20** can be performed, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, formation of amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared from compounds **19** or **20** with an R^{'''} group containing a primary or secondary amine (for example, Example #6, or General Procedures **G**, **H**, **I**, **J**, **J.1**, **XXX**, **EEEE**, **K**, **K.1**, **L**, **DD**,

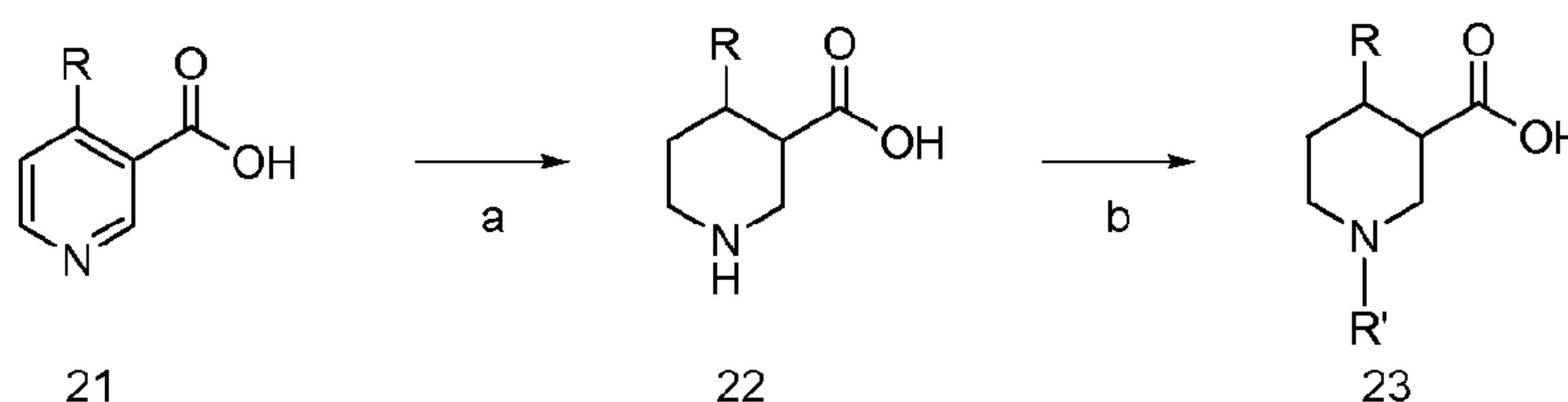
QQ, RR, YY, ZZ followed by **AAA, CCC, YYY, X, X.1, TTTT**, or **EEEE**). Also, deprotection of the R^{'''} group in compounds **19** or **20** to yield an unprotected compound can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above or in General Procedures **E, E.1, F** or **F.1** and the deprotected compounds may then be reacted further as described above.

Scheme III



Methods for preparing 4-substituted piperidine-3-carboxylic acid compounds of the invention are illustrated in Scheme IV. In step a, 4-substituted nicotinic acids **21** may be fully saturated using methods that are known to one skilled in the art (for example, General Procedure **O** or *Bioorganic and Medicinal Chemistry Letters* **2004**, 14(17), 4453-4459). The resulting piperidines **22** may be protected with a suitable amine protecting group (Scheme IV, step b) such as those described in Greene, T.W. and Wuts, P.G.M. "Protective Groups in Organic Synthesis, 3rd Edition", 1999, Wiley-Interscience; Larock, R.C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd edition", 1999, Wiley-VCH or General Procedures **M, M.1**, or **N** to give protected piperidines **23**.

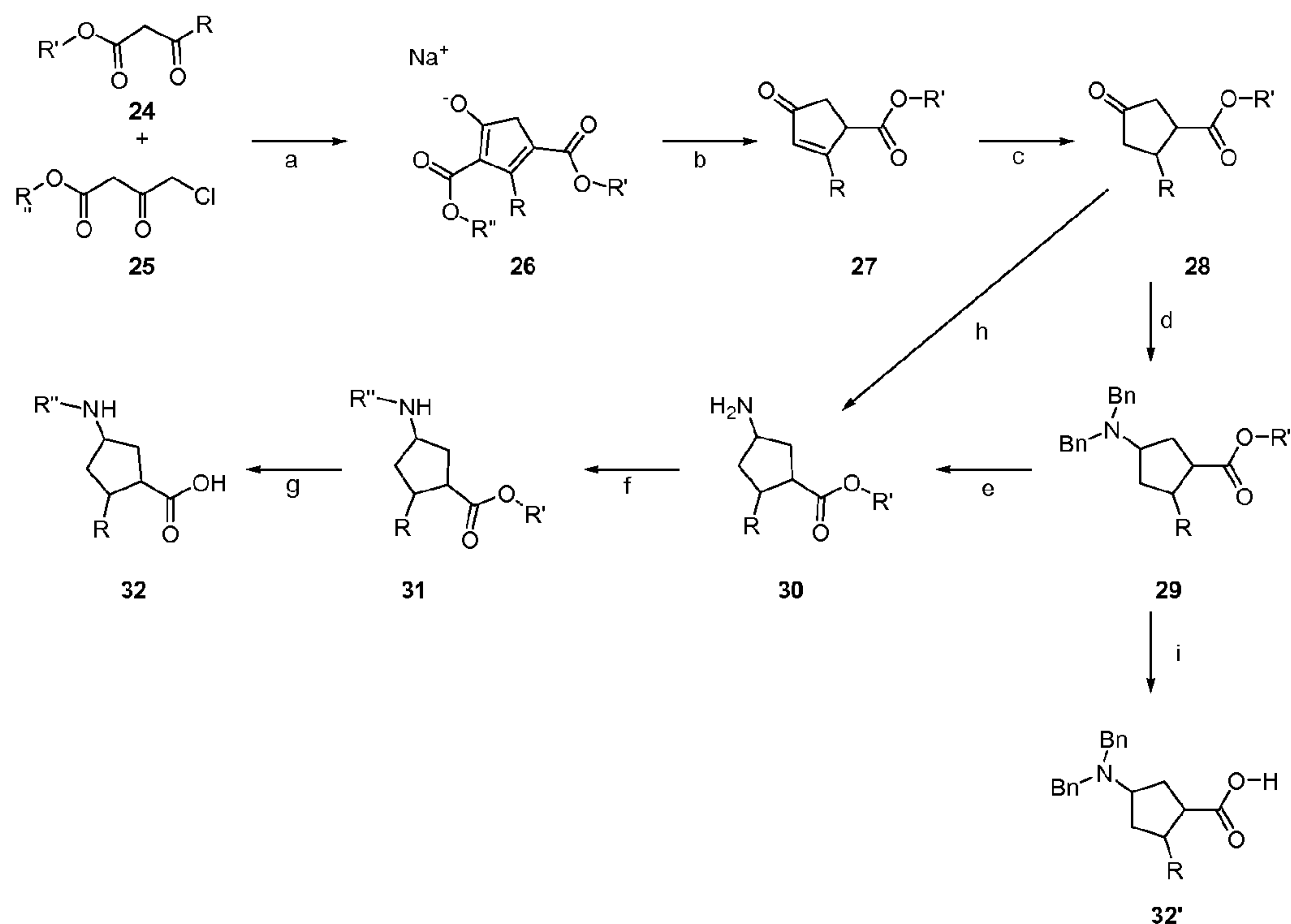
Scheme IV



Methods for preparing amino-substituted cyclopentyl carboxylic acids **32** for use in the preparation of compounds of the invention are illustrated in Scheme V. In step a, β -ketoesters **24**

may be condensed with an alkyl 4-chloroacetoacetate **25** to give cyclic β -ketoester enolate salts **26** (for example, General Procedure U). Decarboxylation of compounds **26** to give α,β -unsaturated ketones **27** (Scheme V, step b) is accomplished by standard methods known to one skilled in the art (for example, General Procedure V). As shown in step c, hydrogenation of α,β -unsaturated ketones **27** provides the saturated ketones **28** (for example, General Procedures W or W.1). Reductive amination of ketones **28** with dibenzylamine yields compounds **29** (Scheme V, step d) using conditions such as those described in General Procedures X or X.1. The debenzylation of compounds **29** may be accomplished via hydrogenation as described in General Procedure Y to give amines **30** (Scheme V, step e). Alternate conditions may be used to access amines **30** from ketones **28**, for example, as described in Larock, R.C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd edition", 1999, Wiley-VCH (Scheme V, step h). Amines **30** may undergo further functionalization using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared from amines **30** (for example, General Procedures G, H, I, J, J.1, XXX, EEEE, K, K.1, L, DD, QQ, RR, YY, ZZ followed by AAA, CCC, YYY, X, X.1, TTTT, or EEEEE) to give compounds **31** (Scheme V, step f). The ester of compounds **31** may be hydrolyzed under aqueous base or acid conditions to give the desired carboxylic acids **32** (Scheme V, step g) using conditions such as those described in General Procedures Z or TT or Larock, R.C. referenced above). Alternatively, the ester of compounds **29** may be hydrolyzed to give intermediate carboxylic acids **32'** as shown in Scheme V, step i, using aqueous base or acid conditions (for example, Preparation #TT.1).

Scheme V

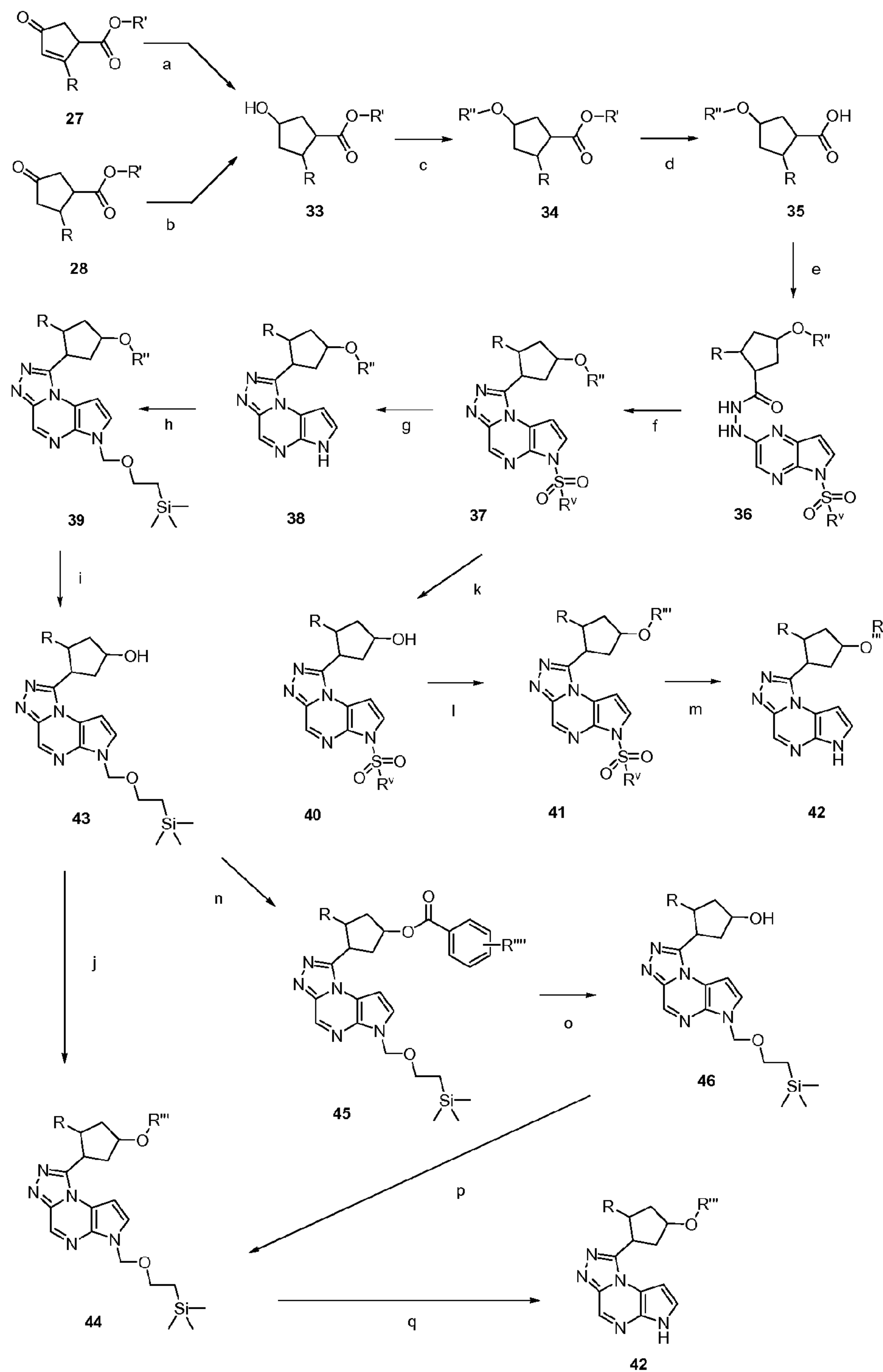


Methods for preparing ether-substituted 1-cyclopentyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazine compounds of the invention are illustrated in Scheme VI. As shown in step a, reduction of α,β -unsaturated ketones **27** with concomitant reduction of the ketone provides the saturated alcohols **33** (for example, the chiral reduction conditions described in Example #4). Alternate conditions may be used to access alcohols **33** from ketones **28** via reduction (Scheme VI, step b) as described in General Procedure **P** or in Larock, R.C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd edition", 1999, Wiley-VCH. The alcohols **33** may be reacted to give ethers **34** (Scheme VI, step c) using conditions such as those described in General Procedure **EE** (which may require first making the 2,2,2-trichloroimidate as described in General Procedure **UU**), **II**, **JJ**, or **VV** followed by General Procedure **FFF** or by methods known to one skilled in the art (for example, *Tet. Lett.* **1983**, 24(48), 5363 or Greene, T.W. and Wuts, P.G.M. "Protective Groups in Organic Synthesis, 3rd Edition", 1999, Wiley-Interscience). The ester of compounds **34** may be hydrolyzed under aqueous base or acid conditions to give the desired carboxylic acids **35** (Scheme VI, step d), using conditions such as those described in General Procedure **Z** or **TT** or Larock, R.C. referenced above. The formation of hydrazides **36** from hydrazinylpyrrolopyrazines **5** and carboxylic acids **35** (Scheme VI, step e) may be accomplished by a variety of methods known to one skilled in the art such as those described in General Procedure **A** or standard peptide coupling methods such as

those found in Larock, R.C. referenced above. The hydrazides **36** may be cyclized to pyrrolotriazolopyrazines **37** (Scheme VI, step f) using conditions such as those described in General Procedures **B** or **ZZZZ** or by methods known to one skilled in the art (for example, *Bioorganic & Medicinal Chemistry Letters* **2007**, 17(12), 3373-3377 or *Journal of Medicinal Chemistry* **1990**, 33(9), 2326-2334). Removal of the sulfonamide protecting group of pyrrolotriazolopyrazines **37** may be accomplished using conditions such as those described in General Procedures **D**, **AAAA**, **BBBB**, or **CCCC** or by methods known to one skilled in the art (for example, the books from Larock, R.C. or Greene, T.W. and Wuts, P.G.M. referenced above) to give pyrrolotriazolopyrazines **38** as final products or intermediates (Scheme VI, step g). The pyrrolotriazolopyrazines **38** may be SEM protected (Scheme VI, step h) using conditions such as those described in General Procedure **KK**, or as described in Greene, T.W. and Wuts, P.G.M. referenced above. If the R" group in pyrrolotriazolopyrazines **37** or **39** is a protecting group, it may be deprotected to yield alcohols **40** (Scheme VI, step k) or **43** (Scheme VI, step i), respectively, using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above. For example, a protecting group such as a *p*-methoxybenzyl (PMB) group can be removed from a PMB-ether to yield the unprotected alcohol (for example General Procedure **FF**) and the deprotected compounds **40** or **43** may then be reacted further. Mitsunobu reaction of alcohols **40** or **43** may be used to prepare ethers or esters **41** (Scheme VI, step l), **44** (Scheme VI, step j), or **45** (Scheme VI, step n) with inversion at the reacting center using conditions such as those described in General Procedure **II** or by methods known to one skilled in the art such as those found in Larock, R. C. referenced above. Additionally, ethers **44** may be prepared from alcohols **43** via alkylation using conditions such as those described in General Procedure **HHHH**. Alternatively, alcohols **40** or **43** may be converted to carbamates **41** or **44** using well-known conditions such as those described in General Procedures **OOO**, **WWW** and **PPPP**. Removal of the sulfonamide protecting group of pyrrolotriazolopyrazines **41** may be accomplished using conditions such as those described in General Procedures **D**, **AAAA**, **BBBB**, **CCCC** or **PPPP**, or by methods known to one skilled in the art (for example, the books from Larock, R.C. or Greene, T.W. and Wuts, P.G.M. referenced above) to give pyrrolotriazolopyrazines **42** (Scheme VI, step m). The ester group of esters **45** may be cleaved to yield the unprotected alcohols **46** (Scheme VI, step o) using conditions such as those described in General Procedure **SS**. The alcohols **46** can be reacted further to form ethers **44** (Scheme VI, step p) via Mitsunobu chemistry (in a manner as described for Scheme VI, step j) or by conditions such as those described in General Procedure **EE** (which may require first making the 2,2,2-trichloroimidate as described in General Procedure **UU**) or **JJ** or by methods known to one skilled in the art (for example, the book from Larock, R.C. referenced above). The SEM protecting group of pyrrolotriazolopyrazines **44** may be removed by methods such as those described in General Procedures **LL** and **LL.1**, or using

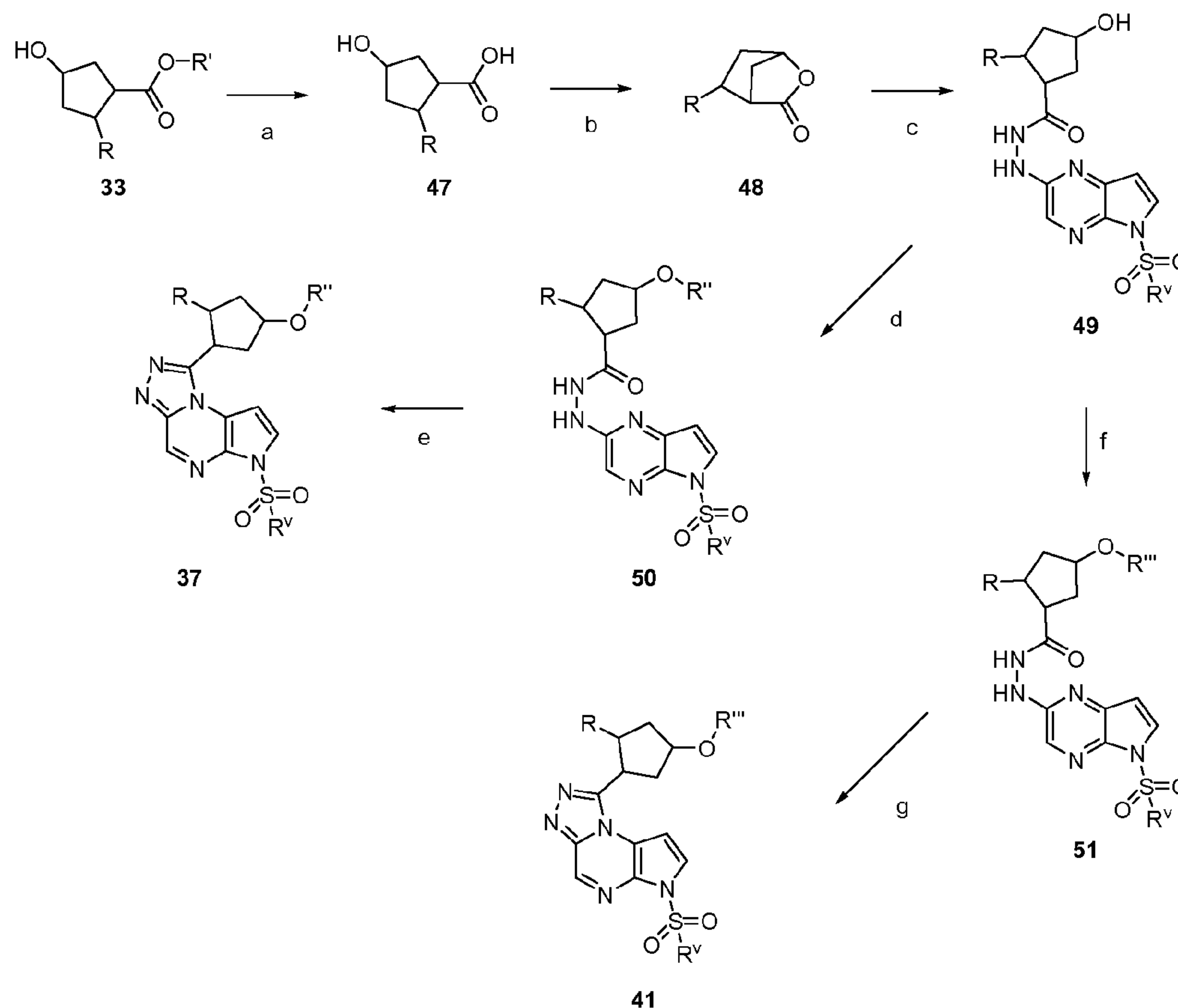
conditions such as described in Greene, T.W. and Wuts, P.G.M. referenced above to give pyrrolotriazolopyrazines **42** (Scheme VI, step q).

Scheme VI



An alternate method for preparing ether-substituted 1-cyclopentyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine compounds of the invention is illustrated in Scheme VII. As shown in step a, the ester of compounds **33** may be hydrolyzed under aqueous base or acid conditions to give the desired carboxylic acids **47**, using conditions such as those described in General Procedures **Z** or **TT** or Larock, R.C. referenced above. The formation of lactones **48** from carboxylic acids **47** (Scheme VII, step b) may be accomplished by methods such as those described in Example #4, General Procedure **GG**, or by methods known to one skilled in the art such as those found in Larock, R.C. referenced above. The formation of hydrazides **49** from hydrazinylpyrrolopyrazines **5** and lactones **48** (Scheme VII, step c) may be accomplished by a variety of methods known to one skilled in the art such as those described in Example #4 or General Procedure **HH**. The alcohols **49** may be reacted to form ethers **50** (Scheme VII, step d) using conditions such as those described in General Procedures **VV** (which may require first making the 2,2,2-trichloroimidate as described in General Procedure **UU**) or **JJ**, or by methods known to one skilled in the art (for example, *Tet. Lett.* **1983**, 24(48), 5363). Mitsunobu reaction of alcohols **49** may be used to prepare ethers **51** (Scheme VII, step f) with inversion at the reacting center using conditions such as those described in Example #4, General Procedure **II**, or by methods known to one skilled in the art such as those found in Larock, R. C. referenced above. The hydrazides **50** or **51** may be cyclized to pyrrolotriazolopyrazines **37** (Scheme VII, step e) or **41** (Scheme VII, step g) using conditions such as those described in Example #4, General Procedures **B** or **ZZZZ**, or by methods known to one skilled in the art (for example, *Bioorganic & Medicinal Chemistry Letters* **2007**, 17(12), 3373-3377 or *Journal of Medicinal Chemistry* **1990**, 33(9), 2326-2334). Further elaboration of **37** or **41** may be performed as described in Scheme VI.

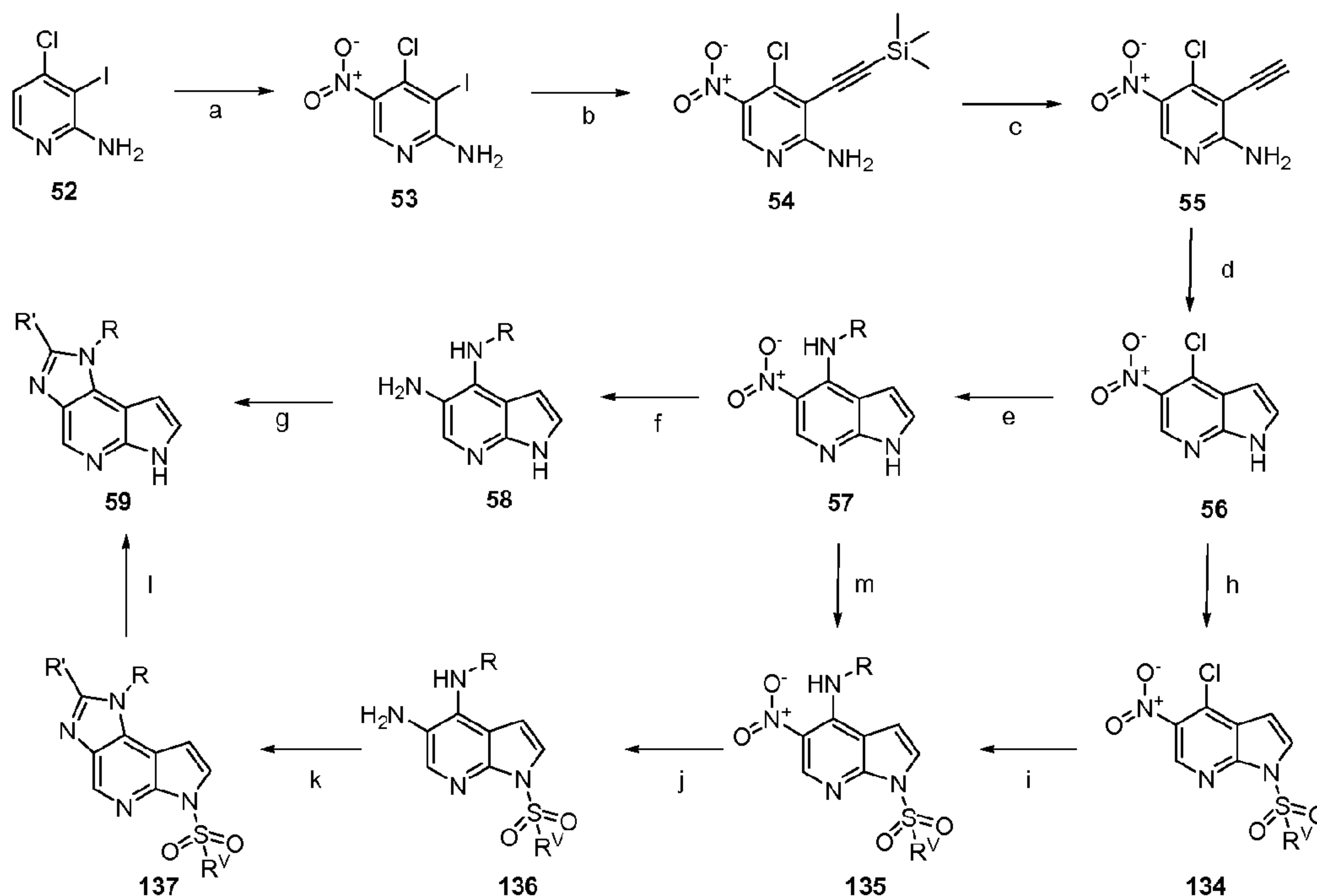
Scheme VII



Methods for preparing 1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine compounds of the invention are illustrated in Scheme VIII. As shown in step a, 4-chloro-3-iodopyridin-2-amine **52** may be nitrated to give 4-chloro-3-iodo-5-nitropyridin-2-amine **53** as described in Example #21 or in Larock, R.C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd edition", 1999, Wiley-VCH. 4-Chloro-3-iodo-5-nitropyridin-2-amine **53** is reacted with a (trimethylsilyl)acetylene via a Sonogashira cross coupling using methods known to one skilled in the art (for example Example #21 or WO2006058120A1) to give 4-chloro-5-nitro-3-((trimethylsilyl)ethynyl)pyridin-2-amine **54** (Scheme VIII, step b). As shown in step c, 4-chloro-5-nitro-3-((trimethylsilyl)ethynyl)pyridin-2-amine **54** is deprotected to give the 4-chloro-3-ethynyl-5-nitropyridin-2-amine **55** as described in Example #21 or using methods known to one skilled in the art (for example, the books from Greene, T.W. and Wuts, P.G.M. "Protective Groups in Organic Synthesis, 3rd Edition", 1999, Wiley-Interscience or Larock, R.C. referenced above). 4-Chloro-3-ethynyl-5-nitropyridin-2-amine **55** is cyclized, as shown in step d, to give 4-chloro-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine **56** as described in Example #21, or by methods known to one skilled in the art (for example, as described in WO2008004117). As shown in step e, amino-substituted 1*H*-pyrrolo[2,3-*b*]pyridines **57** are prepared using methods known to one

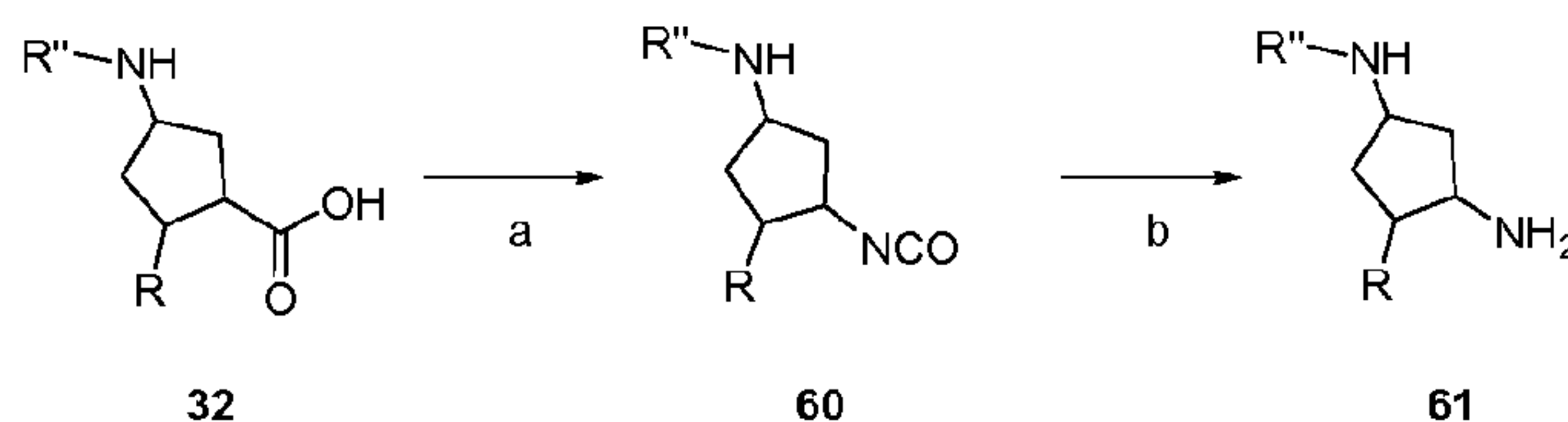
skilled in the art (for example, Example #21 or Larock, R.C. referenced above). Diamino-substituted 1*H*-pyrrolo[2,3-*b*]pyridines **58** (Scheme VIII, step f) are prepared from the reduction of nitro-containing 1*H*-pyrrolo[2,3-*b*]pyridines **57** using methods known to one skilled in the art (for example, Example #21, General Procedure **BBB**, or Larock, R.C. referenced above). As shown in step g, diamino-substituted 1*H*-pyrrolo[2,3-*b*]pyridines **58** can be cyclized as described in Example #21 or General Procedure **DDD** to give 1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridines **59**. Further functionalization of the R group in 1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridines **59** can be performed, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared from 1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridine **59** with an R group containing a primary or secondary amine (for example General Procedures **G**, **H**, **I**, **J**, **J.1**, **XXX**, **EEEE**, **K**, **K.1**, **L**, **DD**, **QQ**, **RR**, **YY**, **ZZ** followed by **AAA**, **CCC**, **YYY**, **X**, **X.1**, **TTTT**, or **EEEEE**). Also, deprotection of the R group in 1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridines **59** to yield an unprotected compound can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above or in General Procedures **E**, **E.1**, **F**, **F.1**, **Y**, or **BB**. For example, a protecting group such as a benzyloxycarbonyl (Cbz) group can be removed from a protected amine to yield the unprotected amine (for example General Procedures **F**, **F.1**, or **Y**) and the deprotected compounds **59** may then be reacted further as described above. Alternatively, intermediates **56** or **57** may be sulfonamide protected using reactions known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above or General Procedure **K.1**) to give sulfonamides **134** and **135** respectively (Scheme VII, steps h and m). As shown in step i, amino-substituted 1*H*-pyrrolo[2,3-*b*]pyridines **135** may also be prepared from chloro-substituted 1*H*-pyrrolo[2,3-*b*]pyridines **134** using methods known to one skilled in the art (for example, Example #23 or Larock, R.C. referenced above). Diamino-substituted 1*H*-pyrrolo[2,3-*b*]pyridines **136** are prepared from the reduction of nitro-containing 1*H*-pyrrolo[2,3-*b*]pyridines **135** using methods known to one skilled in the art (for example, Example #23, General Procedure **BBB**, or Larock, R.C. referenced above). As shown in step k, diamino-substituted 1*H*-pyrrolo[2,3-*b*]pyridines **136** can be cyclized as described in Example #23 or General Procedure **DDD** to give sulfonamide-protected 1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridines **137**. Deprotection of the sulfonamide of compounds **137** to yield 1,6-dihydroimidazo[4,5-*d*]pyrrolo[2,3-*b*]pyridines **59** (Scheme VIII, step l) can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. "Protective Groups in Organic Synthesis, 3rd Edition", 1999, Wiley-Interscience, General Procedures **D**, **XXX**, **AAAA**, **BBBB**, or **CCCC** or Example #23.

Scheme VIII



Methods for preparing substituted cyclopentyl amines **61** for use in the preparation of compounds of the invention are illustrated in Scheme IX. In step a, carboxylic acids **32** are subjected to a Curtius rearrangement as described in General Procedure **NNN** to form isocyanates **60**. The hydrolysis of isocyanates **60** yields amines **61** (for example, General Procedure **OOO**).

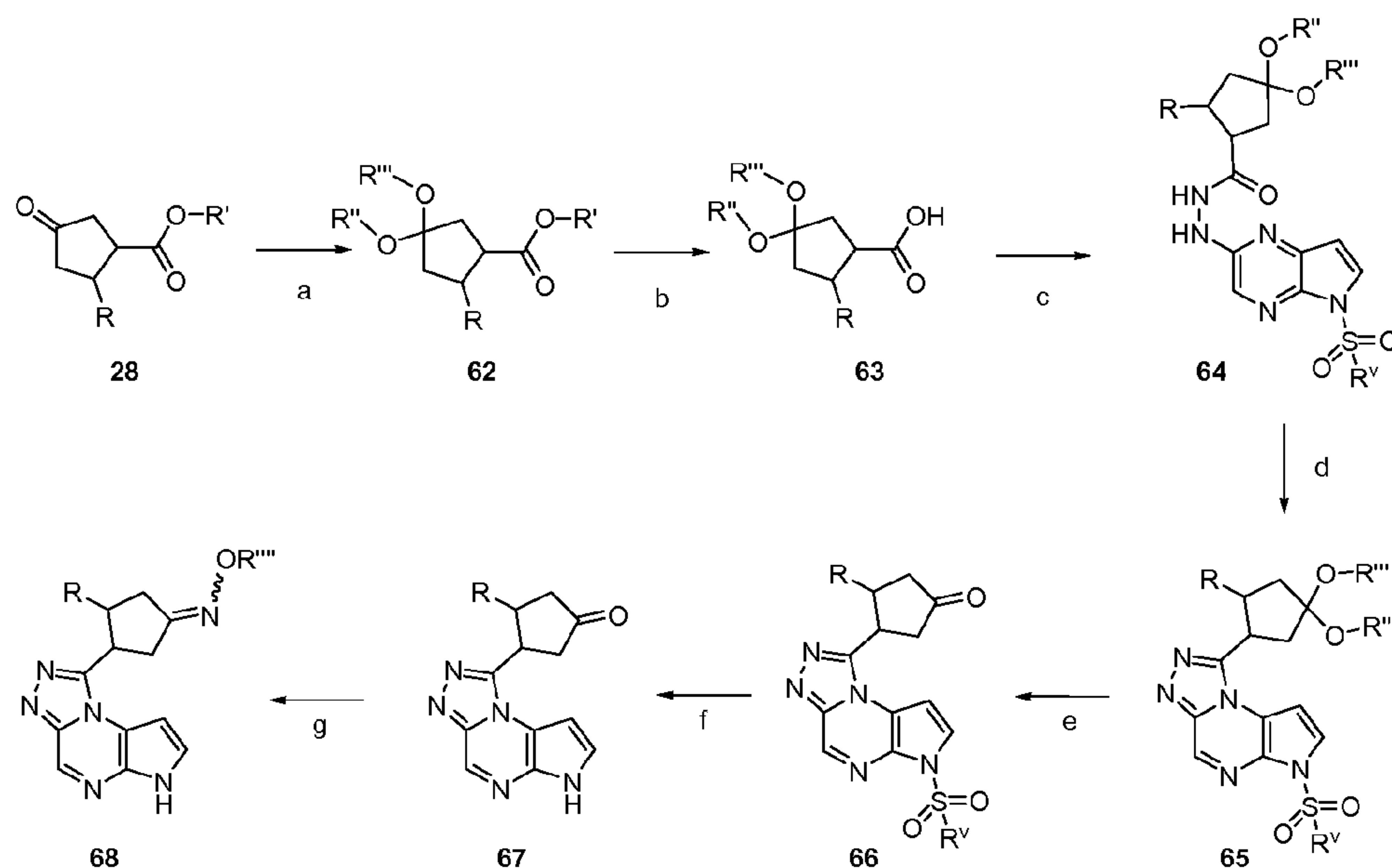
Scheme IX



Methods for preparing 4-(6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanones and their derivatives as compounds of the invention are illustrated in Scheme X. In step a, ketones **28** are protected as ketals **62** using conditions as described in General Procedure **WW** or as those described in Greene, T.W. and Wuts, P.G.M. referenced above. The ester of compounds **62** may be hydrolyzed under aqueous base conditions to give the desired carboxylic acids **63** (Scheme X, step b), using conditions such as those described in General Procedure **Z** or Larock, R.C. referenced above. The formation of hydrazides **64** from hydrazinylpyrrolopyrazines **5** and carboxylic acids **63** (Scheme X, step c) may be accomplished by a variety of methods

known to one skilled in the art such as those described in General Procedure **A** or standard peptide coupling methods such as those found in Larock, R.C. referenced above. The hydrazides **64** may be cyclized to pyrrolotriazolopyrazines **65** (Scheme X, step d) using conditions such as those described in General Procedures **B** or **ZZZZ** or by methods known to one skilled in the art (for example, *Bioorganic & Medicinal Chemistry Letters* **2007**, 17(12), 3373-3377 or *Journal of Medicinal Chemistry* **1990**, 33(9), 2326-2334). Ketals **65** may be deprotected to yield ketones **66** as described in Preparation #25 or Greene, T.W. and Wuts, P.G.M. referenced above. Deprotection of the sulfonamide protecting group of pyrrolotriazolopyrazines **66** may be accomplished using conditions such as those described in General Procedures **D**, **AAAA**, **BBBB**, or **CCCC** or by methods known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above) to give pyrrolotriazolopyrazines **67** as final products or intermediates (Scheme X, step f). For example, step g illustrates the formation of oxime ethers **68** from ketones **67** which may be accomplished using conditions such as those described in General Procedure **PPP** or Larock, R.C. referenced above.

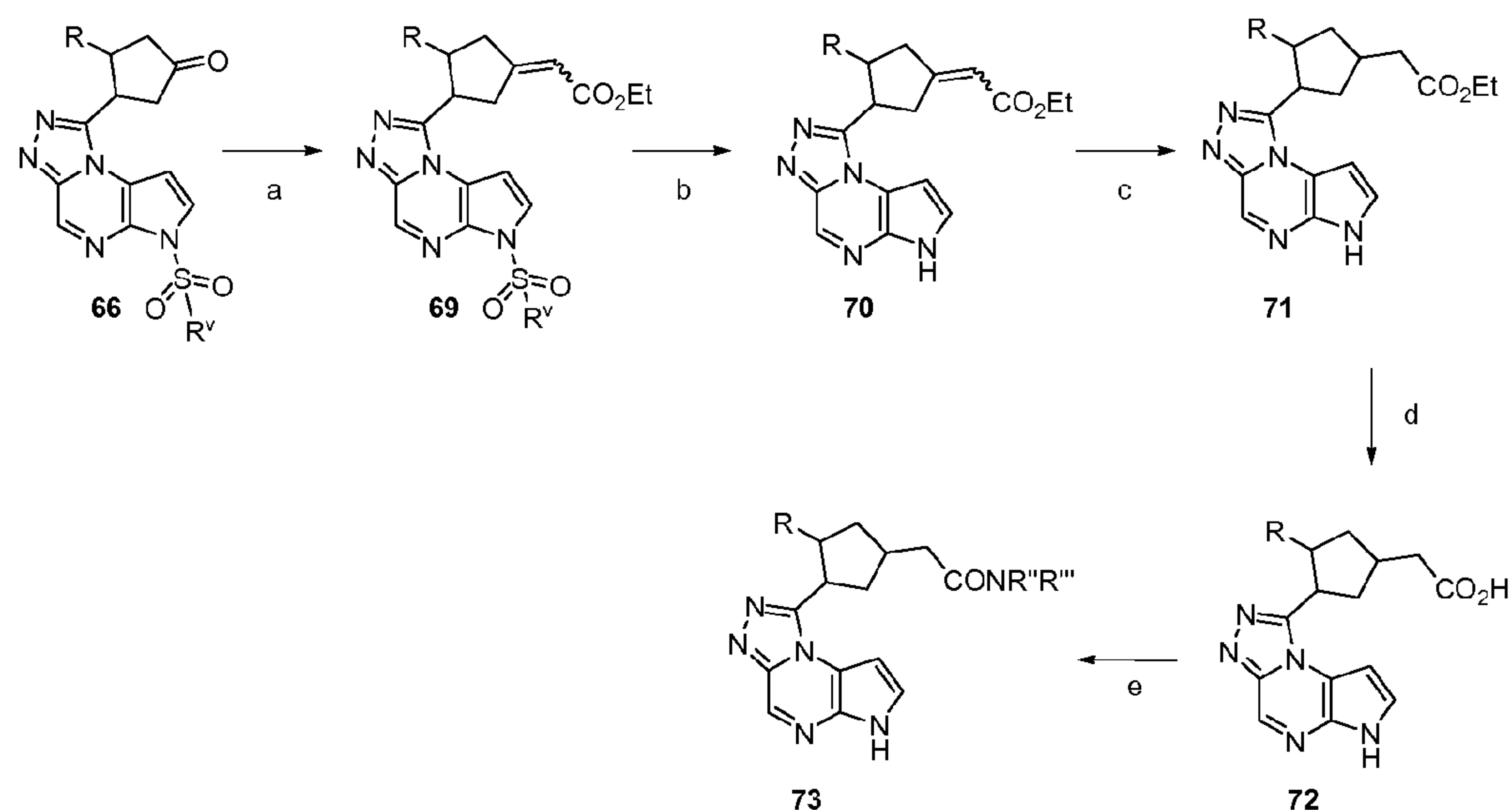
Scheme X



Methods for preparing acetic acid and acetamide derivatives from 4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanones as compounds of the invention are illustrated in Scheme XI. As shown in step a, Horner-Wadsworth-Emmons reaction of ketones **66** to give alkenes **69** may be accomplished using procedures known to one skilled in the art such as those described in General Procedure **III**. Deprotection of the sulfonamide protecting group of

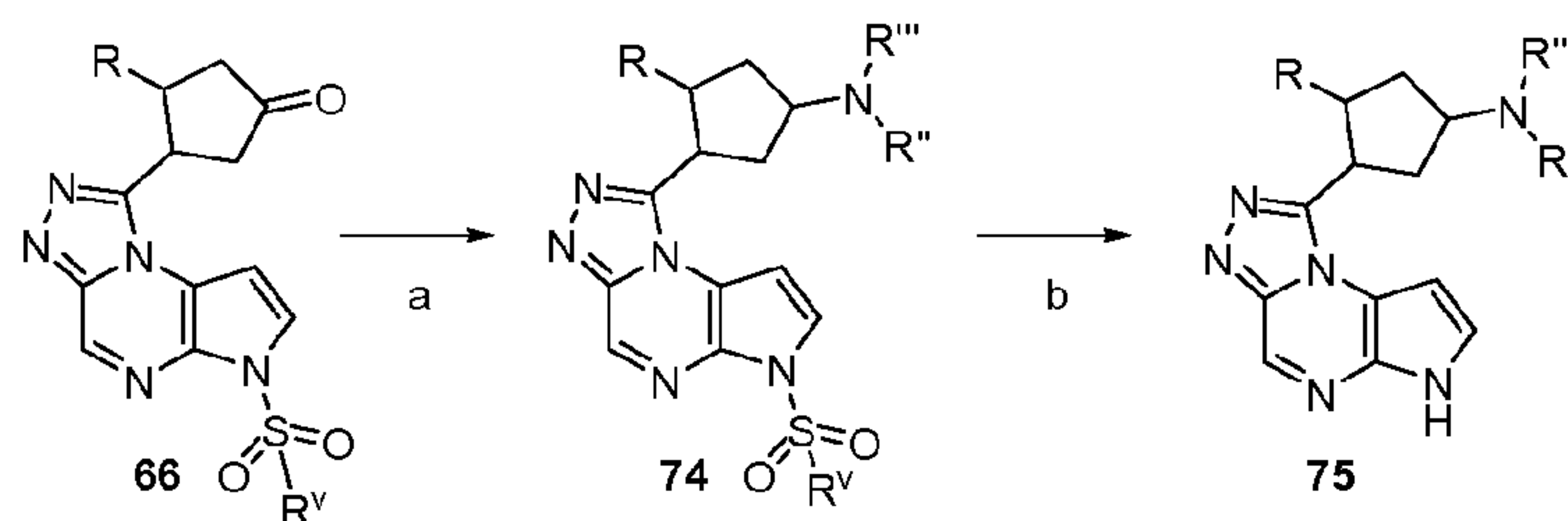
pyrrolotriazolopyrazines **69** may be accomplished using conditions such as those described in General Procedures **D**, **AAAA**, **BBBB**, or **CCCC** or by methods known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above) to give pyrrolotriazolopyrazines **70** (Scheme XI, step b). Hydrogenation of alkenes **70** as described in General Procedures **W** or **W.1** yields pyrrolotriazolopyrazines **71** (Scheme XI, step c). Hydrolysis of esters **71** gives acids **72** (Scheme XI, step d) using well known conditions such as those described in General Procedure **Z**. The acids **72** may be further reacted to give amides **73** as shown in step e using conditions such as those described in General Procedure **H**.

Scheme XI



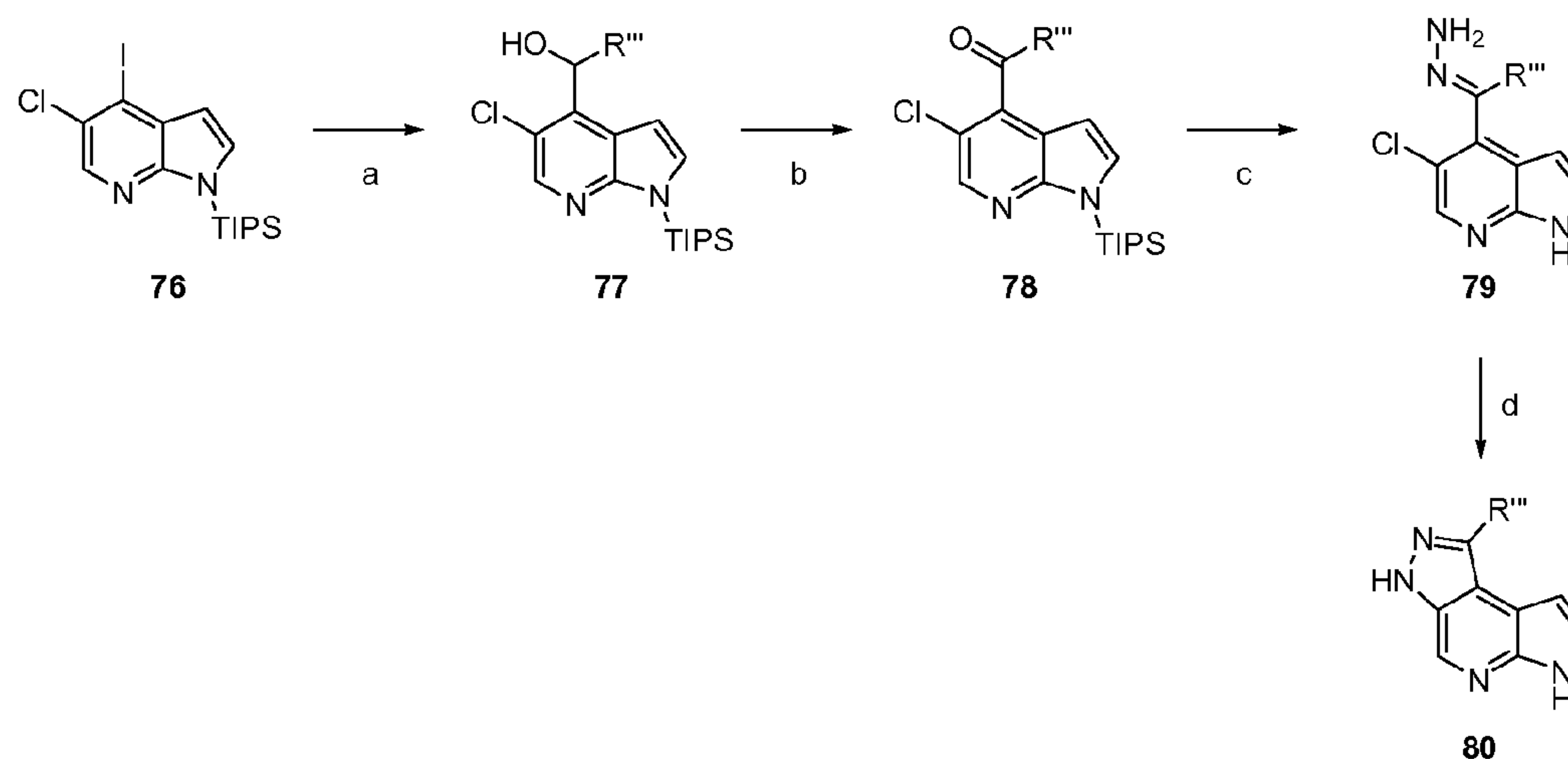
Methods for preparing 4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamines as compounds of the invention are illustrated in Scheme XII. As shown in step a, reductive amination of ketones **66** to give amines **74** may be accomplished using well known conditions such as those described in General Procedures **X** or **X.1**. Deprotection of the sulfonamide protecting group of pyrrolotriazolopyrazines **74** may be accomplished using conditions such as those described in General Procedures **D**, **AAAA**, **BBBB**, or **CCCC** or by methods known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above) to give pyrrolotriazolopyrazines **75** (Scheme XII, step b).

Scheme XII



Methods for preparing dihydropyrazolo[4,3-*d*]pyrrolo[2,3-*b*]pyridine compounds of the invention are illustrated in Scheme XIII. In step a, reaction of 5-chloro-4-iodo-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine **76** with a substituted aldehyde provides alcohols **77** using procedures such as those described in Example #29, Example #30, or in WO2009152133. Preparation of ketones **78** (step b) can be accomplished by treatment of alcohols **77** with an oxidizing agent by methods known to one skilled in the art (for example, Example #29, Example #30, or Larock, R.C. referenced above). Ketones **78** can then be converted to hydrazones **79** with the loss of the TIPS protecting group through reaction with hydrazine using conditions such as those described in Example #29, Example #30 or General Procedure XXXX. Cyclization of hydrazones **79** to provide dihydropyrazolo[4,3-*d*]pyrrolo[2,3-*b*]pyridines **80** can be accomplished via an intramolecular Buchwald-Hartwig cyclization (for example, General Procedure XX or *Organic Letters*, **2008**, 10(18), 4109-4112). Further functionalization of the R''' group in dihydropyrazolo[4,3-*d*]pyrrolo[2,3-*b*]pyridines **80** can be performed, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared from dihydropyrazolo[4,3-*d*]pyrrolo[2,3-*b*]pyridines **80** with an R''' group containing a primary or secondary amine (for example, General Procedures G, H, I, J, J.1, XXX, EEEE, K, K.1, L, DD, QQ, RR, YY, ZZ followed by AAA, CCC, YYY, X, X.1, TTTT, or EEEEE). Also, deprotection of the R''' group in dihydropyrazolo[4,3-*d*]pyrrolo[2,3-*b*]pyridines **80** to yield deprotected compounds **80** can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above or in General Procedures E, E.1, F, F.1, Y, or BB and the deprotected compounds **80** may then be reacted further as described above.

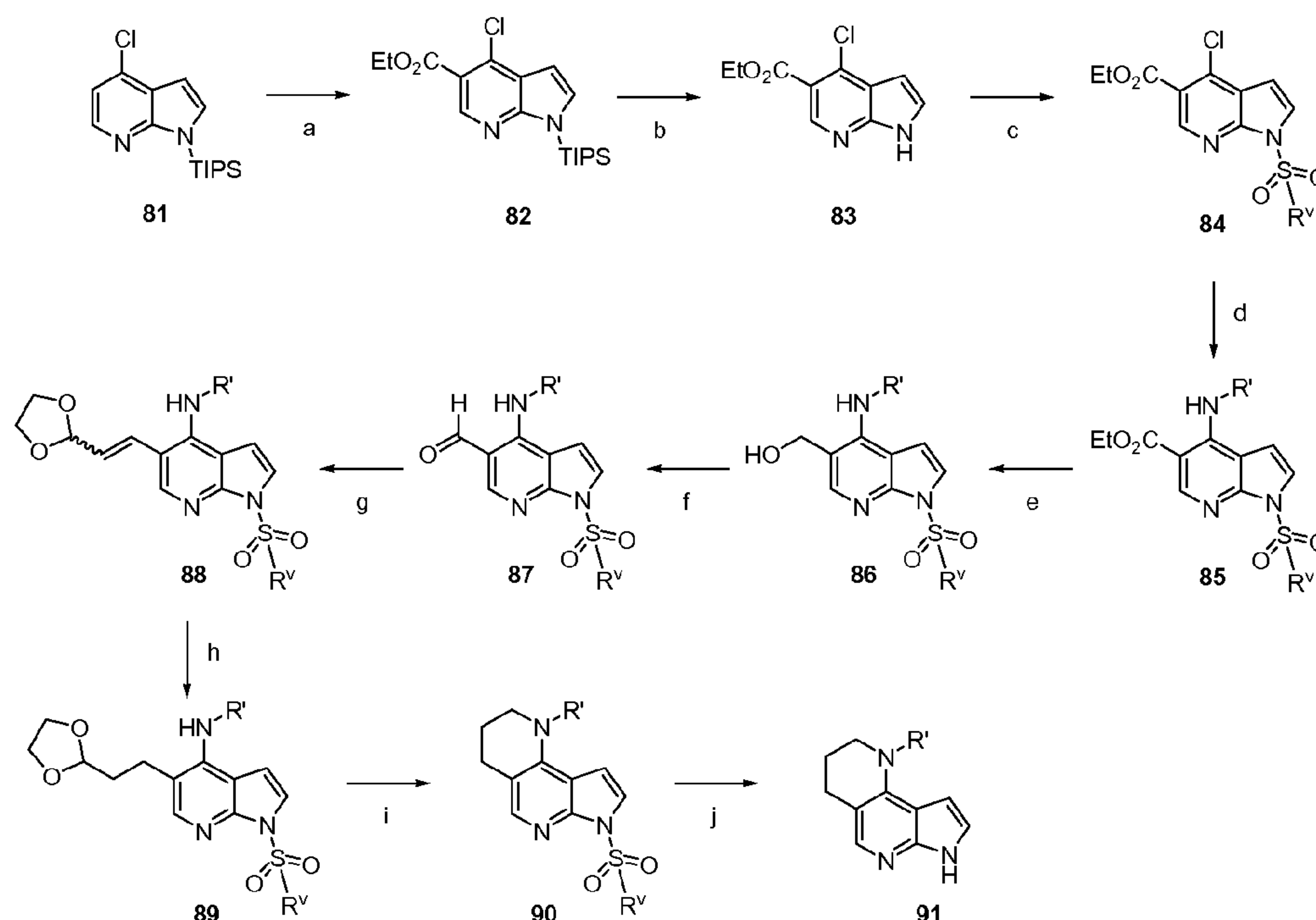
Scheme XIII



Methods for preparing 2,3,4,7-tetrahydro-1*H*-pyrrolo[2,3-*h*][1,6]naphthyridine compounds of the invention are illustrated in Scheme XIV. In step a, *o*-lithiation of 4-chloro-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine **81** followed by trapping of the anion with ethyl chloroformate yields ethyl 4-chloro-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate **82** using conditions described in Example #28. The removal of the TIPS group of **82** may be accomplished as shown in step b to give ethyl 4-chloro-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxylate **83** using conditions well known in the literature (for example, Greene, T.W. and Wuts, P.G.M. referenced above or Example #28). In step c, sulfonamide protected compounds **84** are prepared using reactions known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above or Example #28). As shown in step d, amino-substituted 1*H*-pyrrolo[2,3-*b*]pyridines **85** are prepared using methods known to one skilled in the art (for example, Example #28 or Larock, R.C. referenced above). The reduction of esters **85** to alcohols **86** (Scheme XIV, step e) may be accomplished using conditions well known in the literature (for example, Example #28 or Larock, R.C. referenced above). In step f, alcohols **86** are oxidized to aldehydes **87** using methods known to one skilled in the art (for example, Example #28 or Larock, R.C. referenced above). The Wittig reaction of aldehydes **87** with ((1,3-dioxolan-2-yl)methyl)triphenylphosphonium bromide (Scheme XIV, step g) yields alkenes **88** using conditions such as those described in Example #28. Reduction of alkenes **88** may be accomplished using conditions such as those described in Example #28 or General Procedures **W** or **W.1** (Scheme XIV, step h). The cyclization of aminoacetals **89** to give protected 2,3,4,7-tetrahydro-1*H*-pyrrolo[2,3-*h*][1,6]naphthyridines **90** is accomplished using conditions described in Example #28 (scheme XIV, step i). Deprotection of the sulfonamide protecting group of 2,3,4,7-tetrahydro-1*H*-pyrrolo[2,3-*h*][1,6]naphthyridines **90** may be accomplished using conditions such as those described in General Procedures **D**, **AAAA**, **BBBB**, or **CCCC** or by

methods known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above) to give 2,3,4,7-tetrahydro-1*H*-pyrrolo[2,3-*h*][1,6]naphthyridines **91** (Scheme XIV, step j). Further functionalization of the R' group in 2,3,4,7-tetrahydro-1*H*-pyrrolo[2,3-*h*][1,6]naphthyridines **91** can be performed, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared from 2,3,4,7-tetrahydro-1*H*-pyrrolo[2,3-*h*][1,6]naphthyridines **91** with an R' group containing a primary or secondary amine (for example, General Procedures **G**, **H**, **I**, **J**, **J.1**, **XXX**, **EEEE**, **K**, **K.1**, **L**, **DD**, **QQ**, **RR**, **YY**, **ZZ** followed by **AAA**, **CCC**, **YYY**, **X**, **X.1**, **TTTT**, or **EEEE**). Also, deprotection of the R' group in 2,3,4,7-tetrahydro-1*H*-pyrrolo[2,3-*h*][1,6]naphthyridines **91** to yield deprotected compounds **91** can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above or in General Procedures **E**, **E.1**, **F**, **F.1**, **Y**, or **BB** and the deprotected compounds **91** may then be reacted further as described above.

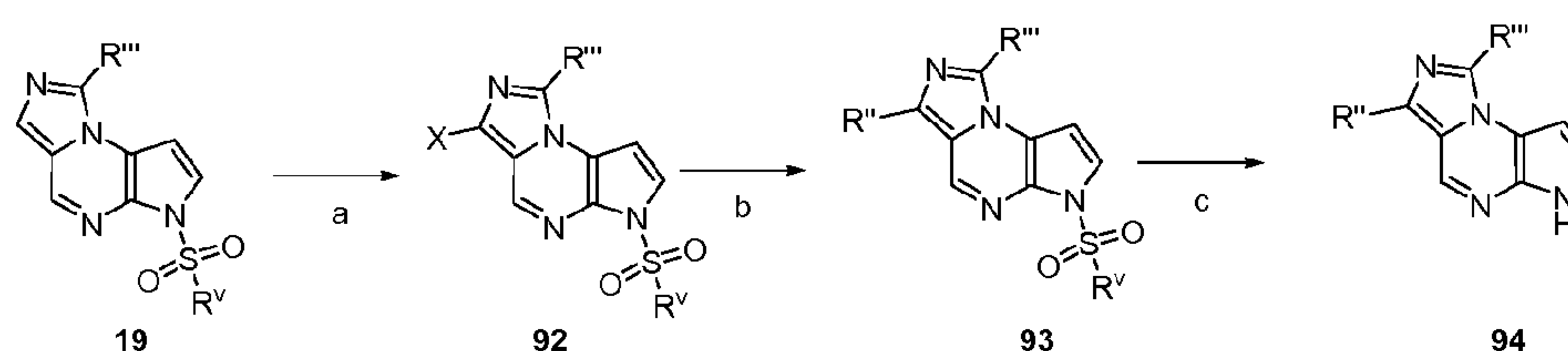
Scheme XIV



Methods for preparing substituted imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines compounds of the invention are illustrated in Scheme XV. As shown in step a, imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines **19** may be halogenated using conditions such as those described in General Procedure **MM** to give 3-halo-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines **92**. The 3-halo-imidazo[1,5-*a*]pyrrolo-

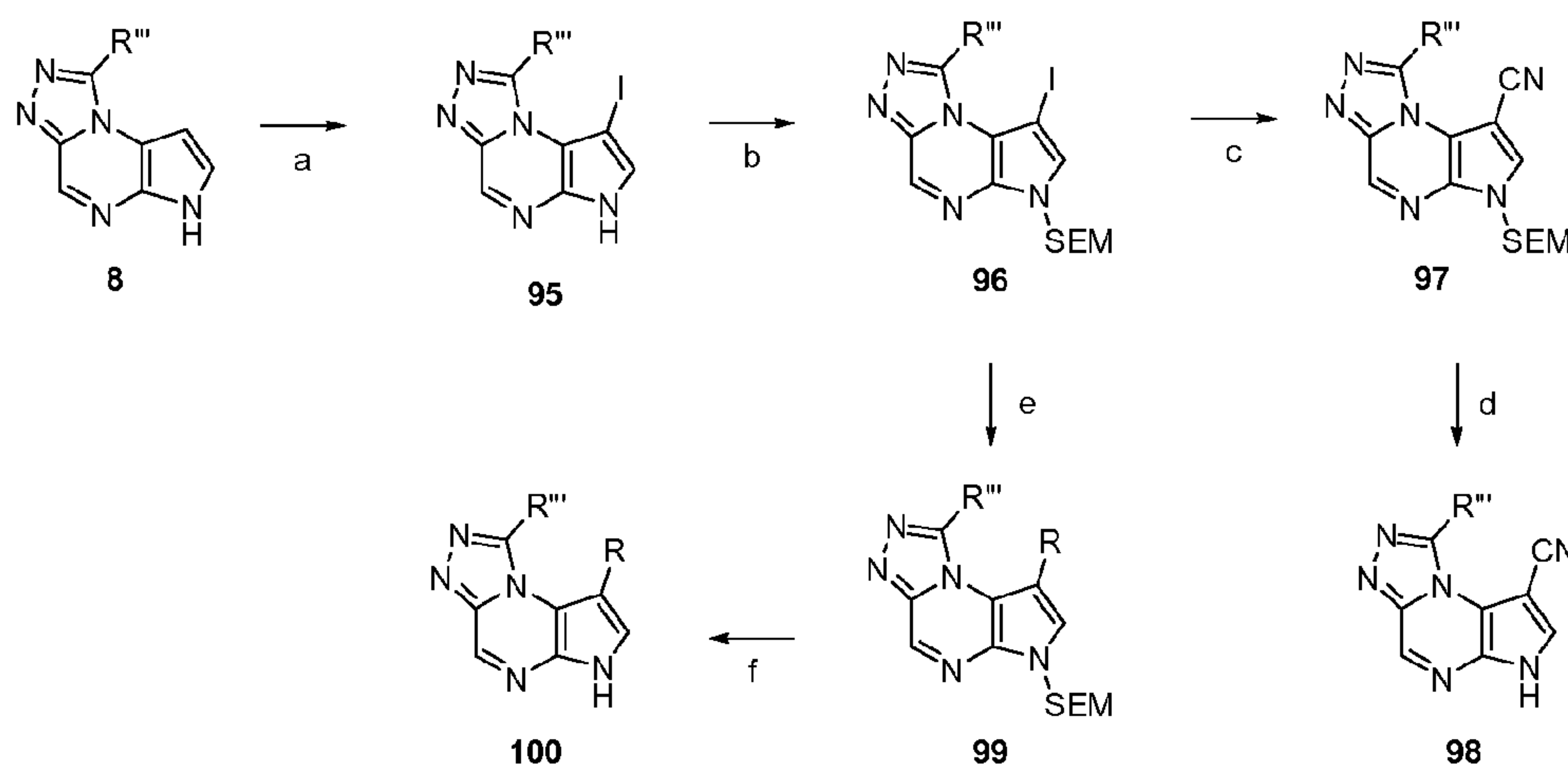
[2,3-*e*]pyrazines **92** may undergo a variety of reactions known to one skilled in the art (for example, , Larock, R.C. referenced above) including, but not limited to, cyanation as described in General Procedure **HHH** (Scheme XVI, step c) or Suzuki coupling reactions such as those described in General Procedures **UUU** or **VVV** (Scheme XV, step b). Deprotection of the sulfonamide protecting group of imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines **93** may be accomplished using conditions such as those described in General Procedures **D**, **UUU**, **AAAA**, **BBBB**, or **CCCC**, or by methods known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above) to give imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazines **94** (Scheme XV, step c).

Scheme XV



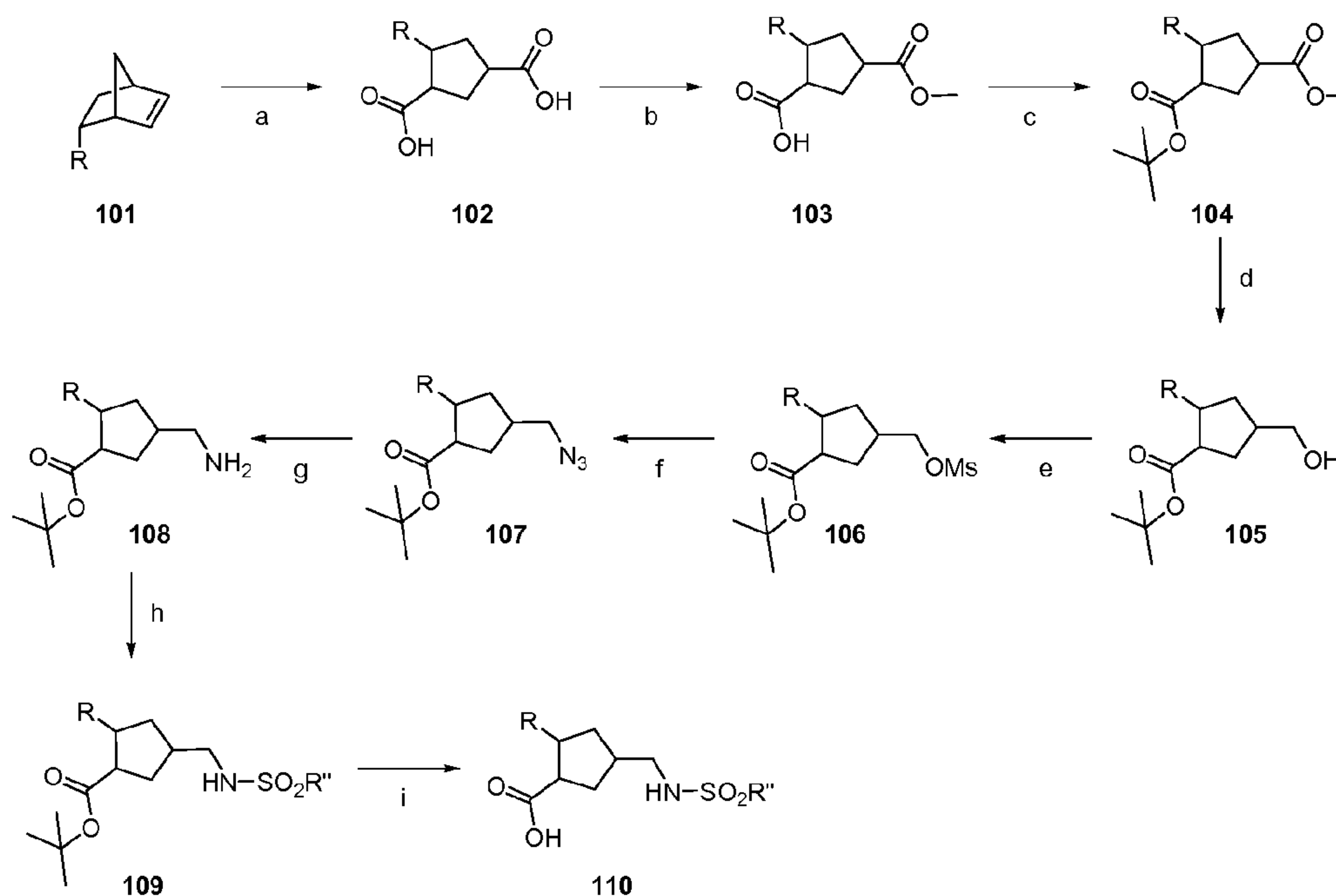
Methods for preparing pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine compounds of the invention are illustrated in Scheme XVI. Pyrrolotriazolopyrazines **8** may be halogenated using conditions such as those described in General Procedures **GGG** or **GGG.1** to give 8-halopyrrolotriazolopyrazines **95** (Scheme XVI, step a). In step b, 8-halopyrrolotriazolopyrazines **95** may be protected with a SEM group using conditions known in the literature such as those found in Greene, T.W. and Wuts, P.G.M. referenced above or as in General Procedure **KK**. The resulting SEM-protected 8-halopyrrolotriazolopyrazines **96** may undergo a variety of reactions known to one skilled in the art (for example, Larock, R.C. referenced above) including, but not limited to, cyanation as described in General Procedure **HHH** (Scheme XVI, step c), Suzuki coupling reactions as described in Preparation #23, formation of a carboxylic ester as described in General Procedure **AAAAA**, or Stille coupling reactions as described in General Procedure **CCCCC** (Scheme XVI, step e). The resulting products **97** or **99** may be deprotected using conditions such as those described in General Procedure **LL**, **LL.1**, or by methods known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above) to give pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazines **98** or **100** (Scheme XV, steps d and f, respectively). Additionally, compounds **99** and **100** may undergo further functionalization, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, for R = CO₂Et, the compound may be hydrolyzed using conditions such as those described in General Procedure **D** and then undergo amide bond formation as described in General Procedure **H**.

Scheme XVI



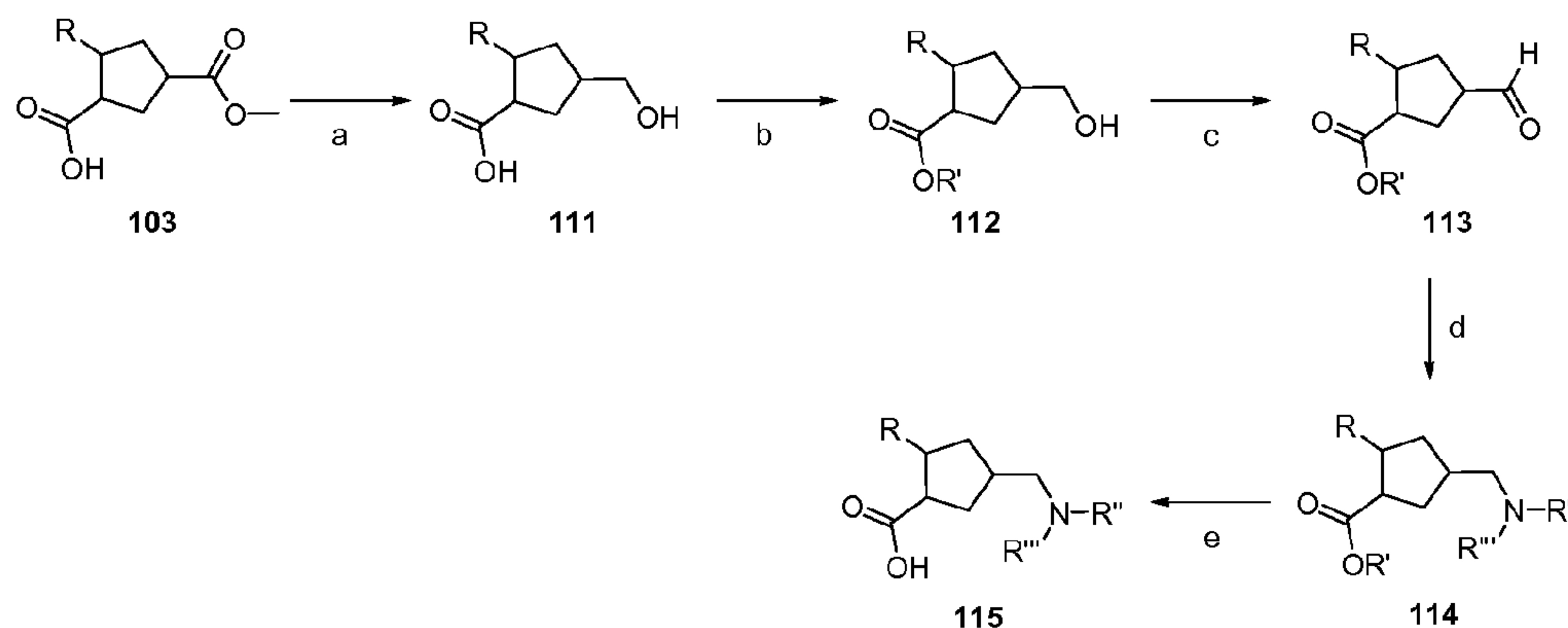
Methods for preparing substituted 4-(sulfonamidomethyl)cyclopentanecarboxylic acids **110** for use in the preparation of compounds of the invention are illustrated in Scheme XVII. In step a, 5-substituted-bicyclo[2.2.1]hept-2-enes **101** are oxidized to dicarboxylic acids **102** using known conditions such as those described in Preparation #11, *Bioorganic & Medicinal Chemistry*, **2007**, 15, 7581, or *Journal of Organic Chemistry*, **1993**, 58, 4745. Formation of the mono-esters **103** are achieved through the cyclic anhydride as described in Preparation #11 (Scheme XVII, step b). The *t*-butyl esters **104** are prepared in step c using standard condition such as those described in Preparation #11 or Larock, R.C. referenced above. Reduction of the methyl ester of compounds **104** to alcohols **105** is achieved using well known conditions such as those found in Preparation #21 (Scheme XVII, step d). The mesylates **106** are prepared as described in Preparation #21 or by methods known to one skilled in the art (Scheme XVII, step e). As shown in step f, the mesylates **106** may be used to form azides **107** using well known conditions such as those described in Preparation #21 or Larock, R.C. referenced above (Scheme XVII, step f). The reduction of azides **107** to amines **108** is a standard transformation that may be accomplished as described in Preparation #21 or using conditions such as those described in General Procedure **TTT** or in Larock, R.C. referenced above (Scheme XVII, step g). Step h shows the formation of sulfonamides **109** from amines **108** which is achieved as described in General Procedures **K** or **K.1** or by methods known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above). The acidic cleavage of *t*-butyl esters **109** to give 4-(sulfonamidomethyl)cyclopentanecarboxylic acids **110** (Scheme XVII, step i) may be done with the conditions described in General Procedure **QQQ** or with methods known to one skilled in the art (for example, the books from Larock, R.C. or Greene, T.W. and Wuts, P.G.M. referenced above).

Scheme XVII



Methods for preparing 4-((dibenzylamino)methyl)-2-substituted-cyclopentanecarboxylic acids **115** for use in the preparation of compounds of the invention are illustrated in Scheme XVIII. Reduction of the methyl ester of compounds **103** to alcohols **111** is achieved using well known conditions such as those found in Preparation #22 or Larock, R.C. referenced above (Scheme XVIII, step a). Step b illustrates the formation of esters **112** which is achieved as described in Preparation #22 or Larock, R.C. referenced above. In step c, alcohols **112** are oxidized to aldehydes **113** using known conditions such as those described in Preparation #22 or Larock, R.C. referenced above. The reductive amination of aldehydes **113** using conditions such as those described in General Procedures **X** or **X.1** gives amines **114** (Scheme XVIII, step d). In step e, esters **114** are hydrolyzed to give 4-((dibenzylamino)methyl)-2-substituted-cyclopentanecarboxylic acids **115** using conditions such as those described in General Procedures **Z** or **TT** or known to one skilled in the art (for example, the books from Larock, R.C. or Greene, T.W. and Wuts, P.G.M. referenced above).

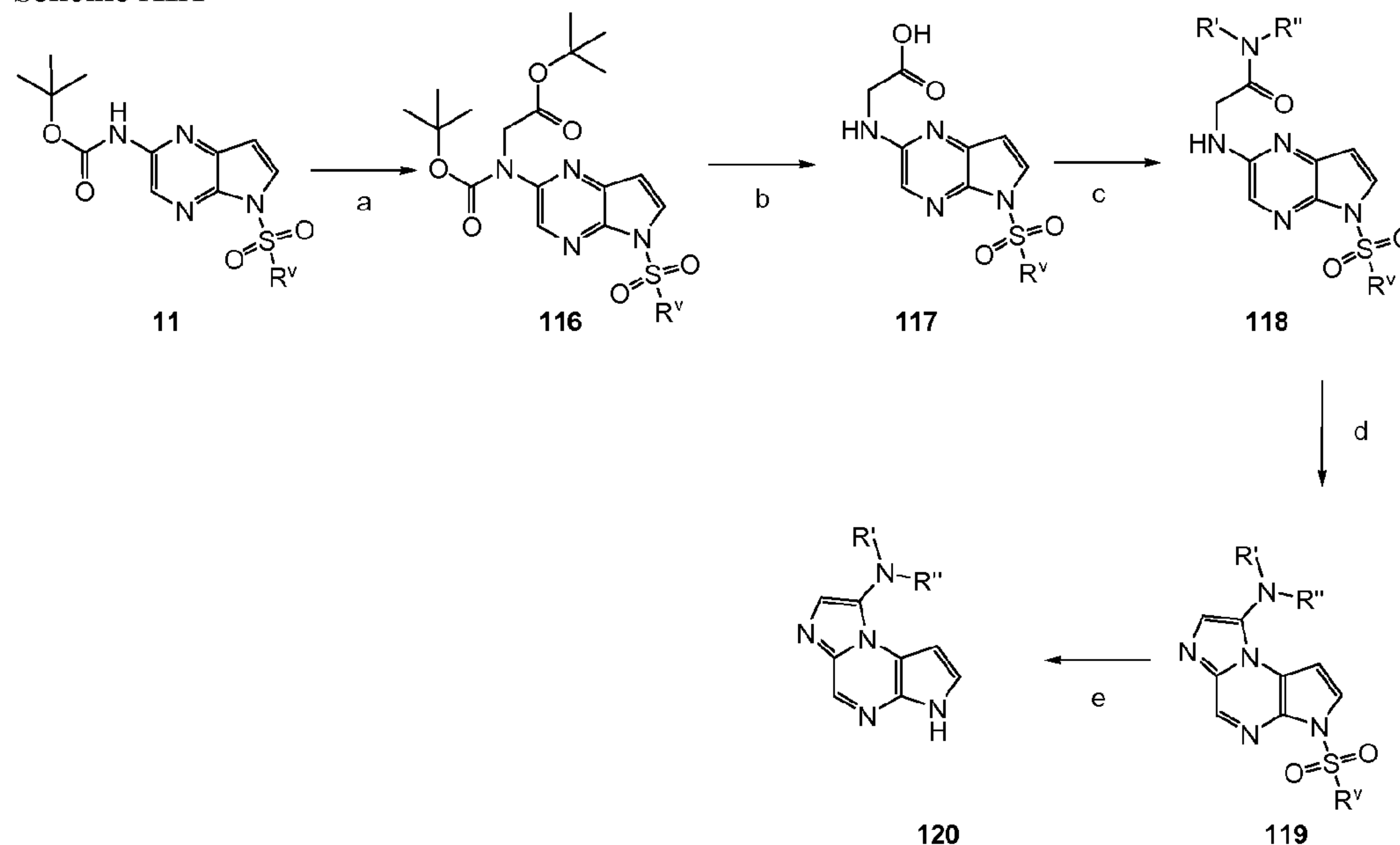
Scheme XVIII



Methods for preparing 3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazin-8-amine compounds of the invention are illustrated in Scheme XIX. Alkylation of pyrrolopyrazin-2-ylcarbamates **11** with *t*-butyl 2-bromoacetate, by methods known to one skilled in the art (for example, General Procedures **S** or **S.1**), gives pyrrolopyrazines **116** (Scheme XIX, step a). The double deprotection of pyrrolopyrazines **116** to aminoacetic acids **117** may be accomplished using conditions such as those described in General Procedures **E**, **E.1**, or **QQQ** (Scheme XIX, step b). The coupling of acids **117** with amines provides amides **118** (Scheme XIX, step c) using well known conditions such as those given in General Procedure **H** or Larock, R.C. referenced above. As shown in step d, the cyclization of amides **118** to imidazopyrrolopyrazin-8-amines **119** may be accomplished using conditions such as those described in General Procedures **OO** or **OO.1**. Further functionalization of the R' or R'' group in imidazopyrrolopyrazin-8-amines **119** can be performed, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared from imidazopyrrolopyrazin-8-amines **119** with an R' or R'' group containing a primary or secondary amine (for example, General Procedures **G**, **H**, **I**, **J**, **J.1**, **XXX**, **EEEE**, **K**, **K.1**, **L**, **DD**, **QQ**, **RR**, **YY**, **ZZ** followed by **AAA**, **CCC**, **YYY**, **X**, **X.1**, **TTTT**, or **EEEE**). Also, deprotection of the of the R' or R'' group in imidazopyrrolopyrazin-8-amines **119** to yield deprotected compounds **119** can be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above or in General Procedures **E**, **E.1**, **F**, **F.1**, **Y**, or **BB** and the deprotected compounds **119** may then be reacted further as described above. Removal of the sulfonamide protecting group of imidazopyrrolopyrazin-8-amines **119** may be accomplished using conditions such as those described in General Procedures **D**, **XXX**, **AAAA**, **BBBB**, or **CCCC** or by methods known to one skilled in the art (for example, the books from Larock, R.C. or Greene, T.W. and

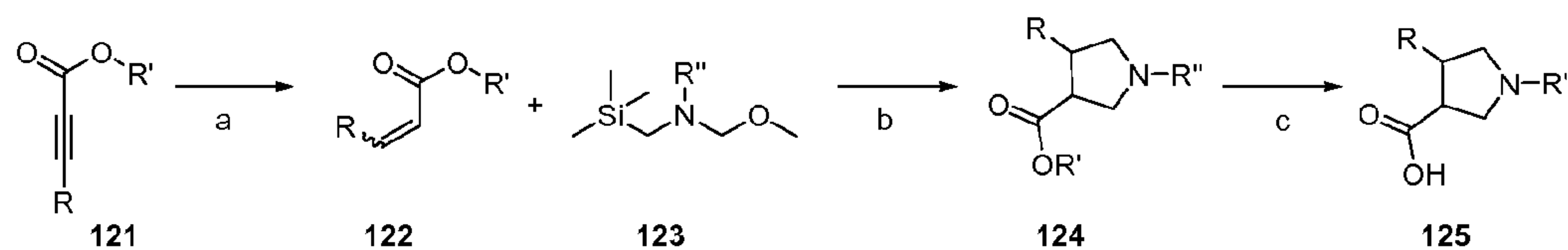
Wuts, P.G.M. referenced above) to give imidazopyrrolopyrazin-8-amines **120** (Scheme XIX, step e).

Scheme XIX



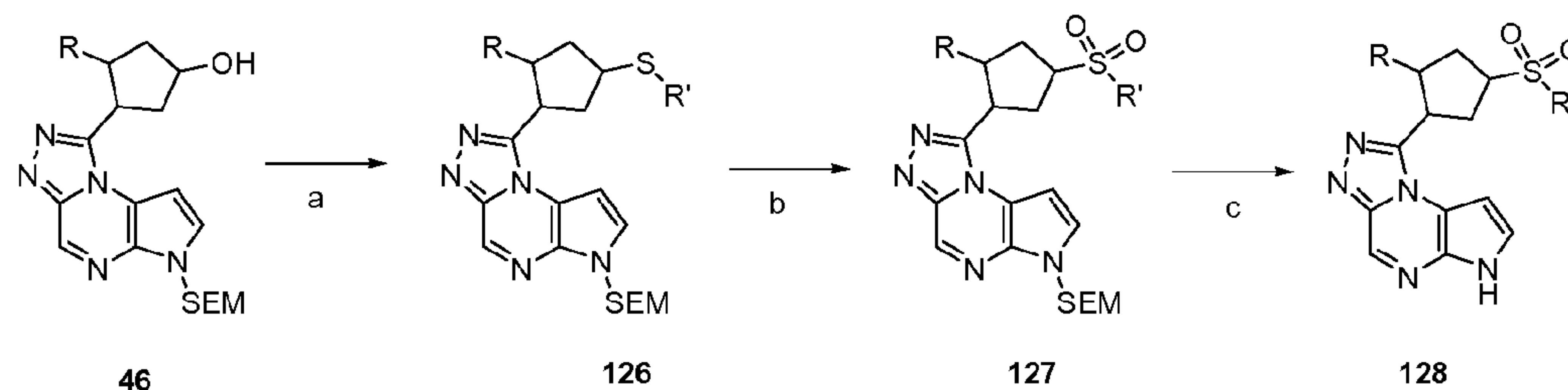
Methods for preparing pyrrolidine-3-carboxylic acids **125** for use in the preparation of compounds of the invention are illustrated in Scheme XX. In step a, alkynes **121** are reduced to alkenes **122** as described in General Procedure **RRR** or using methods known to one skilled in the art (for example, Larock, R.C. referenced above). The 1,3-dipolar cycloaddition of alkenes **122** and *N*-substituted-1-methoxy-*N*-((trimethylsilyl)methyl)methanamine **123** to give pyrrolidines **124** (Scheme XX, step b) can be accomplished by methods known to one skilled in the art (for example, General Procedure **SSS** or *Journal of Medicinal Chemistry*, **2009**, 52(24), 7946-7949). The ester of compounds **124** may be hydrolyzed under aqueous base or acid conditions to give carboxylic acids **125** (Scheme XX, step c) using conditions such as those described in General Procedures **Z** or **TT** or Larock, R.C. referenced above.

Scheme XX



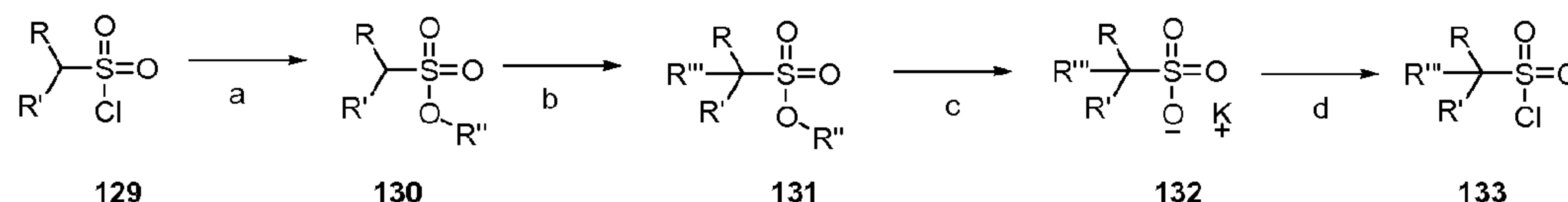
Methods for preparing sulfone-substituted 1-cyclopentyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine compounds of the invention are illustrated in Scheme XXI. As shown in step a, Mitsunobu reaction of alcohols **46** with appropriate thiols gives sulfides **126** using conditions such as those described in General Procedure **MMM** or by methods known to one skilled in the art (for example, Larock, R.C. referenced above). The oxidation of sulfides **126** to sulfones **127** (Scheme XXI, step b) is accomplished as described in General Procedure **LLL** or by methods known to one skilled in the art (for example, Larock, R.C. referenced above). The SEM protecting group of pyrrolotriazolopyrazines **127** may be removed by methods such as those described in General Procedures **LL** and **LL.1**, or using conditions such as described in Greene, T.W. and Wuts, P.G.M. referenced above to give pyrrolotriazolopyrazines **128** (Scheme XXI, step c).

Scheme XXI



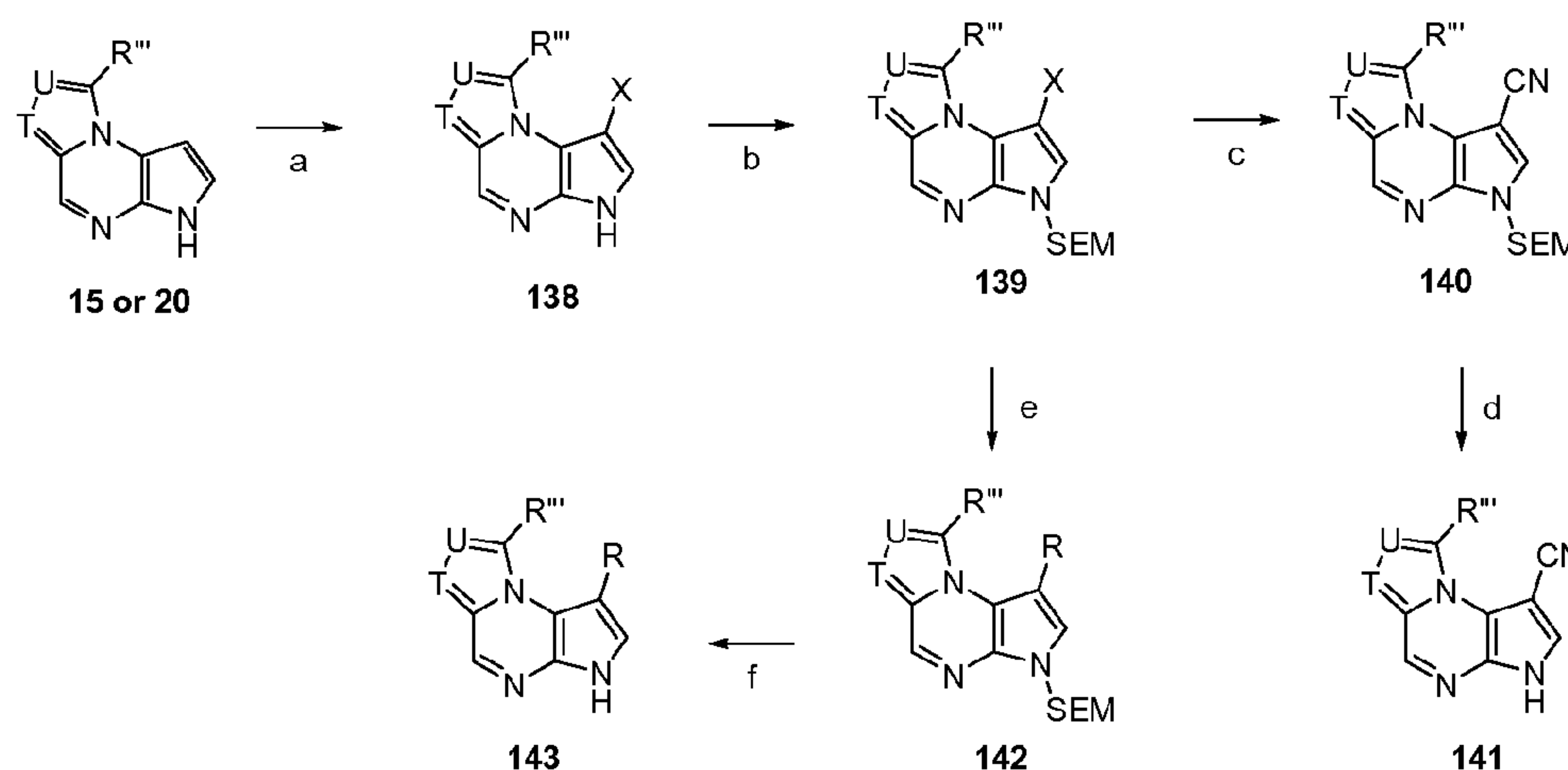
Methods for preparing sulfonyl chlorides **133** for use in the preparation of compounds of the invention are illustrated in Scheme XXII. In step a, sulfonates **130** are prepared from sulfonyl chlorides **129** using known reaction conditions such as those described in Preparation #6 Step A, WO2007014011, or WO2009018238. An additional substituent is added to sulfonates **130** to give sulfonates **131** via alkylation as described in General Procedure **KKK**, WO2007014011, or WO2009018238 (Scheme XXII, step b). In step c, potassium sulfonates **132** are prepared from sulfonates **131** with aqueous potassium cyanate using conditions such as those in General Procedure **JJJ**, WO2007014011, or WO2009018238. Potassium sulfonates **132** are converted to sulfonyl chlorides **133** (Scheme XXII, step d) using thionyl chloride as described in General Procedure **EEE**, WO2007014011, or WO2009018238.

Scheme XXII



Methods for preparing imidazopyrrolo[2,3-*e*]pyrazines compounds of the invention are illustrated in Scheme XXIII. Imidazopyrrolopyrazines **15** [T = N, U = CH] or **20** [T = CH, U = N] may be halogenated using conditions such as those described in General Procedures **GGG** or **GGG.1** to give 8-haloimidazopyrrolopyrazines **138** (Scheme XXIII, step a). In step b, 8-haloimidazopyrrolopyrazines **138** may be protected with a SEM group using conditions known in the literature such as those found in Greene, T.W. and Wuts, P.G.M. referenced above or as in General Procedure **KK**. The resulting SEM-protected 8-haloimidazopyrrolopyrazines **139** may undergo a variety of reactions known to one skilled in the art (for example, Larock, R.C. referenced above) including, but not limited to, cyanation as described in General Procedure **HHH** (Scheme XXIII, step c) or Suzuki coupling reactions as described in General Procedure **VVV** or Stille coupling reactions as described in General Procedure **CCCCC** (Scheme XXIII, step e). The resulting products **140** or **142** may be deprotected using conditions such as those described in General Procedures **LL** and **LL.1**, or by methods known to one skilled in the art (for example, Greene, T.W. and Wuts, P.G.M. referenced above) to give imidazopyrrolo[2,3-*e*]pyrazines **141** or **143** (Scheme XXIII, steps d and f, respectively).

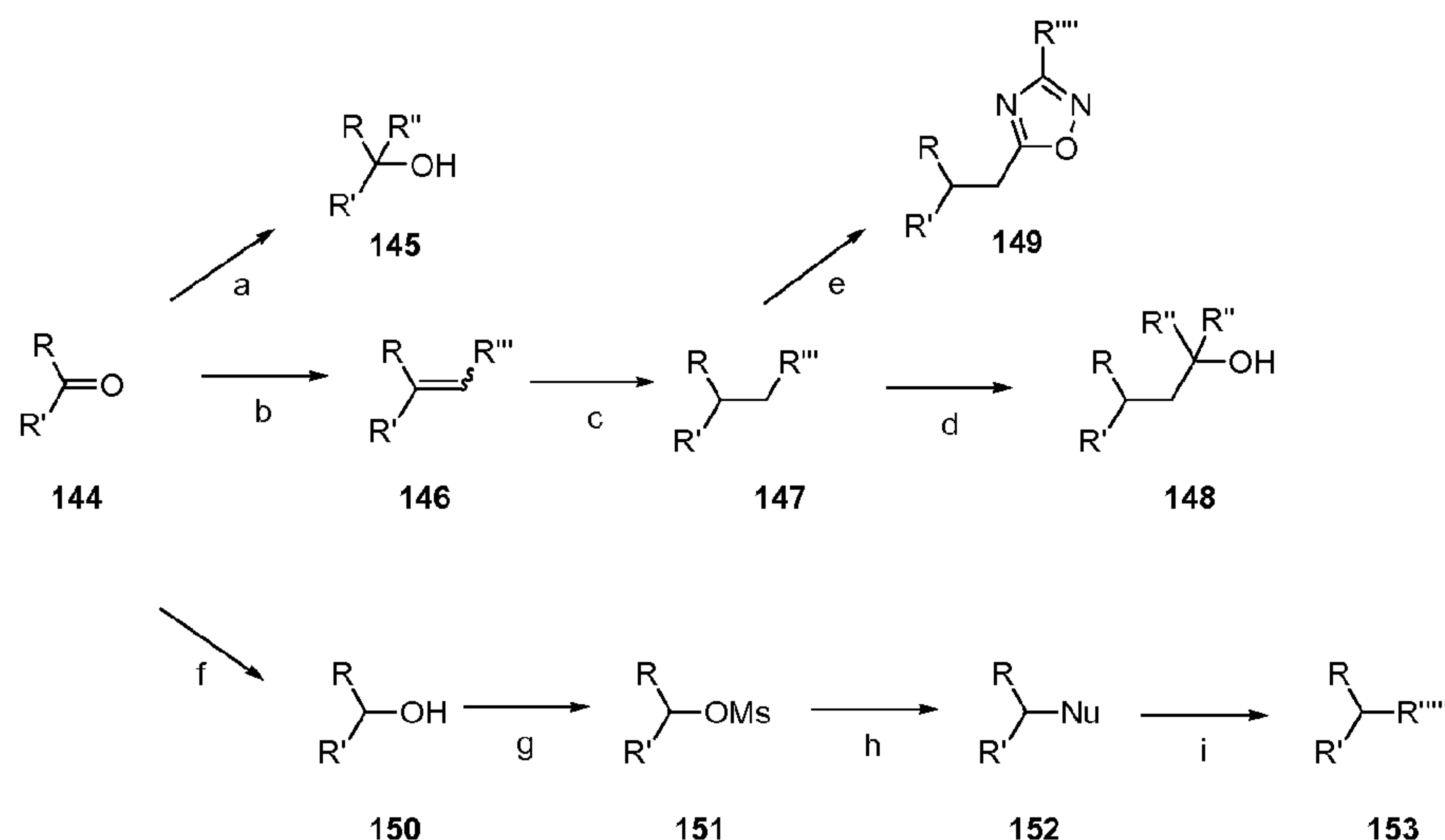
Scheme XXIII



Methods for preparing compounds of the invention from a common ketone intermediate are illustrated in Scheme XXIV. As shown in scheme XXIV, step a, ketones **144** may be reacted with an alkyl lithium or a Grignard reagent to give alcohols **145** using conditions known to one skilled in the art (for example, Larock, R.C. referenced above or General Procedure **ZZZ**). Alternatively, ketones **144** may undergo a Horner-Wadsworth-Emmons reaction with a reagent such as ethyl 2-(diethoxyphosphoryl)acetate (R''' = CO₂Et) or diethyl cyanomethylphosphonate (R''' = CN) as described in General Procedure **III** to give alkenes **146** (Scheme XXIV, step b). Alkenes **146** may be hydrogenated to alkanes **147** using well-known conditions such as those

described in General Procedure **W** and **W.1** (Scheme XXIV, step c). The R''' group may be further functionalized using a variety of reactions such as those described in Larock, R.C. referenced above. For example, for R''' = CO₂Et, alcohols **148** can be prepared as described in General Procedure **ZZZ** (Scheme XXIV, step d) or oxadiazoles **149** may be prepared as described in General Procedure **DDDD** (Scheme XXIV, step e). As shown in scheme XXIV, step f, ketones **144** may also be reduced to alcohols **150** as described in General Procedure **P** or in Larock, R.C. referenced above. Mesylates **151** are formed from alcohols **150** using conditions known to one skilled in the art such as those described in General Procedure **III** (Scheme XXIV, step g) and can be reacted with a variety of nucleophiles (Nu) as described in General Procedure **JJJJ** (Scheme XXIV, step h) to give compounds **152**. Depending on the nucleophile used, further functionalization can be done to give compounds **153** (Scheme XXIV, step i). These functionalizations may be accomplished using methods such as those described in Larock, R.C. referenced above or General Procedures **QQQQ** or **UUUU**.

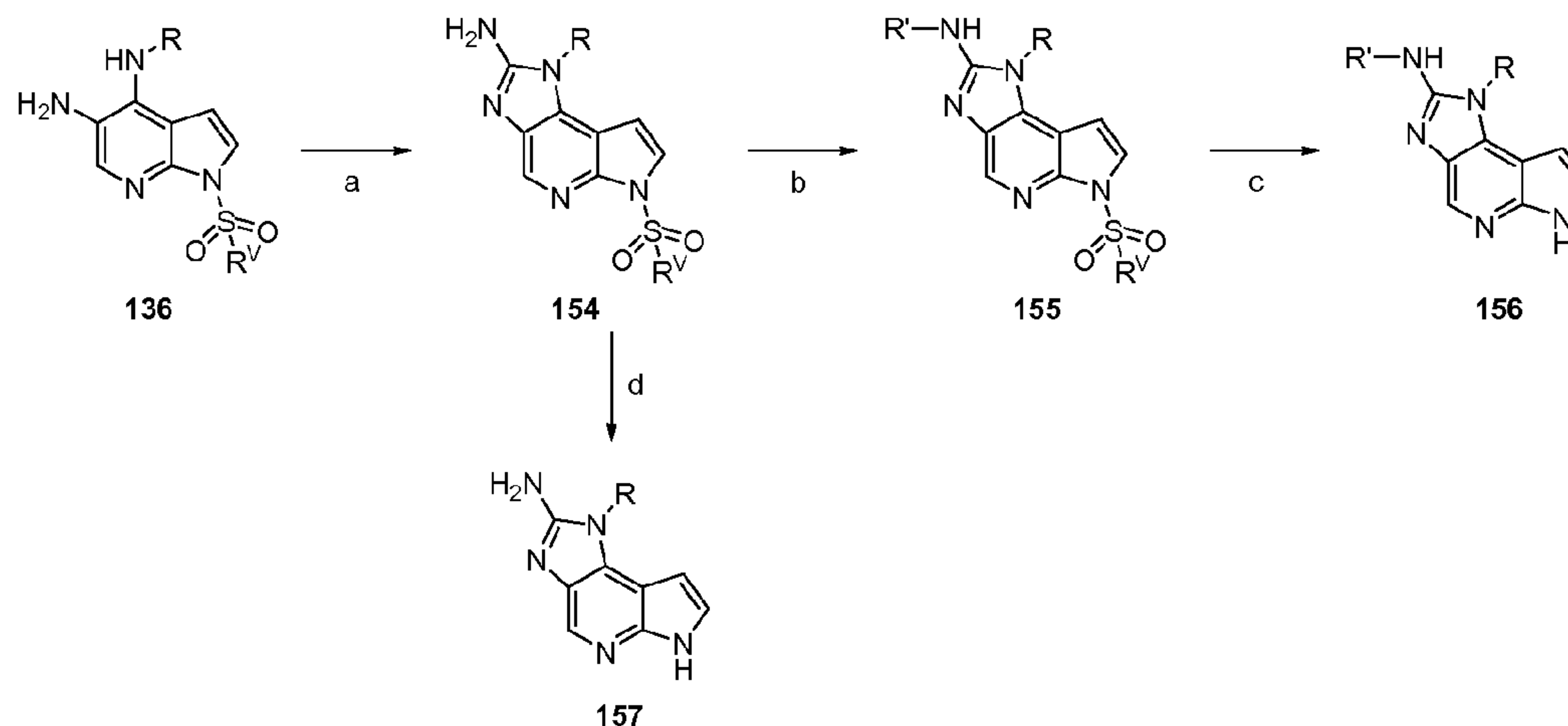
Scheme XXIV



Methods for preparing 1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-amine compounds of the invention are illustrated in Scheme XXV. Diamines **136** (Scheme XVIII) may be reacted with cyanogen bromide as described in General Procedure **RRRR** (Scheme XXV, step a). The resulting 1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-amines **154** may be further functionalized, if desired, using reactions known to one skilled in the art (see, for example, Larock, R.C. above) to give 1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-amines **155** (Scheme XXV, step b). Removal of the sulfonamide protecting group of 1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-amines **155** or **154** may be accomplished using conditions such as those described in General Procedures **D**, **AAAA**, **BBBB**, or **CCCC** or by methods known to one

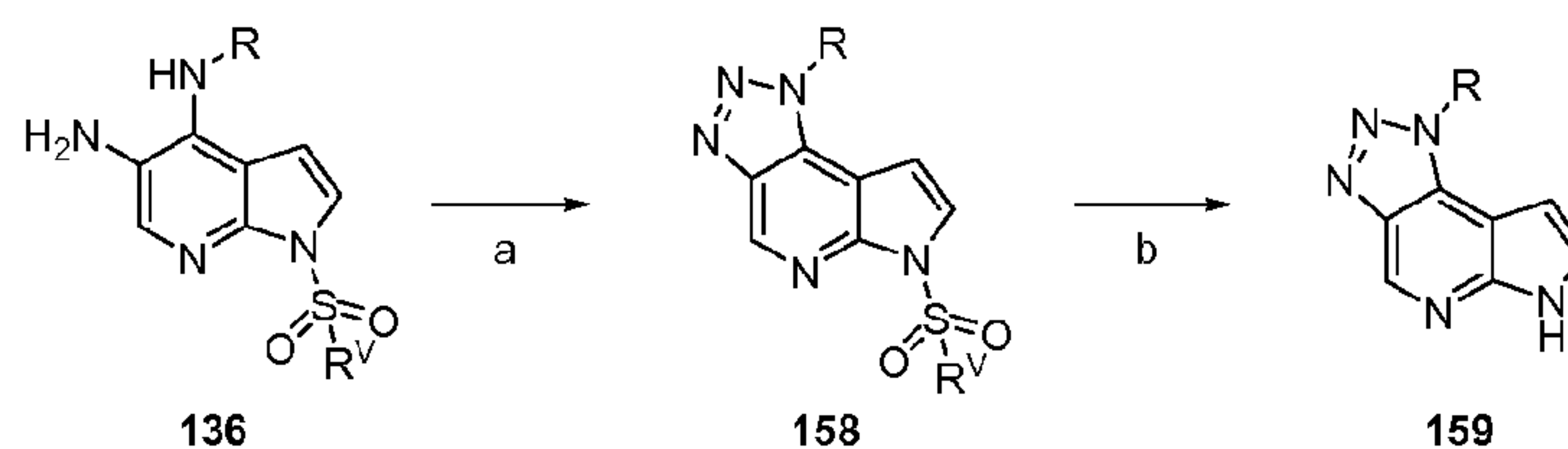
skilled in the art (for example, the books from Larock, R.C. or Greene, T.W. and Wuts, P.G.M. referenced above) to give 1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-amines **156** or **157**, respectively (Scheme XXV, steps c and d).

Scheme XXV



Methods for preparing 1,6-dihydropyrrolo[2,3-b][1,2,3]triazolo[4,5-d]pyridine compounds of the invention are illustrated in Scheme XXV. Diamines **136** (Scheme XVIII) may be reacted with sodium nitrite as described in General Procedure SSSS to give 1,6-dihydropyrrolo[2,3-b][1,2,3]triazolo[4,5-d]pyridines **158** (Scheme XXVI, step a). Removal of the sulfonamide protecting group of 1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2-amines **158** may be accomplished using conditions such as those described in General Procedures D, AAAA, BBBB, or CCCC or by methods known to one skilled in the art (for example, the books from Larock, R.C. or Greene, T.W. and Wuts, P.G.M. referenced above) to give 1,6-dihydropyrrolo[2,3-b][1,2,3]triazolo[4,5-d]pyridines **159** (Scheme XXV, step b).

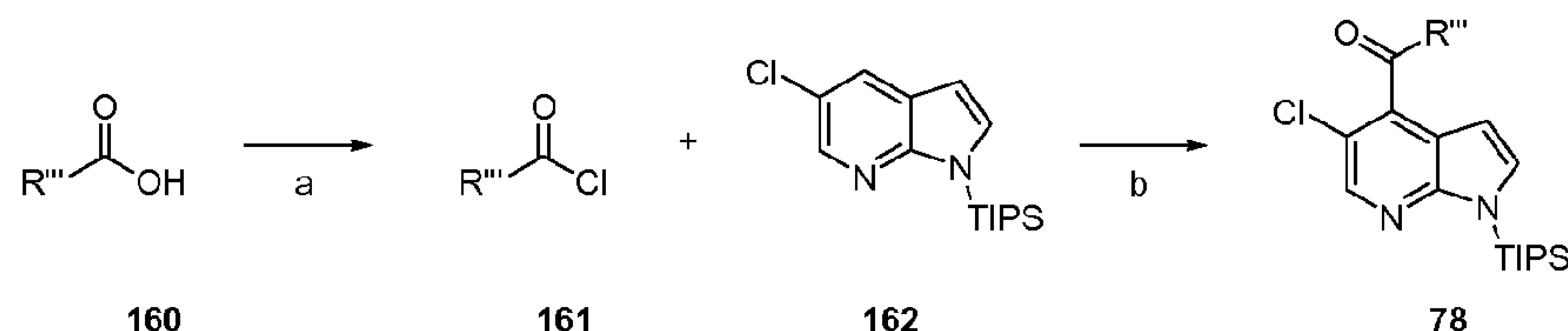
Scheme XXVI



Alternate methods for preparing the ketone intermediate used to make dihydropyrazolo[4,3-d]pyrrolo[2,3-b]pyridine compounds of the invention are illustrated in

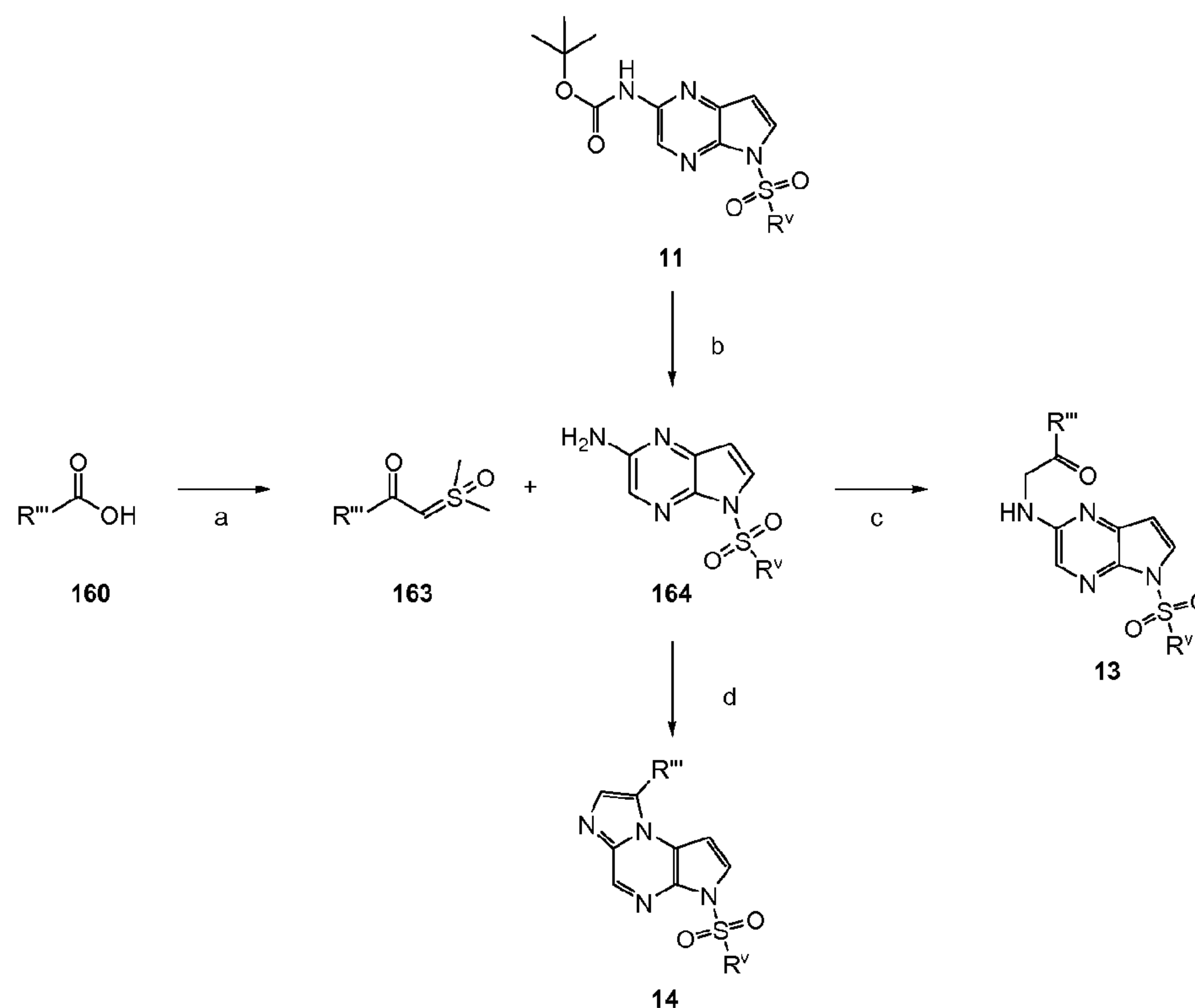
Scheme XXVII. In step a, carboxylic acids **160** are converted to the corresponding acid chlorides **161** using conditions widely known to one skilled in the art such as those described in General Procedure **WWWW**. Acid chlorides **161** are reacted with 5-chloro-1-(triisopropylsilyl)-1*H*-pyrrolo[2,3-*b*]pyridine **162** as described in General Procedure **VVVV** (Scheme XXVII, step b) to give ketones **78** which may be further reacted as described in Scheme XIII.

Scheme XXVII



Alternate methods for preparing imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazines compounds of the invention are illustrated in Scheme XXVIII. In step a, carboxylic acids **160** are converted to the corresponding sulfoxonium ylides **163** using conditions such as those described in General Procedure **FFFFF** or *J. Org. Chem.* **2004**, 69, 1629. Pyrrolopyrazin-2-amines **164** may be prepared from pyrrolopyrazin-2-ylcarbamates **11** (Scheme II) using conditions known to one skilled in the art such as those described in General Procedure **E** or Greene, T.W. and Wuts, P.G.M. referenced above (Scheme XXVIII, step b). Sulfoxonium ylides **163** are reacted with pyrrolopyrazin-2-amines **164** using conditions such as those described in General Procedure **GGGGG** or *Org. Lett.* **2009**, 11, 3566 to give pyrrolopyrazines **13** which may be further reacted as described in Scheme II (Scheme XXVIII, step c). Alternatively, as shown in step d, pyrrolopyrazin-2-amines **164** may be reacted with an α -haloaldehyde using conditions such as those given in General Procedure **YYYY** to give imidazopyrrolopyrazines **14** which may be further reacted as described in Scheme II.

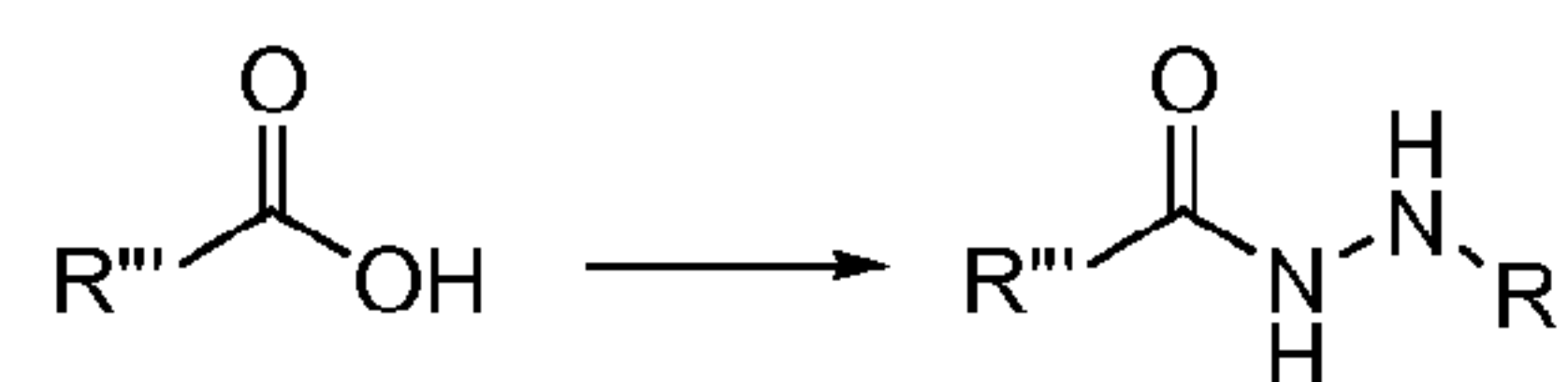
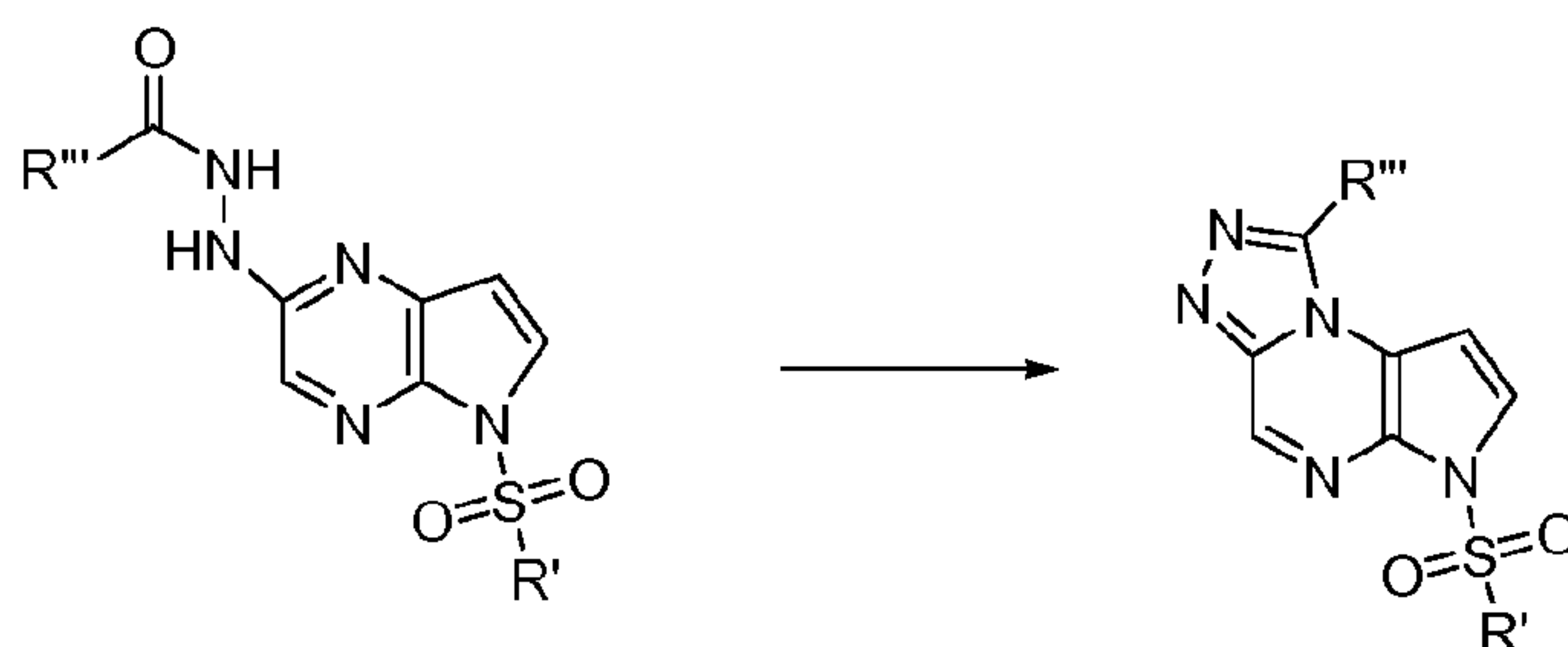
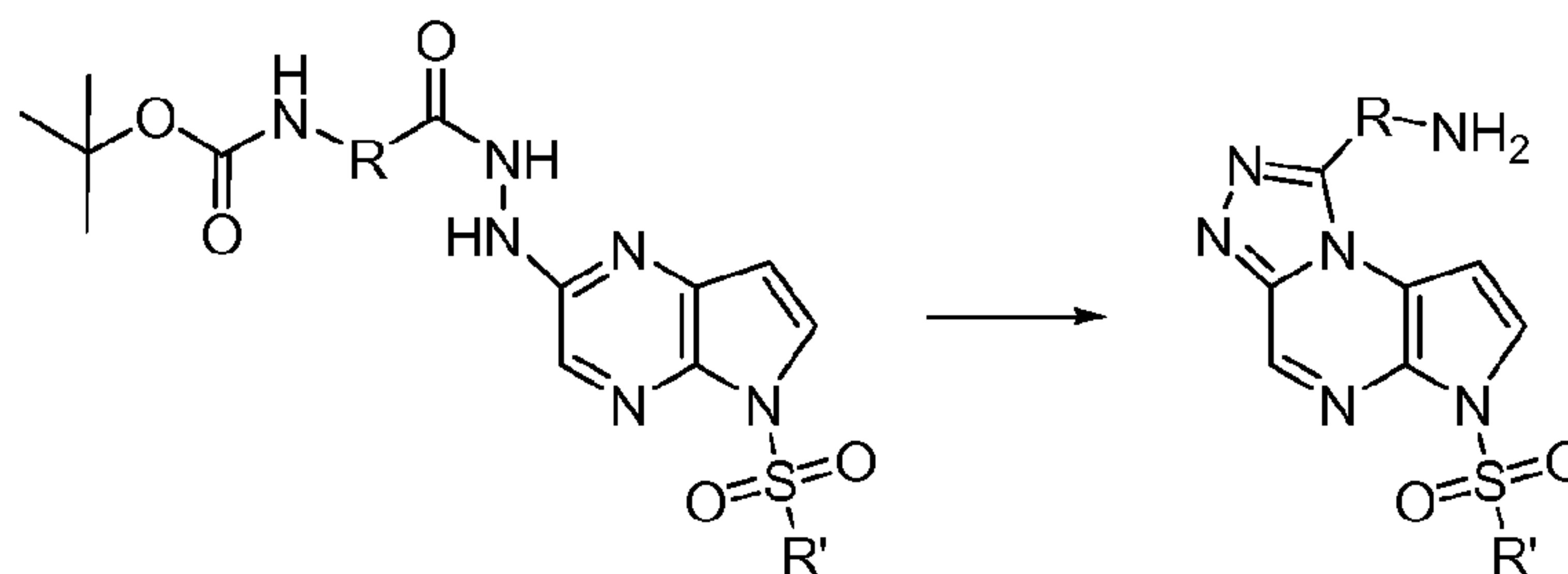
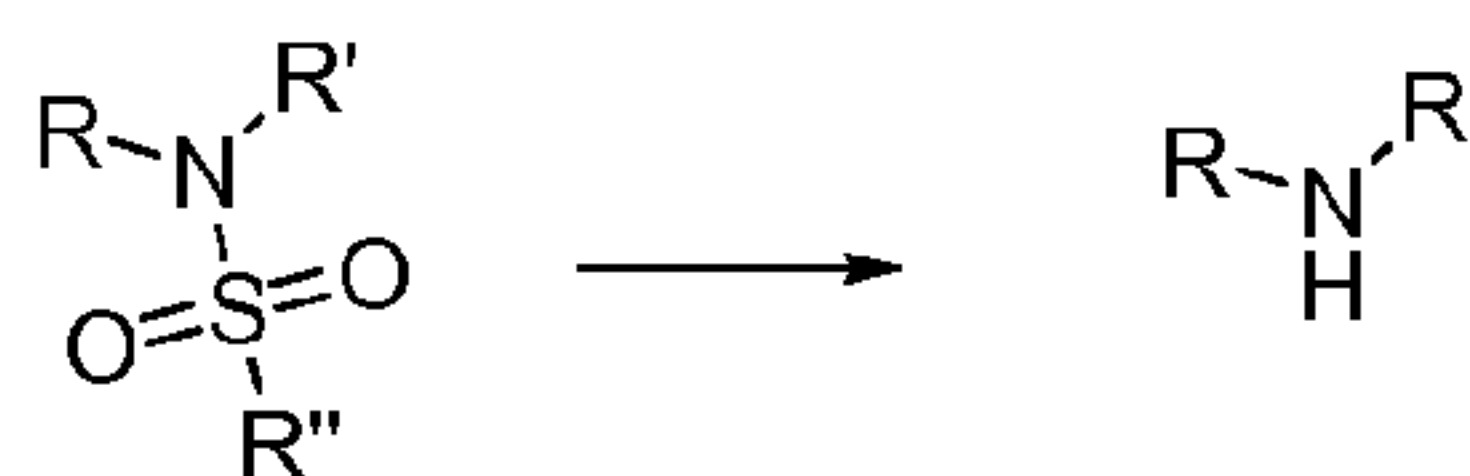
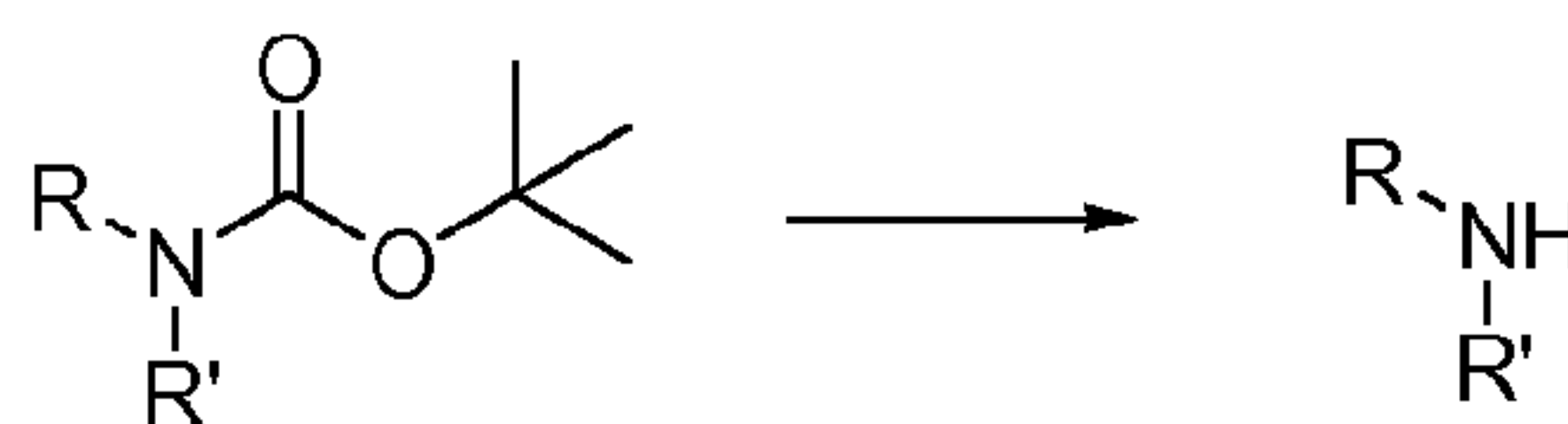
Scheme XXVIII



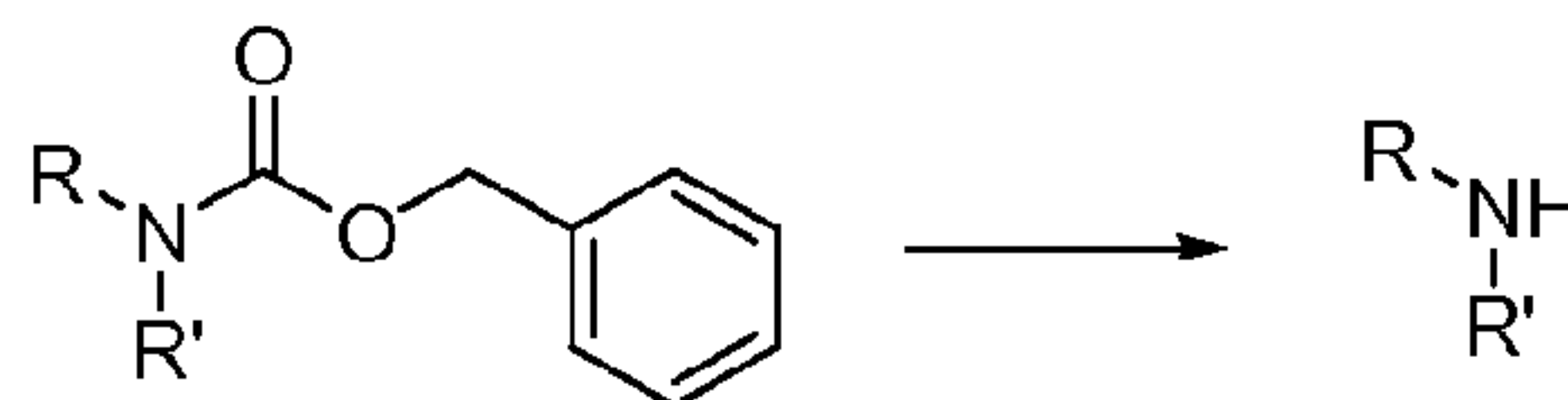
If desired, chiral separation of any of the chiral compounds in Schemes I-XXVIII may be done using methods known to one skilled in the art such as chiral preparative HPLC or chiral SFC (for example, General Procedure **AA**) or crystallization of diastereomeric salts as described in Example #5. Further functionalization of any of the R groups above (e.g. R, R", R"', R''', and R''') can be performed, if desired, using reactions known to one skilled in the art (for example, Larock, R.C. referenced above). For example, formation of amides, ureas, sulfonamides, aryl amines, heteroaryl amines, sulfonyl ureas, substituted amines, squaramides, or guanidines can be prepared with an R group containing a primary or secondary amine (for example, General Procedures **G**, **H**, **I**, **J**, **J.1**, **XXX**, **EEEE**, **K**, **K.1**, **L**, **DD**, **QQ**, **RR**, **YY**, **ZZ** followed by **AAA**, **CCC**, **YYY**, **X**, **X.1**, **TTTT**, or **EEEE**). Also, deprotection of an R group to yield deprotected compounds may be performed using conditions such as those described in Greene, T.W. and Wuts, P.G.M. referenced above or in General Procedures **E**, **E.1**, **F**, **F.1**, **Y**, or **BB** and the deprotected compounds may then be reacted further as described above.

GENERAL PROCEDURES AND EXAMPLES

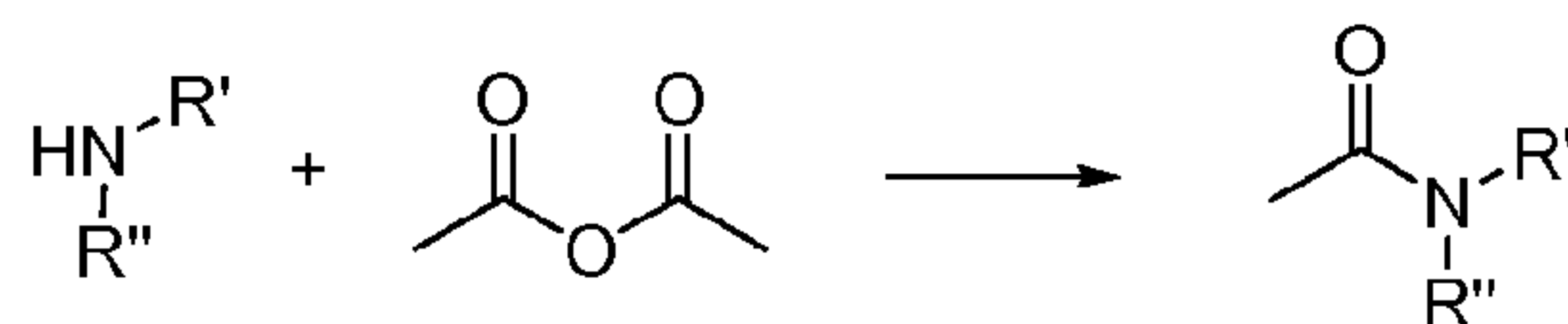
The general synthetic schemes that were utilized to construct the majority of compounds disclosed in this application are described below in Schemes 1-111. These schemes are provided for illustrative purposes only and are not to be construed as limiting the scope of the invention.

Scheme 1. Formation of a hydrazide from a carboxylic acid (General Procedure A)**Scheme 2. Cyclization of a hydrazide (General Procedure B)****Scheme 3. Cyclization of a hydrazide with loss of Boc-protecting group (General Procedure C)****Scheme 4. Hydrolysis of a sulfonamide (General Procedure D)****Scheme 5. Acidic cleavage of a Boc-protected amine (General Procedures E and E.1)**

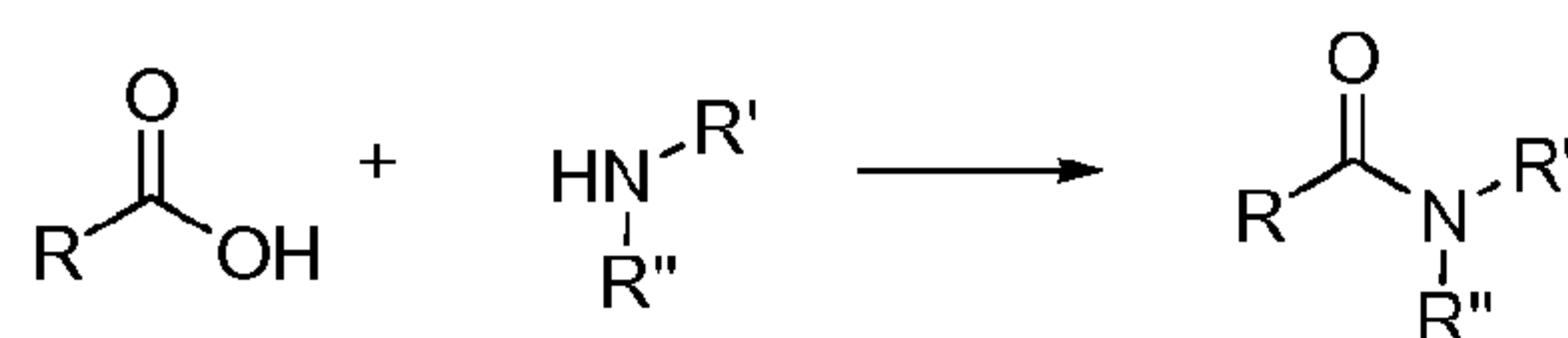
Scheme 6. Deprotection of a Cbz-protected amine using HBr in AcOH (General Procedures F and F.1)



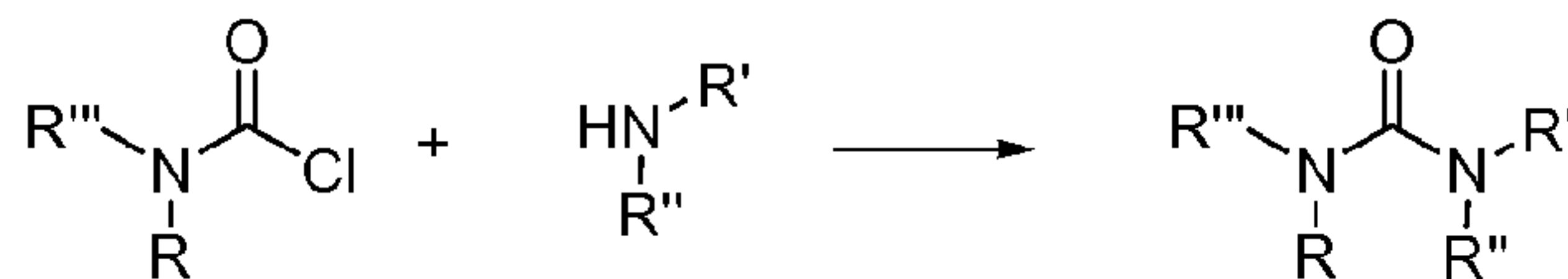
Scheme 7. Formation of an acetamide (General Procedure G)



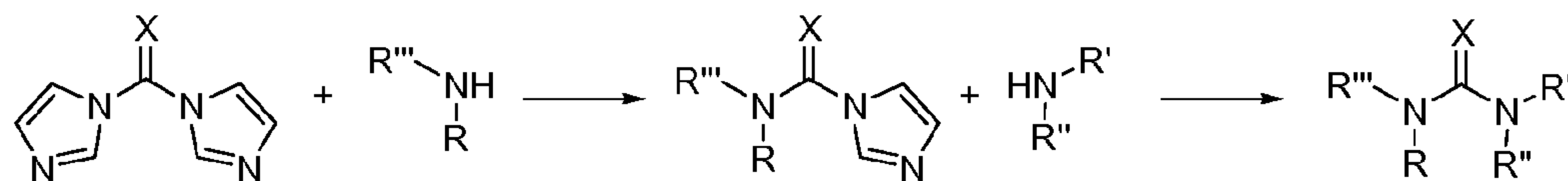
Scheme 8. Formation of an amide from a carboxylic acid and an amine (General Procedure H)



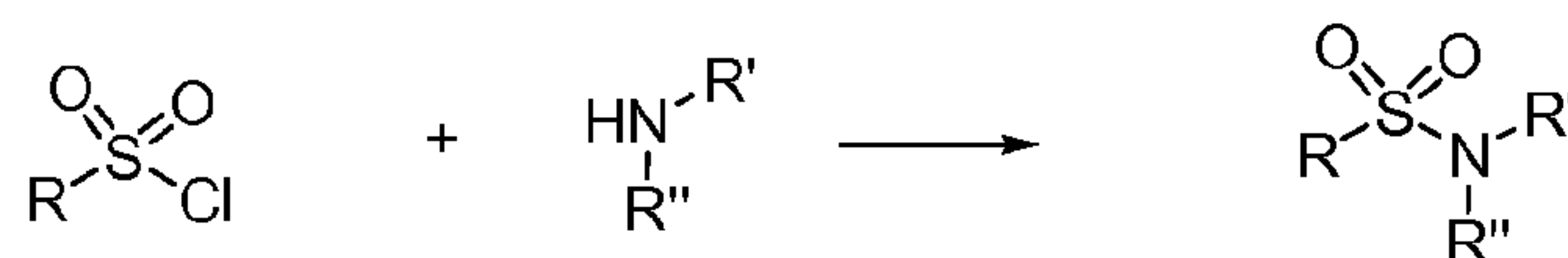
Scheme 9. Formation of a urea from an amine and a carbamoyl chloride (General Procedure I)



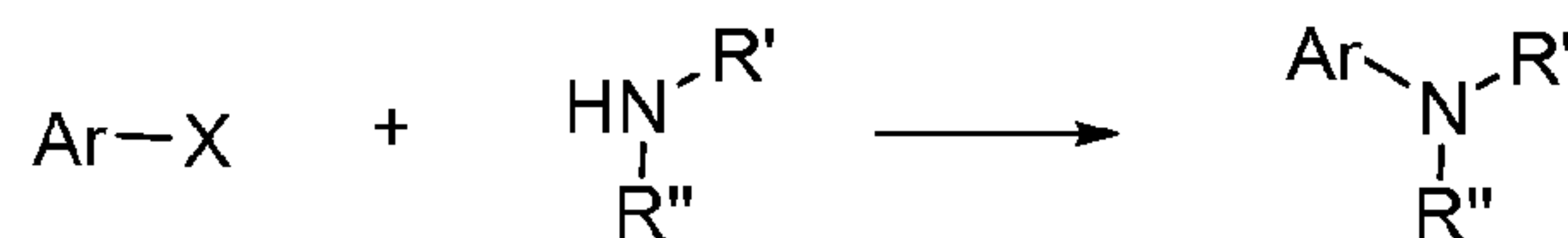
Scheme 10. Formation of a urea (X = O) or thiourea (X = S) using CDI or thiocarbonyl diimidazole, respectively (General Procedures J and J.1)



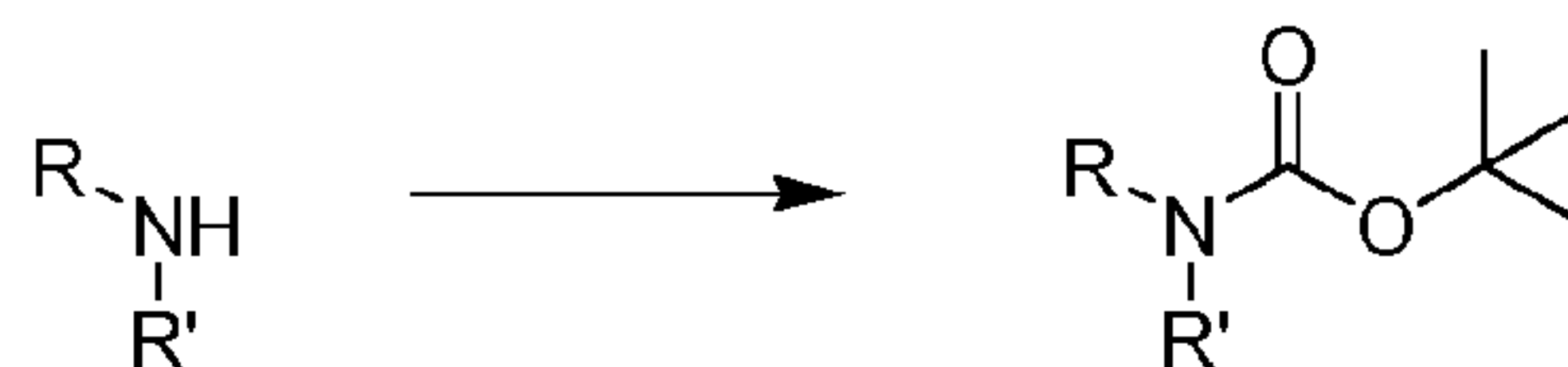
Scheme 11. Formation of a sulfonamide from an amine (General Procedure K and K.1)

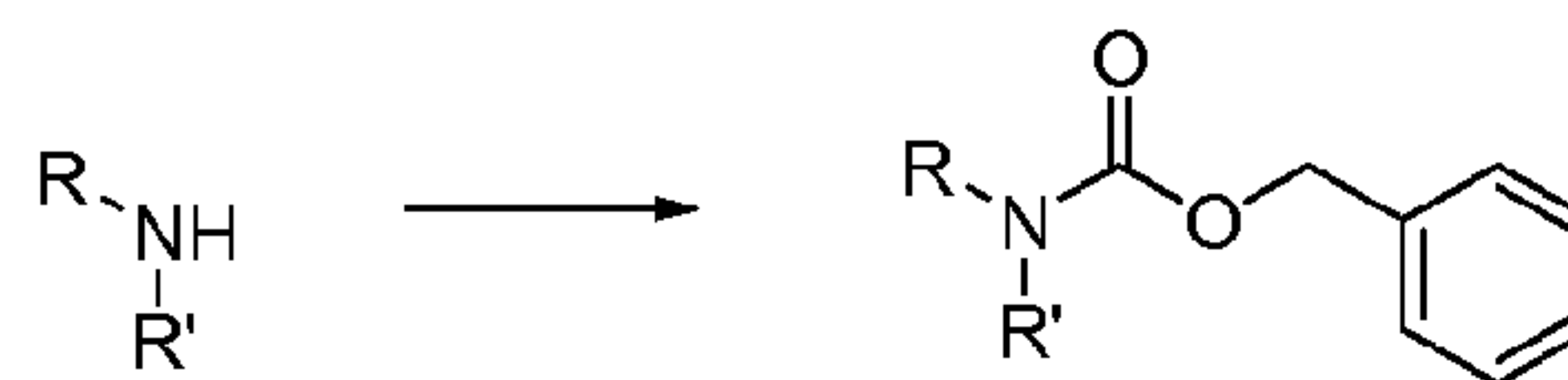
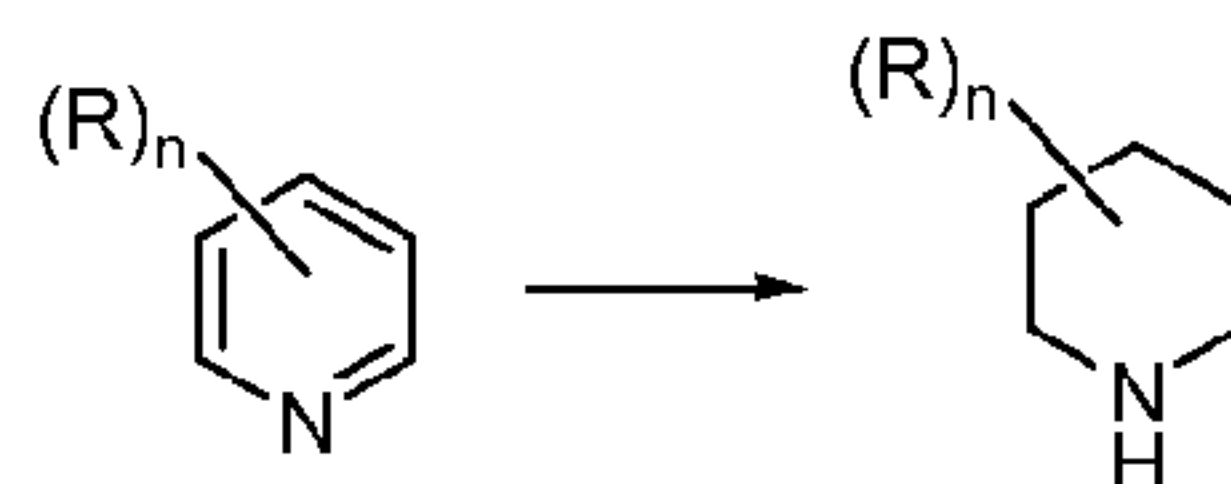
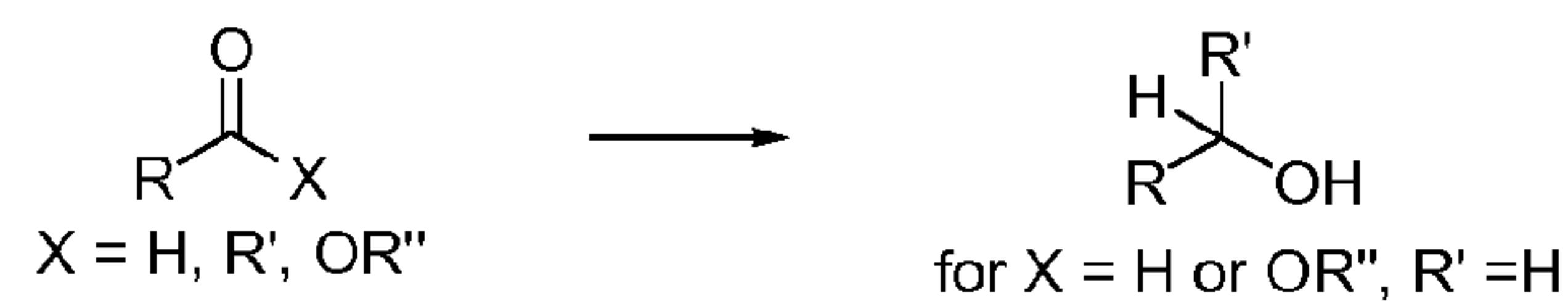
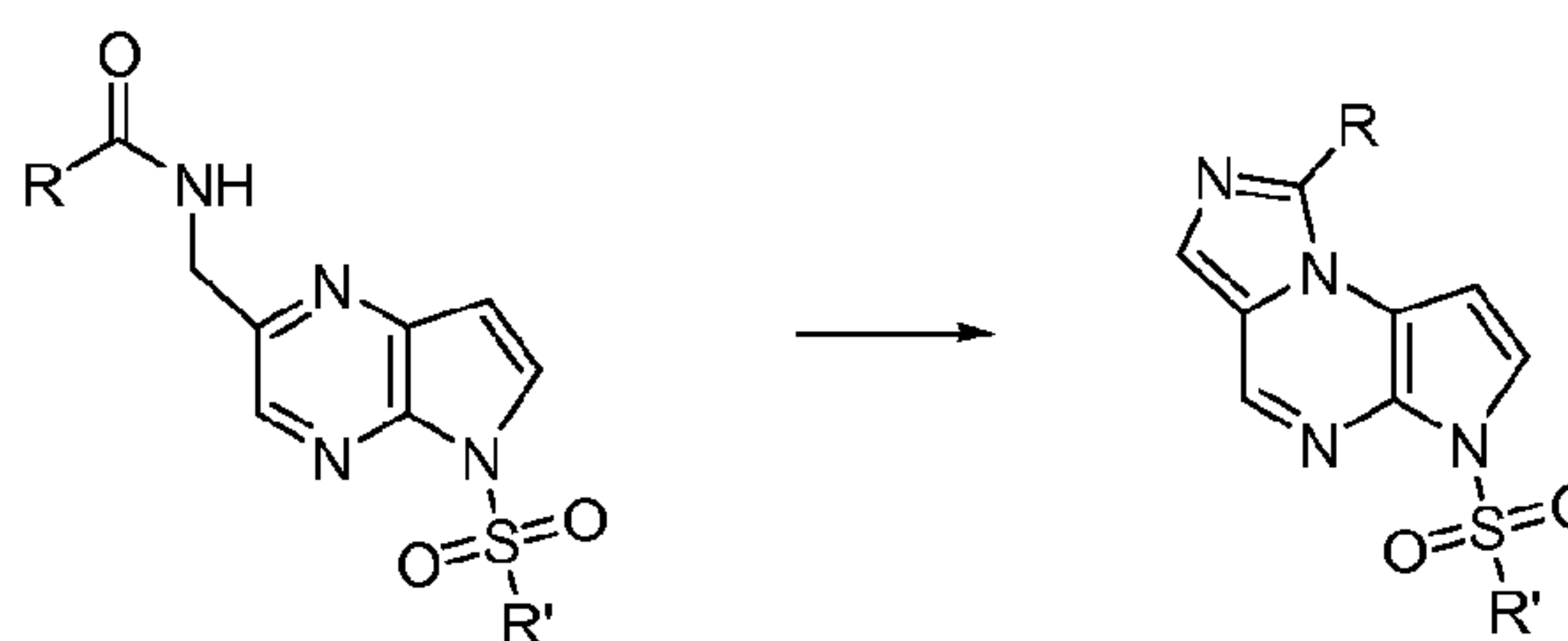
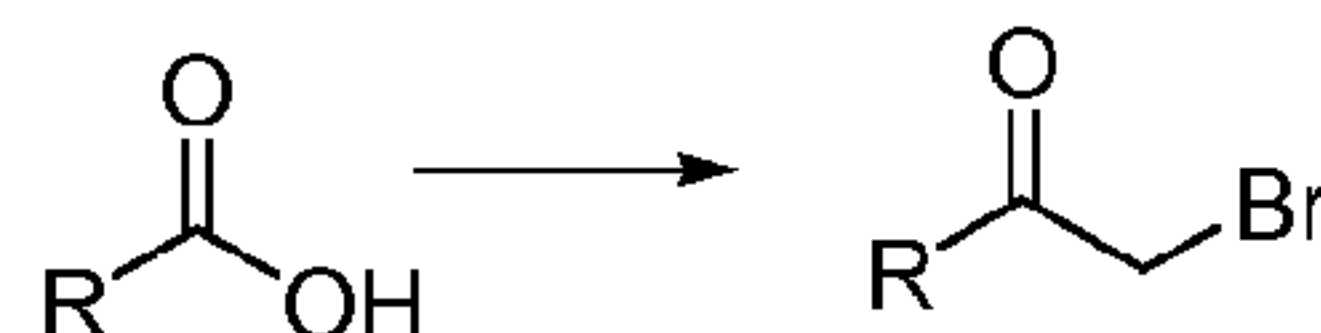
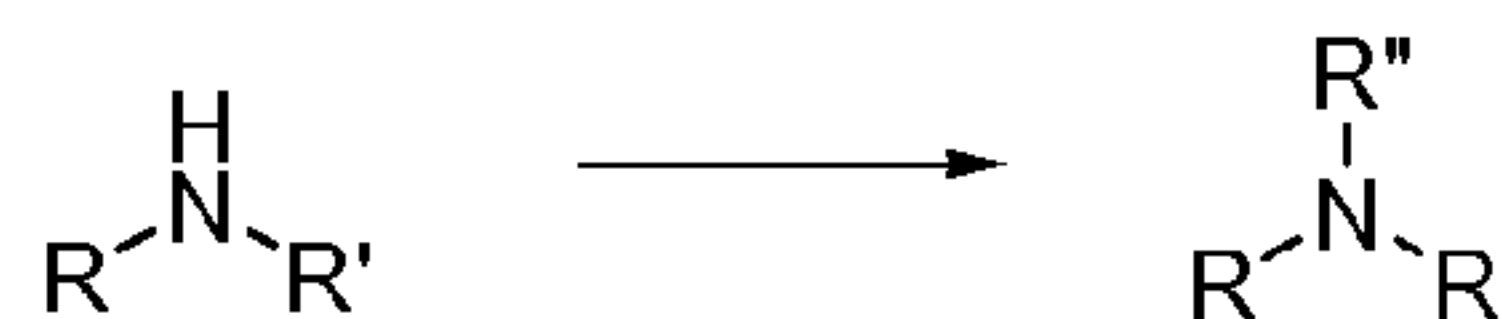
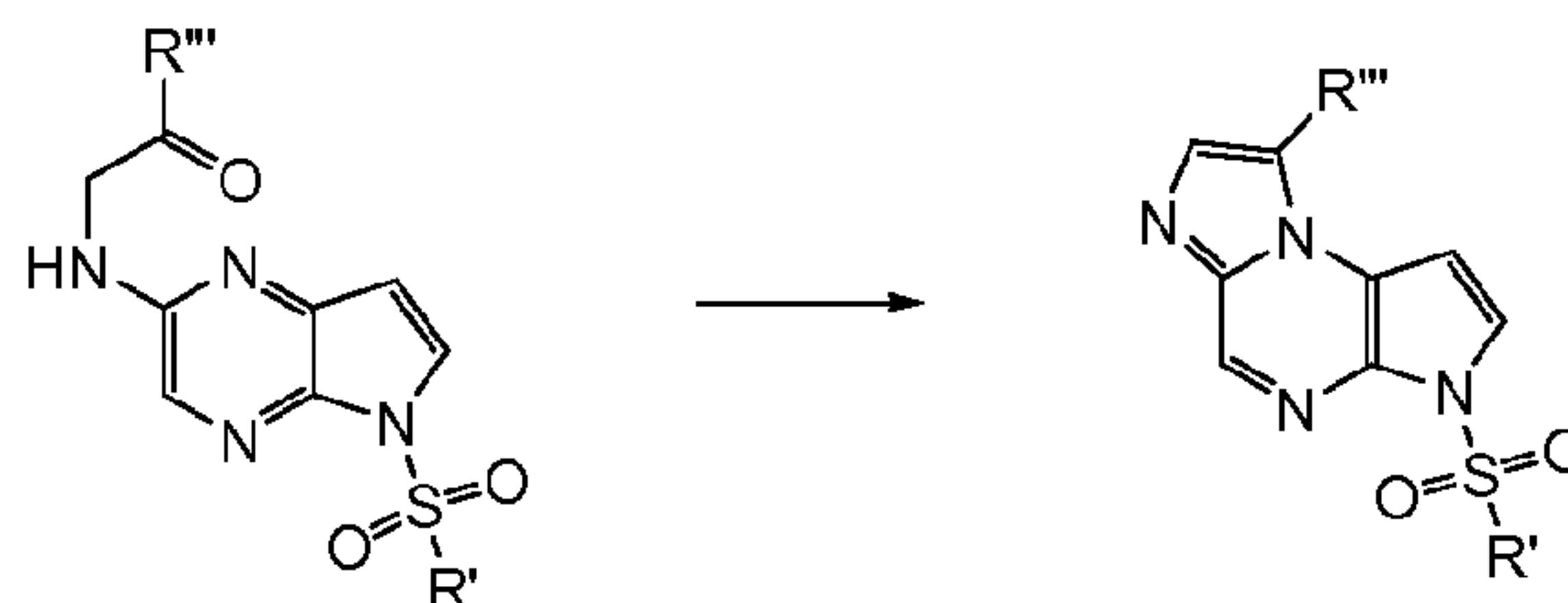


Scheme 12. Displacement of an aryl or heteroaryl halide with an amine (General Procedure L)

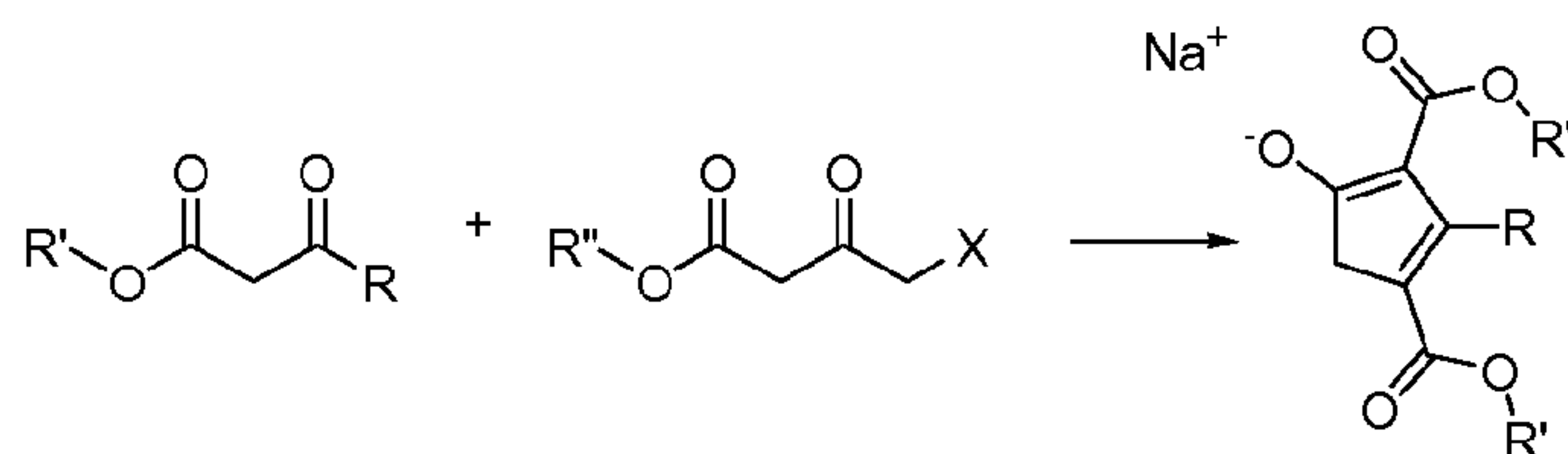


Scheme 13. Boc-protection of an amine (General Procedures M and M.1)

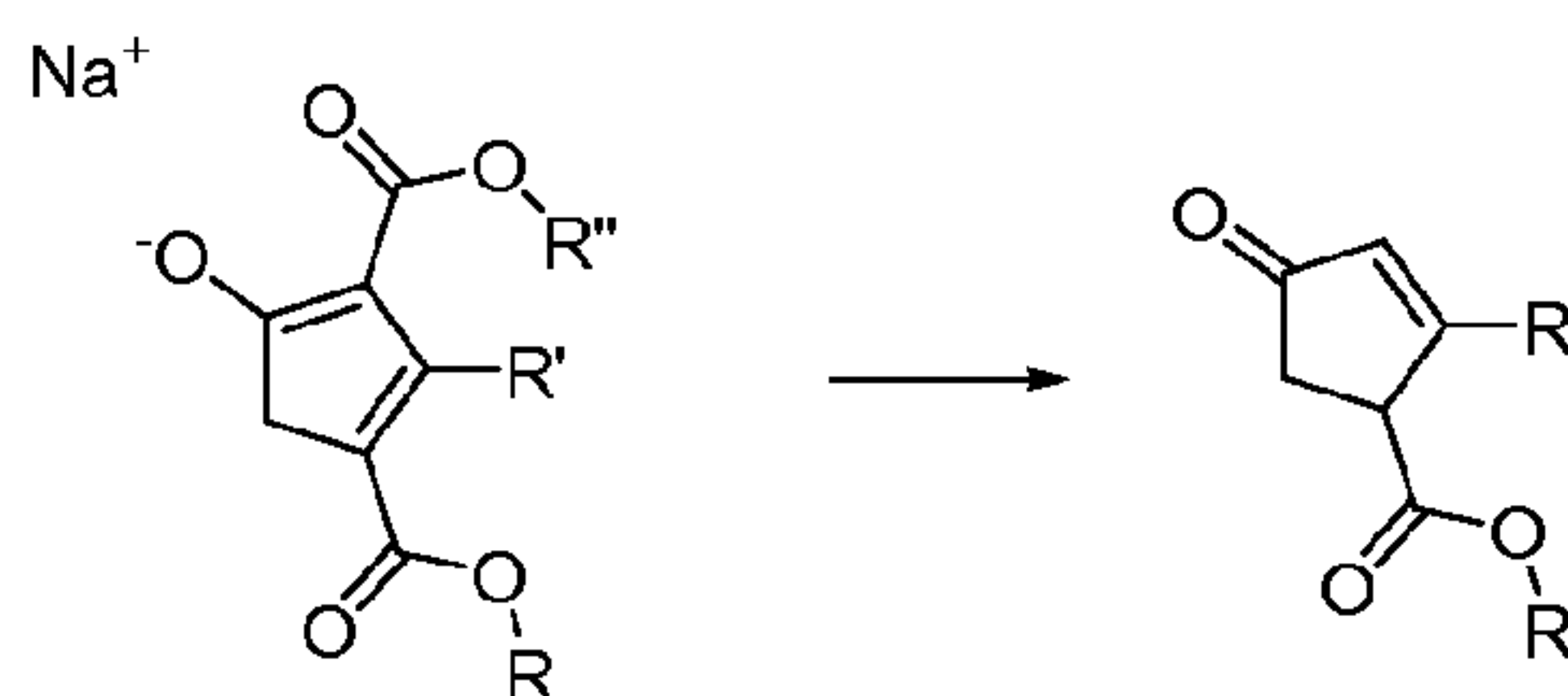


Scheme 14. Cbz-protection of an amine (General Procedure N)**Scheme 15. Reduction of a pyridine (General Procedure O)****Scheme 16. Reduction of a carbonyl to an alcohol (General Procedure P)****Scheme 17. Cyclization of an amide using a dithiaphosphetane reagent (General Procedure Q)****Scheme 18. Formation of a bromomethyl ketone from an acid (General Procedure R)****Scheme 19. N-Alkylation using an alkyl halide, α-haloketone, or α-haloamide (General Procedures S and S.1)****Scheme 20. Cyclization of a ketone using a dithiaphosphetane reagent (General Procedure T)**

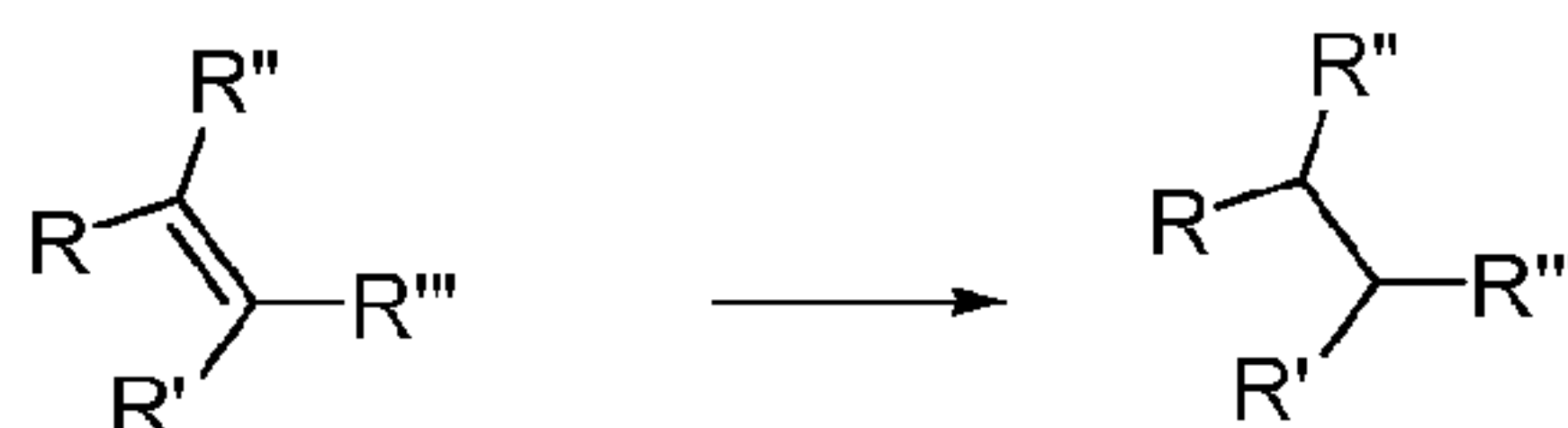
Scheme 21. Knoevenagel condensation to form a substituted cyclopentadiene (General Procedure U)



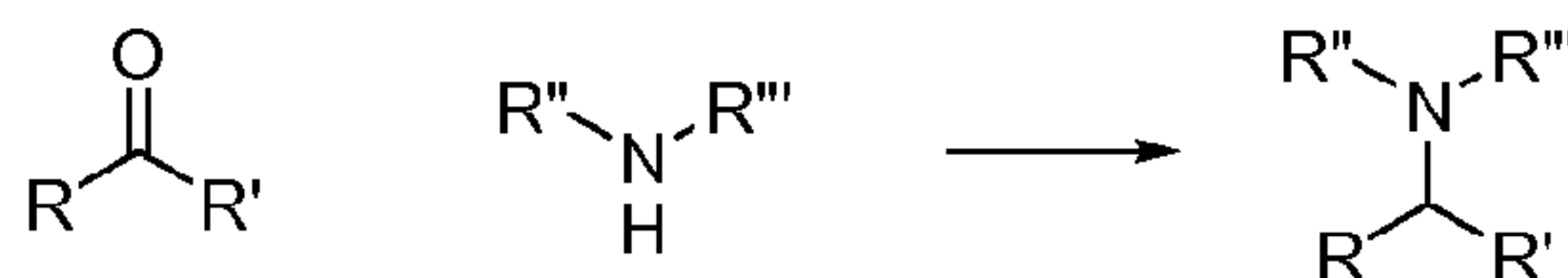
Scheme 22. Decarboxylation of a β -ketoester enolate (General Procedure V)



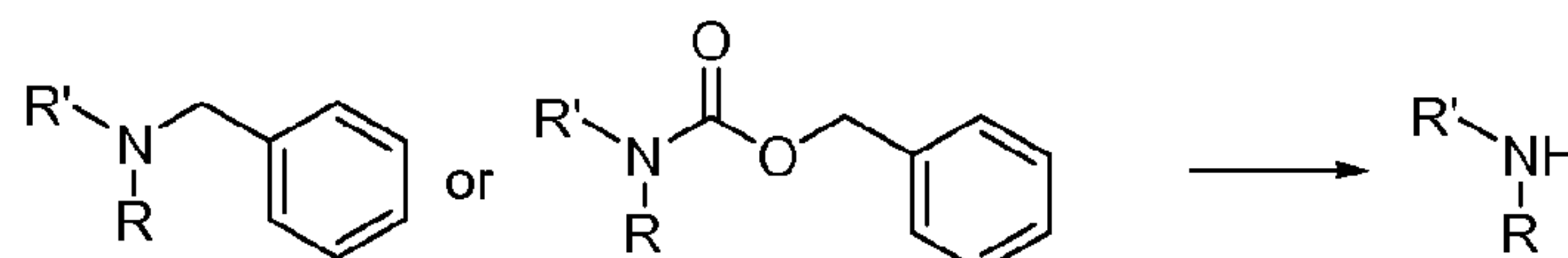
Scheme 23. Hydrogenation of an alkene (General Procedures W and W.1)



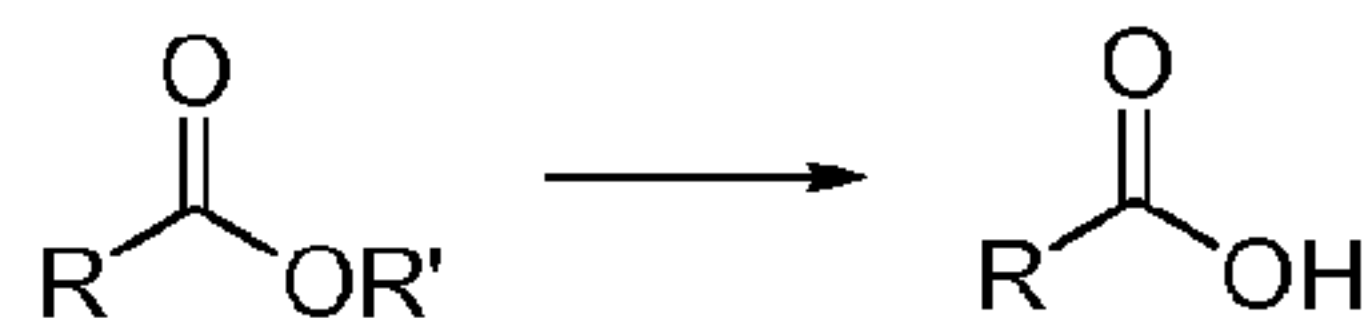
Scheme 24. Reductive amination of a ketone or aldehyde ($R' = H$) (General Procedures X and X.1)



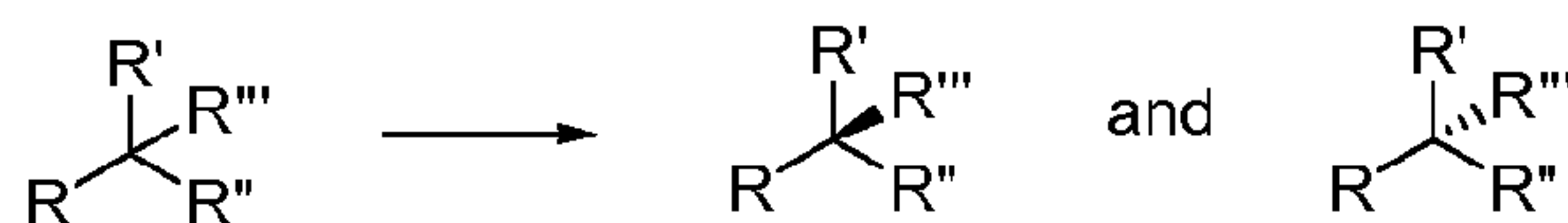
Scheme 25. Hydrogenation of a benzyl- or Cbz-protected amine (General Procedure Y)



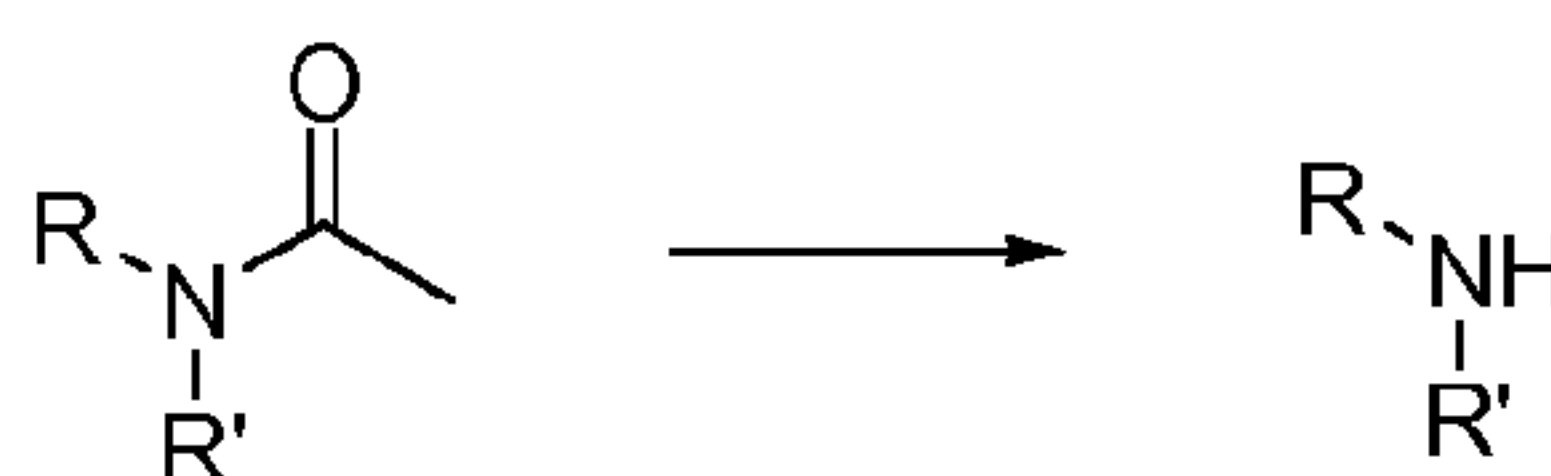
Scheme 26. Basic hydrolysis of an ester to a carboxylic acid (General Procedure Z)

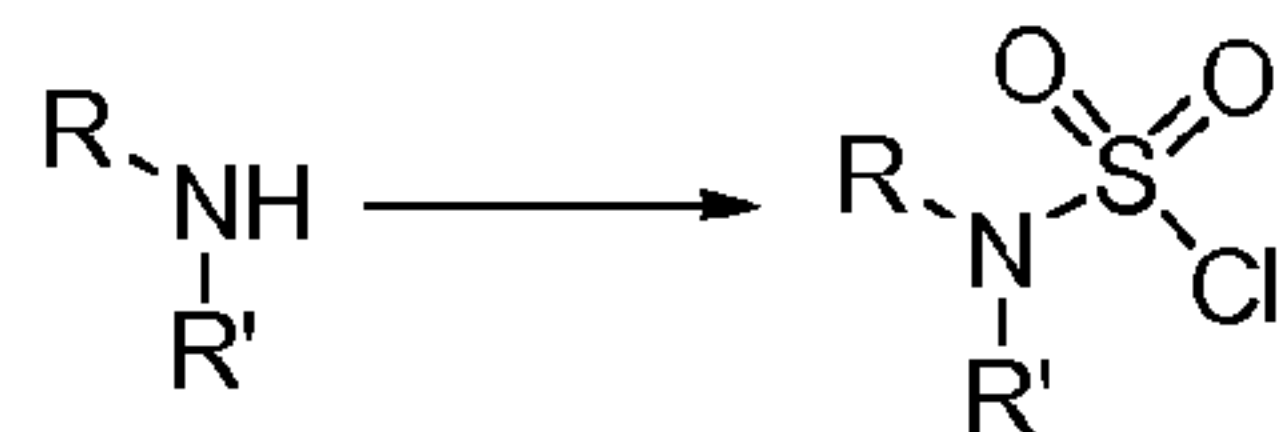
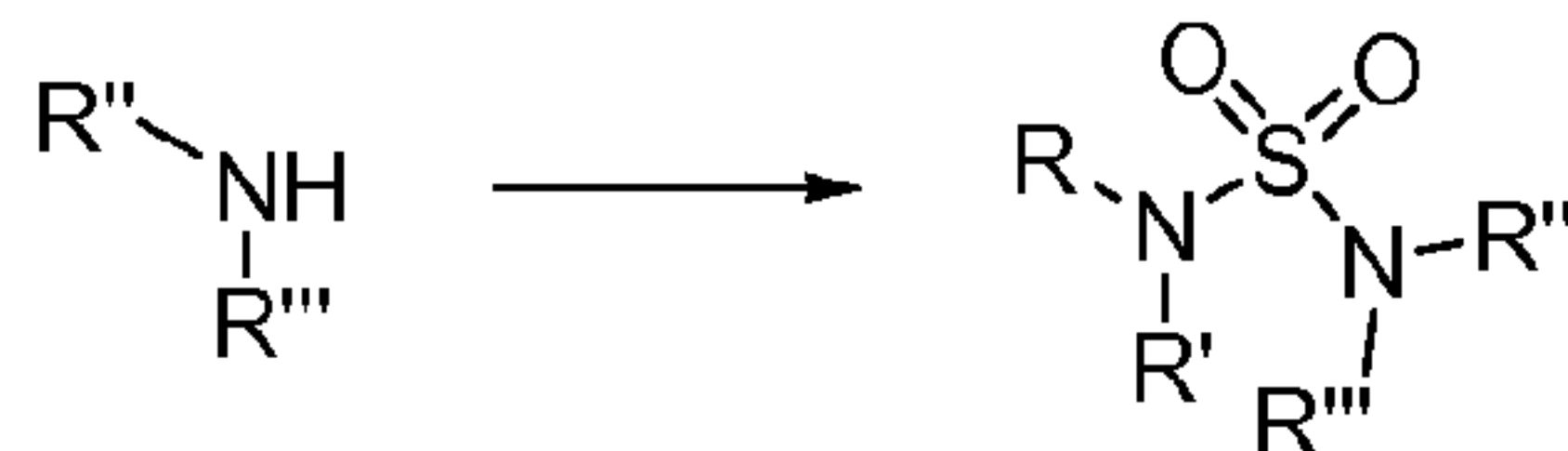
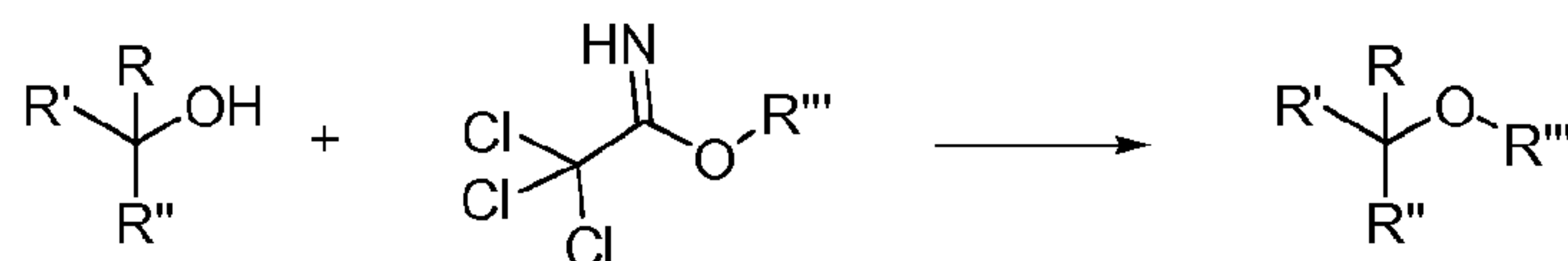
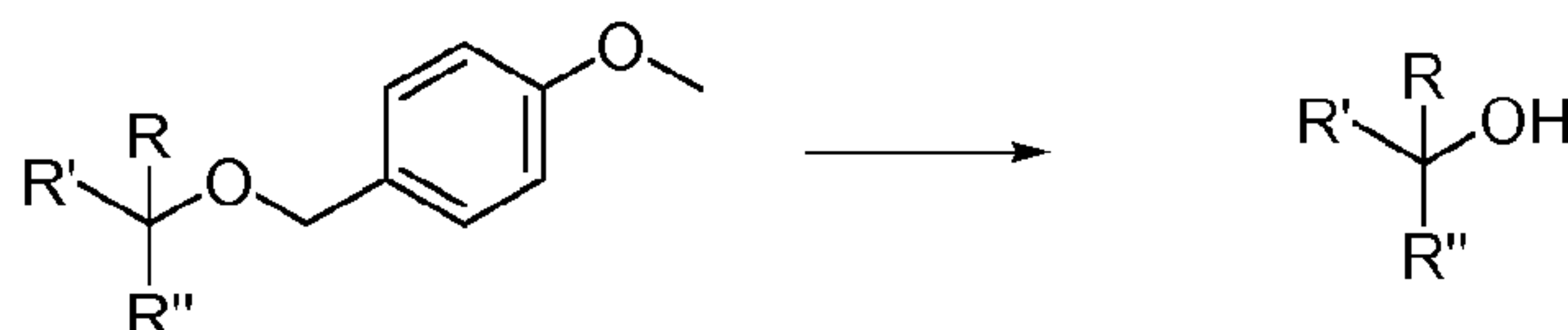
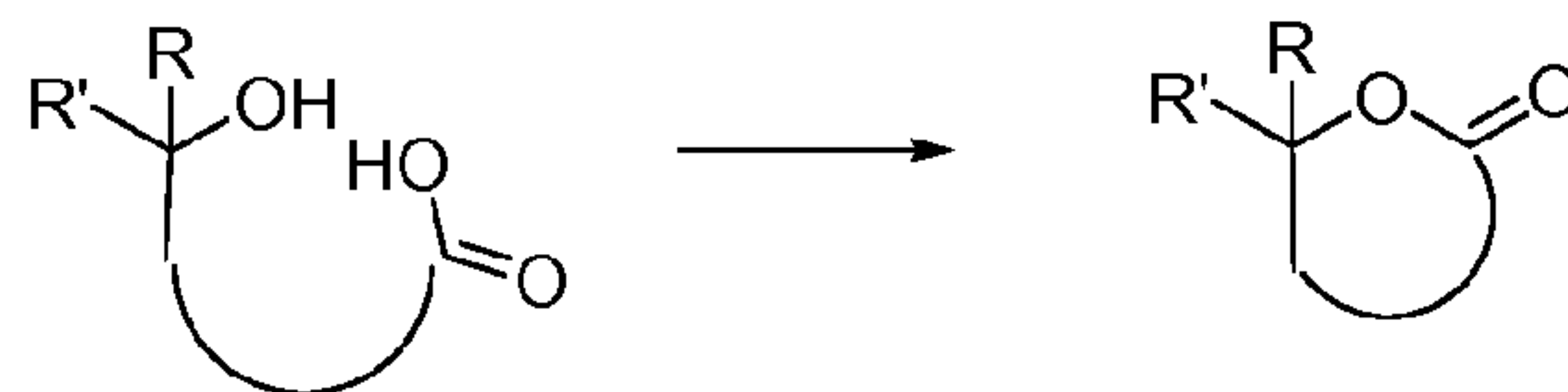
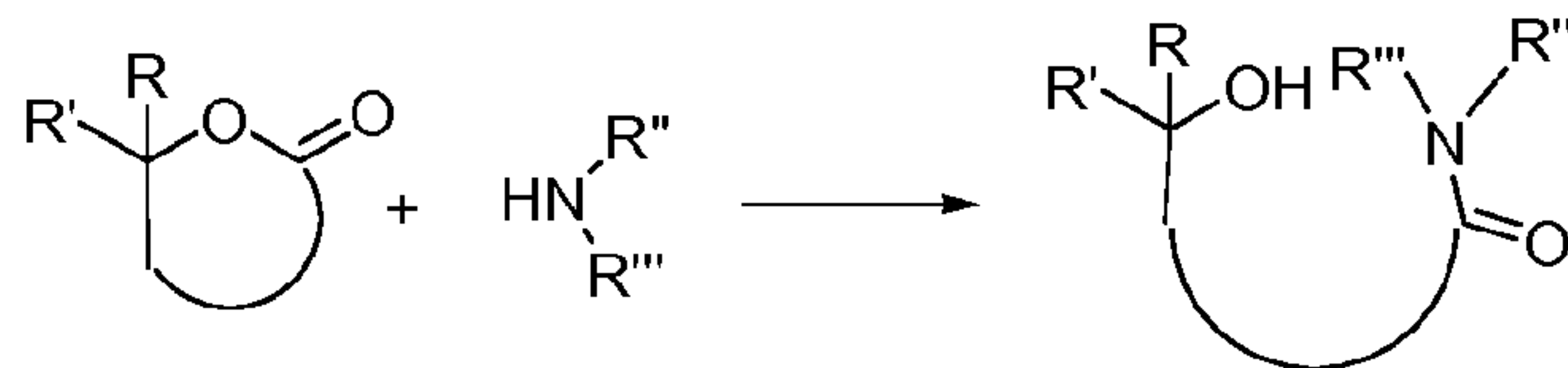
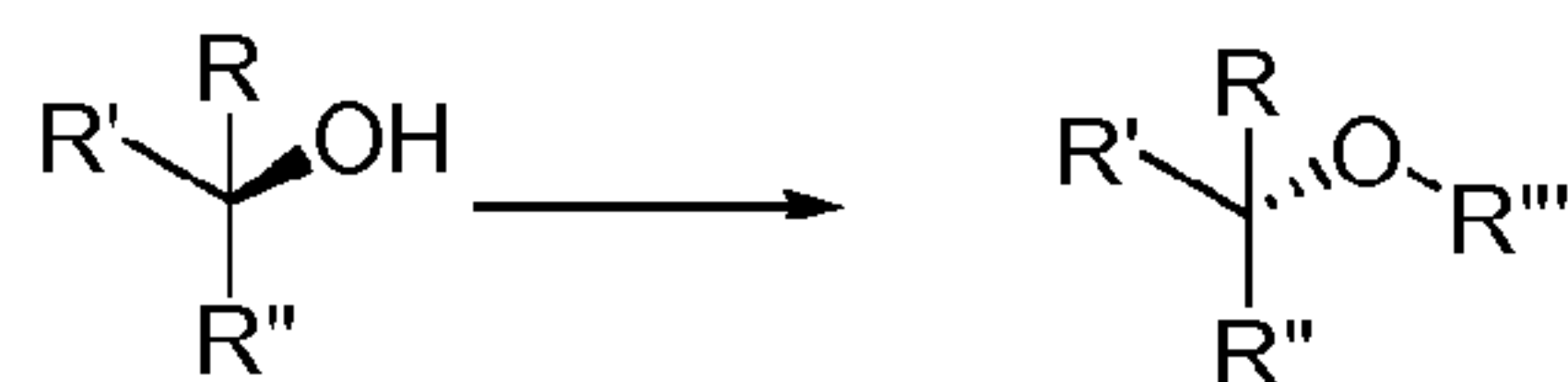


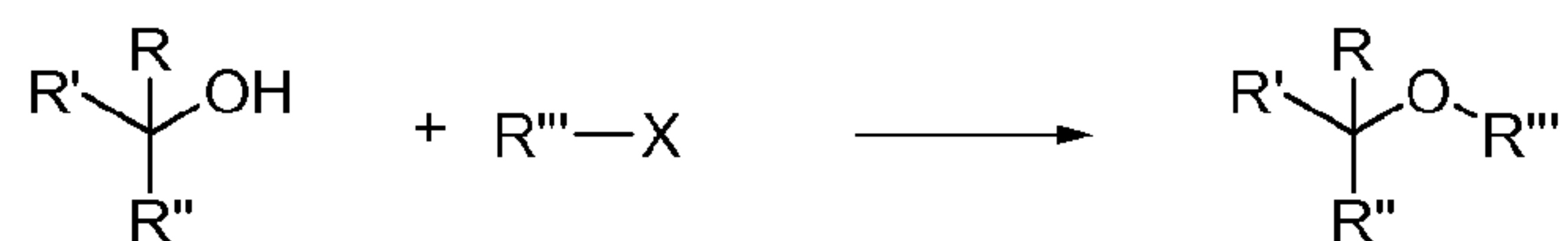
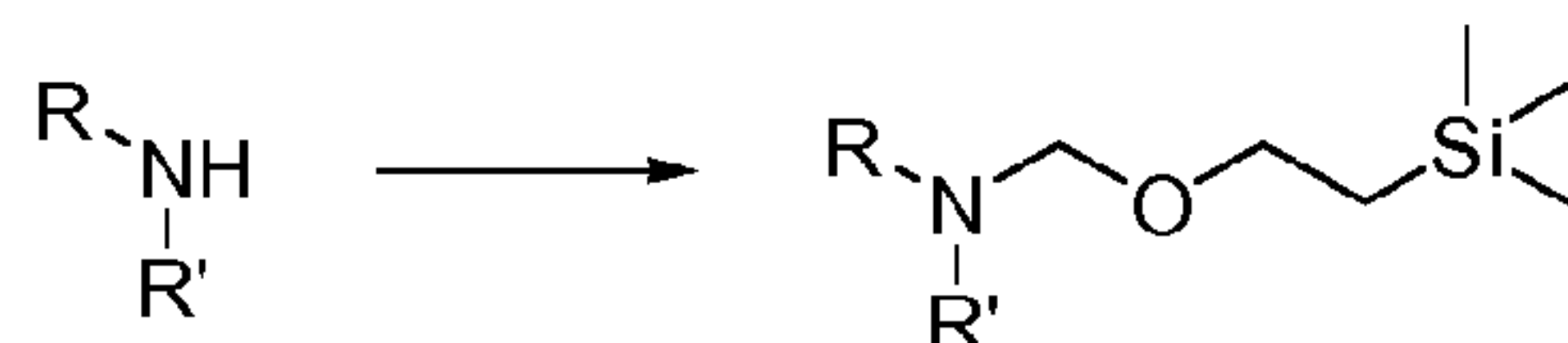
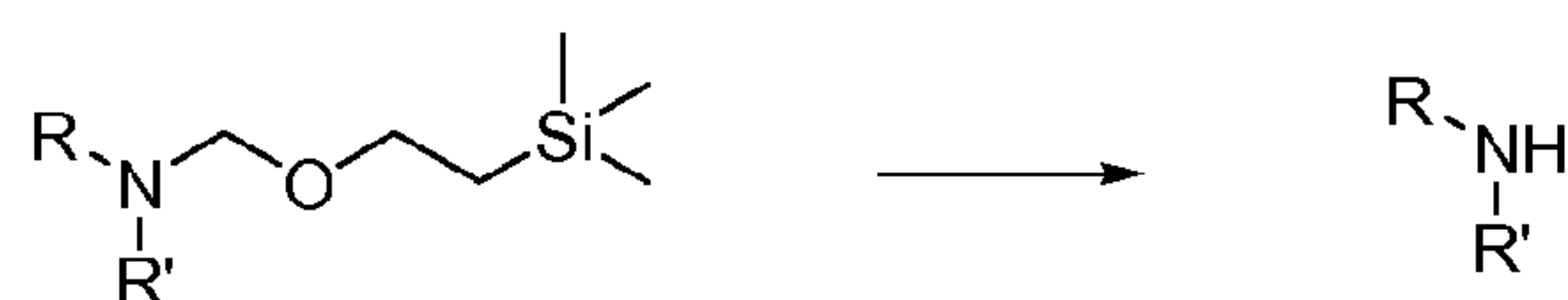
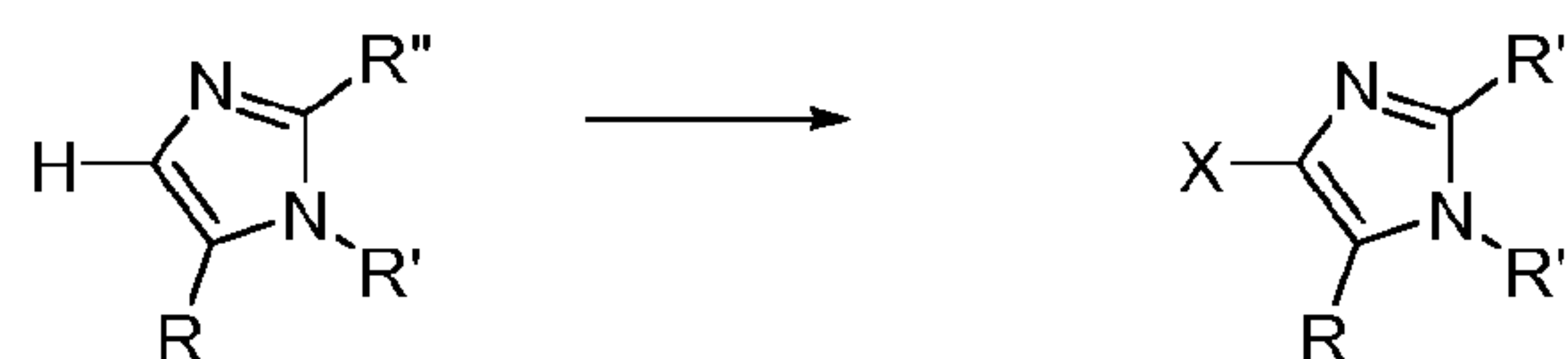
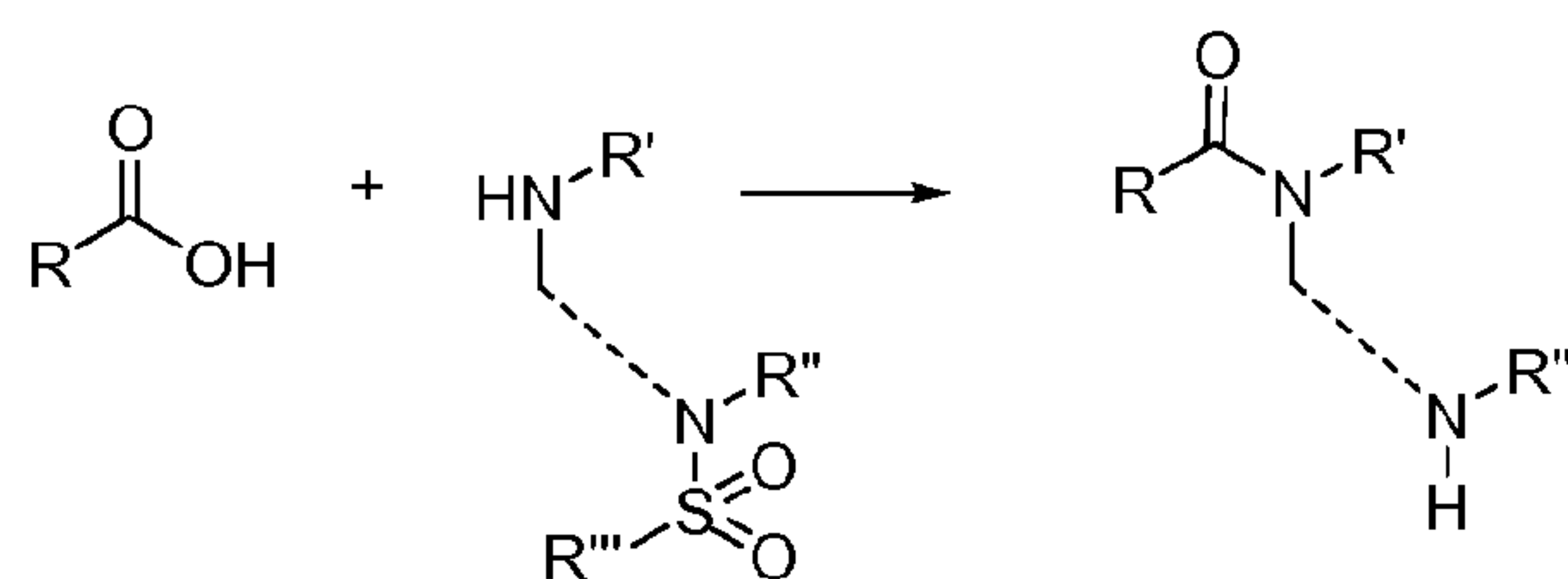
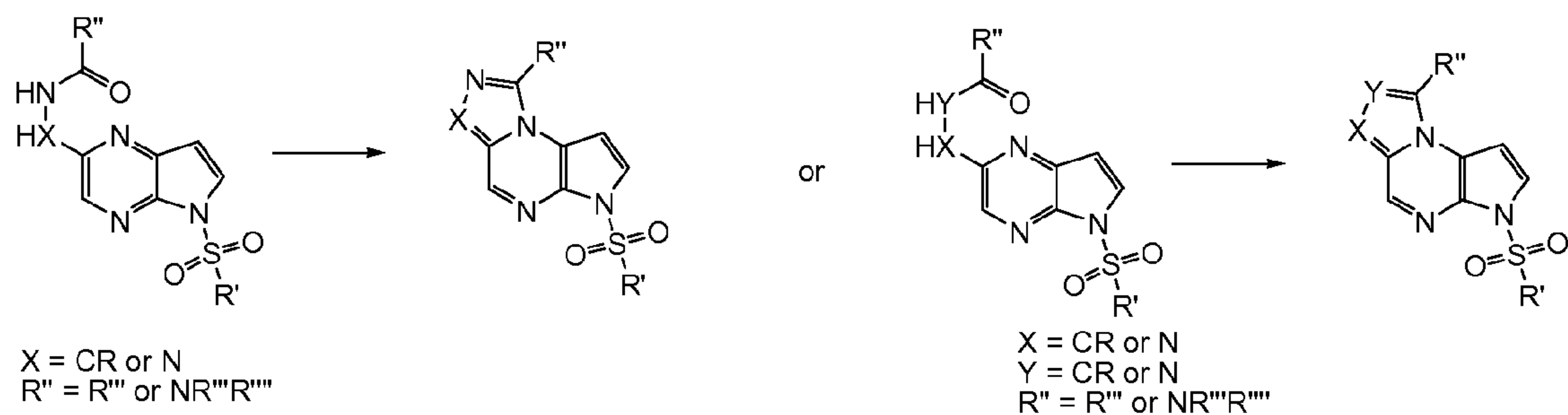
Scheme 27: Chiral preparative HPLC separation of stereoisomers (General Procedure AA)

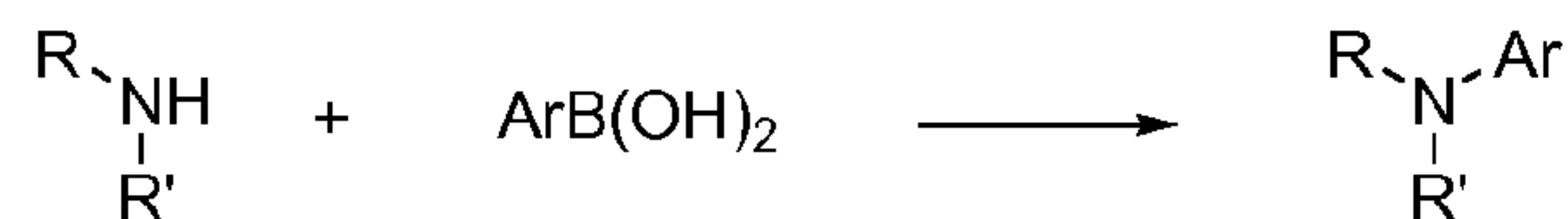
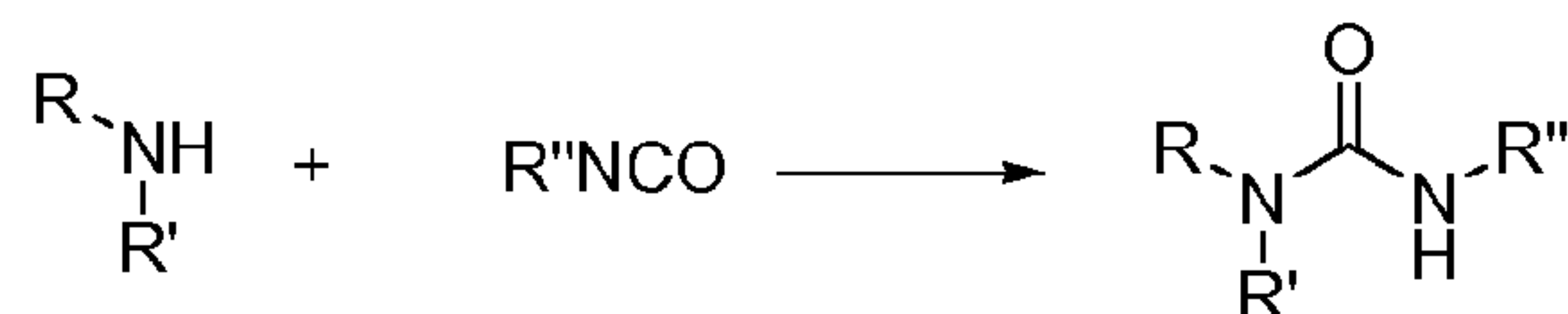
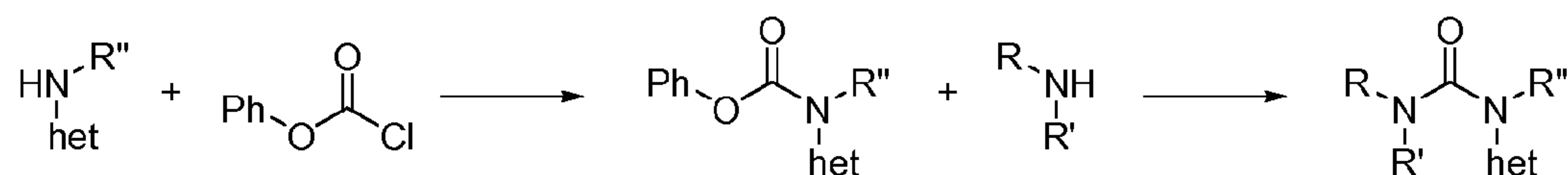
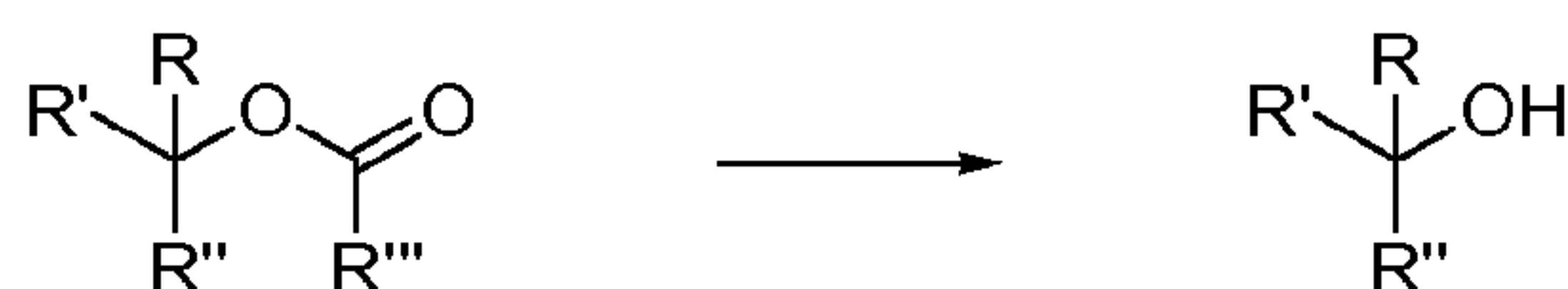
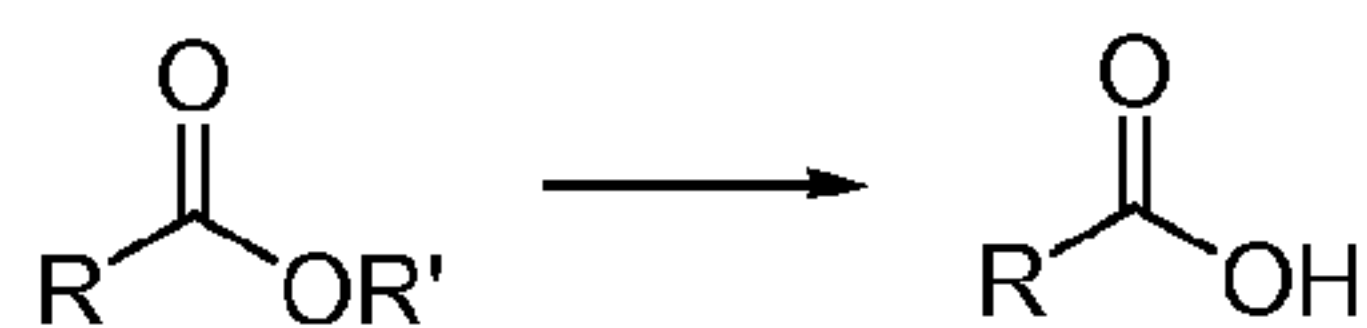
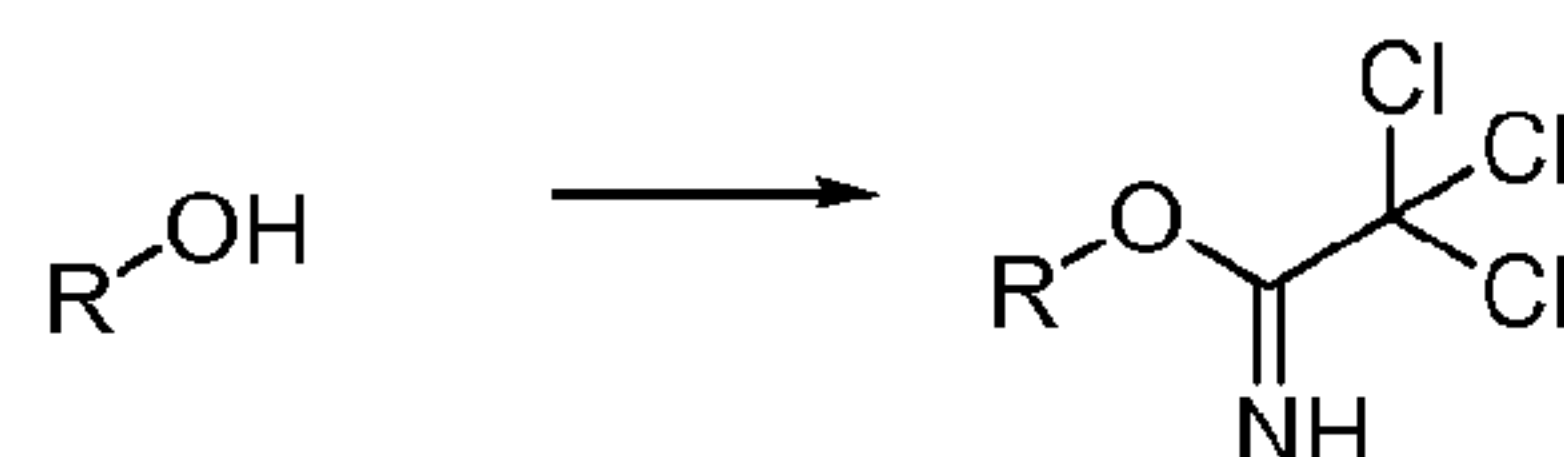
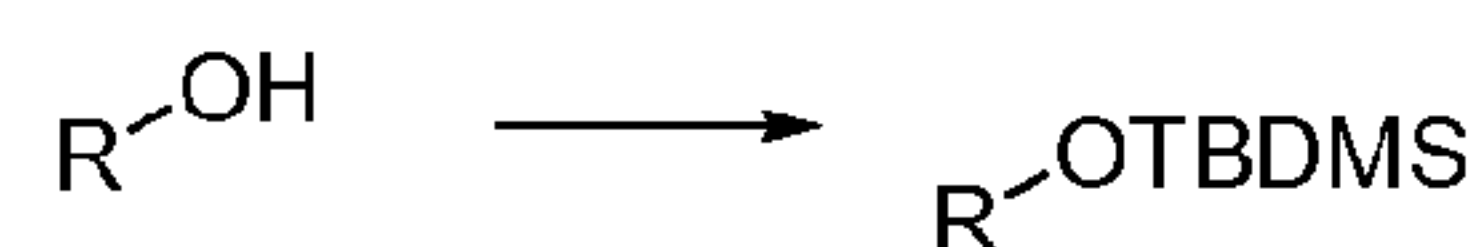
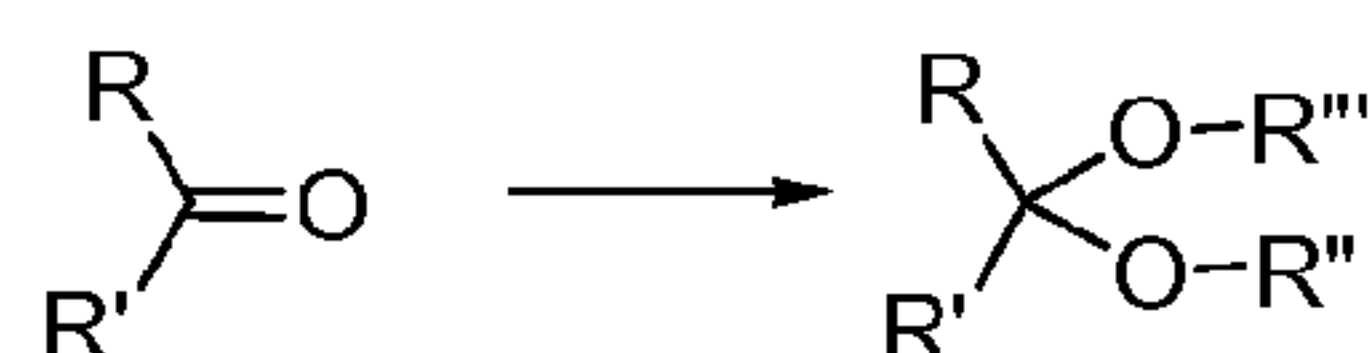


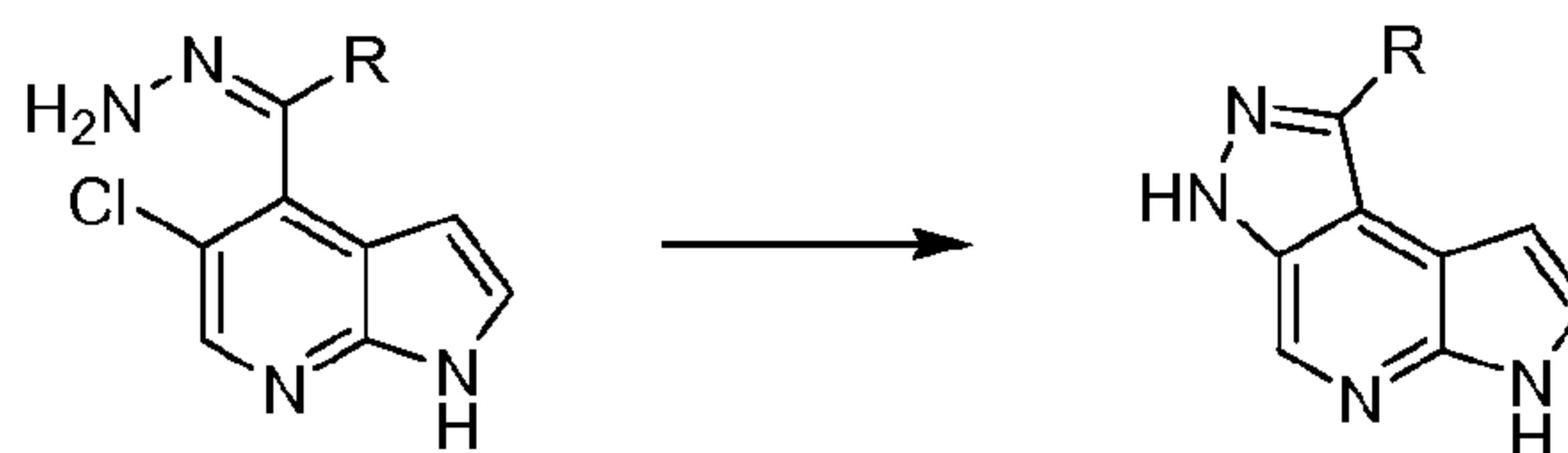
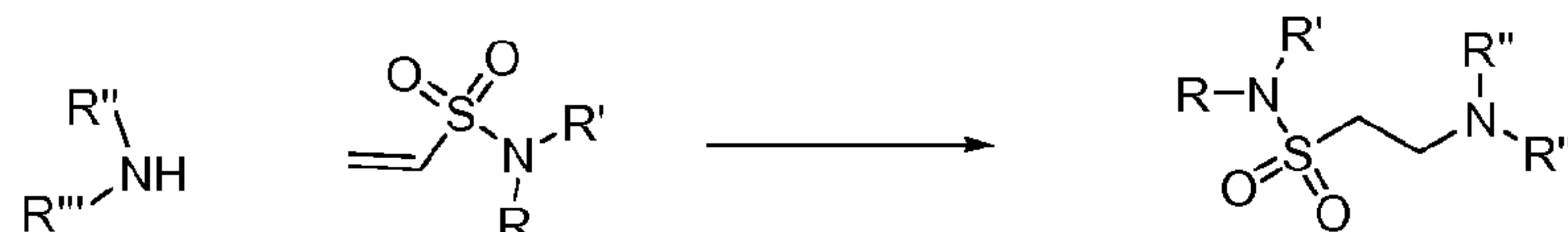
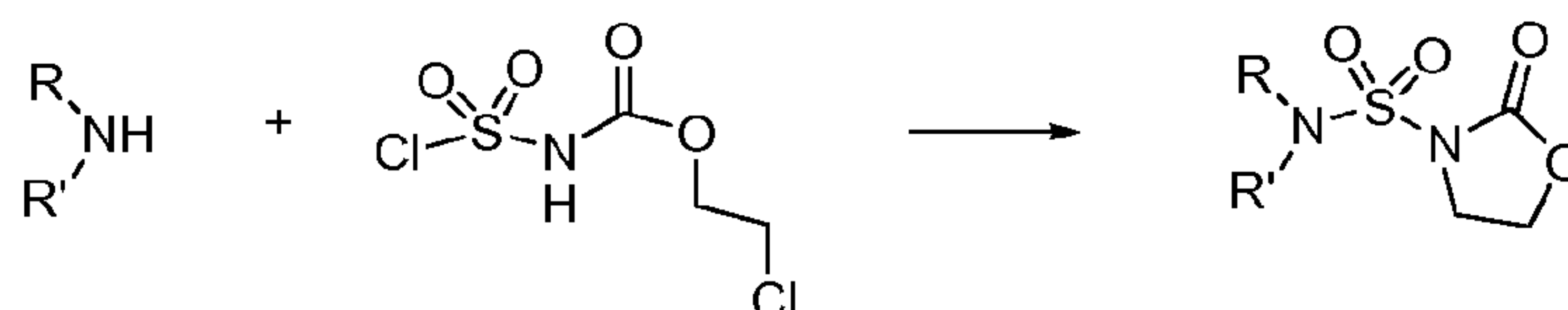
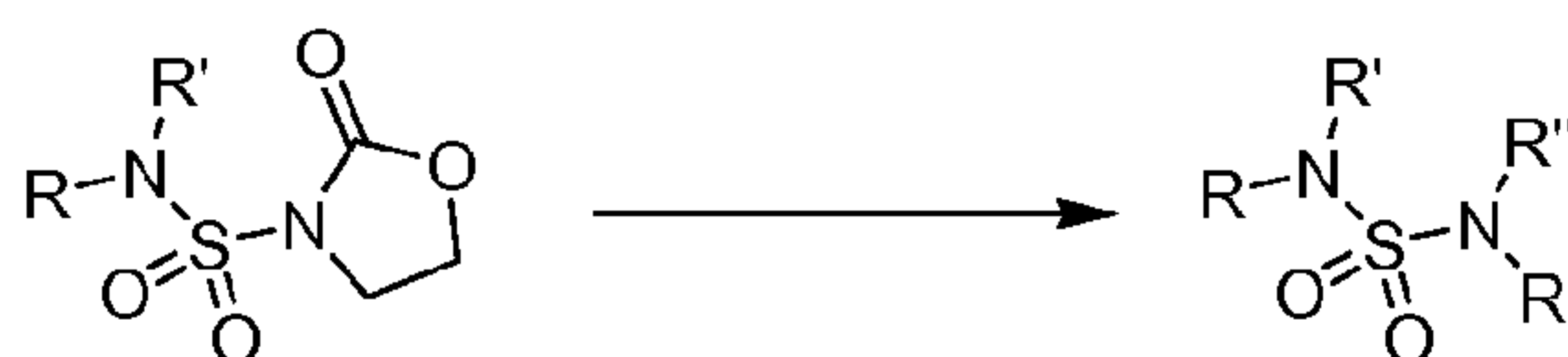
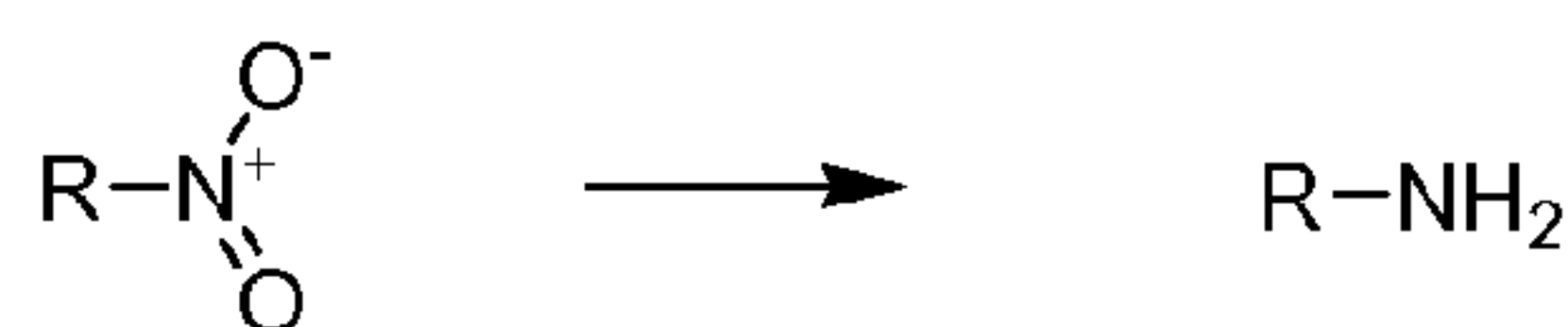
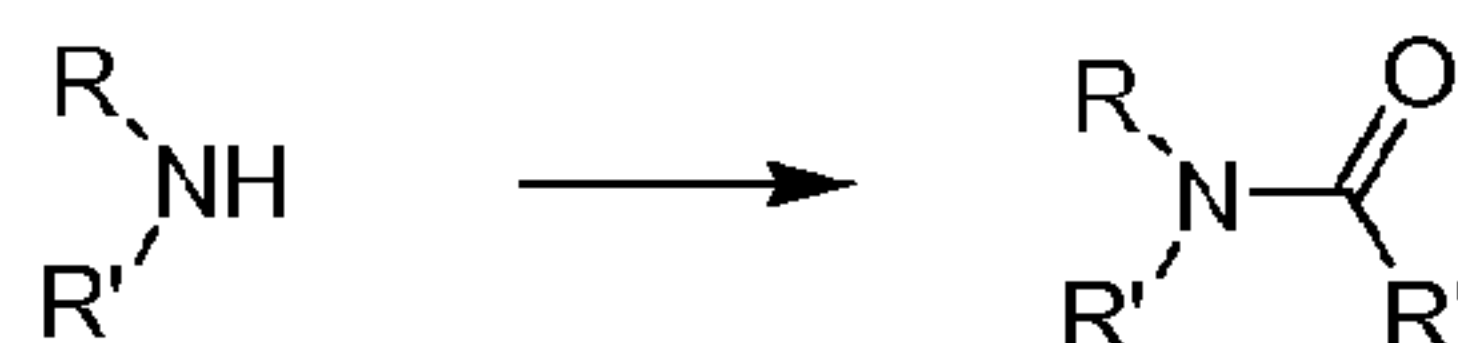
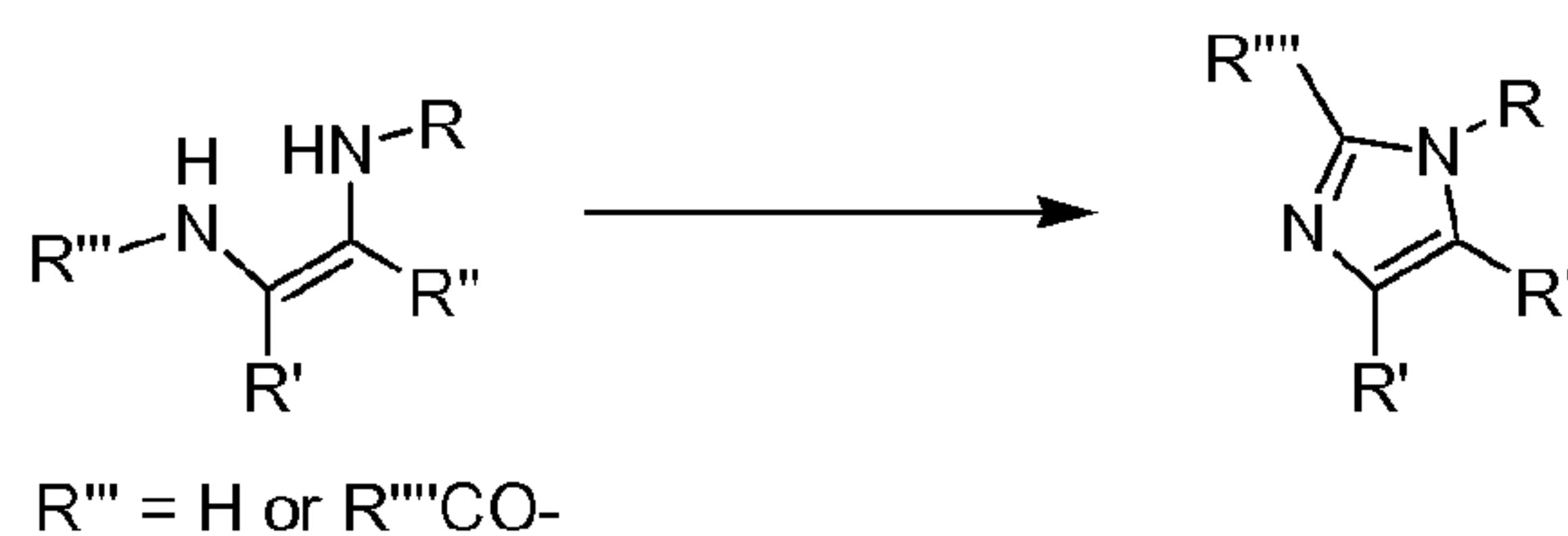
Scheme 28: Acidic hydrolysis of an acetyl protected amine (General Procedure BB)

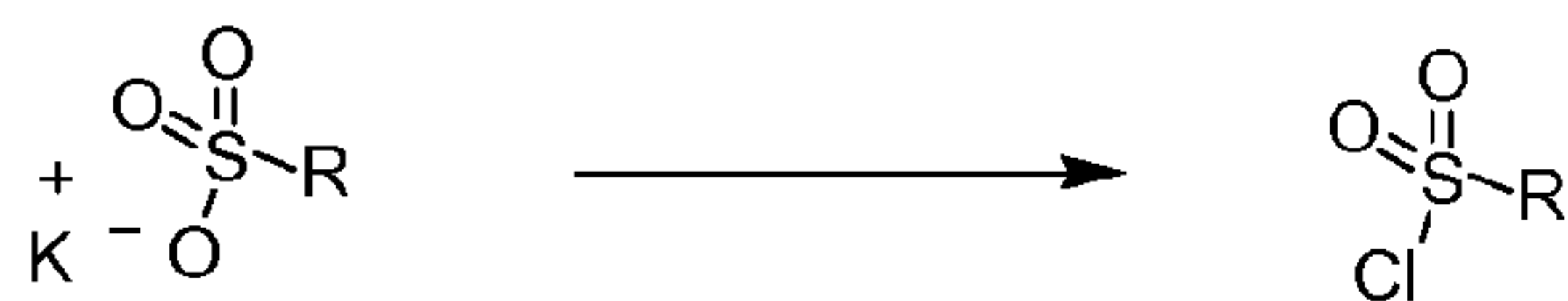
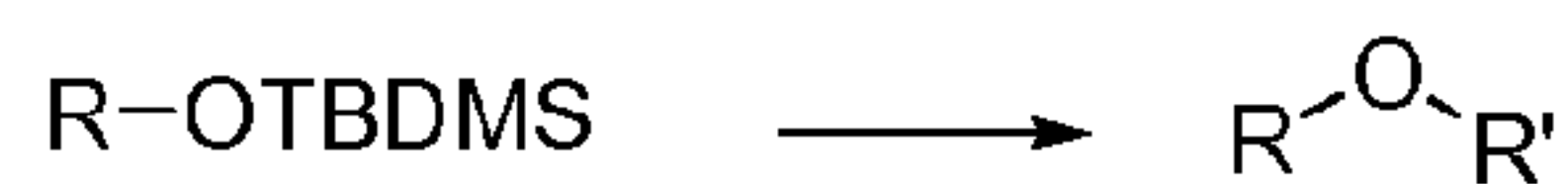
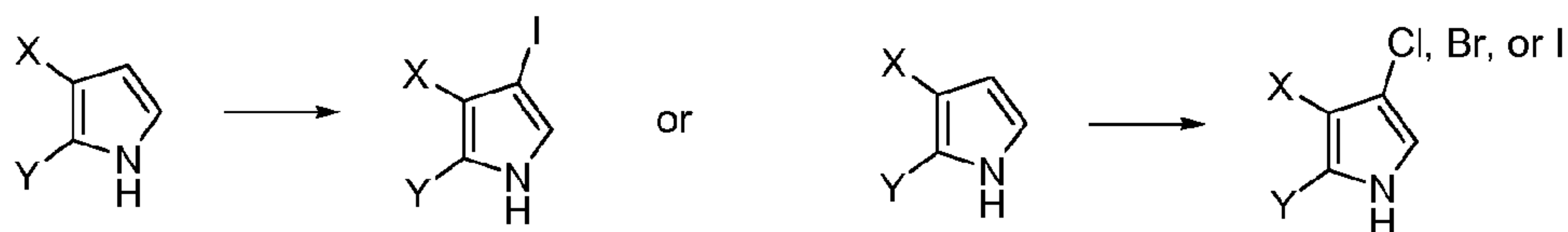
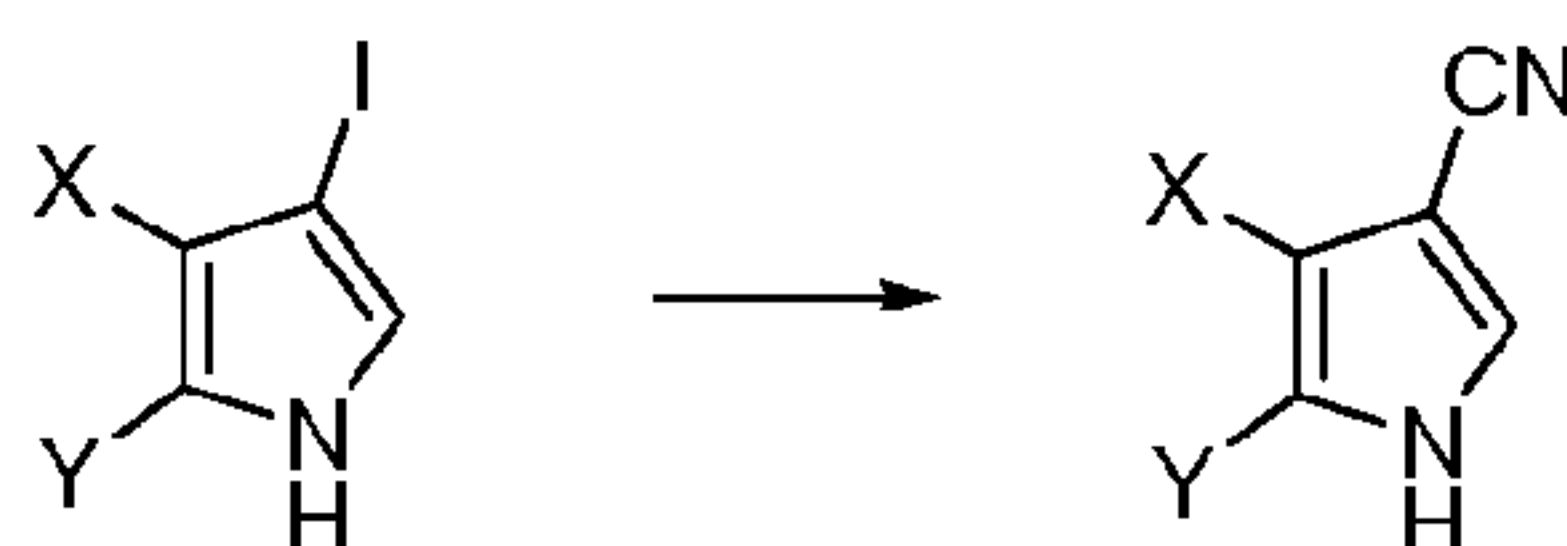
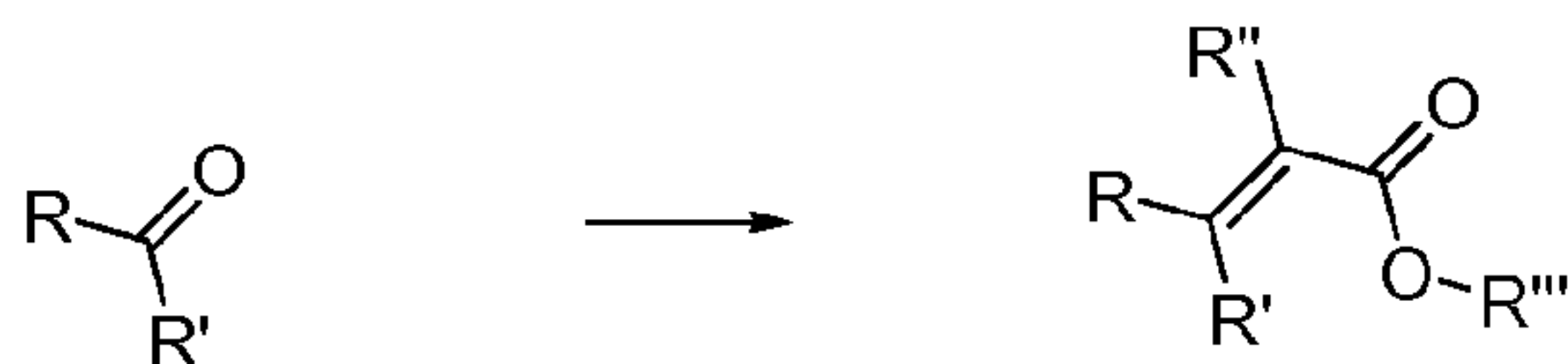
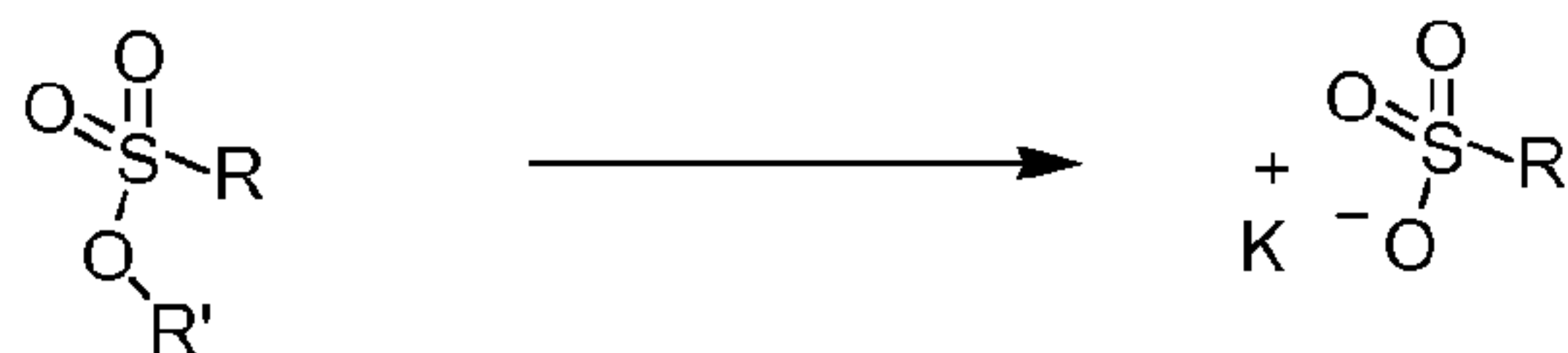
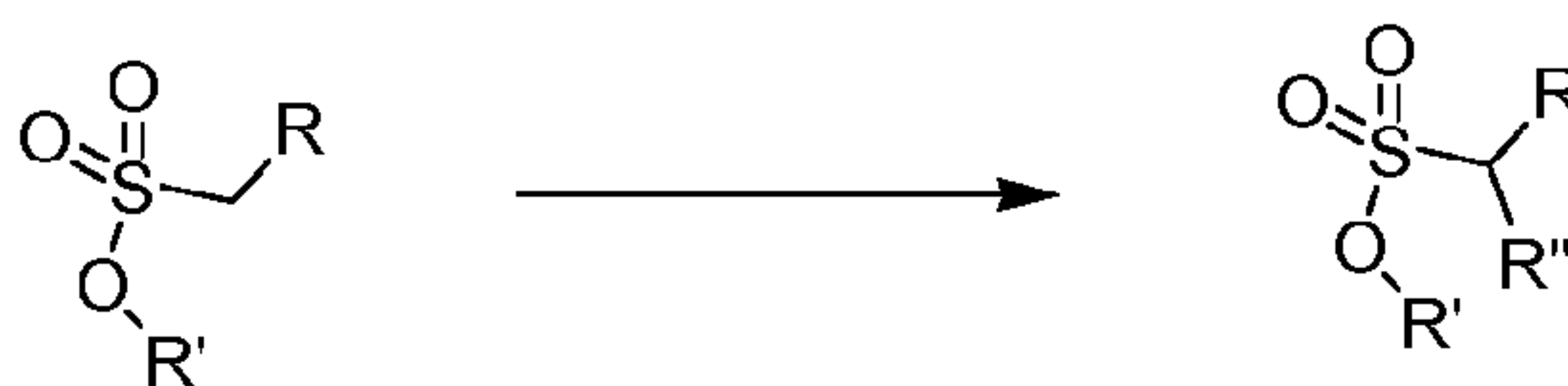
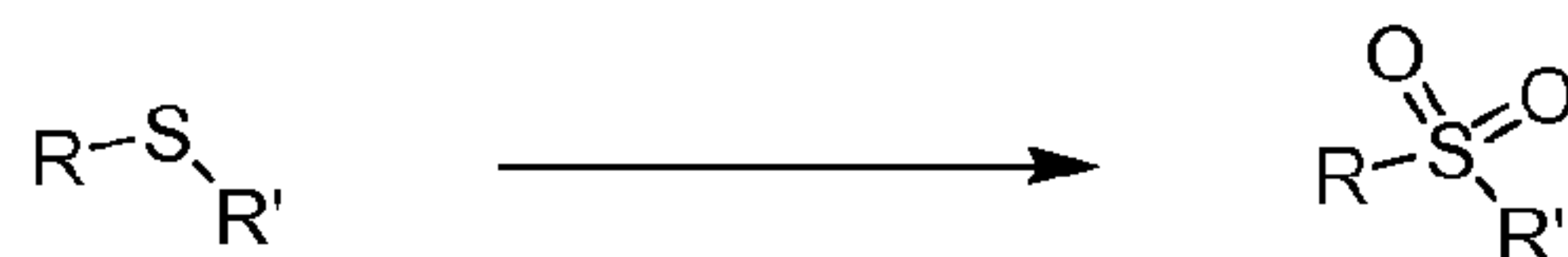
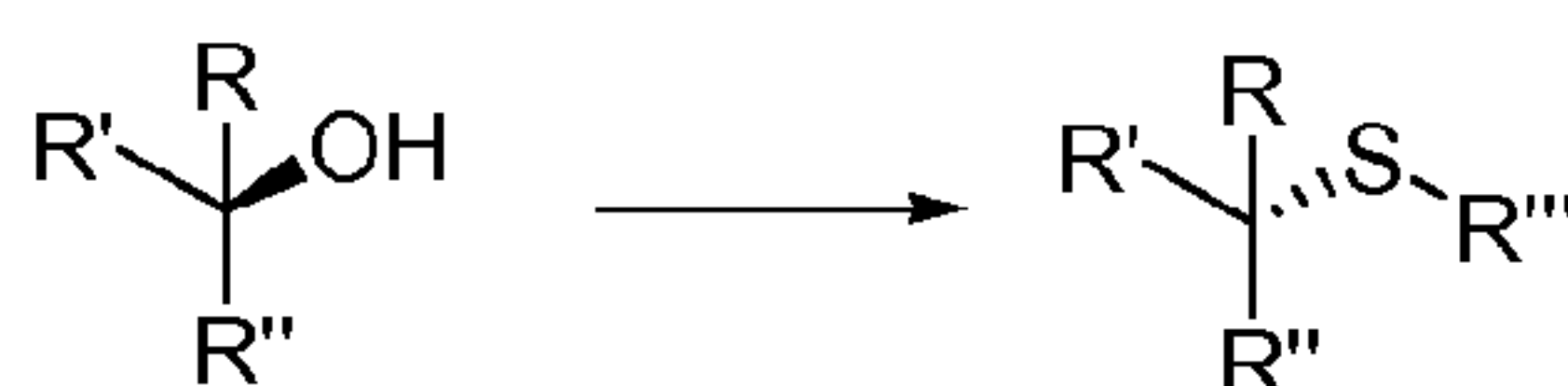


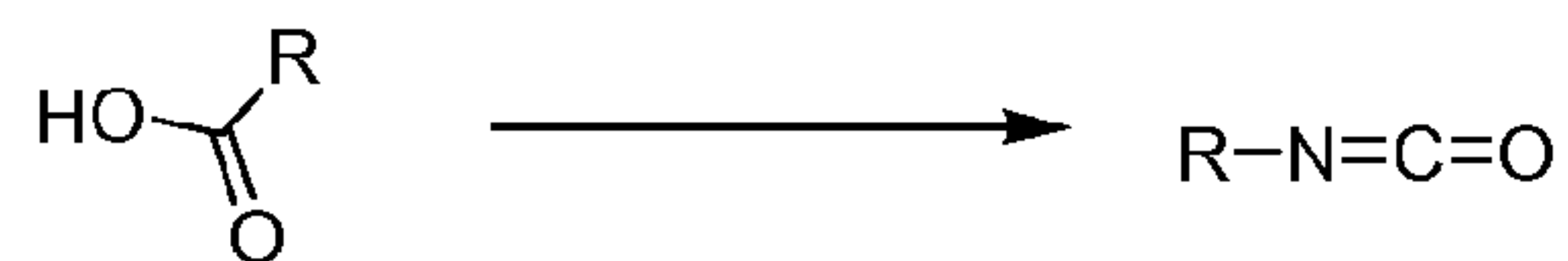
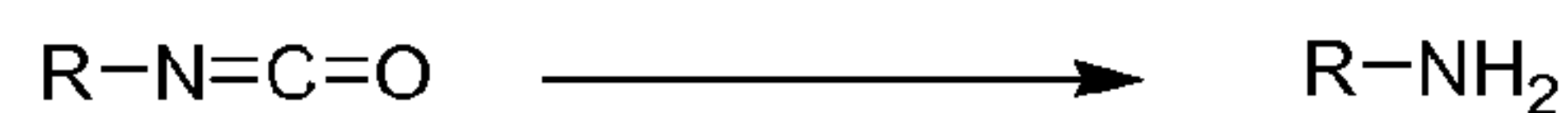
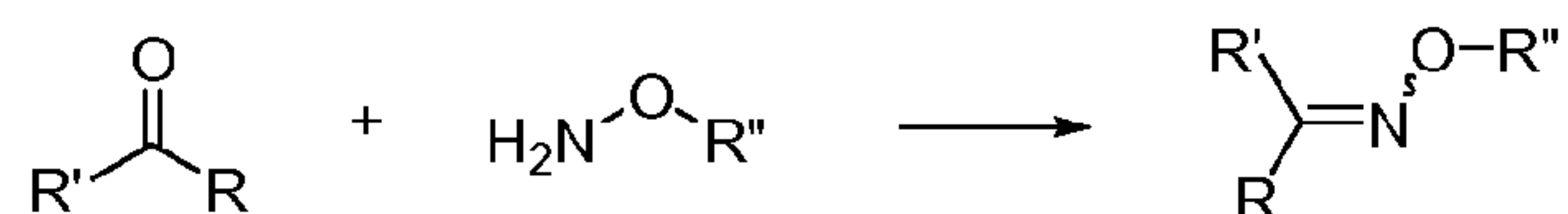
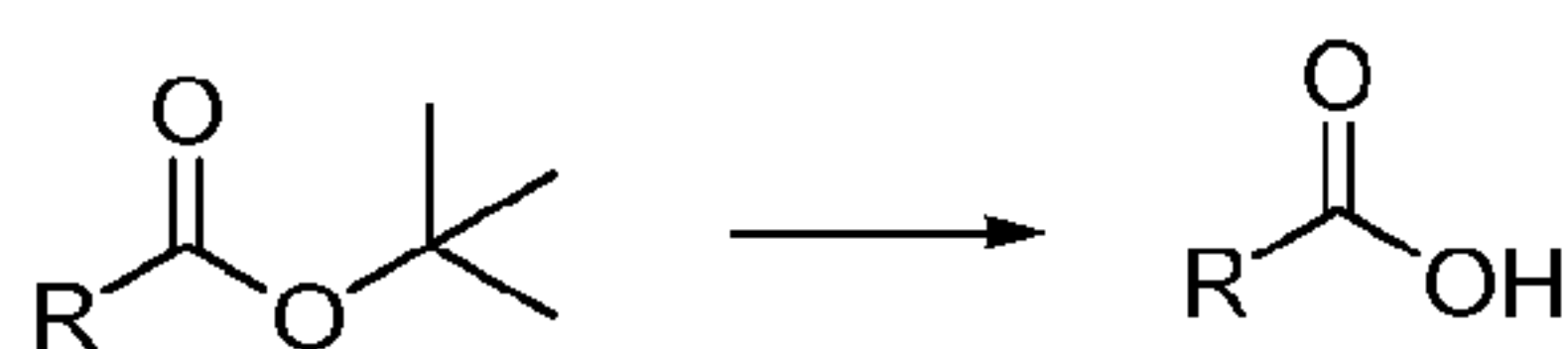
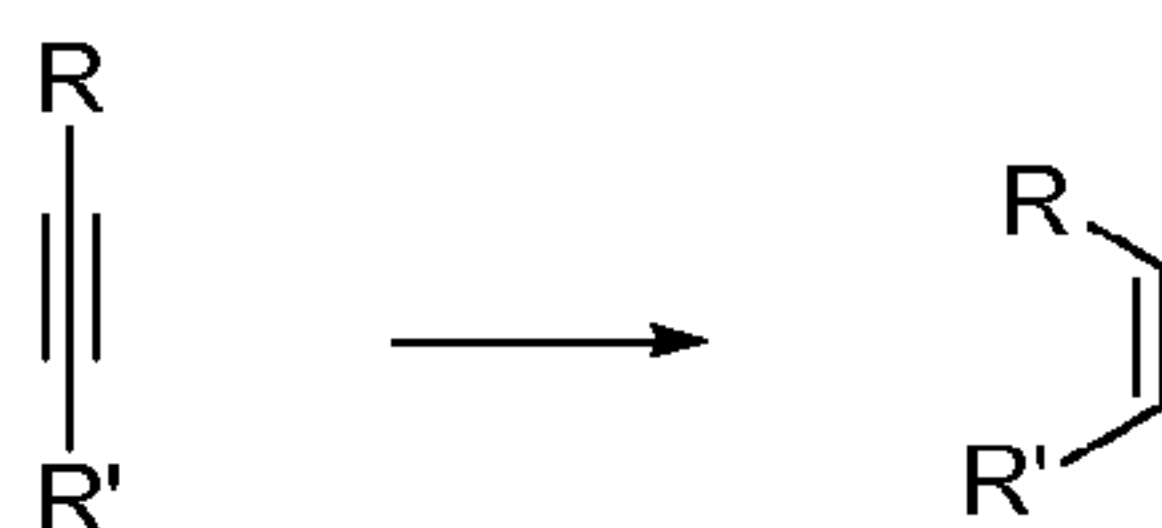
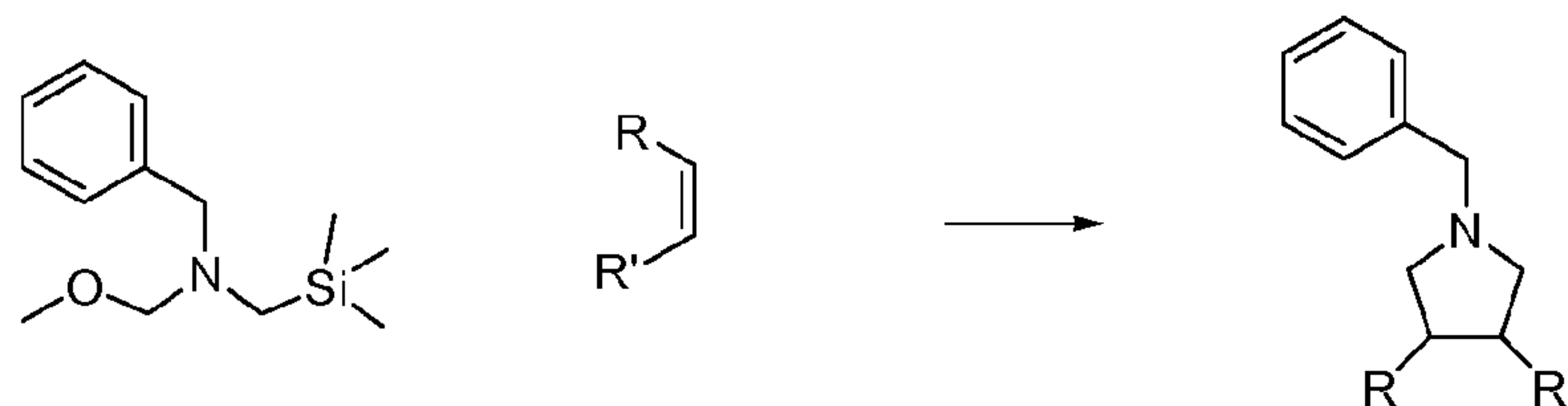
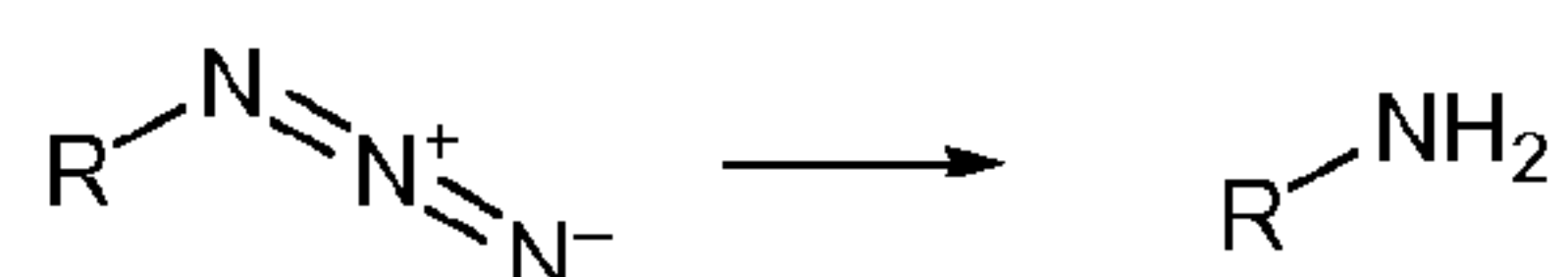
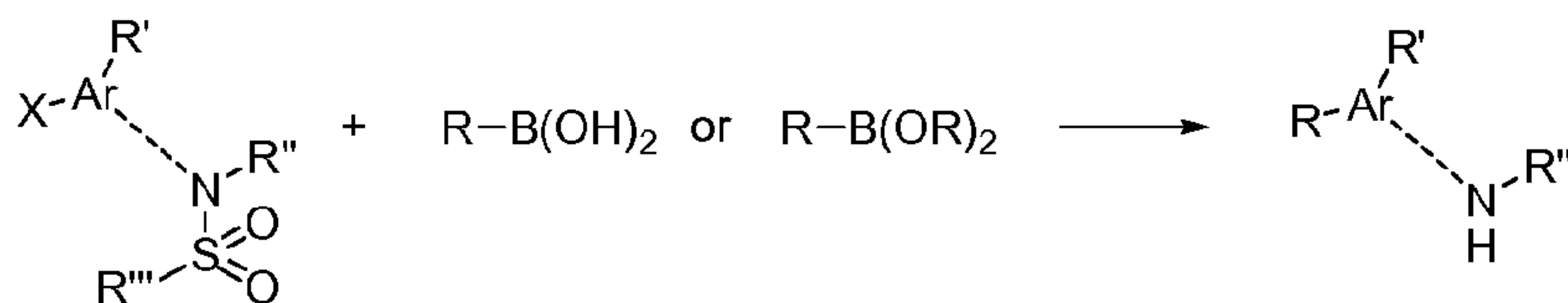
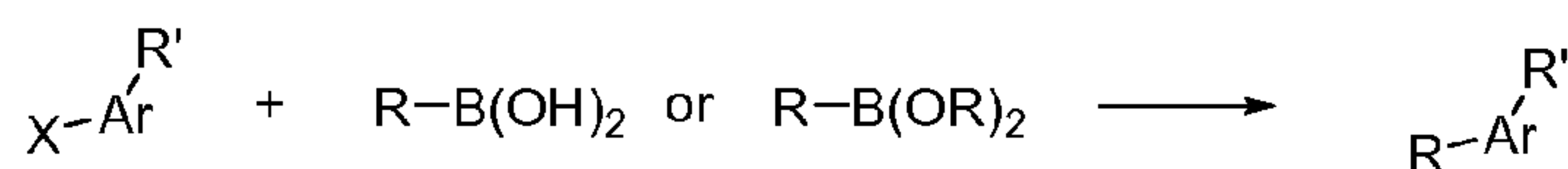
Scheme 29: Formation of a sulfamoyl chloride (General Procedure CC)**Scheme 30: Formation of a sulfonylurea (General Procedure DD)****Scheme 31: Ether formation from a trichloroacetimidate derivative (General Procedure EE)****Scheme 32: Deprotection of a PMB-protected alcohol (General Procedure FF)****Scheme 33: Formation of a lactone (General Procedure GG)****Scheme 34: Opening of a lactone with an amine or hydrazine (General Procedure HH)****Scheme 35: Mitsunobu reaction of an alcohol (General Procedure II)**

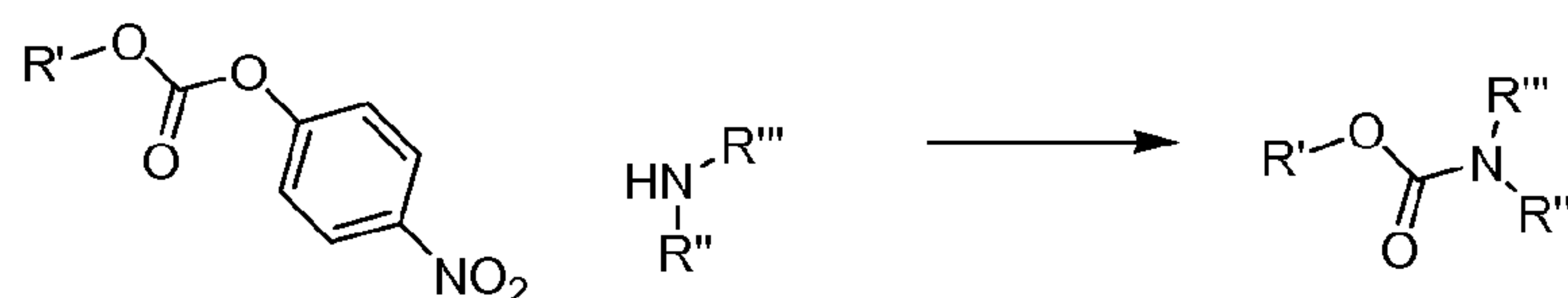
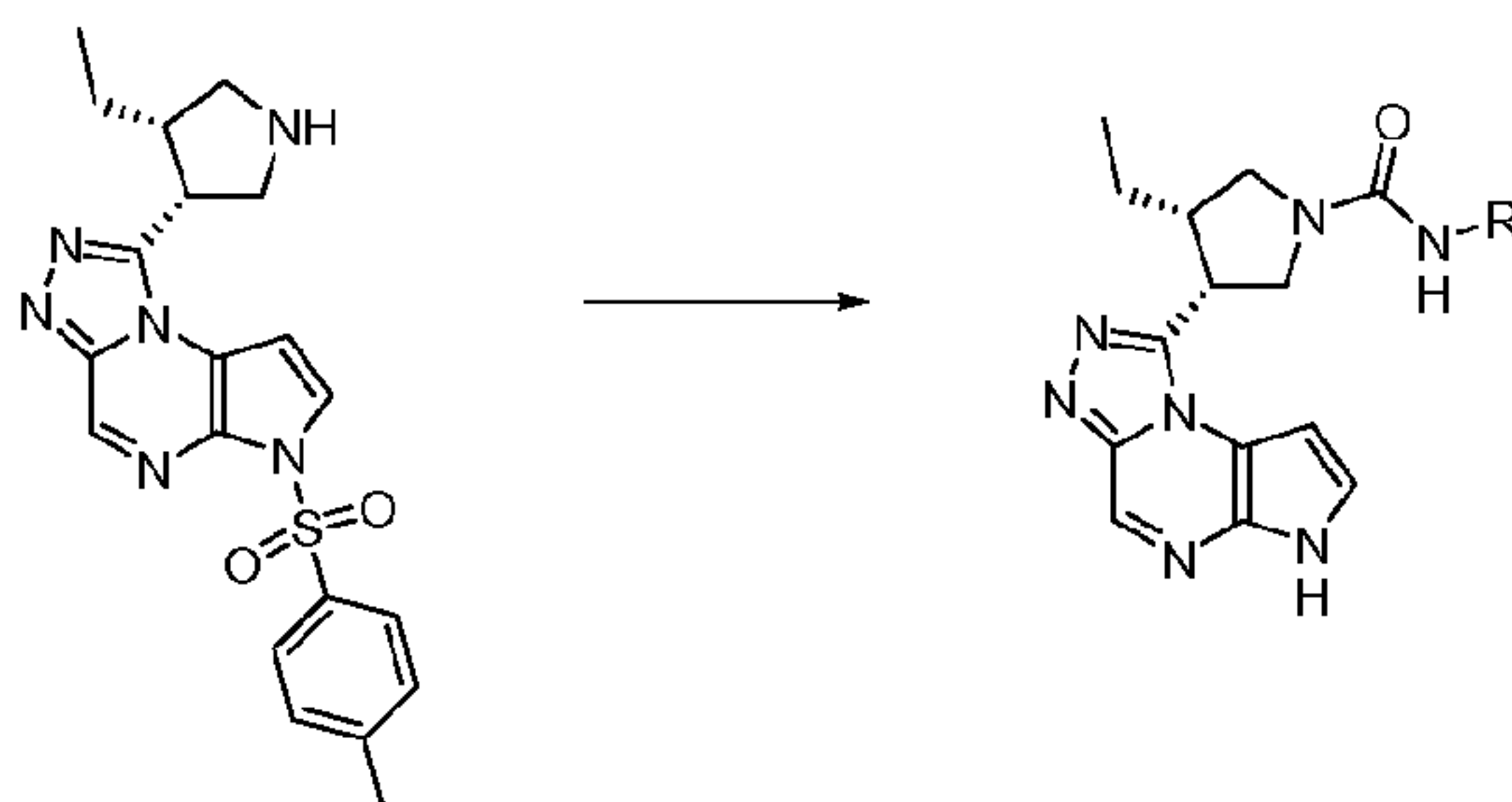
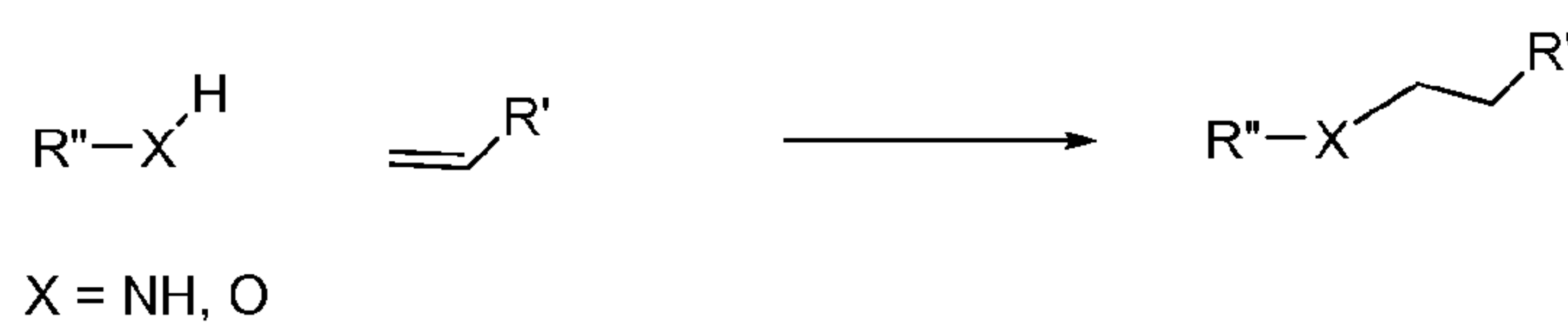
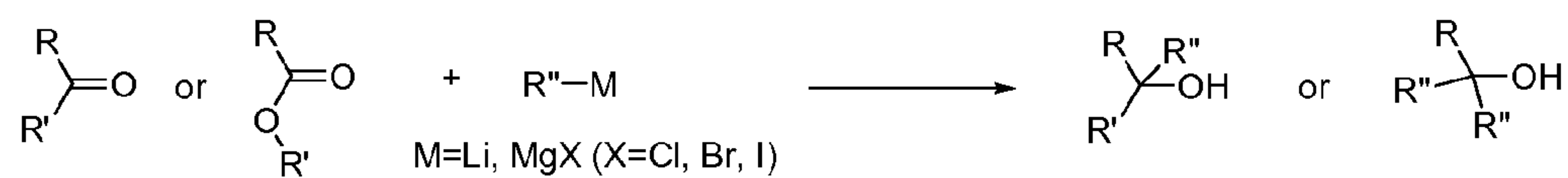
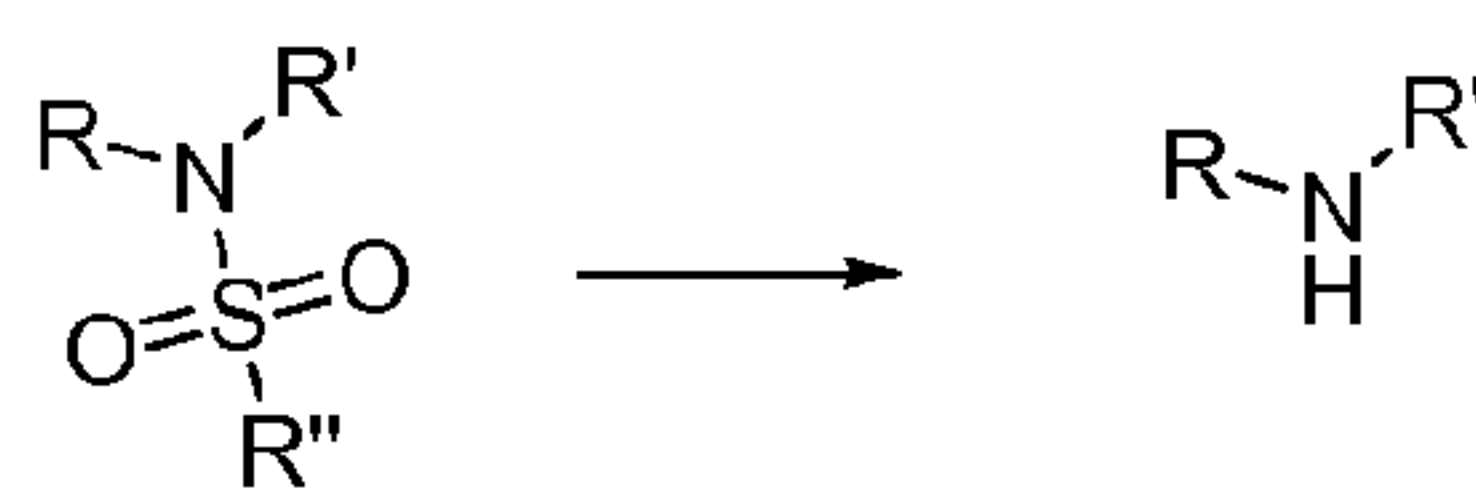
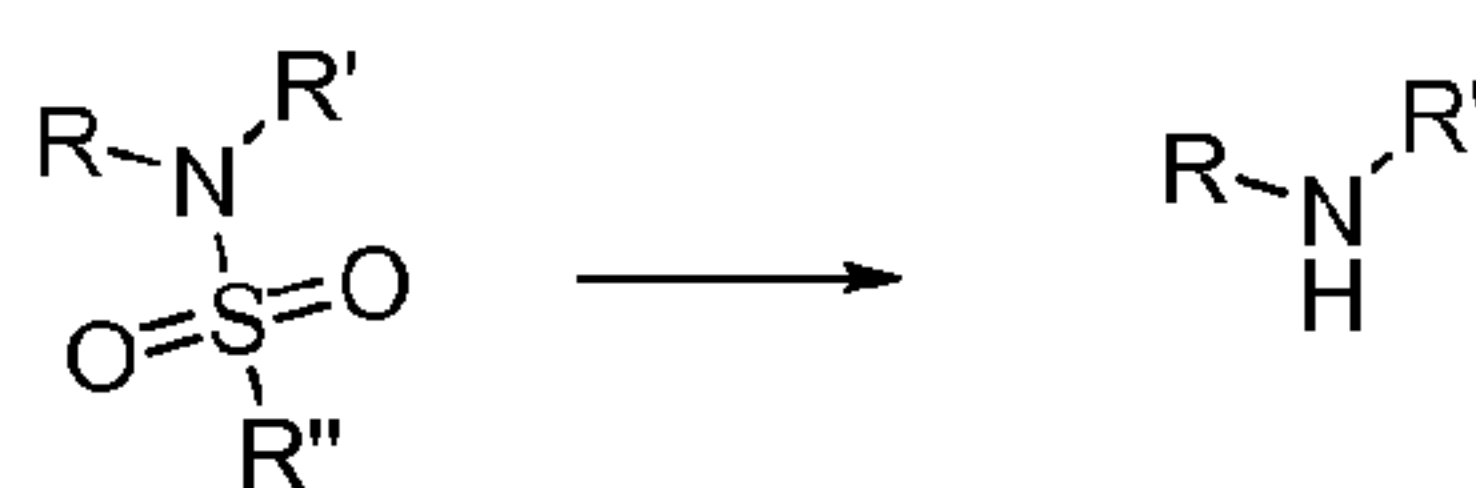
Scheme 36: Displacement of a halide with an alcohol (General Procedure JJ)**Scheme 37: SEM protection of a nitrogen (General Procedure KK)****Scheme 38: SEM deprotection of a nitrogen (General Procedures LL and LL.1)****Scheme 39: Halogenation of an imidazole (General Procedure MM)****Scheme 40: Formation of an amide from a carboxylic acid and an amine with loss of a sulfonamide protecting group (General Procedure NN)****Scheme 41: Cyclization with POCl₃ (General Procedures OO and OO.1)**

Scheme 42: Reaction of an amine with an aryl boronic acid (General Procedure PP)**Scheme 43: Formation of a urea from an amine and an isocyanate (General Procedure QQ)****Scheme 44: Formation of a urea from an amine, a heteroaryl amine and phenyl chloroformate (General Procedure RR)****Scheme 45: Hydrolysis of an ester to an alcohol (General Procedure SS)****Scheme 46: Acid-mediated conversion of an ester to a carboxylic acid (General Procedure TT)****Scheme 47: Formation of a 2,2,2-trichloroacetimidate (General Procedure UU)****Scheme 48: Formation of a TBDMS-protected alcohol (General Procedure VV)****Scheme 49: Formation of a ketal (General Procedure WW)**

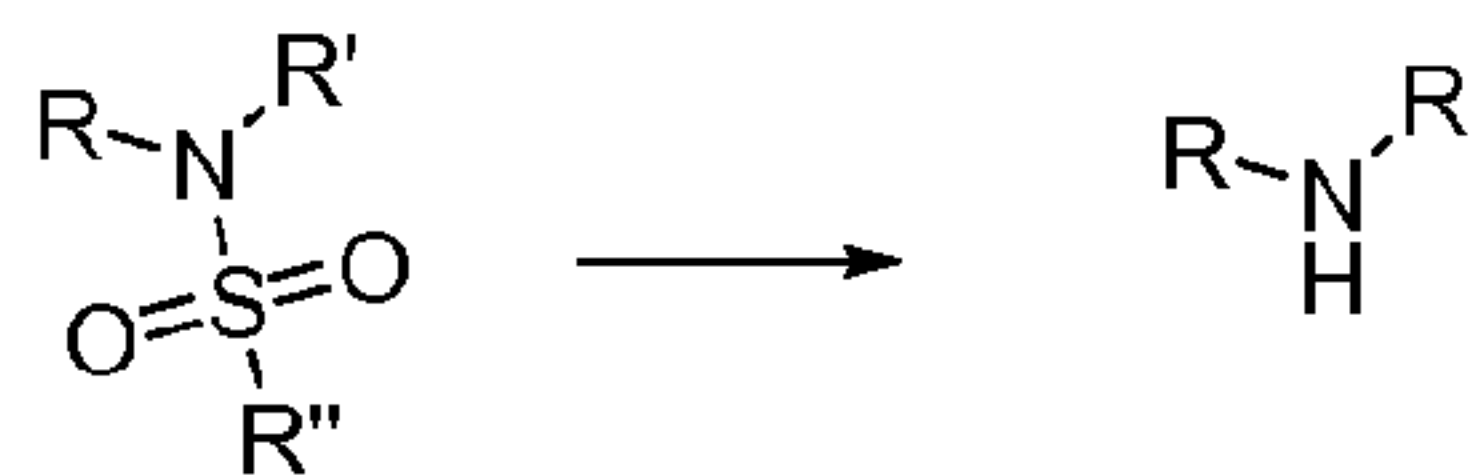
Scheme 50: Palladium catalyzed coupling of a hydrazone (General Procedure XX)**Scheme 51: Michael addition of an amine to an α,β -unsaturated sulfonamide (General Procedure YY)****Scheme 52: Formation of an oxazolidinone sulfonourea (General Procedure ZZ)****Scheme 53: Formation of a sulfonylurea from an oxazolidinone sulfonourea (General Procedure AAA)****Scheme 54: Reduction of a nitro group (General Procedure BBB)****Scheme 55: Formation of an amide (General Procedure CCC)****Scheme 56: Cyclization to form a fused imidazole (General Procedure DDD)**

Scheme 57: Formation of a sulfonyl chloride (General Procedure **EEE**)**Scheme 58: Generation of an ether under reductive conditions** ((General Procedure **FFF**)**Scheme 59: Iodination, chlorination or bromination of a heterocycle or halogenation of a heterocycle** (General Procedures **GGG** and **GGG.1**)**Scheme 60: Cyanation of a heterocycle** (General Procedure **HHH**)**Scheme 61: Horner-Wadsworth-Emmons reaction of a ketone** (General Procedure **III**)**Scheme 62: Formation of a potassium sulfonate** (General Procedure **JJJ**)**Scheme 63: Alkylation of a sulfonate** (General Procedure **KKK**)**Scheme 64: Oxidation of a thioether to a sulfone** (General Procedure **LLL**)**Scheme 65: Mitsunobu reaction using a thiol** (General Procedure **MMM**)

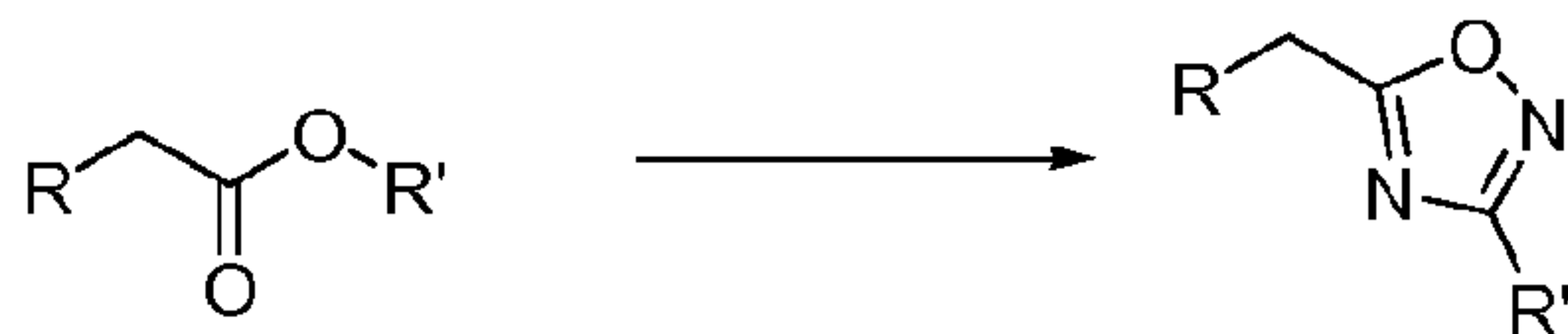
Scheme 66: Curtius reaction to form an isocyanate (General Procedure NNN)**Scheme 67: Hydrolysis of an isocyanate (General Procedure OOO)****Scheme 68: Formation of an oxime ether from a ketone (General Procedure PPP)****Scheme 69: TFA-mediated conversion of an ester to a carboxylic acid (General Procedure QQQ)****Scheme 70: Reduction of an alkyne to an alkene (General Procedure RRR)****Scheme 71: 1,3-dipolar cycloaddition to form a pyrrolidine (General Procedure SSS)****Scheme 72: Hydrogenation of an azide to an amine (General Procedure TTT)****Scheme 73: Reaction of an aryl or heteroaryl halide with a boronic acid or boronate ester followed by tosyl deprotection (General Procedure UUU)****Scheme 74: Reaction of an aryl or heteroaryl halide with a boronic acid or boronate ester (General Procedure VVV)**

Scheme 75: Formation of a carbamate (General Procedure WWW)**Scheme 76:** Urea formation with loss of protecting group (General Procedure XXX)**Scheme 77:** Michael addition (General Procedure YYY)**Scheme 78:** Grignard or alkyl lithium addition to a carbonyl-containing compound (General Procedure ZZZ)**Scheme 79:** Deprotection of a sulfonamide with DBU (General Procedure AAAA)**Scheme 80:** Deprotection of a sulfonamide with TBAF (General Procedure BBBB)

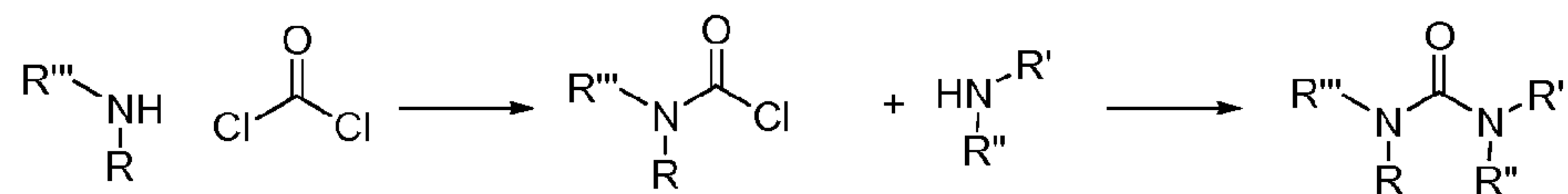
Scheme 81: Deprotection of a sulfonamide with KCN (General Procedure **CCCC**)



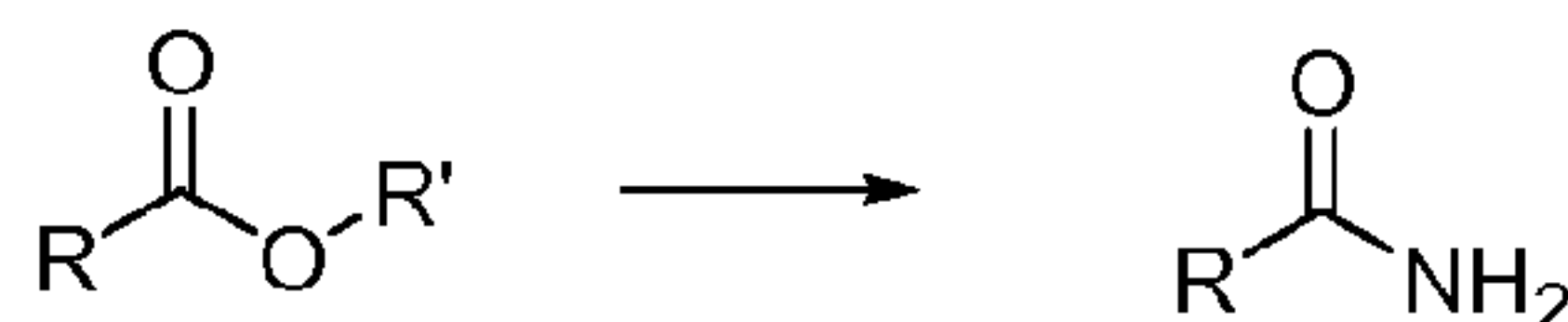
Scheme 82: Formation of an oxadiazole (General Procedure **DDDD**)



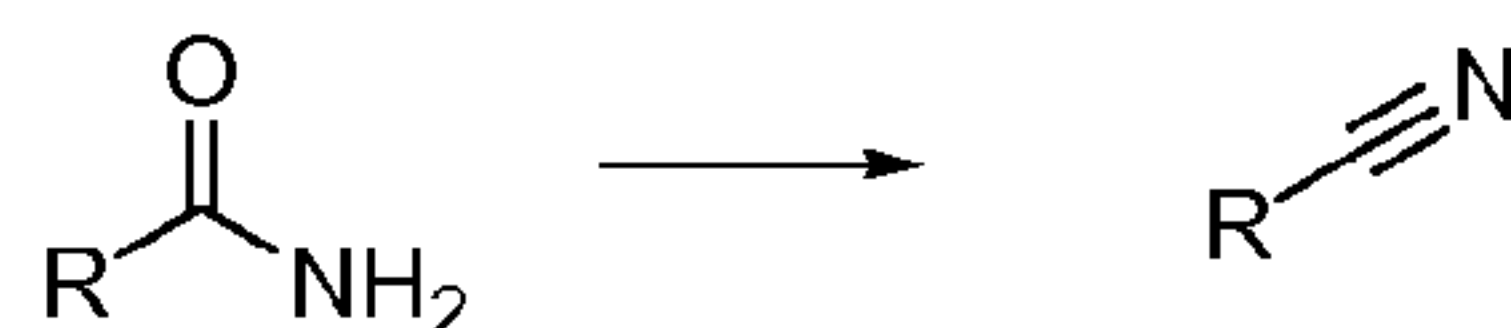
Scheme 83: Formation of a urea using phosgene (General Procedure **EEEE**)



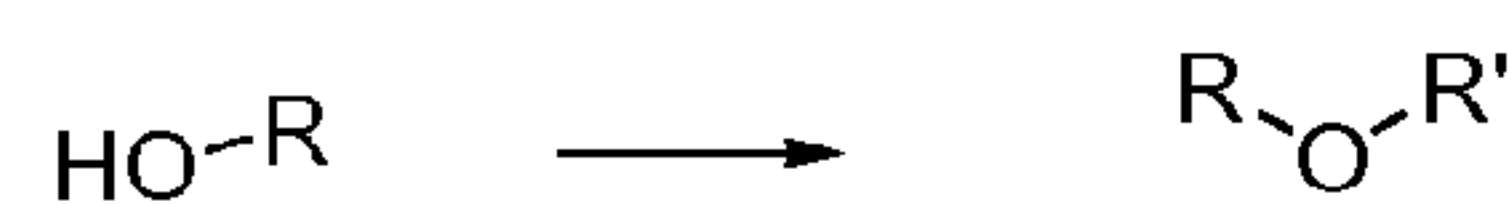
Scheme 84: Formation of an amide from an ester (General Procedure **FFFF**)



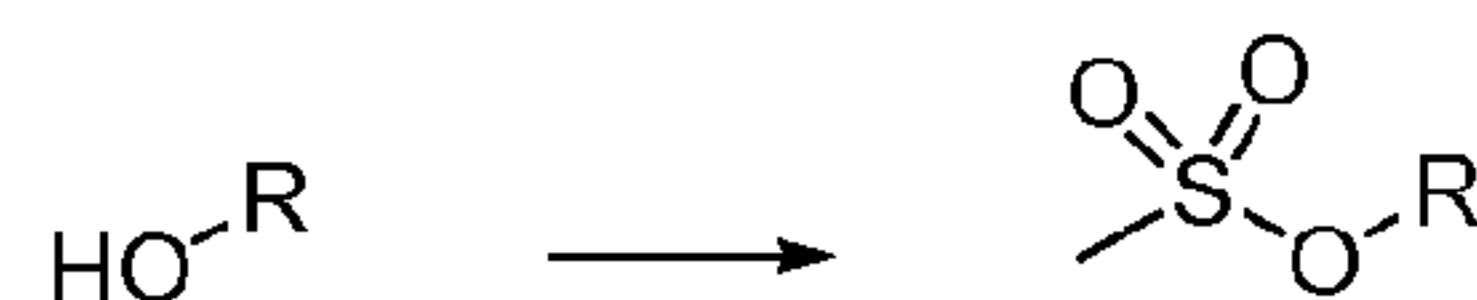
Scheme 85: Formation of a nitrile from a primary amide (General Procedure **GGGG**)



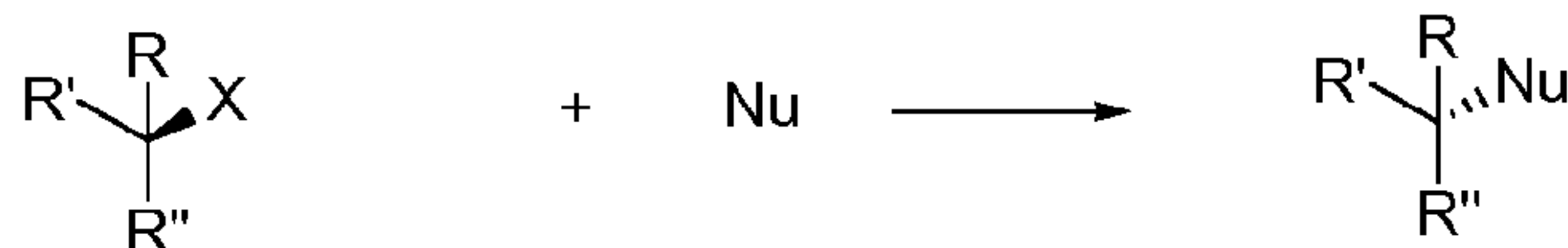
Scheme 86: *O*-alkylation with KOH or NaOH and TBAB (General Procedure **HHHH**)

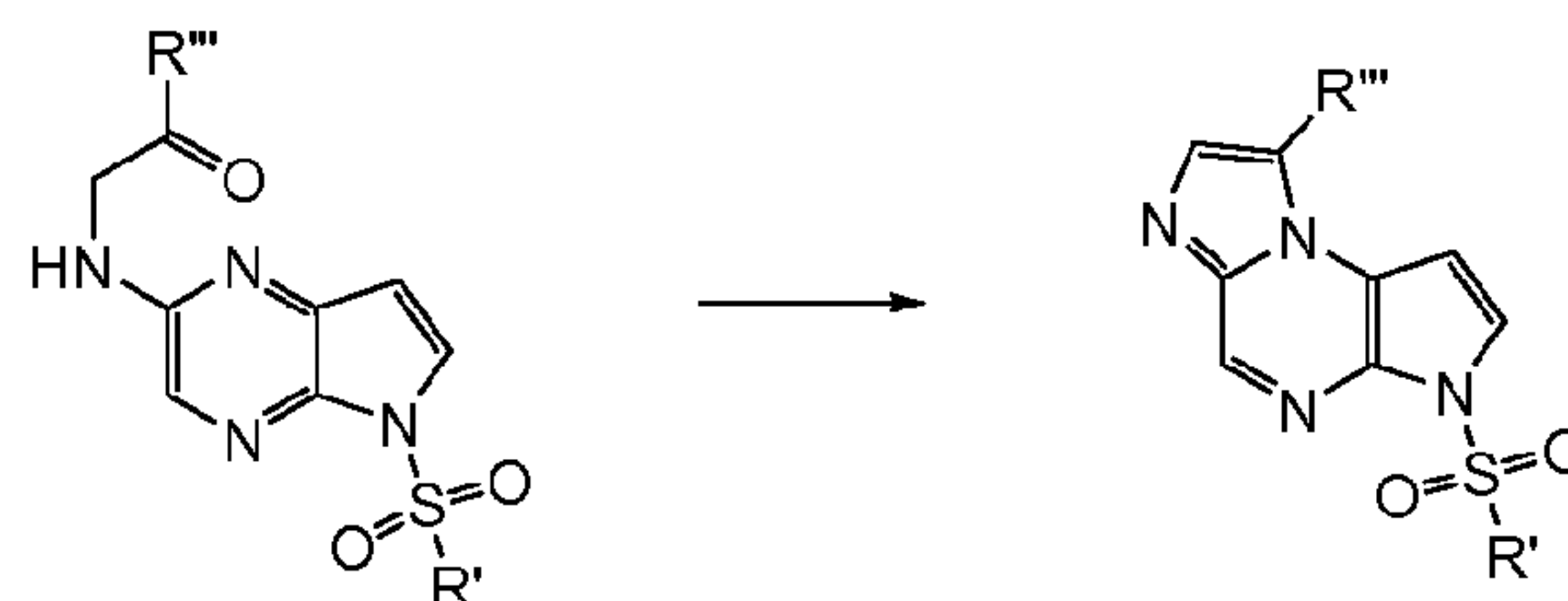
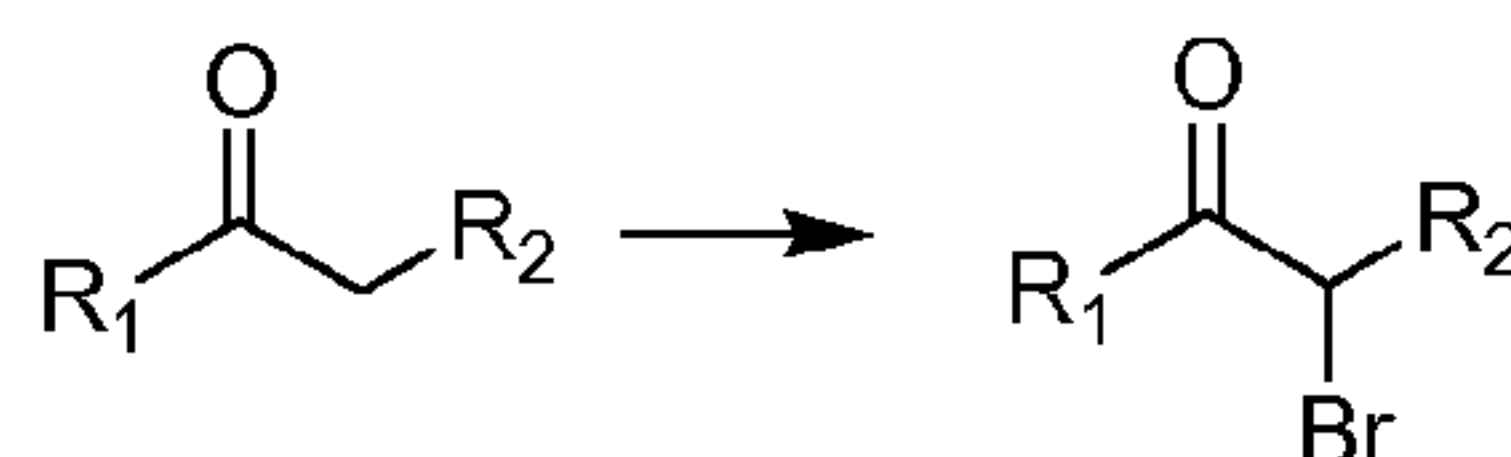
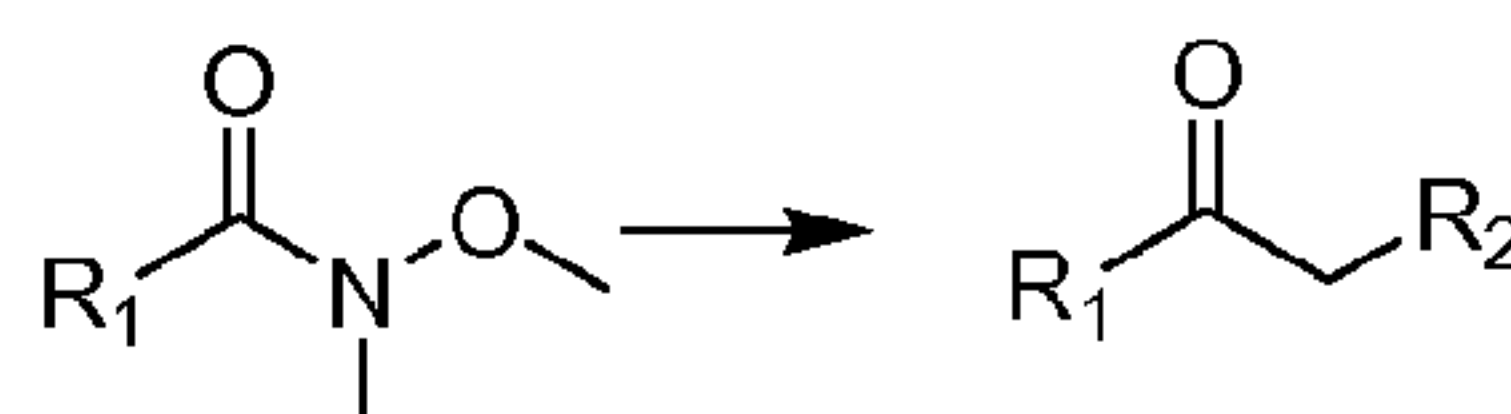
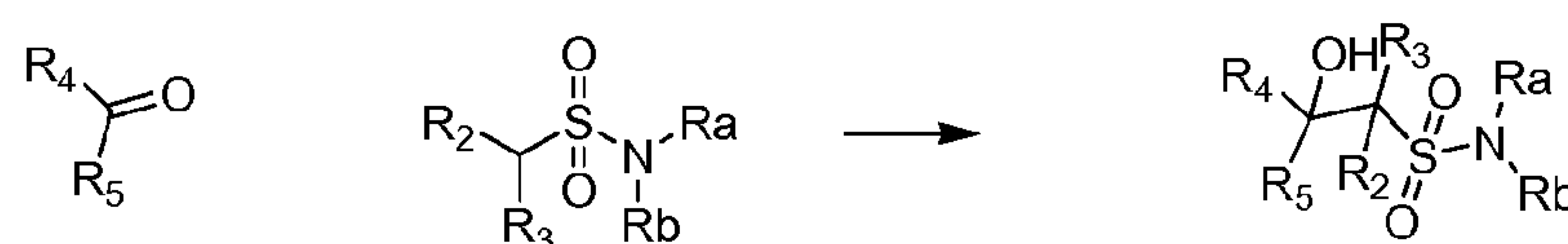
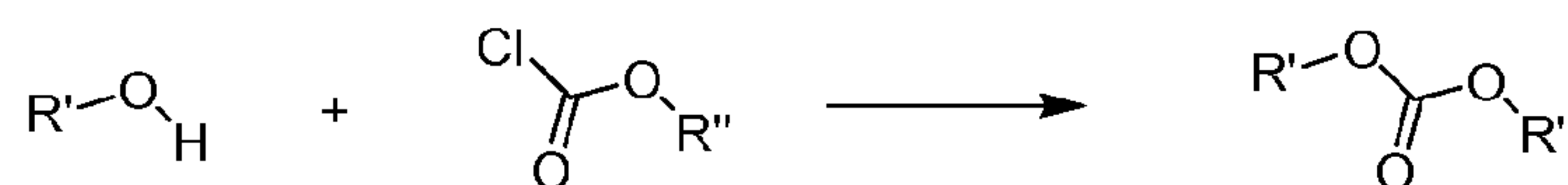
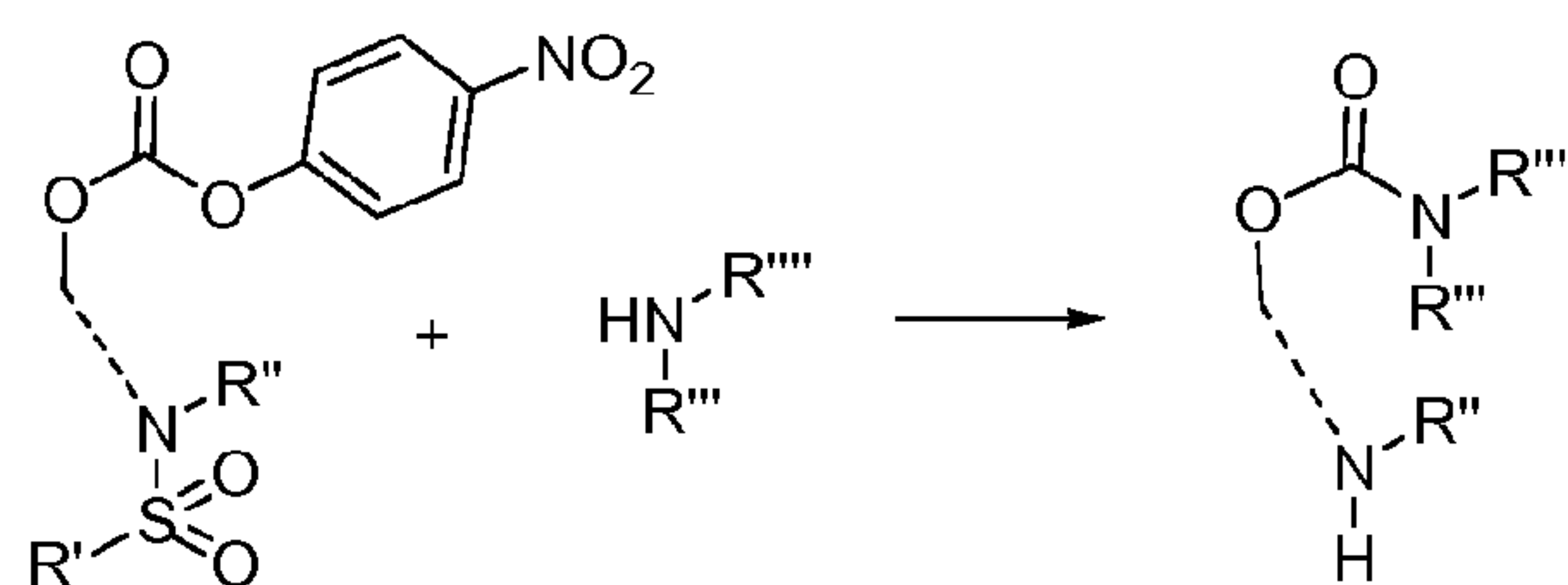
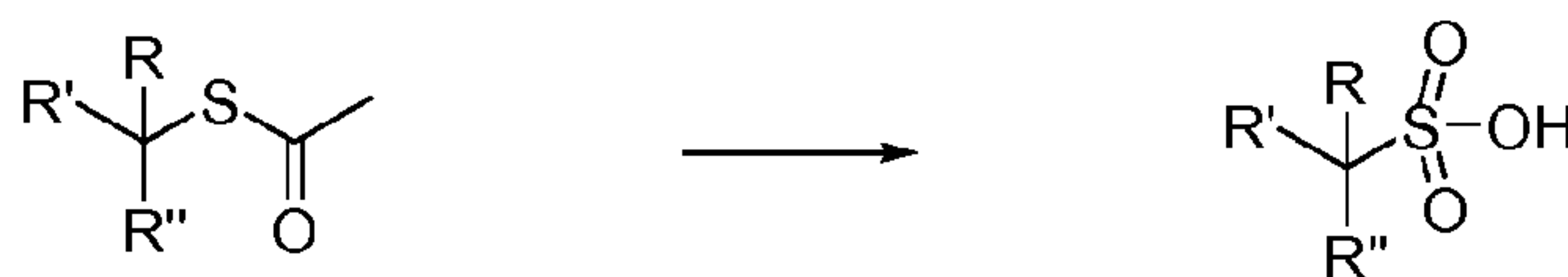


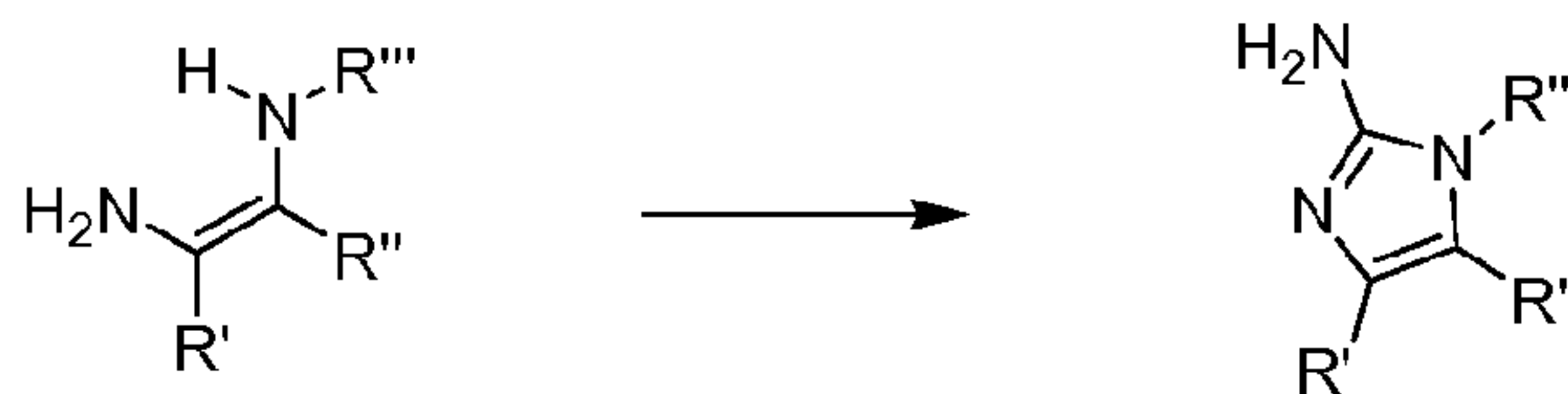
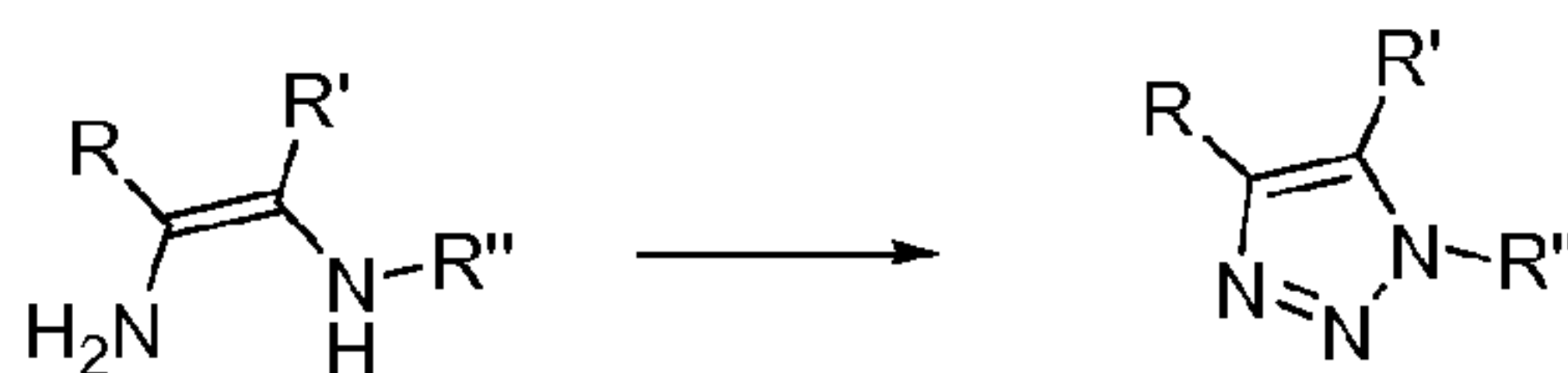
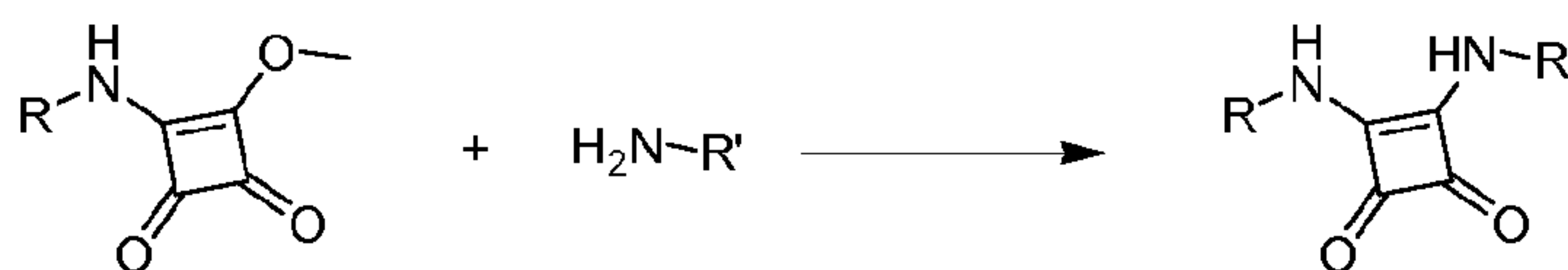
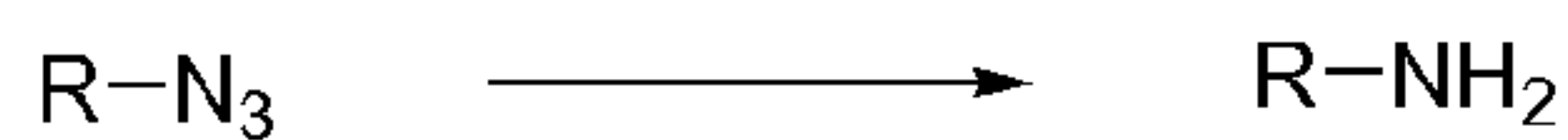
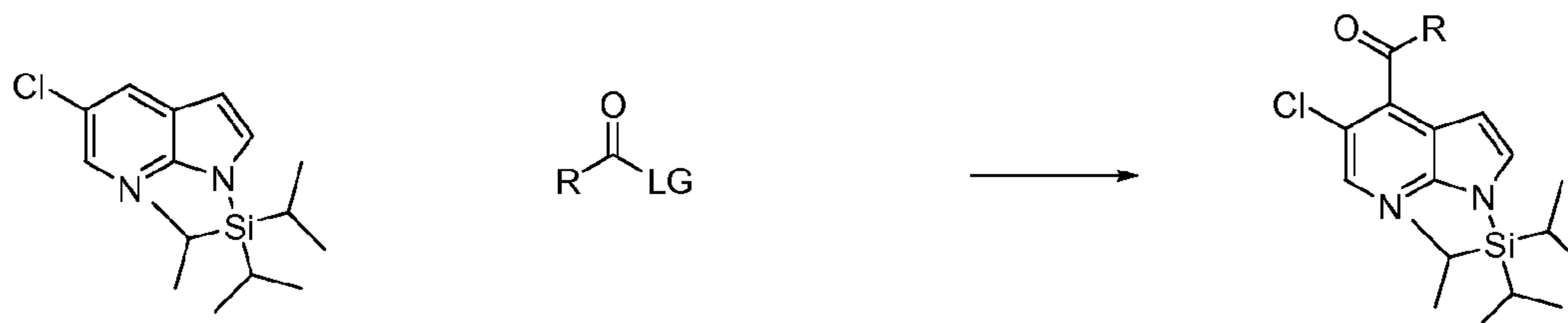
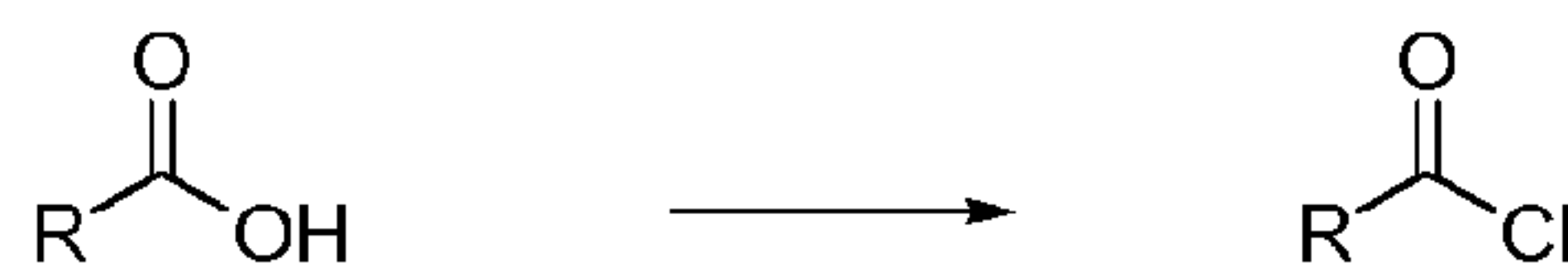
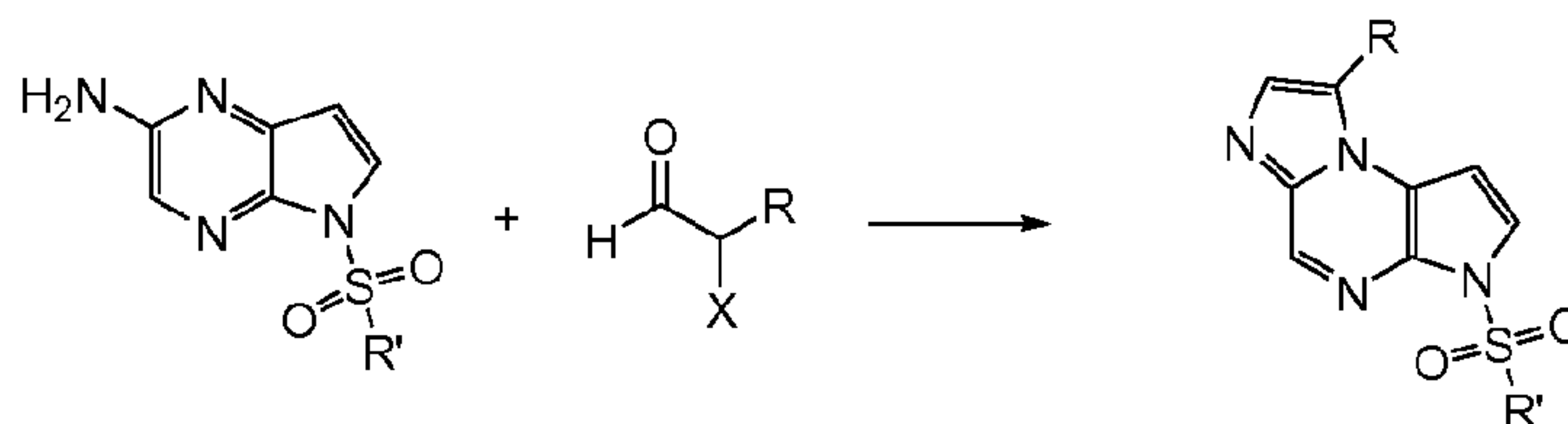
Scheme 87: Formation of a mesylate (General Procedure **IIII**)



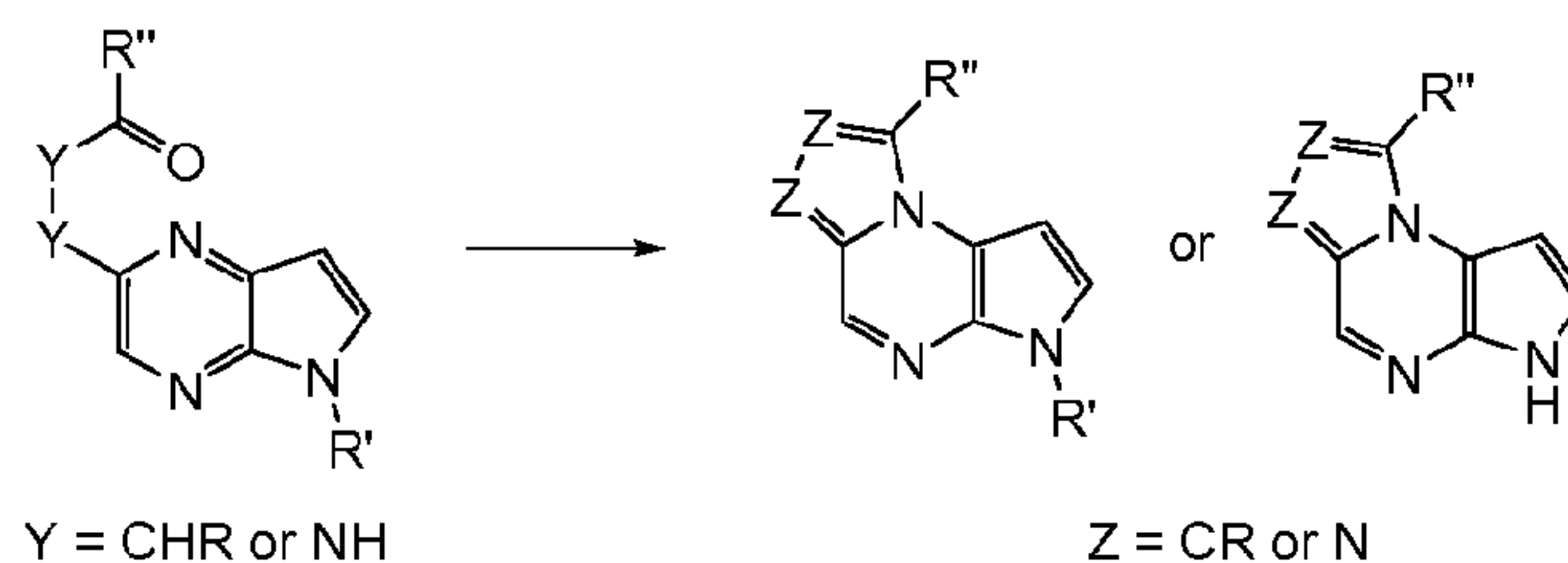
Scheme 88: Displacement of an alkyl mesylate, tosylate, or halide with a nucleophile (General Procedure **JJJJ**)



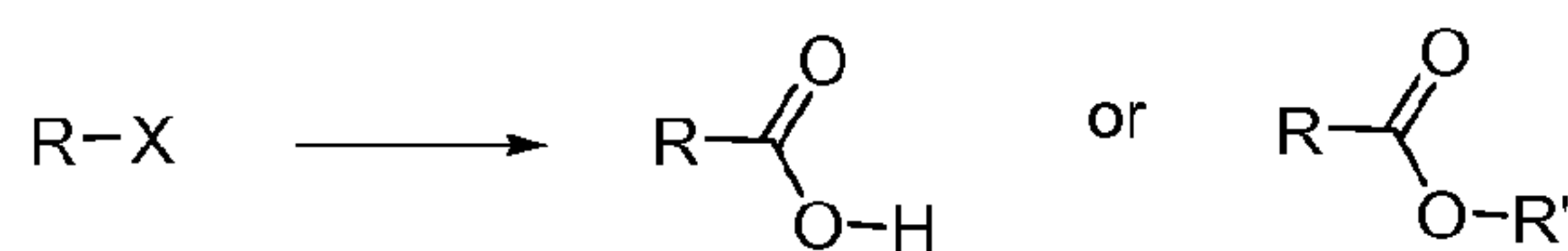
Scheme 89: Cyclization of a ketone using TFAA or PFPAA (General Procedure **KKKK**)**Scheme 90:** Formation of a bromoketone (General Procedure **LLLL**)**Scheme 91:** Formation of a ketone from a Weinreb amide (General Procedure **MMMM**)**Scheme 92:** Formation of β-hydroxysulfonamide from a ketone (General Procedure **NNNN**)**Scheme 93:** Formation of a phenyl carbonate (General Procedure **OOOO**)**Scheme 94:** Formation of a carbamate followed by sulfonamide hydrolysis (General Procedure **PPPP**)**Scheme 95:** Oxidation of an alkyl thioacetate to an alkyl sulfonic acid (General Procedure **QQQQ**)

Scheme 96: Cyclization of a diamine with cyanogen bromide (General Procedure **RRRR**)**Scheme 97:** Cyclization of a diamine with NaNO_2 (General Procedure **SSSS**)**Scheme 98:** Formation of a squaramide (General Procedure **TTTT**)**Scheme 99:** Reduction of an azide to an amine (General Procedure **UUUU**)**Scheme 100:** Formation of a ketone from a heteroaryl halide (General Procedure **VVVV**)**Scheme 101:** Formation of an acid chloride (General Procedure **WWWW**)**Scheme 102:** Formation of a hydrazone (General Procedure **XXXX**)**Scheme 103:** Cyclization with an α -haloaldehyde (General Procedure **YYYY**)

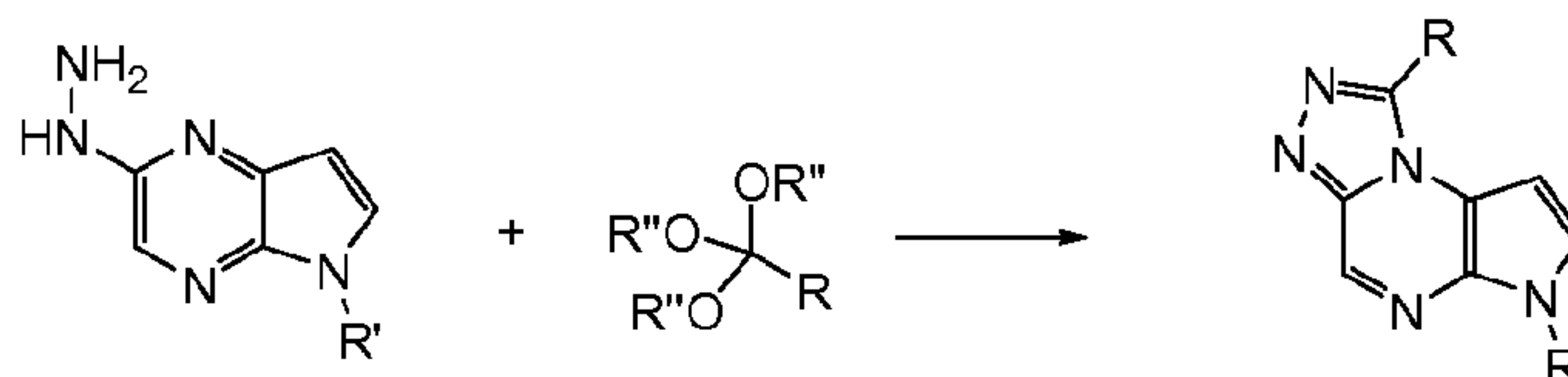
Scheme 104: Cyclization of a hydrazide followed by hydrolysis of a sulfonamide (General Procedure **ZZZZ**)



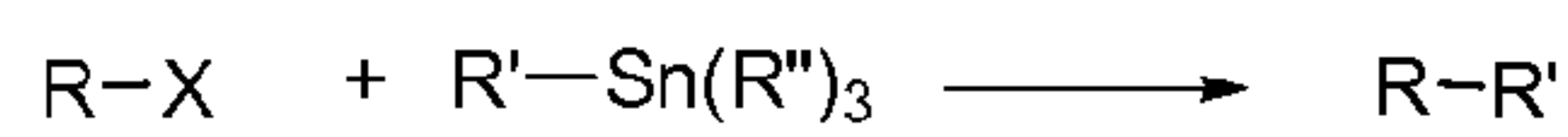
Scheme 105: Formation of a carboxylic acid or ester from an aryl halide (General Procedure **AAAAA**)



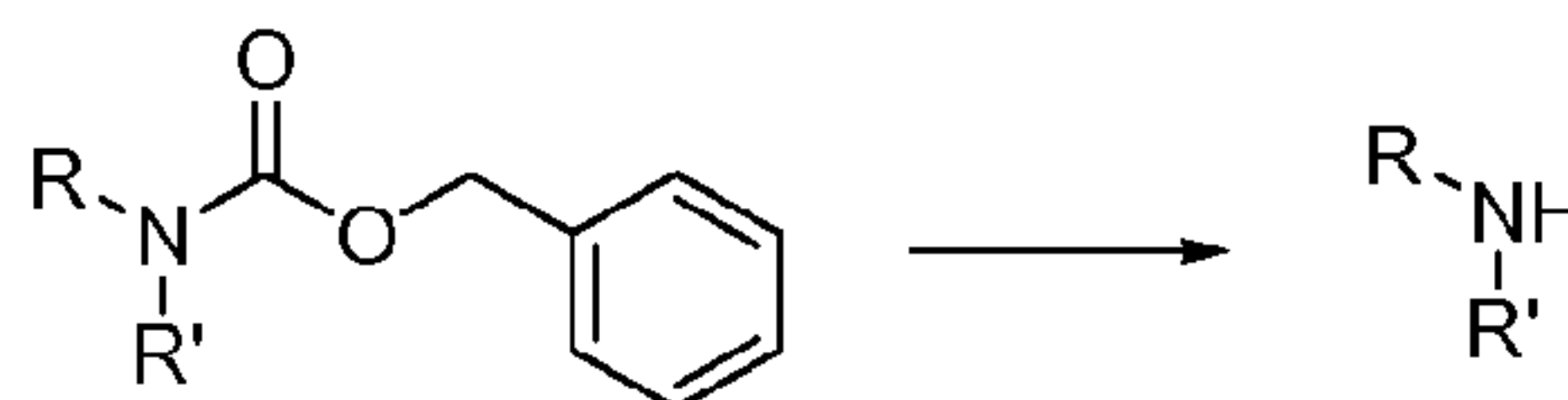
Scheme 106: Cyclization with an orthoformate (General Procedure **BBBBB**)



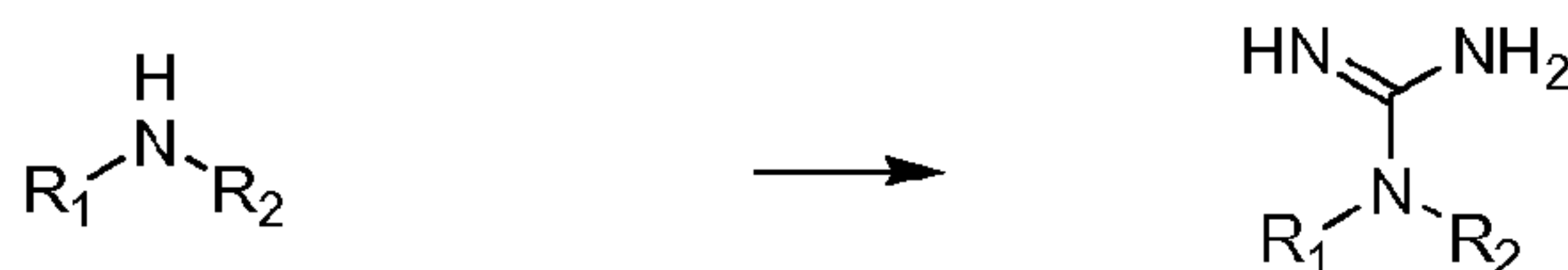
Scheme 107: Stille coupling of an aryl or heteroaryl halide (General Procedure **CCCCC**)



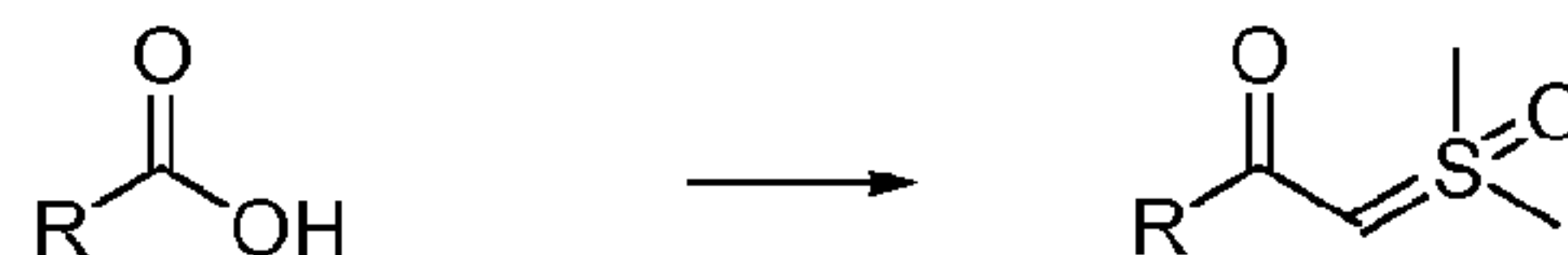
Scheme 108: Deprotection of a Cbz-protected amine using triethylsilane (General Procedure **DDDDD**)



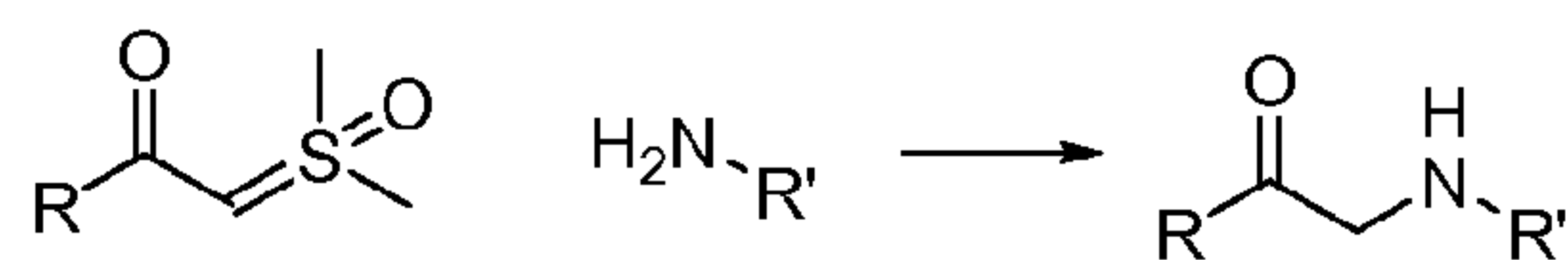
Scheme 109: Formation of a guanidine (General Procedure **EEEEEE**)



Scheme 110: Formation of a sulfoxonium ylide (General Procedure **FFFFF**)



Scheme 111: Reaction of a sulfoxonium ylide with an amine (General Procedure **GGGGG**)



LIST OF GENERAL PROCEDURES

General Procedure A	Formation of a hydrazide from a carboxylic acid
General Procedure B	Cyclization of a hydrazide
General Procedure C	Cyclization of a hydrazide with loss of Boc-protecting group
General Procedure D	Hydrolysis of a sulfonamide
General Procedure E	Acidic cleavage of a Boc-protected amine
General Procedure E.1	Acidic cleavage of a Boc-protected amine
General Procedure F	Deprotection of a Cbz-protected amine using HBr in AcOH
General Procedure G	Formation of an acetamide
General Procedure H	Formation of an amide from a carboxylic acid and an amine
General Procedure I	Formation of a urea from an amine and a carbamoyl chloride
General Procedure J	Formation of a urea or thiourea using CDI or thiocarbonyl diimidazole, respectively
General Procedure K	Formation of a sulfonamide from an amine
General Procedure K.1	Formation of a sulfonamide from an amine or nitrogen containing heterocycle
General Procedure L	Displacement of an aryl or heteroaryl halide with an amine
General Procedure M	Boc-protection of an amine
General Procedure M.1	Boc-protection of a nitrogen-containing compound
General Procedure N	Cbz-protection of an amine
General Procedure O	Reduction of a pyridine
General Procedure P	Reduction of carbonyl to an alcohol
General Procedure Q	Cyclization of an amide using a dithiaphosphetane reagent
General Procedure R	Formation of a bromomethyl ketone from an acid
General Procedure S	<i>N</i> -Alkylation using an alkyl halide or α -haloketone
General Procedure T	Cyclization of a ketone using a dithiaphosphetane reagent
General Procedure U	Knoevenagel condensation to form a substituted cyclopentadiene
General Procedure V	Decarboxylation of a β -ketoester enolate
General Procedure W	Hydrogenation of an alkene
General Procedure W.1	Hydrogenation of an alkene
General Procedure X	Reductive amination of a ketone or aldehyde
General Procedure X.1	Reductive amination of a ketone or aldehyde
General Procedure Y	Hydrogenation of a benzyl- or Cbz-protected amine
General Procedure Z	Basic hydrolysis of an ester to a carboxylic acid
General Procedure AA	Chiral preparative HPLC separation of stereoisomers
General Procedure BB	Acidic hydrolysis of an acetyl protected amine

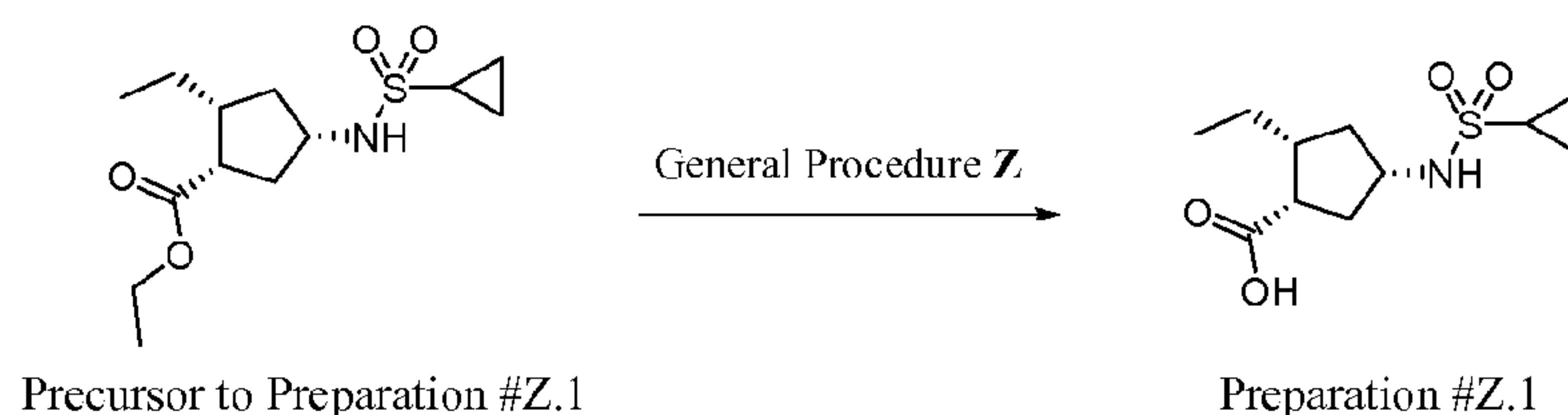
General Procedure CC	Formation of a sulfamoyl chloride
General Procedure DD	Formation of a sulfonylurea
General Procedure EE	Ether formation from a trichloroacetimidate derivative
General Procedure FF	Deprotection of a PMB-protected alcohol
General Procedure GG	Formation of a lactone
General Procedure HH	Opening of a lactone with an amine or hydrazine
General Procedure II	Mitsunobu reaction of an alcohol
General Procedure JJ	Displacement of a halide with an alcohol
General Procedure KK	SEM protection of a nitrogen
General Procedure LL	SEM deprotection of a nitrogen
General Procedure MM	Halogenation of an imidazole
General Procedure NN	Formation of an amide from a carboxylic acid and an amine with loss of a sulfonamide protecting group
General Procedure OO	Cyclization with POCl ₃
General Procedure OO.1	Cyclization with POCl ₃
General Procedure PP	Reaction of an amine with an aryl boronic acid
General Procedure QQ	Formation of a urea from an amine and an isocyanate
General Procedure RR	Formation of a urea from an amine, a heteroaryl amine and phenyl chloroformate
General Procedure SS	Hydrolysis of an ester to an alcohol
General Procedure TT	Acid-mediated conversion of an ester to a carboxylic acid
General Procedure UU	Formation of a 2,2,2-trichloroacetimidate
General Procedure VV	Formation of a TBDMS-protected alcohol
General Procedure WW	Formation of a ketal
General Procedure XX	Palladium catalyzed coupling of a hydrazone
General Procedure YY	Michael addition of an amine to an α,β -unsaturated sulfonamide
General Procedure ZZ	Formation of an oxazolidinone sulfonourea
General Procedure AAA	Formation of a sulfonylurea from an oxazolidinone sulfonourea
General Procedure BBB	Reduction of a nitro group
General Procedure CCC	Formation of an amide
General Procedure DDD	Cyclization to form a fused imidazole
General Procedure EEE	Formation of a sulfonyl chloride
General Procedure FFF	Generation of an ether under reductive conditions
General Procedure GGG	Iodination, chlorination or bromination of a heterocycle or halogenation of a heterocycle
General Procedure GGG.1	Iodination of a heterocycle or halogenation of a heterocycle
General Procedure HHH	Cyanation of a heterocycle

General Procedure III	Horner-Wadsworth-Emmons reaction of a ketone
General Procedure JJJ	Formation of a potassium sulfonate
General Procedure KKK	Alkylation of a sulfonate
General Procedure LLL	Oxidation of a thioether to a sulfone
General Procedure MMM	Mitsunobu reaction using a thiol
General Procedure NNN	Curtius reaction to form an isocyanate
General Procedure OOO	Hydrolysis of an isocyanate
General Procedure PPP	Formation of an oxime ether from a ketone
General Procedure QQQ	TFA-mediated conversion of a <i>t</i> -butyl ester to a carboxylic acid
General Procedure RRR	Reduction of an alkyne to an alkene
General Procedure SSS	1,3-Dipolar cycloaddition to form a pyrrolidine
General Procedure TTT	Hydrogenation of an azide to an amine
General Procedure UUU	Reaction of an aryl or heteroaryl halide with a boronic acid or boronate ester followed by tosyl deprotection
General Procedure VVV	Reaction of an aryl or heteroaryl halide with a boronic acid or boronate ester
General Procedure WWW	Formation of a carbamate
General Procedure XXX	Urea formation with loss of protecting group
General Procedure YYY	Michael addition
General Procedure ZZZ	Grignard or alkyl lithium addition to a carbonyl-containing compound
General Procedure AAAA	Deprotection of a sulfonamide with DBU
General Procedure BBBB	Deprotection of a sulfonamide with TBAF
General Procedure CCCC	Deprotection of a sulfonamide with KCN
General Procedure DDDD	Formation of an oxadiazole
General Procedure EEEE	Formation of a urea using phosgene
General Procedure FFFF	Formation of an amide from an ester
General Procedure GGGG	Formation of a nitrile from a primary amide
General Procedure HHHH	<i>O</i> -alkylation with KOH or NaOH and TBAB
General Procedure IIII	Formation of a mesylate
General Procedure JJJJ	Displacement of an alkyl mesylate, tosylate, or halide with a nucleophile
General Procedure KKKK	Cyclization of a ketone using TFAA or PFPA
General Procedure LLLL	Formation of a bromoketone from a ketone or an aldehyde
General Procedure MMMM	Formation of a ketone from a Weinreb amide
General Procedure NNNN	Formation of β -hydroxysulfonamide from a ketone
General Procedure OOOO	Formation of a phenyl carbonate

General Procedure PPPP	Formation of a carbamate followed by sulfonamide hydrolysis
General Procedure QQQQ	Oxidation of an alkyl thioacetate to an alkyl sulfonic acid
General Procedure RRRR	Cyclization of a diamine with cyanogen bromide
General Procedure SSSS	Cyclization of a diamine with NaNO ₂
General Procedure TTTT	Formation of a squaramide
General Procedure UUUU	Reduction of an azide to an amine
General Procedure VVVV	Formation of a ketone from a heteroaryl halide
General Procedure WWWW	Formation of an acid chloride
General Procedure XXXX	Formation of a hydrazone
General Procedure YYYY	Cyclization with an α -haloaldehyde
General Procedure ZZZZ	Cyclization of a hydrazide followed by hydrolysis of a sulfonamide
General Procedure AAAAA	Formation of a carboxylic acid or ester from an aryl halide
General Procedure BBBBB	Cyclization with an orthoformate
General Procedure CCCCC	Stille coupling of an aryl or heteroaryl halide
General Procedure DDDDD	Deprotection of a Cbz-protected amine using triethylsilane
General Procedure EEEEE	Formation of a guanidine
General Procedure FFFFF	Formation of a sulfoxonium ylide
General Procedure GGGGG	Reaction of a sulfoxonium ylide with an amine

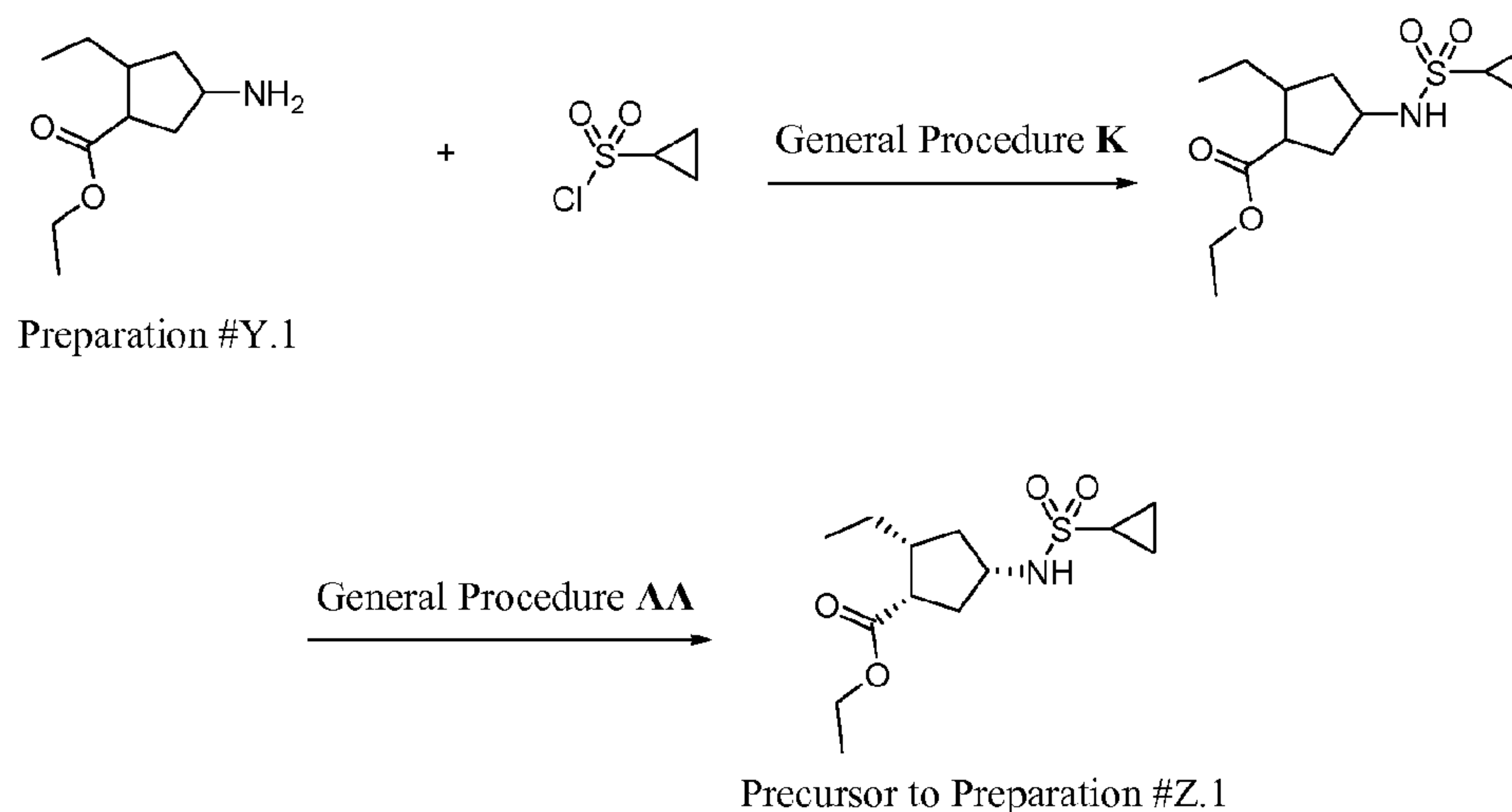
The following examples are ordered according to the final general procedure used in their preparation. The synthetic routes to any novel intermediates are detailed by sequentially listing the general procedure (letter codes) in parentheses after their name with additional reactants or reagents as appropriate. A worked example of this protocol is given below using Preparation #Z.1 as a non-limiting illustration. Preparation #Z.1 is (1*S*,2*R*,4*S*)-4-(cyclopropanesulfonamido)-2-ethylcyclopentane-carboxylic acid, which was prepared from (1*S*,2*R*,4*S*)-ethyl 4-(cyclopropanesulfonamido)-2-ethylcyclopentane carboxylate using General Procedure **Z** as represented in Scheme A.

Scheme A



The precursor to Preparation #Z.1, (1*S*,2*R*,4*S*)-ethyl 4-(cyclopropanesulfonamido)-2-ethylcyclopentane-carboxylate, was prepared (as shown in Scheme B) by initially reacting ethyl 4-amino-2-ethylcyclopentanecarboxylate (Preparation #Y.1) with the commercially available cyclopropanesulfonyl chloride, following the conditions given in General Procedure **K**, to give ethyl 4-(cyclopropanesulfonamido)-2-ethylcyclopentane-carboxylate as a mixture of stereoisomers. This mixture of stereoisomers is separated as described in General Procedure **AA**, using the conditions from Method **1** in Table 2, to give the precursor to Preparation #Z.1, (1*S*,2*R*,4*S*)-ethyl 4-(cyclopropanesulfonamido)-2-ethylcyclopentane-carboxylate as a single enantiomer with a retention time of 9.5 minutes and a negative optical rotation. The reaction sequence to synthesize the precursor to Preparation #Z.1, (1*S*,2*R*,4*S*)-ethyl 4-(cyclopropanesulfonamido)-2-ethylcyclopentane-carboxylate, (detailed above) is consequently translated in the preparations and examples section to: (1*S*,2*R*,4*S*)-ethyl 4-(cyclopropanesulfonamido)-2-ethylcyclopentane-carboxylate (prepared using **K** from Preparation #Y.1 and cyclopropanesulfonyl chloride, **AA** [Table 2, Method **1**, R_t = 9.5 min, or = negative]). Hence the Preparation #Z.1 would be written as: Preparation #Z.1 was prepared from (1*S*,2*R*,4*S*)-ethyl 4-(cyclopropanesulfonamido)-2-ethylcyclopentane carboxylate (prepared using **K** from Preparation #Y.1 and cyclopropanesulfonyl chloride, **AA** [Table 2, Method **1**, R_t = 9.5 min, or = negative]) using General Procedure **Z**.

Scheme B



Analytical Methods

Analytical data was included within the procedures below, in the illustrations of the general procedures, or in the tables of examples. Unless otherwise stated, all ^1H NMR data were collected on a Varian Mercury Plus 400 MHz or a Varian Inova 600 MHz instrument and chemical shifts

are quoted in parts per million (ppm). LC/MS and HPLC data are referenced to the table of LC/MS and HPLC conditions using the lower case method letter provided in Table 1.

Table 1. LC/MS and HPLC methods

Method	Conditions
a	LC/MS: The gradient was 5-60% B in 1.5 min then 60-95% B to 2.5 min with a hold at 95% B for 1.2 min (1.3 mL/min flow rate). Mobile phase A was 10 mM NH ₄ OAc, mobile phase B was HPLC grade MeCN. The column used for the chromatography is a 4.6 x 50 mm MAC-MOD Halo C18 column (2.7 µm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.
b	LC/MS: The gradient was 5-60% B in 1.5 min then 60-95% B to 2.5 min with a hold at 95% B for 1.2 min (1.3 mL/min flow rate). Mobile phase A was 10 mM NH ₄ OAc, mobile phase B was HPLC grade MeCN. The column used for the chromatography is a 4.6 x 50 mm MAC-MOD Halo C8 column (2.7 µm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.
c	LC/MS: The gradient was 5-60% B in 0.75 min then 60-95% B to 1.15 min with a hold at 95% B for 0.75 min (1.3 mL/min flow rate). Mobile phase A was 10 mM NH ₄ OAc, mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 4.6 x 50 mm MAC-MOD Halo C8 column (2.7 µm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.
d	HPLC: The gradient was 5-100% B over 40 min, hold at 100% for 5 min, 2 min back to 5% B, hold at 5% B for 4 min (21 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 21.2 x 250 mm Hypersil C18 HS column (8 µm particles). Detection method was UV.
e	HPLC: The gradient was 1-5% B over 3 min then 5-55% B over 6 min with a hold at 55% B for 0.10 min then 55-95% B over 1.5 min (22.5 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN, the column used for the chromatography was a 19 x 50 mm Waters Atlantis T3 OBD C18 column (5 µm particles), detection methods are Photodiode array DAD and Waters ZQ 2000 mass spectrometer.
f	HPLC: The gradient was 10-75% B over 9 min with a hold at 75% for 0.10 min then 75%-100% B over 1.5 min (22.5 mL/min flow rate). Mobile phase A was 50 mM

Method	Conditions
	NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN, the column used for the chromatography was a 19 x 50 mm Waters Atlantis T3 OBD C18 column (5 µm particles), detection methods were Photodiode array DAD and Waters ZQ 2000 mass spectrometer.
g	HPLC: The gradient was 10% B over 2.5 min then 10-15% B over 0.50 min then 15-75% B over 3 min then 75-85% B over 3.10 min then 85%-100% B over 1.5 min (22.5 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN, the column used for the chromatography was a 19 x 50 mm Waters Atlantis T3 OBD C18 column (5 µm particles), detection methods were Waters 2996 photodiode array DAD and Waters ZQ 2000 mass spectrometer.
h	HPLC: The gradient was 10-85% B over 9.00 min then 85-95% B over 0.10 min then held at 95% B for 1.50 min (25.0 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN, the column used for the chromatography was a 19 x 50 mm Waters Atlantis T3 OBD C18 column (5 µm particles), detection methods were Waters 2996 photodiode array DAD and Waters ZQ 2000 mass spectrometer.
i	HPLC: The gradient was 10-35% B over 45 min (25 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 21.2 x 250 mm Hypersil C18 HS column (8 µm particles). Detection method was UV.
j	HPLC: The gradient was 5-75% B over 25 min (21 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 21.2 x 250 mm Hypersil C18 HS column (8 µm particles). Detection method was UV.
k	HPLC: The gradient was 20-40% B over 30 min (21 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 21.2 x 250 mm Hypersil C18 HS column (8 µm particles). Detection method was UV.
l	HPLC: The gradient was 0-100% B over 30 min (21 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 21.2 x 250 mm Hypersil C18 HS column (8 µm particles). Detection method was UV.

Method	Conditions
m	HPLC: The gradient was 5% B, hold for 5 min, 5-100% B over 40 min, hold at 100% for 5 min, 2 min back to 5% B, hold at 5% B for 4 min, (21 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 21.2 x 250 mm Hypersil C18 HS column (8 µm particles). Detection method was UV.
n	LC/MS: The gradient was 5-60% B in 0.60 min then 60-95% B to 1.0 min with a hold at 95% B for 0.30 min (1.25 mL/min flow rate). Mobile phase A was 10 mM NH ₄ OAc, mobile phase B was HPLC grade MeCN. The column used for the chromatography is 2.1 x 30 mm Acquity UPLC HSS T3 column (1.8 µm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.
o	LC/MS: The gradient was 60-95% B in 1.15 min with a hold at 95% B for 3 min (1.3 mL/min flow rate). Mobile phase A was 10 mM NH ₄ OAc, mobile phase B was HPLC grade MeCN. The column used for the chromatography is a 4.6 x 50 mm MAC-MOD Halo C8 column (2.7 µm particles). Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.
p	LC/MS: The gradient was 5% B, hold for 0.2 min, 5-95% B over 1.7 min, hold at 95% for 1.3 min, back to 5% B within 0.01 min, (2.3 mL/min flow rate). Mobile phase A was water (0.05% TFA) and mobile phase B was HPLC grade MeCN (0.05% TFA). The column used for the chromatography was a 4.6 x 50 mm XBridge C18 column (3.5 µm particles). Temperature 50 °C. Detection method was UV.
q	HPLC: The gradient was 10-75% B over 10 min (22.5 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN, the column used for the chromatography was a 19 x 50 mm Waters Atlantis T3 OBD C18 column (5 µm particles), detection methods were Photodiode array DAD and Waters ZQ 2000 mass spectrometer.
r	LC/MS: The gradient was 80-65% B in 1.80 min then 65-40% B to 2.80 min with a hold at 40% for another 1.20 min (1.3 mL/min flow rate). The column used for the chromatography is a 4.6 x 50 mm X-bridge hilic column (3.5 µm particles). Mobile phase A was 10 mM ammonium acetate, mobile phase B was HPLC grade acetonitrile. Detection methods are diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive/negative electrospray ionization.

Method	Conditions
s	HPLC: The gradient was 0-100% B over 15 min, hold at 100% for 15 min (21 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 21.2 x 250 mm Hypersil C18 HS column (8 µm particles). Detection method was UV.
t	HPLC: The gradient was 24% B over 2 min then 24-55% B over 7.6 min then 55-98% B over 1 min (25 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN, the column used for the chromatography was a 19 x 50 mm Waters Atlantis T3 OBD C18 column (5 µm particles), detection methods were Waters 2996 photodiode array DAD and Waters ZQ 2000 mass spectrometer.
u	LC/MS: The gradient was 0-0.1 min 10% A, 0.1-1.1 min 10-100% A, 1.1-1.3 min 100% A, then 1.3-1.4 min 100-10% A. Flow rate was 1 mL/min. Mobile phase A was HPLC grade acetonitrile and mobile phase B was 0.1% trifluoroacetic acid in water. The column used was a Waters BEH C8, 1.7 µm (2.1mm × 30mm) at a temperature of 55°C. Detection methods were diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive APCI ionization.
v	The gradient was 0-0.1 min 10% A, 0.1-2.6 min 10-100% A, 2.6-2.9 min 100% A, 2.9-3.0 min 100-10% A then 0.5min post-run delay. Flow rate was 2 mL/min. Mobile phase A was HPLC grade acetonitrile and mobile phase B was 0.1% trifluoroacetic acid in water. The column used for the chromatography was a Phenomenex Luna Combi-HTS C8(2) 5 µm 100Å (2.1 mm × 50 mm), at a temperature of 55 °C. Detection methods were diode array (DAD) and evaporative light scattering (ELSD) detection as well as positive APCI ionization.
w	HPLC: The gradient was 15% B over 3.5 min then 15-46% B over 6.1 min then 46-98% B over 1.2 min (25 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN, the column used for the chromatography was a 19 x 50 mm Waters Atlantis T3 OBD C18 column (5 micron particles), detection methods were Waters 2996 photodiode array DAD and Waters ZQ 2000 mass spectrometer.
x	HPLC: The gradient was 0-80% B over 5 min, hold at 80% for 4 min, 0.1 min at 90% B, then 90 to 0% B for 2.9 min, hold at 0 % B for 2 min (1 mL/min flow rate). Mobile phase A was 0.1% H ₃ PO ₄ in water and mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 4.6 x 150 mm Ascentis Express column (2.8 µm particles). Detection method was UV.

Method	Conditions
y	HPLC: The gradient was 0-50% B over 45 min (25 mL/min flow rate). Mobile phase A was 50 mM NH ₄ OAc (pH 4.5) and mobile phase B was HPLC grade MeCN. The column used for the chromatography was a 21.2 x 250 mm Hypersil C18 HS column (8 µm particles). Detection method was UV.

Table 2. Chiral HPLC methods

Method	Conditions
1	Isocratic 50% A for 25 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
2	Isocratic 100% EtOH (200 proof) for 13 min (10 mL/min flow rate). The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
3	Isocratic 20% A for 10-23 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
4	Isocratic 70% A for 25 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
5	Isocratic 50% A for 20 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.

<u>Method</u>	Conditions
6	Isocratic 25% A for 18 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
7	Isocratic 30% A for 18 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
8	The gradient was 15-54% A in 16 min then step to 90% A in 0.5 min, with a hold at 90% for 4.3 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
9	The gradient was 10-70% A in 16 min then re-equilibrated at 10% A for 9 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were UV, λ = 315 nm.
10	The gradient was 10-50% A in 19 min with a hold at 50% for 2 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
11	Isocratic 60% A for 20 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were UV, λ = 300 nm.

<u>Method</u>	Conditions
12	Isocratic 30% A for 25 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
13	Isocratic 20% A for 20 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
14	Isocratic 100% EtOH (200 proof) for 20 min (13 mL/min flow rate). The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
15	Isocratic 50% A for 20 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
16	Isocratic 30% A for 18 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
17	The gradient was 10-50% A in 19 min with a hold at 50% for 2 min then re-equilibrated at 10% A for 11 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
18	The gradient was 10-50% A in 19 min with a hold at 50% for 1.5 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection

<u>Method</u>	Conditions
	methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
19	The gradient was 10-50% A in 19 min then re-equilibrated at 10% A for 6 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
20	Isocratic 40% A for 16 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
21	Isocratic 40% A for 15-25 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
22	The gradient was 10-40% A in 19 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IB, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
23	The gradient was 15-70% A in 19 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
24	Isocratic 15% A for 14 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
25	Isocratic 30% A for 10 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine

<u>Method</u>	Conditions
	added. The column used for the chromatography was a Daicel IB, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
26	Isocratic 40% A for 5 min then gradient 40 to 95% A in 2 min, with a hold at 95% for 11 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
27	The gradient was 10-50% A in 19 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IB, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
28	Isocratic 15% A for 35 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
29	The gradient was 10-50% A in 19 min with a hold at 50% for 3 min then re-equilibrate at 10% A for 13 min (1 mL/min flow rate). Mobile phase A was IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IC, 4.6 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
30	Isocratic 20% A for 20 min (1 mL/min flow rate). Mobile phase A was IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IC, 4.6 x 250 mm column (5 μ m particles). Detection methods were UV, λ = 230 nm as well as positive electrospray ionization.
31	Isocratic 20% A for 10 min (20 mL/min flow rate). Mobile phase A was ethanol (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.

<u>Method</u>	Conditions
32	The gradient was 10-70% A in 19 min then re-equilibrate at 10% A for 11 min (20 mL/min flow rate). Mobile phase A was ethanol (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were ELSD and optical rotation.
33	Isocratic 30% A for 20-30 min (20 mL/min flow rate). Mobile phase A was ethanol (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
34	Isocratic 40% A for 10-30 min (20 mL/min flow rate). Mobile phase A was ethanol (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
35	Isocratic 15% A for 22.5 min then step to 60% A and hold for 5 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection method was UV, λ = 325 nm
36	Isocratic 40% A for 20 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
37	The gradient was 10-70% A in 19 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
38	Isocratic 35% A for 25 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm

<u>Method</u>	Conditions
	column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
39	Isocratic 70% A for 7 min then gradient 70-95% A in 3min and hold at 95% A for 12 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
40	Isocratic 25% A for 25 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection method was UV, λ = 325 nm
41	Isocratic 10% A for 25 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection method was UV, λ = 320 nm
42	Isocratic 20% A for 20 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
43	Isocratic 15% A for 30 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IB, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
44	Isocratic 25% A for 25 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
45	The gradient was 10-60% A in 20 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IC, 20

<u>Method</u>	Conditions
	x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
46	The gradient was 10-50% A in 13 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
47	The gradient was 10-50% A in 17 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
48	The gradient was 15-60% A in 17 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
49	Isocratic 25% A for 17 min then step to 60% A and hold for 10 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 μ m particles). Detection method was UV, λ = 340 nm
50	Isocratic 20% A for 20 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.1% diethylamine added. The column used for the chromatography was a Daicel IB, 20 x 250 mm column (5 μ m particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
51	Isocratic 10% A for 60 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 μ m particles). Detection

<u>Method</u>	Conditions
	methods were evaporative light scattering (ELSD) detection as well as optical rotation.
52	Isocratic 50% A for 20 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
53	The gradient was 30-70% A in 18 min with a hold at 70% for 4 min then re-equilibrate at 30% A for 13 min (20 mL/min flow rate). Mobile phase A was IPA, mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection as well as optical rotation.
54	Isocratic 30% A for 30 min (20 mL/min flow rate). Mobile phase A was ethanol (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
55	Isocratic 30% A for 30 min (20 mL/min flow rate). Mobile phase A was ethanol (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a (R,R) Whelk-O1, 21 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
56	Isocratic 35% A for 30 min (20 mL/min flow rate). Mobile phase A was ethanol (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
57	Isocratic 30% A for 30 min (20 mL/min flow rate). Mobile phase A was a 50:50 mixture of HPLC grade MeOH and EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.

<u>Method</u>	Conditions
58	Isocratic 15% A for 11 min then step to 50% A in 0.5 min and hold for 4.5 min (20 mL/min flow rate). Mobile phase A was HPLC grade ethanol (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
59	The gradient was 10-95% A in 17 min with a hold at 95% for 2 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
60	Isocratic 20% A for 10 min then step to 60% A in 0.5 min and hold at 60% for 5.5 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
61	The gradient was 10-20% A in 28 min, hold at 20% for 2 min then 20-70% A in 5min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
62	Isocratic 22% A for 30 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IB, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
63	Isocratic 25% A for 30 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IB, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
64	Isocratic 65% A for 30 min (20 mL/min flow rate). Mobile phase A was ethanol

<u>Method</u>	Conditions
	(200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a (R,R) Whelk-O1, 21 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
65	Isocratic 65% A for 6 min then step to 90% A in 0.5 min and hold at 90% for 6.5 min (20 mL/min flow rate). Mobile phase A was ethanol (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a (R,R) Whelk-O1, 21 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
66	Isocratic 30% A for 30 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
67	Isocratic 55% A for 8 min then step to 90% A in 1 min and hold at 90 for 7 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
68	The gradient was 60-90% A in 4 min with a hold at 90% for 6 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
69	Isocratic 20% A for 12 min then step to 50% A in 0.5 min and hold at 50% for 3.5 min (20 mL/min flow rate). Mobile phase A was EtOH (200 proof), mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IA, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.
70	The gradient was 20-50% B over 10 min (0.6 mL/min flow rate). Mobile phase A was 10 mM KH ₂ PO ₄ buffer (pH = 6.9) and mobile phase B was HPLC grade

<u>Method</u>	Conditions
	MeCN. The column used for the chromatography was a 4.6 x 150 mm Chiralpak AS-RH, Diacel col. Detection method was UV.
71	The gradient was 15-85% A in 37 min with a hold at 85% A for 0.5 min (20 mL/min flow rate). Mobile phase A was HPLC grade IPA, mobile phase B was HPLC grade heptane with 0.12% diethylamine added. The column used for the chromatography was a Daicel IC, 20 x 250 mm column (5 µm particles). Detection methods were evaporative light scattering (ELSD) detection, and/or UV (variable wavelength) as well as optical rotation.

Purification Methods

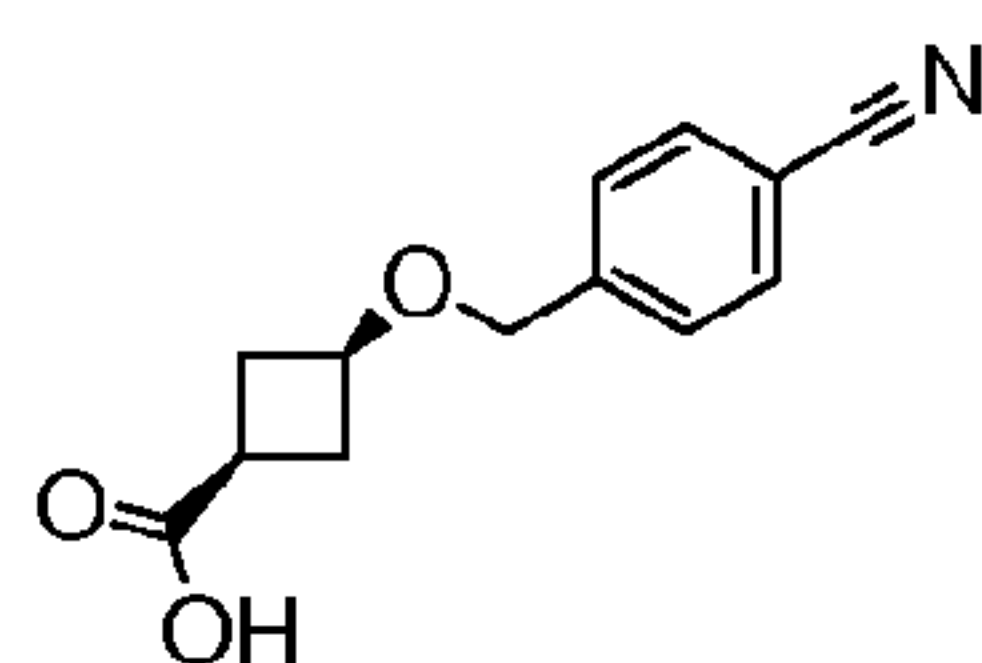
For the general procedures, the intermediates and final compounds may be purified by any technique or combination of techniques known to one skilled in the art. Some examples that are not limiting include flash chromatography with a solid phase (e.g. silica gel, alumina, etc.) and a solvent (or combination of solvents) that elutes the desired compounds (e.g. heptane, EtOAc, DCM, MeOH, MeCN, water, etc.); preparatory TLC with a solid phase (e.g. silica gel, alumina etc.) and a solvent (or combination of solvents) that elutes the desired compounds (e.g. heptane, EtOAc, DCM, MeOH, MeCN, water, etc.); reverse phase HPLC (see Table 1 for some non-limiting conditions); recrystallization from an appropriate solvent or combination of solvents (e.g. MeOH, EtOH, IPA, EtOAc, toluene, etc.) or combination of solvents (e.g. EtOAc/heptane, EtOAc/MeOH, etc.); chiral LC with a solid phase and an appropriate solvent (see Table 2 for some non-limiting conditions) to elute the desired compound; chiral SFC with a solid phase and CO₂ with an appropriate modifier (e.g. MeOH, EtOH, IPA with or without additional modifier such as diethylamine, TFA, etc.); precipitation from a combination of solvents (e.g. DMF/water, DMSO/DCM, EtOAc/heptane, etc.); trituration with an appropriate solvent (e.g. EtOAc, DCM, MeCN, MeOH, EtOH, IPA, *n*-IPA, etc.); extractions by dissolving a compound in a liquid and washing with an appropriately immiscible liquid (e.g. DCM/water, EtOAc/water, DCM/saturated aqueous NaHCO₃, EtOAc/saturated aqueous NaHCO₃, DCM/10% aqueous HCl, EtOAc/10% aqueous HCl, etc.); distillation (e.g. simple, fractional, Kugelrohr, etc.); gas chromatography using an appropriate temperature, carrier gas and flow rate; sublimation at an appropriate temperature and pressure; filtration through a media (e.g. Florosil[®], alumina, Celite[®], silica gel, etc.) with a solvent (e.g. heptane, hexanes, EtOAc, DCM, MeOH, etc.) or combination of solvents; salt formation with solid support (resin based, e.g. ion exchange) or without. Compounds of interest may be isolated as a salt without the use of a specific salt formation purification method. For example, on occasions where purification is accomplished with reverse phase HPLC with an aqueous TFA buffer, the TFA salt may be isolated. Some descriptions of

these techniques can be found in the following references: Gordon, A. J. and Ford, R. A.. "The Chemist's Companion", 1972; Palleros, D. R. "Experimental Organic Chemistry", 2000; Still, W. C., Kahn and M. Mitra, A. *J. Org. Chem.* 1978, 43, 2923; Yan, B. "Analysis and Purification Methods in Combinatorial Chemistry", 2003; Harwood, L. M., Moody, C. J. and Percy, J. M. "Experimental Organic Chemistry: Standard and Microscale, 2nd Edition", 1999; Stichlmair, J. G. and Fair, J. R. "Distillation; Principles and Practices", 1998; Beesley, T. E. and Scott, R. P. W. "Chiral Chromatography", 1999; Landgrebe, J. A. "Theory and Practice in the Organic Laboratory, 4th Ed.", 1993; Skoog, D. A. and Leary, J. J. "Principles of Instrumental Analysis, 4th Ed.", 1992; G. Subramanian, "Chiral Separation Techniques, 3rd Edition", 2007; Y. Kazakevich, R. Lobrutto, "HPLC for Pharmaceutical Scientists", 2007.

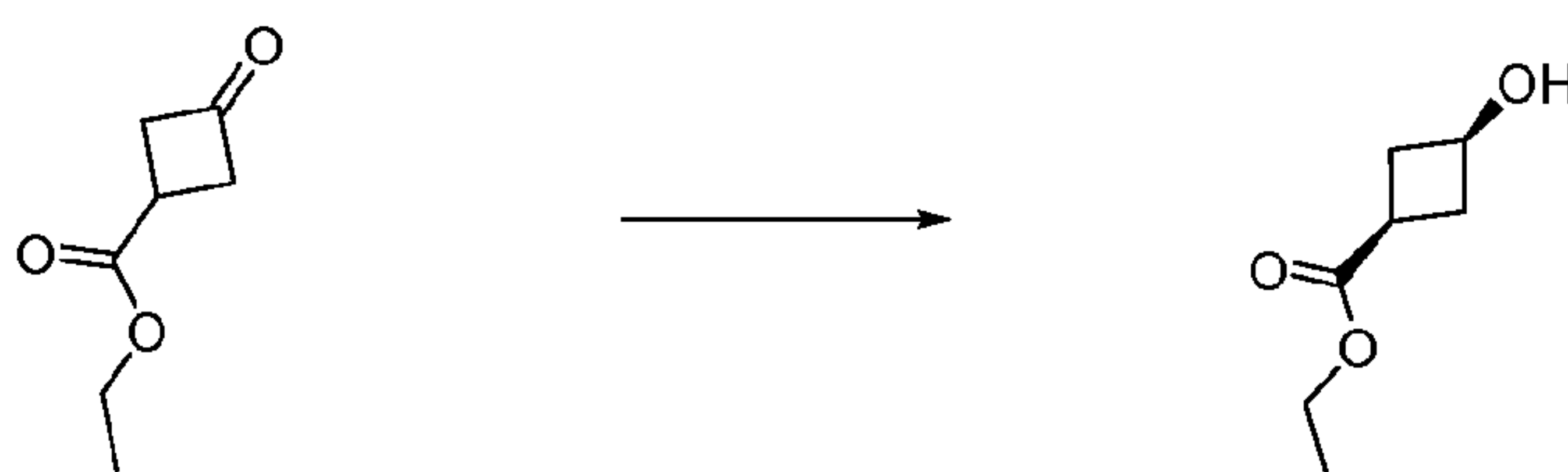
Preparations and Examples

The general synthetic methods used in each General Procedure follow and include an illustration of a compound that was synthesized using the designated General Procedure. None of the specific conditions and reagents noted herein are to be construed as limiting the scope of the invention and are provided for illustrative purposes only. All starting materials are commercially available from Sigma-Aldrich (including Fluka and Discovery CPR) unless otherwise noted after the chemical name. Reagent/reactant names given are as named on the commercial bottle or as generated by IUPAC conventions, CambridgeSoft[®] ChemDraw Ultra 9.0.7, CambridgeSoft[®] Chemistry E-Notebook 9.0.127, or AutoNom 2000. Compounds designated as salts (e.g. hydrochloride, acetate) may contain more than one molar equivalent of the salt. Compounds of the invention where the absolute stereochemistry has been determined by the use of a commercially available enantiomerically pure starting material or a stereochemically defined intermediate, or by X-ray diffraction are denoted by an asterisk after the example number.

Preparation #1: *cis*-3-(4-cyanobenzyloxy)cyclobutanecarboxylic acid

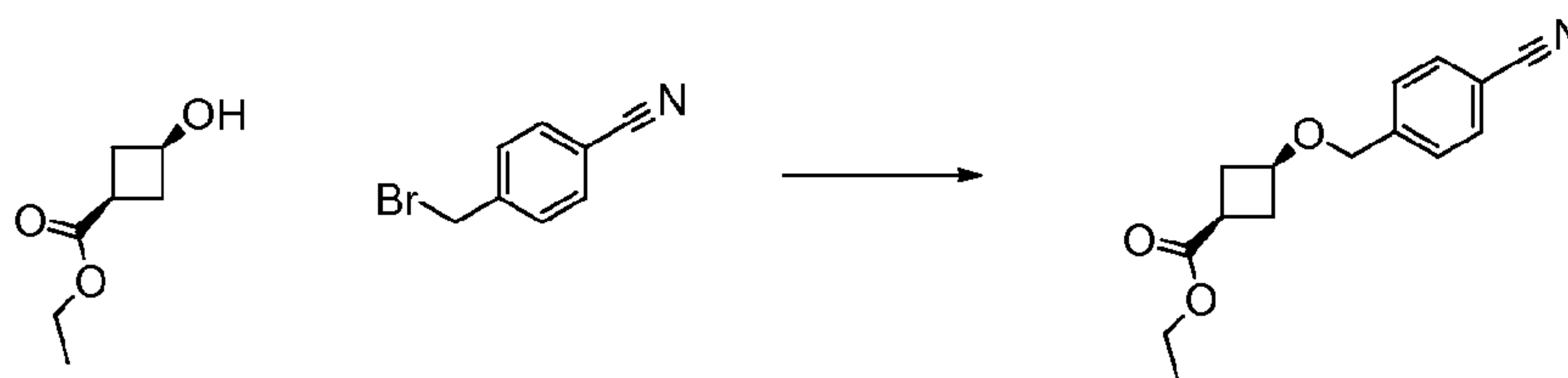


Step A: *cis*-ethyl 3-hydroxycyclobutanecarboxylate



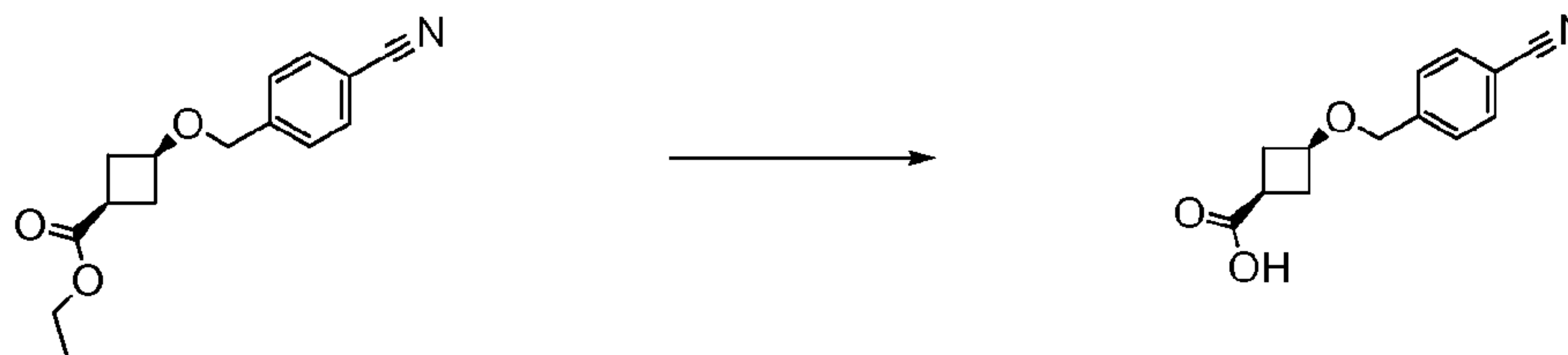
A solution of ethyl 3-oxocyclobutanecarboxylate (2.90 g, 20.4 mmol, Parkway) in EtOH (30 mL) at ambient temperature was treated with NaBH₄ (0.77 g, 20 mmol). The reaction was stirred for about 1 h and then 2 N aqueous HCl was added to adjust the pH to about 2. The reaction was concd *in vacuo*. The reaction was partitioned with DCM (50 mL) and brine (50 mL). The organic layer was separated, dried over anhydrous Na₂SO₄, filtered then concd *in vacuo*. The resulting residue was purified on silica gel (80 g) using 20-40% EtOAc in DCM to give *cis*-ethyl 3-hydroxycyclobutanecarboxylate (2.75 g, 66%) as a clear oil: ¹H NMR (DMSO-*d*₆) δ 5.17 (d, 1H), 4.09-3.99 (m, 2H), 3.99-3.90 (m, 1H), 2.57-2.47 (m, 1H), 2.42-2.29 (m, 2H), 1.98-1.89 (m, 2H), 1.17 (m, 3H).

Step B: *cis*-ethyl 3-(4-cyanobenzyloxy)cyclobutanecarboxylate



To a solution of *cis*-ethyl 3-hydroxycyclobutanecarboxylate (0.17 g, 1.2 mmol) in DMF (4 mL) was added K₂CO₃ (0.24 g, 1.8 mmol) followed by 4-(bromomethyl)benzonitrile (0.28 g, 1.4 mmol). The reaction was stirred at about 25 °C for about 16 h. The reaction was partitioned between EtOAc (50 mL) and brine (50 mL). The layers were separated and the organic layer was washed with additional brine (50 mL). The organic layer was then dried over anhydrous Na₂SO₄, filtered, and concd *in vacuo* to give *cis*-ethyl 3-(4-cyanobenzyloxy)-cyclobutanecarboxylate (0.29 g, 95%) as an oil: ¹H NMR (DMSO-*d*₆) δ 7.82 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 4.75 (s, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.93 (m, 1H), 2.58-2.45 (m, 1H), 2.41-2.28 (m, 2H), 1.98-1.85 (m, 2H), 1.20-1.08 (t, *J* = 7.1 Hz, 3H).

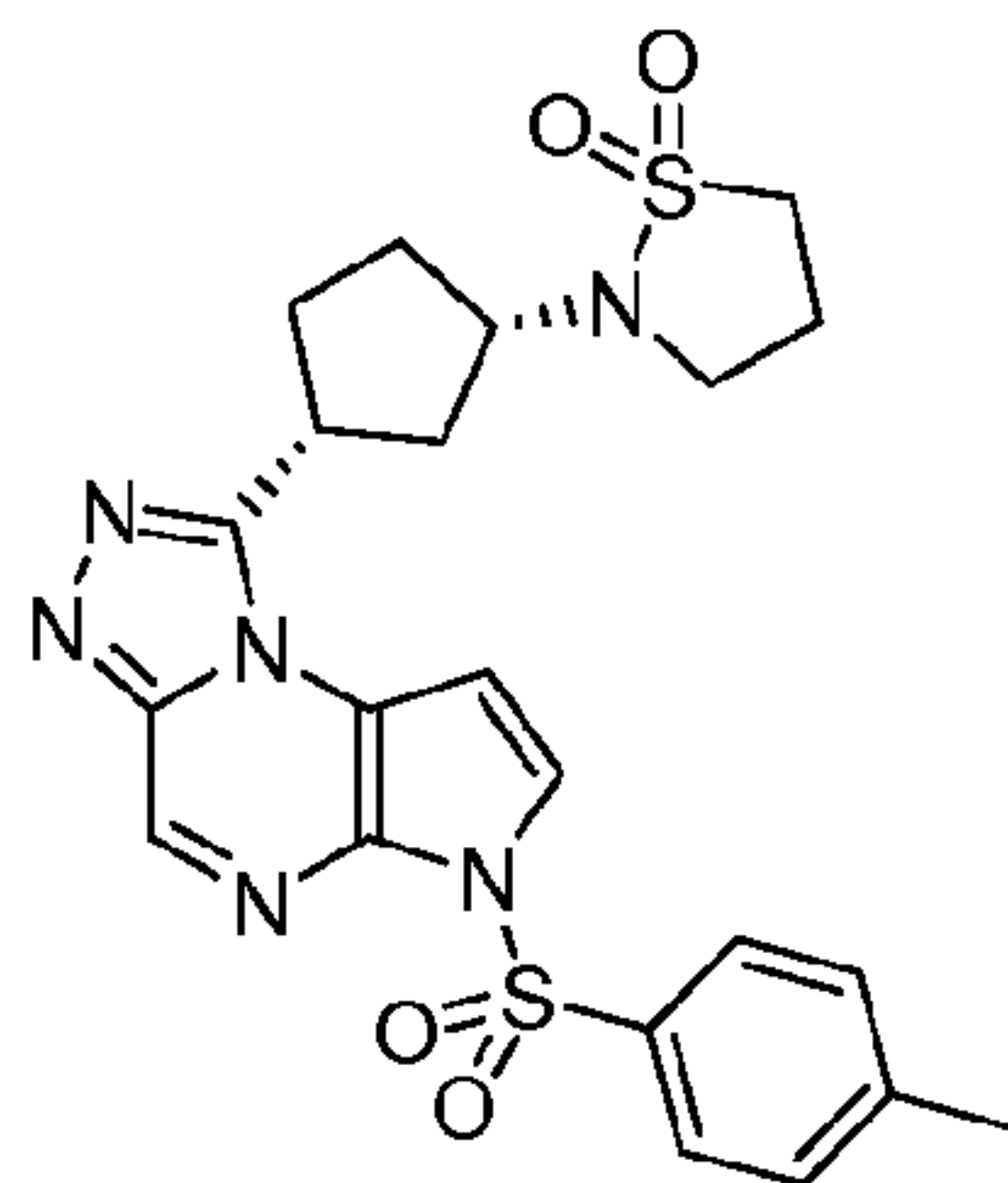
Step C: *cis*-3-(4-cyanobenzyloxy)cyclobutanecarboxylic acid



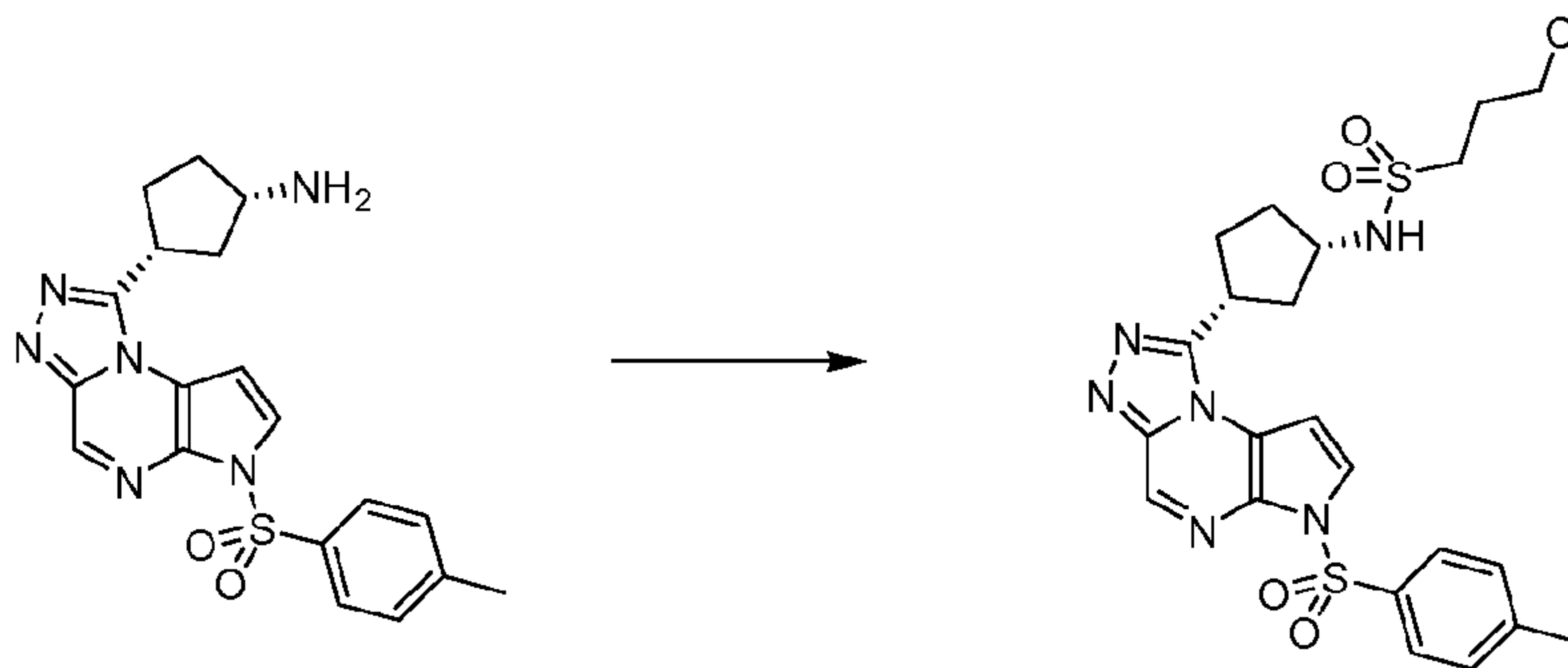
To a solution of *cis*-ethyl 3-(4-cyanobenzyloxy)cyclobutanecarboxylate (0.44 g, 1.70 mmol) in 1,4-dioxane (10 mL) was added aqueous NaOH (1 N, 2.0 mL). The reaction was stirred at about 25 °C for about 16 h. The reaction was partitioned between 10% aqueous AcOH (20 mL) and EtOAc (25 mL). The layers were separated and the aqueous layer was extracted with additional EtOAc (25 mL). The combined organic extracts were washed with brine (20 mL), dried over

anhydrous Na_2SO_4 , filtered then concd *in vacuo* to give *cis*-3-(4-cyanobenzyloxy)-cyclobutanecarboxylic acid (0.24 g, 60%): LC/MS (Table 1, Method b) $R_t = 1.67$ min; MS m/z : 232 ($\text{M}+\text{H}$)⁺.

Preparation #2*: (1*S*,3*R*)-1-[3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-isothiazolidin-2-yl-1,1-dioxide]cyclopentane

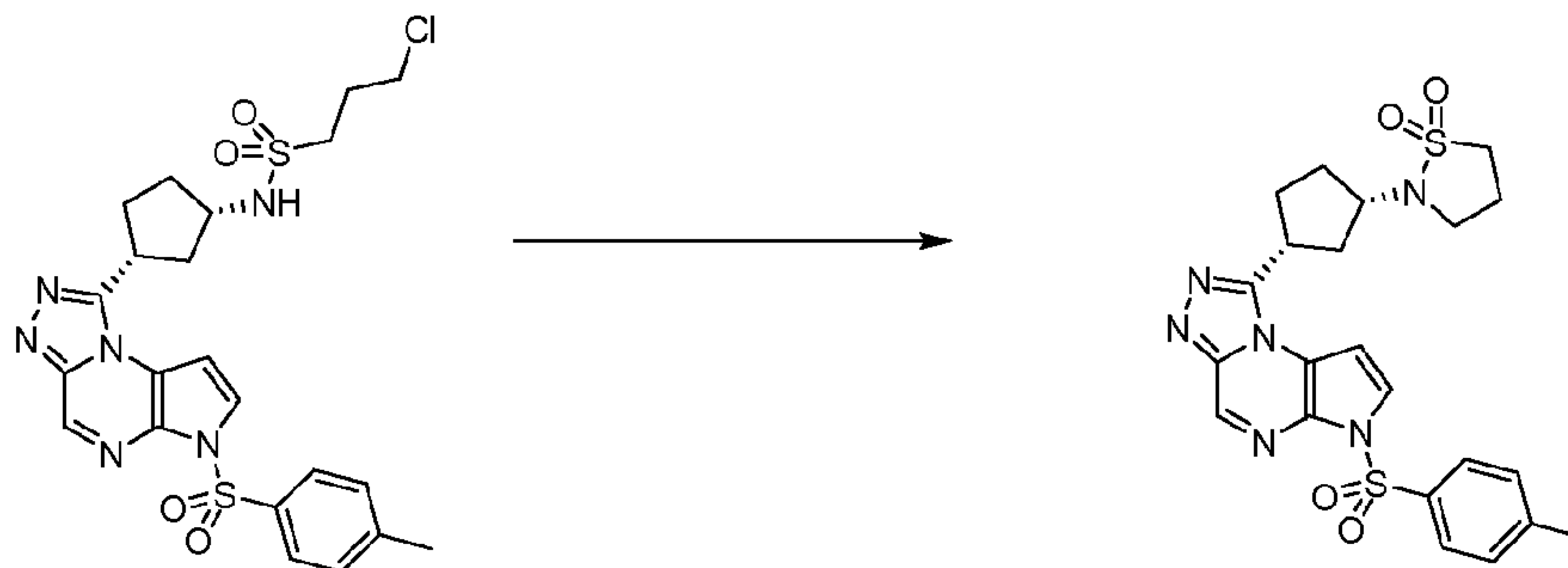


Step A: 3-chloro-*N*-((1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide



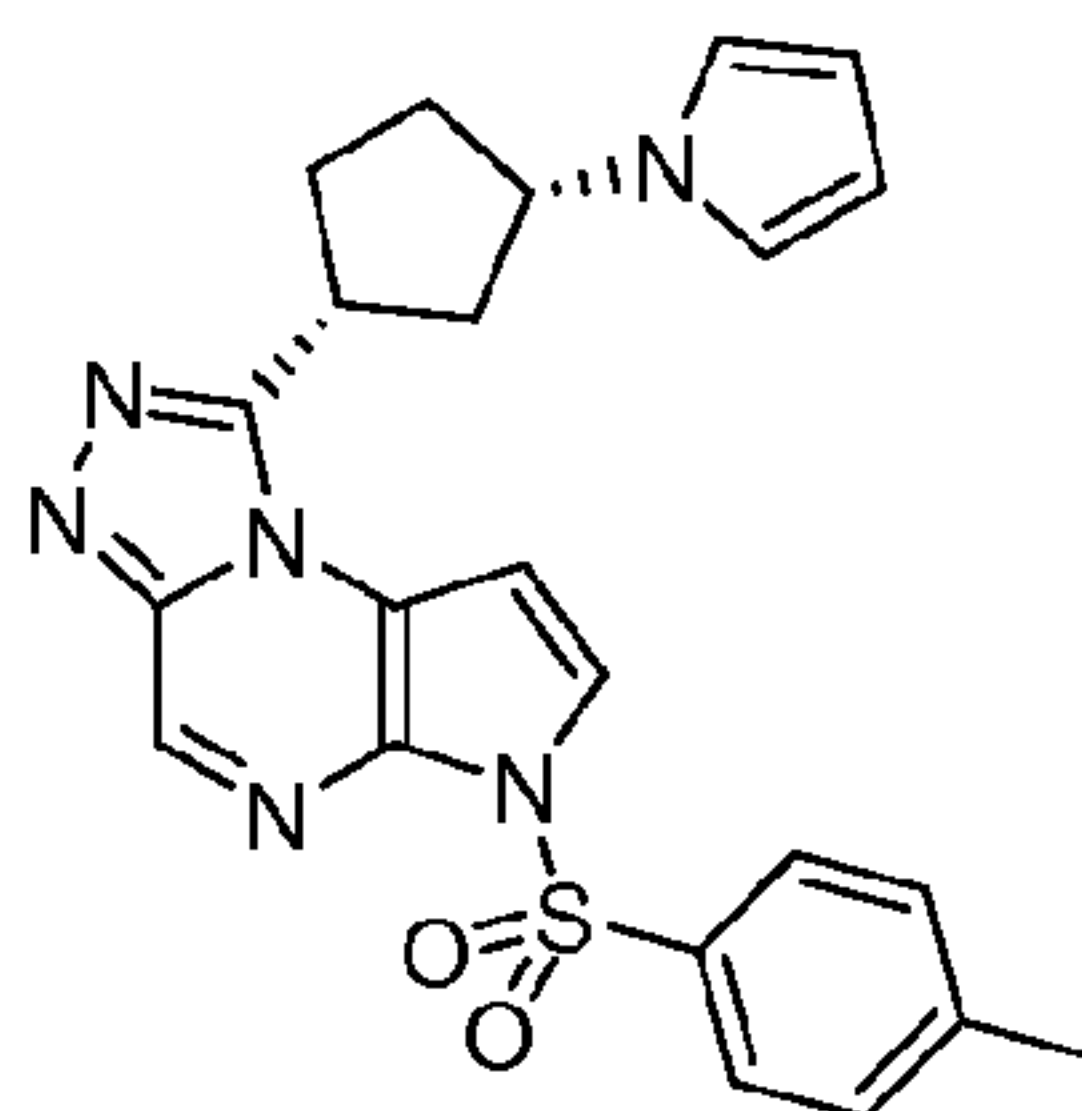
To a suspension of (1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine hydrochloride (0.05 g, 0.11 mmol, prepared using **E** from Preparation #B.1 and HCl) and TEA (0.03 mL, 0.21 mmol) in DCM (5 mL) at about 0 °C was added 3-chloropropane-1-sulfonyl chloride (0.02 g, 0.11 mmol) dropwise. The reaction mixture was stirred at about 0 °C for about 1.5 h. The reaction mixture was diluted with 5% aqueous citric acid (10 mL), and the layers were separated. The organic layer was washed with saturated aqueous NaHCO_3 (10 mL), water (10 mL), brine (10 mL), dried over anhydrous MgSO_4 , filtered, and concd under reduced pressure to give 3-chloro-*N*-((1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide (0.052 g, 91%) as a brown residue: LC/MS (Table 1, Method a) $R_t = 2.18$ min; MS m/z : 537 ($\text{M}+\text{H}$)⁺.

Step B: (1*S*,3*R*)-1-[3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-isothiazolidin-2-yl-1,1-dioxide]cyclopentane



To a solution of 3-chloro-*N*-((1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide (0.11 g, 0.21 mmol) in DMF (5 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.04 mL, 0.27 mmol crude). The reaction mixture was stirred at ambient temperature for about 16 h. The solvent was removed under reduced pressure to give (1*S*,3*R*)-1-[3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)-isothiazolidin-2-yl-1,1-dioxide]cyclopentane (0.106 g, 99%): LC/MS (Table 1, Method **a**) R_t = 2.04 min; MS m/z : 501 (M+H)⁺.

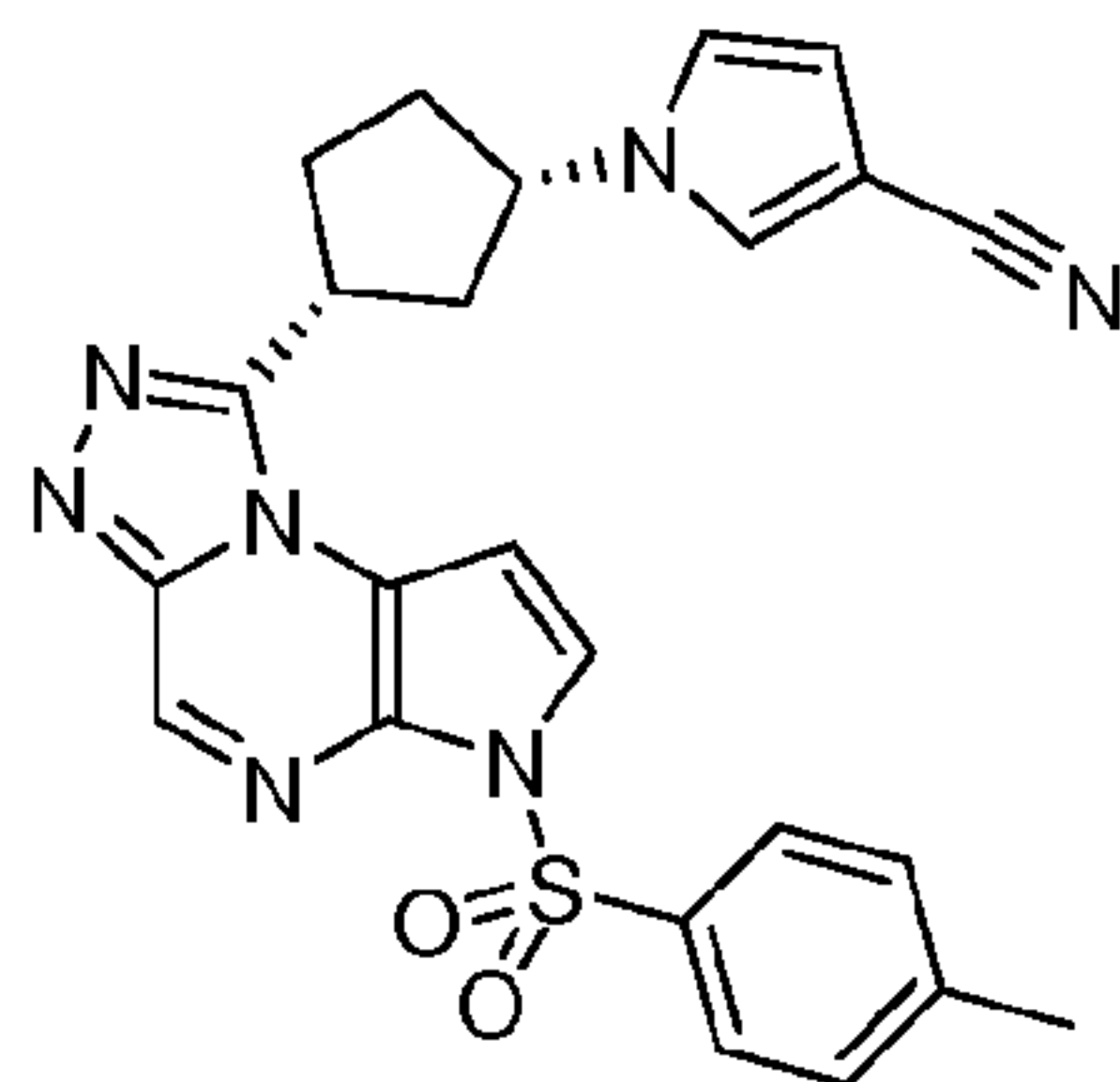
Preparation #3*: 1-((1*R*,3*S*)-3-(1*H*-pyrrol-1-yl)cyclopentyl)-6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine



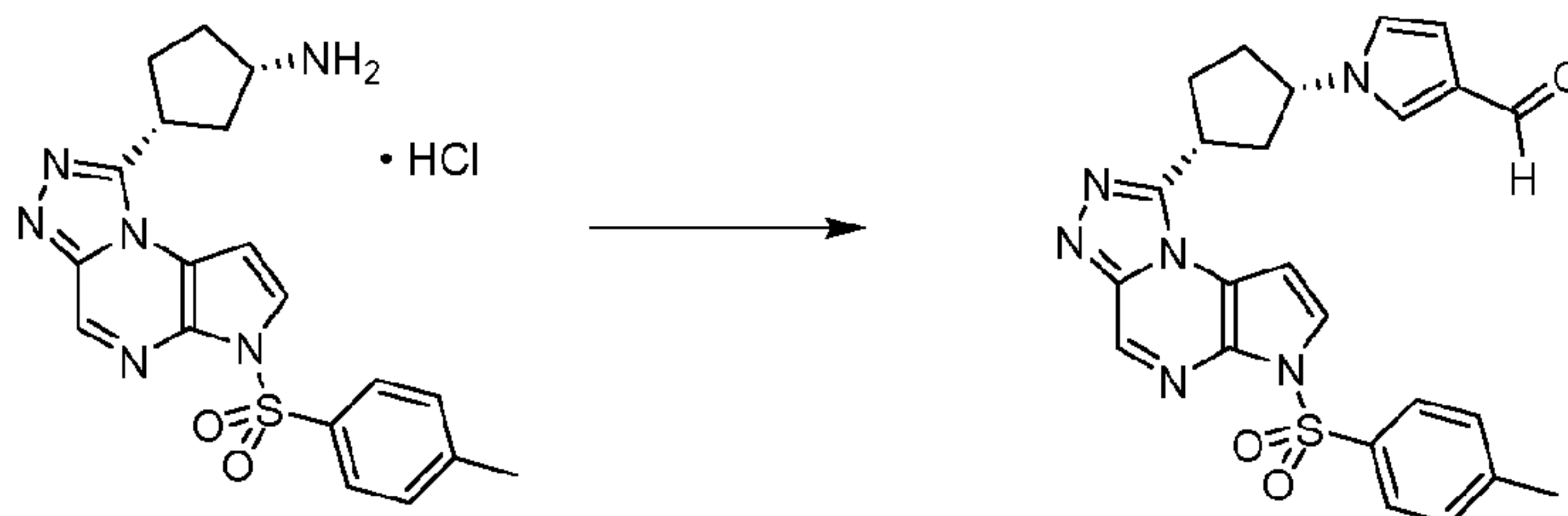
A solution of 2,5-dimethoxytetrahydrofuran (0.14 g, 1.1 mmol) in water (3 mL) was heated at about 100 °C for about 1.5 h. The solution was cooled to ambient temperature. A suspension of (1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine hydrochloride (0.10 g, 0.21 mmol, prepared using **E** from Preparation #B.1 and HCl) and NaOAc (0.05 g, 0.61 mmol) in DCM (5 mL) was added to the aqueous solution. The reaction mixture was stirred at ambient temperature for about 1 h followed by addition of additional 2,5-dimethoxytetrahydrofuran (0.14 g, 1.1 mmol). The reaction mixture was heated to about 40 °C for about 15 h. Additional 2,5-dimethoxytetrahydrofuran (0.14 g, 1.1 mmol) was added and the reaction mixture was stirred at about 40 °C for about 8 h then at about 35 °C for about 48 h. The reaction was diluted with DCM (10 mL) and water (10 mL). The layers were separated and the organic layer was washed with water (2 x 10 mL) and brine (10 mL), dried over anhydrous MgSO₄, filtered, and the solvent was removed under reduced pressure to give 1-((1*R*,3*S*)-3-(1*H*-

*pyrrol-1-yl)cyclopentyl)-6-tosyl-6H-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine* (0.095 g, 99%) as a yellow residue: LC/MS (Table 1, Method **a**) $R_t = 2.42$ min; MS m/z : 447 (M+H)⁺.

Preparation #4*: 1-((1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-1*H*-pyrrole-3-carbonitrile

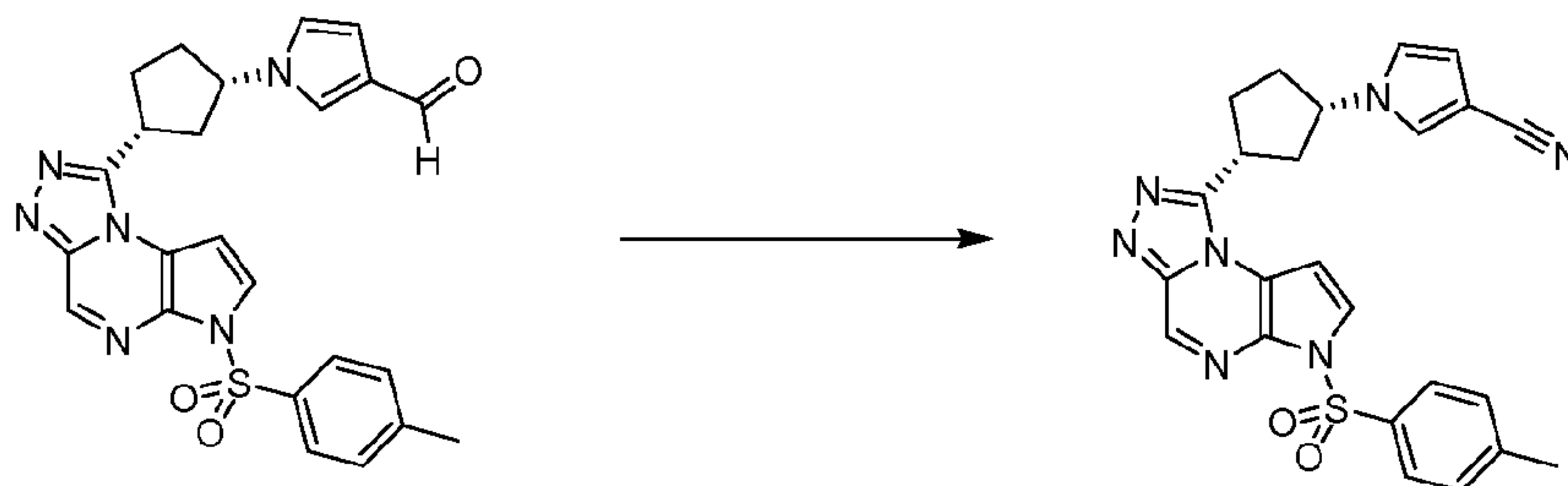


Step A: 1-((1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-1*H*-pyrrole-3-carbaldehyde



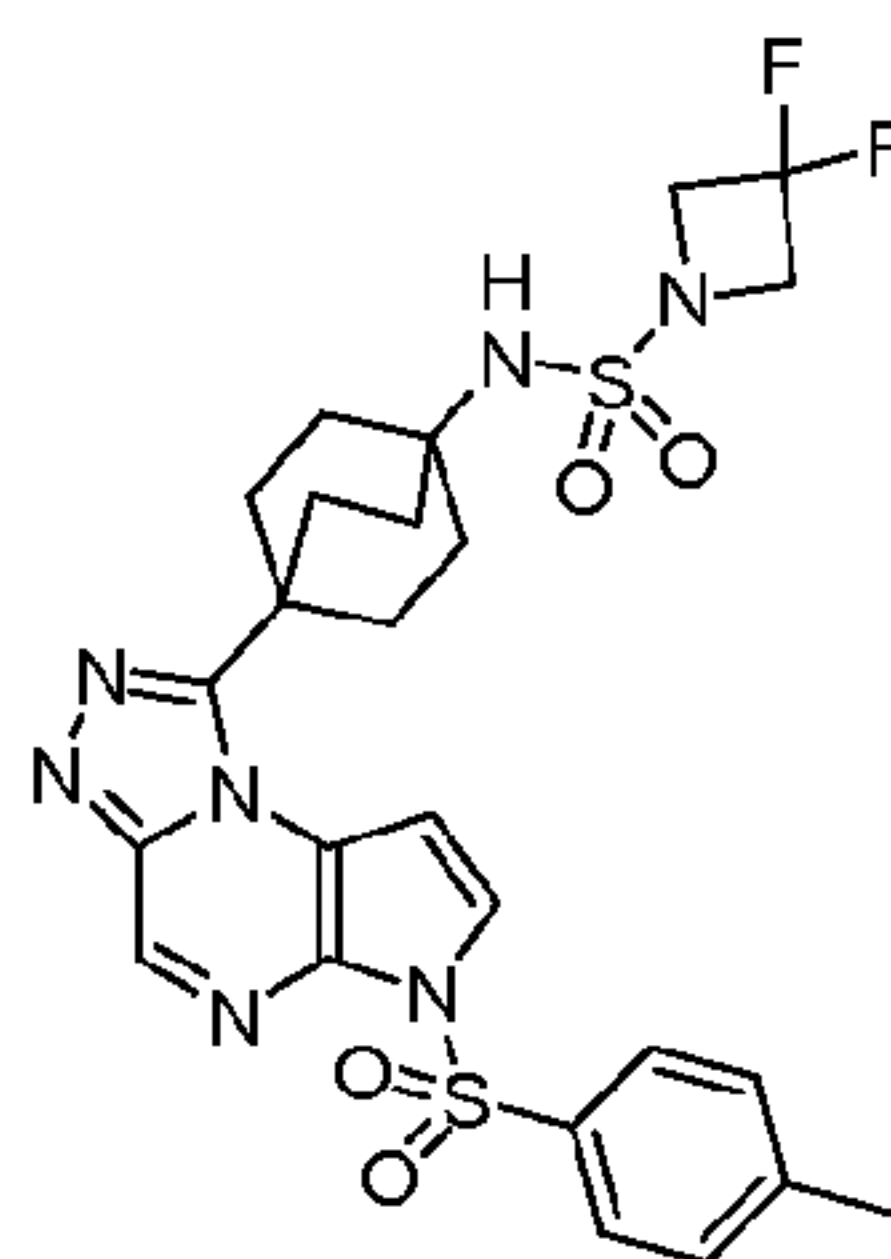
To a suspension of (1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine hydrochloride (0.175 g, 0.373 mmol, prepared using **E** from Preparation #B.1 and HCl) and NaOAc (0.100 g, 1.22 mmol) in DCM (3 mL) and water (2 mL) was added 2,5-dimethoxytetrahydrofuran-3-carbaldehyde (0.600 g, 3.37 mmol). The reaction was heated to about 40 °C for about 24 h. The reaction mixture was diluted with DCM (30 mL) and washed with water (4 x 20 mL). The organic layer was dried over anhydrous MgSO₄, filtered, and the solvent was removed under reduced pressure to give a brown residue. The crude material was purified by flash chromatography on silica gel eluting with a gradient of 20-100% EtOAc in DCM to give 1-((1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-1*H*-pyrrole-3-carbaldehyde (0.059 g, 33%) as a yellow amorphous solid: LC/MS (Table 1, Method **a**) $R_t = 2.10$ min; MS m/z : 475 (M+H)⁺.

Step B: 1-((1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-1*H*-pyrrole-3-carbonitrile

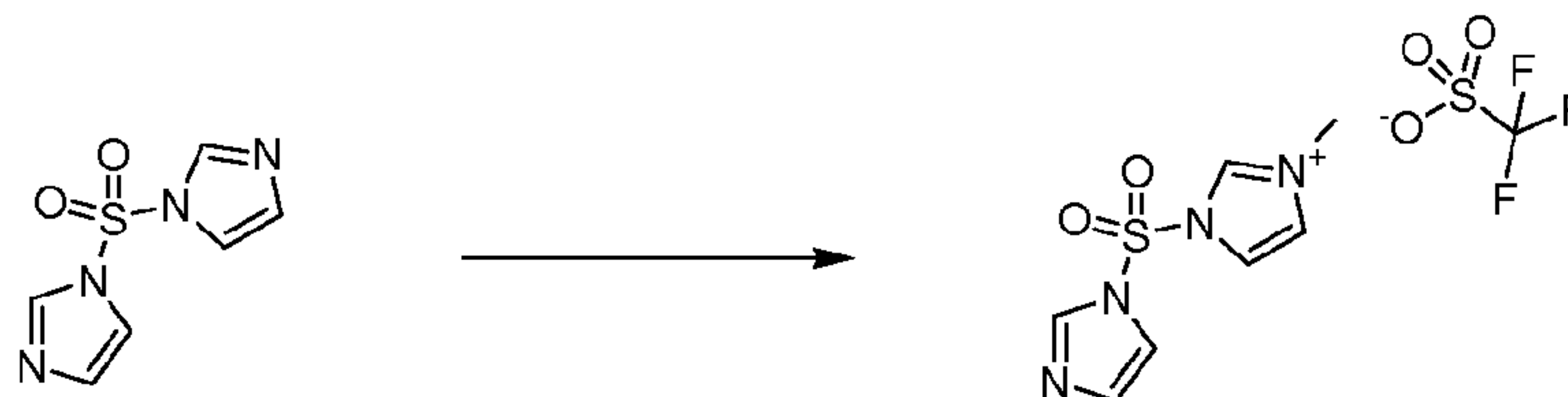


To a solution of 1-((1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-1*H*-pyrrole-3-carbaldehyde (0.050 g, 0.105 mmol) in THF (2 mL) was added iodine (0.083 g, 0.327 mmol) and aqueous NH₄OH (28-30% w/v, 0.733 mL, 5.27 mmol). The reaction mixture was stirred at ambient temperature for about 24 h. The reaction mixture was diluted with saturated aqueous Na₂SO₃ (30 mL) and EtOAc (30 mL). The layers were partitioned and the organic layer was dried over anhydrous MgSO₄, filtered, and the solvent was removed under reduced pressure to give 1-((1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-1*H*-pyrrole-3-carbonitrile (0.05 g, 100%): LC/MS (Table 1, Method a) R_t = 2.33 min; MS *m/z*: 472 (M+H)⁺.

Preparation #5: 3,3-difluoro-*N*-(4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)azetidine-1-sulfonamide



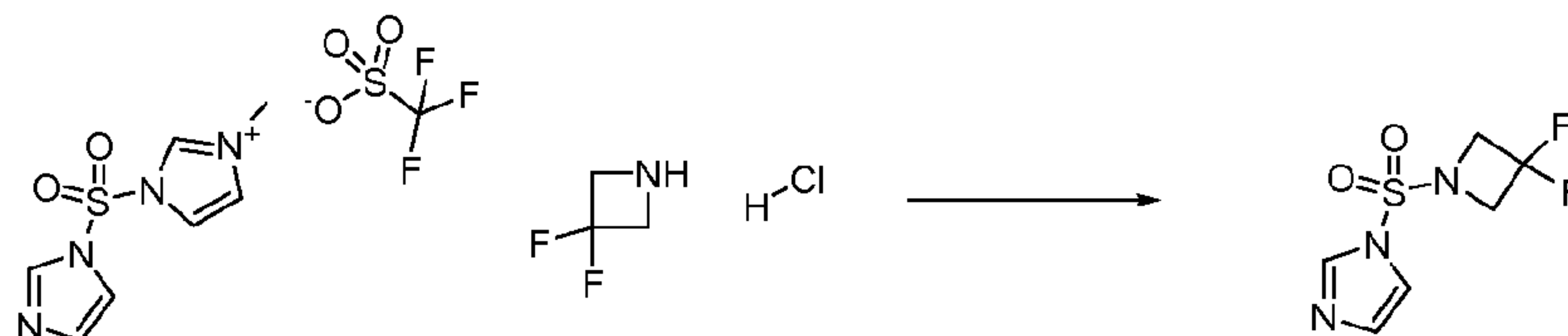
Step A: 1-(1*H*-imidazol-1-ylsulfonyl)-3-methyl-1*H*-imidazol-3-ium trifluoromethanesulfonate



To a solution of 1,1'-sulfonyldiimidazole (3.50 g, 17.7 mmol) in DCM (75 mL) at about 0 °C was added methyl trifluoromethanesulfonate (1.94 mL, 17.7 mmol). The reaction mixture was stirred at about 0 °C for about 1 h, then warmed to ambient temperature and stirred for about 5 h. The

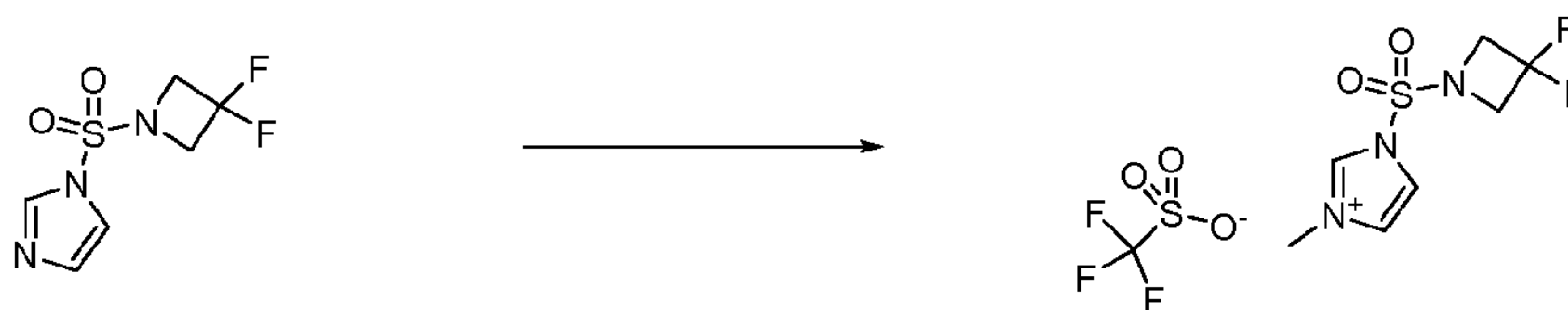
solid was collected by vacuum filtration and washed with DCM (10 mL) to give *1-(1H-imidazol-1-ylsulfonyl)-3-methyl-1H-imidazol-3-ium trifluoromethanesulfonate* (6.35 g, 98%) as a white solid: LC/MS (Table 1, Method **a**) $R_t = 0.082$ min; MS m/z 213 ($M+H$)⁺.

Step B: 1-(3,3-difluoroazetidin-1-ylsulfonyl)-1H-imidazole



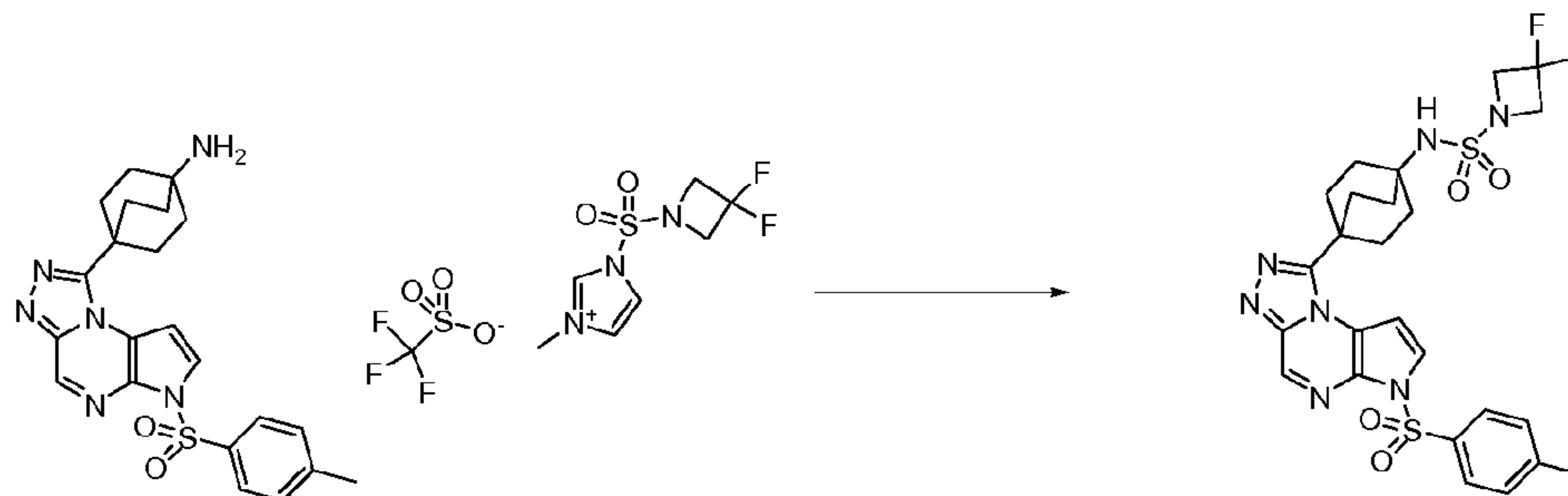
A solution of 3,3-difluoroazetidine hydrochloride (1.00 g, 7.72 mmol) and DIEA (1.5 mL, 8.6 mmol) in MeCN (5 mL) was stirred for about 5 min and then was added to a solution of 1-(1H-imidazol-1-ylsulfonyl)-3-methyl-1H-imidazol-3-ium trifluoromethanesulfonate (4.20 g, 11.6 mmol) in MeCN (10 mL) at about 0 °C. The reaction mixture was stirred at about 0 °C for about 1 h, and then warmed to ambient temperature and stirred for about 16 h. The reaction mixture was then concd under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with a gradient of 5-100% EtOAc in DCM to give *1-(3,3-difluoroazetidin-1-ylsulfonyl)-1H-imidazole* (0.95 g, 55%) as a yellow solid: LC/MS (Table 1, Method **c**) $R_t = 1.16$ min; MS m/z 224 ($M+H$)⁺.

Step C: 1-(3,3-difluoroazetidin-1-ylsulfonyl)-3-methyl-1H-imidazol-3-ium trifluoromethanesulfonate



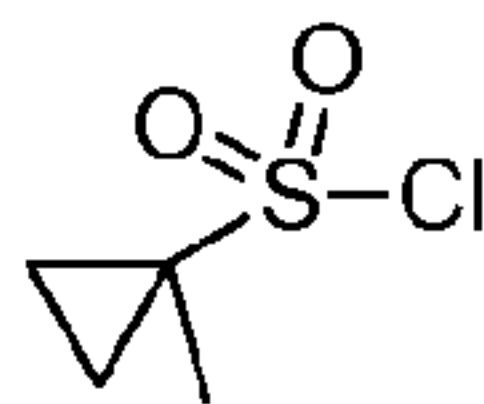
To a solution of 1-(3,3-difluoroazetidin-1-ylsulfonyl)-1H-imidazole (0.500 g, 2.24 mmol) in DCM (5 mL) at about 0 °C was added methyl trifluoromethanesulfonate (0.27 mL, 2.46 mmol) dropwise over about 3 min. The reaction mixture was stirred at about 0 °C for about 2 h. The solid was collected by vacuum filtration, washed with DCM (10 mL), and dried under vacuum to give *1-(3,3-difluoroazetidin-1-ylsulfonyl)-3-methyl-1H-imidazol-3-ium trifluoromethanesulfonate* (0.79 g, 90%) as a white solid: LC/MS (Table 1, Method **c**) $R_t = 1.12$ min; MS m/z 238 ($M+H$)⁺.

Step D: 3,3-difluoro-N-(4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)azetidine-1-sulfonamide

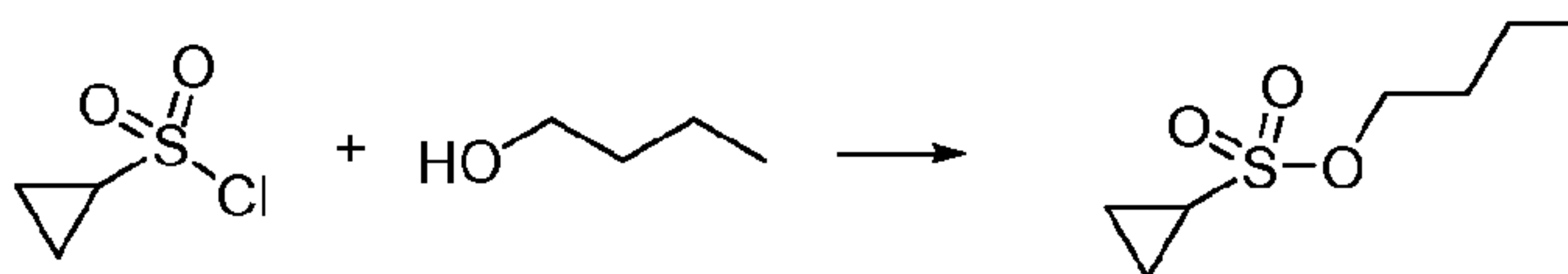


To a solution of 4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)bicyclo[2.2.2]octan-1-amine (0.20 g, 0.46 mmol, Example #9, Step F) in MeCN (5 mL) was added 1-(3,3-difluoroazetidin-1-yl)sulfonyl)-3-methyl-1H-imidazol-3-ium trifluoromethanesulfonate (0.19 g, 0.50 mmol). The reaction mixture was heated to about 70 °C for about 24 h. The solvent was removed under reduced pressure. The residue was partitioned between EtOAc (30 mL) and water (10 mL). The layers were separated and the organic layer was washed with water (10 mL) and brine (2 x 10 mL), dried over anhydrous MgSO₄, filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash chromatography on silica gel eluting with a gradient of 0-10% MeOH in DCM to give 3,3-difluoro-N-(4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)azetidine-1-sulfonamide (0.119 g, 38%): LC/MS (Table 1, Method a) R_t = 2.32 min; MS *m/z* 592 (M+H)⁺.

Preparation #6: 1-methylcyclopropane-1-sulfonyl chloride



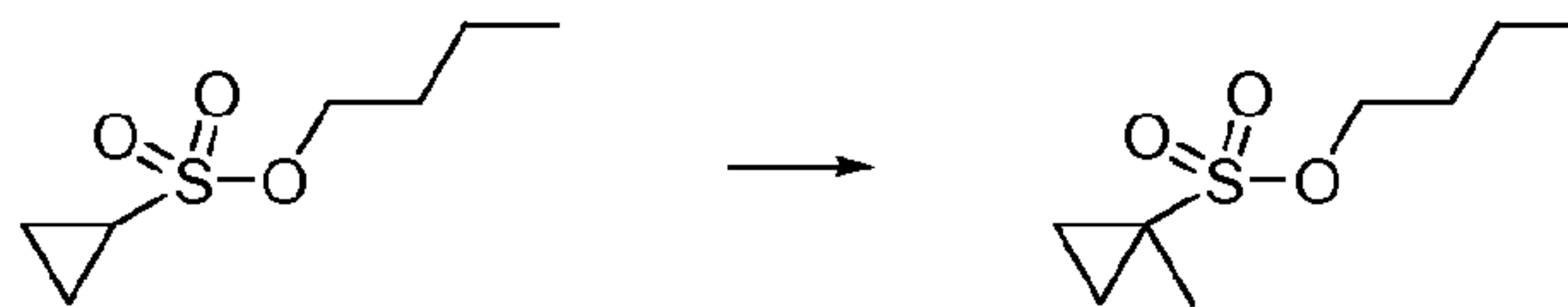
Step A: butyl cyclopropanesulfonate



To a solution of cyclopropanesulfonyl chloride (5.00 g, 35.6 mmol) in *n*-BuOH (20 mL) at -20 °C, pyridine (5.75 mL, 71.1 mmol) was added dropwise. The resulting mixture was stirred for about 16 h while warming slowly to ambient temperature. The solvents were removed under reduced pressure and the residue was partitioned between DCM and water (50 mL each). The organic phase was further washed with brine (40 mL), dried over anhydrous MgSO₄ and concd under reduced pressure to yield *butyl cyclopropanesulfonate* (4.7 g, 74%) as a yellow oil. ¹H

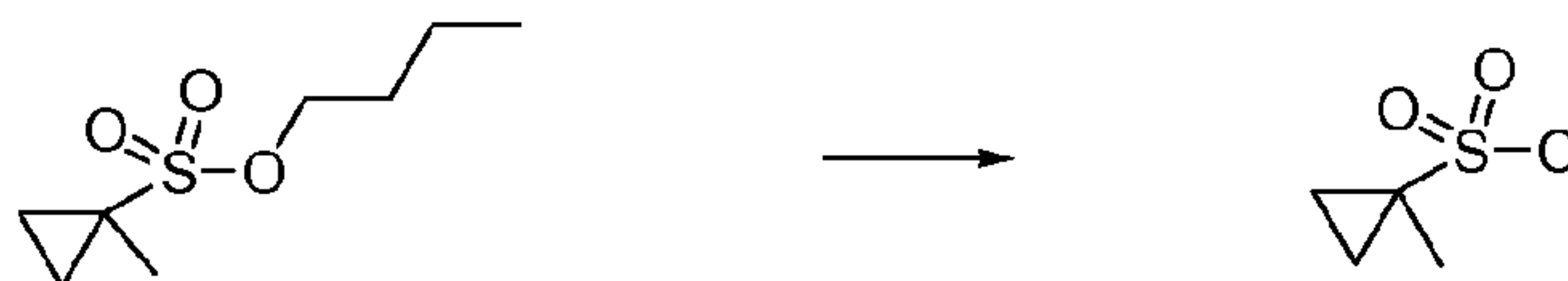
NMR (DMSO- d_6) δ 4.2 (t, 2H), 2.82 (m, 1H), 1.64 (m, 2H), 1.35 (m, 2H), 1.08 (m, 2H), 1.01 (m, 2H), 0.89 (t, 3H).

Step B: butyl 1-methylcyclopropane-1-sulfonate



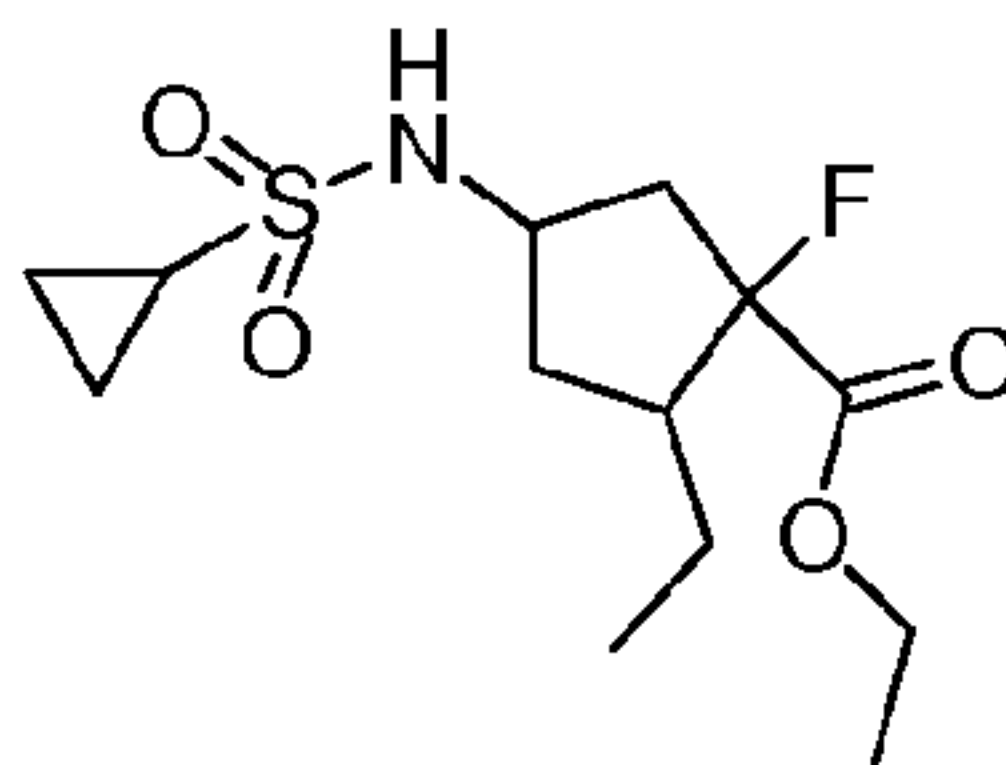
To a solution of butyl cyclopropanesulfonate (1.5 g, 8.4 mmol) in THF (8 mL) at about -78 °C, *n*-BuLi (1.6 M in hexanes, 5.26 mL, 8.42 mmol) and iodomethane (0.684 mL, 10.9 mmol) were added simultaneously and the resulting mixture was stirred at about -78 °C for about 2 h and then at ambient temperature for about 2 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl (7 mL) and the layers were separated. The aqueous layer was back extracted with EtOAc (15 mL) and the combined organic extracts were dried over anhydrous MgSO₄ and concd under reduced pressure. The residue was subjected to silica gel column chromatography (5 to 25% EtOAc in heptane over 30 min) to yield *butyl 1-methylcyclopropane-1-sulfonate* (0.8 g, 49%) as a colorless oil. ¹H NMR (DMSO- d_6) δ 4.17 (t, 2H), 1.62 (m, 2H), 1.43 (s, 3H), 1.35 (m, 2H), 1.22 (m, 2H), 0.94 (m, 2H), 0.88 (t, 3H).

Step C: 1-methylcyclopropane-1-sulfonyl chloride



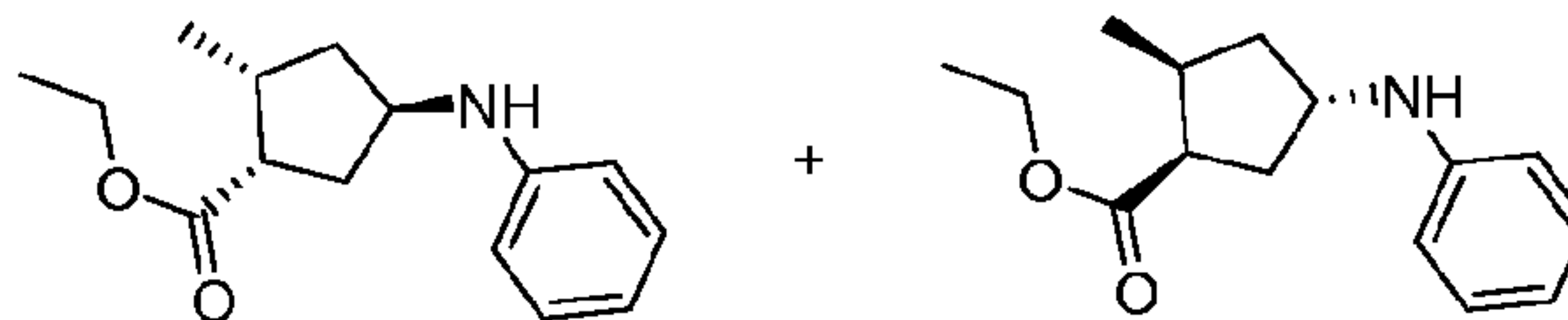
A mixture of butyl 1-methylcyclopropane-1-sulfonate (0.80 g, 4.2 mmol) and potassium thiocyanate (0.404 g, 4.16 mmol) in 1,4-dioxane/water (1:1, 10 mL) was heated at reflux for about 8 h. The reaction was cooled to ambient temperature and the solvents were concd under reduced pressure to yield crude potassium 1-methylcyclopropane-1-sulfonate which was suspended in thionyl chloride (7 mL). DMF (0.05 mL) was added and the mixture was heated at reflux for about 8 h and then cooled. The volatiles were removed under reduced pressure and the residue was dissolved in DCM (20 mL), washed with water (15 mL), dried over anhydrous MgSO₄ and concd under reduced pressure to yield *1-methylcyclopropane-1-sulfonyl chloride* (0.56 g, 86%) as a yellow oil. ¹H NMR (DMSO- d_6) δ 1.82 (br s, 2H), 1.79 (s, 3H), 1.15 (m, 2H).

Preparation #7: ethyl 4-(cyclopropanesulfonamido)-2-ethyl-1-fluorocyclopentanecarboxylate



A solution of ethyl 4-(cyclopropanesulfonamido)-2-ethylcyclopentanecarboxylate (0.630 g, 2.18 mmol, prepared using **K** from Preparation #Y.1 and cyclopropanesulfonyl chloride) in THF (14.5 mL) was cooled to about -78 °C and then LDA (1.8 M in THF/hexane, 3.63 mL, 6.53 mmol) was added dropwise to the reaction mixture over about 30 min. The reaction mixture was stirred at about -78 °C for about 50 min before a solution of *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (2.06 g, 6.53 mmol) in THF (7.3 mL) was added dropwise over about 30 min. The reaction mixture was stirred at about -78 °C for about 1 h and then was warmed to ambient temperature and stirred for about 16 h. Saturated aqueous NH₄Cl (100 mL) was added. The reaction mixture was partitioned with EtOAc (50 mL). The aqueous layer was further extracted with EtOAc (2 x 50 mL). The combined organic layers were concd under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of 0-60% EtOAc in heptane to yield *ethyl 4-(cyclopropanesulfonamido)-2-ethyl-1-fluorocyclopentanecarboxylate* (0.41 g, 46%) as clear oil: LC/MS (Table 1, Method **b**) R_t = 2.12 min; MS *m/z*: 306 (M-H)⁻.

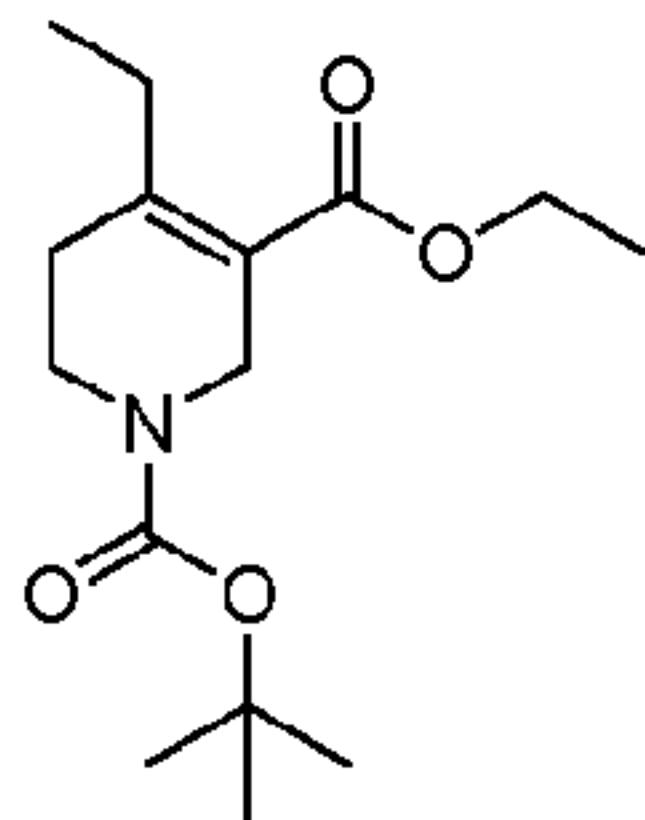
Preparation #8: (1*S*,2*R*,4*R*)-ethyl 2-methyl-4-(phenylamino)cyclopentanecarboxylate and (1*R*,2*S*,4*S*)-ethyl 2-methyl-4-(phenylamino)cyclopentanecarboxylate



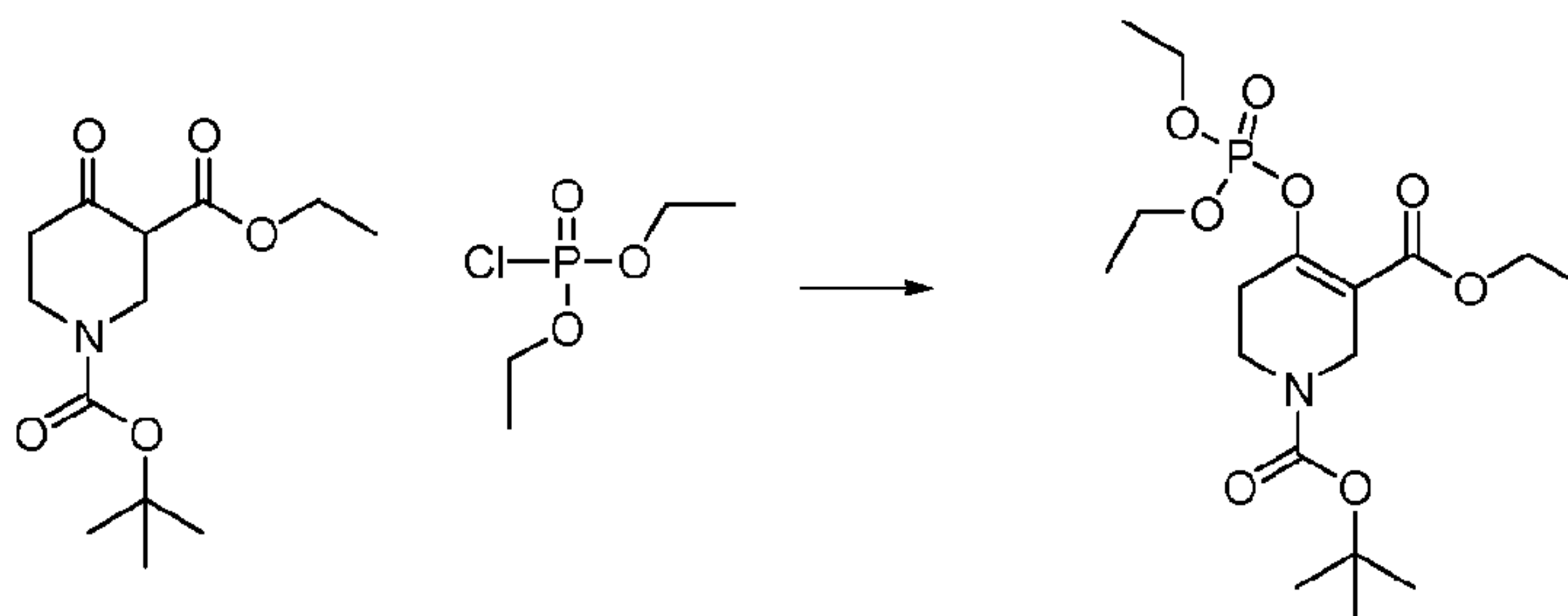
A solution of ethyl 4-hydroxy-2-methylcyclopentanecarboxylate (1.81 g, 10.5 mmol, prepared using **P** from Example #7, step G and NaBH₄) and pyridine (1.28 mL, 15.8 mmol) in THF (52.5 mL) was cooled to about 0 °C. Methanesulfonyl chloride (0.90 mL, 12 mmol) was added dropwise. The reaction mixture was stirred at ambient temperature for about 16 h then partitioned between water (50 mL) and DCM (30 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 30 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concd under reduced pressure to give a white solid. The resulting solid was mixed with aniline (78.0 g, 841 mmol) and heated at about 90 °C for about 16 h. The reaction mixture

was concd under reduced pressure and purified by silica gel chromatography eluting with a gradient of 20-100% EtOAc in DCM to yield *(1S,2R,4R)*-ethyl 2-methyl-4-(phenylamino)cyclopentanecarboxylate and *(1R,2S,4S)*-ethyl 2-methyl-4-(phenylamino)cyclopentanecarboxylate with 29 mol% aniline as an excipient (2.73 g, 75%) as a dark oil: LC/MS (Table 1, Method **b**) $R_t = 2.67$ min; MS m/z : 248 (M+H)⁺.

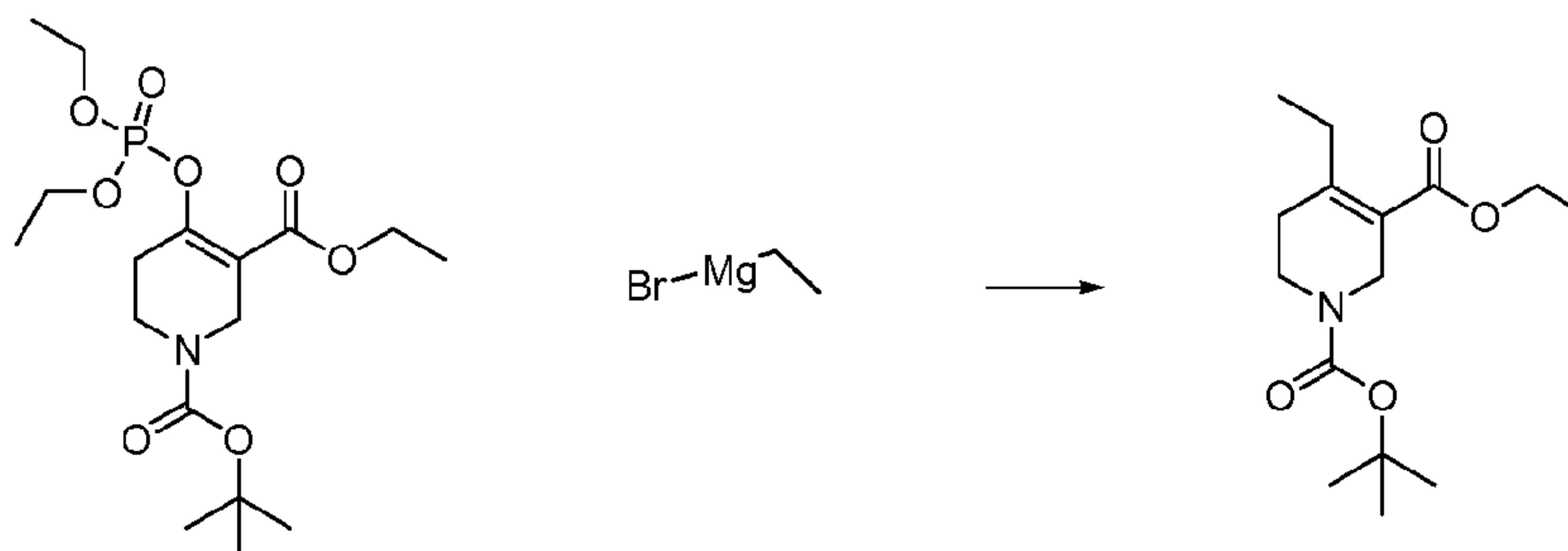
Preparation #9: 1-*tert*-butyl 3-ethyl 4-ethyl-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate



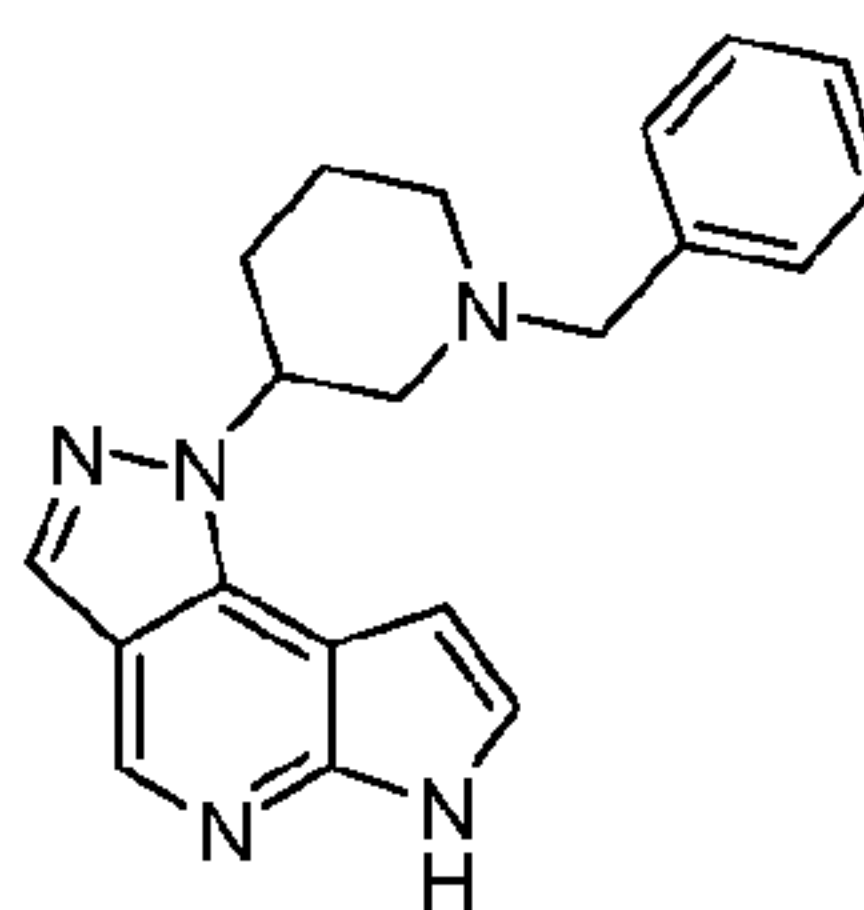
Step A: 1-*tert*-butyl 3-ethyl 4-(diethoxyphosphoryloxy)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate

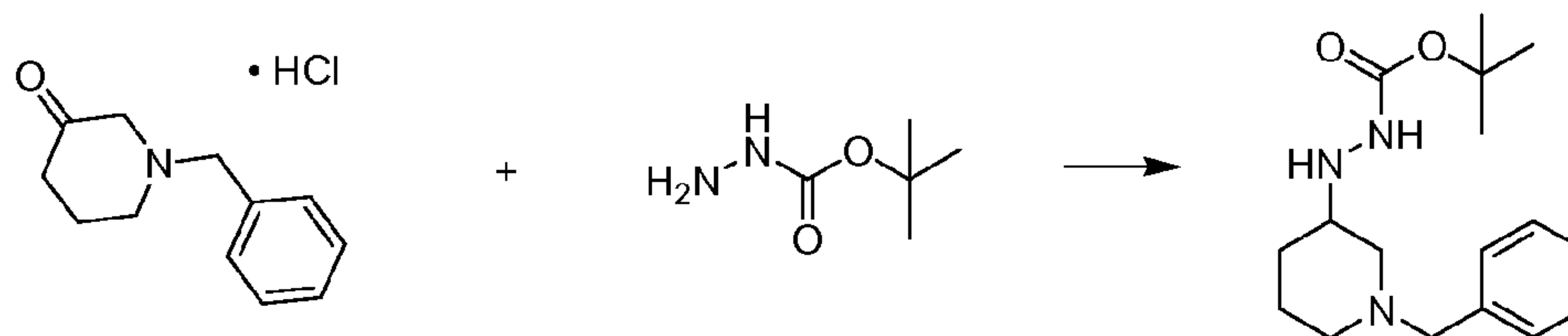


To a solution of 1-*tert*-butyl 3-ethyl 4-oxopiperidine-1,3-dicarboxylate (11.50 g, 42.4 mmol, ASDI) in MTBE (500 mL) at about -78 °C was added NaHMDS (1 M in THF, 53.0 mL, 53.0 mmol). After about 1 h, diethyl phosphorochloridate (7.62 mL, 53.0 mmol) was added to the reaction mixture. After about 30 min, the reaction mixture was allowed to warm to ambient temperature and stirred for about 16 h. The reaction mixture was partitioned between saturated aqueous NH₄Cl (100 mL) and EtOAc (50 mL). The layers were separated. The aqueous layer was further extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concd under reduced pressure. The crude material was purified by silica gel chromatography eluting with a gradient of 0-100% EtOAc in heptane to yield 1-*tert*-butyl 3-ethyl 4-(diethoxyphosphoryloxy)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (8.55 g, 49%) as a yellow oil: LC/MS (Table 1, Method **b**) $R_t = 2.35$ min; MS m/z : 408 (M+H)⁺.

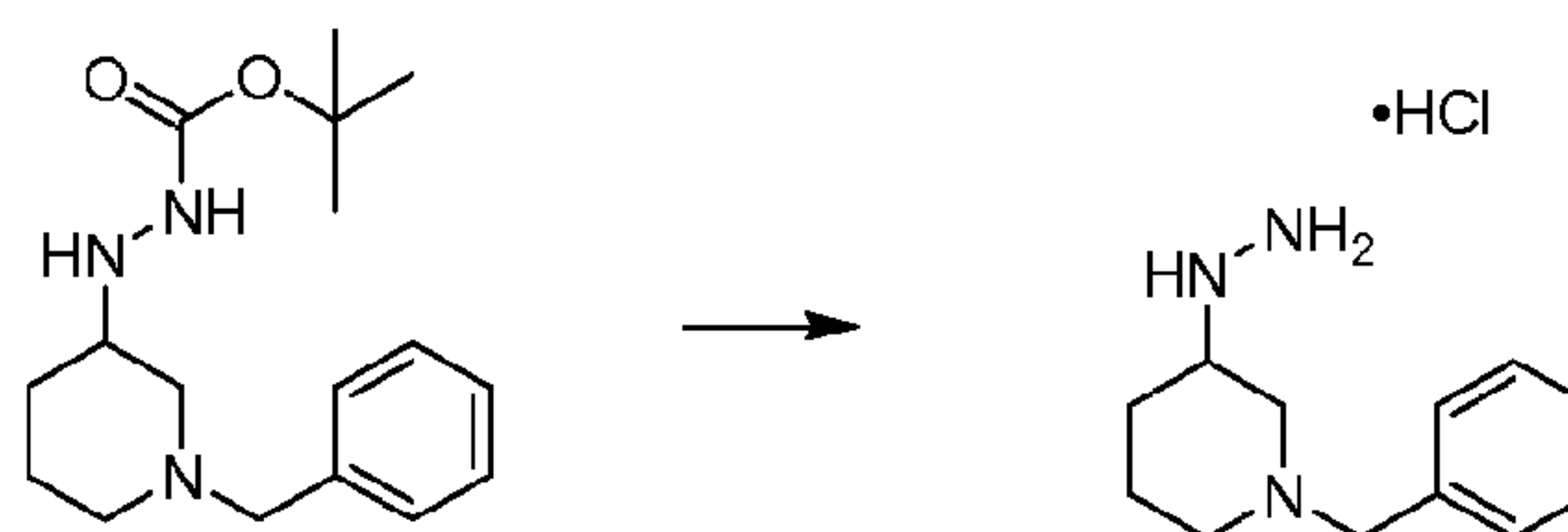
Step B: 1-*tert*-butyl 3-ethyl 4-ethyl-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate

To a slurry of CuI (4.21 g, 22.12 mmol) in THF (61.4 mL) at about 0 °C was added ethylmagnesium bromide (1.0 M in THF, 44.2 mL, 44.2 mmol) dropwise. After about 30 min, the reaction mixture was cooled to about -78 °C and a solution of 1-*tert*-butyl 3-ethyl 4-(diethoxyphosphoryloxy)-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (7.51 g, 18.43 mmol) in THF (61 mL) was added slowly. The reaction mixture was stirred at about -78 °C for about 1 h then warmed to about 0 °C. The reaction mixture was stirred at about 0 °C for about 1.5 h, then warmed to ambient temperature and stirred for about 1 h. The reaction mixture was cooled to about -78 °C and saturated aqueous NH₄Cl (100 mL) was slowly added. The reaction mixture was allowed to warm to ambient temperature and stirred for about 16 h. The mixture was extracted with Et₂O (100 mL). The aqueous layer was further extracted with Et₂O (2 x 50 mL). The organic layers were combined, washed with saturated aqueous NH₄Cl (50 mL), dried over anhydrous Na₂SO₄, filtered, concd under reduced pressure and purified by silica gel chromatography eluting with a gradient of 0-30% EtOAc in heptane to yield 1-*tert*-butyl 3-ethyl 4-ethyl-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (0.785 g, 15%) as a clear oil: ¹H NMR (CDCl₃) δ 4.23 (d, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 3.48 (t, *J* = 5.8 Hz, 2H), 2.52 (q, *J* = 7.5 Hz, 2H), 2.28 (t, *J* = 5.8 Hz, 2H), 1.51 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.09 (t, *J* = 7.5 Hz, 3H).

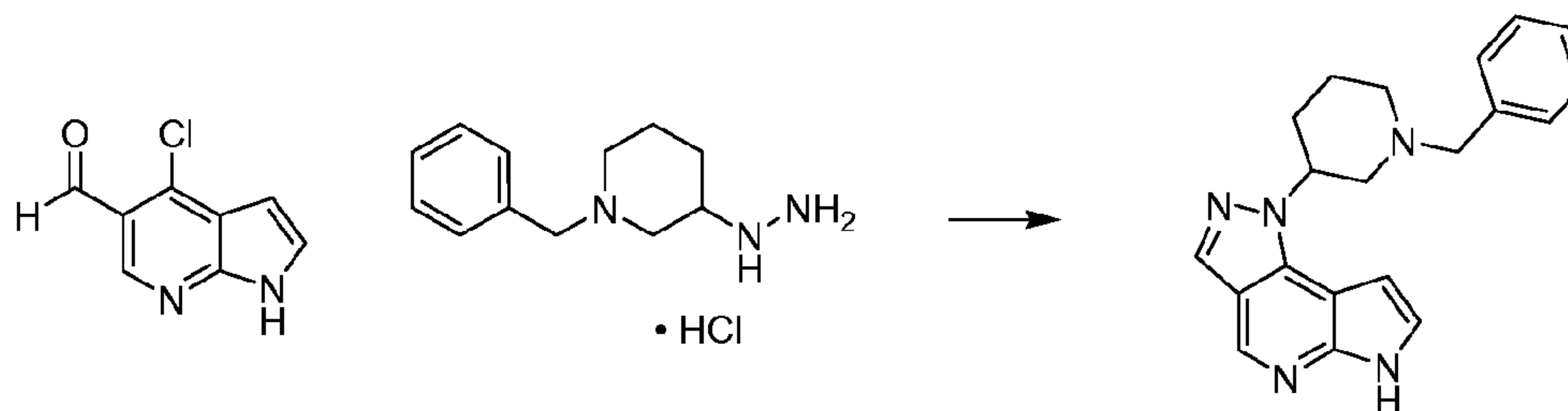
Preparation #10: 1-(1-benzylpiperidin-3-yl)-1,6-dihydropyrazolo[3,4-*d*]pyrrolo[2,3-*b*]pyridine

Step A: *tert*-butyl 2-(1-benzylpiperidin-3-yl)hydrazinecarboxylate

A mixture of 1-benzylpiperidin-3-one hydrochloride (1.00 g, 4.10 mmol), *tert*-butyl hydrazinecarboxylate (0.596 g, 4.51 mmol), and AcOH (0.470 mL, 8.21 mmol) in DCE (20 mL) was stirred at ambient temperature for about 1 h then NaCNBH₃ (0.258 g, 4.10 mmol) was added. The reaction mixture was stirred at ambient temperature for about 16 h. The reaction mixture was quenched by the addition of saturated aqueous NaHCO₃ (50 mL). The organic layer was separated, concd under reduced pressure and purified by RP-HPLC (Table 1, Method **h**) to afford *tert*-butyl 2-(1-benzylpiperidin-3-yl)hydrazinecarboxylate (1.25 g, 100%) as a clear oil: LC/MS (Table 1, Method **b**) R_t = 1.66 min; MS *m/z*: 306 (M+H)⁺.

Step B: 1-benzyl-3-hydrazinylpiperidine hydrochloride

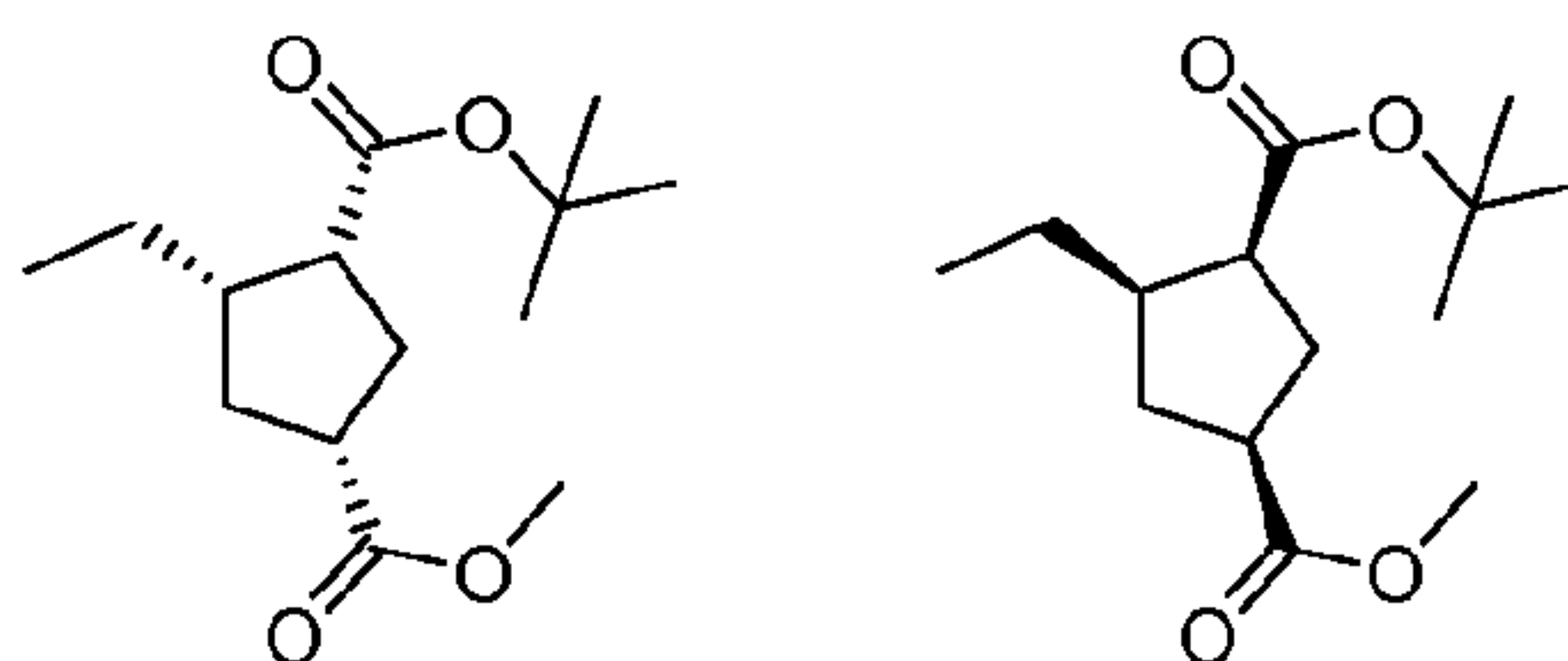
A solution of *tert*-butyl 2-(1-benzylpiperidin-3-yl)hydrazinecarboxylate (1.25 g, 4.10 mmol) in aqueous HCl (6 N, 6.83 mL, 41.0 mmol) was stirred at ambient temperature for about 8 h. The solvent was removed under reduced pressure to give crude 1-benzyl-3-hydrazinylpiperidine hydrochloride (1.45 g, 112%) as a white solid which was used without further purification: LC/MS (Table 1, Method **b**) R_t = 0.66 min; MS *m/z*: 206 (M+H)⁺.

Step C: 1-(1-benzylpiperidin-3-yl)-1,6-dihydropyrazolo[3,4-*d*]pyrrolo[2,3-*b*]pyridine

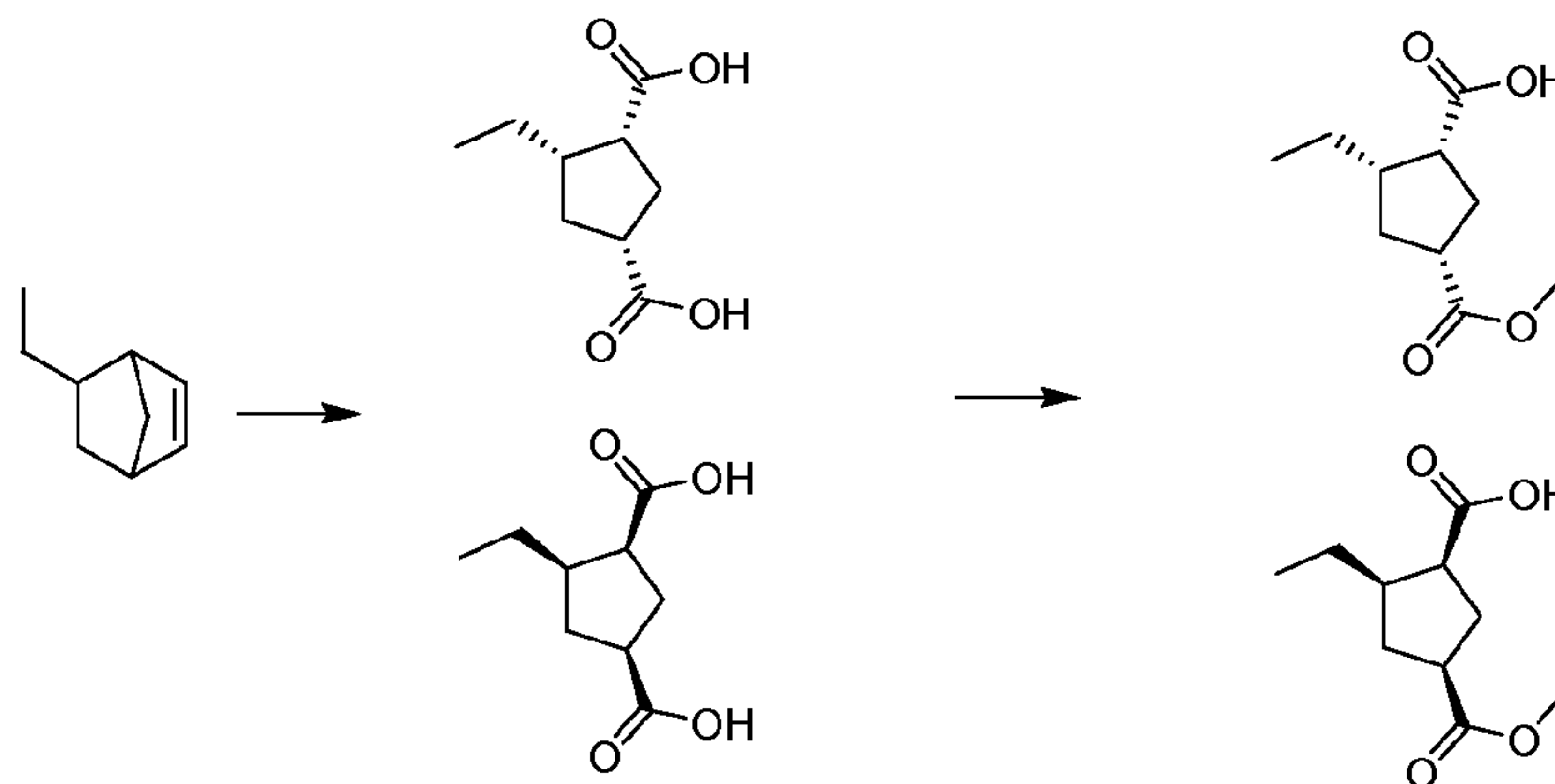
4-Chloro-1H-pyrrolo[2,3-*b*]pyridine-5-carbaldehyde (0.40 g, 2.21 mmol, Adcis) and 1-benzyl-3-hydrazinylpiperidine hydrochloride (1.39 g, 4.43 mmol) were suspended in *n*-BuOH (11.1 mL).

The mixture was heated at about 90 °C for about 3 h and then heated at about 120 °C for about 5 h. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of 0-5% MeOH in DCM to yield *1-(1-benzylpiperidin-3-yl)-1,6-dihydropyrazolo[3,4-d]pyrrolo[2,3-b]pyridine* (0.105 g, 14%) as a brown oil: LC/MS (Table 1, Method **b**) $R_t = 1.53$ min; MS m/z : 332 (M+H)⁺.

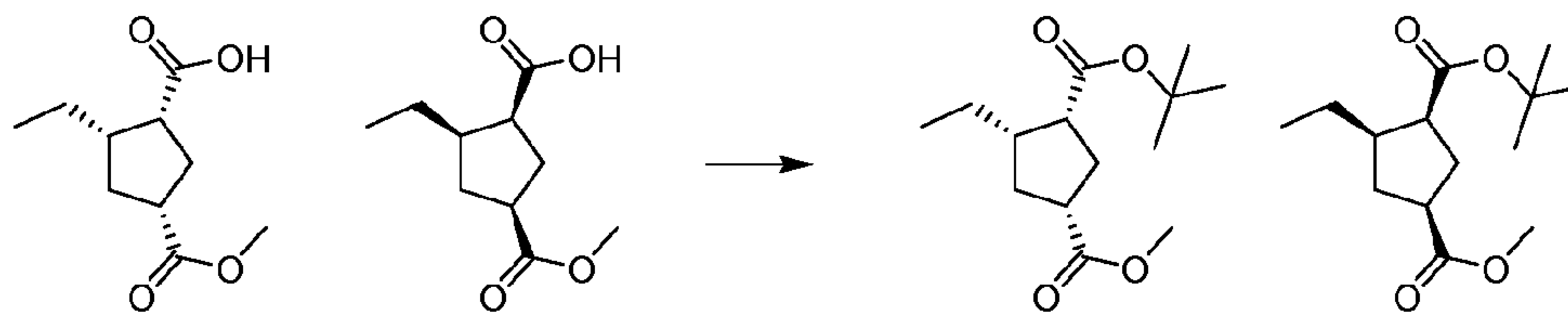
Preparation #11: *cis*-3-*tert*-butyl 1-methyl 4-ethylcyclopentane-1,3-dicarboxylate



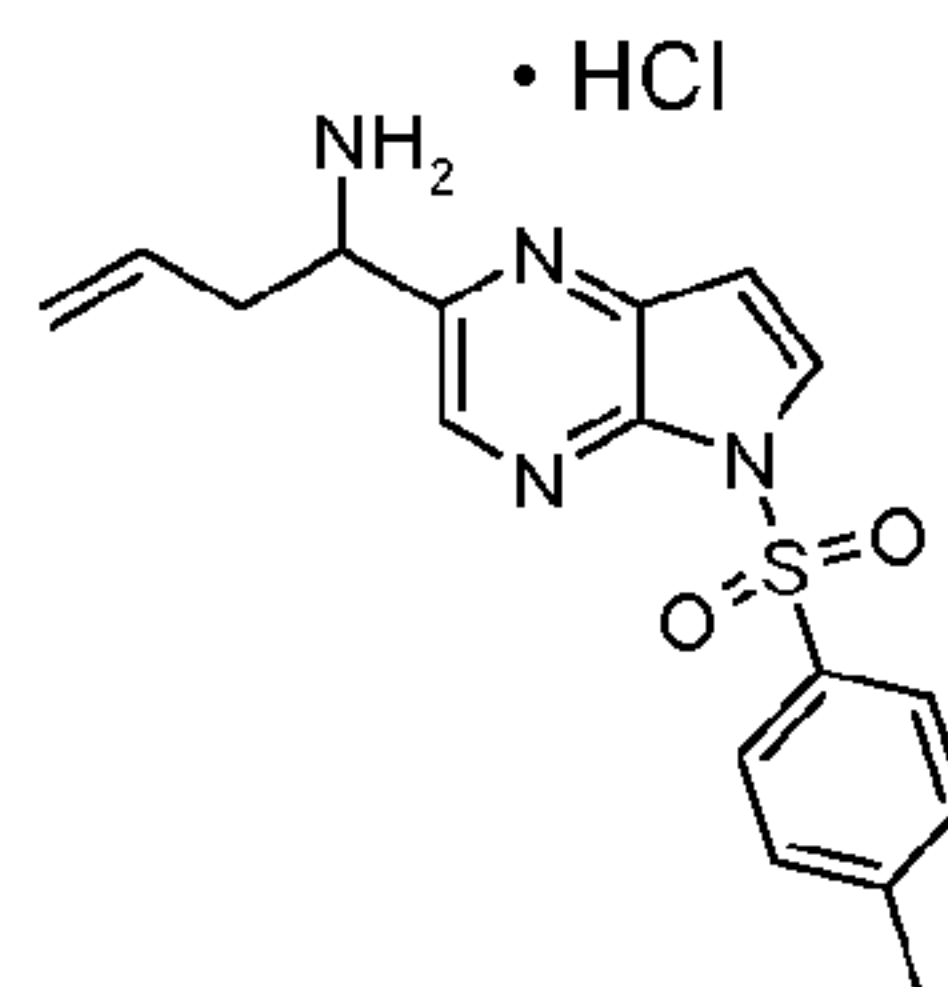
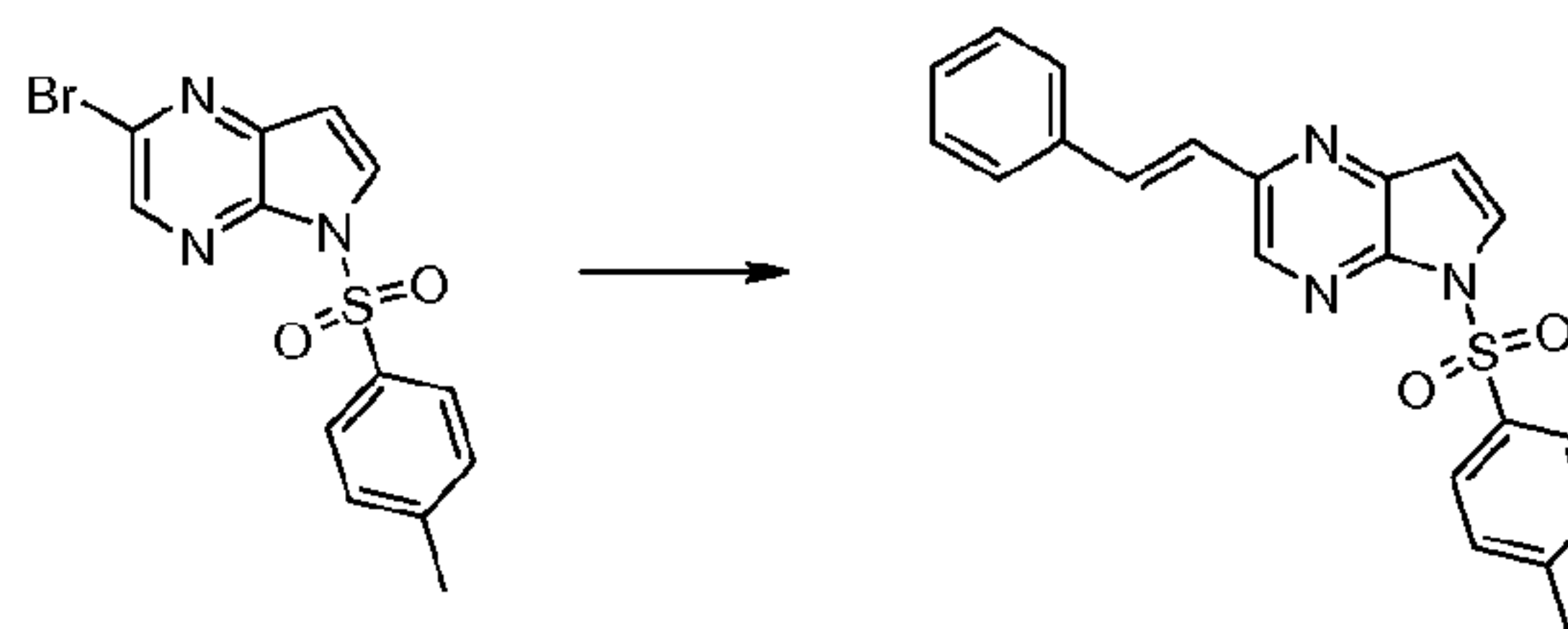
Step A: *cis*-2-ethyl-4-(methoxycarbonyl)cyclopentanecarboxylic acid



Ruthenium (III) chloride hydrate (0.203 g, 0.900 mmol) was added to a mixture of 5-ethylbicyclo[2.2.1]hept-2-ene (5.00 g, 40.9 mmol, ChemSampCo) and sodium periodate (35.0 g, 164 mmol) in water (117 mL), MeCN (78 mL) and EtOAc (78 mL). The reaction mixture was stirred at ambient temperature for about 16 h. The reaction mixture was filtered, extracted with Et₂O (2 x 100 mL). The aqueous layer was further extracted with Et₂O (3 x 100 mL). The organic layers were combined, washed with brine (100 mL), dried over anhydrous MgSO₄, filtered, and concd under reduced pressure. The residue was dissolved in Ac₂O (20 mL, 24 mmol) and heated at reflux for about 4 h. The reaction mixture was cooled to ambient temperature and the solvent was removed under reduced pressure. MeOH (40 mL) was added and the reaction mixture was heated at reflux for about 6 h. The solvent was removed under reduced pressure to yield *cis*-2-ethyl-4-(methoxycarbonyl)cyclopentanecarboxylic acid (4.84 g, 59%) as a brown oil: LC/MS (Table 1, Method **b**) $R_t = 1.91$ min; MS m/z : 201 (M+H)⁺.

Step B: *cis*-3-*tert*-butyl 1-methyl 4-ethylcyclopentane-1,3-dicarboxylate

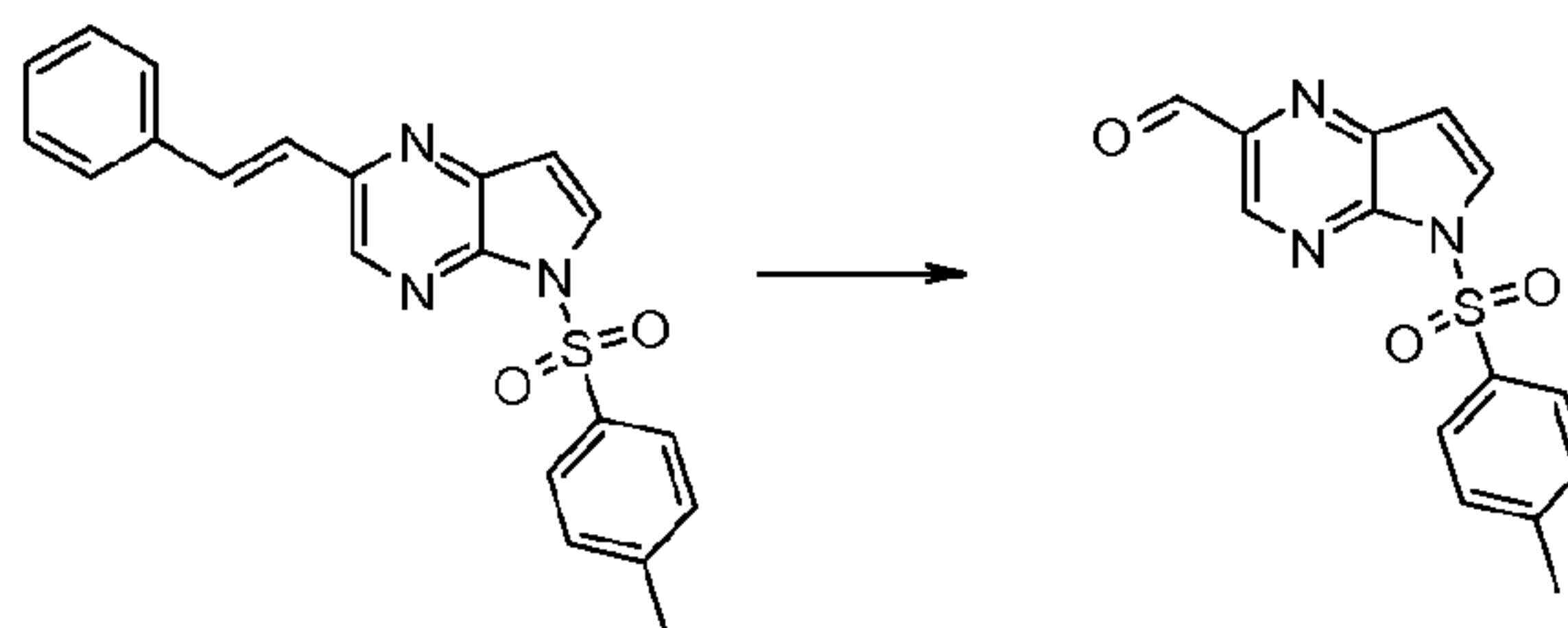
A mixture of *cis*-2-ethyl-4-(methoxycarbonyl)cyclopentanecarboxylic acid (4.50 g, 22.47 mmol) in SOCl_2 (8.20 mL, 112 mmol) was stirred at ambient temperature for about 16 h. The solvent was removed under reduced pressure. The resulting residue was dissolved in *t*-BuOH (22.5 mL). The reaction mixture was stirred at ambient temperature for about 16 h. The solvent was removed under reduced pressure. The residue was dissolved in water (50 mL) and DCM (100 mL). The organic layer was separated, washed with saturated aqueous NaHCO_3 (50 mL), dried over anhydrous Na_2SO_4 , filtered, and concd under reduced pressure to give *cis*-3-*tert*-butyl 1-methyl 4-ethylcyclopentane-1,3-dicarboxylate (3.94 g, 68%) as a dark brown oil: LC/MS (Table 1, Method b) $R_t = 2.86$ min; MS m/z : 257 ($\text{M}+\text{H}$)⁺.

Preparation #12: 1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)but-3-en-1-amine hydrochloride**Step A: (*E*)-2-styryl-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine**

To a solution of 2-bromo-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine (3.1 g, 8.8 mmol, Example #1, Step B), $\text{PdCl}_2(\text{dppf}) \cdot \text{DCM}$ (0.719 g, 0.880 mmol) and (*E*)-styrylboronic acid (2.60 g, 17.6 mmol) in THF (3 mL) and water (2 mL) was added Na_2CO_3 (2.33 g, 22.0 mmol). The reaction mixture was degassed with argon for about 5 min. The reaction mixture was heated at about 50 °C. After about 24 h, additional $\text{PdCl}_2(\text{dppf}) \cdot \text{DCM}$ (0.719 g, 0.880 mmol), (*E*)-styrylboronic acid (2.60 g, 17.6 mmol) and Na_2CO_3 (2.33 g, 22.0 mmol) were added to the reaction mixture. After heating at about 50 °C for about 48 h, the reaction mixture was cooled to ambient temperature and diluted with DCM (200 mL) and water (200 mL). The organic layer was separated, dried over anhydrous

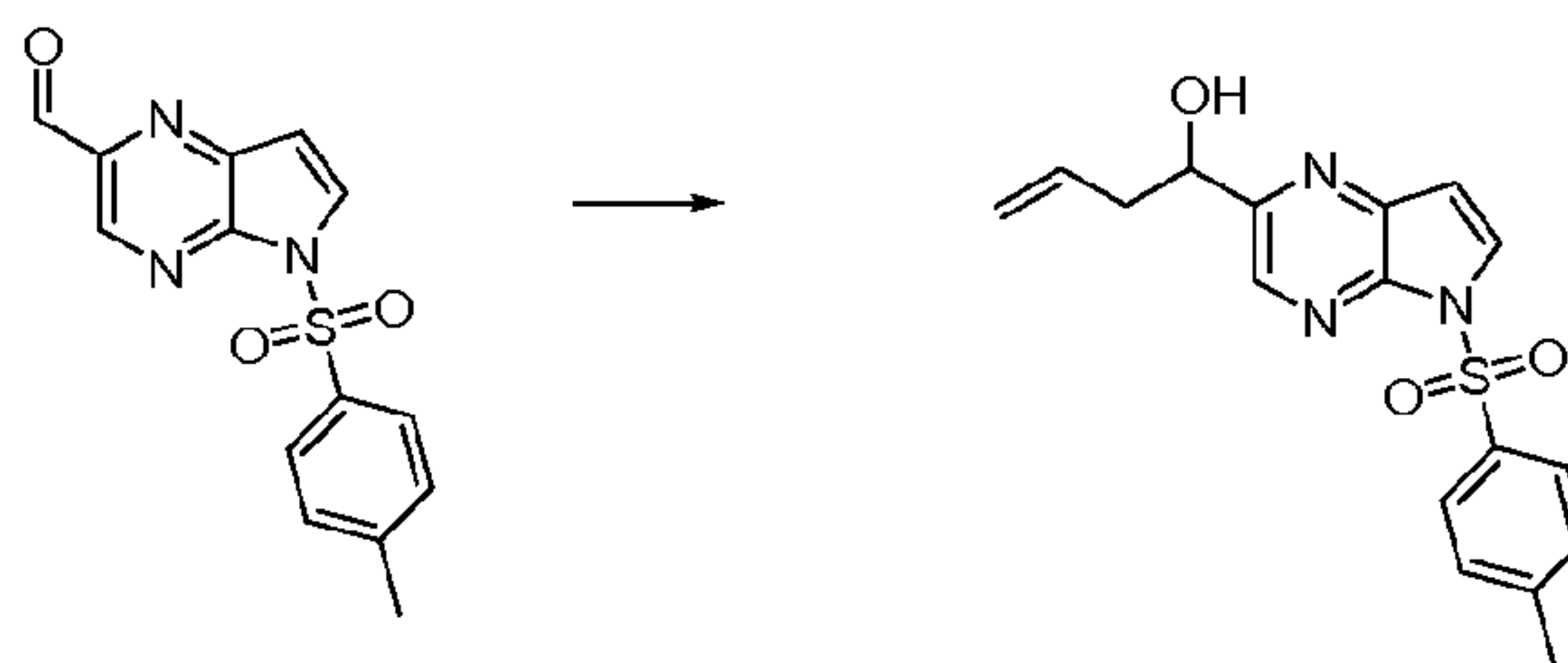
Na₂SO₄, filtered, and concd under reduced pressure. Purification by chromatography over silica gel eluting with a gradient of 20-60% EtOAc in heptane containing 5% DCM provided (*E*)-2-styryl-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine as a yellow solid (1.2 g, 36%): LC/MS (Table 1, Method **a**) R_t = 2.99 min; MS *m/z*: 376 (M+H)⁺.

Step B: 5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine-2-carbaldehyde



To a solution of (*E*)-2-styryl-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine (1.2 g, 3.2 mmol) in 1,4-dioxane (20 mL) and water (2.0 mL) was added sodium periodate (2.73 g, 12.8 mmol) followed by osmium tetroxide (2.5 wt% in *t*-BuOH, 4.01 mL, 0.320 mmol). The reaction mixture was stirred for about 1 day at ambient temperature and then additional sodium periodate (2.73 g, 12.78 mmol) and osmium tetroxide (2.5 wt% in *t*-BuOH, 4.01 mL, 0.320 mmol) were added. After stirring for about 2 days, a solution of 10% aqueous Na₂S₂O₃ (100 mL) and EtOAc (100 mL) was added. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concd under reduced pressure to give a solid, which was triturated with heptane to remove benzaldehyde. The resulting solid was dried *in vacuo* to provide 5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine-2-carbaldehyde as a brown solid (0.77 g, 80%): LC/MS (Table 1, Method **a**) R_t = 2.01 min; MS *m/z*: 334 (M+H)⁺.

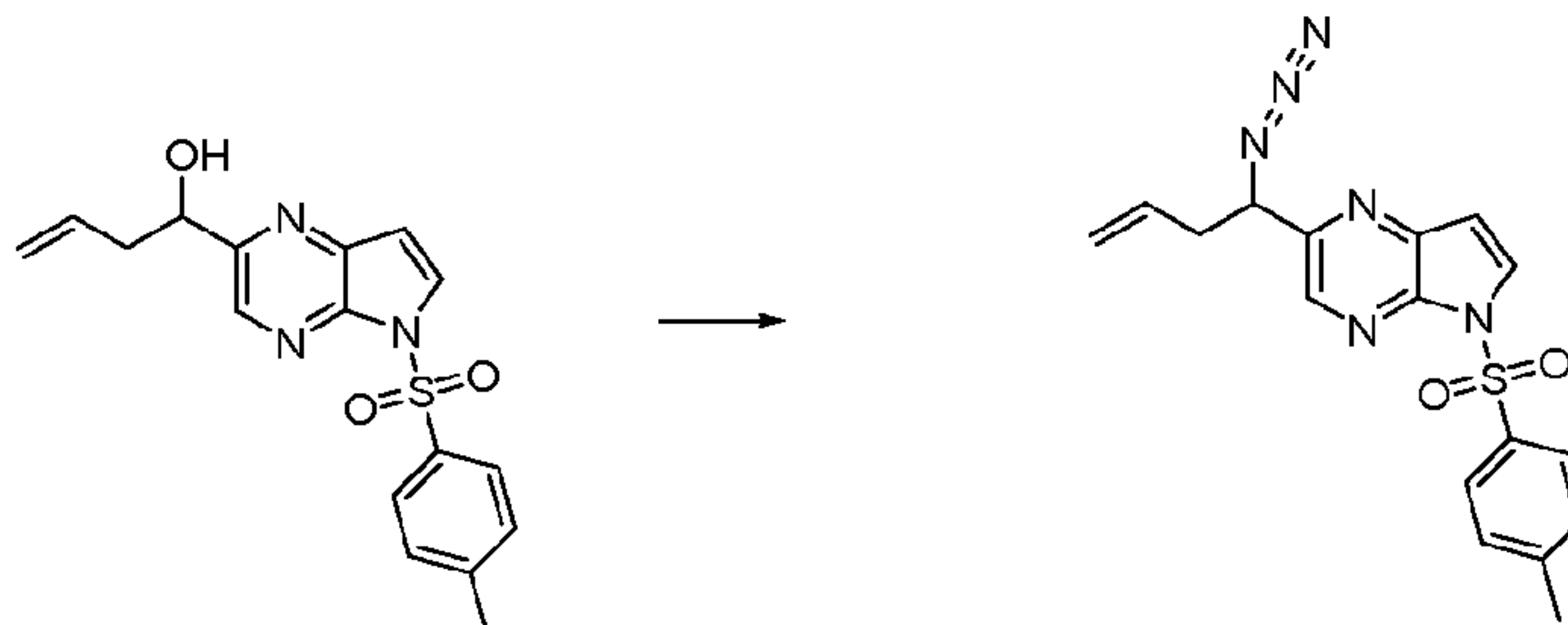
Step C: 1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)but-3-en-1-ol



To a solution of 5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine-2-carbaldehyde (5.1 g, 17 mmol) in THF (100 mL) and water (33.3 mL) was added 3-bromoprop-1-ene (2.86 mL, 33.9 mmol) followed by indium (3.89 g, 33.9 mmol). The reaction mixture was stirred for about 15 h at ambient temperature and then aqueous HCl (1 N, 150 mL) and EtOAc (150 mL) were added. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered, concd *in vacuo* and purified by chromatography on silica gel eluting with 20-60% EtOAc in heptane to provide 1-(5-tosyl-5*H*-

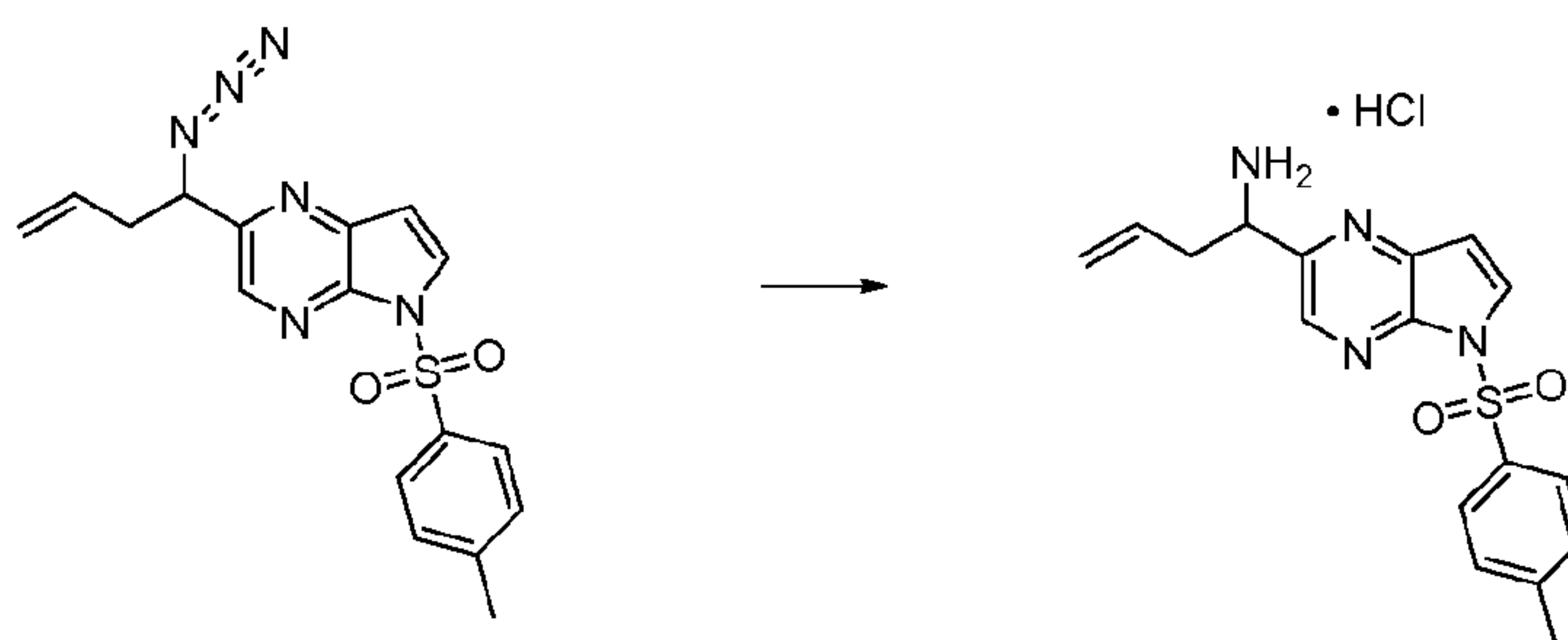
*pyrrolo[2,3-*b*]pyrazin-2-yl)but-3-en-1-ol* (4 g, 69%) as a thick oil: LC/MS (Table 1, Method **a**) $R_t = 2.30$ min; MS m/z : 344 (M+H)⁺.

Step D: 2-(1-azidobut-3-enyl)-5-tosyl-5H-pyrrolo[2,3-*b*]pyrazine



To a solution of 1-(5-tosyl-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)but-3-en-1-ol (0.14 g, 0.41 mmol) in DCM (10 mL) was added thionyl chloride (0.045 mL, 0.61 mmol). The reaction mixture was stirred for about 8 h at ambient temperature and then EtOAc and saturated aqueous NaHCO₃ (10 mL each) were added. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered and coned *in vacuo*. The crude chloride was dissolved in DMF (10 mL) and sodium azide (0.159 g, 2.45 mmol) was added to the reaction mixture. The reaction mixture was stirred for about 15 h at ambient temperature and then EtOAc and saturated aqueous NaHCO₃ (10 mL each) were added to the reaction mixture. The organic layer was separated, coned *in vacuo*, and purified by chromatography on silica gel eluting with 10-60% EtOAc in heptane to provide 2-(1-azidobut-3-enyl)-5-tosyl-5H-pyrrolo[2,3-*b*]pyrazine (0.153 g, 87%) as an oil: LC/MS (Table 1, Method **a**) $R_t = 2.84$ min; MS m/z : 369 (M+H)⁺.

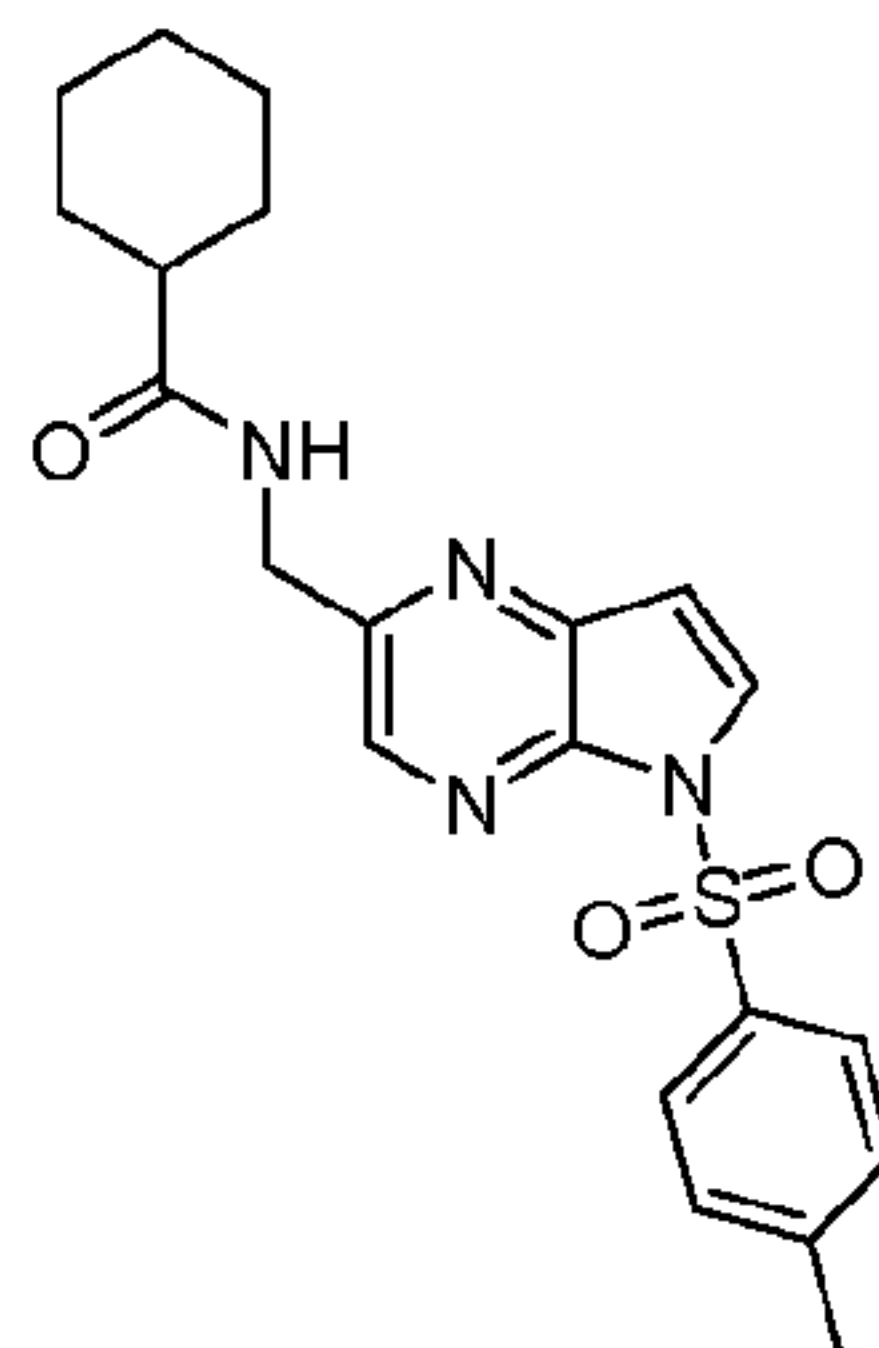
Step E: 1-(5-tosyl-5H-pyrrolo[2,3-*b*]pyrazin-2-yl)but-3-en-1-amine hydrochloride



To a solution of 2-(1-azidobut-3-enyl)-5-tosyl-5H-pyrrolo[2,3-*b*]pyrazine (3.90 g, 10.6 mmol) in THF (60 mL) and water (30 mL) was added triphenylphosphine (3.33 g, 12.7 mmol). The reaction mixture was heated to about 50 °C for about 15 h. The reaction mixture was cooled to ambient temperature and coned *in vacuo*. The residue was dissolved in EtOAc (30 mL) and HCl (gas) was added until a pH of about 1 was maintained followed by the addition of Et₂O to induce precipitate formation. After stirring for about 15 h, the precipitate was collected by filtration to

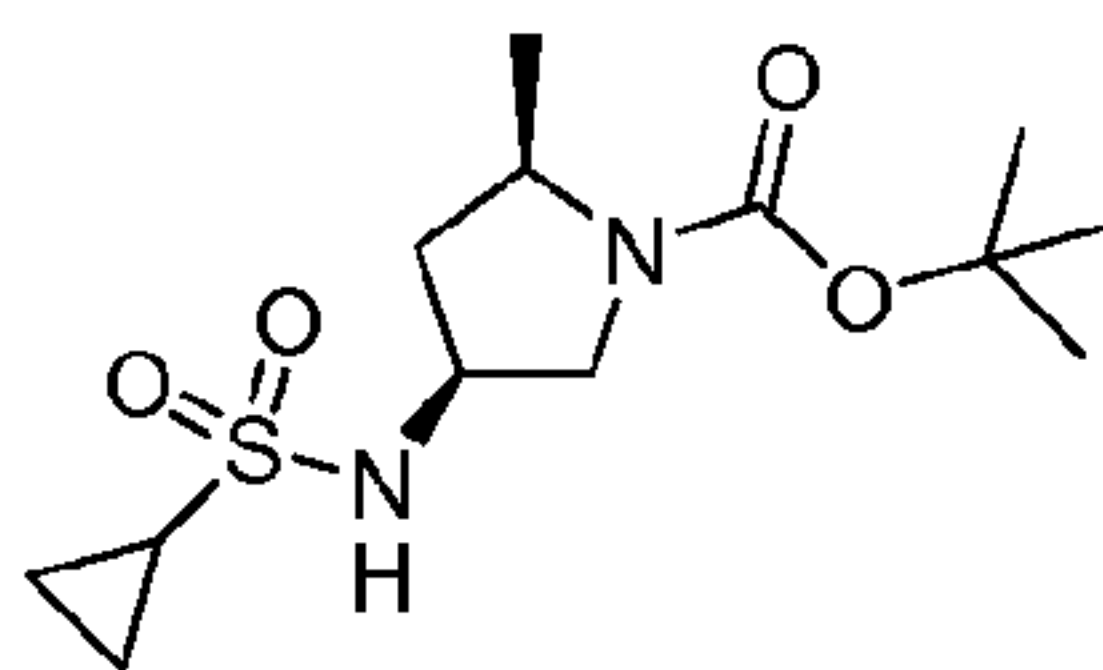
provide *1-(5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)but-3-en-1-amine hydrochloride* (2.5 g, 62%) as a tan solid: LC/MS (Table 1, Method **a**) R_t = 1.80 min; MS m/z : 343 (M+H)⁺.

Preparation #13: *N-((5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)methyl)cyclohexanecarboxamide*



To a slurry of (5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)methanamine hydrochloride (0.50 g, 1.476 mmol, Example #5, Step C) in DCM (10 mL) was added cyclohexanecarbonyl chloride (0.221 mL, 1.623 mmol) followed by DIEA (0.644 mL, 3.69 mmol). The reaction mixture was stirred for about 4 h at ambient temperature and then saturated aqueous NaHCO₃ (20 mL) and DCM (20 mL) were added to the reaction mixture. The organic layer was separated, concd *in vacuo*, and purified by chromatography on silica gel (40 g) eluting with 20-80% EtOAc in DCM to provide *N-((5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)methyl)cyclohexanecarboxamide* (0.49 g, 80%) as a colorless solid: LC/MS (Table 1, Method **a**) R_t = 2.40 min; MS m/z : 413 (M+H)⁺.

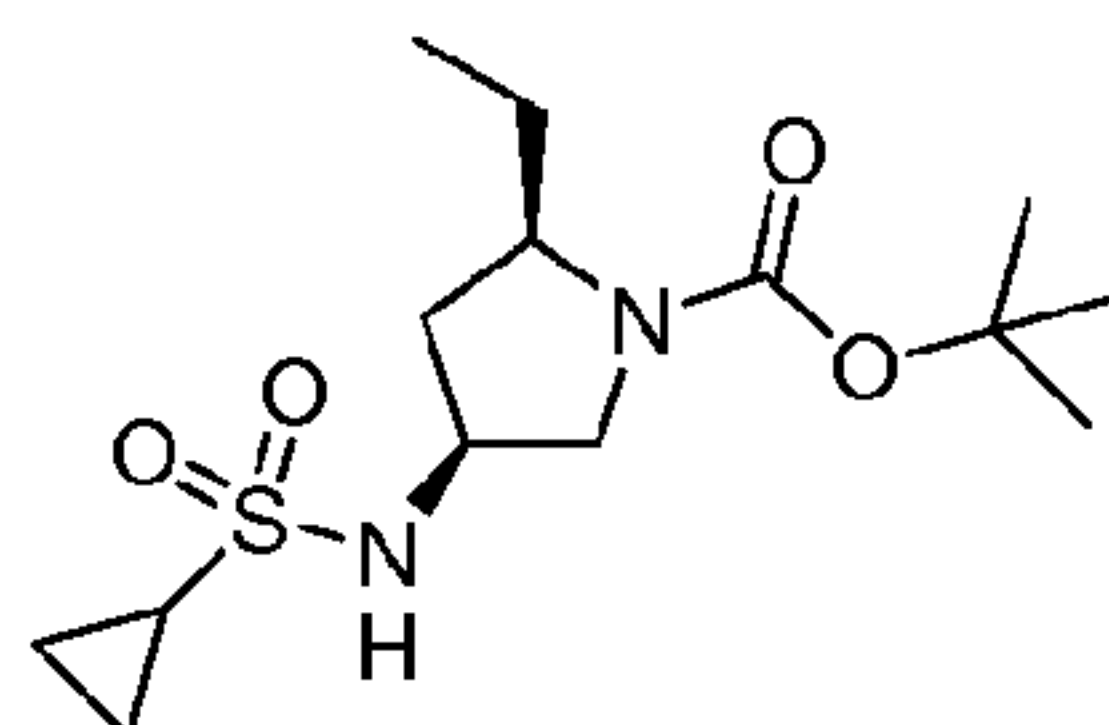
Preparation #14*: (2*R*,4*S*)-*tert*-butyl 4-(cyclopropanesulfonamido)-2-methylpyrrolidine-1-carboxylate



To a slurry of 20 wt% Pd(OH)₂ on C (0.605 g, 0.862 mmol) in EtOH (75 mL) was added a solution of (2*R*,4*S*)-*tert*-butyl 4-azido-2-methylpyrrolidine-1-carboxylate (3.9 g, 17 mmol, synthesized as described in Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Cepa, V. G.; Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1598-1611) in EtOH (25 mL). The reaction mixture was sparged with hydrogen and an atmosphere of hydrogen was maintained via balloon. The reaction mixture was stirred for about 2 h at ambient temperature and then was filtered and concd *in vacuo*. The residue was dissolved in DCM (100 mL), cooled to about 0 °C and TEA (6.01 mL, 43.1 mmol) was added followed by cyclopropanesulfonyl chloride (2.67 g, 19.0 mmol). The reaction mixture was stirred at ambient temperature for about 15 h, saturated

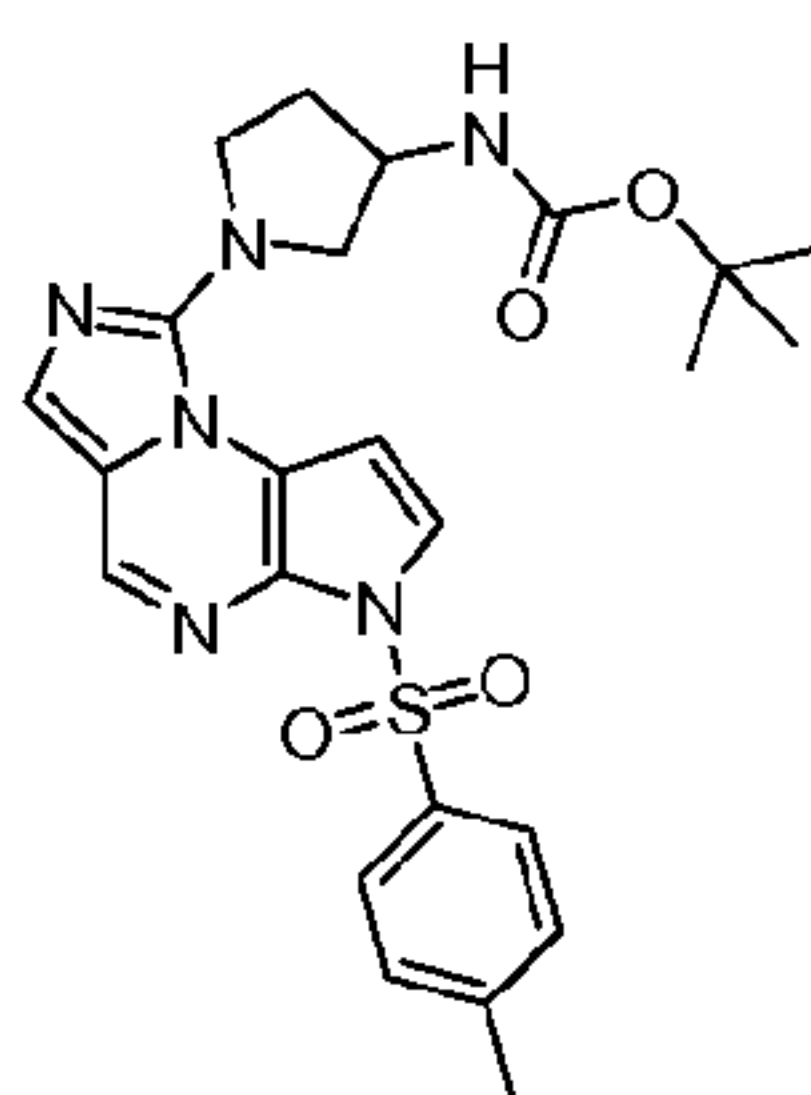
aqueous NaHCO₃ (50 mL) was added to the reaction mixture and the organic layer was separated, coned *in vacuo*, and purified by chromatography on silica gel (80 g) eluting with 20-80% EtOAc in heptane to provide *(2R,4S)*-*tert*-butyl 4-(cyclopropanesulfonamido)-2-methylpyrrolidine-1-carboxylate (2.55 g, 48%) as an oil: LC/MS (Table 1, Method a) R_t = 1.98 min (ELSD); MS *m/z*: 305 (M+H)⁺.

Preparation #15*: *(2R,4S)*-*tert*-butyl 4-(cyclopropanesulfonamido)-2-ethylpyrrolidine-1-carboxylate



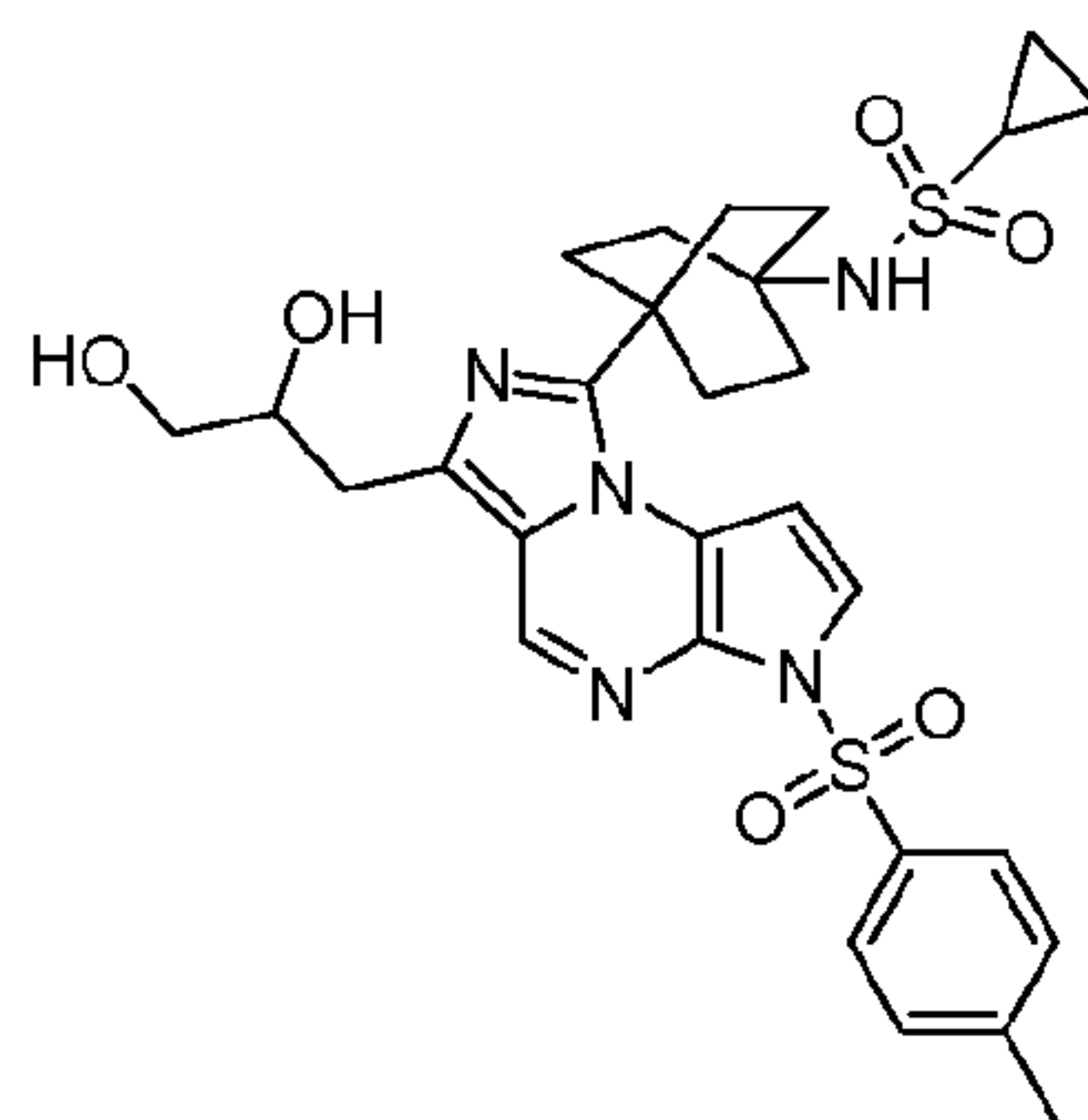
To a slurry of 20 wt% Pd(OH)₂ on C (0.044 g, 0.062 mmol) in EtOH (30 mL) was added a solution of *(2R,4S)*-*tert*-butyl 4-azido-2-ethylpyrrolidine-1-carboxylate (1.5 g, 6.2 mmol, synthesized as described in Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Cepa, V. G.; Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1598-1611) in EtOH (10 mL). The reaction mixture was sparged with hydrogen and an atmosphere of hydrogen was maintained via balloon. The reaction mixture was stirred for about 4 h at ambient temperature and then was filtered and coned *in vacuo*. The residue was dissolved in pyridine (30 mL) and cyclopropanesulfonyl chloride (1.05 g, 7.49 mmol) was added. The reaction mixture was stirred for about 15 h at ambient temperature and then was partitioned between EtOAc (50 mL) and saturated aqueous CuSO₄ (50 mL). The organic layer was separated, washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered, coned *in vacuo*, and purified by chromatography on silica gel (80g) eluting with 20-80% EtOAc in heptane to provide *(2R,4S)*-*tert*-butyl 4-(cyclopropanesulfonamido)-2-ethylpyrrolidine-1-carboxylate (0.95 g, 48%) as an oil: LC/MS (Table 1, Method a) R_t = 2.12 min (ELSD); MS *m/z*: 319 (M+H)⁺.

Preparation #16: *tert*-butyl 1-(6-tosyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-3-ylcarbamate

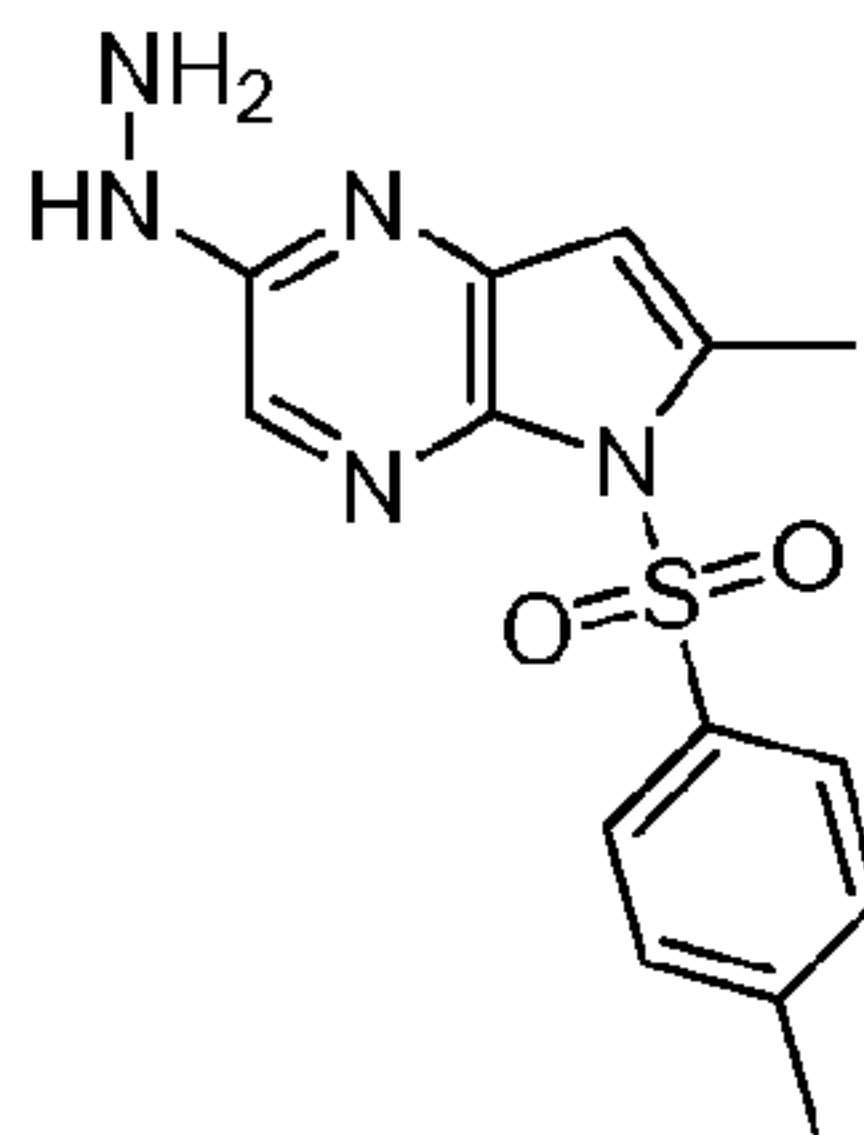


To a solution of *tert*-butyl 1-((5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)methylcarbamothioyl)-pyrrolidin-3-ylcarbamate (0.54 g, 1.0 mmol, Preparation #J.1) in THF (15 mL) was added DIEA (0.444 mL, 2.54 mmol) followed by mercury (II) trifluoroacetate (0.478 g, 1.12 mmol). The reaction mixture was stirred at ambient temperature for about 2 h and then saturated aqueous NaHCO₃ (30 mL) and EtOAc (30 mL) were added. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concd *in vacuo*. The crude material was purified by chromatography on silica gel (40 g) eluting with 10-40% EtOAc in DCM to provide *tert*-butyl 1-(6-tosyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)pyrrolidin-3-ylcarbamate (0.411 g, 81%) as a yellow glass: LC/MS (Table 1, Method **a**) *R*_t = 2.50 min; MS *m/z*: 497 (M+H)⁺.

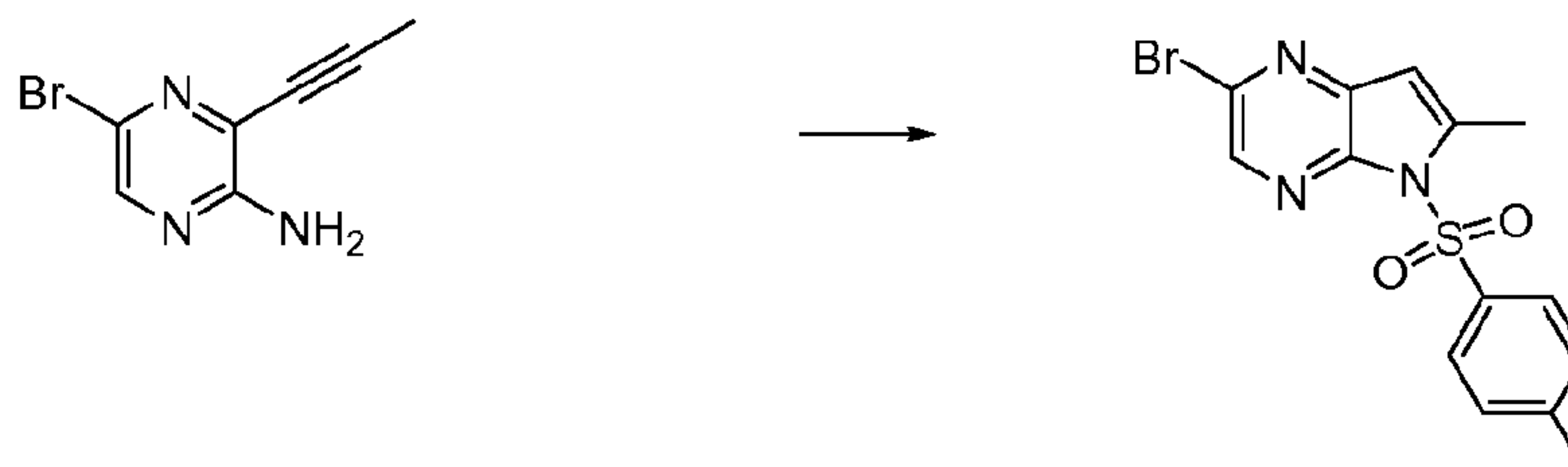
Preparation #17: *N*-(4-(3-(2,3-dihydroxypropyl)-6-tosyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide



To a solution of *N*-(4-(3-allyl-6-tosyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide (0.27 g, 0.47 mmol, prepared using **E** with 4-(*tert*-butoxycarbonylamino)bicyclo[2.2.2]octane-1-carboxylic acid [Prime Organics], **K** with cyclopropylsulfonyl chloride, **H** from Preparation #12, HATU and DIEA, **Q** with Lawesson's reagent and mercury (II) trifluoroacetate) in 1,4-dioxane (10 mL) and water (1 mL) was added *N*-methylmorpholine-*N*-oxide (0.22 g, 1.8 mmol) followed by osmium tetroxide (4 wt% in water, 0.36 mL, 0.047 mmol). The reaction mixture was stirred for about 15 h and then DCM (20 mL) and water (10 mL) were added to the reaction mixture. The organic layer was separated, concd *in vacuo*, and purified by chromatography on silica gel eluting with 10-50% MeCN in DCM, to provide *N*-(4-(3-(2,3-dihydroxypropyl)-6-tosyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide (0.009 g, 3%): LC/MS (Table 1, Method **a**) *R*_t = 1.90 min; MS *m/z*: 612 (M-H)⁺.

Preparation #18: 2-hydrazinyl-6-methyl-5-tosyl-5H-pyrrolo[2,3-b]pyrazine**Step A: 5-bromo-3-(prop-1-ynyl)pyrazin-2-amine**

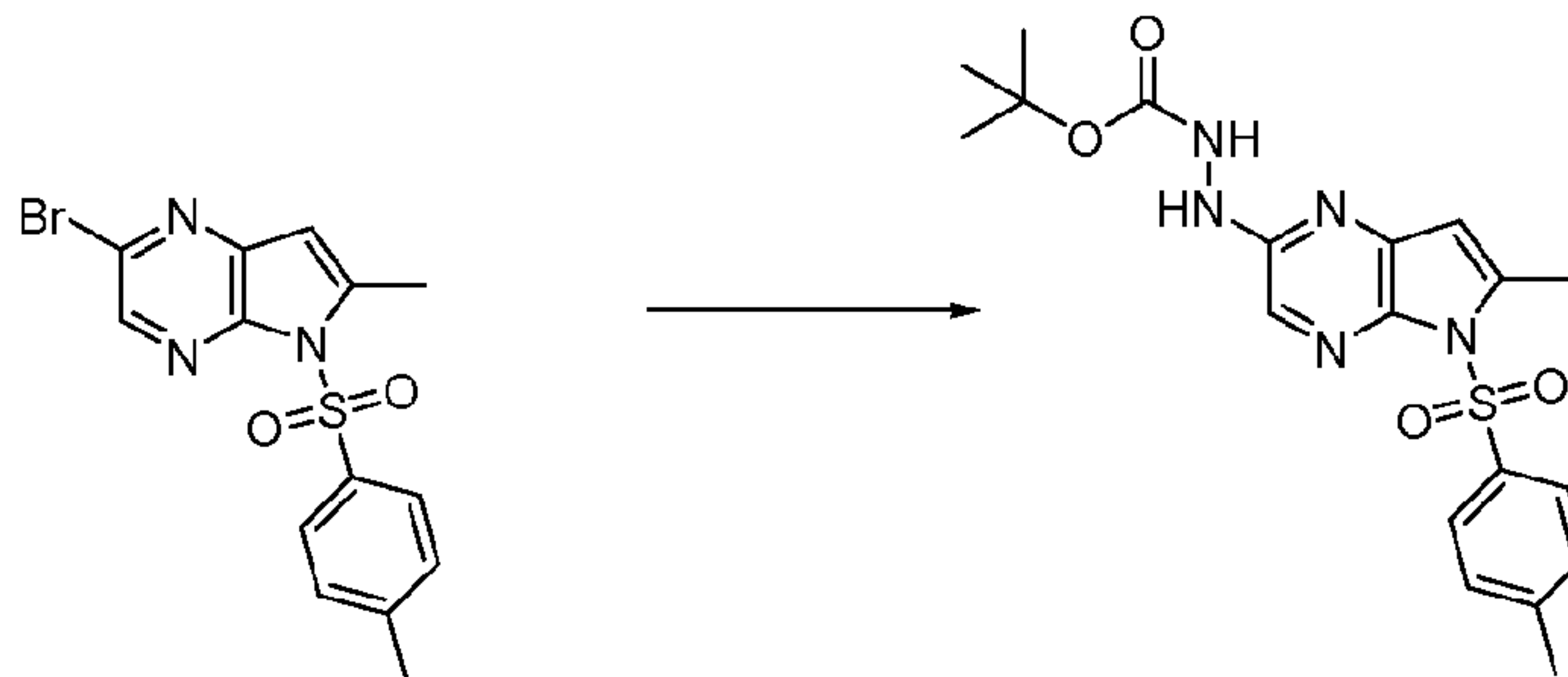
To a solution of 3,5-dibromopyrazin-2-amine (10.0 g, 39.5 mmol) in THF (200 mL) was added copper (I) iodide (0.377 g, 1.98 mmol), bis (triphenylphosphine)palladium (II) dichloride (1.39 g, 1.98 mmol) and TEA (16.5 mL, 119 mmol). The reaction mixture was cooled to about 0 °C and degassed with Ar. The reaction mixture was stirred for about 5 min and then the reaction mixture was sparged with propyne and a propyne atmosphere was maintained via balloon. The reaction mixture was stirred for about 30 min at about 0 °C and then was allowed to warm to ambient temperature. The reaction mixture was stirred for about 2 h and then EtOAc (100 mL) and water (100 mL) were added to the reaction mixture. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered, and concd *in vacuo*. The crude mixture was purified by chromatography on silica gel (120 g) eluting with 10-60% EtOAc in DCM (dry loaded) to provide 5-bromo-3-(prop-1-ynyl)pyrazin-2-amine (7.05 g, 84%) as a yellow solid: LC/MS (Table 1, Method a) R_t = 1.79 min; MS *m/z*: 212, 214 (1:1) (M+H)⁺.

Step B: 2-bromo-6-methyl-5-tosyl-5H-pyrrolo[2,3-b]pyrazine

To a slurry of NaH (60% dispersion in mineral oil, 2.00 g, 49.9 mmol) in NMP (100 mL) was slowly added a solution of 5-bromo-3-(prop-1-ynyl)pyrazin-2-amine (7.05 g, 33.2 mmol) in NMP (20 mL). The reaction mixture was stirred at ambient temperature for about 20 min and then a solution of *p*-toluenesulfonyl chloride (6.97 g, 36.6 mmol) in NMP (20 mL) was added. The reaction mixture was stirred at ambient temperature for about 20 h and then aqueous HCl (1 N, 100 mL) was added to the reaction mixture. The resulting solids were collected by filtration. The

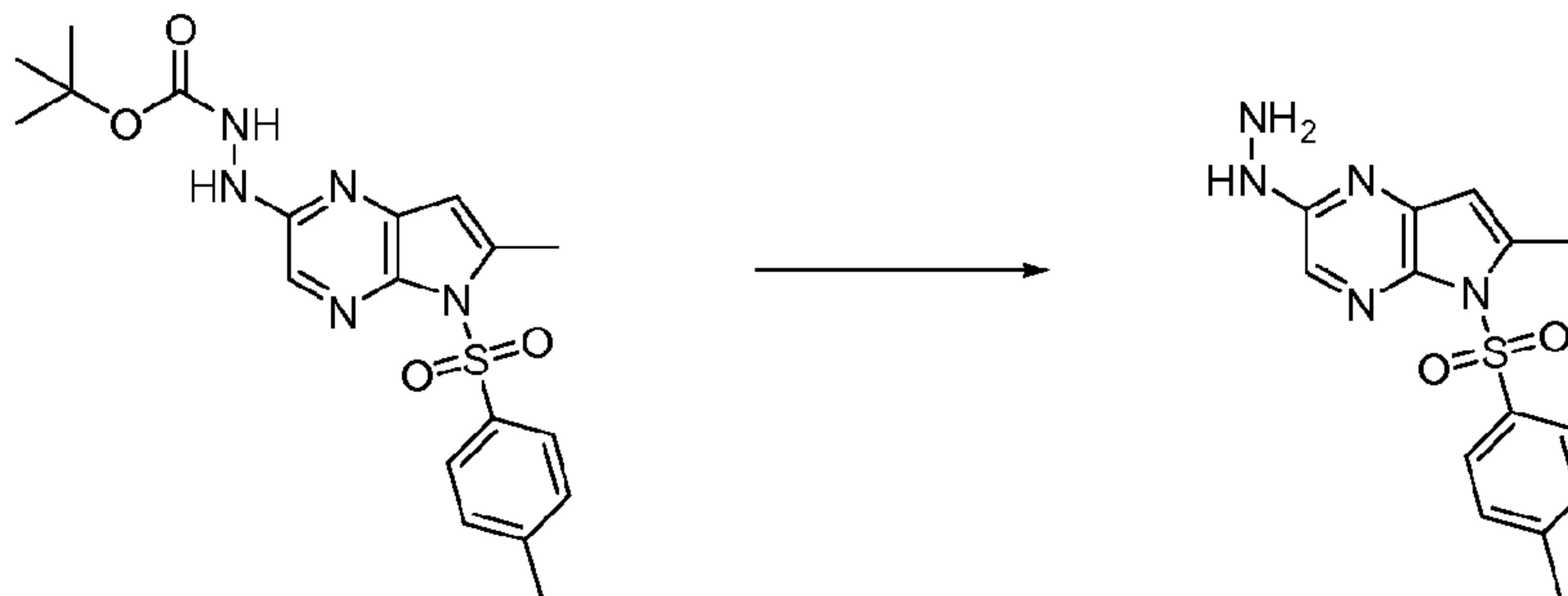
brown solid was triturated with DCM/EtOAc (1:1, 30 mL) and collected by filtration to provide 2-bromo-6-methyl-5-tosyl-5H-pyrrolo[2,3-b]pyrazine (9.0 g, 74%) as a brown solid: LC/MS (Table 1, Method a) $R_t = 2.68$ min; MS m/z : 366, 368 (1:1) ($M+H$)⁺.

Step C: *tert*-butyl 2-(6-methyl-5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)hydrazinecarboxylate



Tris(dibenzylideneacetone)dipalladium(0) (0.250 g, 0.273 mmol) and 2-di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl (0.232 g, 0.546 mmol) were combined in 1,4-dioxane (15 mL). The flask was evacuated with some bubbling of solvent and then carefully refilled with nitrogen (3 times). Nitrogen was then bubbled directly into the reaction mixture. The mixture was then heated at about 80 °C for about 10 min and then removed from the heating source. 2-Bromo-6-methyl-5-tosyl-5H-pyrrolo[2,3-b]pyrazine (1.0 g, 2.73 mmol), *tert*-butyl hydrazinecarboxylate (0.541 g, 4.10 mmol) and NaOt-Bu (0.501 mL, 4.10 mmol) were added and the reaction was heated at about 80 °C for about 1 h. The reaction was cooled to ambient temperature and the solvents removed under reduced pressure. The black residue was then taken up in EtOAc (50 mL) and filtered. The filtrate was washed with saturated aqueous NH₄Cl (50 mL), EDTA (1.0 M aqueous, 50 mL) and saturated aqueous NaHCO₃ (50 mL). The solution was dried over anhydrous Na₂SO₄, filtered, and concd under reduced pressure. The material was purified by chromatography on silica gel (80g) eluting with 25-100% EtOAc in heptane to provide *tert*-butyl 2-(6-methyl-5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)hydrazinecarboxylate (0.160 g, 14%) as a brown oil: LCMS (Table 1, Method a) $R_t = 2.51$ min; MS m/z : 418 ($M+H$)⁺.

Step D: 2-hydrazinyl-6-methyl-5-tosyl-5H-pyrrolo[2,3-b]pyrazine

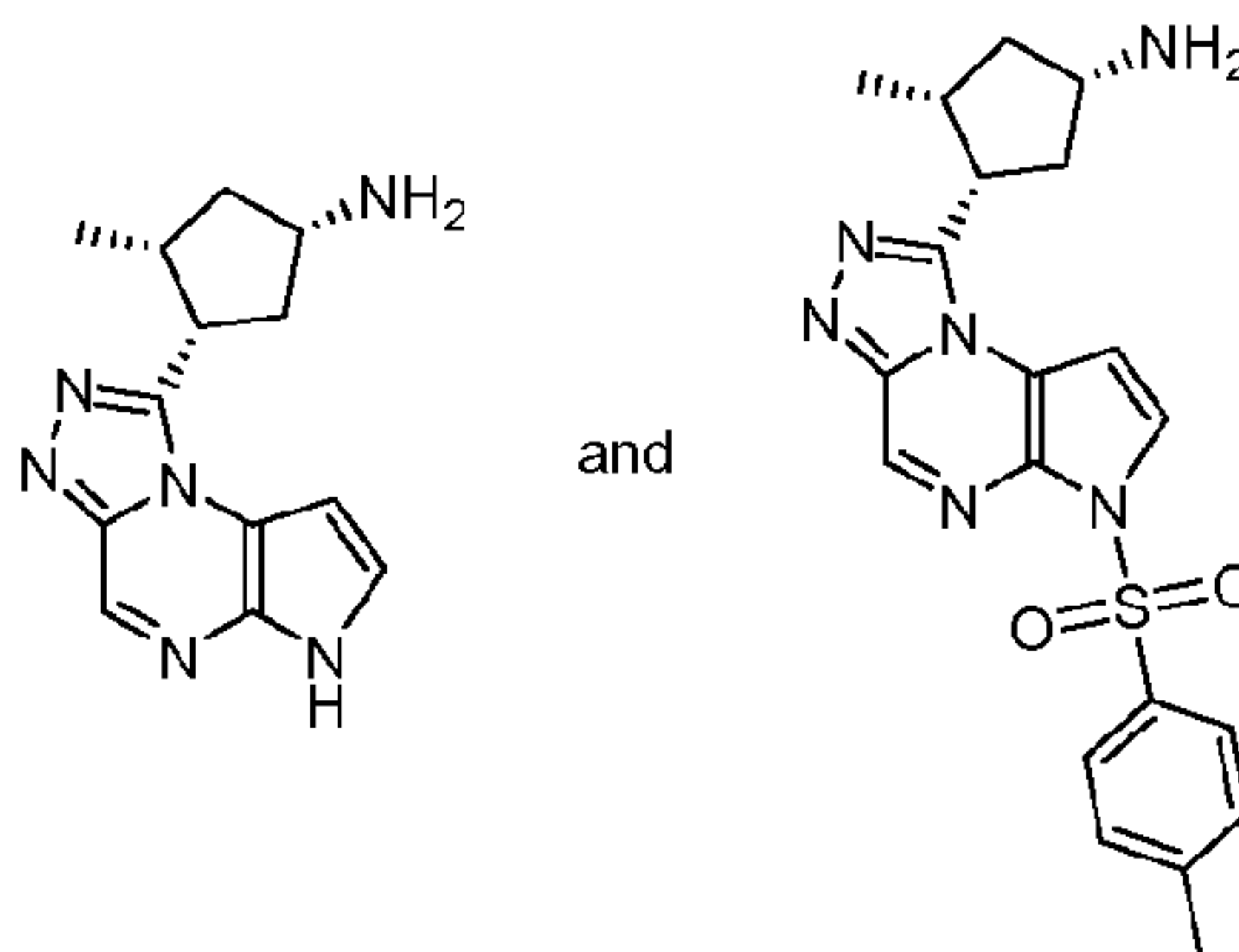


tert-Butyl 2-(6-methyl-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)hydrazinecarboxylate (0.16 g, 0.38 mmol) was stirred in 1,4-dioxane (1.9 mL) in a sealed vial to give a brown solution. HCl (4 M in 1,4-dioxane, 0.958 mL, 3.83 mmol) was added and the reaction stirred at ambient temperature for about 20 h. The solvents were removed under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous Na₂SO₄, filtered, and concd *in vacuo* to provide 2-hydrazinyl-6-methyl-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine (0.089 g, 73%): LC/MS (Table 1, Method **a**) *R*_t = 1.92 min; MS *m/z*: 318 (M+H)⁺.

Preparation #19:

Preparation #19.1: (1*S*,3*R*,4*S*)-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine

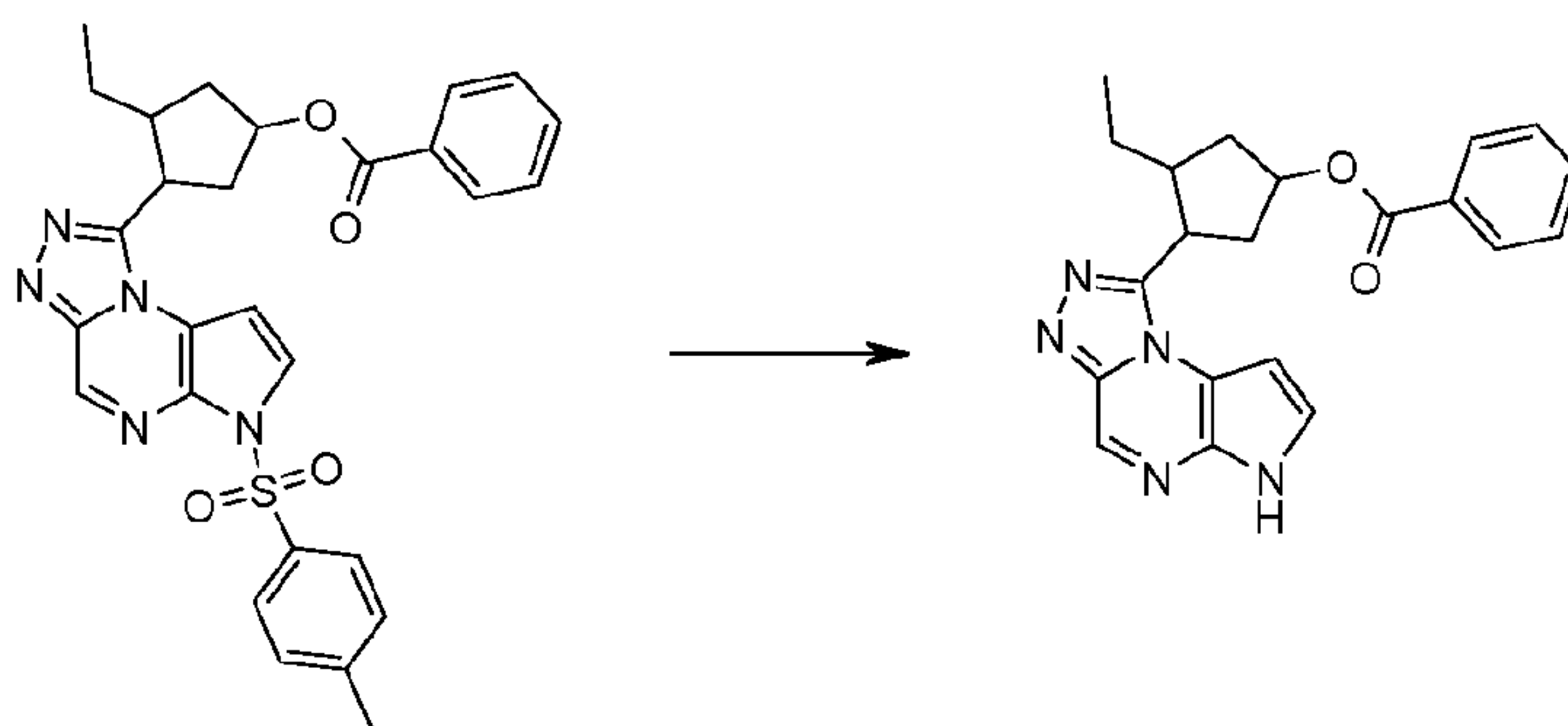
Preparation #19.2: (1*S*,3*R*,4*S*)-3-methyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine



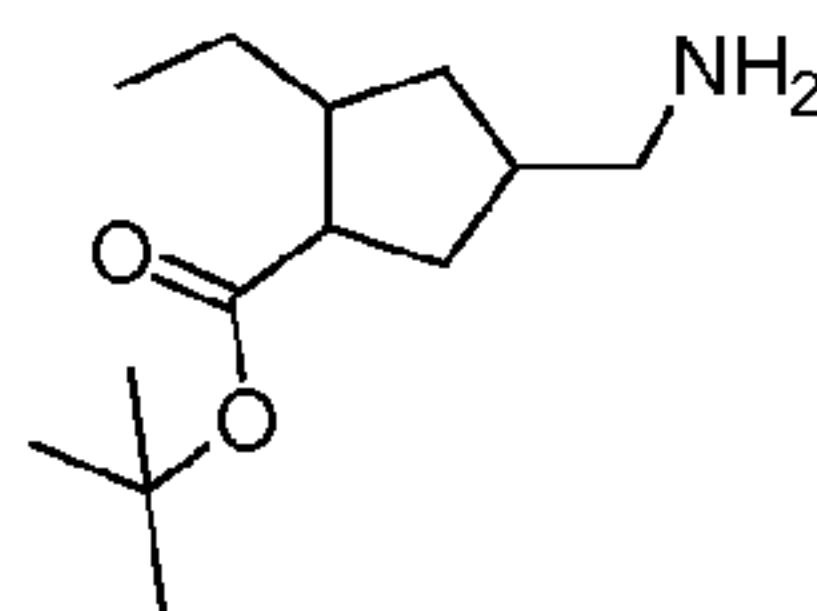
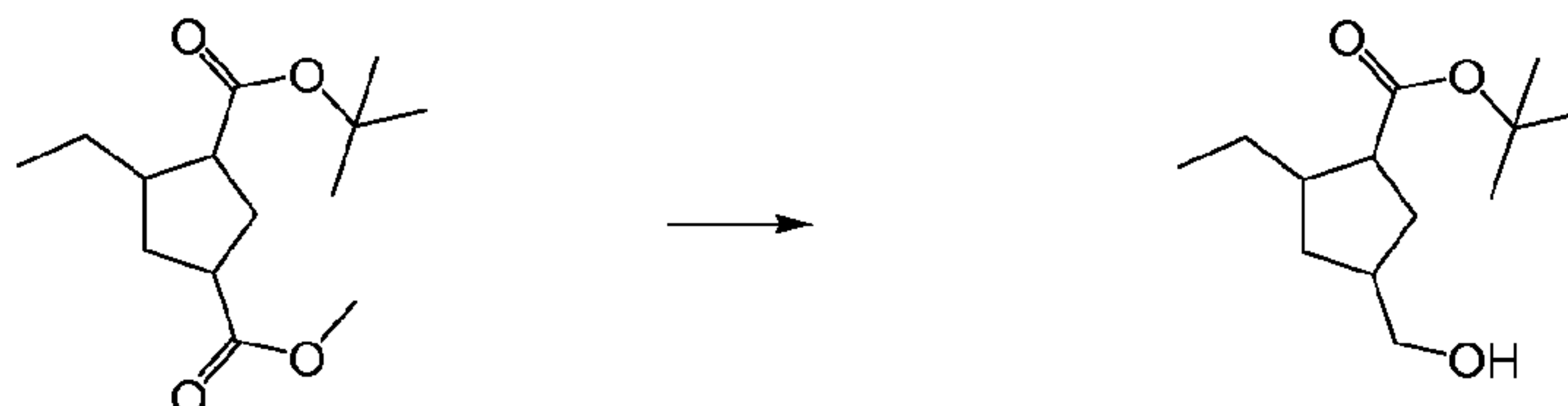
To a mixture of *N*-((1*S*,3*R*,4*S*)-3-methyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)acetamide (1.52 g, 3.36 mmol, prepared using **Y** from Example #7, step H and Pd/C, **G**, **AA** [Table 2, Method 3, *R*_t = 6.1 min, or = ND], **Z** with NaOH, **A** with Example #1 Step D, HATU, and TEA, and **B** with TEA) and 1,4-dioxane (25 mL) was added aqueous HCl (6 N, 25 mL, 150 mmol). The reaction was heated at about 100 °C for about 14 h and then was cooled to ambient temperature and concd under reduced pressure. To the resulting brown residue was added MeOH (30 mL) and the solution was concd under reduced pressure. To the resulting residue was added MeOH (5 mL) followed by slow addition of Et₂O (20 mL). Initially a cloudy solution formed and then a dark oil/gum formed and the mixture was concd under reduced pressure. To the resulting brown residue was added MeOH (30 mL), (1*S*,3*R*,4*S*)-3-methyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentan-amine (1.35 g, 2.50 mmol, UV purity 75%) from a separate reaction, and silica gel (7 g). The mixture was concd under reduced pressure and purified by silica gel chromatography eluting with a gradient of 0-100% (DCM/[2 M NH₃ in MeOH] (9:1)) in DCM, the column was further flushed with MeOH

then MeOH/aqueous NH_4OH (9:1), to give *(1S,3R,4S)*-3-methyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine [Preparation #19.1] (0.092 g, 5%) as a dark brown solid: LC/MS (Table 1, Method **a**) R_t = 1.35 min; MS m/z : 257 ($\text{M}+\text{H}$)⁺ and 2.9 g of brown residue that was partitioned between DCM and saturated aqueous NaHCO_3 (50 mL each). The layers were separated and the aqueous layer was extracted with additional DCM (2 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 , filtered, and concd under reduced pressure to give *(1S,3R,4S)*-3-methyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine [Preparation #19.2] (1.94 g, 78%) as a taupe foam: LC/MS (Table 1, Method **a**) R_t = 1.80 min; MS m/z : 411 ($\text{M}+\text{H}$)⁺.

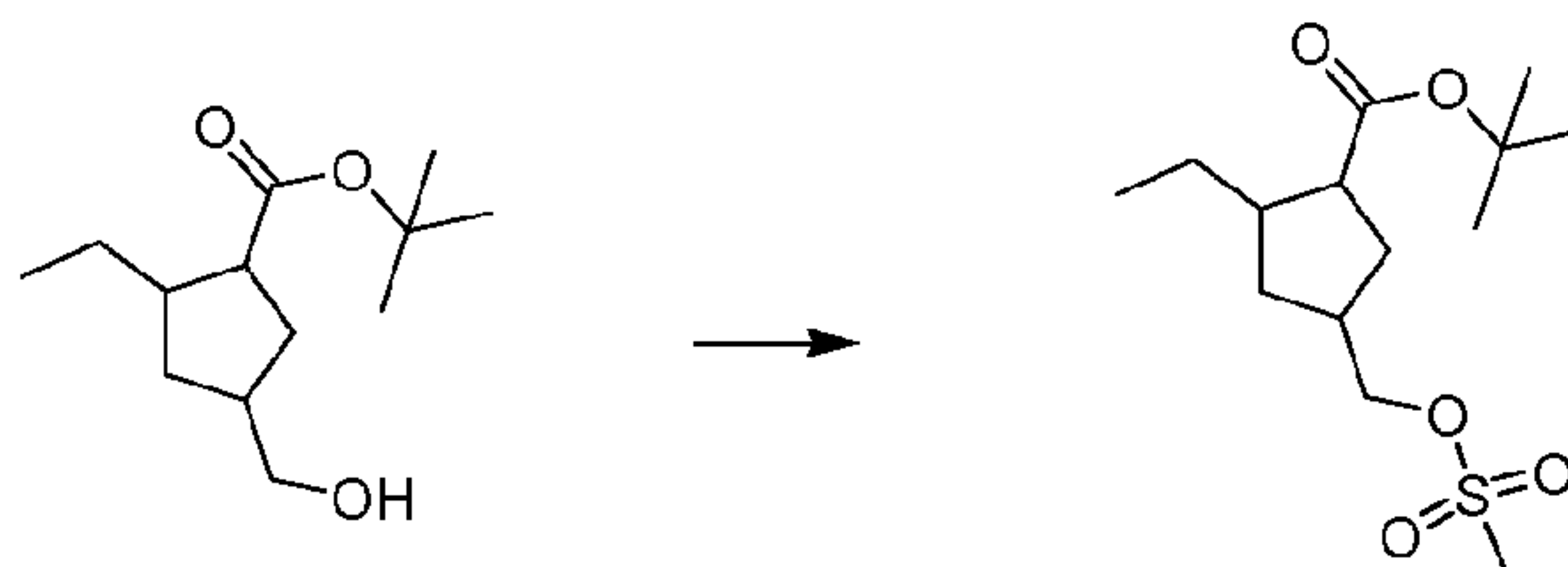
Preparation #20: 3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl benzoate



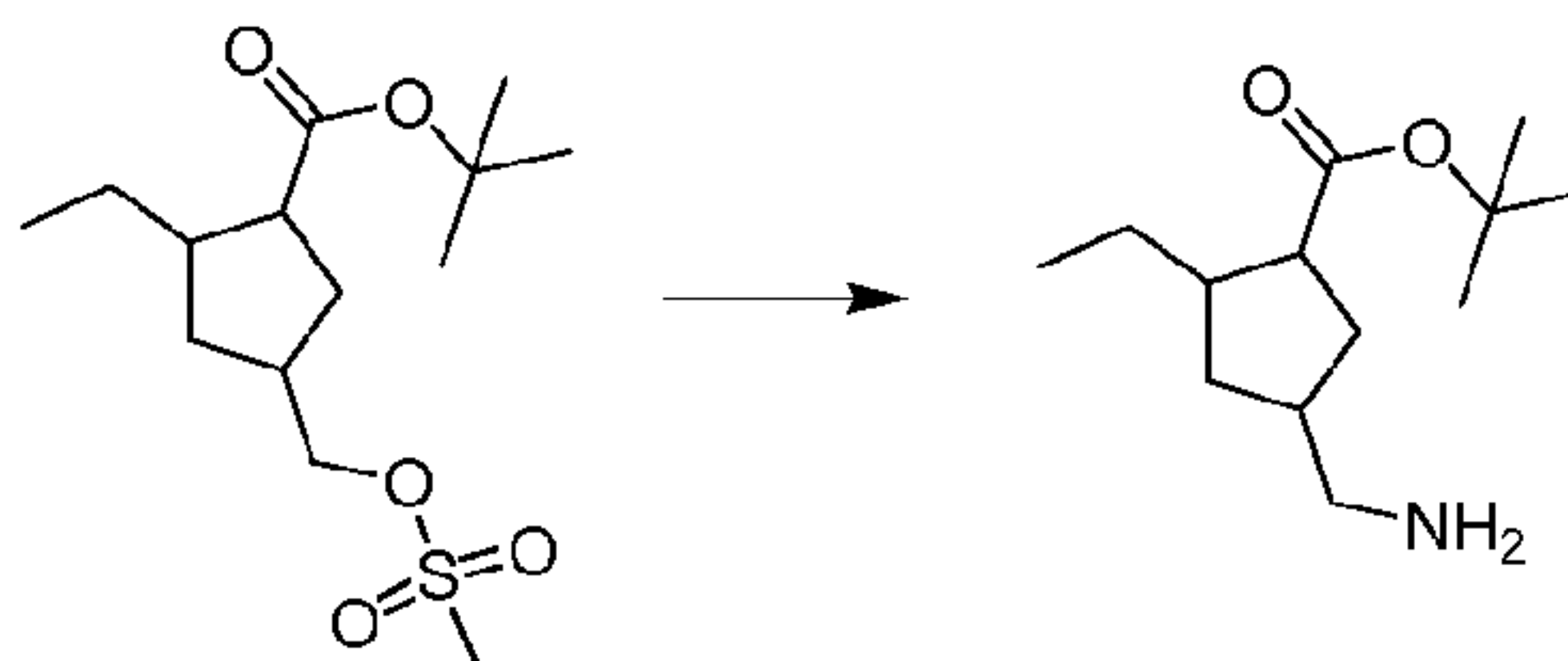
To a mixture of 3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl benzoate (5.00 g, 7.84 mmol, prepared from Example #4 Step J using **II** with benzoic acid, and **B**) in MeOH (16 mL) was added a solution of potassium cyanide (0.74 mL, 17.2 mmol) in MeOH (16 mL). The reaction was stirred at ambient temperature for about 16 h. The reaction mixture was concd under reduced pressure to afford a residue. The residue was partitioned between water (20 mL) and DCM (20 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 10 mL). The extract was then washed with saturated aqueous NaHCO_3 , dried over anhydrous MgSO_4 , filtered, and concd under reduced pressure to afford a crude oil. The crude material was purified by silica gel chromatography eluting with a gradient of 0-10% MeOH in DCM to 3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl benzoate (2.30 g, 78%) as a red tinted solid. LC/MS (Table 1, Method **a**) R_t = 2.08 min; MS m/z : 376 ($\text{M}+\text{H}$)⁺.

Preparation #21: *tert*-butyl 4-(aminomethyl)-2-ethylcyclopentanecarboxylate**Step A: *tert*-butyl 2-ethyl-4-(hydroxymethyl)cyclopentanecarboxylate**

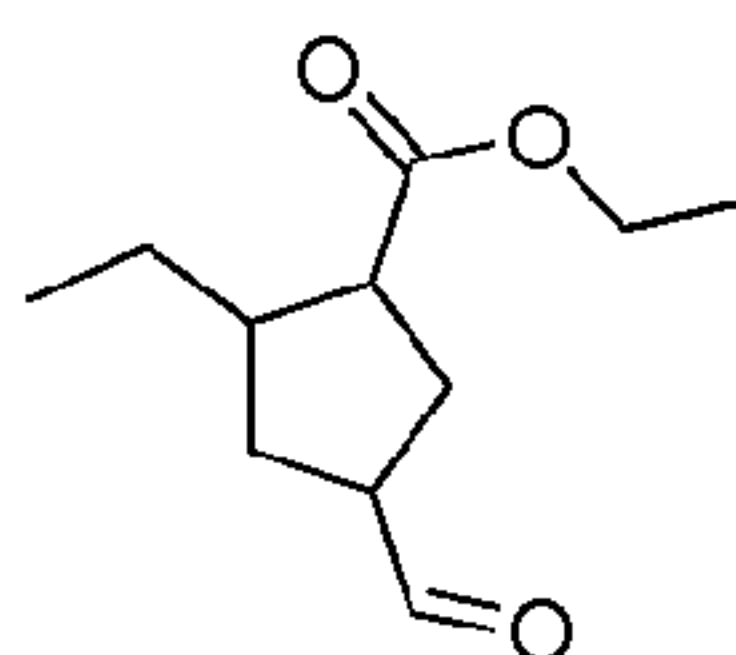
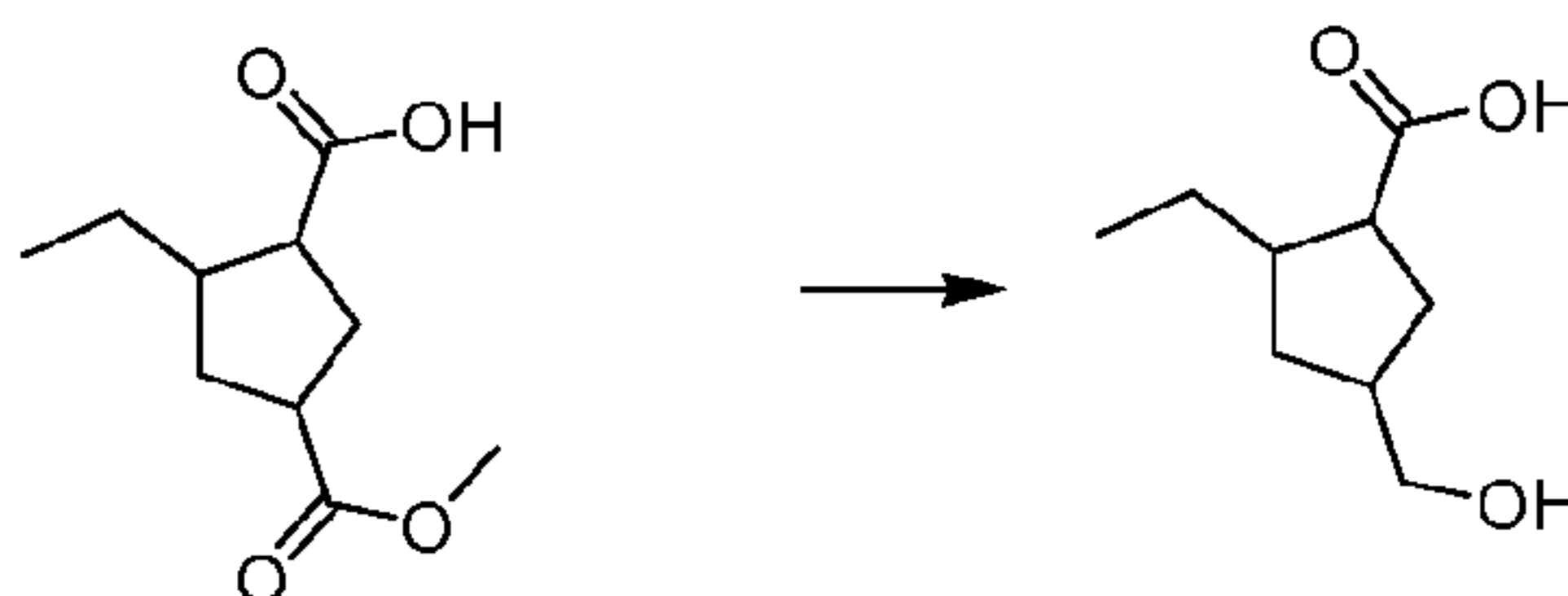
A solution of 3-*tert*-butyl 1-methyl 4-ethylcyclopentane-1,3-dicarboxylate (3.88 g, 15.1 mmol, Preparation #11, Step B) in Et₂O (150 mL) was cooled to about -40 °C. LAH (2 N in THF, 8.32 mL, 16.6 mmol) was added dropwise. The reaction mixture was stirred at about -40 °C for about 1 hour. The reaction mixture was partitioned between saturated aqueous NaHCO₃ (50 mL) and EtOAc (3 x 50 mL). The combined organic extracts were concd under reduced pressure. The crude material was purified by silica gel chromatography eluting with a gradient of 0-100% EtOAc/heptane to give *tert*-butyl 2-ethyl-4-(hydroxymethyl)cyclopentanecarboxylate (1.00 g, 29%) as a brown oil: LC/MS (Table 1, Method **a**) R_t = 2.37 min; MS *m/z*: 229 (M+H)⁺.

Step B: *tert*-butyl 2-ethyl-4-((methylsulfonyloxy)methyl)cyclopentanecarboxylate

To a solution of *tert*-butyl 2-ethyl-4-(hydroxymethyl)cyclopentanecarboxylate (0.220 g, 0.964 mmol) in DCM (5 mL) was added TEA (0.16 mL, 1.15 mmol) and methanesulfonyl chloride (0.083 mL, 1.06 mmol) at about 0 °C. The reaction mixture was allowed to warm to about 25 °C and stirred at about 25 °C for about 16 h. The reaction mixture was partitioned between water (20 mL) and DCM (20 mL). The aqueous solution was washed with DCM (2 x 20 mL). The combined organic extracts were dried over anhydrous MgSO₄, filtered, and concd under reduced pressure to give *tert*-butyl 2-ethyl-4-((methylsulfonyloxy)methyl)cyclopentanecarboxylate (0.295 g, 100%): LC/MS (Table 1, Method **b**) R_t = 2.55 min; MS *m/z*: 307 (M+H)⁺.

Step C: *tert*-butyl 4-(aminomethyl)-2-ethylcyclopentanecarboxylate

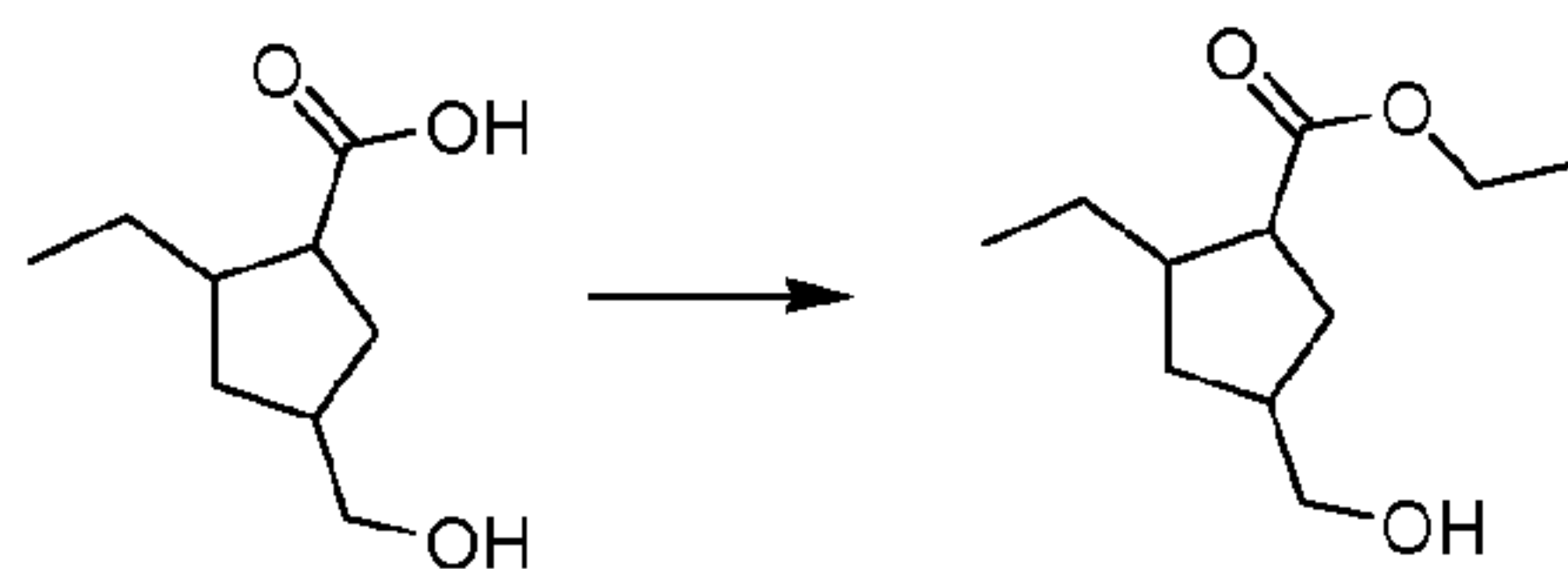
To a solution of *tert*-butyl 2-ethyl-4-((methylsulfonyloxy)methyl)cyclopentanecarboxylate (0.295 g, 0.964 mmol) in DMF (5 mL) was added sodium azide (0.313 g, 4.82 mmol). The reaction was heated at about 50 °C for about 16 h and then cooled to about 15-20 °C. Water (40 mL) was added to the reaction mixture. The aqueous solution was extracted with DCM (3 x 30 mL). The combined organic extracts were dried over anhydrous MgSO₄, filtered, and concd under reduced pressure to give a dark brown oil. The brown oil was dissolved in THF (6.5 mL) and water (3.5 mL). Triphenylphosphine (0.316 g, 1.205 mmol) was added. The reaction mixture was stirred at about 25 °C for about 15 h. The organic solvent was removed under reduced pressure and the residue partitioned between saturated aqueous NaHCO₃ (20 mL) and DCM (20 mL). The organic phase was concd under reduced pressure. The resulting residue was purified using silica gel chromatography eluting with a gradient of 0-20% (20% (7 N ammonium in MeOH) in MeOH) in DCM to give *tert*-butyl 4-(aminomethyl)-2-ethylcyclopentanecarboxylate (0.102 g, 46%) as a brown oil: LC/MS (Table 1, Method b) R_t = 1.72 min; MS *m/z*: 228 (M+H)⁺.

Preparation #22: ethyl 2-ethyl-4-formylcyclopentanecarboxylate**Step A: 2-ethyl-4-(hydroxymethyl)cyclopentanecarboxylic acid**

To a solution of 2-ethyl-4-(methoxycarbonyl)cyclopentanecarboxylic acid (8.34 g, 41.7 mmol, Preparation #11, Step A) in THF (208 mL) was added LiBH₄ (0.907 g, 41.7 mmol) at about -20 °C. The reaction mixture was stirred at about -20 °C for about 1 h. The reaction mixture was allowed to warm to about 25 °C then was stirred at about 25 °C for about 16 h. Additional LiBH₄ (0.907 g, 41.7 mmol) was added. The reaction mixture was stirred at about 25 °C for about 4 h. Water (10 mL) was added slowly to quench the reaction. The solid was removed by vacuum

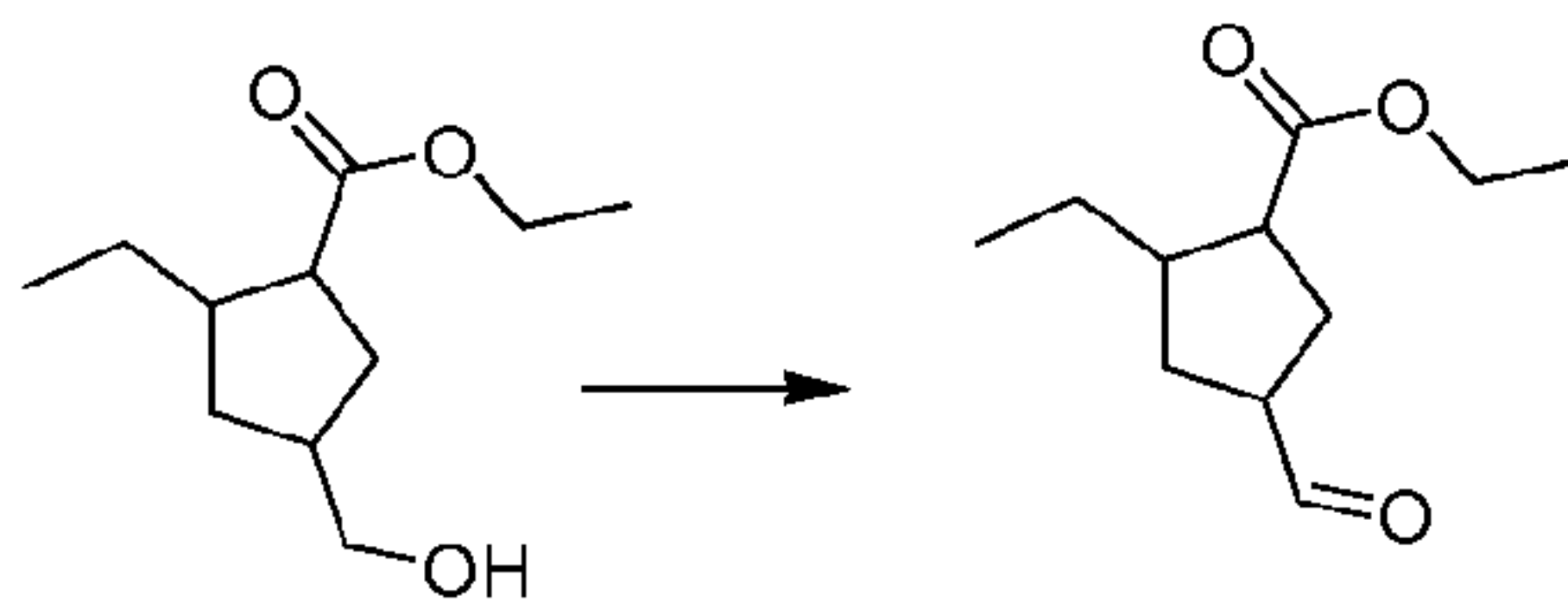
filtration. The filtrate was concd under reduced pressure. The resulting residue was partitioned between water (50 mL) and DCM (3 x 50 mL). The combined organic extracts were dried over anhydrous MgSO_4 , filtered, and concd under reduced pressure to give *2-ethyl-4-(hydroxymethyl)cyclopentanecarboxylic acid* (7.29 g, 100%): LC/MS (Table 1, Method n) R_t = 0.44 min; MS m/z : 173 ($M+H$)⁺.

Step B: ethyl 2-ethyl-4-(hydroxymethyl)cyclopentanecarboxylate



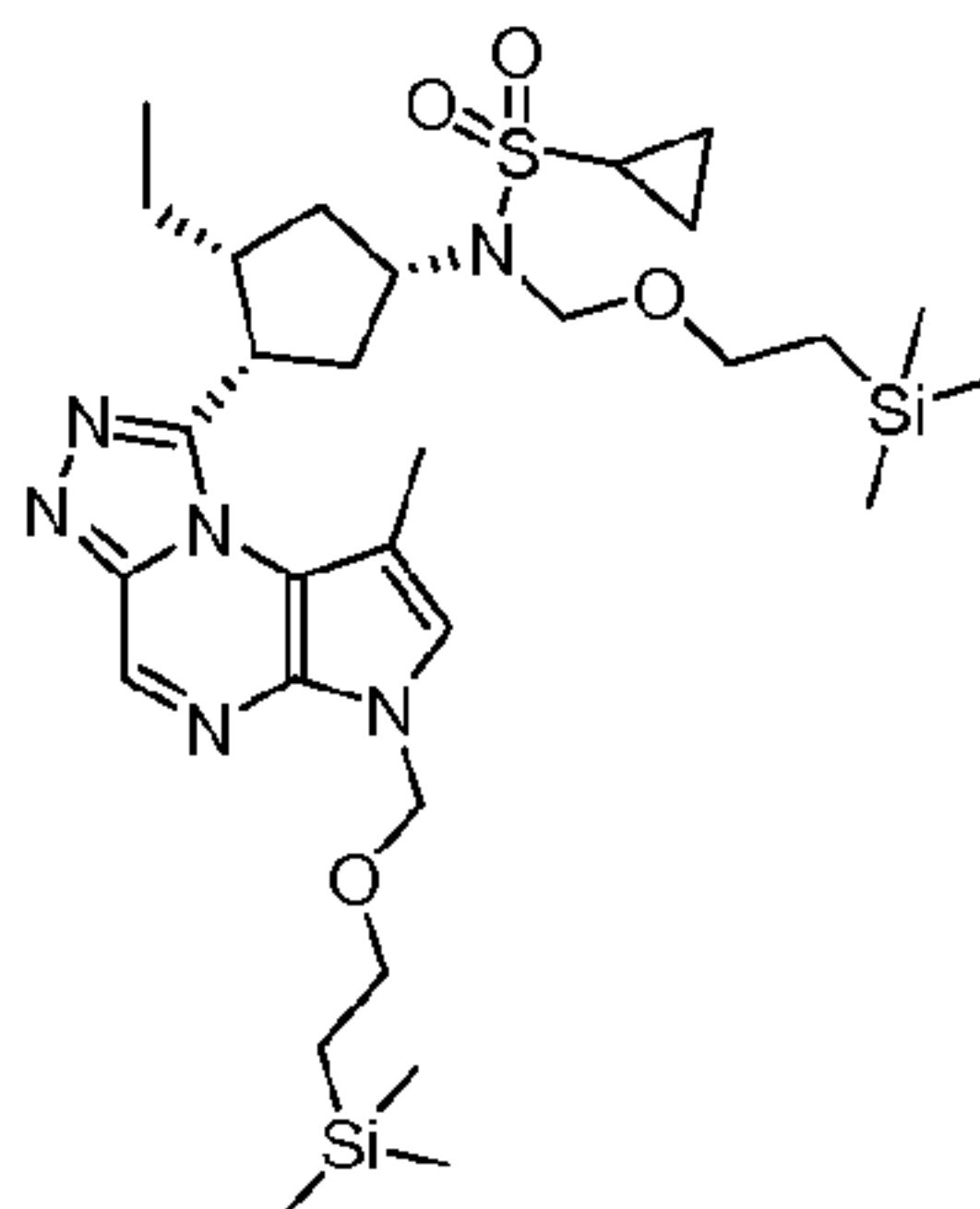
HCl gas was bubbled through a solution of 2-ethyl-4-(hydroxymethyl)cyclopentanecarboxylic acid (7.29 g, 42.3 mmol) in EtOH (60 mL) at about 25 °C for about 10 min. The reaction mixture was stirred at about 25 °C for about 72 h. The solvent was removed under reduced pressure. The crude residue was partitioned between water (30 mL) and DCM (3 x 30 mL). The combined organic extracts were concd under reduced pressure. The crude material was purified by silica gel chromatography eluting with a gradient of 0-100% EtOAc/heptane to give *ethyl 2-ethyl-4-(hydroxymethyl)cyclopentanecarboxylate* (4.89 g, 58%) as a yellow oil: ^1H NMR (CDCl_3) δ 4.23 – 4.02 (m, 2H), 3.74 – 3.47 (m, 2H), 2.96 – 2.83 (m, 1H), 2.31 – 2.17 (m, 1H), 2.15 – 1.98 (m, 2H), 1.97 – 1.84 (m, 1H), 1.79 – 1.66 (m, 1H), 1.65 – 1.50 (m, 1H), 1.49 – 1.37 (m, 1H), 1.30 – 1.21 (m, 5H), 1.04 – 0.82 (m, 3H).

Step C: ethyl 2-ethyl-4-formylcyclopentanecarboxylate



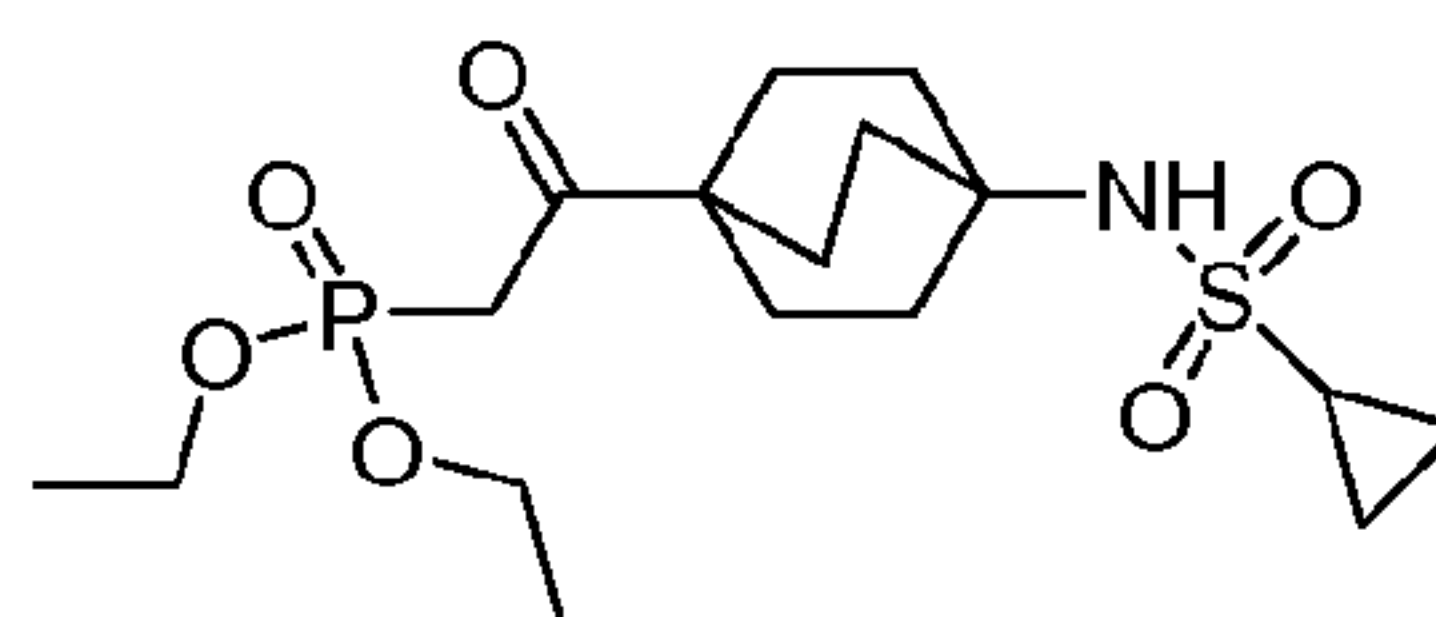
To a solution of ethyl 2-ethyl-4-(hydroxymethyl)cyclopentanecarboxylate (4.84 g, 24.2 mmol) in DCM (100 mL) was added pyridinium chlorochromate (10.42 g, 48.3 mmol). The reaction mixture was stirred at about 25 °C for about 3 h. Silica gel (1 g) was added. The mixture was stirred at about 25 °C for about 30 min. The solid was removed by vacuum filtration, while rinsing with DCM (100 mL). The filtrate was concd under reduced pressure. The resulting residue was purified using silica gel chromatography eluting with a gradient of 0-40% EtOAc/Heptane to give *ethyl 2-ethyl-4-formylcyclopentanecarboxylate* (3.03 g, 63%) as a clear oil: ^1H NMR ($\text{DMSO}-d_6$) δ 9.66 – 9.47 (m, 1H), 4.12 – 3.94 (m, 2H), 2.94 – 2.73 (m, 2H), 2.19 – 1.90 (m, 4H), 1.55 – 1.65 (m, 1H), 1.37 – 1.23 (m, 1H), 1.23 – 1.06 (m, 4H), 0.96 – 0.82 (m, 3H).

Preparation #23: *N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(8-methyl-6-((2-(trimethylsilyl)ethoxy)methyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)cyclopropanesulfonamide

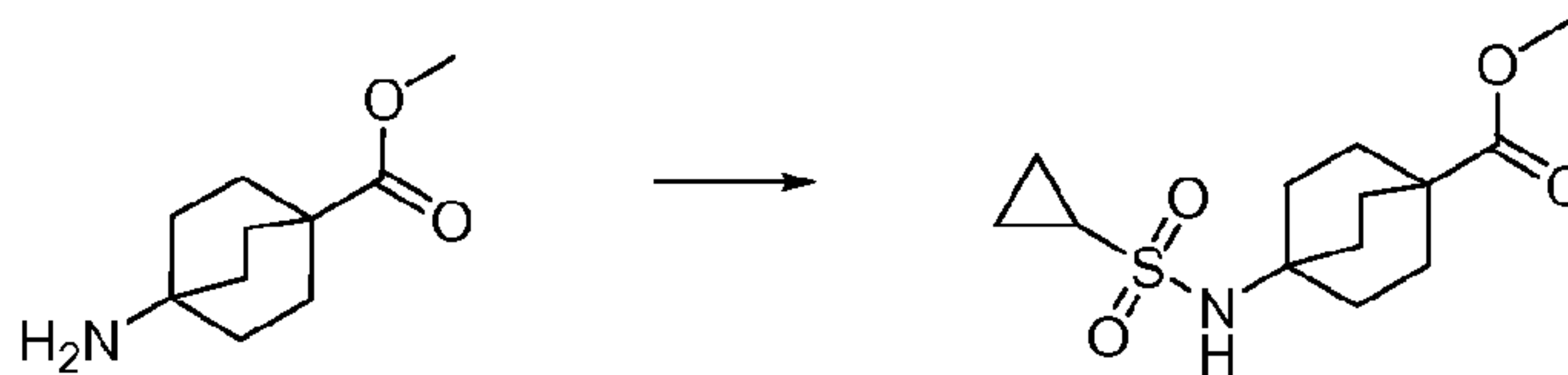


Cesium carbonate (0.274 g, 0.841 mmol), tricyclohexylphosphine (20 wt% solution in toluene, 0.094 g, 0.067 mmol), Pd₂(dba)₃ (0.039 g, 0.042 mmol) and trimethylborate (0.069g, 0.547 mmol) were added to a solution of *N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(8-iodo-6-((2-(trimethylsilyl)ethoxy)methyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)cyclopropanesulfonamide (0.32 g, 0.421 mmol, prepared using **KK** from Preparation #**GGG.1**) in 1,4-dioxane (8 mL). The mixture was degassed and heated at about 85 °C for about 2 h. The solvent was removed and the residue was partitioned between EtOAc and water (20 mL each). The organic phase was washed with brine (15 mL), dried over anhydrous MgSO₄, filtered and concd. The resulting mixture was purified by silica gel flash chromatography (40 to 100% of EtOAc in heptane) to yield *N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(8-methyl-6-((2-(trimethylsilyl)ethoxy)methyl)-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)cyclopropanesulfonamide (0.21 g, 77%) as a yellow amorphous solid. LC/MS (Table 1, Method **a**) R_t = 3.39 min; MS *m/z*: 650 (M+H)⁺.

Preparation #24: diethyl 2-(4-(cyclopropanesulfonamido)bicyclo[2.2.2]octan-1-yl)-2-oxoethylphosphonate

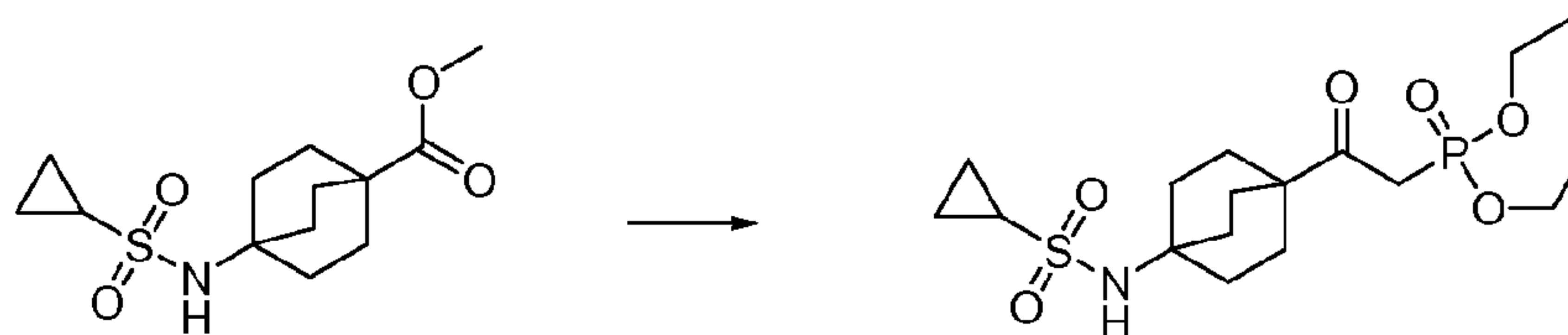


.Step A: methyl 4-(cyclopropanesulfonamido)bicyclo[2.2.2]octane-1-carboxylate



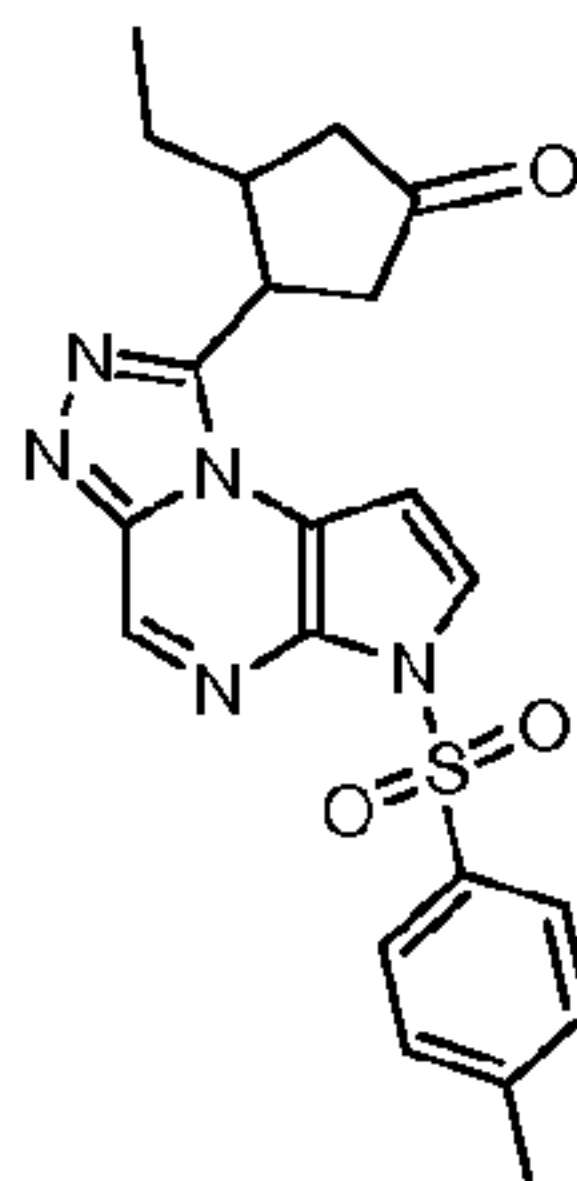
To a solution of methyl 4-aminobicyclo[2.2.2]octane-1-carboxylate (500 mg, 2.73 mmol) (Yeh, V. S. C.; Kurukulasuriya, R.; Madar, D.; Patel, J. R.; Fung, S.; Monzon, K.; Chiou, W.; Wang, J.; Jacobson, P.; Sham, H. L.; Link, J. T. *Bioorg. and Med. Chem. Let.*, **2006**, vol. 16, # 20 p. 5408 - 5413) in DCM (10 mL) at rt was added TEA (0.76 mL, 5.46 mmol) and DMAP (50 mg, 0.41 mmol). Cyclopropanesulfonyl chloride (764 mg, 5.46 mmol, Matrix) was added dropwise by syringe. The reaction mixture was stirred for about 15 h at rt. The mixture was washed with water (10 mL), and the aqueous layer was extracted with DCM (2 x 10 mL), the organic layers were combined and dried over anhydrous Na₂SO₄, filtered and coned *in vacuo*. The crude materials was purified by silica gel chromatography eluting with a gradient of 20-35% EtOAc in hexanes to afford *methyl 4-(cyclopropanesulfonamido)bicyclo[2.2.2]octane-1-carboxylate* (410 mg, 52% yeild). LC/MS (Table 1, Method **p**) R_t = 1.68 min; MS *m/z*: 288 (M+H)⁺.

Step B: diethyl (4-(cyclopropanesulfonamido)bicyclo[2.2.2]octan-1-yl)methylphosphonate

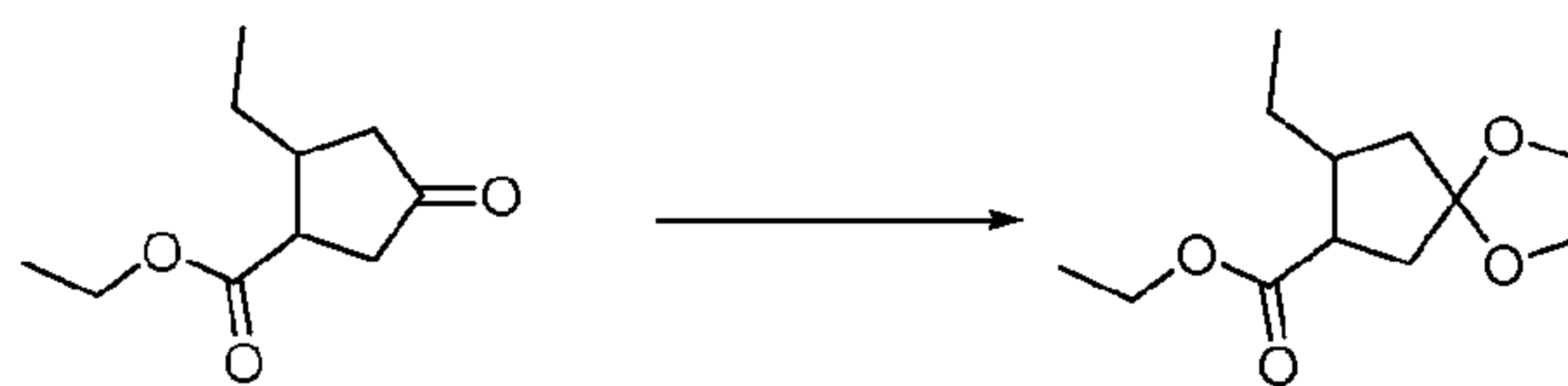


A solution of diethyl methylphosphonate (1.27 g, 8.36 mmol) was dissolved in THF (20 mL) and cooled to about -78 °C in a dry ice-acetone bath under nitrogen. Then *n*-BuLi (9.77 mmol, 3.9 mL, 2.5M in hexane) was added dropwise over about 5 min. The reaction mixture was stirred for about 3 h, keeping the temperature below about -70 °C. Then a solution of methyl 4-(cyclopropanesulfonamido)bicyclo[2.2.2]octane-1-carboxylate (800 mg, 2.79 mmol) in THF (10 mL) was added, keeping the temperature at about -78 °C. The solution was stirred for about 15 h, allowing the temperature to rise slowly to rt. To the reaction mixture was added saturated aqueous NH₄Cl (30 mL) and extracted with EtOAc (3 x 30 mL). The organic layers were combined and washed with brine, dried over anhydrous Na₂SO₄ and coned to provide *diethyl (4-(cyclopropanesulfonamido)bicyclo[2.2.2]octan-1-yl)methylphosphonate* (1.30 g, 100% yield). The crude product was used in next step without further purification. LC/MS (Table 1, Method **p**) R_t = 1.62 min; MS *m/z*: 408 (M+H)⁺.

Preparation #25: 3-ethyl-4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)cyclopentanone

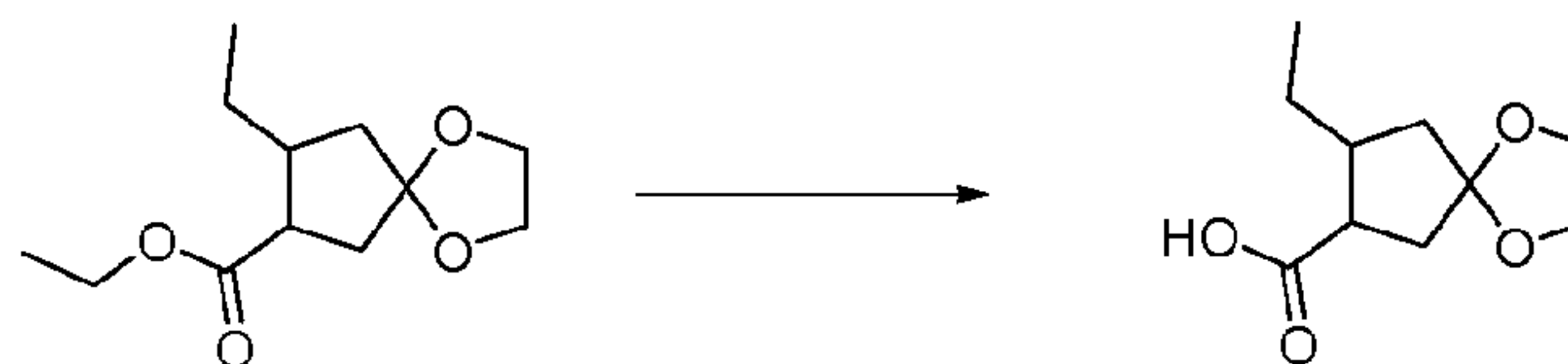


Step A: ethyl 2-ethyl-4-oxocyclopentanecarboxylate



A round bottom flask was charged with ethyl 2-ethyl-4-oxocyclopentanecarboxylate (1.5 g, 8.1 mmol, Example #22, Step B) in DCM (22 mL). To the flask were added ethylene glycol (0.91 mL, 16 mmol), triethylorthoformate (2.0 mL, 12 mmol), and *p*-toluenesulfonic acid monohydrate (0.31 g, 1.6 mmol). The reaction mixture was stirred at rt for about 24 h. The solution was concd under reduced pressure to give a brown oil that was dissolved in EtOAc and purified by flash silica gel chromatography (Silicycle 25 g column) eluting with a gradient of 0-50% EtOAc in heptane. The product containing fractions were combined and concd to dryness under reduced pressure to give *ethyl 2-ethyl-4-oxocyclopentanecarboxylate* as a light yellow oil (1.6 g, 83%): LC/MS (Table 1, Method c) MS m/z 229 (M+H)⁺; ¹H NMR (CDCl₃) δ 4.14 (q, 2 H), 3.90 (m, 4 H), 2.99 (q, 1 H), 2.32-2.27 (m, 1 H), 2.26-2.11 (m, 1 H), 2.05-1.99 (m, 1 H), 1.96-1.91 (m, 1 H), 1.83-1.78 (m, 1 H), 1.46-1.39 (m, 1 H), 1.31-1.24 (m, 1 H), 1.26 (t, 3 H), 0.90 (t, 3 H).

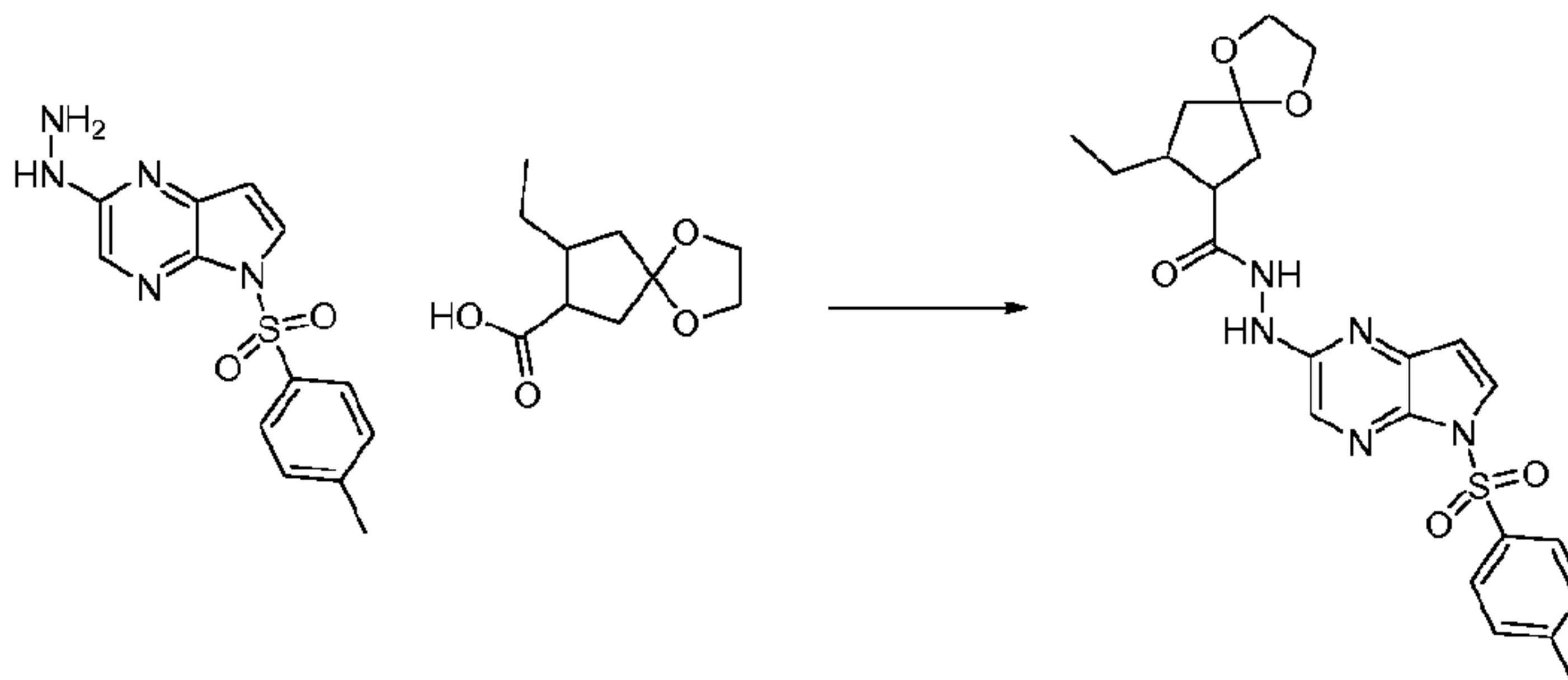
Step B: 8-ethyl-1,4-dioxaspiro[4.4]nonane-7-carboxylic acid



A round bottom flask was charged with ethyl 8-ethyl-1,4-dioxaspiro[4.4]nonane-7-carboxylate (0.32 g, 1.4 mmol) and aqueous 1 N sodium hydroxide (14.0 mL, 14.0 mmol). The solution was stirred overnight at rt. To the solution was added DCM (30 mL) followed by the addition of 20% aqueous citric acid (about 20 mL) to reach pH of about 2. The layers were separated and the aqueous solution was extracted with DCM (2x30 mL) and DCM/EtOAc (1:1, 30 mL). The combined extracts were dried over anhydrous MgSO₄, filtered, and concd under reduced pressure

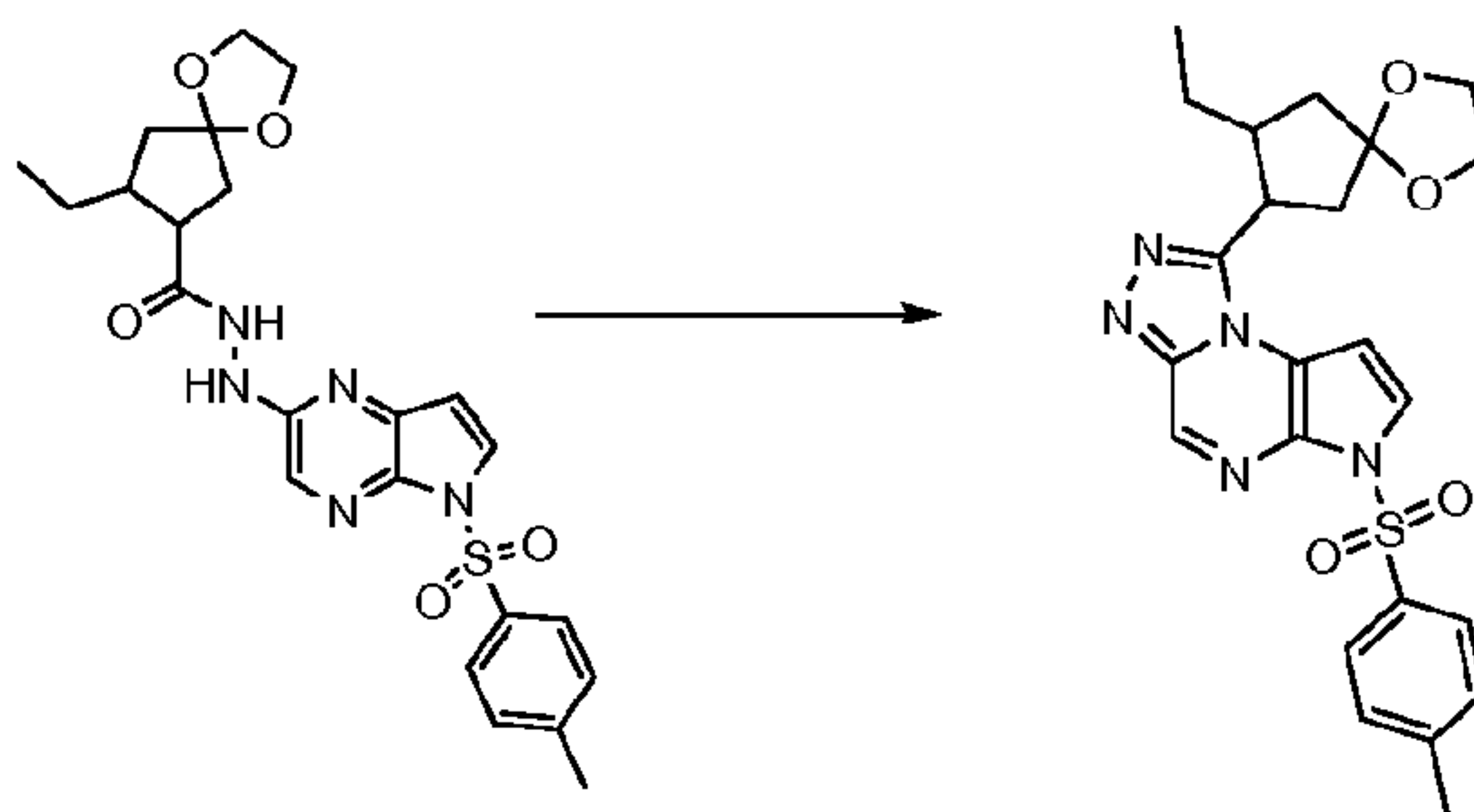
to give *8-ethyl-1,4-dioxaspiro[4.4]nonane-7-carboxylic acid* as a clear, colorless oil (0.27 g, 96%): LC/MS (Table 1, Method c) $R_t = 1.20$ min; MS m/z : 201 ($M+H$)⁺.

Step C: 8-ethyl-*N'*-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)-1,4-dioxaspiro[4.4]nonane-7-carbohydrazide



A 50 mL round bottom flask was charged with 2-hydrazinyl-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine (0.350 g, 1.16 mmol, Example #1, Step D), 8-ethyl-1,4-dioxaspiro[4.4]nonane-7-carboxylic acid (0.250 g, 1.25 mmol), and DCM (6.0 mL). To the reaction mixture was added HATU (0.483 g, 1.27 mmol) and TEA (0.64 mL, 4.6 mmol) and the resulting yellow suspension was stirred at rt for about 3 h. To the reaction solution was added DCM (25 mL) and the solution was washed with water and brine (20 mL each). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concd under reduced pressure to give a brown oil. The crude product was purified by flash silica gel chromatography (25 g Silicycle column) eluting with a gradient of: 0-10% MeOH in DCM over 25 min. The product containing fractions were concd under reduced pressure to give *8-ethyl-N'-(5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)-1,4-dioxaspiro[4.4]nonane-7-carbohydrazide* as a foam (0.50 g, 89%): LC/MS (Table 1, Method c) $R_t = 1.49$ min; MS m/z : 486 ($M+H$)⁺.

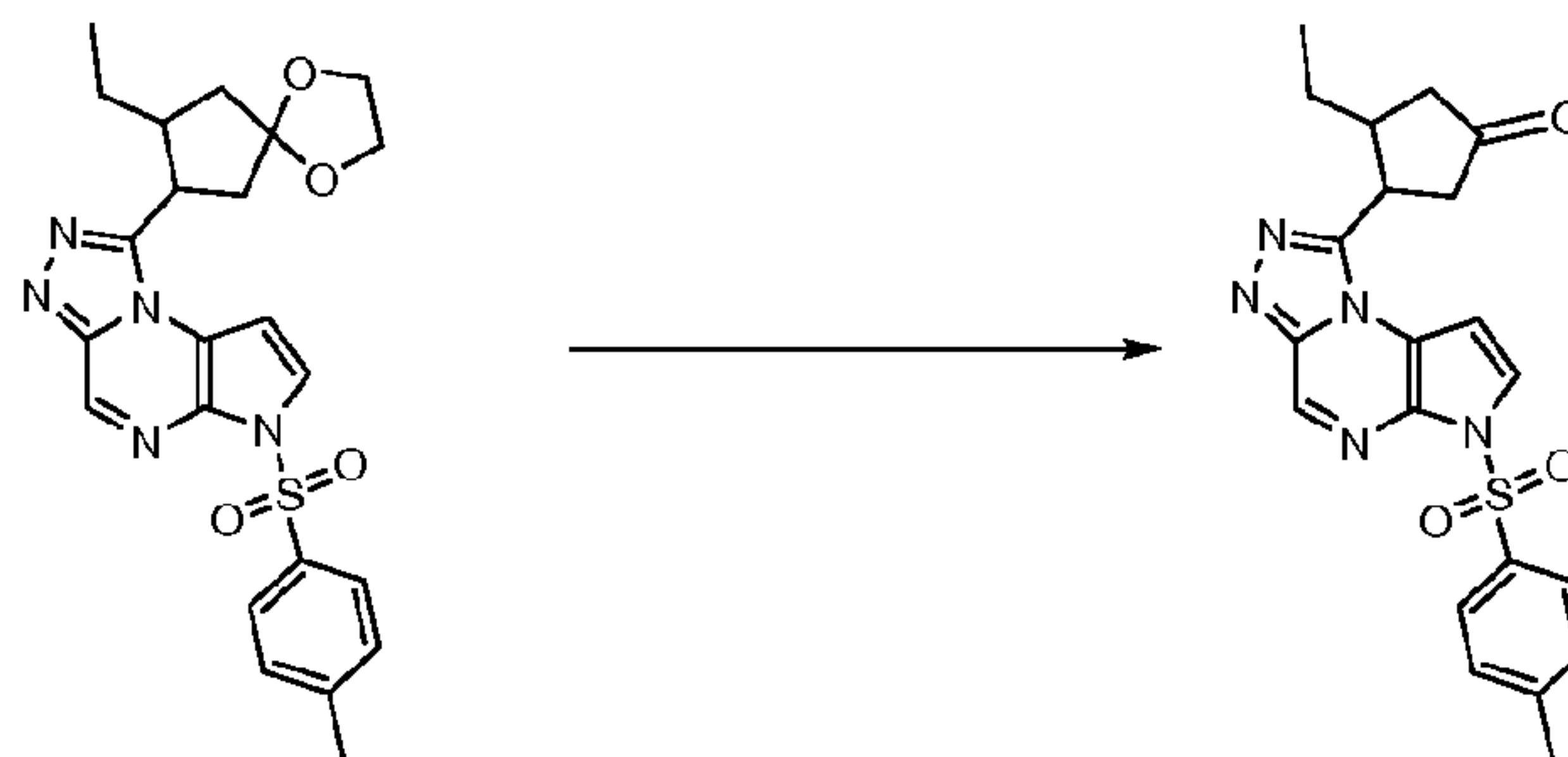
Step D: 1-(8-ethyl-1,4-dioxaspiro[4.4]nonan-7-yl)-6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine



A round bottom flask was charged with 8-ethyl-*N'*-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)-1,4-dioxaspiro[4.4]nonane-7-carbohydrazide (4.90 g, 10.1 mmol) and 1,4-dioxane (50 mL). To the flask was added DIEA (8.81 mL, 50.5 mmol) followed by the addition of thionyl chloride (0.770

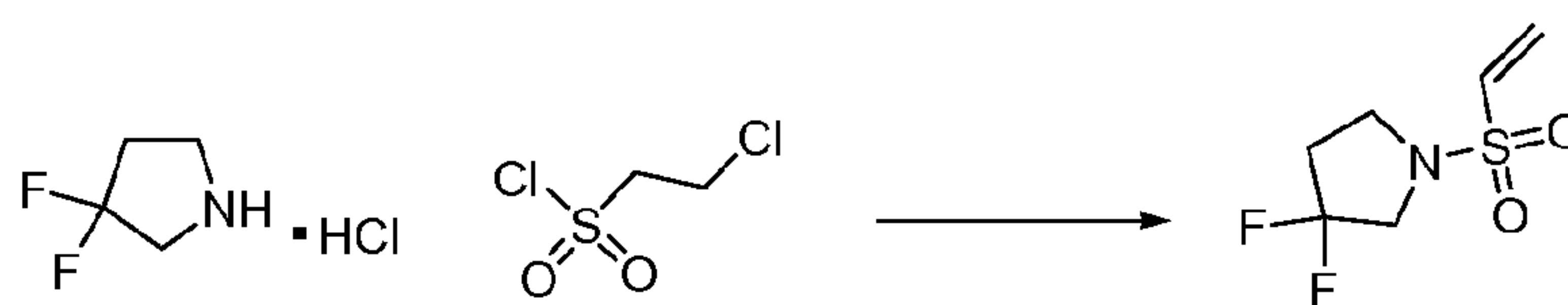
mL, 10.6 mmol). The mixture was heated to about 75 °C for about 90 min. Additional thionyl chloride (0.074 mL, 1.0 mmol) was added and heating was continued for about 1 h. The reaction was cooled to rt and stirred overnight. The solution was diluted with DCM (75 mL) and washed with water (50 mL). The layers were separated and the organic layer was dried over anhydrous MgSO_4 , filtered, and concd under reduced pressure to give a dark brown oil. The crude product was purified via flash silica gel chromatography eluting with a gradient of 0-60% acetone in heptane with a hold at 60% acetone in heptane. The product containing fractions were combined and concd to give material that was loaded onto a second column (Silicycle, 40 g column), eluting with a gradient of 0-60% acetone in heptane. The product containing fractions were combined and concd under reduced pressure to give *1-(8-ethyl-1,4-dioxaspiro[4.4]nonan-7-yl)-6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazine* as a tan powder (3.0 g, 64%): LC/MS (Table 1, Method c) $R_t = 1.44$ min; MS m/z : 468 ($\text{M}+\text{H}$)⁺.

Step E: 3-ethyl-4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)cyclopentanone



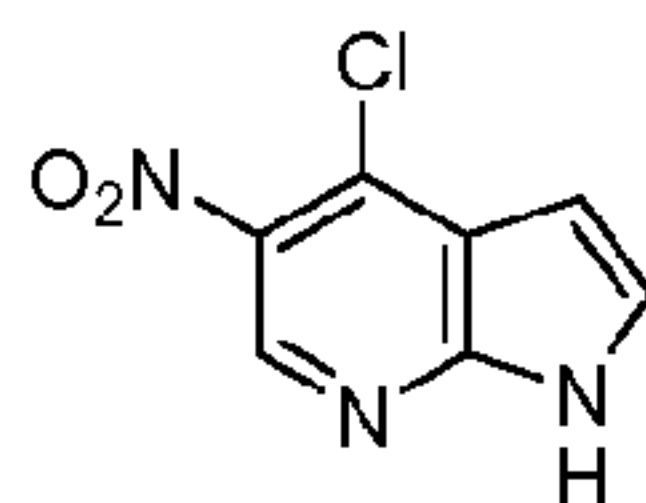
A round bottom flask was charged with 1-((7*S*,8*R*)-8-ethyl-1,4-dioxaspiro[4.4]nonan-7-yl)-6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazine (3.56 g, 7.61 mmol) and THF (20 mL). To the solution was added aqueous HCl (6N, 3.81 mL, 22.8 mmol) and the mixture was stirred at rt for about 2 h. The solvent was removed under reduced pressure and DCM (75 mL) and water (50 mL) were added. The layers were separated and the organic solution was dried over anhydrous MgSO_4 , filtered, and concd under reduced pressure to give *3-ethyl-4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)cyclopentanone* as a brown foam (2.99 g, 93%): LC/MS (Table 1, Method c) $R_t = 1.40$ min; MS m/z : 424 ($\text{M}+\text{H}$)⁺.

Preparation #26: 3,3-difluoro-1-(vinylsulfonyl)pyrrolidine

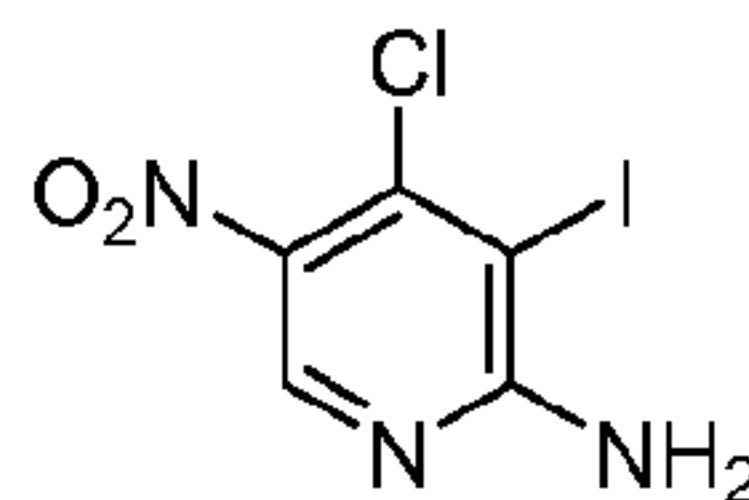


A solution of 3,3-difluoropyrrolidine hydrochloride (0.3 g, 2.1 mmol, Matrix) and DIEA (0.37 mL, 2.1 mmol) in MeCN (5 mL) was stirred at about 50 °C for about 30 min. The reaction was cooled to ambient temperature and concd under reduced pressure. The solid was dissolved in MeCN (2 mL) and a solution of 2-chloroethanesulfonyl chloride (0.22 mL, 2.1 mmol) in Et₂O (3 mL) was added at about -78 °C and stirred for about 2 h. To the reaction mixture was added DIEA (0.6 mL, 3.4 mmol) and stirred for about 1 h. The reaction was warmed to ambient temperature and the solvent was removed under reduced pressure. The residue was partitioned between DCM (5 mL) and water (2 x 2 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered and concd under reduced pressure to give crude *3,3-difluoro-1-(vinylsulfonyl)pyrrolidine* (0.11 g, 27%) which was used without further purification: LC/MS (Table 1, Method **b**) *R*_t = 2.04 min; MS *m/z*: 198 (M+H)⁺.

Preparation #27: 4-chloro-5-nitro-1*H*-pyrrolo[2,3-*b*]pyridine

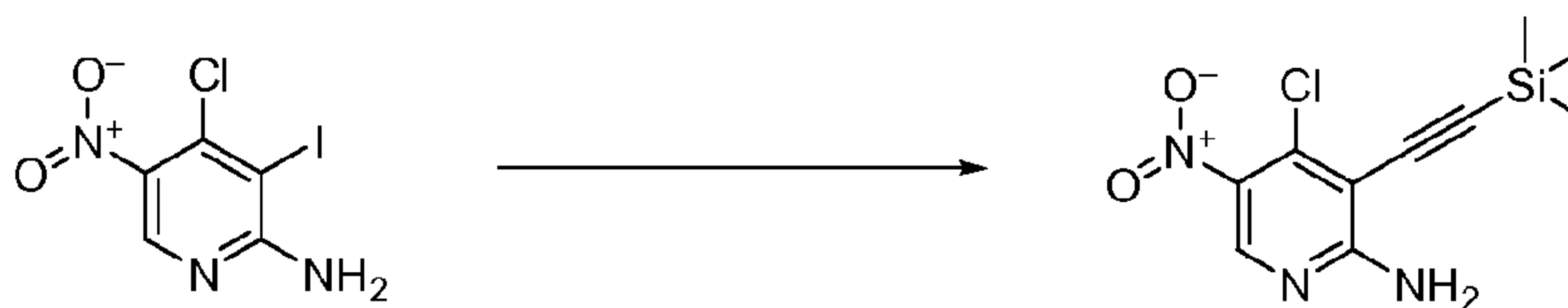


Step A: 4-chloro-3-iodo-5-nitropyridin-2-amine



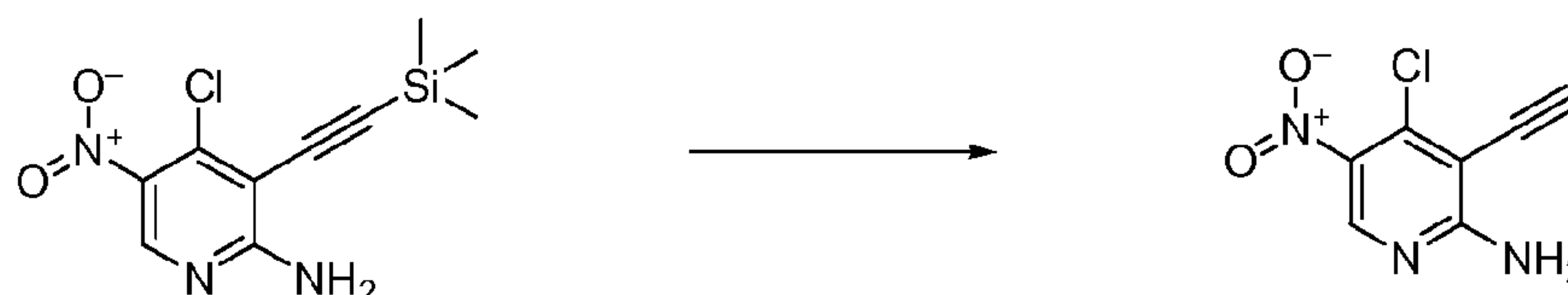
A solution of 4-chloro-3-iodopyridin-2-amine (0.25 g, 0.982 mmol, Boa Pharma) in concd H₂SO₄ (1.95 mL) was cooled to about 0 °C before the portion wise addition of potassium nitrate (0.21 g, 2.2 mmol) over 10 min. The reaction was stirred for about 4 h at about 0 °C. The reaction mixture was slowly pipetted over a solution of ammonium hydroxide and crushed ice (10 mL) in an ice bath. The pH of the reaction was maintained above 9 by the incremental addition of ammonium hydroxide. The resulting precipitate was filtered and dried to afford *4-chloro-3-iodo-5-nitropyridin-2-amine* (0.085 g, 29%) as a green-tinted solid LC/MS (Table 1, Method **n**) *R*_t = 0.64 min; MS *m/z*: 298 (M-H)⁻.

Step B: 4-chloro-5-nitro-3-((trimethylsilyl)ethynyl)pyridin-2-amine



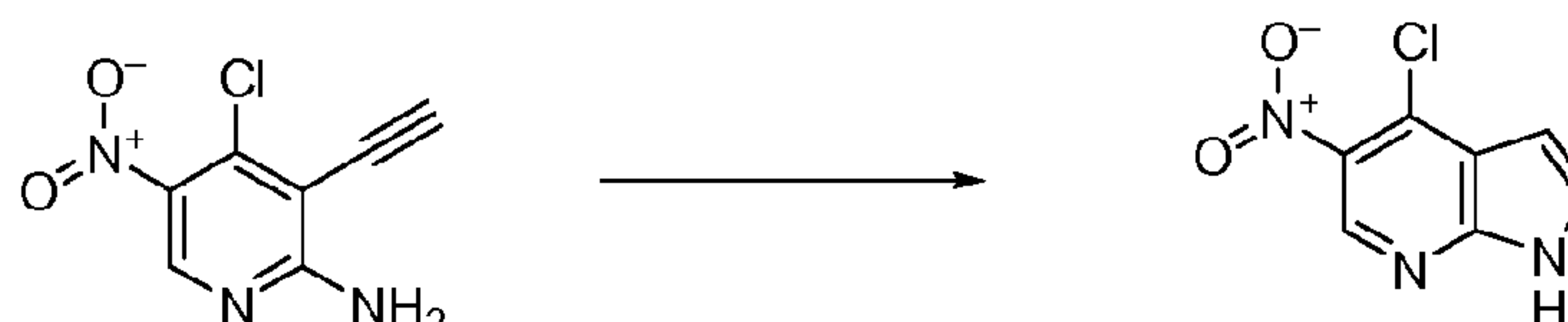
To a solution of 4-chloro-3-iodo-5-nitropyridin-2-amine (5.30 g, 17.7 mmol) in THF (90 mL) was added TEA (15.0 mL, 108 mmol). The reaction mixture was degassed and purged with nitrogen 3 times. Bis(triphenylphosphine)-palladium(II)dichloride (0.62 g, 0.88 mmol, Strem), copper(I) iodide (0.17 g, 0.89 mmol), and trimethylsilylacetylene (5.4 mL, 39 mmol) were added to the reaction mixture. The mixture was degassed and purged 3 times with nitrogen. The reaction was heated at about 60 °C for about 16 h. The reaction mixture was cooled to ambient temperature. The reaction mixture was filtered and washed with THF (200 mL). The filtrate was concd under reduced pressure. DCM (100 mL) was added to the residue and the precipitate that formed was filtered and collected to give 4-chloro-5-nitro-3-((trimethylsilyl)ethynyl)pyridin-2-amine (0.77 g). The remaining filtrate was concd under reduced pressure and the crude material was purified by flash chromatography on silica gel eluting with a gradient of 0-100% EtOAc in DCM. The purified material was combined with the 0.77 g of precipitate to afford 4-chloro-5-nitro-3-((trimethylsilyl)ethynyl)pyridin-2-amine (2.22 g, 47%) as a yellow solid: LC/MS (Table 1, Method c) R_t = 1.62 min; MS m/z 268 (M-H)⁻.

Step C: 4-chloro-3-ethynyl-5-nitropyridin-2-amine



To a solution of 4-chloro-5-nitro-3-((trimethylsilyl)ethynyl)pyridin-2-amine (1.98 g, 7.34 mmol) in DMF (25 mL) was added potassium fluoride on alumina (40 wt%, 2.67 g, 18.35 mmol). The suspension was stirred at ambient temperature for about 1 h. Activated charcoal (0.3 g) was added and the suspension was filtered through Celite[®], washing with DMF (150 mL). The solvent was removed under reduced pressure and the crude material was purified by silica gel chromatography eluting with a gradient of 0-10% MeOH in DCM to afford 4-chloro-3-ethynyl-5-nitropyridin-2-amine (1.03 g, 71%) as a yellow solid: LC/MS (Table 1, Method n) R_t = 0.59 min; MS m/z : 196 (M-H)⁻.

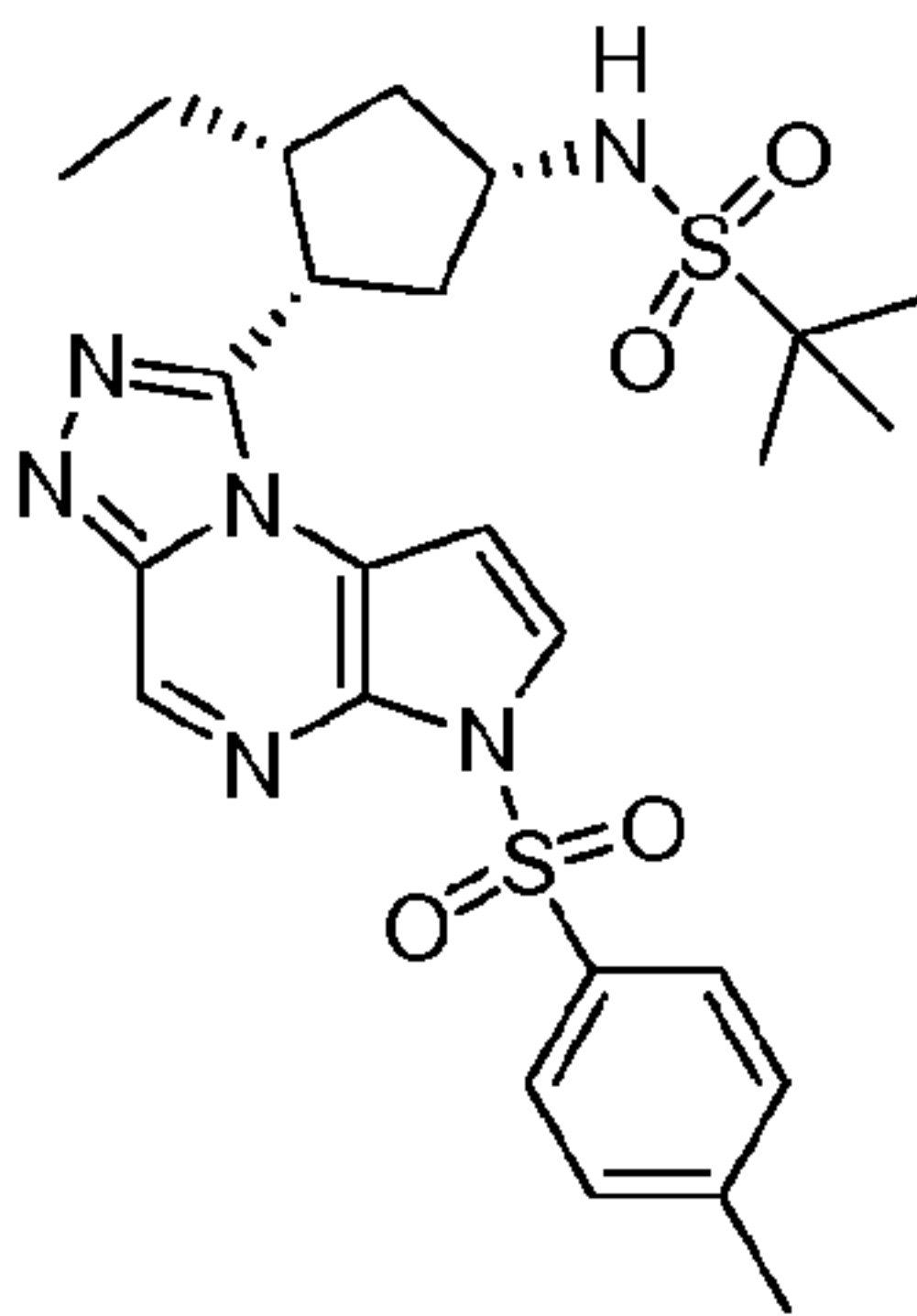
Step D: 4-chloro-5-nitro-1H-pyrrolo[2,3-b]pyridine



To a solution of 4-chloro-3-ethynyl-5-nitropyridin-2-amine (0.16 g, 0.81 mmol) in DMF (3 mL) was added chloro(1,5-cyclooctadiene) rhodium (I) dimer (0.02 g, 0.04 mmol) and tris(4-fluorophenyl)phosphine (0.128 g, 0.405 mmol). The reaction mixture was degassed by bubbling

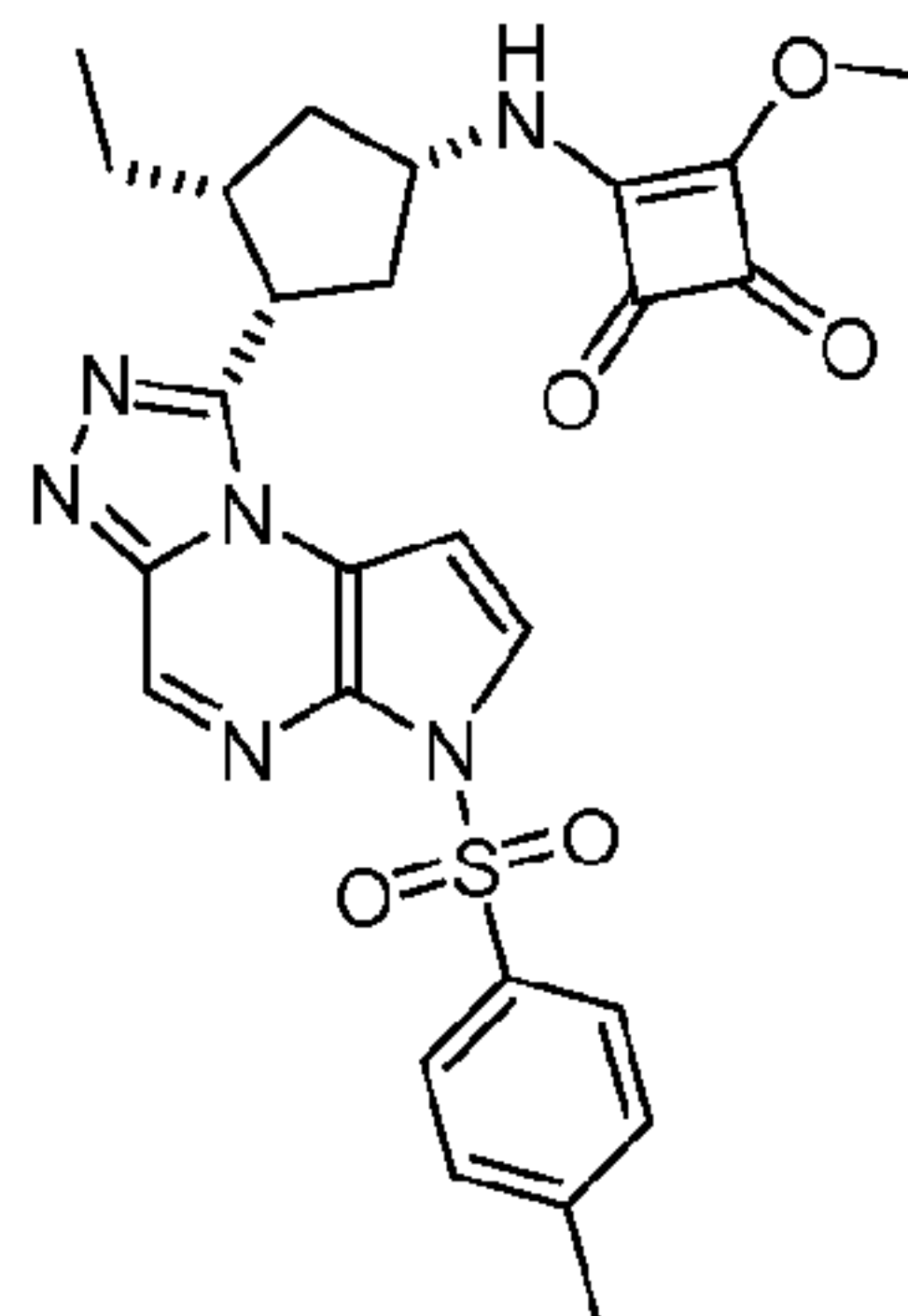
argon for 15 min. The reaction mixture was heated at about 80 °C for about 45 min. The reaction was cooled to ambient temperature and the solvent was removed under reduced pressure and the residue was suspended in ether (10 mL). The precipitate was collected by filtration and dried to give *4-chloro-5-nitro-1H-pyrrolo[2,3-*b*]pyridine* (0.132 g, 83%, contains approximately 6% mol of DMF and approximately 3% mol of tris(4-fluorophenyl)phosphine) as a brown solid: LC/MS (Table 1, Method **a**) $R_t = 2.05$ min; MS m/z 198 (M+H)⁺.

Preparation #28*: *N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-methylpropane-2-sulfonamide*



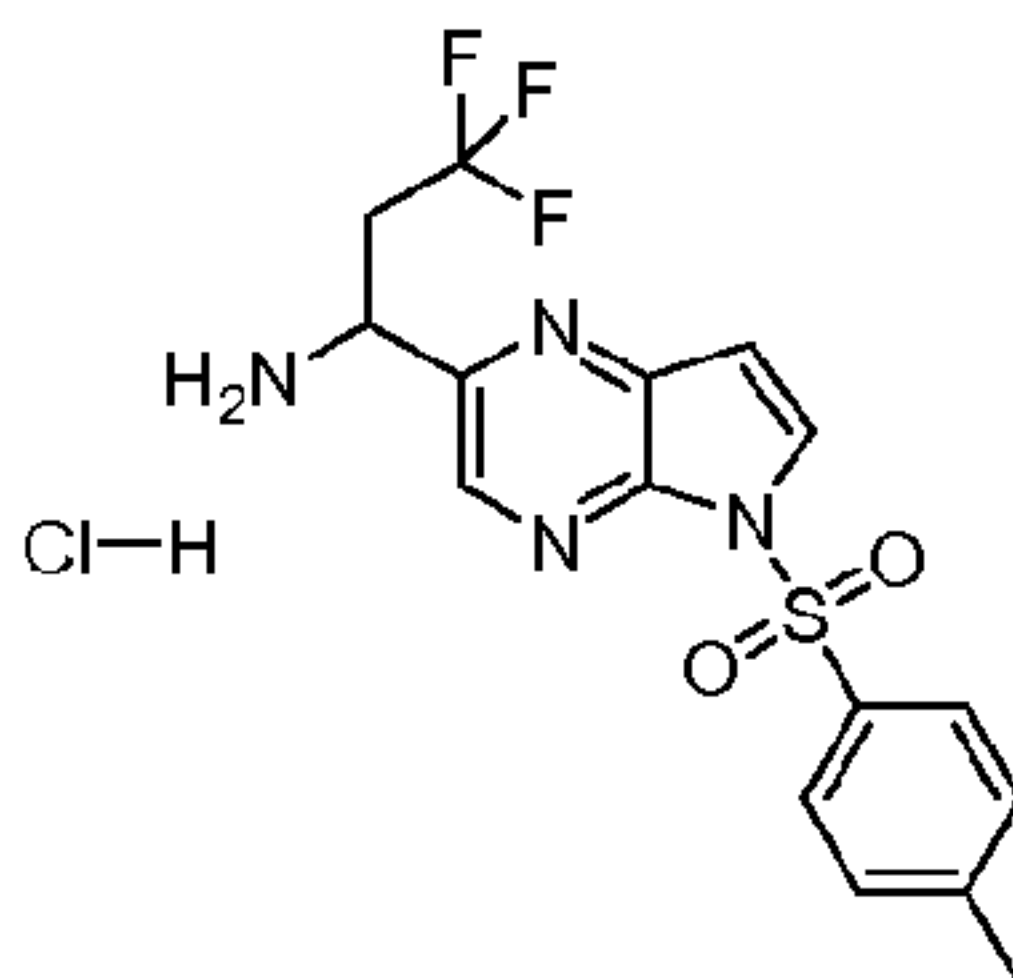
To a solution of (1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine (115 mg, 0.271 mmol, Preparation #BB.1*) in DCM (1.5 mL) was added DIEA (0.071 mL, 0.406 mmol) followed by 2-methylpropane-2-sulfinic chloride (0.037 mL, 0.298 mmol). After about 4h the reaction mixture was diluted with EtOAc (10 mL) and aqueous saturated NaHCO₃ (10 mL). The organic layer was separated, dried over anhydrous Na₂SO₄, filtered and coned *in vacuo*. The crude residue was dissolved in DCM (1.5 mL) and a freshly prepared solution of *m*-chloroperbenzoic acid (0.271 mL, 0.271 mmol, 1M in DCM) was added. After about 2h the reaction mixture was diluted with EtOAc (10 mL) and saturated aqueous NaHCO₃ (10 mL). The organic layer was separated, dried over anhydrous Na₂SO₄, filtered and coned *in vacuo*. The crude residue was purified by chromatography on silica gel eluting with EtOAc to provide *N-((1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)-2-methylpropane-2-sulfonamide* (95 mg, 64% yield) as an oil. LC/MS (Table 1, Method **a**) $R_t = 2.40$ min; MS m/z : 545 (M+H)⁺.

Preparation #29*: 3-((1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)-4-methoxycyclobut-3-ene-1,2-dione

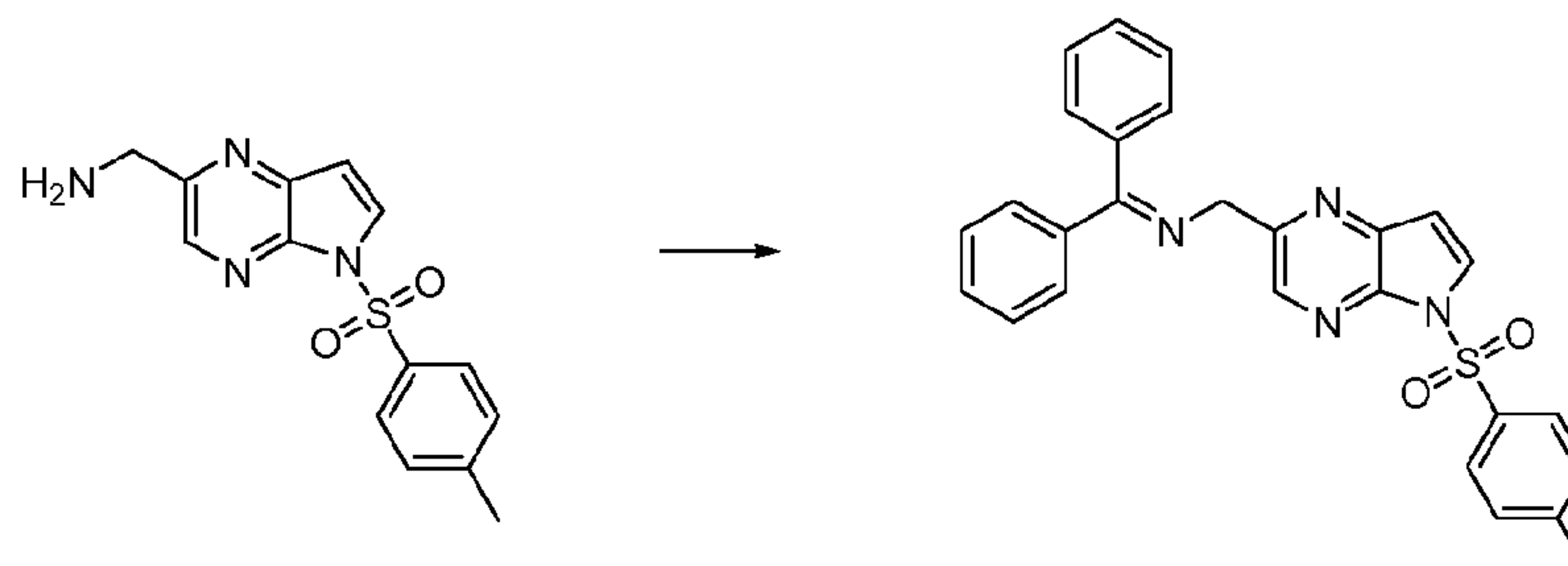


To a solution of (1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine (0.40 g, 0.942 mmol, Example #8 Step M) in MeOH (3 mL) was added 3,4-dimethoxycyclobut-3-ene-1,2-dione (0.14 g, 0.98 mmol) and DIEA (0.18 mL, 1.0 mmol). The reaction was stirred at rt for about 16.5 h. Then the solid from the reaction mixture was collected via vacuum filtration, while washing with cold MeOH (about 4 °C, 10 mL), and dried in a vacuum oven at about 60 °C to give crude 3-((1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylamino)-4-methoxycyclobut-3-ene-1,2-dione (0.36 g, 73%, 90% purity): LC/MS (Table 1, Method **a**) R_t = 2.13 min; MS m/z : 535 (M+H)⁺.

Preparation #30: 3,3,3-trifluoro-1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)propan-1-amine hydrochloride



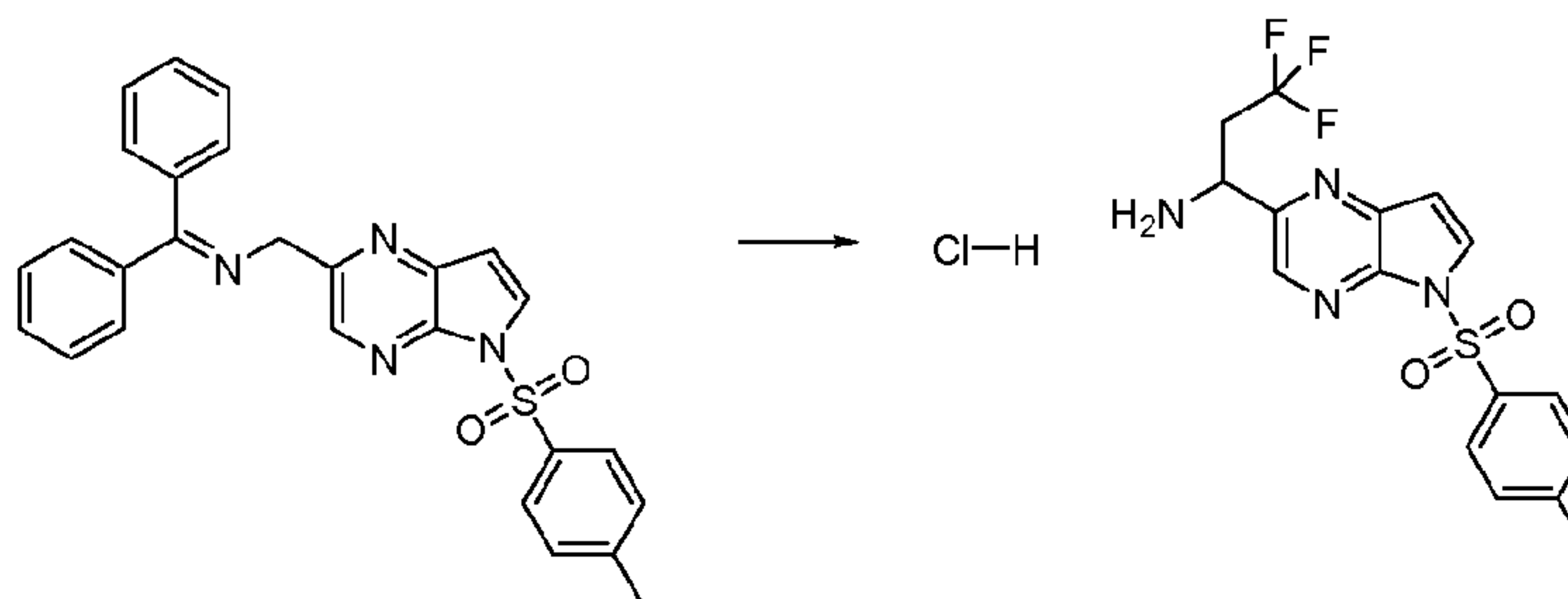
Step A: *N*-(diphenylmethylene)-1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)methanamine



To a solution of (5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)methanamine (2.00 g, 6.61 mmol, Example #5 Step C) in DCM (30 mL) was added diphenylmethanimine (1.16 mL, 6.61 mmol).

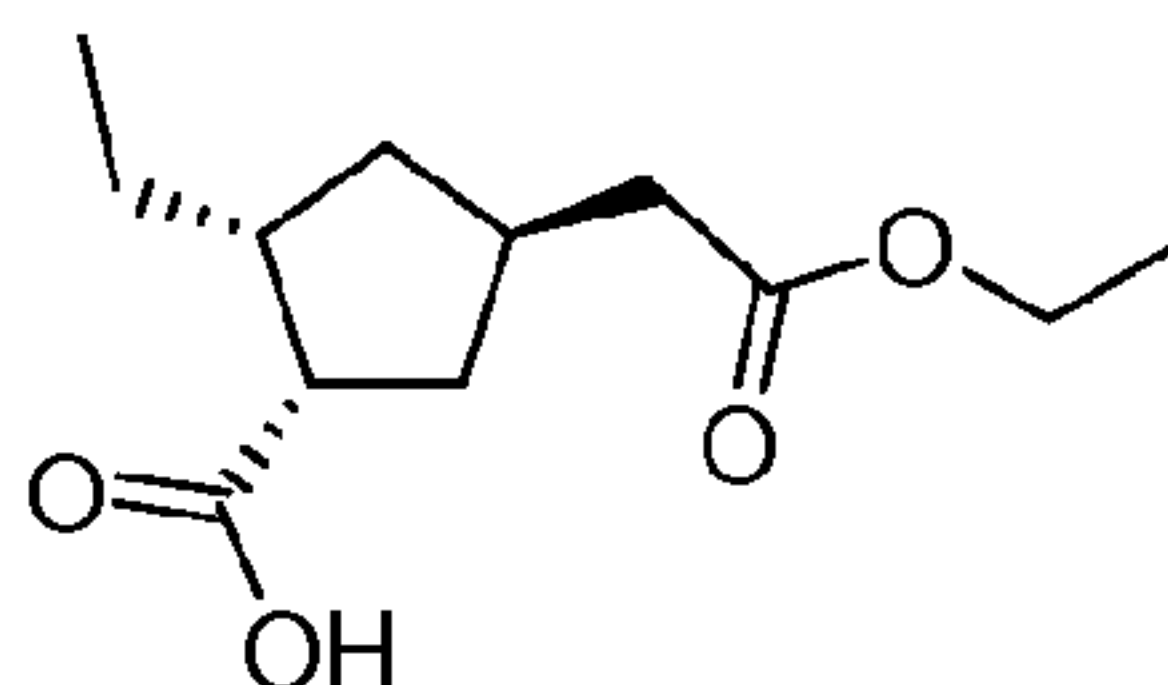
After about 2 d, the reaction mixture was concd *in vacuo* to provide *N*-(diphenylmethylene)-1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)methanamine (2.75 g, 89%) as a foam and used without further purification. LC/MS (Table 1, Method **a**) $R_t = 3.02$ min; MS m/z : 467 (M+H)⁺.

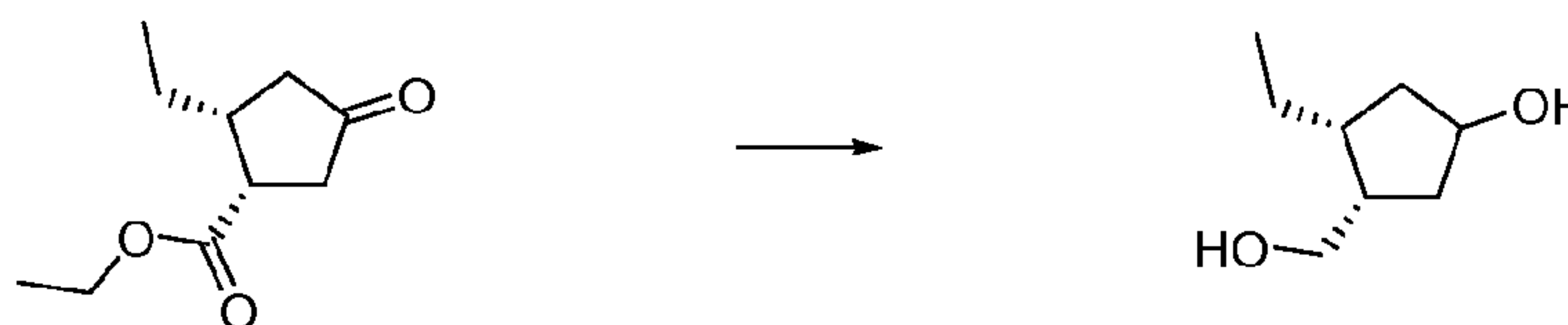
Step B: 3,3,3-trifluoro-1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)propan-1-amine, hydrochloride



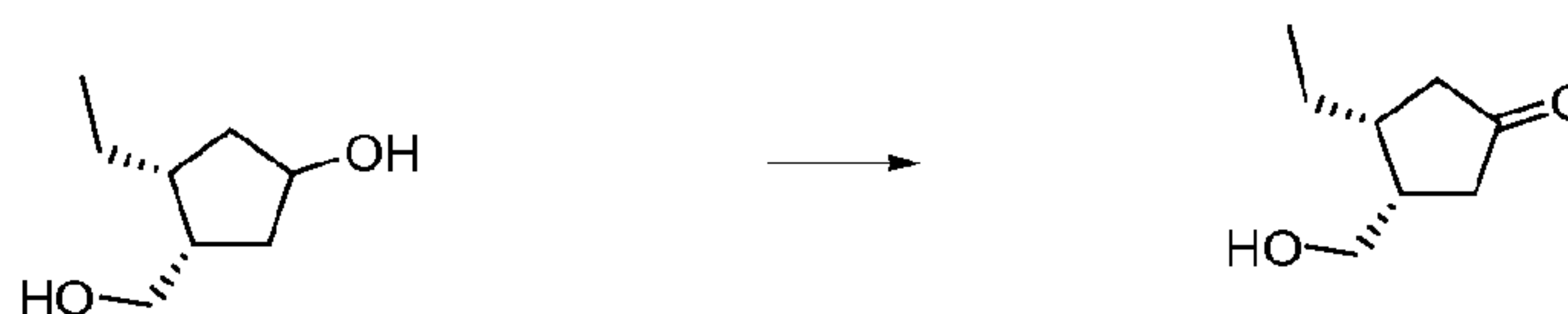
To a solution of *N*-(diphenylmethylene)-1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)methanamine (0.722 g, 1.55 mmol) in THF (3 mL) at about -78 °C was added NaHMDS (0.5 M in THF, 1.55 mL, 1.55 mmol). After about 30 min, 1,1,1-trifluoro-2-iodoethane (1.51 mL, 15.5 mmol) was added to the reaction mixture. After about 4 h, the reaction mixture was allowed to warm to rt slowly over night. After about 15 h, EtOAc (30 mL) and saturated aqueous NaHCO₃ (30 mL) were added. The organic layer was separated, concd *in vacuo* and purified by chromatography on silica gel eluting with EtOAc/heptane (20-50%) to provide the crude alkylated imine. The imine was dissolved in isopropyl acetate (30 mL) and concd HCl (0.50 mL) was added. The reaction mixture was spun on a rotory evaporator for 1 h prior to partial concentration to approx 10 mL. Additional isopropyl acetate (30 mL) was added and the solvent was partially removed *in vacuo* until approx. 10 mL remained. Et₂O (30 mL) was added and the solution was allowed to age for about 30 min. The resulting solids were collected by filtration and dried *in vacuo* to provide 3,3,3-trifluoro-1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)propan-1-amine hydrochloride (0.150 g, 23%) as a colorless solid. LC/MS (Table 1, Method **a**) $R_t = 1.88$ min; MS m/z 385 (M+H)⁺.

Preparation #31: (1*S*,2*R*,4*R*)-4-(2-ethoxy-2-oxoethyl)-2-ethylcyclopentanecarboxylic acid

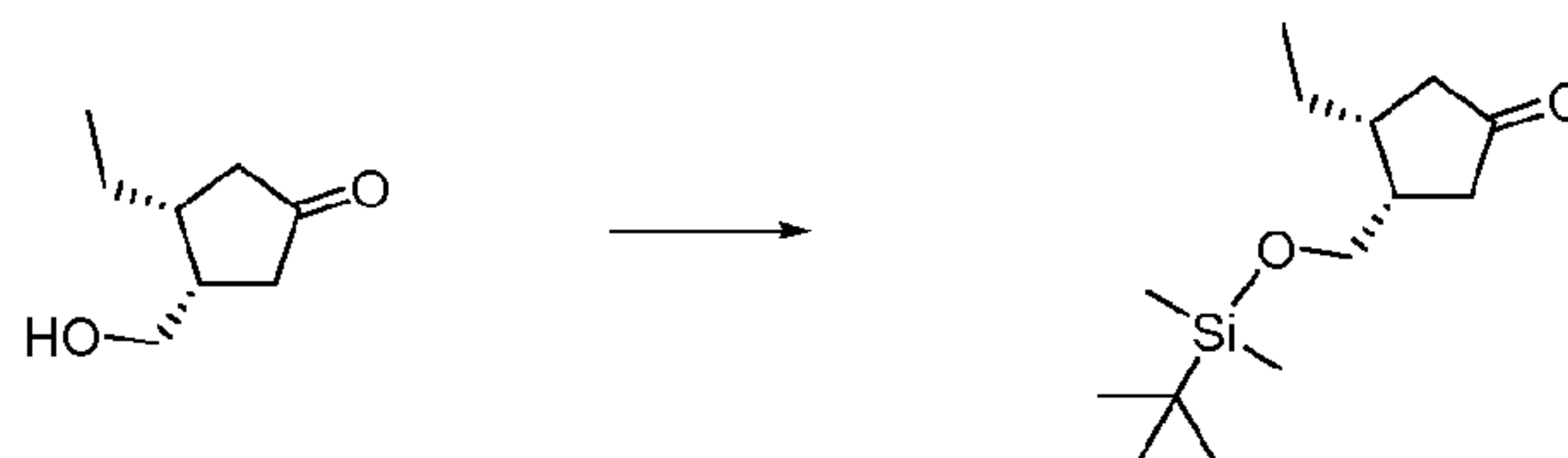


Step A: (3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentanol

To a solution of (1*S*,2*R*)-ethyl 2-ethyl-4-oxocyclopentanecarboxylate (5 g, 27.1 mmol, Example #22 step B) in THF (100 mL) at about -78 °C was added LAH (2 M in THF, 54.3 mL, 109 mmol). After about 1 h, the reaction mixture was allowed to warm to rt slowly. After about 4 h, water (4.8 mL) followed by aqueous NaOH (15% w/v, 4.8 mL) followed by water (9.6 mL) was added to the reaction mixture. After about 15 h, anhydrous Na₂SO₄ was added and the slurry was filtered and coned in vacuo to provide crude (3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentanol (3.9 g, 100%) as an oil which was used without further purification. LC/MS (Table 1, Method **a**) R_t = 2.40 min; MS *m/z*: 145 (M+H)⁺.

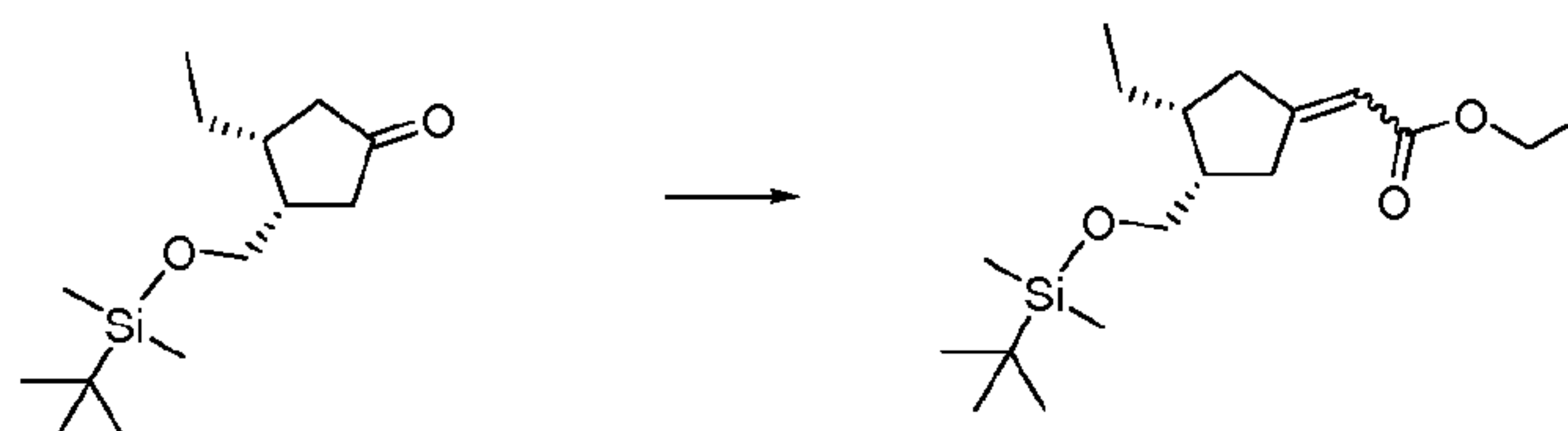
Step B: (3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentanone

To a solution of (3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentanol (4.00 g, 27.7 mmol) in MeCN (70 mL) and water (30.0 mL) was added potassium bromate (1.487 mL, 29.1 mmol) and CAN (0.760 g, 1.387 mmol). The reaction mixture was heated to about 80 °C. After about 2 h, the reaction mixture was cooled to rt and Et₂O (100 mL) was added. The organic layer was separated, washed with brine (30 mL), coned *in vacuo* and purified by chromatography on silica gel eluting with EtOAc/heptane (20-60%) to provide (3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentanone (2.4 g, 61%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 3.79 (dd, *J* = 10.5, 5.3 Hz, 1H), 3.70 (dd, *J* = 10.5, 6.5 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.41 – 2.25 (m, 4H), 2.15 – 2.05 (m, 1H), 1.55 – 1.65 (m, 2H), 1.43 – 1.30 (m, 1H), 0.97 (t, *J* = 7.3 Hz, 3H).

Step C: (3*S*,4*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-4-ethylcyclopentanone

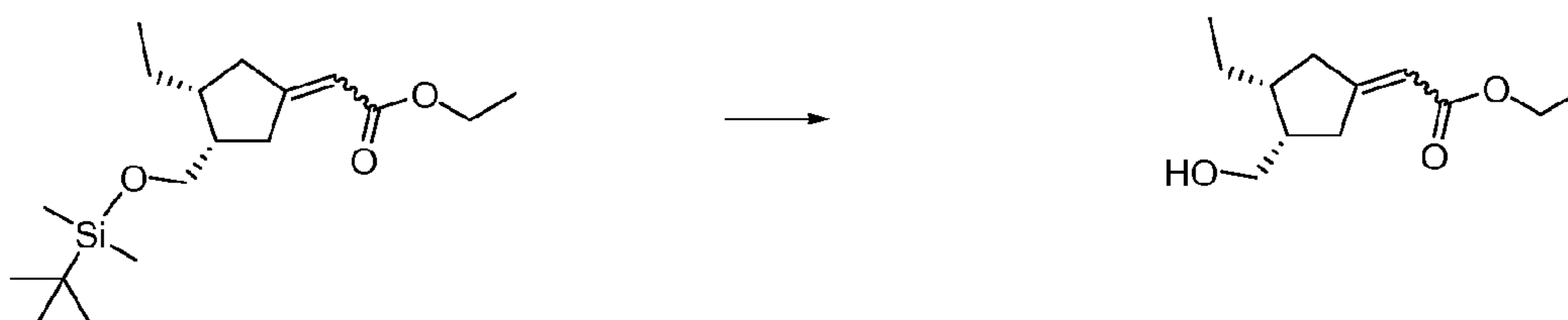
To a solution of (3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentanone (2.60 g, 18.3 mmol) in DMF (30 mL) was added imidazole (1.87 g, 27.4 mmol) followed by *tert*-butylchlorodimethylsilane (3.03 g, 20.1 mmol). After about 4 h, heptane (50 mL) was added. The heptane layer was removed and washed with brine. The brine layer was combined with the DMF layer and extracted with EtOAc/heptane (1:1, 30 mL). The heptane and EtOAc layers were combined, concd *in vacuo* and purified by chromatography on silica gel eluting with EtOAc/heptane (0-30%) to provide (3*S*,4*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-4-ethylcyclopentanone (3.5 g, 75%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.77 (dd, *J* = 10.5, 4.3 Hz, 1H), 3.64 (dd, *J* = 10.5, 4.0 Hz, 1H), 2.40 – 2.20 (m, 5H), 2.18 – 2.02 (m, 1H), 1.65 – 1.55 (m, 1H), 1.52 – 1.37 (m, 1H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.87 (s, 9H), 0.43 (s, 3H), 0.03 (s, 3H).

Step D: ethyl 2-((3*S*,4*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-4-ethylcyclopentylidene)acetate



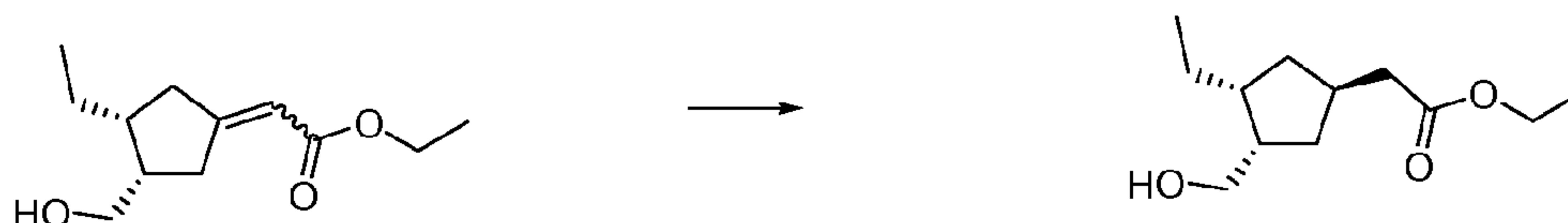
To a slurry of NaH (60% dispersion in mineral oil, 0.608 g, 15.2 mmol) in THF (50 mL) was added ethyl 2-(diethoxyphosphoryl)acetate (3.25 mL, 16.2 mmol). After about 30 min, the phosphonate solution was added to a flask charged with (3*S*,4*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-4-ethylcyclopentanone (2.6 g, 10.14 mmol). After about 20 h, EtOAc (20 mL) and saturated aqueous NH₄Cl (20 mL) were added. The organic layer was removed concd *in vacuo* and purified by chromatography on silica gel eluting with EtOAc/heptane (20-60%) to provide ethyl 2-((3*S*,4*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-4-ethylcyclopentylidene)acetate (3.3 g, 100%) as an oil. LC/MS (Table 1, Method a) *R*_t = 3.91, 3.96 min; MS *m/z*: 327 (M+H)⁺.

Step E: ethyl 2-((3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentylidene)acetate



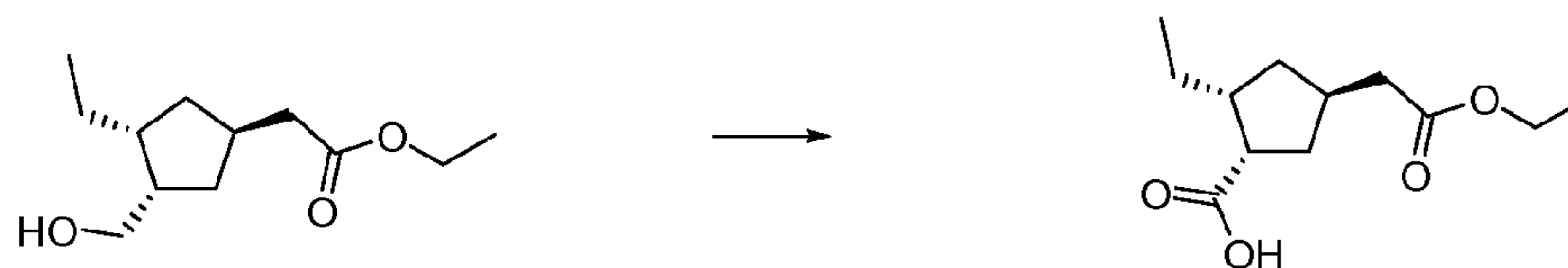
To a solution of ethyl 2-((3*S*,4*R*)-3-((*tert*-butyldimethylsilyloxy)methyl)-4-ethylcyclopentylidene)acetate (1.00 g, 3.06 mmol) in THF (20 mL) was added TBAF (1M in THF, 4.59 mL, 4.59 mmol). After 6 h, EtOAc and water were added. The organic layer was separated, concd *in vacuo* and purified by chromatography on silica gel eluting with EtOAc/heptane to provide ethyl 2-((3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentylidene)acetate (0.620 g, 95%) as an oil. LC/MS (Table 1, Method **a**) R_t = 1.96, 2.08 min; MS m/z : 213 (M+H)⁺.

Step F: ethyl 2-((1*R*,3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentyl)acetate



To a solution of ethyl 2-((3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentylidene)acetate (0.160 g, 0.754 mmol) in DCM (3 mL) was added Crabtree's catalyst (0.030 g, 0.038 mmol). The reaction mixture was sparged with hydrogen for about 5 min and an atmosphere of hydrogen was maintained via balloon. After about 24 h, the reaction mixture was concd *in vacuo* and purified by chromatography on silica gel eluting with EtOAc/heptane (30-80%) to provide ethyl 2-((1*R*,3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentyl)acetate (0.140 g, 87%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 4.12 (q, J = 7.1 Hz, 2H), 3.71 – 3.64 (dd, J = 10.5, 8.0 Hz, 1H), 3.47 (dd, J = 10.5, 8.0 Hz, 1H), 2.55 – 2.41 (m, 1H), 2.32 (d, J = 6.7 Hz, 2H), 2.02 – 1.89 (m, 1H), 1.88 – 1.76 (m, 1H), 1.70 – 1.60 (m, 1H), 1.48 – 1.33 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.22 – 1.07 (m, 1H), 0.90 (t, J = 7.4 Hz, 3H).

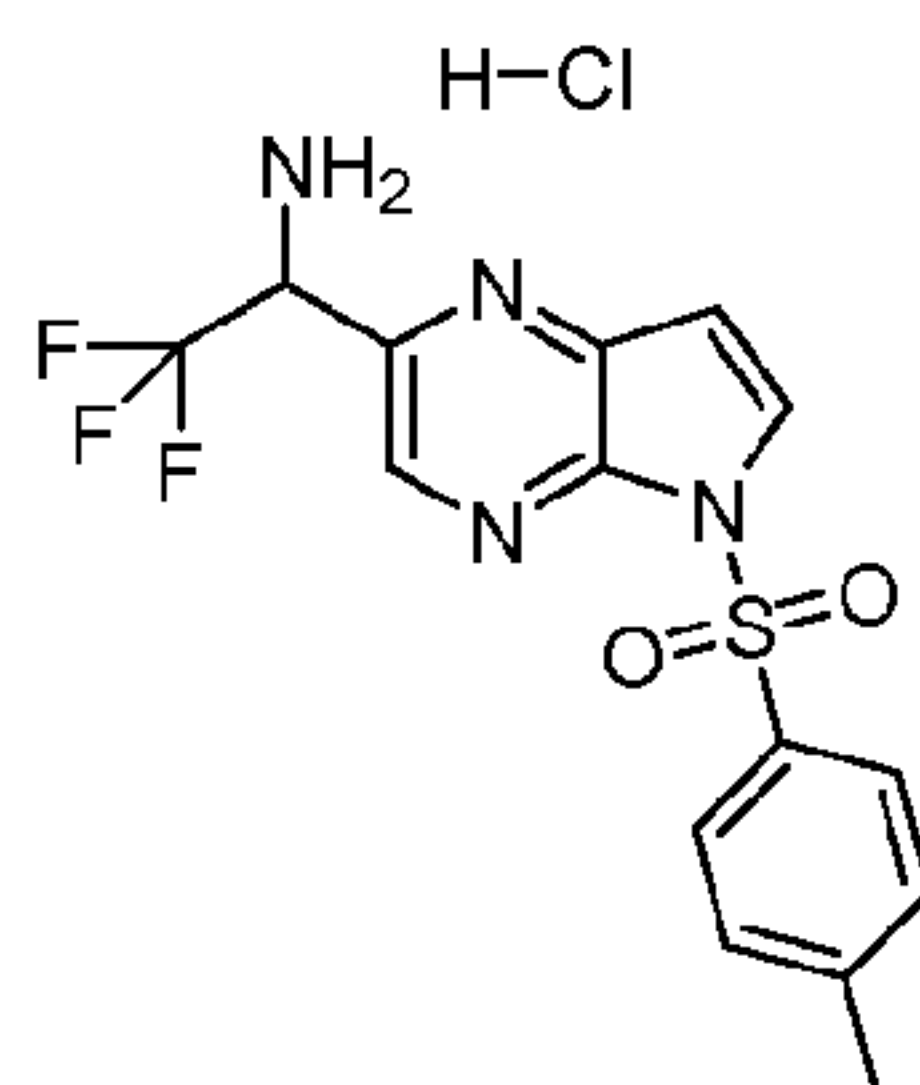
Step G: (1*S*,2*R*,4*R*)-4-(2-ethoxy-2-oxoethyl)-2-ethylcyclopentanecarboxylic acid



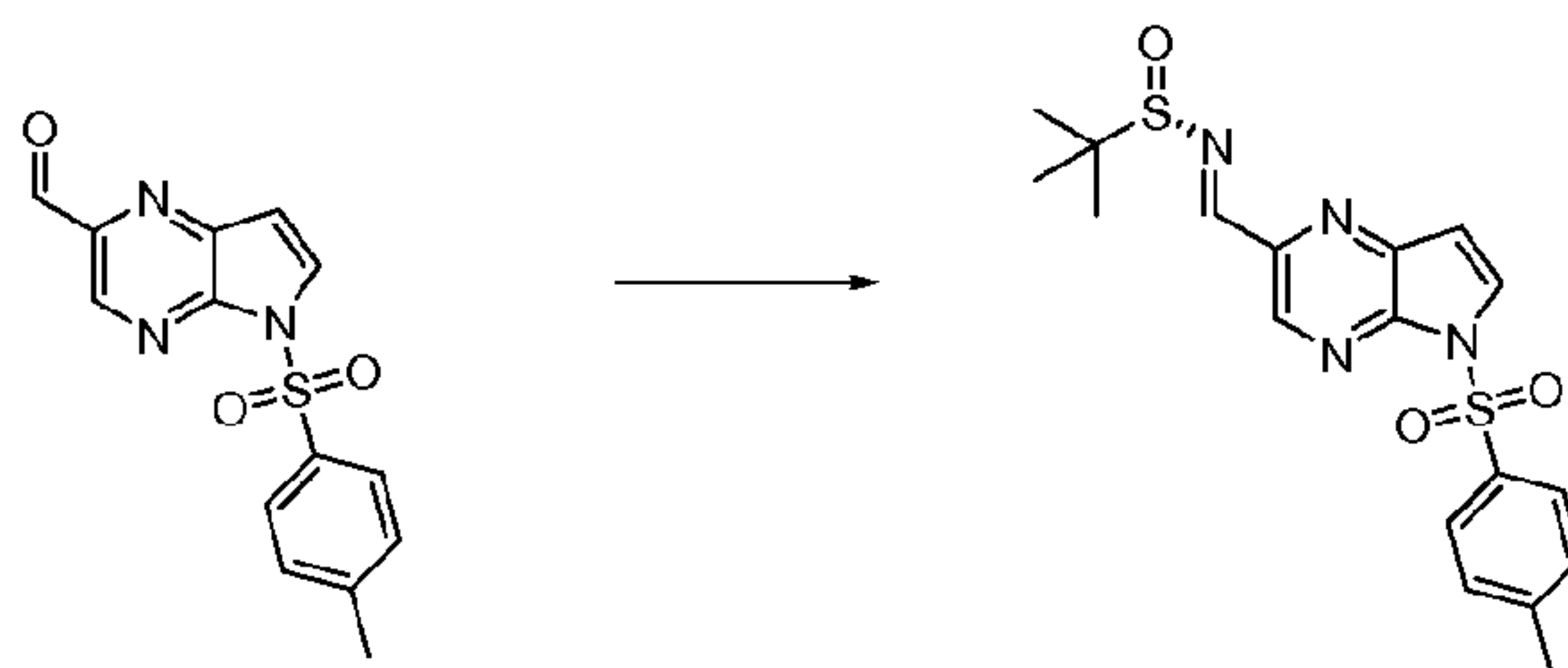
To a solution of ethyl 2-((1*R*,3*R*,4*S*)-3-ethyl-4-(hydroxymethyl)cyclopentyl)acetate (0.140 g, 0.653 mmol) in MeCN (2 mL), water (4 mL) and EtOAc (2 mL) was added sodium periodate (0.349 g, 1.633 mmol) followed by ruthenium(III) chloride hydrate (0.0015 g, 0.0065 mmol). After about 2 h, the reaction mixture was diluted with EtOAc (20 mL) and water (10 mL). The organic layer was separated and extracted with aqueous NaOH (1 N, 10 mL). The pH of the

aqueous layer was adjusted to about 1 with concd HCl and extracted with EtOAc (20 mL). The organic layer was dried over anhydrous MgSO_4 , filtered, and concd *in vacuo* to provide (1*S*,2*R*,4*R*)-4-(2-ethoxy-2-oxoethyl)-2-ethylcyclopentanecarboxylic acid (0.150 g, 101%) as an oil which was used without further purification. ^1H NMR (600 MHz, CDCl_3) δ 10.68 (bs, 1H), 4.13 (q, $J = 7.1$ Hz, 2H), 2.99 – 2.95 (m, 1H), 2.76 – 2.64 (m, 1H), 2.31 (d, $J = 7.6$ Hz, 2H), 2.24 (ddd, $J = 13.5, 8.7, 4.8$ Hz, 1H), 2.18 – 2.11 (m, 1H), 1.81 (dt, $J = 13.0, 8.4$ Hz, 1H), 1.55 – 1.45 (m, 3H), 1.31 – 1.27 (m, 1H), 1.25 (t, $J = 7.0$ Hz, 3H), (t, $J = 7.4$ Hz, 3H).

Preparation #32: 2,2,2-trifluoro-1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)ethanamine, hydrochloride

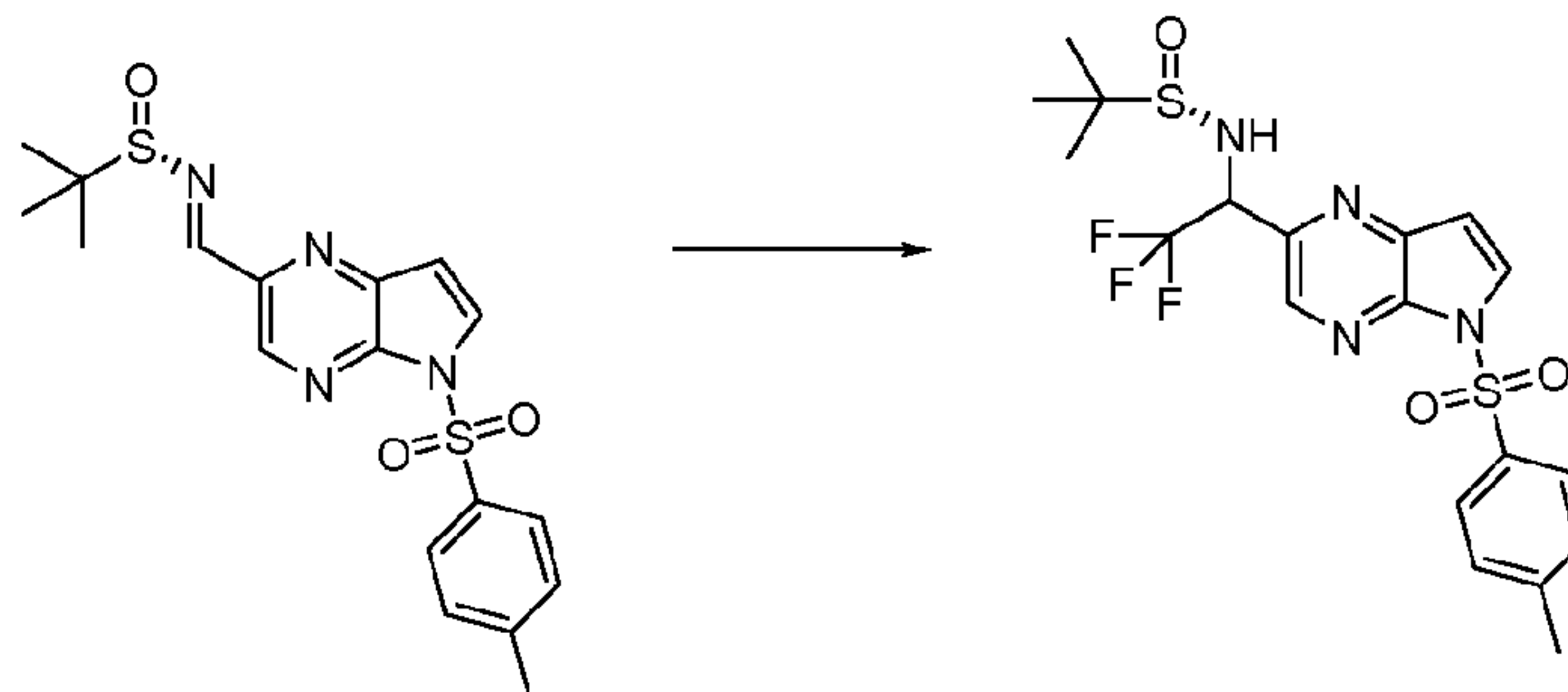


Step A: (*S,E*)-2-methyl-*N*-((5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)methylene)propane-2-sulfinamide



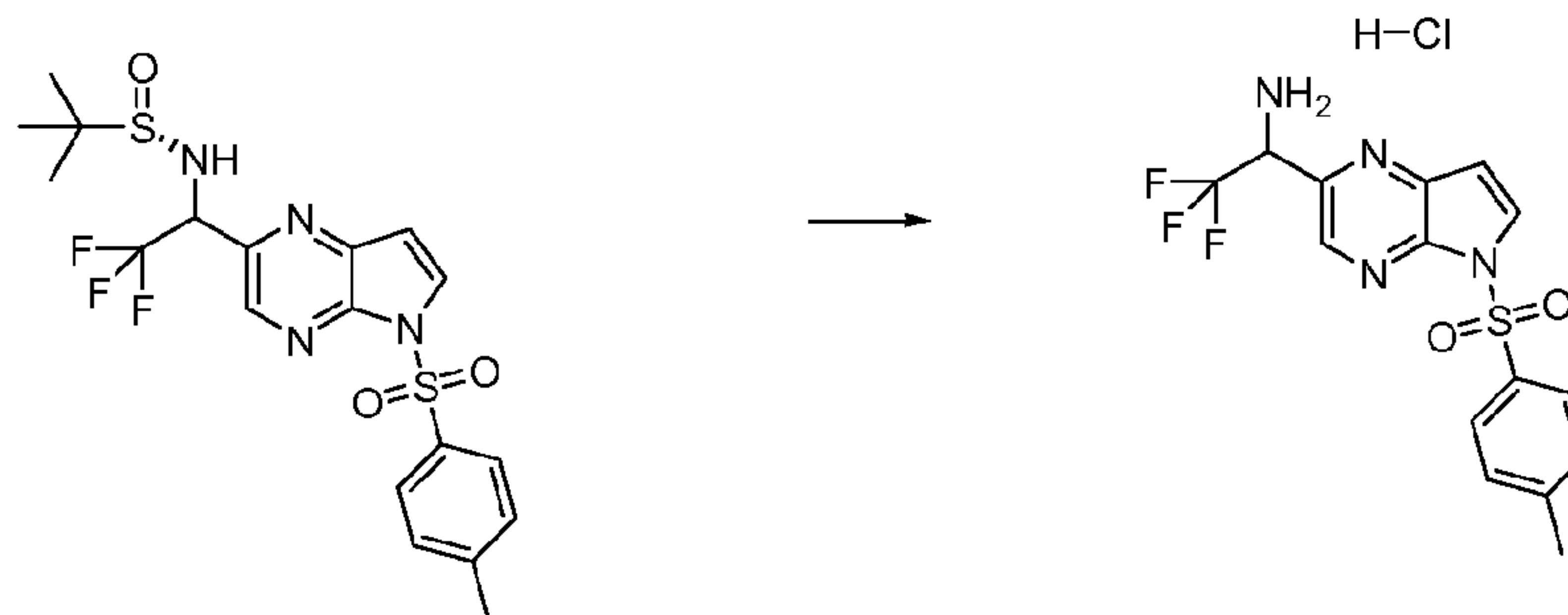
To a solution of 5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine-2-carbaldehyde (8.66 g, 28.7 mmol, Preparation #12 Step B) and (*S,E*)-2-methylpropane-2-sulfinamide (4.18 g, 34.5 mmol) in DCM (20 mL) at ambient temperature was added anhydrous powdered copper(II) sulfate (13.8 g, 86 mmol). After about 20 h, the reaction mixture was filtered and partially concd *in vacuo*. Heptane was added to the solution and the resulting solids were collected by filtration and dried *in vacuo* to provide (*S,E*)-2-methyl-*N*-((5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)methylene)propane-2-sulfinamide (11.5 g, 99%) as a solid. LC/MS (Table 1, Method a) $R_t = 2.50$ min; MS m/z : 405 ($\text{M}+\text{H}$) $^+$.

Step B: (S)-2-methyl-N-(2,2,2-trifluoro-1-(5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)ethyl)propane-2-sulfinamide



To a dry flask charged with 4 Å molecular sieves (5 g) and tetramethyl-ammonium fluoride (0.553 g, 5.93 mmol) was added THF (20 mL). The reaction mixture was stirred for about 30 min after which it was cooled to about -78 °C and a solution of (*S,E*)-2-methyl-*N*-((5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)methylene)propane-2-sulfinamide (1.20 g, 2.97 mmol) in THF (10 mL) was added. After about 15 min trimethyl(trifluoromethyl)silane (0.877 mL, 5.93 mmol) was added to the reaction mixture. The mixture was allowed to warm to -35 to -45 °C. After about 3 h, the reaction mixture was cooled to -78 °C and aqueous NH₄Cl was added. The reaction mixture was allowed to warm to rt. EtOAc (30 mL) and brine (30 mL) were added. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered and concd *in vacuo* to provide crude (*S*)-2-methyl-*N*-(2,2,2-trifluoro-1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)ethyl)propane-2-sulfinamide (1.4 g, 99%) as a foamsulfonamide which was used without further purification. LC/MS (Table 1, Method a) R_t = 2.49 min; MS *m/z* 475 (M+H)⁺.

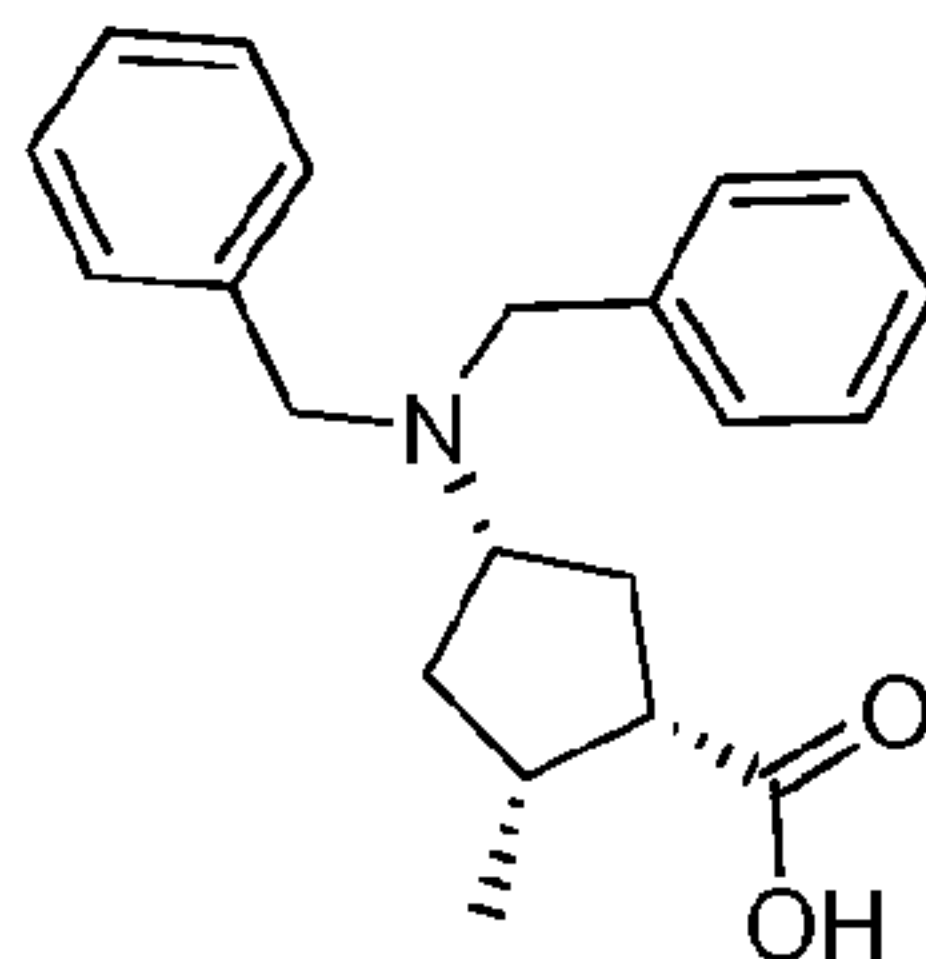
Step C: 2,2,2-trifluoro-1-(5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)ethanamine hydrochloride



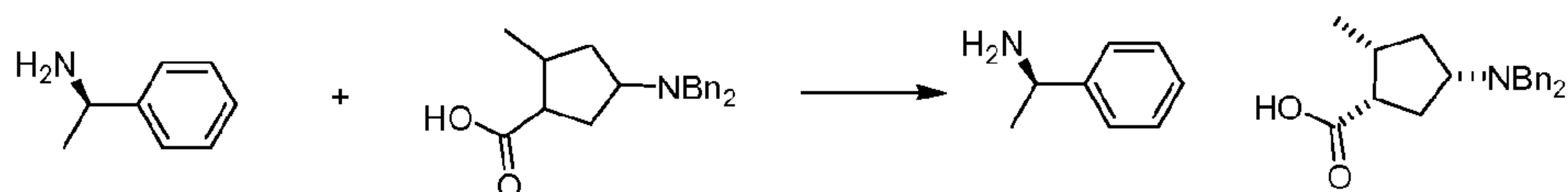
To a solution of (*S*)-2-methyl-*N*-(2,2,2-trifluoro-1-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)ethyl)propane-2-sulfinamide (1.40 g, 2.95 mmol) in MeOH (20 mL) was added HCl (4 N in 1,4-dioxane, 7.38 mL, 29.5 mmol). After about 2 h, the reaction mixture was partially concd *in vacuo* and diluted with Et₂O until solids began to form. After about 30 min, the resulting solids were collected by filtration and dried *in vacuo* to provide 2,2,2-trifluoro-1-(5-tosyl-5*H*-

*pyrrolo[2,3-*b*]pyrazin-2-yl)ethanamine hydrochloride* (0.840 g, 70%) as a solid. LC/MS (Table 1, Method **a**) $R_t = 2.16$ min; MS m/z 371 (M+H)⁺.

Preparation #33: (1*S*,2*R*,4*S*)-4-(dibenzylamino)-2-methylcyclopentanecarboxylic acid

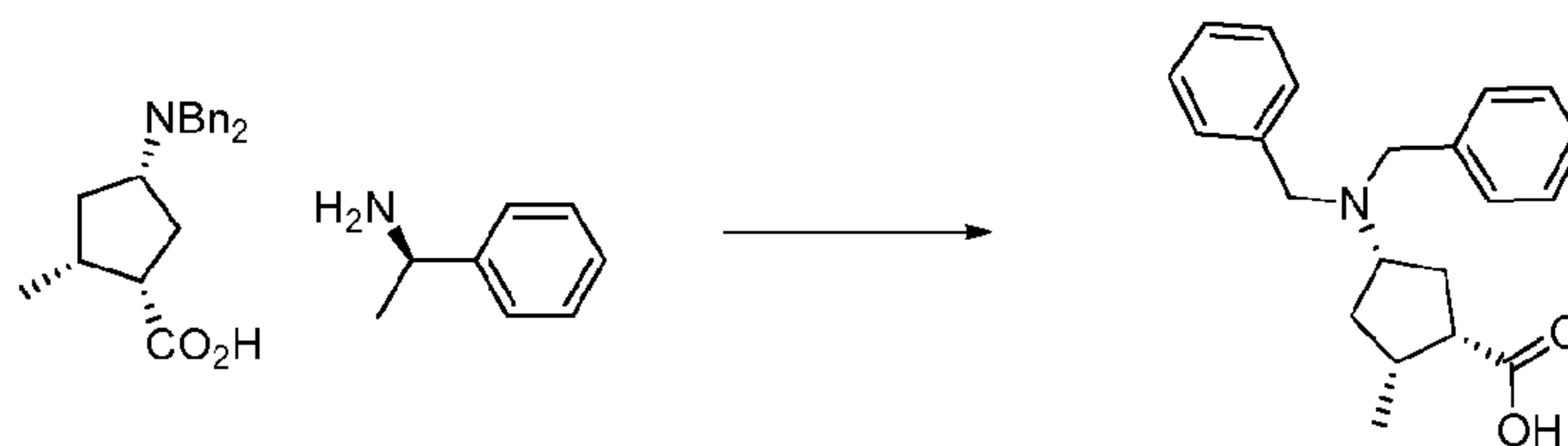


Step A: (1*S*,2*R*,4*S*)-4-(dibenzylamino)-2-methylcyclopentanecarboxylate · (*R*)-1-phenylethanamine



To a solution of 4-(dibenzylamino)-2-methylcyclopentanecarboxylic acid (1240 g, 1499 mmol, prepared using **X** with Example #24 Step H and dibenzylamine and **TT**) in THF (8.0 L) was added (*R*)-(+)-1-phenylethylamine (0.193 L, 1499 mmol). The mixture was warmed to reflux to dissolve the solids, and was then cooled to ambient temperature. After about 15 h, the reaction mixture was filtered, washed THF (800 mL) and dried in a vacuum oven to afford (1*S*,2*R*,4*S*)-4-(dibenzylamino)-2-methylcyclopentanecarboxylate · (*R*)-1-phenylethanamine (565 g, 85%, 97.5% ee): LC/MS (Table 2, Method **70**) $R_t = 8.49$ min. The mother liquor was concd. The residue was dissolved in THF (1 L), heated to dissolve the solids, and cooled to ambient temperature. After about 15 h, the reaction mixture was filtered, washed THF (800 mL) and dried in a vacuum oven to afford additional (1*S*,2*R*,4*S*)-4-(dibenzylamino)-2-methylcyclopentanecarboxylate · (*R*)-1-phenylethanamine (78.5 g, 12%, 95.2% ee): HPLC (Table 2, Method **70**) $R_t = 8.57$ min

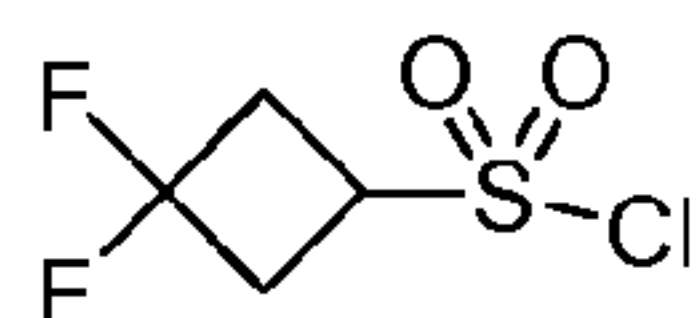
Step B: (1*S*,2*R*,4*S*)-4-(dibenzylamino)-2-methylcyclopentanecarboxylic acid



Phosphoric acid (11.40 mL, 196 mmol) was added to a flask containing water (500 mL). The solution was stirred for about 5 min. (1*S*,2*R*,4*S*)-4-(dibenzylamino)-2-

methylcyclopentanecarboxylate · (*R*)-1-phenylethanamine (83 g, 187 mmol) was added to the solution in small portions. MTBE (500 mL) was added and the contents were mixed well, dissolving the solid. The phases were settled and separated. The aqueous layer was back extracted with MTBE (150 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to afford (*1S,2R,4S*)-4-(dibenzylamino)-2-methylcyclopentanecarboxylic acid (60 g, 99%) as an oil: HPLC (Table 1, Method x) $R_t = 4.57$ min.

Preparation #34: 3,3-difluorocyclobutane-1-sulfonyl chloride

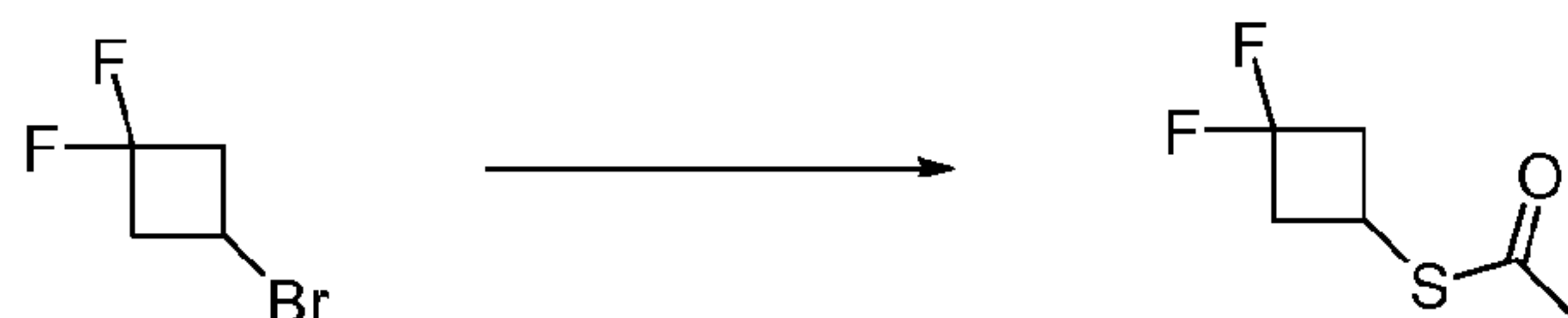


Step A: 3-bromo-1,1-difluorocyclobutane



To a vigorously stirred solution of 3-bromocyclobutanone (18.0 g, 121 mmol, prepared as described in *J. Am. Chem. Soc.*, **1971**, 93, 2481) in DCM (375 mL) at about 0 °C was added dropwise via an addition funnel DAST (36.9 mL, 279 mmol) over about 1 h. The reaction mixture continued stirring at about 0 °C for about 2 h and at ambient temperature for about 14 h. The reaction was cooled to about -5 °C in an ice/acetone bath and a saturated aqueous solution of NaHCO₃ (400 mL) was added dropwise via addition funnel. The bilayers remained vigorously stirring for about 1 h. The layers were partitioned and the aqueous layer was extracted with DCM (4 x 200 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, and solvent removed under reduced pressure (180 mm Hg maximum, 30 °C water bath) to afford 3-bromo-1,1-difluorocyclobutane (15.3 g, 59%) as a light brown oil as product: ¹H NMR (400 MHz, CDCl₃) δ 4.28 - 4.14 (m, 1H), 3.35 - 3.16 (m, 2H), 3.06 - 2.87 (m, 2H).

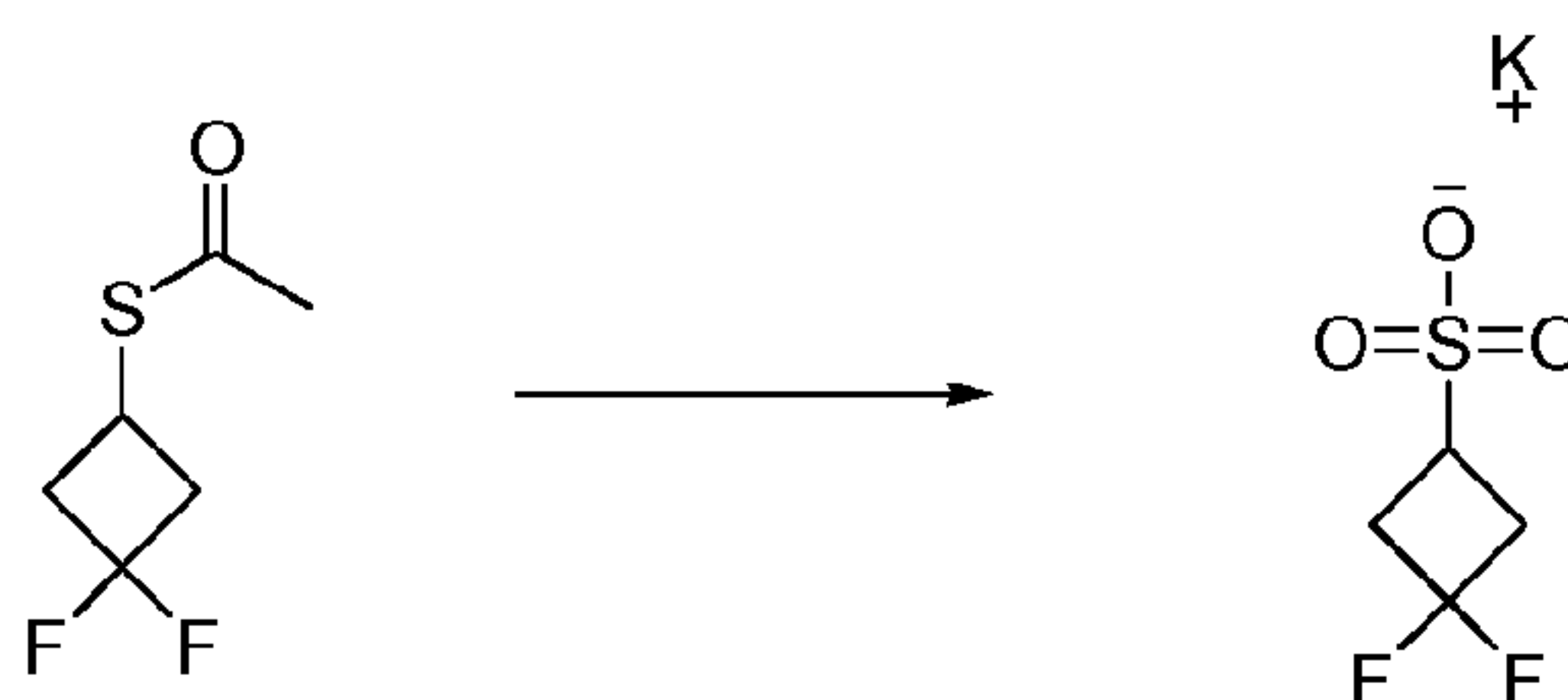
Step B: S-3,3-difluorocyclobutyl ethanethioate



To a solution of 3-bromo-1,1-difluorocyclobutane (13.8 g, 64.7 mmol) in DMSO (24.6 mL) was added potassium thioacetate (22.2 g, 194 mmol). The solution was heated at about 45 °C for about 16 h. Water (20 mL) and Et₂O (50 mL) were added. The layers were partitioned and the aqueous layer was extracted with Et₂O (7 x 50 mL). The combined organic layers were dried

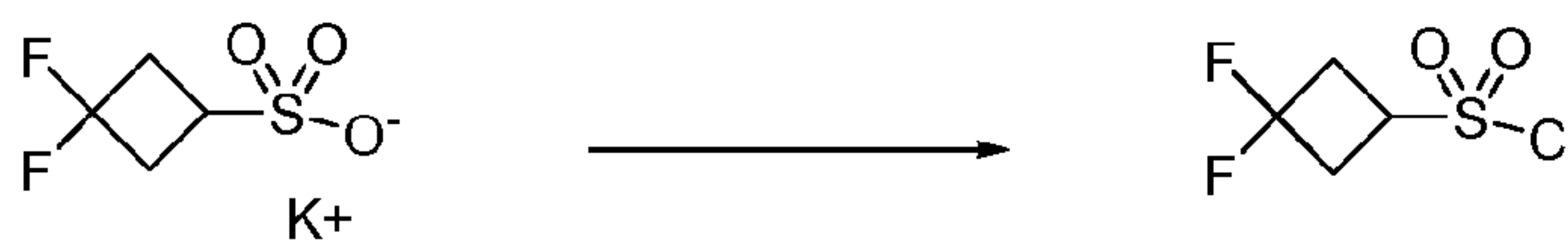
over anhydrous MgSO_4 , filtered, and solvent removed under reduced pressure (60 mm Hg maximum, 30 °C water bath) to afford crude *S*-3,3-difluorocyclobutyl ethanethioate (13.09 g, 78%) as an oil: ^1H NMR (400 MHz, d_6 -DMSO) δ 3.84 - 3.69 (m, 1H), 3.14 (ddd, J = 13.0, 7.5, 3.9 Hz, 2H), 2.66 - 2.55 (m, 2H), 2.33 (s, 3H).

Step C: potassium 3,3-difluorocyclobutane-1-sulfonate



To a solution of crude *S*-3,3-difluorocyclobutyl ethanethioate (13.0 g, 39.1 mmol) in acetic acid (100 mL) was added H_2O_2 (24.0 mL, 235 mmol, 30 % in water). After about 4 h, an exotherm was noted which generated enough heat to reflux the reaction mixture. After about 20 h, the reaction mixture was diluted with toluene (500 mL) and partially concd *in vacuo*. This process was repeated (5x). The solution was diluted with EtOH (about 500 mL) and KOH (4.4 g, 78 mmol) was added to the reaction mixture. The precipitate was collected by filtration and discarded. Additional KOH (4.4 g, 78 mmol) was added to the filtrate and the precipitate was collected by filtration. The solution was partially concd *in vacuo*. The solution was diluted with EtOH (approx. 500 mL) and partially concd again (3x). The precipitate was collected by filtration. The last 2 collected solids were dried *in vacuo* and combined to provide *potassium 3,3-difluorocyclobutane-1-sulfonate* (3.5 g, 42.6%). Additional KOH (4.39 g, 78 mmol) and the solution was partially concd *in vacuo*. The solution was diluted with EtOH (approx. 500 mL) and concd again (3x). The resulting solids were collected by filtration to provide *potassium 3,3-difluorocyclobutane-1-sulfonate* (1.6 g, 19%): ^1H NMR (400 MHz, d_6 -DMSO) δ 3.01 (ddd, J = 13.5, 6.3, 2.5 Hz, 1H), 2.72 - 2.59 (m, 4H).

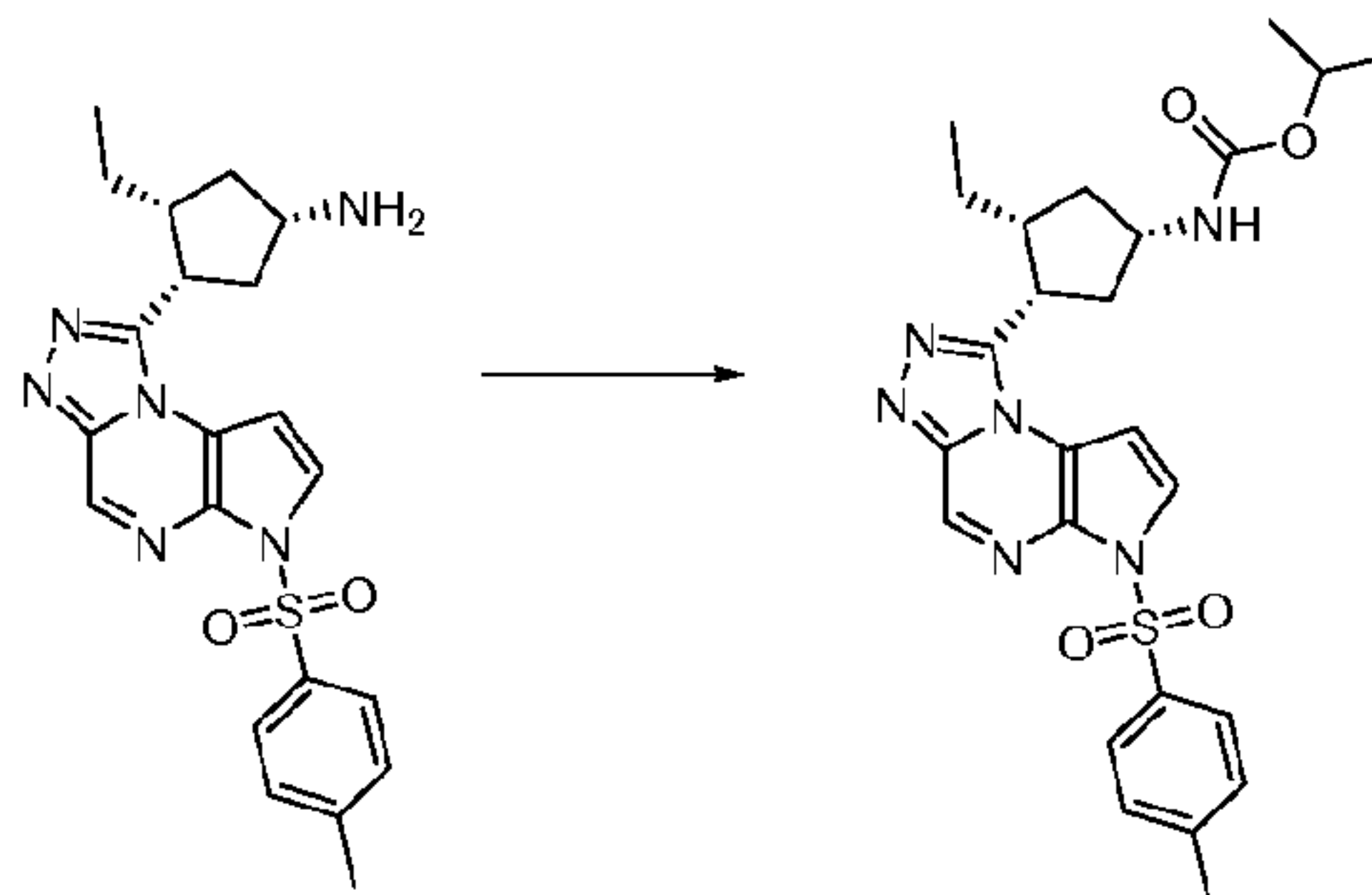
Step D: 3,3-difluorocyclobutane-1-sulfonyl chloride



To a suspension of potassium 3,3-difluorocyclobutane-1-sulfonate (0.250 g, 1.189 mmol) in thionyl chloride (2.60 mL, 35.7 mmol) was added DMF (3 drops). The reaction was heated to about 60 °C for about 21 h. The solvent was removed under reduced pressure and the residue was used in the next reaction without further workup or purification to afford crude 3,3-

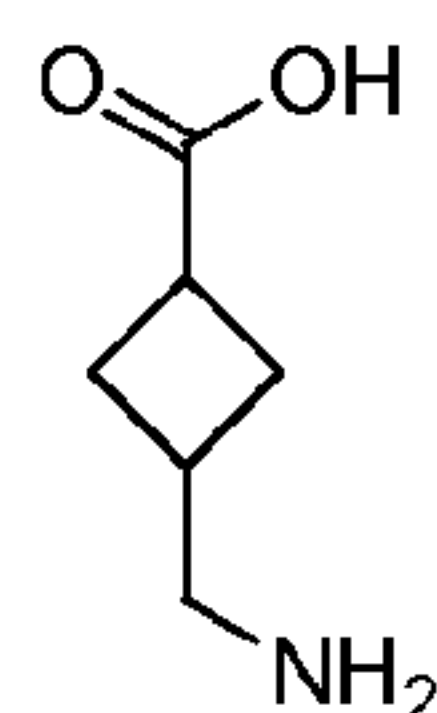
difluorocyclobutane-1-sulfonyl chloride (0.227 g, 100%) as product. ^1H NMR (400 MHz, CDCl_3) δ 4.33 - 4.17 (m, 1H), 3.28 (dd, $J = 11.1, 7.6$ Hz, 2H), 3.21 - 3.05 (m, 2H).

Preparation #35: isopropyl (1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylcarbamate



To a solution of (1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine (0.080 g, 0.19 mmol, Preparation #BB.1*) in THF (2 mL) was added TEA (0.079 mL, 0.565 mmol) and the solution was stirred at ambient temperature for about 10 min. To the reaction was added isopropyl chloroformate (1 M in toluene, 0.18 mL, 0.18 mmol) and the reaction mixture was stirred for about 1 h. The solvent was removed under reduced pressure and DCM (5 mL) and saturated aqueous NaHCO_3 (2 mL) were added. The layers were separated and the organic layer was washed with brine (2 mL), dried over MgSO_4 , filtered and concentrated under reduced pressure to give crude *isopropyl* (1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylcarbamate (0.080 g, 60%) which was used without further purification: LC/MS (Table 1, Method **b**) $R_t = 2.33$ min; MS m/z : 511 ($\text{M}+\text{H}$) $^+$.

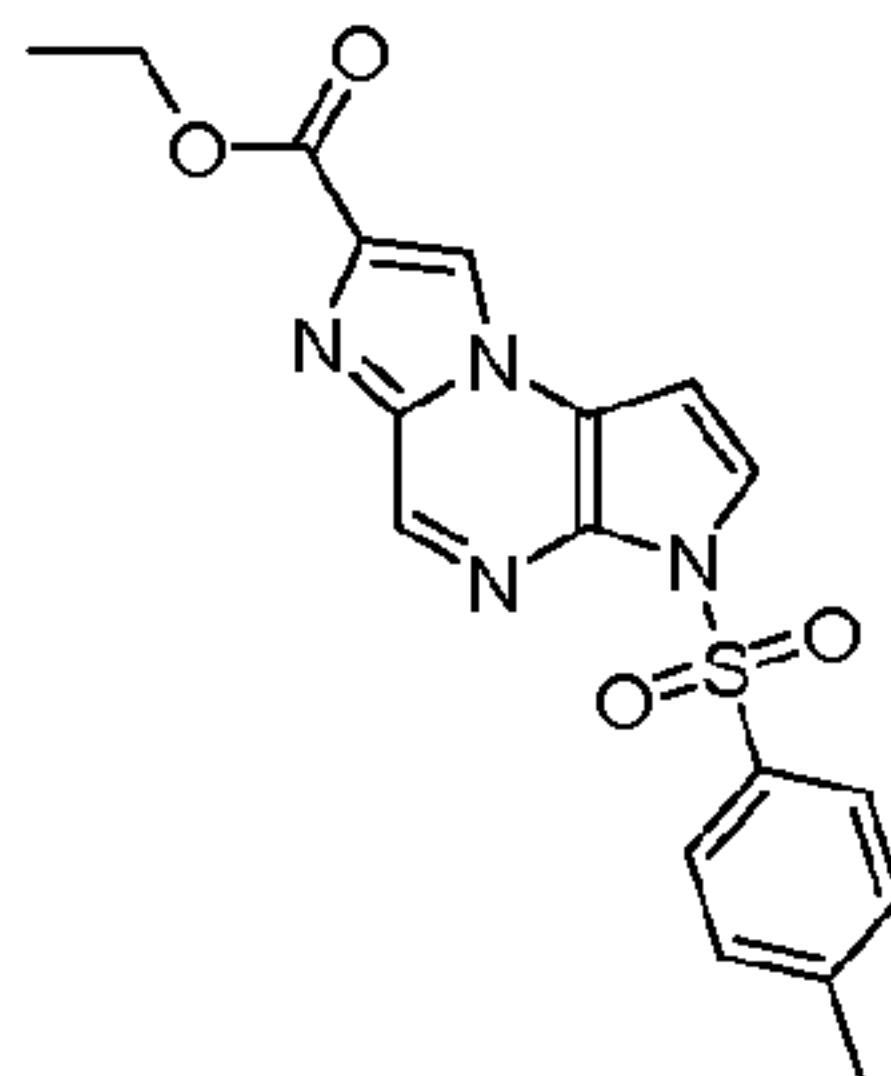
Preparation #36: 3-(aminomethyl)cyclobutanecarboxylic acid



To a flask charged with 10% palladium on carbon (0.20 g, 0.19 mmol) was added a solution of benzyl 3-(azidomethyl)cyclobutanecarboxylate (2.00 g, 8.15 mmol, prepared using **IIII** from benzyl 3-(hydroxymethyl)cyclobutanecarboxylate (Parkway Scientific), **JJJJ** with sodium azide) in MeOH (100 mL). The reaction mixture was sparged with hydrogen and an atmosphere of hydrogen was maintained via a balloon. The reaction mixture was stirred for about 4 h at ambient temperature and then was filtered through a pad of Celite[®], washed with MeOH and concentrated

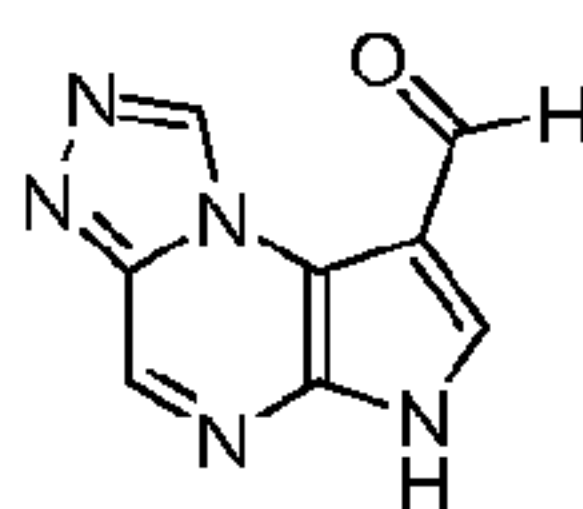
in vacuo to give the crude *3-(aminomethyl)cyclobutanecarboxylic acid* (1.08 g, 100%) which was used without further purification: LC/MS (Table 1, Method **r**) R_t = 2.41 min (ELSD); MS m/z : 130 (M+H)⁺.

Preparation #37: ethyl 3-tosyl-3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazine-7-carboxylate

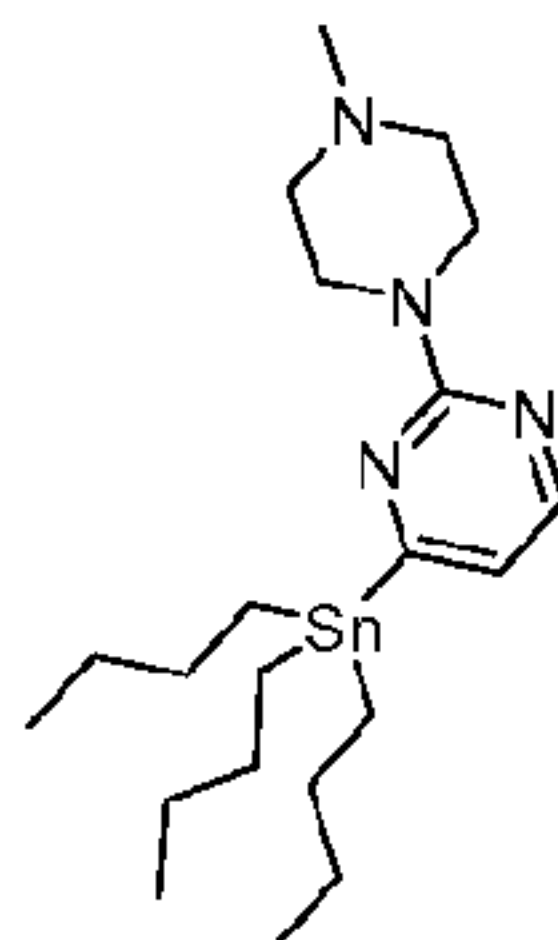


3-Bromo-2-oxo-propionic acid ethyl ester (0.090 mL, 0.72 mmol) was added to a mixture of 5-tosyl-5*H*-pyrrolo[3,2-*b*]pyrazin-2-amine (0.180 g, 0.624 mmol, prepared using **E** from Example #3 Step E and HCl) and 1,4-dioxane (3.5 mL) under nitrogen. After about 3 days, the volatiles were removed under reduced pressure. The residue was slurried in Et₂O (5 mL) and then filtered to afford a tan powder. The solid was slurried in MeCN (3.50 mL) under nitrogen. PFPA (0.40 mL, 2.1 mmol) was added. After about 30 min, the volatiles were removed under reduced pressure. The residue was dissolved in DCM (20 mL) and washed with saturated aqueous NaHCO₃/water (2:1, 20 mL). The aqueous layer was extracted with DCM (20 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of 20-100% EtOAc/heptane to afford *ethyl 3-tosyl-3H-imidazo[1,2-a]pyrrolo[2,3-e]pyrazine-7-carboxylate* (0.181 g, 75%): LC/MS (Table 1, Method **n**) R_t = 0.70 min; MS m/z : 385 (M+H)⁺.

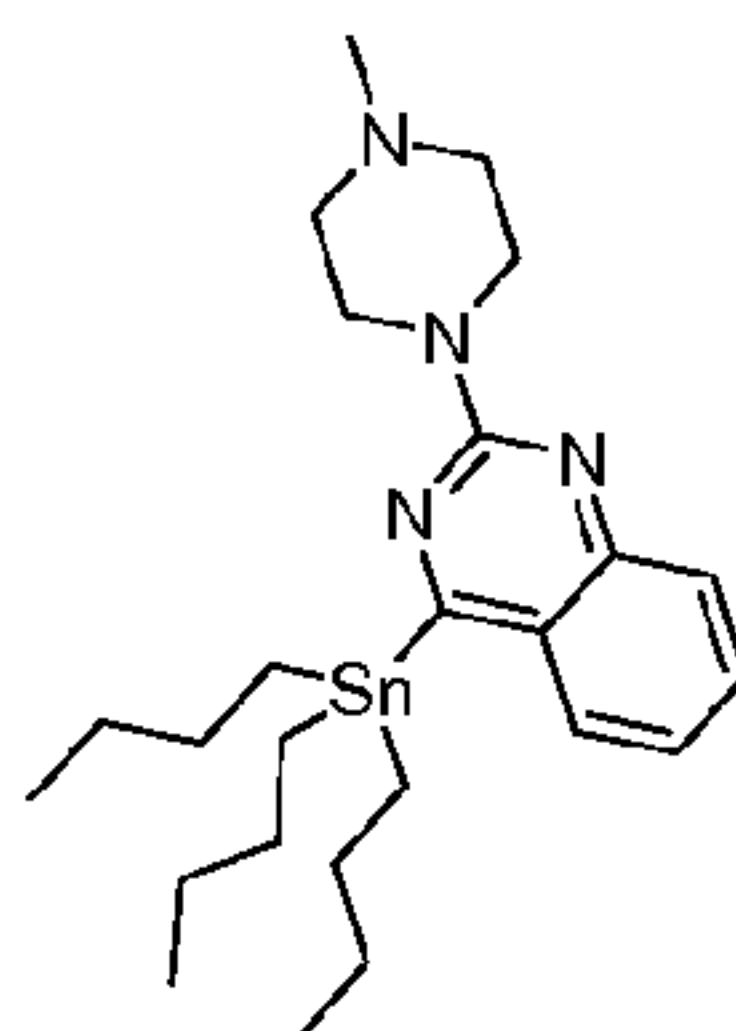
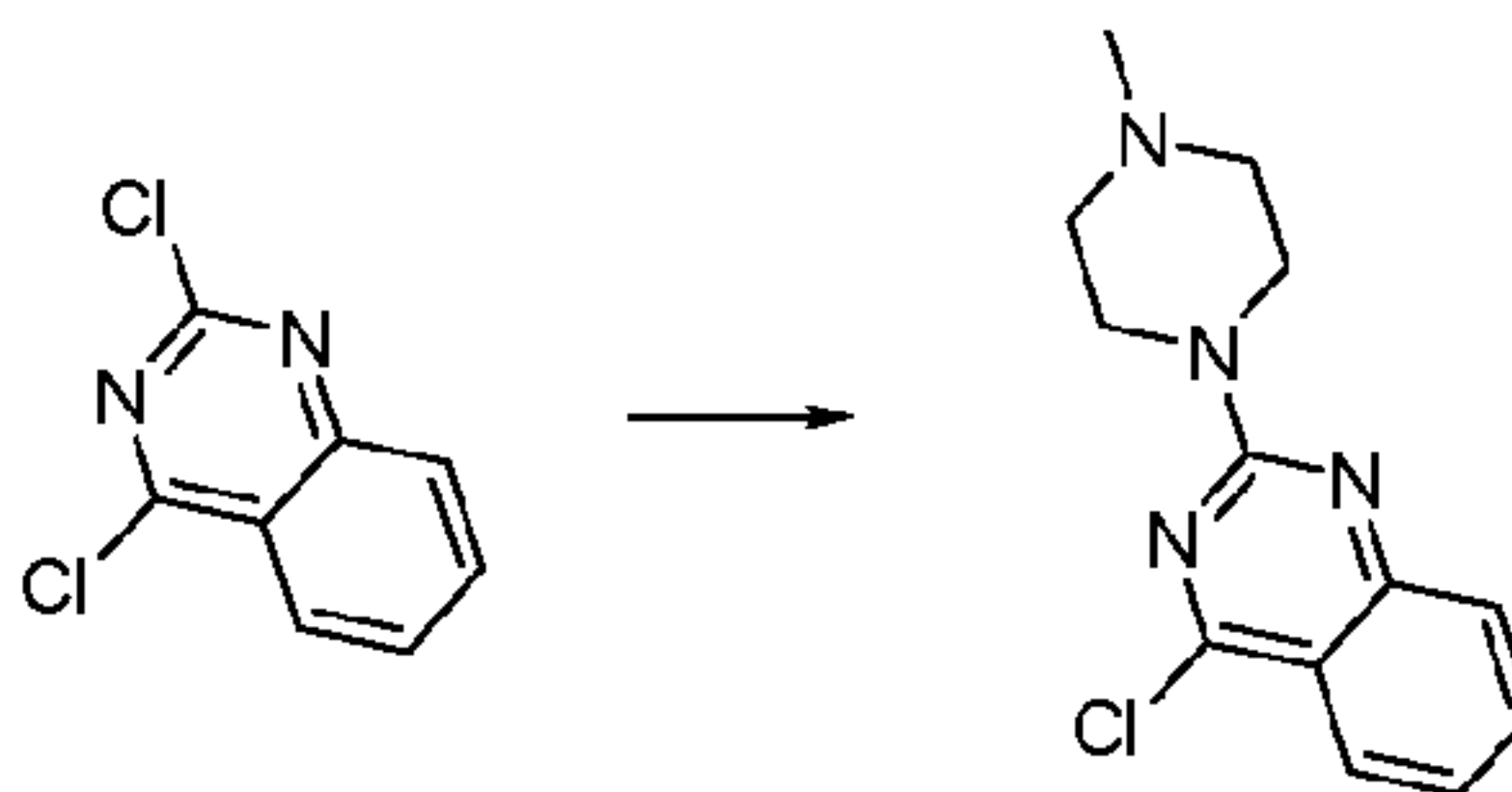
Preparation #38: 6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine-8-carbaldehyde



Water (1.0 mL) was added to a mixture of 6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazine (0.200 g, 1.26 mmol, prepared using **D** from Preparation #BBBBB.1 and NaOH) and hexamethylenetetramine (0.264 g, 1.89 mmol). Acetic acid (0.5 mL) was added. The reaction vessel was sealed and the mixture was warmed to about 100 °C. After about 8 h, the solution was allowed to cool to ambient temperature. After sitting for about 13 h, the mixture was cooled to about 0 °C. The resulting mixture was diluted with water (1 mL) and then filtered rinsing with water. The solid was dried to afford *6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazine-8-carbaldehyde* (0.041 g, 18%): LC/MS (Table 1, Method **n**) R_t = 0.23 min; MS m/z 188 (M+H)⁺.

Preparation #39: 2-(4-methylpiperazin-1-yl)-4-(tributylstannyl)pyrimidine

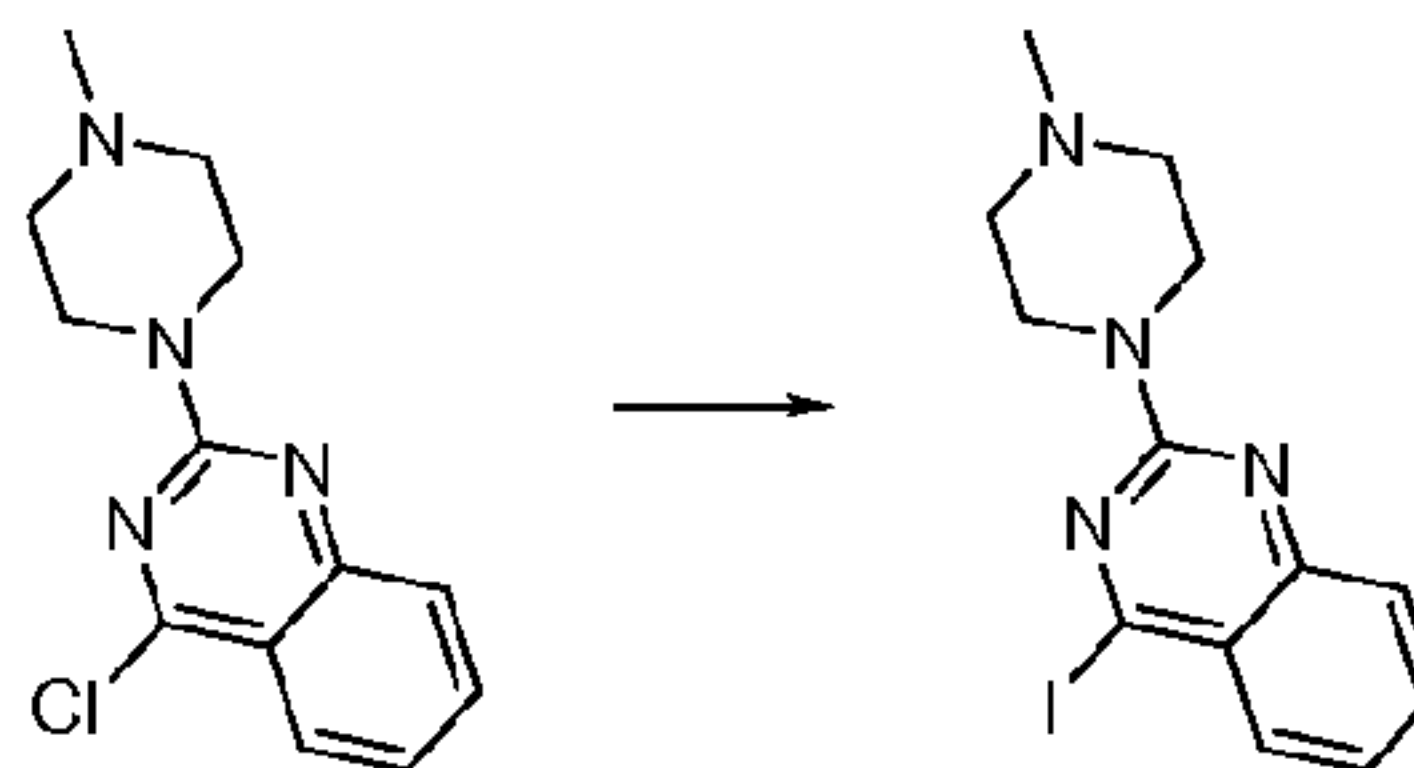
1-Methylpiperazine (0.160 mL, 1.44 mmol) was added to a solution of 2-(methylsulfonyl)-4-(tributylstannyl)pyrimidine (0.250 g, 0.481 mmol, synthesized as described in Majeed, A. J., *et al. Tetrahedron* **1989**, 45, 993-1006) and 1,4-dioxane (1.0 mL) under nitrogen. After about 2 h, the solution was warmed to about 50 °C. After about 30 min, the solution was warmed to about 80 °C. After about 30 min, a reflux condenser was attached and the solution was warmed to about 100 °C. After about 16 h, the brown solution was allowed to cool to ambient temperature. Water (5 mL) was added. The mixture was extracted with EtOAc (2 x 5 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered, and concentrated. The residue was purified by silica gel chromatography eluting with a gradient of 2-10% MeOH/DCM to afford 2-(4-methylpiperazin-1-yl)-4-(tributylstannyl)pyrimidine (0.127 g, 56%): ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, *J* = 4.6 Hz, 1H), 6.63 (d, *J* = 4.6 Hz, 1H), 3.98 - 3.82 (m, 4H), 2.63 - 2.48 (m, 4H), 2.40 (s, 3H), 1.70 - 1.43 (m, 6H), 1.42 - 1.20 (m, 6H), 1.18 - 0.97 (m, 6H), 0.88 (t, *J* = 7.3 Hz, 9H).

Preparation #40: 2-(4-methylpiperazin-1-yl)-4-(tributylstannyl)quinazoline**Step A: 4-chloro-2-(4-methylpiperazin-1-yl)quinazoline**

2,4-Dichloroquinazoline (2.00 g, 10.1 mmol, prepared as described in Prasad, M., *et al. Org. Process Res. Dev.* **2004**, 8, 330-340) was slurried in 1,4-dioxane (20.0 mL). 1,4-Dimethylpiperazine (1.44 mL, 10.6 mmol) was added. The mixture was heated in a CEM microwave at about 150 °C for about 5 min. The material was poured into saturated aqueous

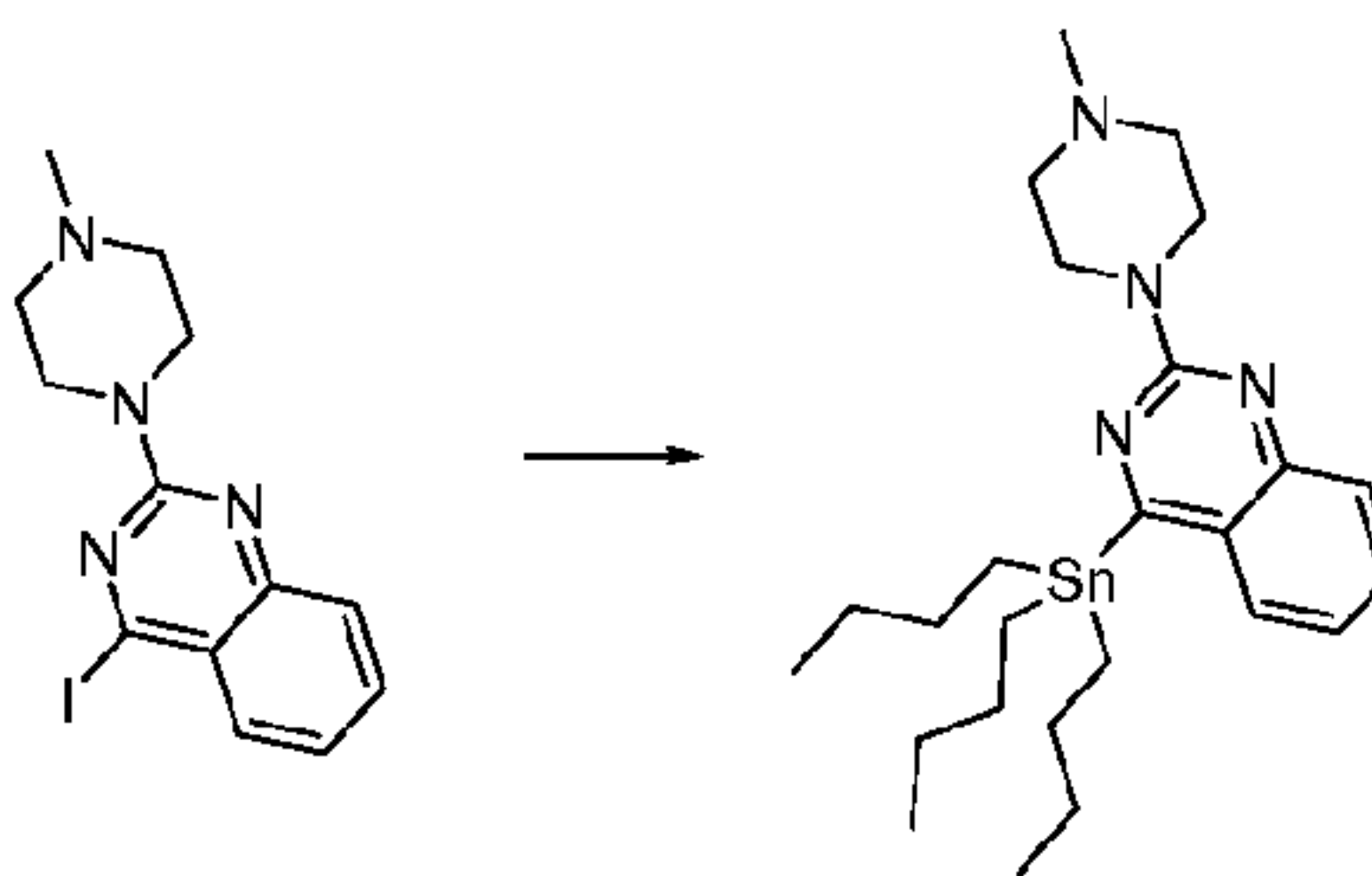
NaHCO₃/water (1:1, 150 mL). The mixture was extracted with EtOAc (5 x 100 mL). 20 g of silica gel was added to the combined organics and the volatiles were removed under reduced pressure. The resulting solid was purified by silica gel chromatography eluting with a gradient of 2-10% MeOH/DCM to afford *4-chloro-2-(4-methylpiperazin-1-yl)quinazoline* (1.36 g, 52%): LC/MS (Table 1, Method **n**) R_t = 0.51 min; MS *m/z* 263 (M+H)⁺.

Step B: 4-iodo-2-(4-methylpiperazin-1-yl)quinazoline



Hydrogen iodide (55% aqueous solution, 4.00 mL, 29.3 mmol) was slowly added to 4-chloro-2-(4-methylpiperazin-1-yl)quinazoline (1.36 g, 5.18 mmol) under air while cooling in an ambient temperature water bath. After about 5 min, the bath was removed, the reaction vessel was wrapped in aluminum foil, and the mixture was stirred at ambient temperature for about 5 h. DCM (4.0 mL) was added and the mixture was stirred for about 39 h. Hydrogen iodide (55% aqueous solution, 8.0 mL, 110 mmol) was added and the mixture was stirred for about 71 h. The mixture was slowly added to saturated aqueous NaHCO₃ (200 mL) and EtOAc (200 mL). After completion of the quench, the layers were separated. The organics were washed with saturated aqueous NaHCO₃/water (1:1, 200 mL). The organics were dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of 2-5% MeOH/DCM to afford (1.18 g, 69%) as a 3:1 mixture of *4-iodo-2-(4-methylpiperazin-1-yl)quinazoline* to *4-chloro-2-(4-methylpiperazin-1-yl)quinazoline*. *4-iodo-2-(4-methylpiperazin-1-yl)quinazoline*: LC/MS (Table 1, Method **n**) R_t = 0.55 min; MS *m/z* 355 (M+H)⁺.

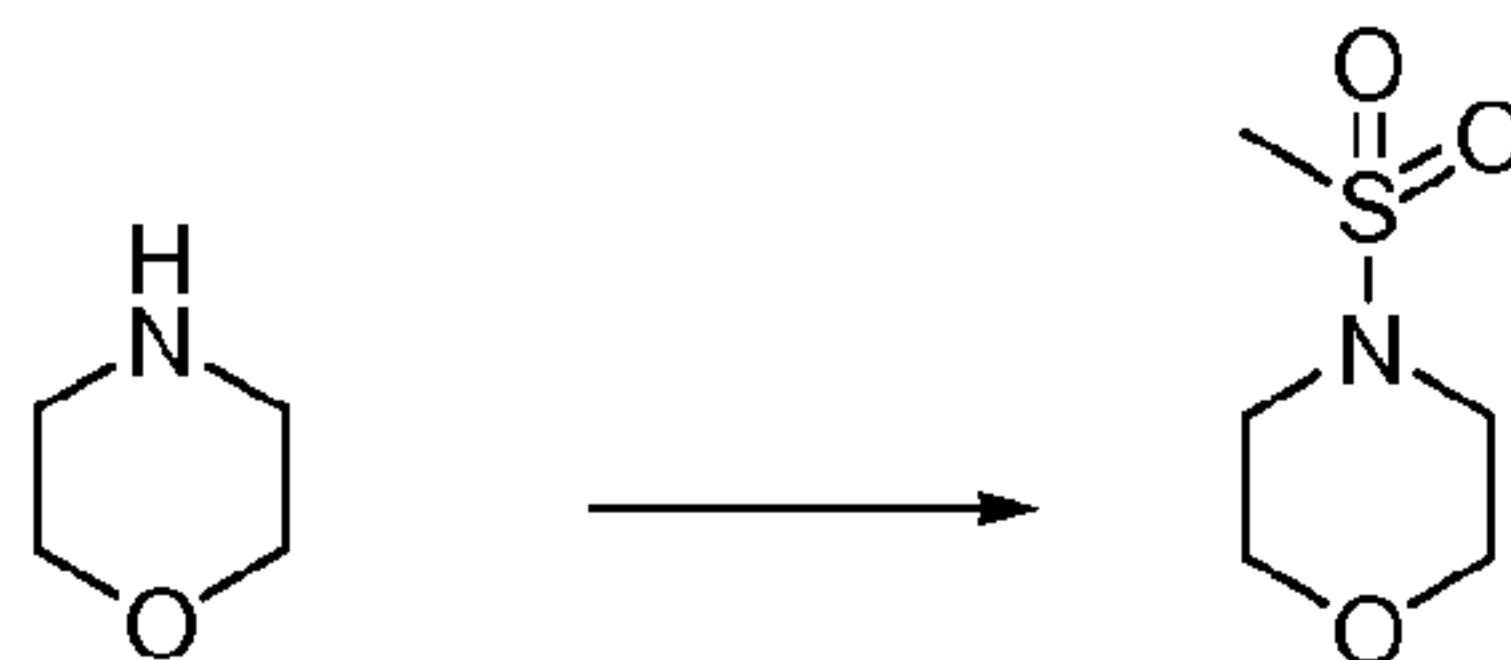
Step C: 2-(4-methylpiperazin-1-yl)-4-(tributylstannyl)quinazoline



Bis(triphenylphosphine)palladium(II) acetate (0.063 g, 0.085 mmol) was added to 3:1 mixture of 4-iodo-2-(4-methylpiperazin-1-yl)quinazoline:4-chloro-2-(4-methylpiperazin-1-yl)quinazoline (0.300 g) under nitrogen. Bis(tributyltin) (0.855 mL, 1.69 mmol) was added. TBAF (1.0 M solution in THF, 2.54 mL, 2.54 mmol) was added. The mixture was purged with nitrogen for

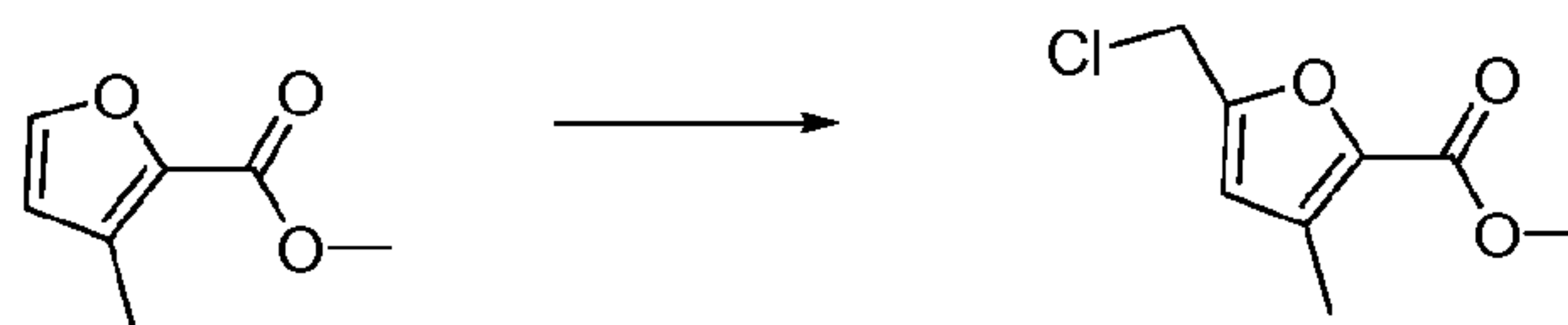
about 20 min and then stirred under nitrogen at ambient temperature for about 7 h. Saturated aqueous NaHCO_3 /water (1:1, 20 mL) and EtOAc (50 mL) were added. The mixture was filtered through a syringe filter, the layers were separated and the organics were washed with water (2 x 10 mL). The organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography eluting with a gradient of 5-10% MeOH/DCM to afford a sticky brown solid. The material was dissolved in EtOAc (10 mL) and washed with water (2 x 5 mL). The organics were dried over anhydrous Na_2SO_4 , filtered, and concentrated to afford a 1:1 mix of 2-(4-methylpiperazin-1-yl)-4-(tributylstannyl)quinazoline:4-chloro-2-(4-methylpiperazin-1-yl)quinazoline (0.058 g, 17%). 2-(4-methylpiperazin-1-yl)-4-(tributylstannyl)quinazoline: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 7.69 - 7.64 (m, 1H), 7.61 - 7.57 (m, 1H), 7.49 - 7.44 (m, 1H), 7.31 - 7.26 (m, 1H), 3.95 - 3.83 (m, 4H), 2.44 - 2.35 (m, 4H), 2.22 (s, 3H), 1.66 - 1.48 (m, 6H), 1.37 - 1.18 (m, 12H), 0.82 (t, $J = 7.3$ Hz, 9H).

Preparation #41: 4-(methylsulfonyl)morpholine



To a solution of morpholine (2.00 mL, 22.96 mmol) in DCM (40 mL) was added TEA (3.20 mL, 22.96 mmol) at about -20 $^{\circ}\text{C}$, then methanesulfonyl chloride (2.68 mL, 34.4 mmol) was added dropwise at about -20 $^{\circ}\text{C}$. The reaction mixture was stirred at about -20 $^{\circ}\text{C}$ for about 2 h, then warmed to rt. The mixture was partitioned with saturated aqueous NH_4Cl (100 mL) and DCM (3 x 50 mL). The combined organic layers were concentrated and purified by silica gel chromatography eluting with a gradient of 0-100% EtOAc / heptane to give 4-(methylsulfonyl)morpholine (3.95 g, 100%) as a white solid: ^1H NMR ($\text{DMSO}-d_6$) δ 3.70 - 3.60 (m, 4H), 3.12 - 3.04 (m, 4H), 2.89 (s, 3H).

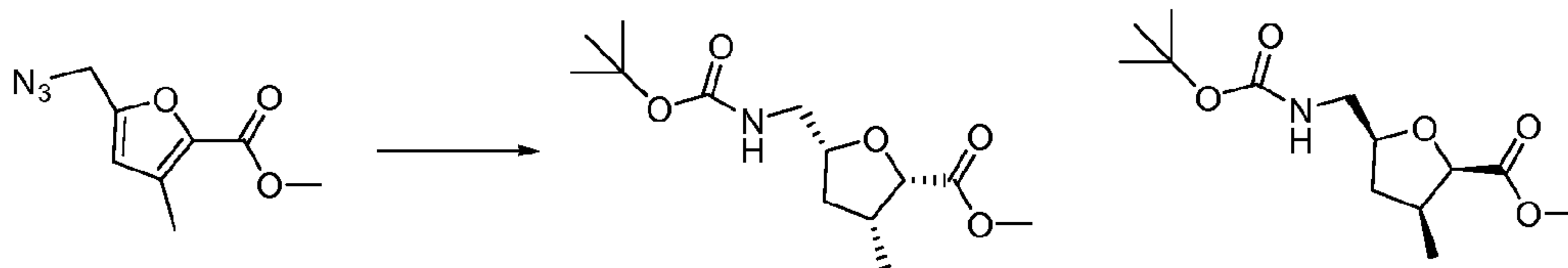
Preparation #42: methyl 5-(chloromethyl)-3-methylfuran-2-carboxylate



To a solution of methyl 3-methylfuran-2-carboxylate (8.00 g, 57.1 mmol) in DCM (285 mL) was added zinc chloride (2.14 g, 15.7 mmol) and paraformaldehyde (2.2 mL, 82 mmol). The solution was warmed to about 35 $^{\circ}\text{C}$. HCl gas was bubbled through the reaction mixture for about 20 min.

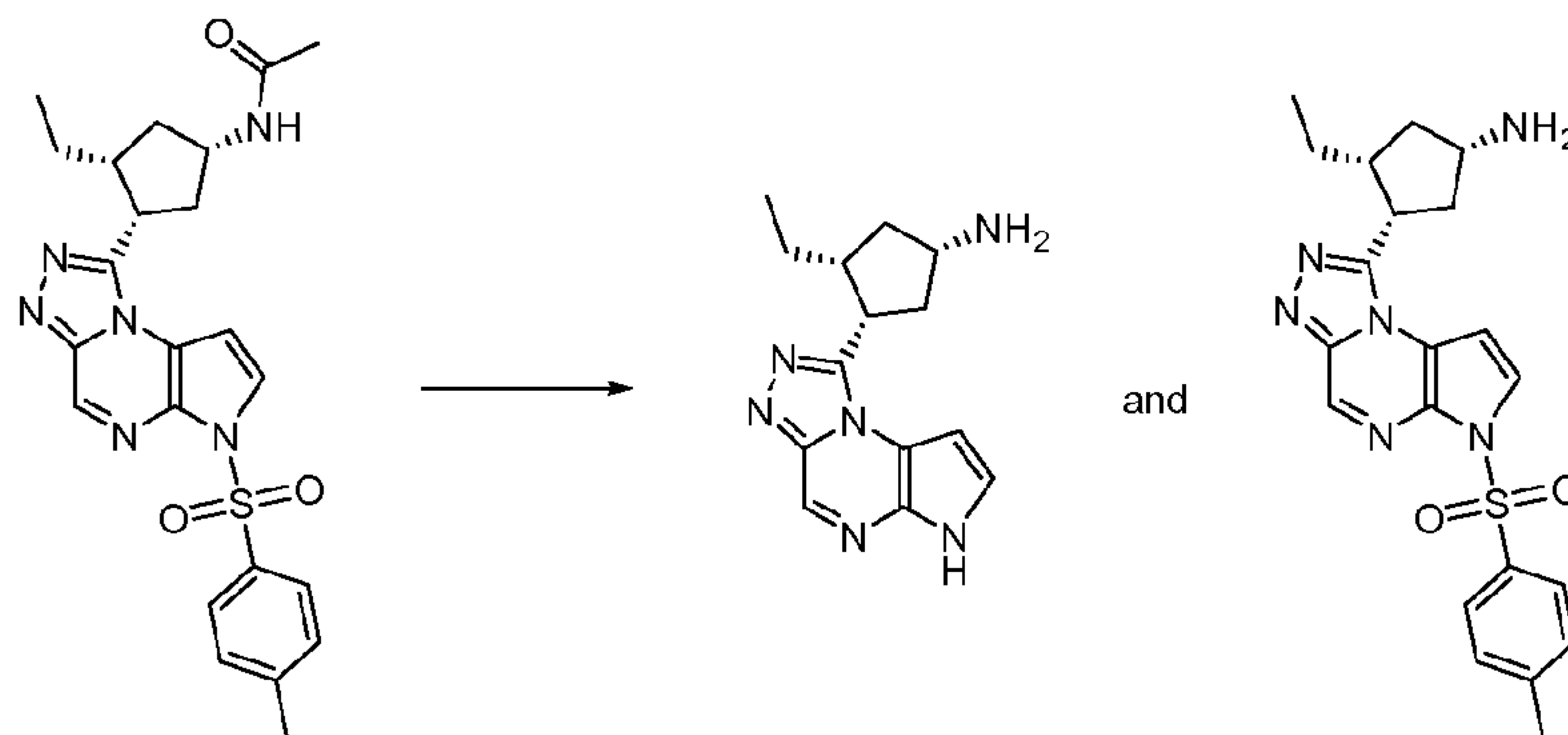
The mixture was partitioned with water (50 mL) and DCM (3 x 30 mL). The combined organic layers were concentrated and purified by silica gel chromatography eluting with a gradient of 0-50% EtOAc / heptane to give *methyl 5-(chloromethyl)-3-methylfuran-2-carboxylate* (8.24 g, 77%) as a white solid: LC/MS (Table 1, Method n) $R_t = 0.69$ min; MS m/z : 189 (M+H)⁺.

Preparation #43: *cis*-methyl 5-((*t*-butoxycarbonylamino)methyl)-3-methyltetrahydrofuran-2-carboxylate



A solution of methyl 5-(azidomethyl)-3-methylfuran-2-carboxylate (3.10 g, 15.88 mmol, prepared using General Procedure **JJJJ** from Preparation #42 and sodium azide) in MeOH (50 mL) was added to a suspension of 5% Rh/C (0.31 g, 3.01 mmol) and di-*tert*-butyl dicarbonate (4.16 g, 19.06 mmol) in a 50 mL pressure bottle. The reaction mixture was stirred under 40 psi of hydrogen at about 50 °C for about 3.5 days. The mixture was filtered through a nylon membrane. The organic solvent was concentrated under reduced pressure to give *cis*-methyl 5-((*t*-butoxycarbonylamino)methyl)-3-methyltetrahydrofuran-2-carboxylate (4.19 g, 81%) as a brown oil: ¹H NMR (CDCl₃) δ 5.70 (s, 1H), 4.43 – 4.46 (d, 1H), 4.28 – 4.12 (m, 1H), 3.75 (s, 3H), 3.50 – 3.30 (m, 2H), 2.75 – 2.55 (m, 1H), 1.95 – 2.05 (m, 1H), 1.65 – 1.48 (m, 1H), 1.45 (s, 9H), 1.03 – 0.97 (d, 3H).

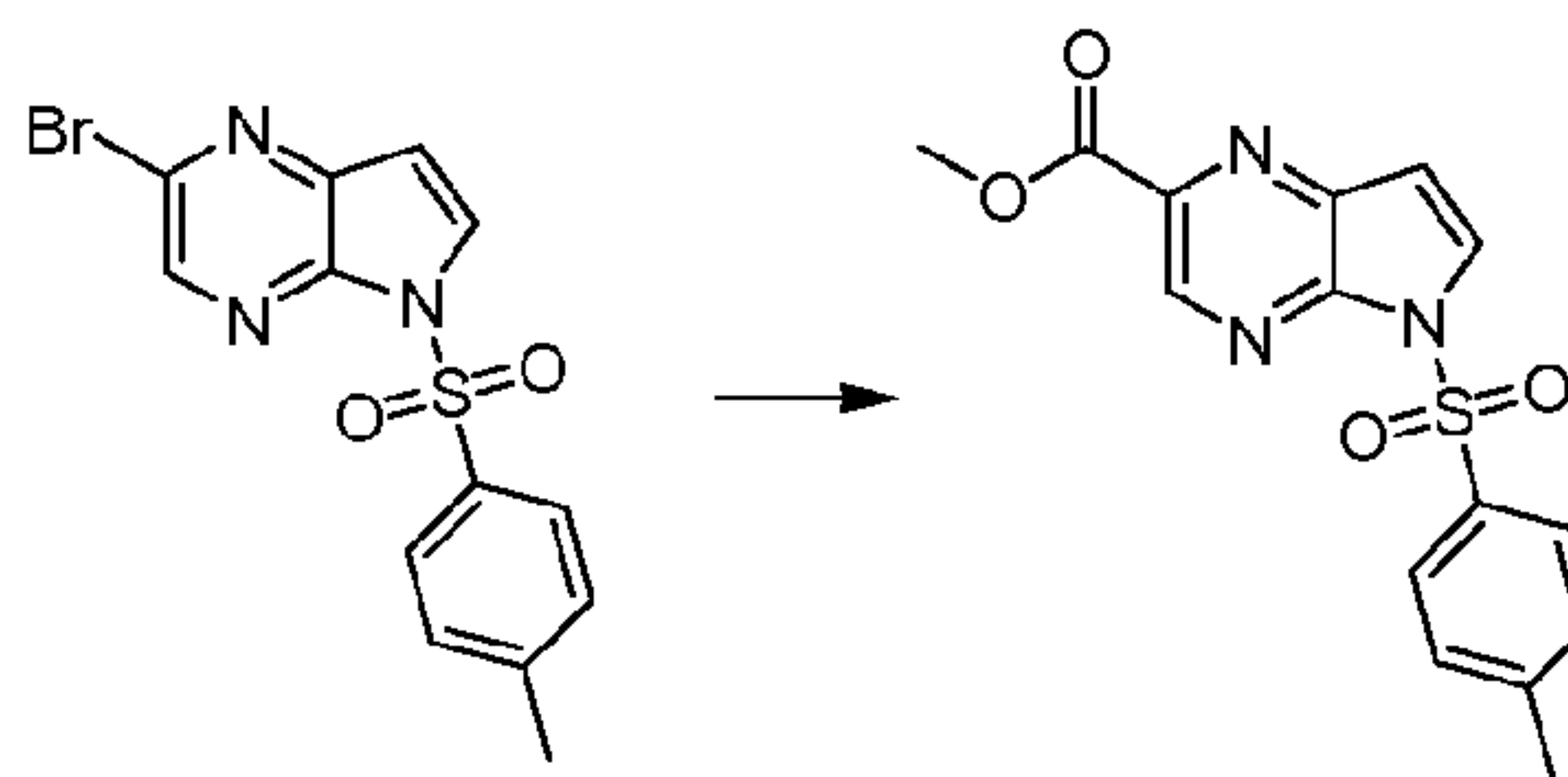
Preparation #44: (1*S*,3*R*,4*S*)-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine and (1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine



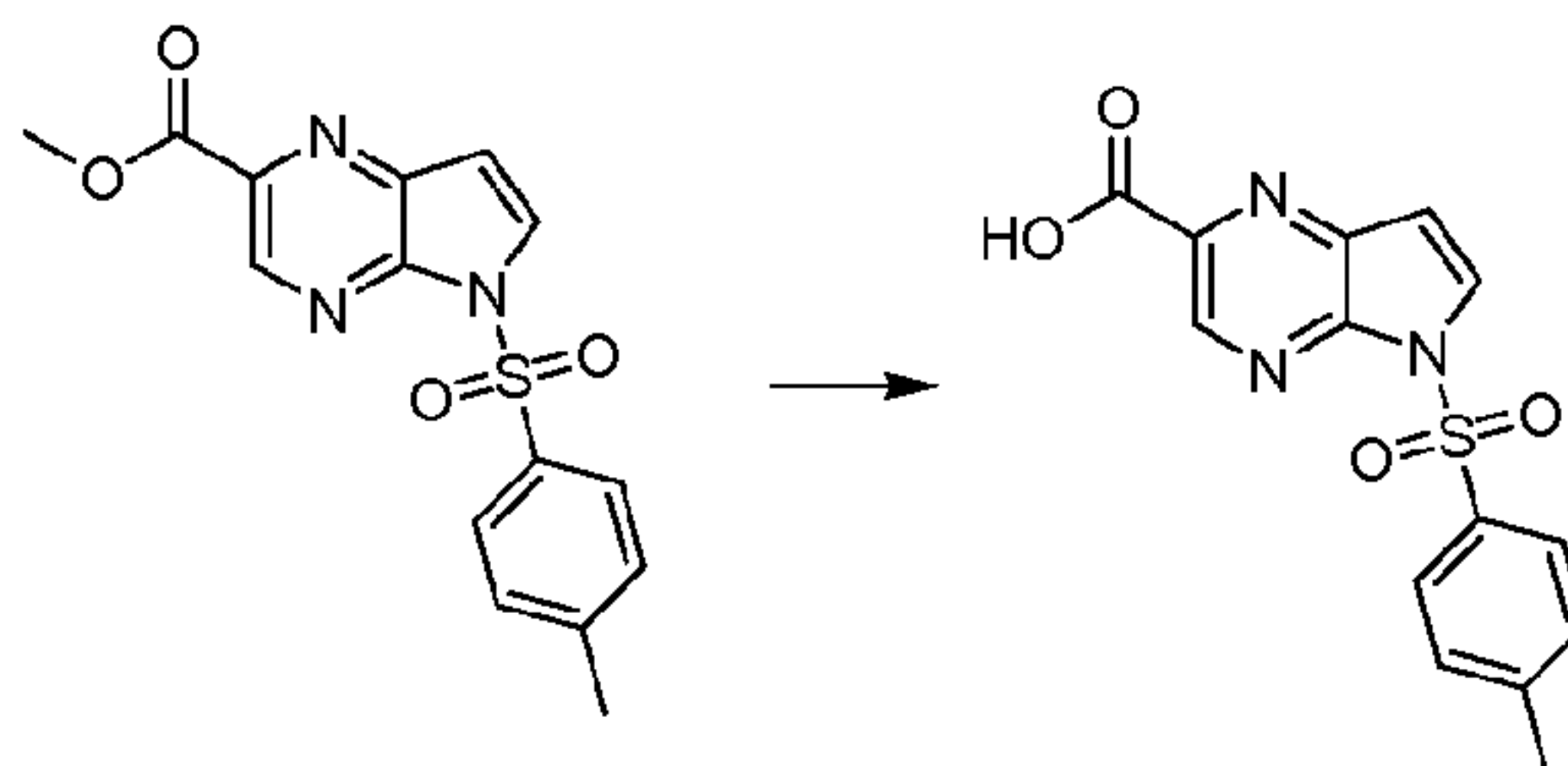
To a mixture of *N*-((1*S*,3*R*,4*S*)-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentyl)acetamide (5.0 g, 10.7 mmol, Example #8 Step L) and THF (110 mL) was added aqueous HCl (6 N, 63 mL, 375 mmol). The reaction was heated at about 95 °C for about 20 h and

then cooled to ambient temperature and concd under reduced pressure. To the resulting brown residue was added DCM (100 mL) and the solution was washed with saturated NaHCO_3 (3 x 50 mL). The aqueous portion was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous MgSO_4 , filtered, and concd under reduced pressure. The material was purified by chromatography on silica gel eluting with 0-100% DCM/MeOH/ NH_4OH (950:45:5) to give a mixture of *(1S,3R,4S)*-3-ethyl-4-(6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine and *(1S,3R,4S)*-3-ethyl-4-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentanamine (3.2 g, 70%) in a 1:10 ratio based on H-NMR as an off-white solid: LC/MS (Table 1, Method **a**) $R_t = 1.75$ min; MS m/z : 425 ($\text{M}+\text{H}$)⁺.

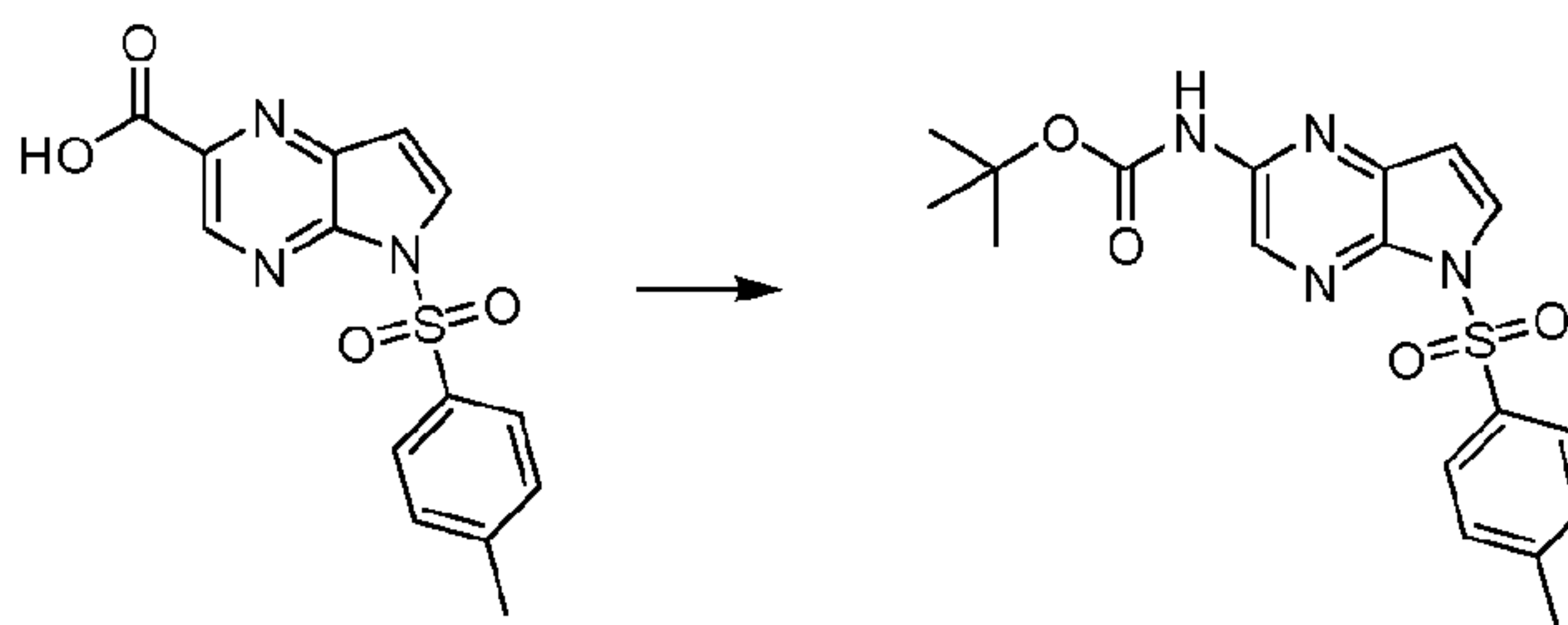
Preparation #45: Methyl 5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine-2-carboxylate



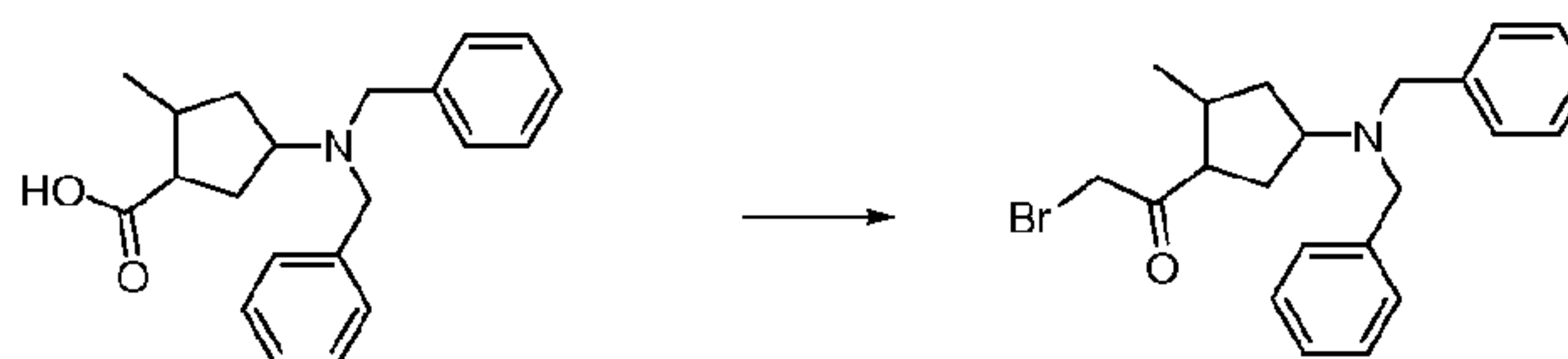
CO was bubbled into an orange solution of 2-bromo-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine (50.0 g, 142 mmol, Example #7, step B) in DMF (2.50 L) within a 5 L round bottom flask for about 2 min. Bis(triphenylphosphine)-palladium(II) dichloride (9.96 g, 14.2 mmol), TEA (59 mL, 423 mmol) and MeOH (173.0 mL, 4259 mmol) were added and the flask was fitted with a balloon of CO . The mixture was heated at about 95 °C under an atmosphere of CO (1 atmosphere). After stirring overnight, the reaction mixture was cooled to ambient temperature overnight and poured into ice water (3.2 L). The mixture was stirred for about 10 min and the precipitate was collected by filtration, while washing with water, and dried for 1 h. The crude material was dissolved in DCM, separated from residual water, dried over anhydrous MgSO_4 , filtered, added silica gel, and concd under reduced pressure to prepare for chromatography. The crude material was purified by silica gel column chromatography eluting with 0-5% MeOH in DCM to yield *methyl 5-tosyl-5H-pyrrolo[2,3-*b*]pyrazine-2-carboxylate* with 5 mol% DCM as an excipient (40.7 g, 86%, 93% purity): LC/MS (Table 1, Method **a**) $R_t = 2.35$ min; MS m/z 332 ($\text{M}+\text{H}$)⁺.

Preparation #46: 5-Tosyl-5H-pyrrolo[2,3-b]pyrazine-2-carboxylic acid

HCl (6 N aqueous, 714 mL) was added to a yellow solution of methyl 5-tosyl-5H-pyrrolo[2,3-b]pyrazine-2-carboxylate (17.8 g, 53.6 mmol, Preparation #45) in 1,4-dioxane (715 mL) within a 2 L round bottom flask, and the mixture was heated at about 60 °C for about 16 h. The reaction mixture was cooled to ambient temperature. The organic solvent was removed under reduced pressure and the precipitate was collected, washed with water, and dried to yield 5-tosyl-5H-pyrrolo[2,3-b]pyrazine-2-carboxylic acid (14.4 g, 85%) as a yellow solid: LC/MS (Table 1, Method a) R_t = 1.63 min; MS m/z 316 (M-H)⁻.

Preparation #47: *tert*-Butyl 5-tosyl-5H-pyrrolo[2,3-b]pyrazine-2-ylcarbamate

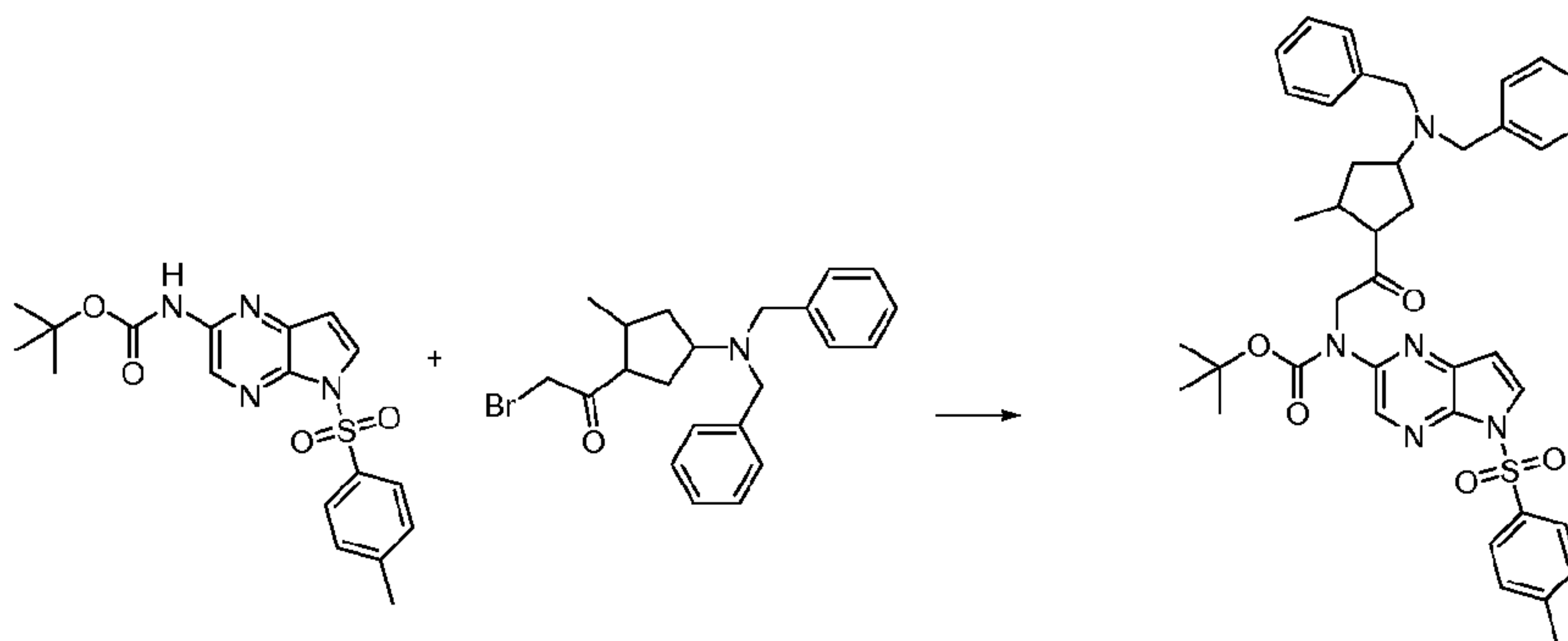
In a 500 mL round bottom flask, 5-tosyl-5H-pyrrolo[2,3-b]pyrazine-2-carboxylic acid (14.4 g, 45.3 mmol, Preparation #46), diphenylphosphoryl azide (9.78 mL, 45.3 mmol) and TEA (13.9 mL, 100 mmol) in *t*-BuOH (200 mL) were added to give an orange suspension. The mixture was heated at about 70 °C for about 16 h, cooled to ambient temperature and the insoluble material was filtered off. The solvent was removed under reduced pressure and the crude material was purified by silica gel column chromatography eluting with 25-60% EtOAc in heptane over 30 min to yield *tert*-butyl 5-tosyl-5H-pyrrolo[2,3-b]pyrazine-2-ylcarbamate (9.75 g, 54%) as an off-white solid: LC/MS (Table 1, Method a) R_t = 2.79 min; MS m/z 389 (M+H)⁺.

Preparation #48: 2-bromo-1-(4-(dibenzylamino)-2-methylcyclopentyl)ethanone

Oxalyl chloride (4.37 mL, 49.9 mmol) was slowly added to a solution of 4-(dibenzylamino)-2-methylcyclopentanecarboxylic acid (7.34 g, 22.7 mmol, Example #7, step I) in DCM (100 mL),

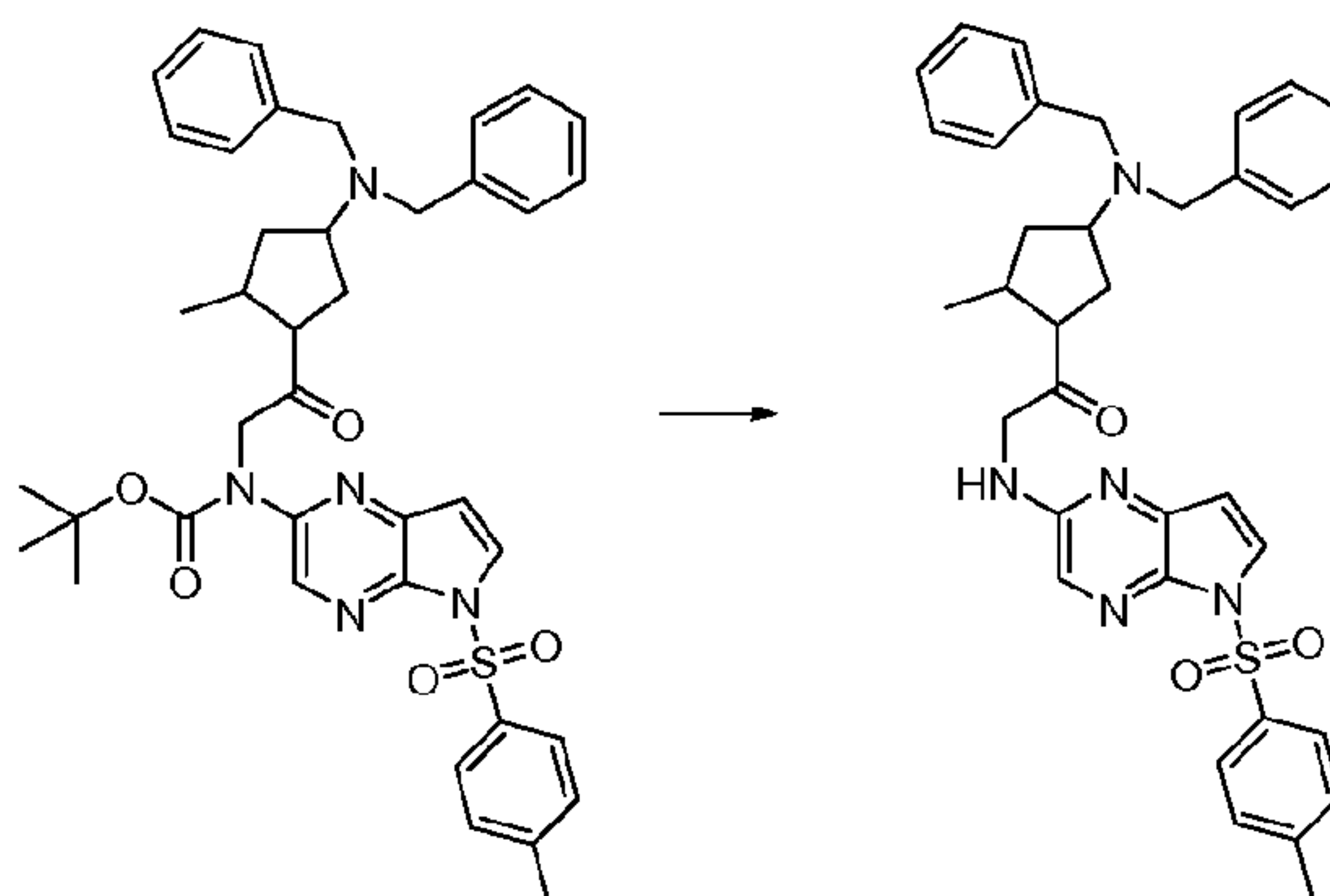
(note: mild gas evolution) followed by a dropwise addition of DMF (0.26 mL, 3.41 mmol). The mixture was stirred at ambient temperature for about 14 h. The solvent was removed under reduced pressure to yield a beige amorphous solid, which was dissolved in THF and MeCN (1:1, 100 mL) and added to a solution of trimethylsilyldiazomethane (2 M in Et₂O, 39.7 mL, 79 mmol) in THF and MeCN (1:1, 100 mL) at about 0 °C. The resulting mixture was stirred at about 0 °C for about 3 h and then was quenched by a dropwise addition of HBr (48% aqueous, 25 mL, 221 mmol). The resulting mixture was neutralized by a dropwise addition of saturated aqueous NaHCO₃ (300 mL) and the layers were separated. The organic layer was dried over anhydrous MgSO₄ and concd under reduced pressure. The residue was purified by silica gel flash chromatography eluting with 5% to 45% of EtOAc in heptane to yield *2-bromo-1-(4-(dibenzylamino)-2-methylcyclopentyl)ethanone* (6.3 g, 69%) as a yellow oil: LC/MS (Table 1, Method a) R_t = 2.90 min; MS *m/z* 400, 402 (M+H)⁺.

Preparation #49: *tert*-Butyl 2-(4-(dibenzylamino)-2-methylcyclopentyl)-2-oxoethyl(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)carbamate



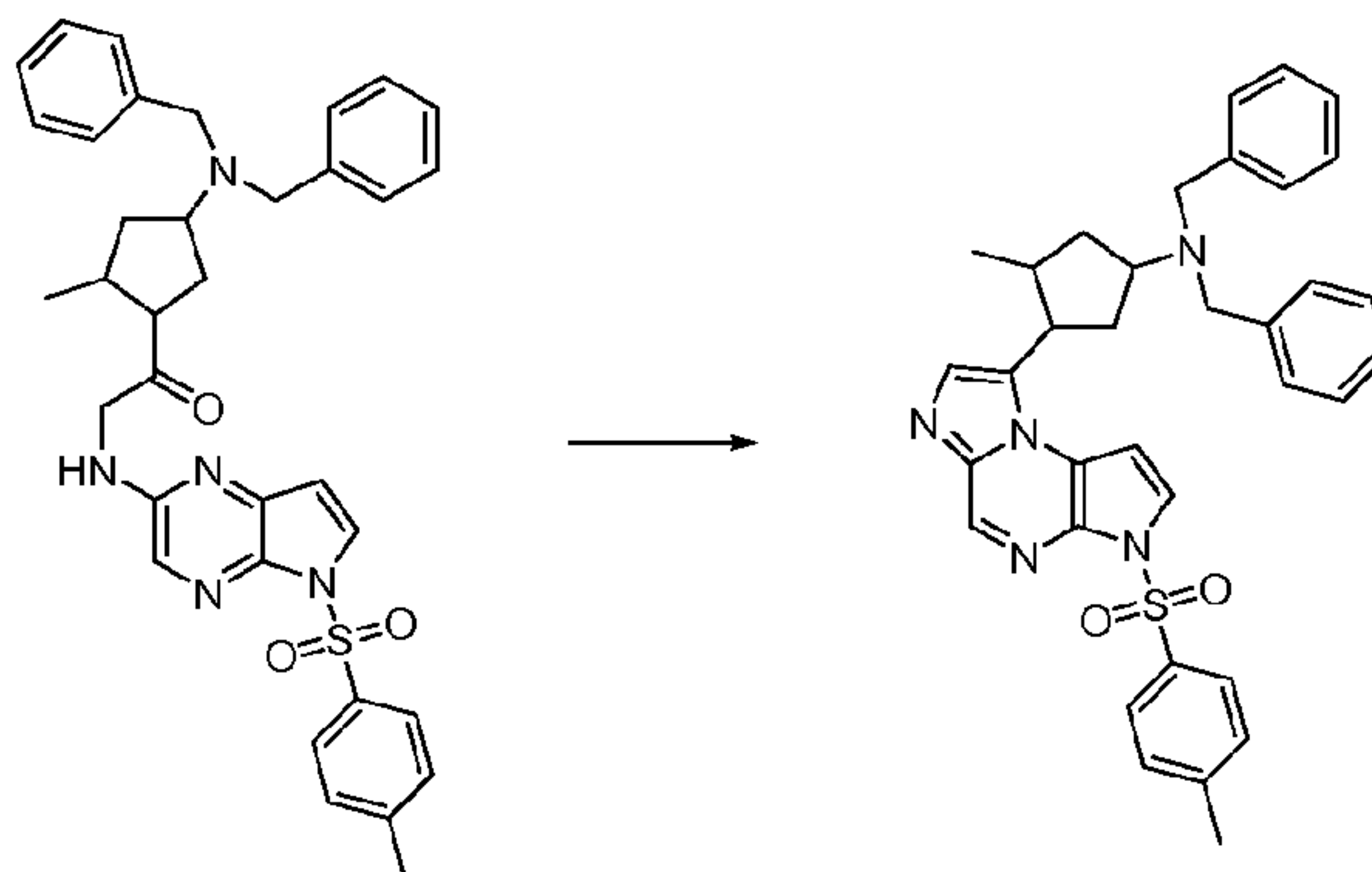
A solution of *tert*-butyl 5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-ylcarbamate (0.59 g, 1.519 mmol, Example #7, Step C) in DMF (5 mL) was added dropwise to a suspension of NaH (60% dispersion in mineral oil, 0.058 g, 1.45 mmol) in DMF (5 mL), at about 0 °C. The resulting mixture was stirred at about 0 °C for about 30 min and then added dropwise to a solution of 2-bromo-1-(4-(dibenzylamino)-2-methylcyclopentyl)ethanone (0.73 g, 1.8 mmol) in DMF (10 mL) at about 0 °C. The resulting mixture was stirred at about 0 °C for about 1 h and the solvent was removed under reduced pressure. The residue was partitioned between saturated aqueous NaHCO₃ and EtOAc (100 mL each). The organic phase was separated, dried over anhydrous MgSO₄ and concd under reduced pressure to yield *tert*-butyl 2-(4-(dibenzylamino)-2-methylcyclopentyl)-2-oxoethyl(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)carbamate (1.04 g, 97%) as a yellow amorphous solid: LC/MS (Table 1, Method a) R_t = 3.30 min; MS *m/z* 708 (M+H)⁺.

Preparation #50: 1-(4-(dibenzylamino)-2-methylcyclopentyl)-2-(5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-ylamino)ethanone



tert-Butyl 2-(4-(dibenzylamino)-2-methylcyclopentyl)-2-oxoethyl(5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)carbamate (6.19 g, 8.75 mmol, Preparation #49) was dissolved in HCl (4 N in 1,4-dioxane, 25 mL). The reaction mixture was stirred at ambient temperature for about 2 h. The solvent was removed under reduced pressure and the residue partitioned between saturated aqueous NaHCO₃ and EtOAc (100 mL each). The organic phase was washed with brine (80 mL), dried over anhydrous MgSO₄ and concd under reduced pressure to yield 1-(4-(dibenzylamino)-2-methylcyclopentyl)-2-(5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-ylamino)ethanone (5.2 g, 98%) as a brown amorphous solid: LC/MS (Table 1, Method a) R_t = 3.00 min; MS *m/z* 608 (M+H)⁺.

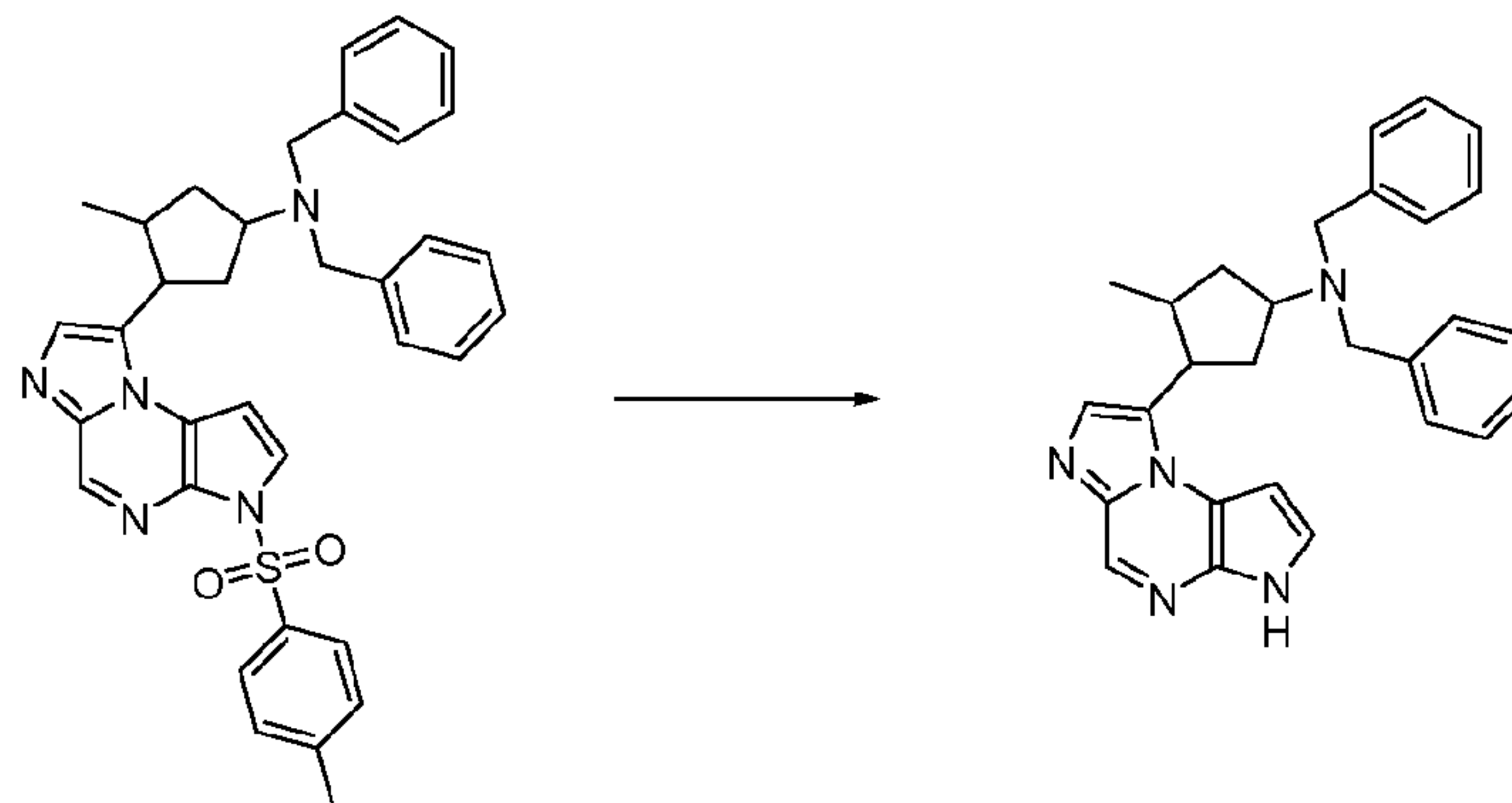
Preparation #51: *N,N*-dibenzyl-3-methyl-4-(3-tosyl-3H-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentanamine



A mixture of 1-(4-(dibenzylamino)-2-methylcyclopentyl)-2-(5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-ylamino)ethanone (5.32 g, 8.75 mmol, Preparation #50) and Lawesson's reagent (1.88 g, 4.64 mmol) was heated at about 60 °C for about 2 h. Lawesson's reagent (1.88 g, 4.64 mmol) was added. The reaction mixture was stirred at about 60 °C for about 1 h. The solvent was removed under reduced pressure and the residue purified by silica gel flash chromatography eluting with a gradient of 0-8% MeOH in DCM to yield *N,N*-dibenzyl-3-methyl-4-(3-tosyl-3H-imidazo[1,2-

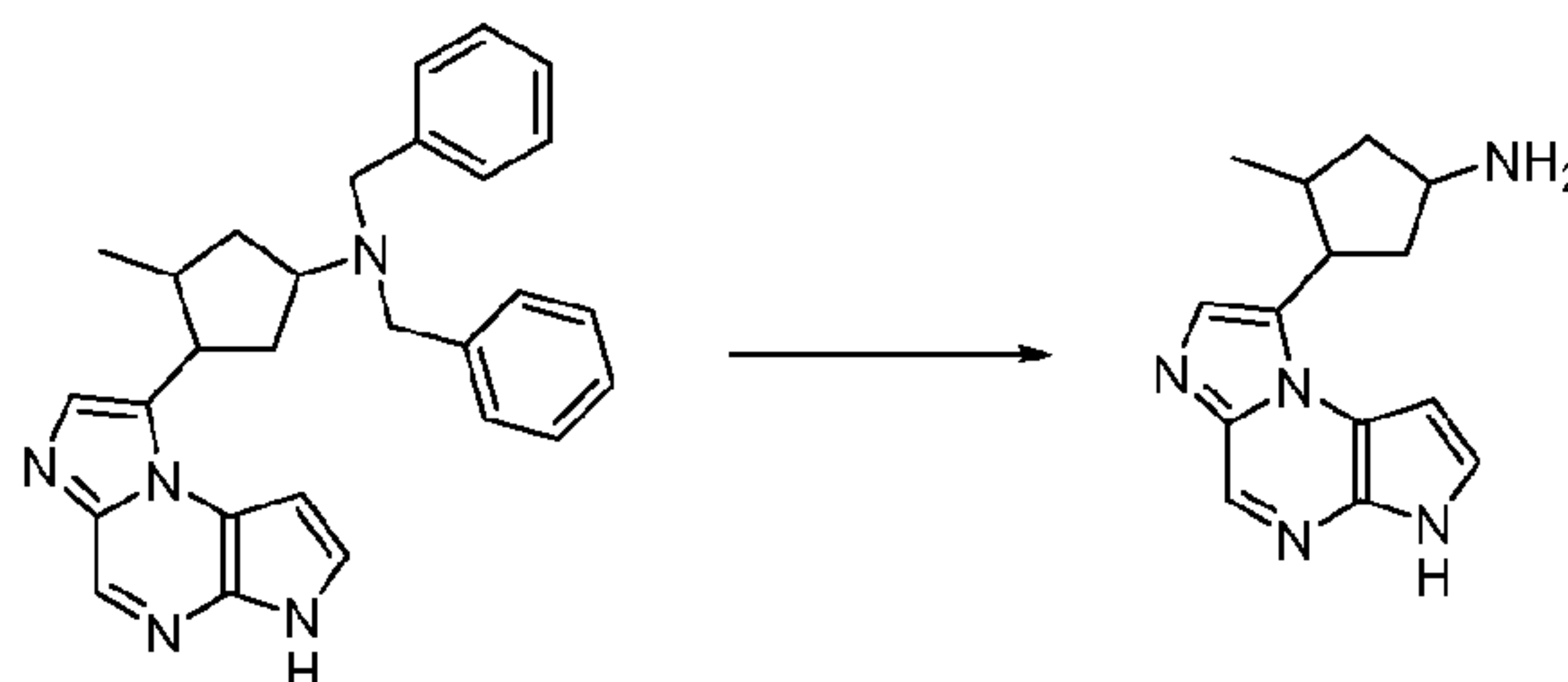
a]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentanamine (4.47 g, 87%) as a brown amorphous solid: LC/MS (Table 1, Method **a**) R_t = 2.99 min; MS m/z 590 (M+H)⁺.

Preparation #52: *N,N*-dibenzyl-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentanamine



N,N-Dibenzyl-3-methyl-4-(3-tosyl-3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)cyclopentanamine (4.47 g, 7.58 mmol, Preparation #51) was dissolved in 1,4-dioxane (40 mL). NaOH (2 N aqueous, 4 mL) was added and the reaction mixture was heated at about 90 °C for about 80 min. The organic solvent was removed under reduced pressure and the residue was treated with saturated aqueous NH₄Cl (70 mL) and extracted with DCM (2 x 60 mL). The combined organic extracts were washed with brine (70 mL), dried over anhydrous MgSO₄ and concd under reduced pressure. Purification by silica gel flash chromatography eluting with a gradient of 0-8% MeOH in DCM yielded *N,N*-dibenzyl-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentanamine (1.84 g, 56%) as a yellow oil: LC/MS (Table 1, Method **a**) R_t = 2.31 min; MS m/z 436 (M+H)⁺.

Preparation #53: 3-(3*H*-Imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentanamine

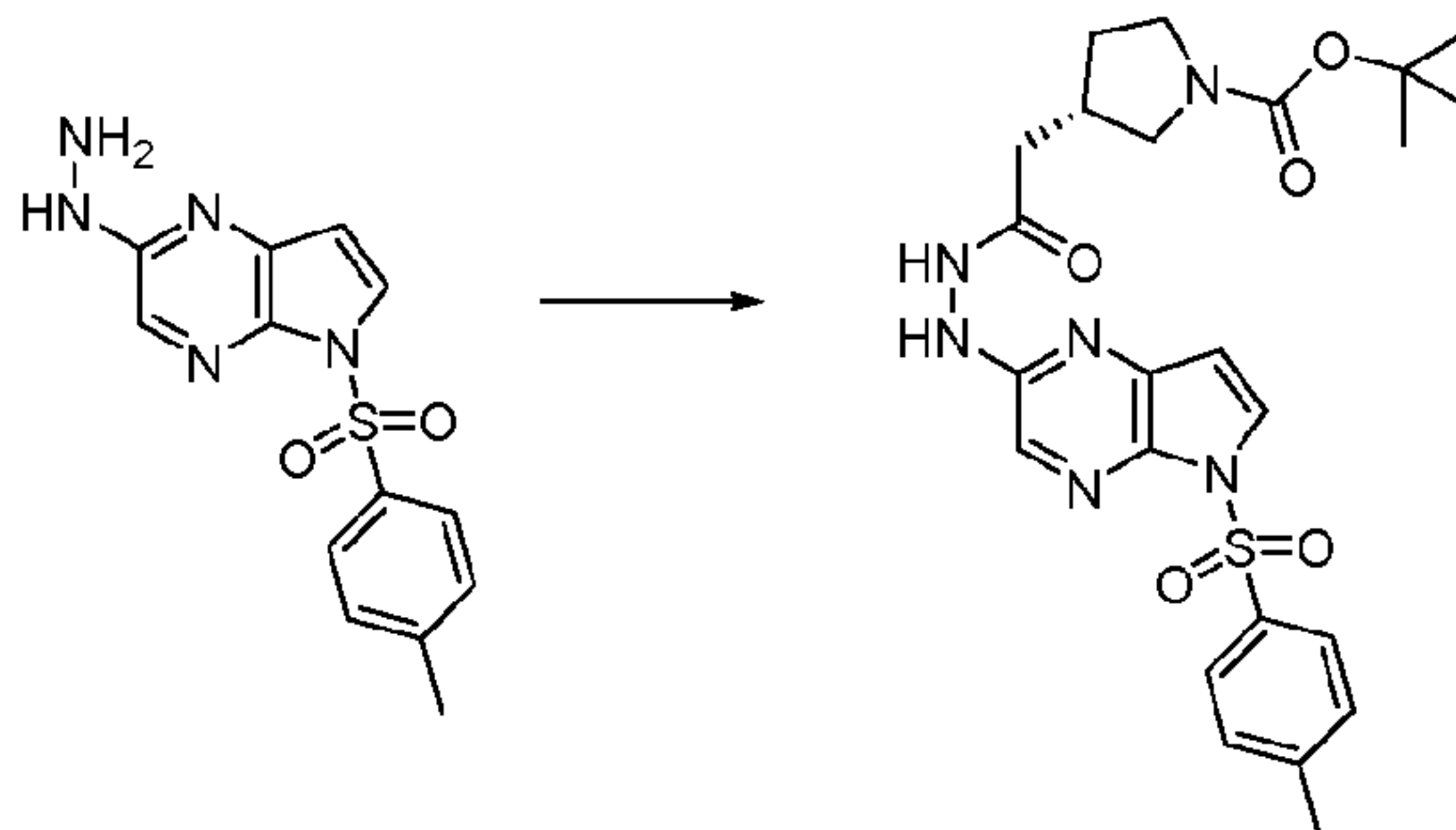


To a mixture of *N,N*-dibenzyl-3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentanamine (1.84 g, 4.22 mmol, Preparation #52) in EtOH (50 mL) was added 20 wt% Pd(OH)₂ on C (0.43 g, 0.61 mmol) and the resulting mixture was shaken under hydrogen pressure of about 50 psi on a Parr shaker at about 50 °C for about 2 h. The catalyst was filtered off using a pad of

Celite[®], 20 wt% Pd(OH)₂ on C (0.43 g, 0.61 mmol) was added, and the mixture was shaken under hydrogen pressure of about 50 psi on a Parr shaker at about 50 °C for about 16 h. The catalyst was filtered off using a pad of Celite[®], 20 wt% Pd(OH)₂ on C (0.43 g, 0.61 mmol) was added, and the mixture was shaken under hydrogen pressure of about 50 psi on a Parr shaker at about 50 °C for about 4 h. The catalyst was filtered off using a pad of Celite[®] and the filtrate was concd under reduced pressure to yield 3-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-4-methylcyclopentanamine (0.88 g, 82%) as an off-white amorphous solid: LC/MS (Table 1, Method a) R_t = 0.75 min and 0.87 min; MS *m/z* 256 (M+H)⁺.

General Procedure A: Formation of a hydrazide from a carboxylic acid

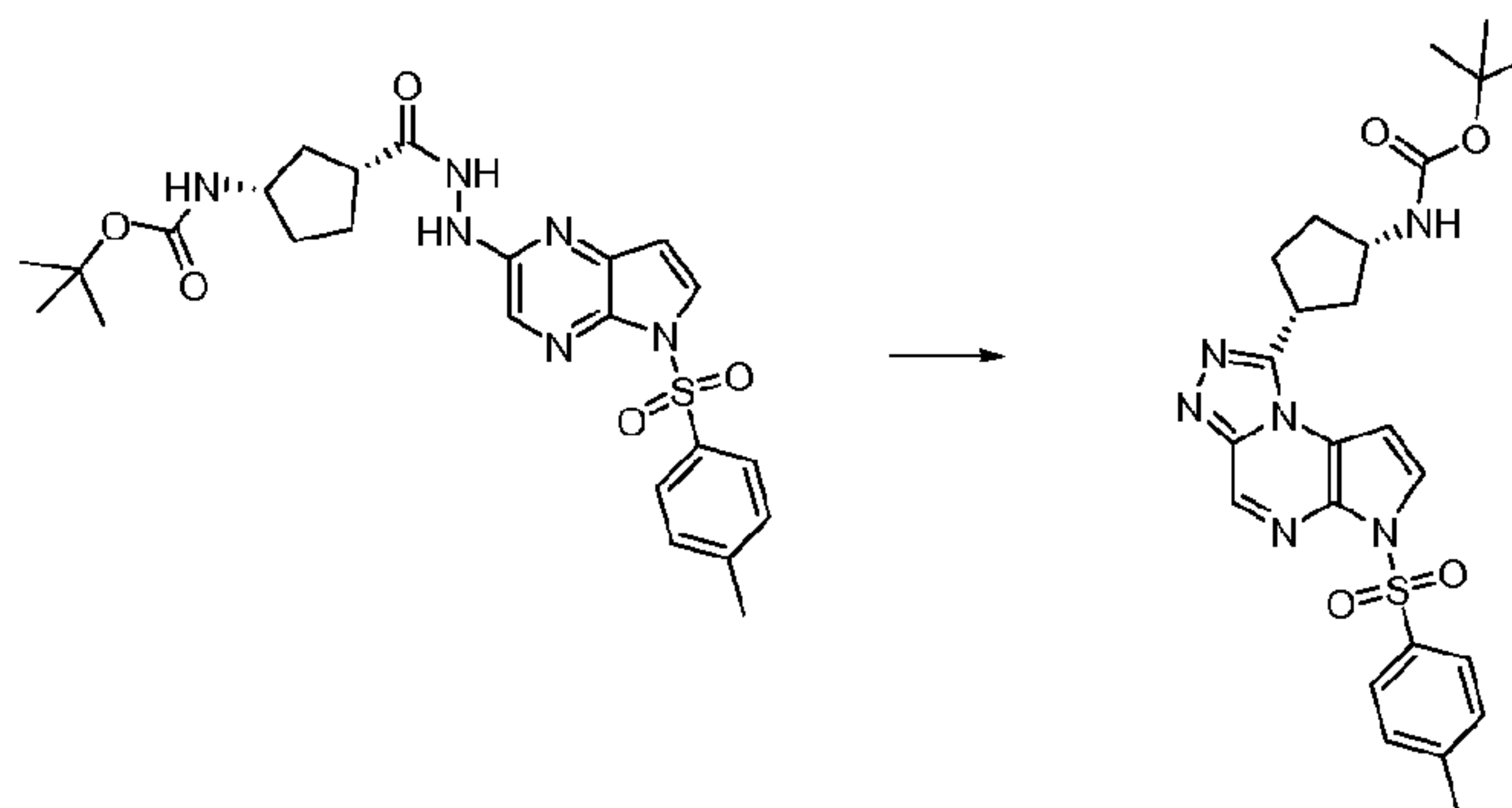
To a mixture of a 2-hydrazinylpyrrolo[2,3-*b*]pyrazine (preferably 1 equiv) and a carboxylic acid (1-2 equiv, preferably 1.1-1.3 equiv) in an organic solvent (such as DCM, DMF or THF, preferably DMF) is added a coupling agent such as EDC•HCl or HATU (1.0-2.0 equiv, preferably 1.2-1.6 equiv) with or without an organic base (such as TEA or DIEA, 2-5 equiv, preferably 3-4 equiv). After about 1-72 h (preferably 2-16 h) at about 20-60 °C (preferably about ambient temperature), the reaction is worked up using one of the following methods. If DMF is the solvent, the reaction is first concd under reduced pressure. Method 1: Water is added and the layers are separated. Optionally, the mixture may be filtered through Celite[®] prior to the separation of the layers. The aqueous layer is then extracted with an organic solvent such as EtOAc or DCM. The combined organic layers are optionally washed with brine, dried over anhydrous Na₂SO₄ or MgSO₄, filtered or decanted, and concd under reduced pressure. Method 2: The reaction is diluted with an organic solvent such as EtOAc or DCM and is washed with either water or brine or both. The aqueous layer is optionally further extracted with an organic solvent such as EtOAc or DCM. Then the organic layer or combined organic layers are optionally washed with brine, dried over anhydrous Na₂SO₄ or MgSO₄, filtered or decanted, and concd under reduced pressure. Method 3: The reaction is diluted with an organic solvent such as EtOAc or DCM and water is added. The layers are separated and the organic layer is concd under reduced pressure and directly purified by chromatography.

Illustration of General Procedure A**Preparation #A.1*: (*S*)-*tert*-butyl 3-(2-oxo-2-(2-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)hydrazinyl)ethyl)pyrrolidine-1-carboxylate**

To a solution of (*S*)-3-carboxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.756 g, 3.30 mmol, AstaTech) and 2-hydrazinyl-5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazine (1.0 g, 3.3 mmol, Example #1, Step D) in DMF (33 mL) was added TEA (1.38 mL, 9.89 mmol) followed by the addition of HATU (1.25 g, 3.30 mmol). The resulting mixture was stirred at ambient temperature for about 15 h then concd under reduced pressure. The residue was taken up in EtOAc (100 mL) and washed with water (100 mL). The organic portion was separated, washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concd under reduced pressure to give (*S*)-*tert*-butyl 3-(2-oxo-2-(2-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)hydrazinyl)ethyl)pyrrolidine-1-carboxylate as a sticky brown solid (1.90 g, 100%). This material was used without further purification: LC/MS (Table 1, Method c) R_t = 1.38 min; MS *m/z*: 515 (M+H)⁺.

General Procedure B: Cyclization of a hydrazide

To a solution of a 2-hydrazidyl-5*H*-pyrrolo[2,3-*b*]pyrazine (preferably 1 equiv) in an organic solvent (for example 1,4-dioxane) is added a base (such as TEA or DIEA, 1-5 equiv, preferably 2-4 equiv) and SOCl₂ (1-5 equiv, preferably 1-2 equiv). The mixture is heated at about 60-100 °C (preferably about 80 °C) for about 1-16 h (preferably about 1-2 h). The reaction mixture is cooled to ambient temperature and worked up using one of the following methods. Method 1: An organic solvent (such as EtOAc or DCM) and water are added. The layers are separated and the aqueous layer is optionally extracted with additional organic solvent. The combined organic layers may be optionally washed with aqueous base (such as NaHCO₃) and/or brine, dried over anhydrous Na₂SO₄ or MgSO₄, then decanted or filtered prior to concentrating under reduced pressure. Method 2: An organic solvent (such as EtOAc or DCM) is added and the organic layer is optionally washed with brine or water, dried over anhydrous MgSO₄ or Na₂SO₄, filtered or decanted, and concd under reduced pressure. Method 3: The reaction mixture is partitioned between an organic solvent (such as EtOAc or DCM) and saturated aqueous NaHCO₃ or brine, dried over anhydrous Na₂SO₄ or MgSO₄, then decanted or filtered prior to concentrating under reduced pressure.

Illustration of General Procedure B**Preparation #B.1*: *tert*-butyl (1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylcarbamate**

To a solution of *tert*-butyl (1*S*,3*R*)-3-(2-(5-tosyl-5*H*-pyrrolo[2,3-*b*]pyrazin-2-yl)hydrazinecarbonyl)cyclopentylcarbamate (9.30 g, 18.1 mmol, prepared using **A** from Example #1 Step D, and (1*R*,3*S*)-3-*tert*-butoxycarbonylamino)cyclopentanecarboxylic acid [Peptech]) in 1,4-dioxane (100 mL) was added TEA (10.0 mL, 72.3 mmol) and SOCl₂ (2.11 mL, 28.9 mmol). The mixture was heated at about 80 °C for about 1.5 h. The reaction mixture was cooled to ambient temperature, EtOAc (200 mL) and water (200 mL) were added, and the layers were separated. The aqueous portion was extracted with EtOAc (2 x 100 mL) and the combined organic extracts were washed with saturated aqueous NaHCO₃ (100 mL) and brine (100 mL), dried over anhydrous Na₂SO₄, filtered, and concd under reduced pressure. The crude material was purified by silica gel chromatography eluting with a gradient of 25-100% EtOAc in DCM to give *tert*-butyl-(1*S*,3*R*)-3-(6-tosyl-6*H*-pyrrolo[2,3-*e*][1,2,4]triazolo[4,3-*a*]pyrazin-1-yl)cyclopentylcarbamate (7.65 g, 85%): LC/MS (Table 1, Method **a**) R_t = 2.37 min; MS *m/z*: 497 (M+H)⁺.

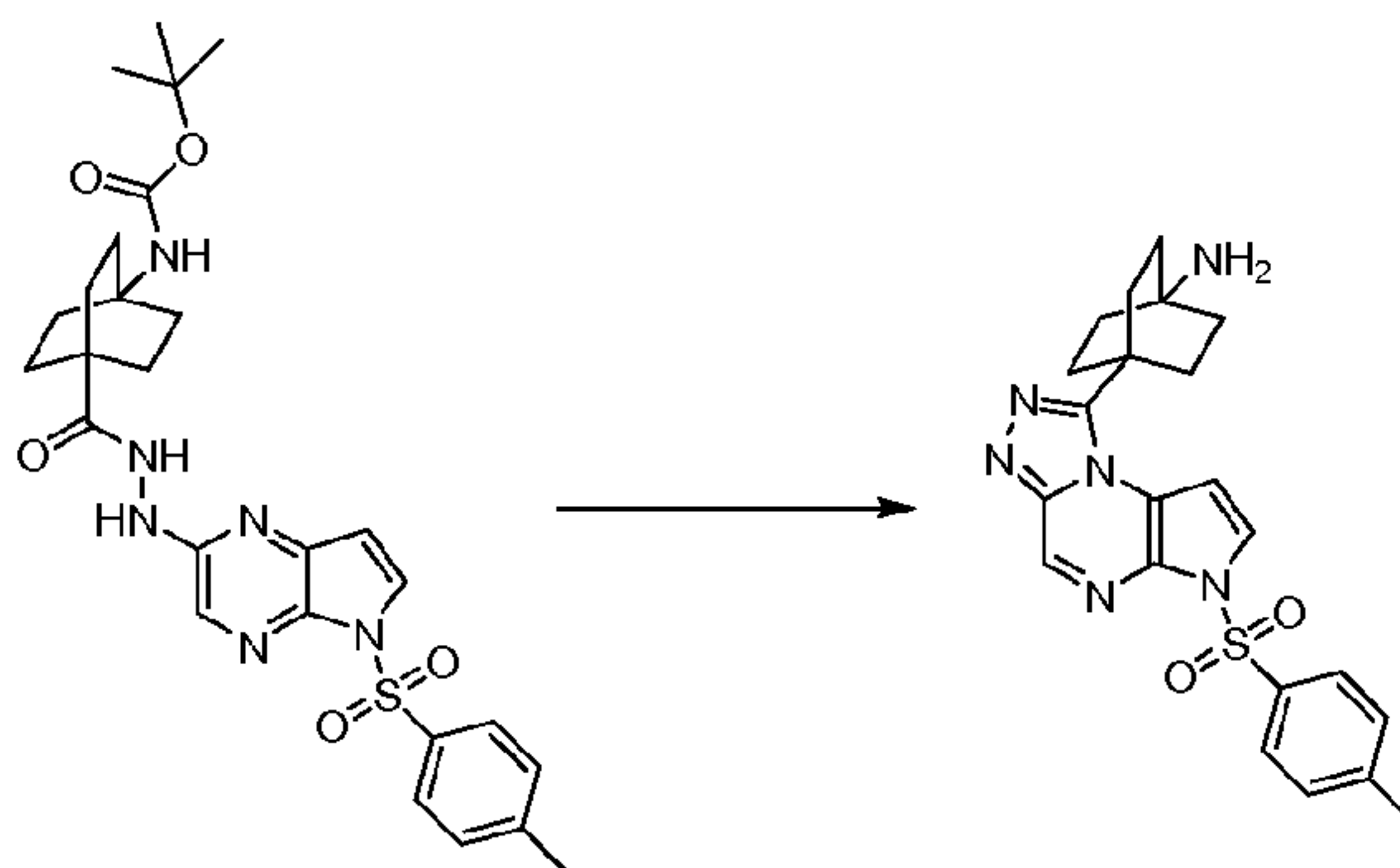
General Procedure C: Cyclization of a hydrazide with loss of Boc-protecting group

To a solution of an appropriately substituted 2-hydrazidyl-5*H*-pyrrolo[2,3-*b*]pyrazine containing a Boc protecting group (preferably 1 equiv) and TEA or DIEA (0-6 equiv, preferably 4 equiv) in an organic solvent (such as 1,4-dioxane or DCM, preferably 1,4-dioxane) is added SOCl₂ (2.0-6.0 equiv, preferably 2.5 equiv). The reaction is heated at about 60-120 °C (preferably about 80-90 °C) for about 1-8 h (preferably about 2-4 h) and then worked up using one of the following methods. Method 1: The reaction mixture is filtered and washed with a suitable organic solvent (such as EtOAc or DCM) to give the target compound with no further purification. Method 2: The crude material is diluted with a suitable organic solvent (such as EtOAc or DCM) and saturated aqueous NaHCO₃ is added, the layers are separated and the organic portion is dried over anhydrous Na₂SO₄ or MgSO₄, filtered, and concd under reduced pressure. Method 3: The

reaction mixture is washed with a basic aqueous solution (preferably saturated aqueous NaHCO_3) and filtered to give the Boc-protected target compound with no further purification. If partial Boc-deprotection occurs, the filtrate is extracted with a suitable organic solvent (such as EtOAc or DCM), the layers are separated and the organic portion is dried over anhydrous Na_2SO_4 or MgSO_4 , filtered, and concd under reduced pressure to give the remaining Boc-protected compound. The crude Boc-protected material or partially Boc-protected material obtained above is dissolved in 1,4-dioxane or DCM (preferably 1,4-dioxane) and added to a solution of HCl in an organic solvent (1-6 N, preferably 4 N HCl in 1,4-dioxane) and heated to about 30-60 °C (preferably about 50 °C) for about 1-5 h (preferably about 3 h). If a precipitate forms, it is collected and then dissolved in a suitable organic solvent (such as EtOAc or DCM) and washed with a basic aqueous solution (preferably saturated aqueous NaHCO_3). If no precipitate forms, the reaction mixture is washed with a basic aqueous solution (preferably saturated aqueous NaHCO_3). In either case, the layers are separated and the organic portion is dried over anhydrous Na_2SO_4 or MgSO_4 , filtered, and concd under reduced pressure.

Illustration of General Procedure C

Preparation #C.1 4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)bicyclo[2.2.2]octan-1-amine

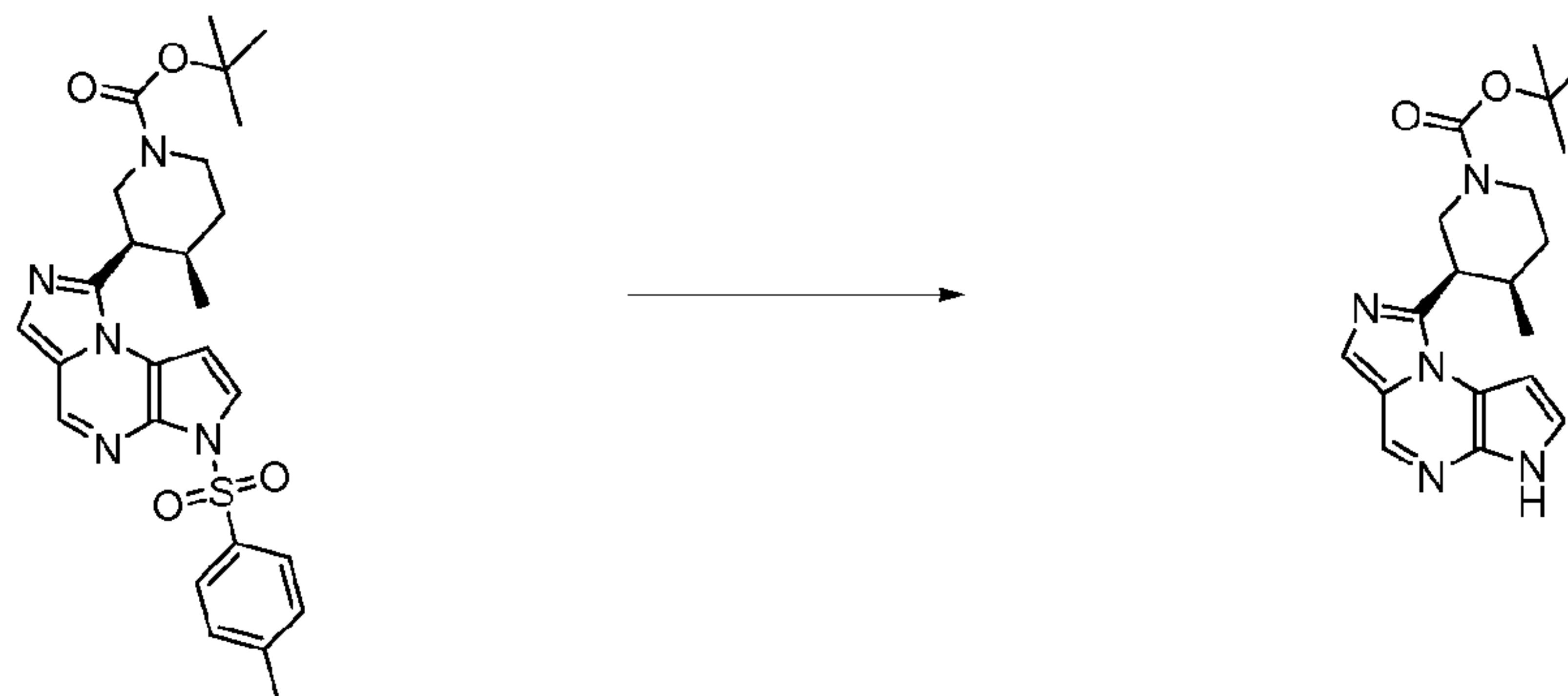


To a solution of *tert*-butyl 4-(2-(5-tosyl-5H-pyrrolo[2,3-b]pyrazin-2-yl)hydrazinecarbonyl)-bicyclo[2.2.2]octan-1-ylcarbamate (6.1 g, 11.0 mmol, Example #9, Step E), and TEA (6.1 mL, 44.0 mmol) in 1,4-dioxane (110 mL) was added SOCl_2 (2.0 mL, 27.5 mmol). The reaction mixture was heated at about 80 °C for about 2 h then cooled to ambient temperature. The reaction mixture was washed with saturated aqueous NaHCO_3 (3 x 50 mL). The layers were separated and the aqueous portion was filtered to give 4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)bicyclo[2.2.2]-octan-1-amine as a brown solid (1.17 g, 24%); LC/MS (Table 1, Method a) R_t = 1.28 min; MS m/z : 437 ($\text{M}+\text{H}$)⁺. The remaining filtrate was extracted with EtOAc (10 mL). The combined organic layer was dried over anhydrous MgSO_4 , filtered, and concd under reduced pressure to afford crude *tert*-butyl 4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)bicyclo[2.2.2]octan-1-ylcarbamate (3.5 g). The crude Boc-protected material was

dissolved in 1,4-dioxane (38 mL) and HCl (4 N in 1,4-dioxane, 8 mL) was added. The reaction mixture was heated to about 50 °C for about 3 h. The precipitate formed was collected by filtration. The solid was dissolved in DCM (50 mL), and washed with saturated aqueous NaHCO₃ (3 x 20 mL). The layers were separated and the organic portion was dried over anhydrous MgSO₄, filtered, and concd under reduced pressure to give additional 4-(6-tosyl-6H-pyrrolo[2,3-e][1,2,4]triazolo[4,3-a]pyrazin-1-yl)bicyclo[2.2.2]octan-1-amine as a brown solid (2.3 g, 50% over 2 steps): LC/MS (Table 1, Method a) R_t = 1.28 min; MS m/z: 437 (M+H)⁺.

General Procedure D: Hydrolysis of a sulfonamide

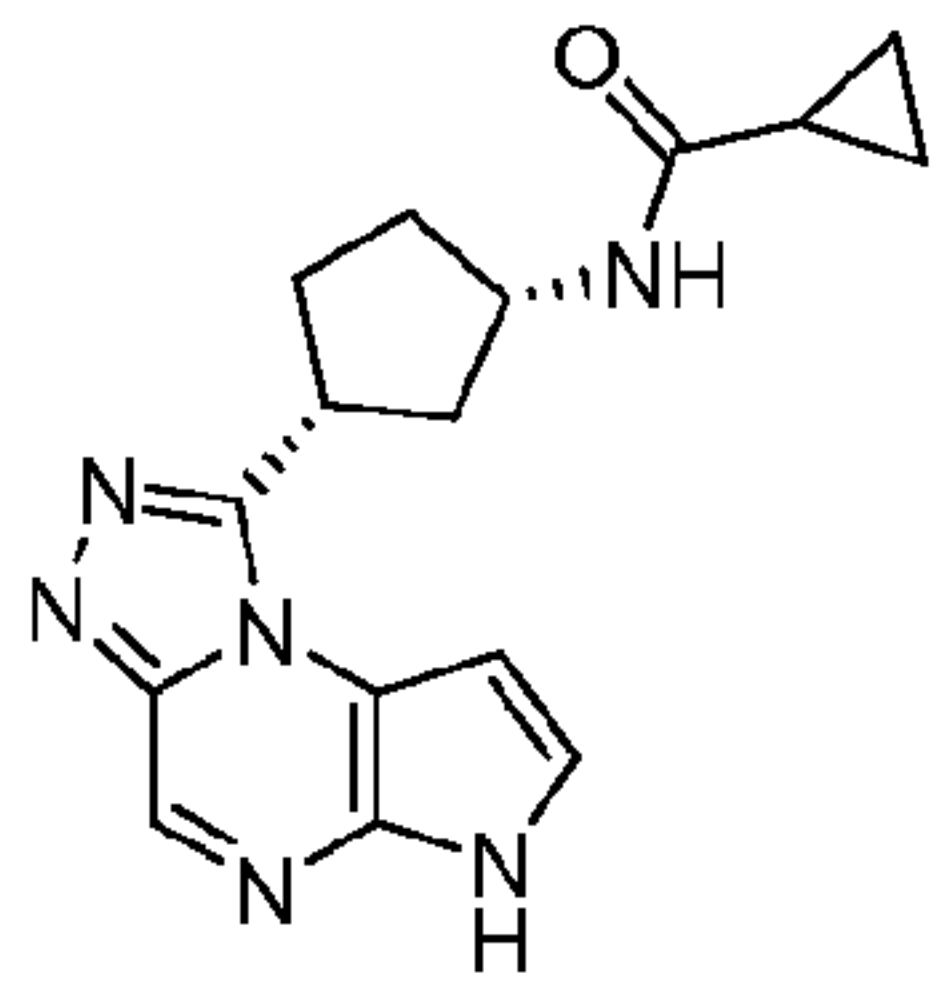
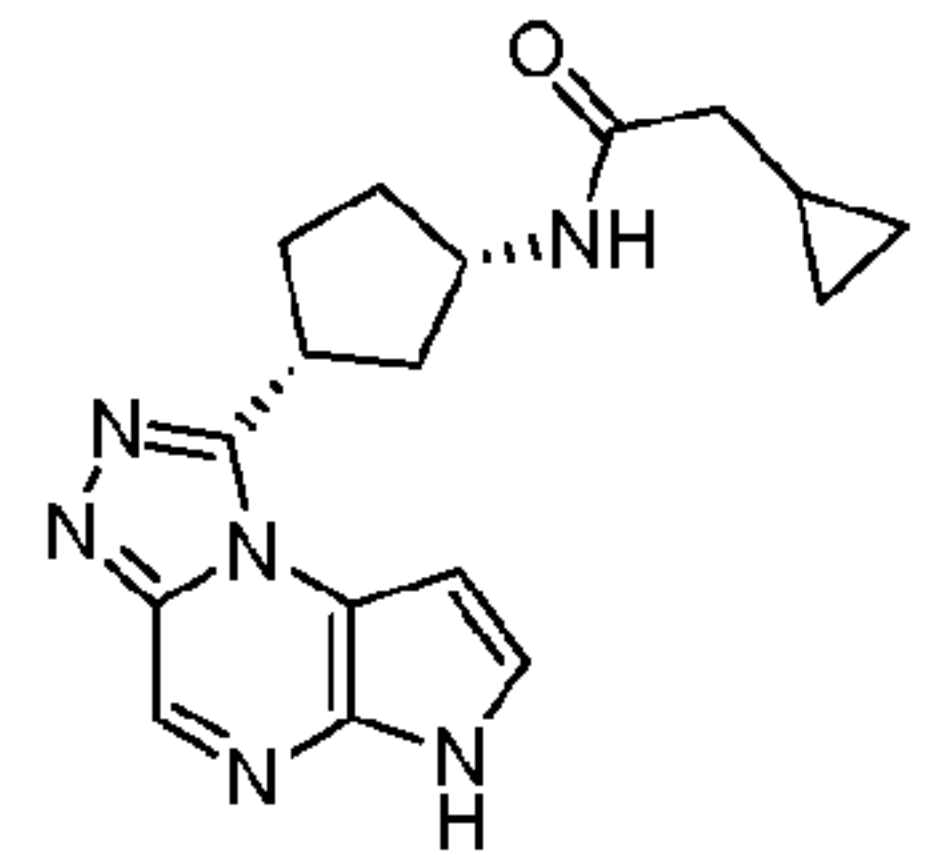
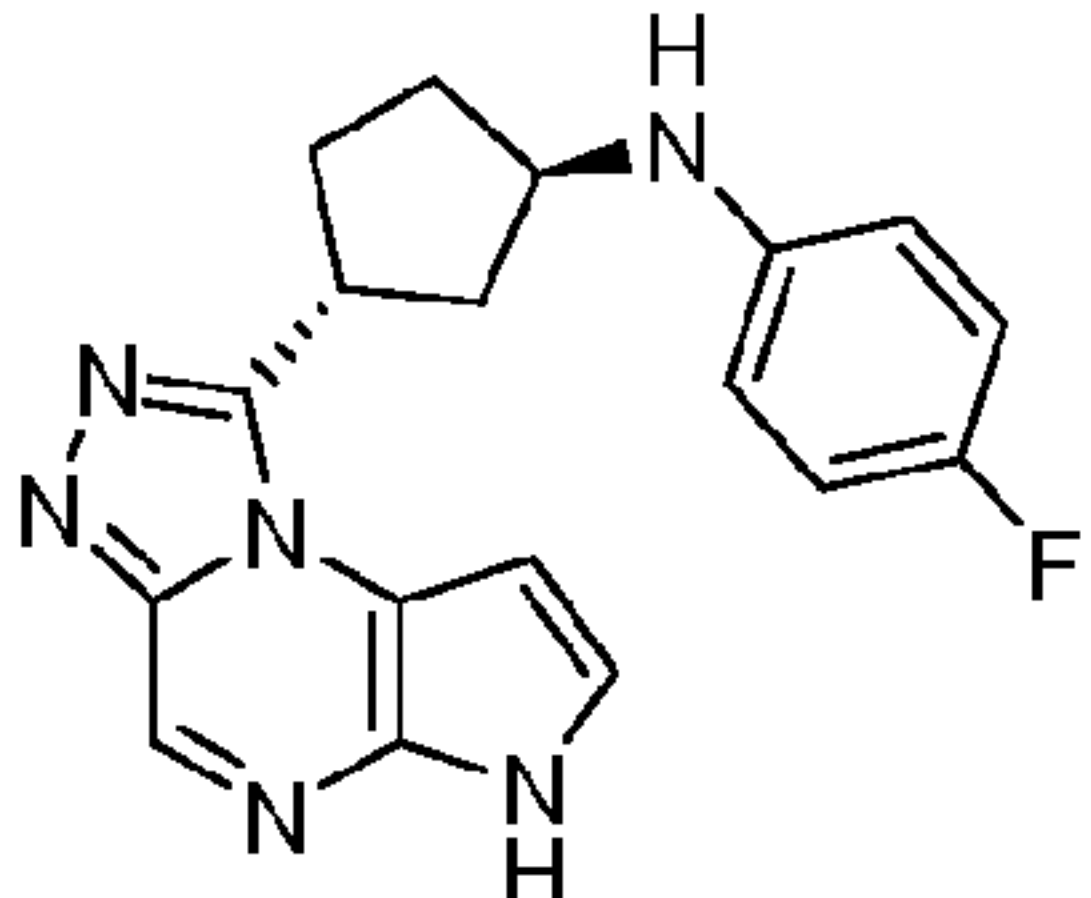
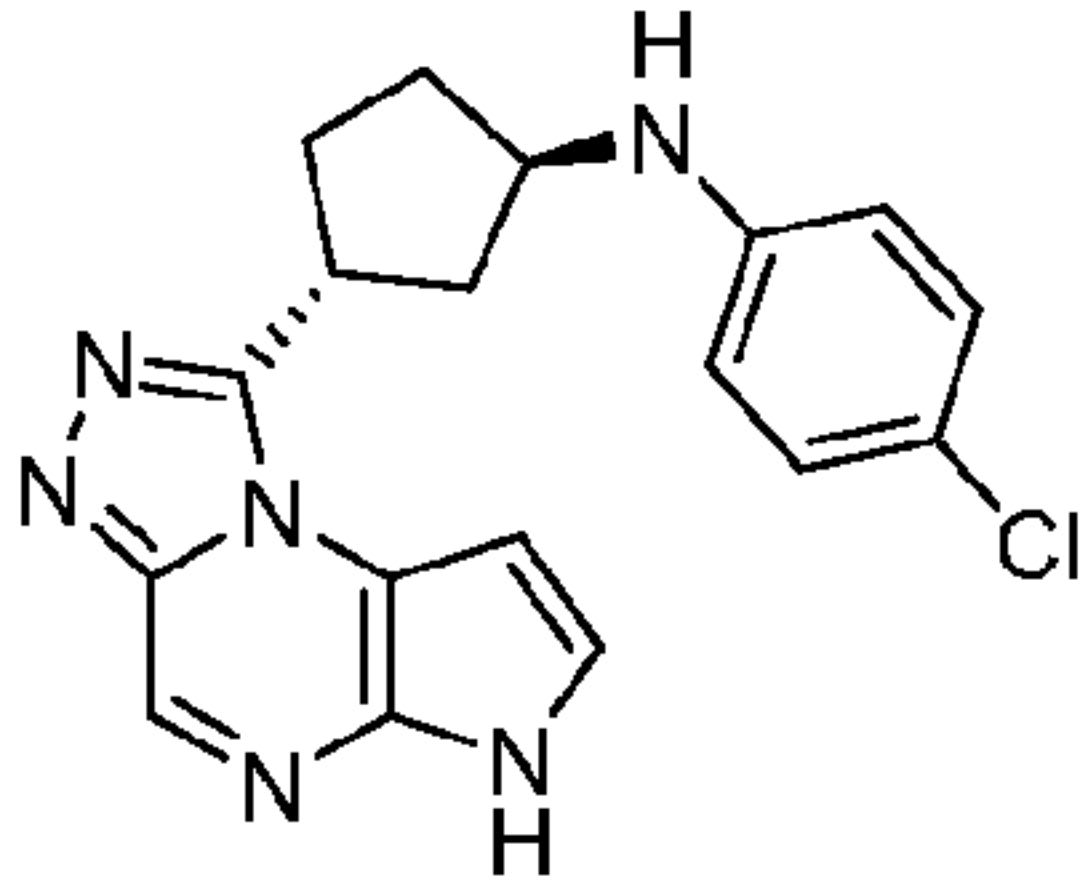
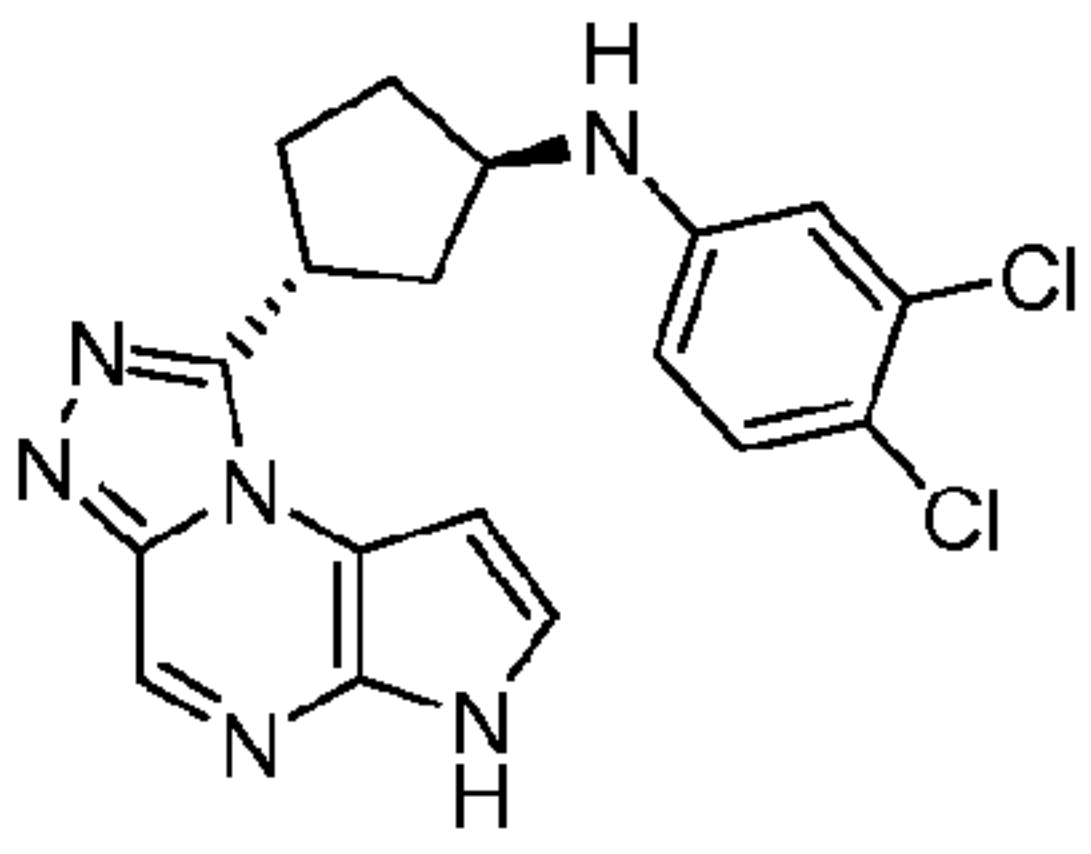
To a flask containing a sulfonamide, for example, a sulfonyl-protected pyrrole, (preferably 1 equiv) in an organic solvent (such as 1,4-dioxane, MeOH, or THF/MeOH, preferably 1,4-dioxane) is added an aqueous base (such as aqueous Na₂CO₃ or aqueous NaOH, 1-30 equiv, preferably 2-3 equiv for aqueous NaOH, preferably 15-20 equiv for aqueous Na₂CO₃). The mixture is stirred at about 25-100 °C (preferably about 60 °C) for about 1-72 h (preferably about 1-16 h). In cases where the reaction does not proceed to completion as monitored by TLC, LC/MS, or HPLC, additional aqueous base (such as aqueous Na₂CO₃, 10-20 equiv, preferably 10 equiv or aqueous NaOH, 1-5 equiv, preferably 1-2 equiv) and/or a cosolvent (such as EtOH) is added. The reaction is continued at about 25-100 °C (preferably about 60 °C) for about 0.25-3 h (preferably about 1-2 h). In any case where an additional base labile group is present (for example, an ester a trifluoromethyl, or a cyano group), this group may also be hydrolyzed. The reaction is worked up using one of the following methods. Method 1. The organic solvent is optionally removed under reduced pressure and the aqueous solution is neutralized with the addition of a suitable aqueous acid (such as aqueous HCl). A suitable organic solvent (such as EtOAc or DCM) and water are added, the layers are separated, and the organic solution is dried over anhydrous Na₂SO₄ or MgSO₄, filtered, and concd to dryness under reduced pressure to give the target compound. Method 2. The organic solvent is optionally removed under reduced pressure, a suitable organic solvent (such as EtOAc or DCM) and water are added, the layers are separated, and the organic solution is dried over anhydrous Na₂SO₄ or MgSO₄, filtered, and concd to dryness under reduced pressure to give the target compound. Method 3. The reaction mixture is concd under reduced pressure and directly purified by one of the subsequent methods.

Illustration of General Procedure D**Preparation #D.1*: (3*R*,4*R*)-*tert*-butyl-3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carboxylate**

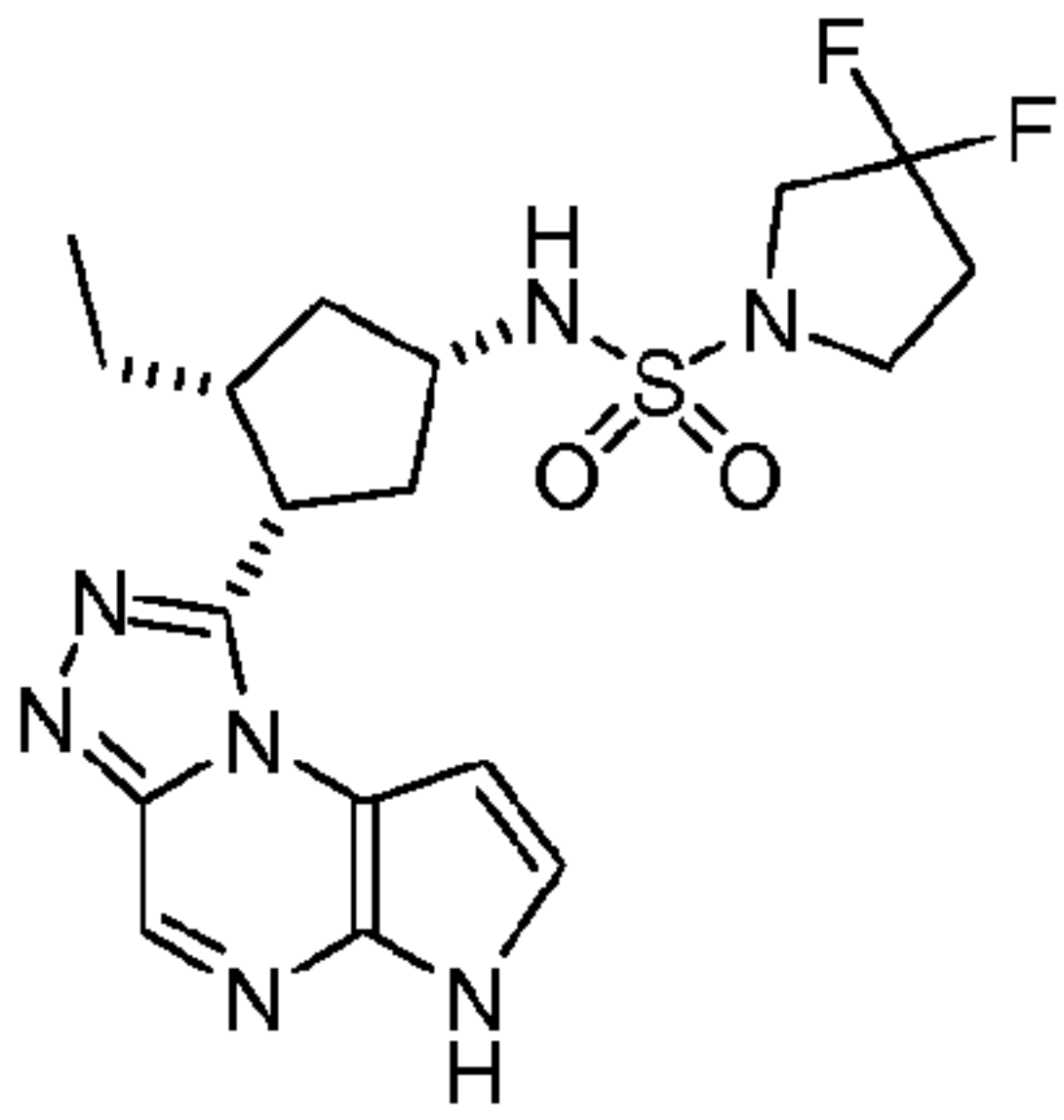
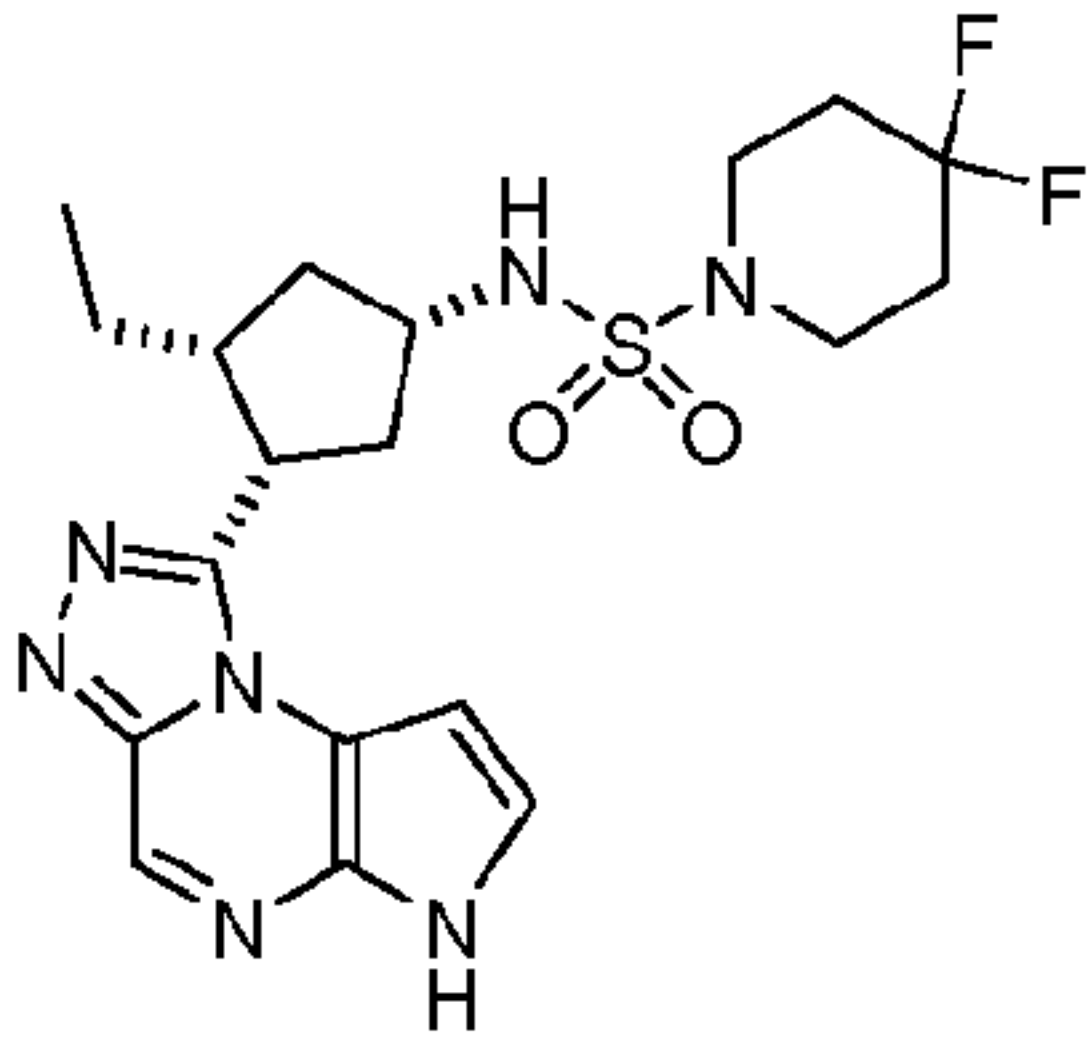
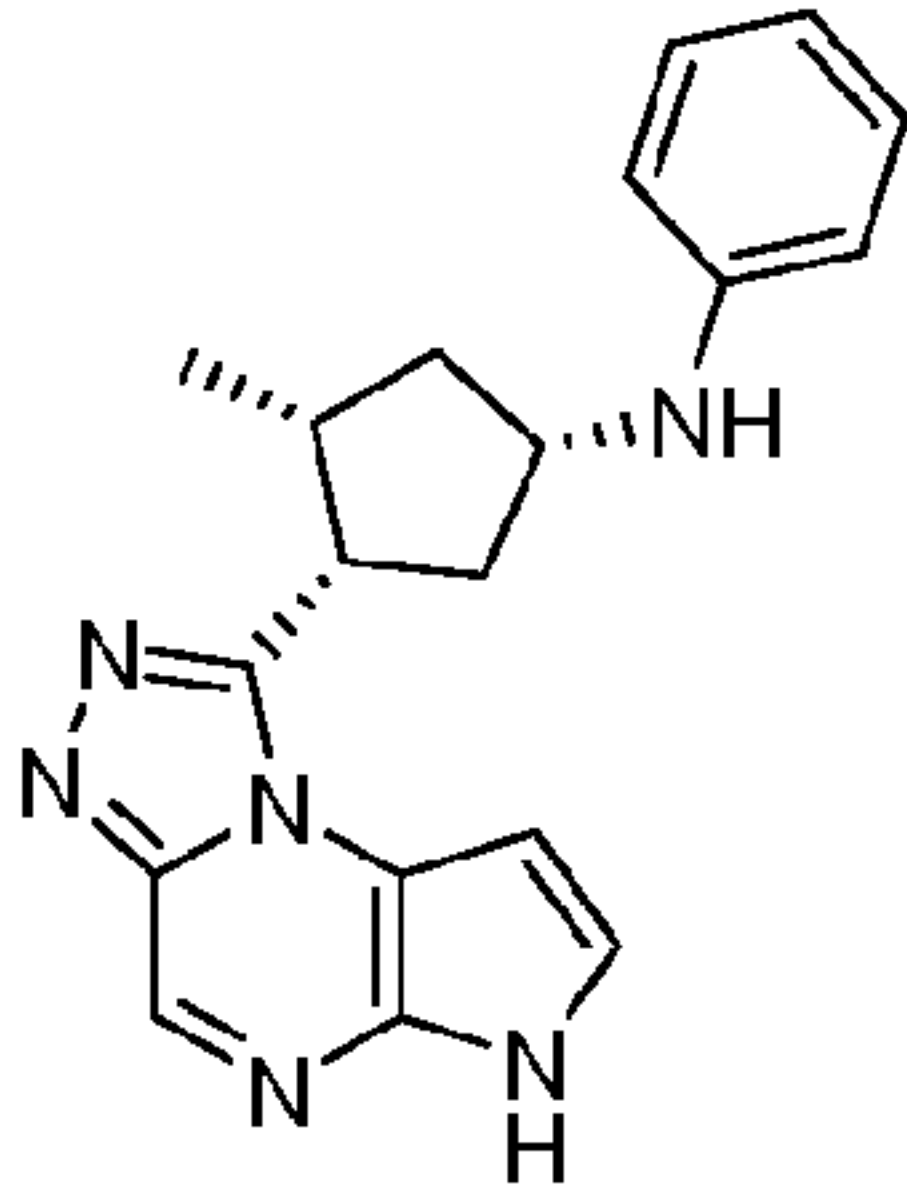
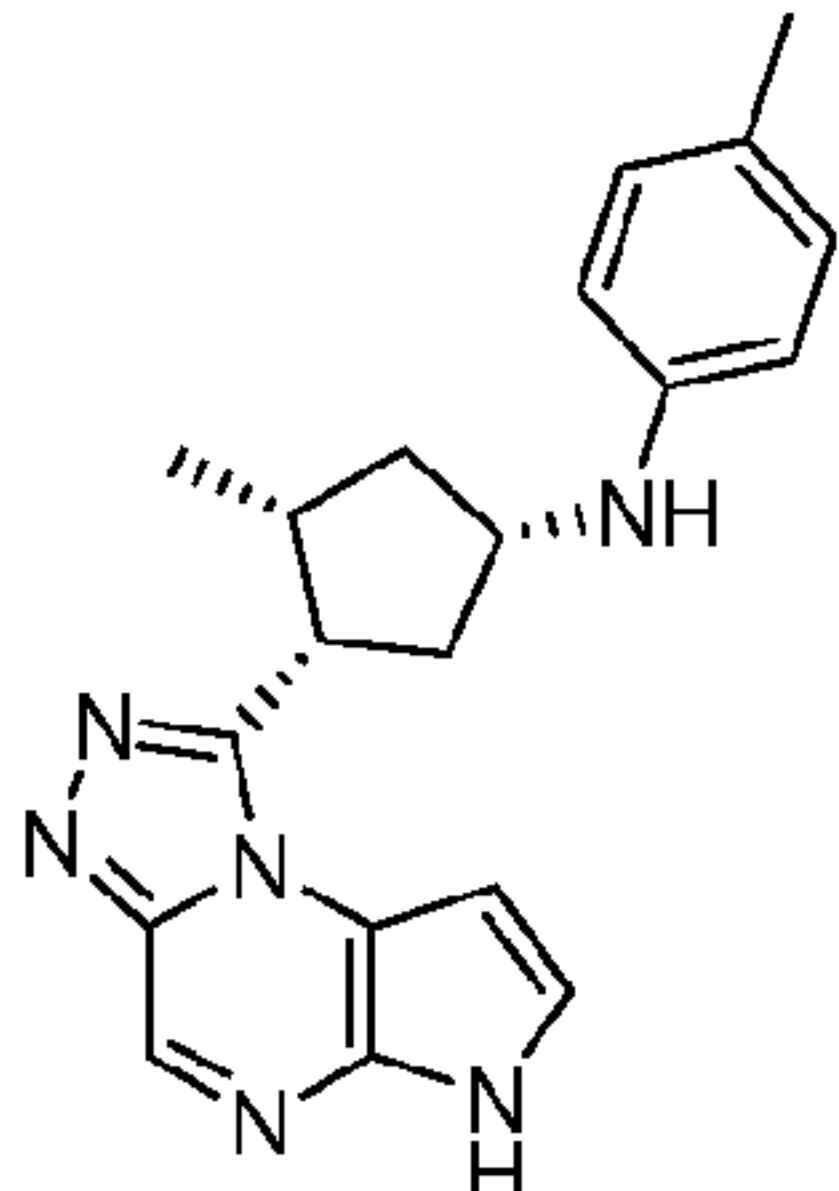
To a solution of (3*R*,4*R*)-*tert*-butyl 4-methyl-3-(6-tosyl-6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)piperidine-1-carboxylate (40 g, 78 mmol, Example #5 Step H) in 1,4-dioxane (160 mL) was added NaOH (1 N aqueous, 157 mL). The reaction was heated at about 60 °C for about 1 h. The reaction was allowed to cool to ambient temperature. The reaction was neutralized with aqueous HCl (4 N, 50 mL). The layers and extracted with DCM (2 x 300 mL). The combined organic extracts were washed with brine (400 mL), dried over anhydrous Na₂SO₄, filtered then concd *in vacuo*. The product was purified by chromatography on silica gel (330 g) using 1-5% MeOH in DCM to give (3*R*,4*R*)-*tert*-butyl 3-(6*H*-imidazo[1,5-*a*]pyrrolo[2,3-*e*]pyrazin-1-yl)-4-methylpiperidine-1-carboxylate (30 g, 99%); LC/MS (Table 1, Method b) *R*_t = 2.00 min; MS *m/z*: 356 (M+H)⁺.

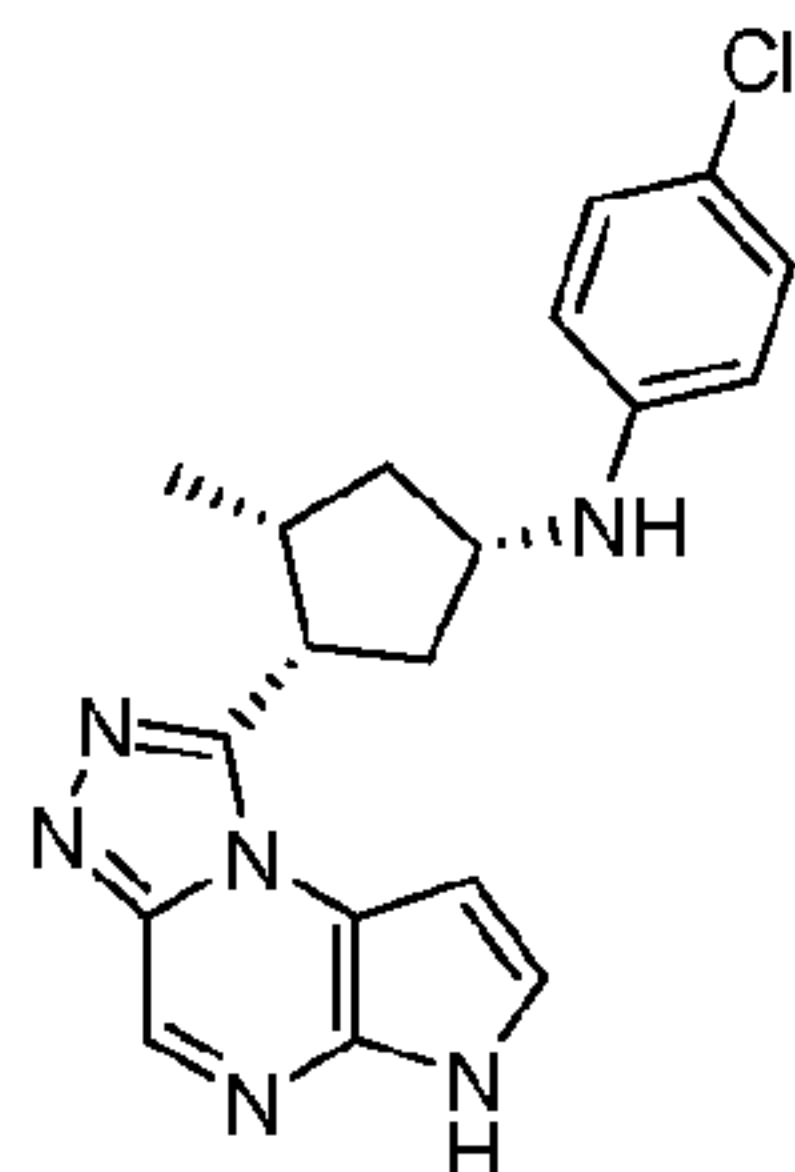
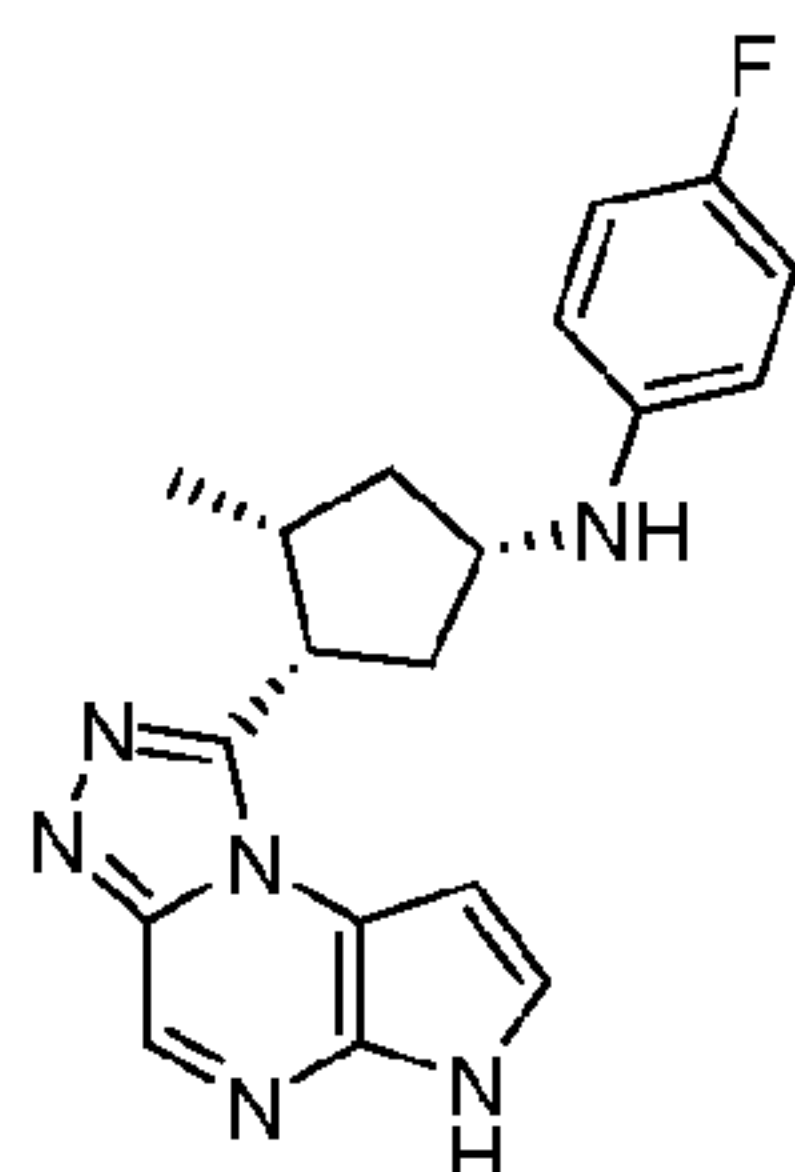
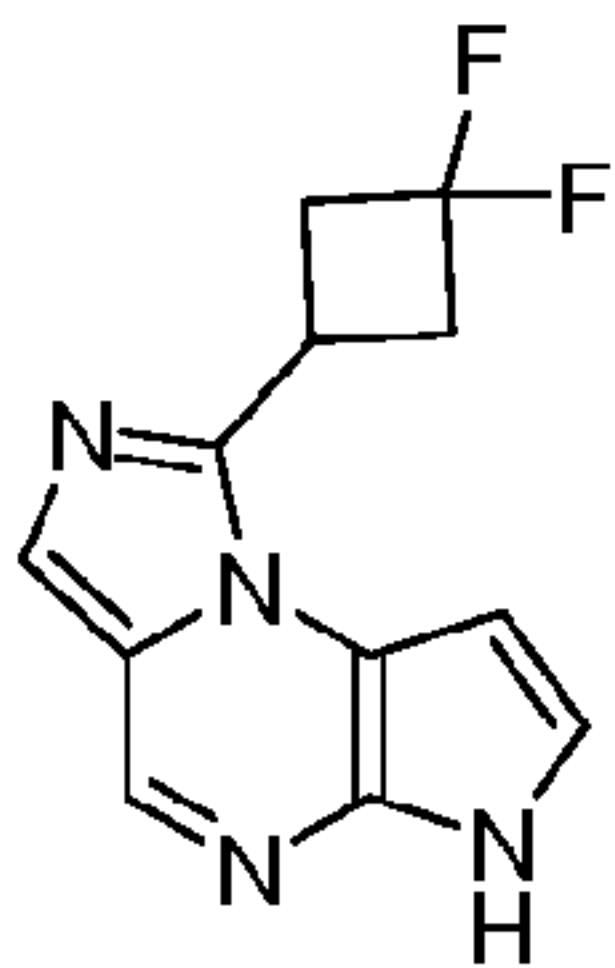
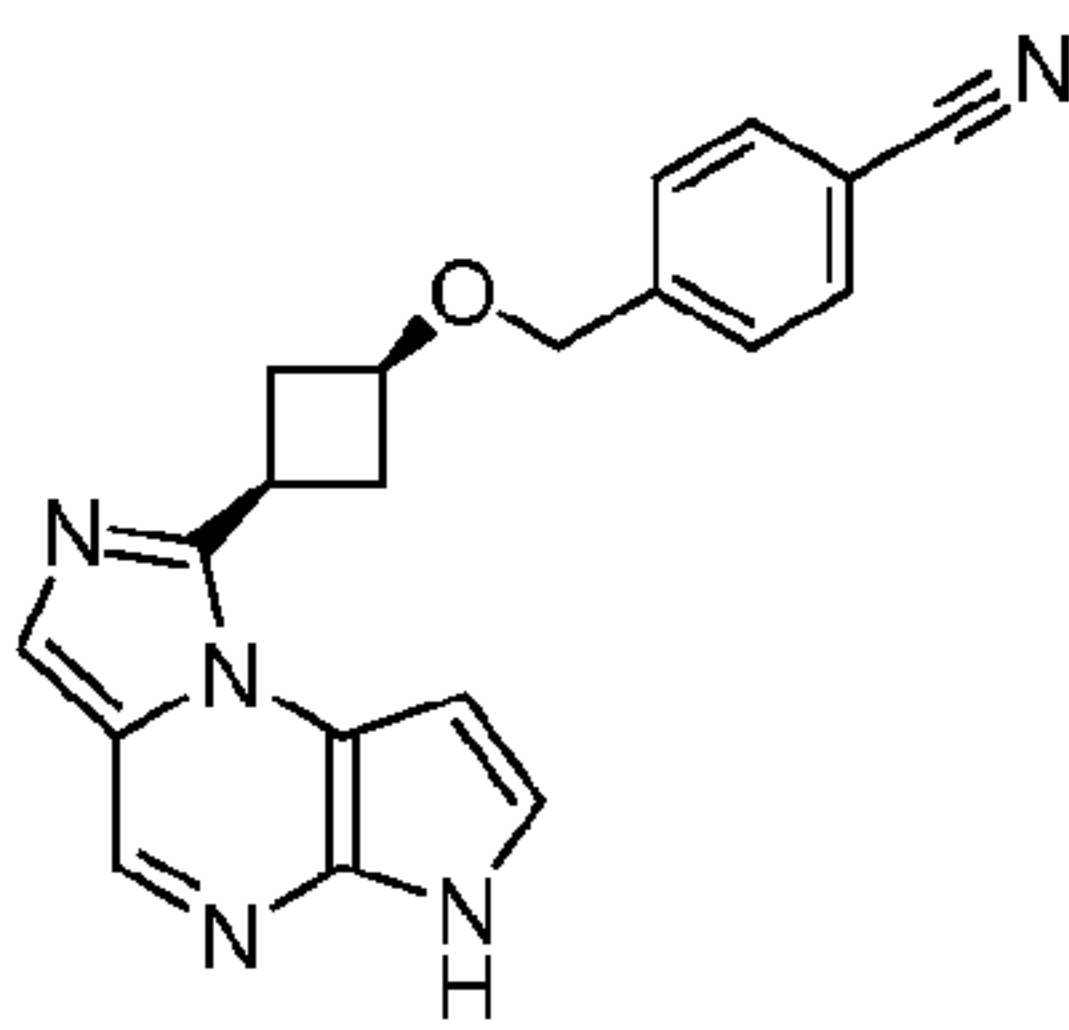
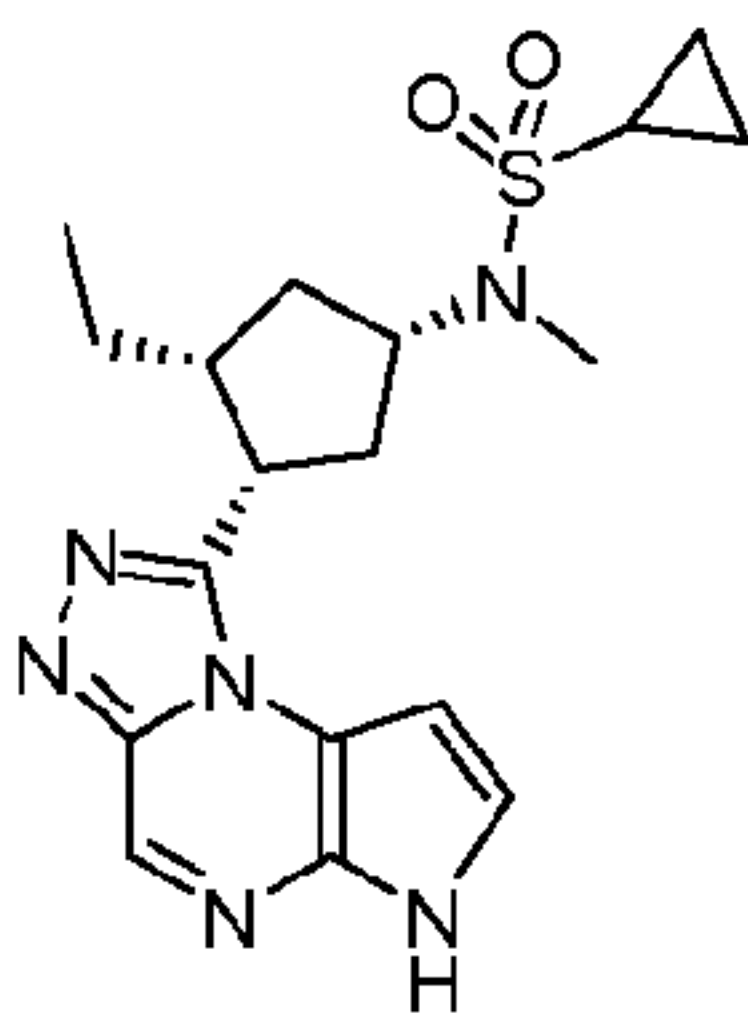
Table D.1 Examples prepared using General Procedure D with NaOH

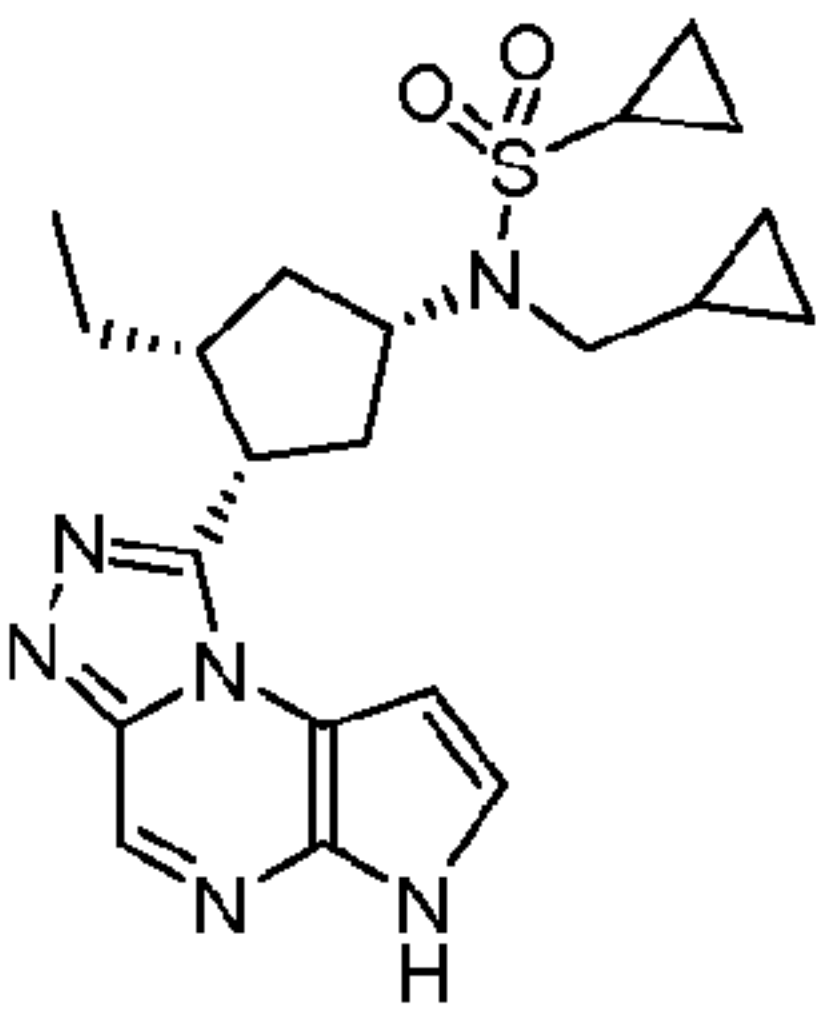
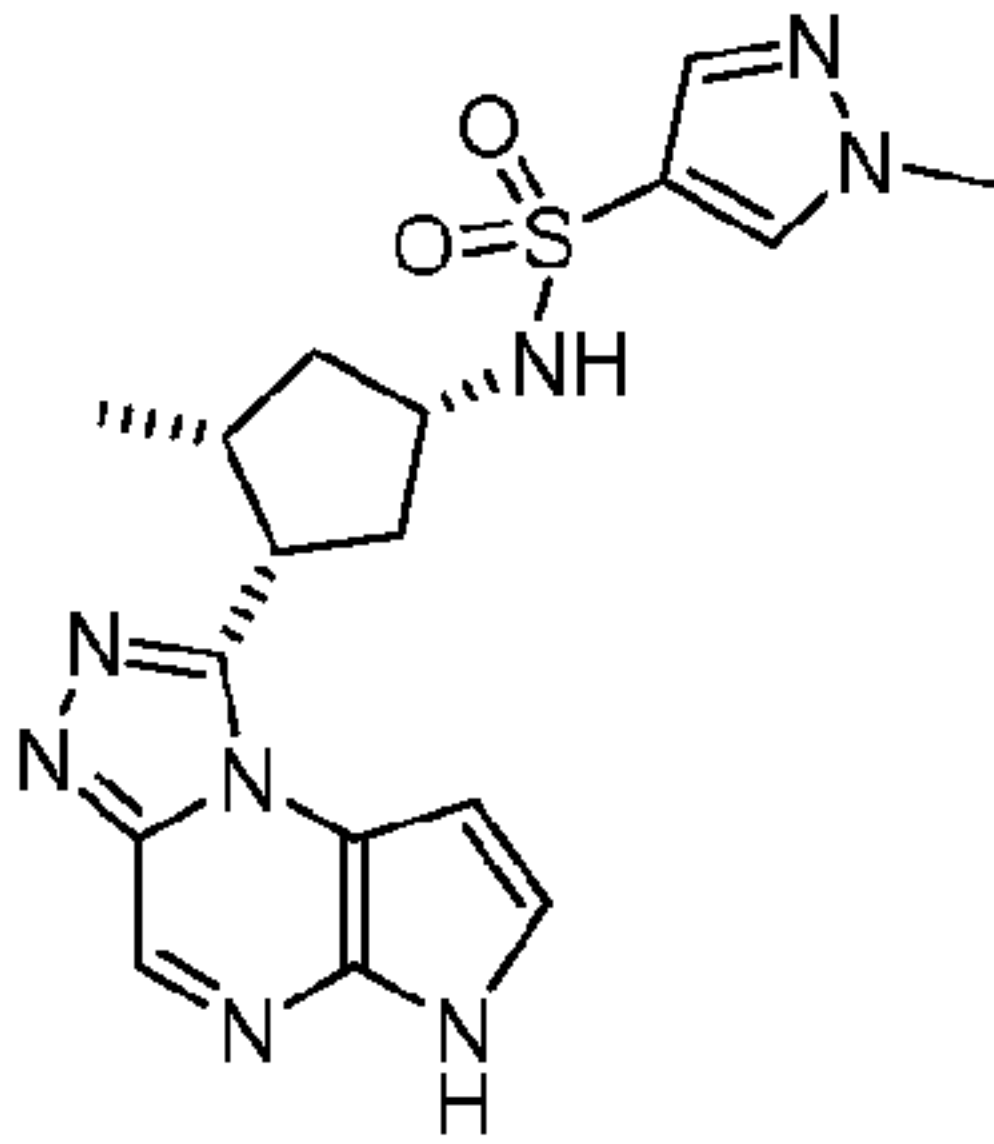
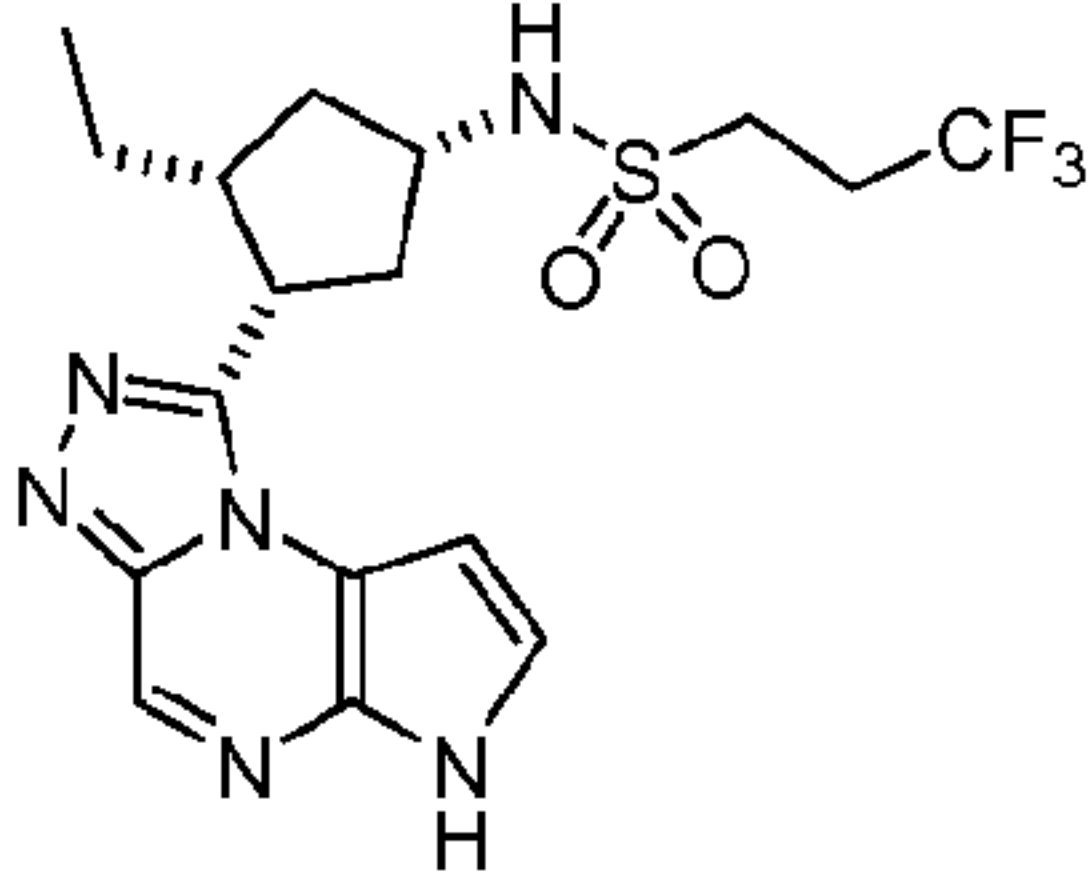
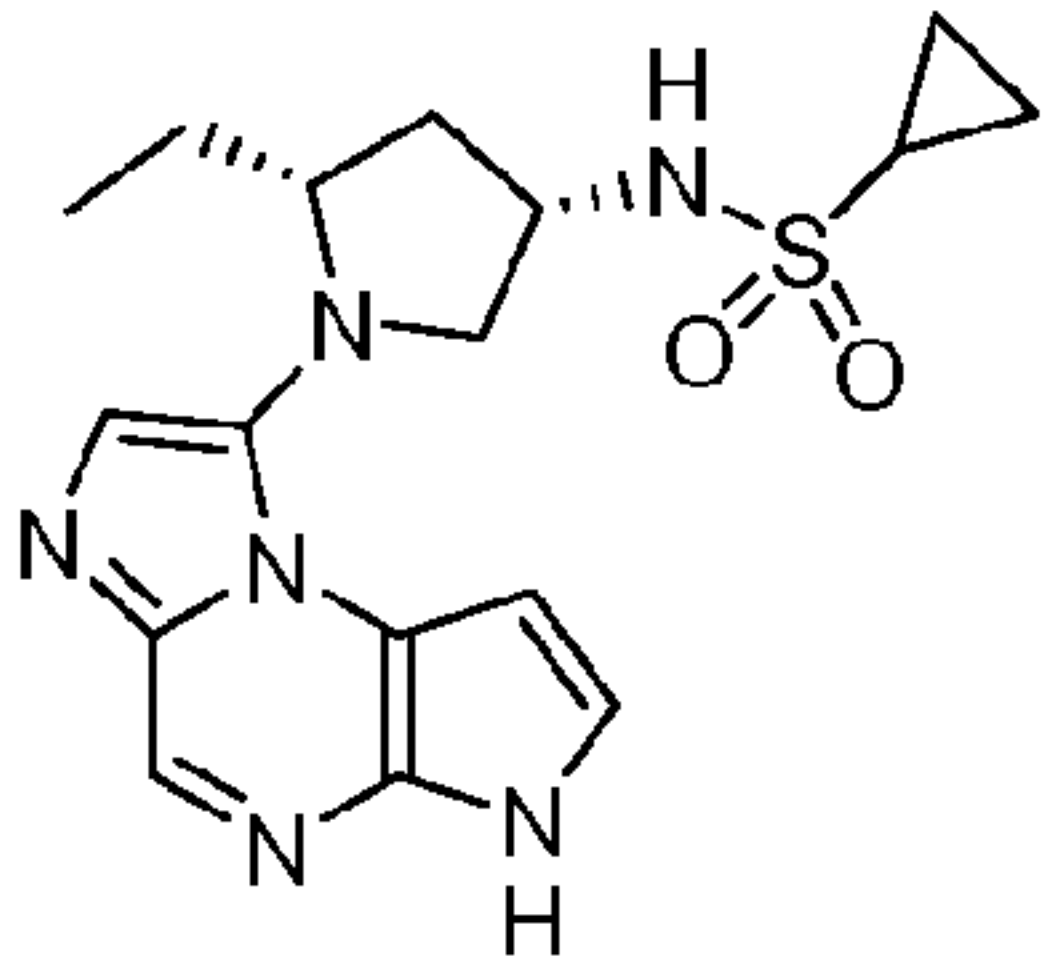
Sulfonamide	Product	Ex #	<i>R</i> _t min (Table 1, Method)	<i>m/z</i> ESI+ (M+H) ⁺
(<i>S</i>)-1-((1-(cyclopropylsulfonyl)pyrrolidin-3-yl)methyl)-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo [4,3- <i>a</i>]pyrazine (prepared using C from Preparation #A.1, and K with cyclopropanesulfonyl chloride and TEA)		D.1.1*	1.34 (a)	347
<i>N</i> -(1-((6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>] pyrazin-1-yl)methyl)cyclobutyl)-cyclopropanesulfonamide (prepared using A from Example #1 Step D and 2-(1-(<i>tert</i> -butoxycarbonyl-amino) cyclobutyl)acetic acid [prepared as described in <i>Eur. J. Med.Chem</i> , 1999 , 34, 363])		D.1.2	1.60 (a)	347

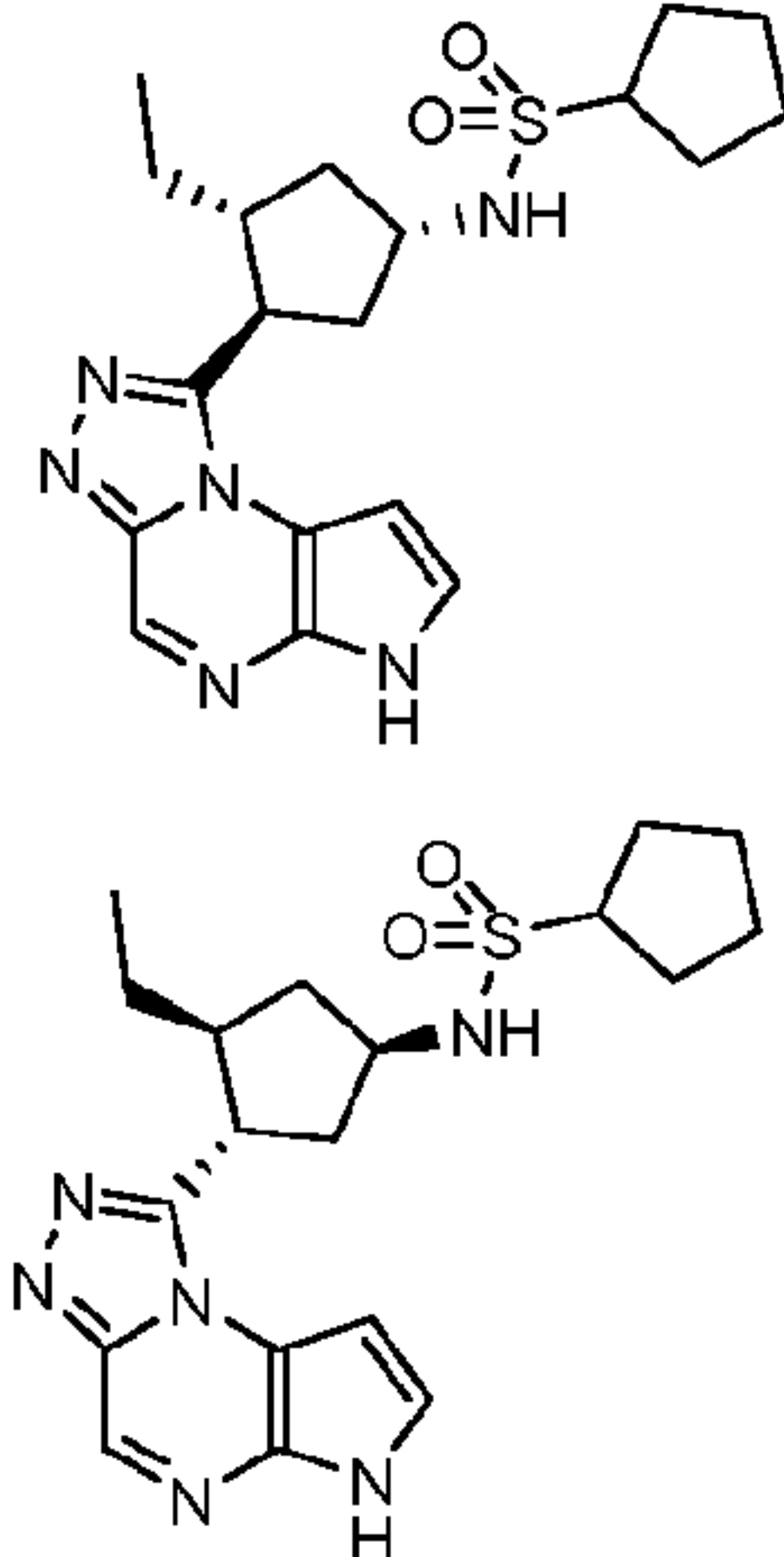
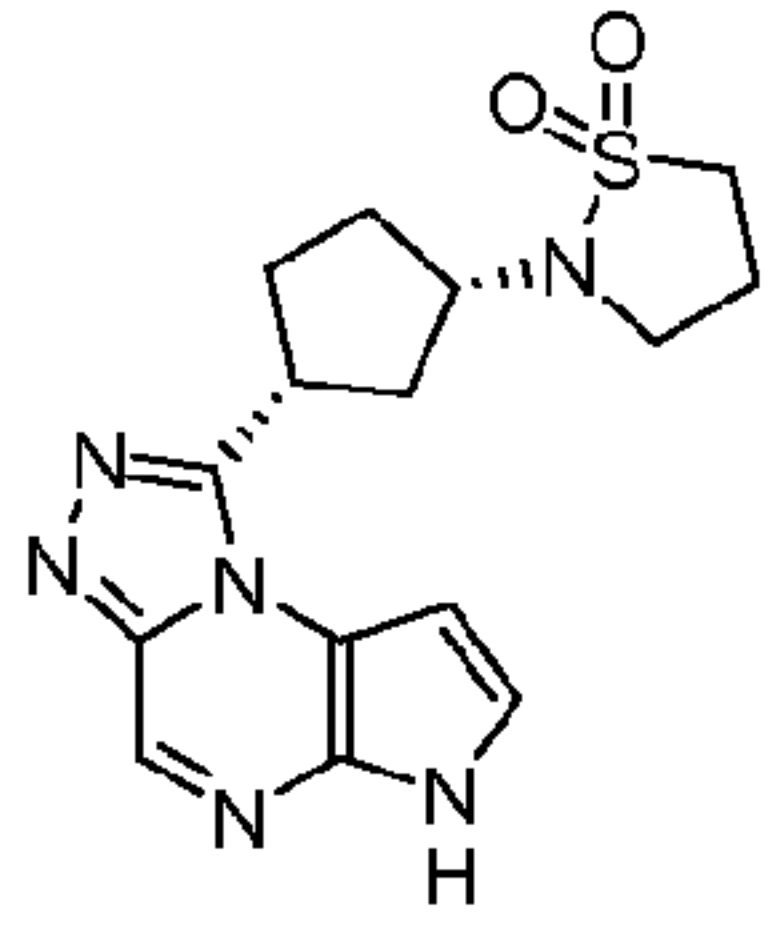
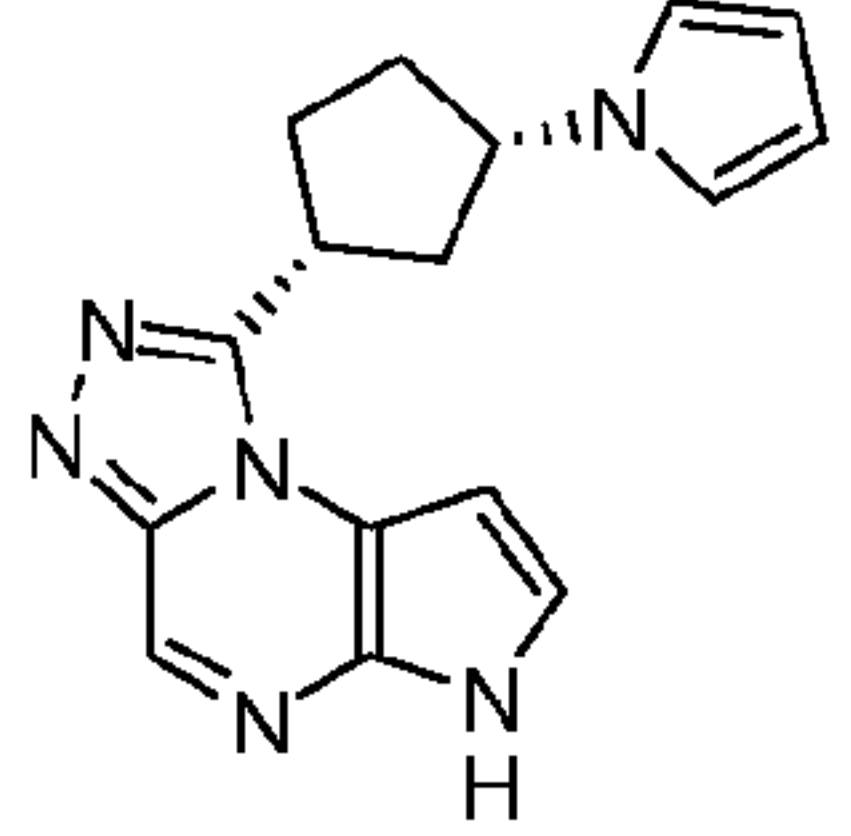
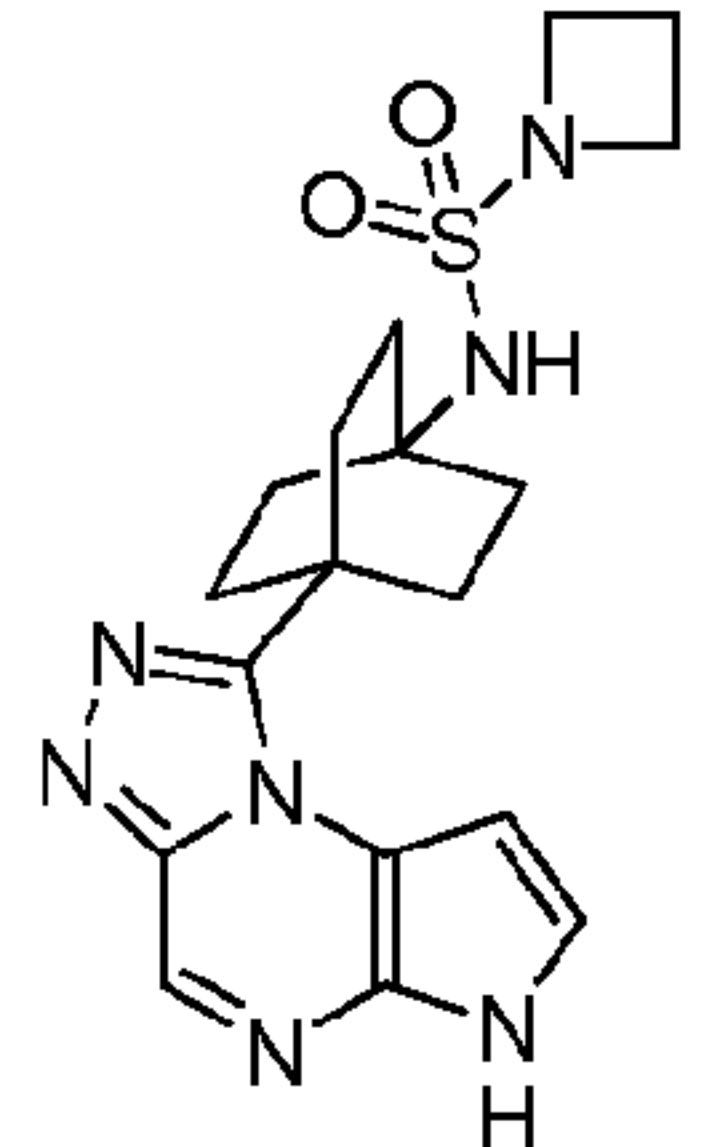
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
with EDC·HCl, B with TEA, E with HCl, K with cyclopropanesulfonyl chloride and DIEA)				
<i>N</i> -((1 <i>S</i> ,3 <i>R</i>)-3-(6-tosyl-6 <i>H</i> - pyrrolo[2,3- <i>e</i>][1,2,4]triazolo [4,3- <i>a</i>]pyrazin-1- yl)cyclopentyl)cyclo- propanecarboxamide (prepared using E from Preparation #B.1 with HCl, H with cyclopropanecarboxylic acid, EDC, and DIEA)		D.1.3*	1.15 (c)	311
2-cyclopropyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i>)-3-(6- tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1- yl)cyclopentyl)acetamide (prepared using using E from Preparation #B.1 with HCl, H with cyclopropylacetic acid [Lancaster], EDC, and DIEA)		D.1.4*	1.17 (c)	325
4-fluoro- <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-(6-tosyl- 6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1- yl)cyclopentyl)aniline (prepared using PP with Example #2 Step F, 4- fluorophenyl boronic acid, and DIEA)		D.1.5*	1.91 (a)	337
4-chloro- <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-(6-tosyl- 6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1- yl)cyclopentyl)aniline (prepared using PP with Example #2 Step F, 4- chlorophenylboronic acid and DIEA)		D.1.6*	2.07 (a)	353
3,4-dichloro- <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-(6- tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1- yl)cyclopentyl)aniline (prepared using PP with Example #2 Step F, 3,4- dichlorophenylboronic acid and DIEA)		D.1.7*	2.24 (a)	387

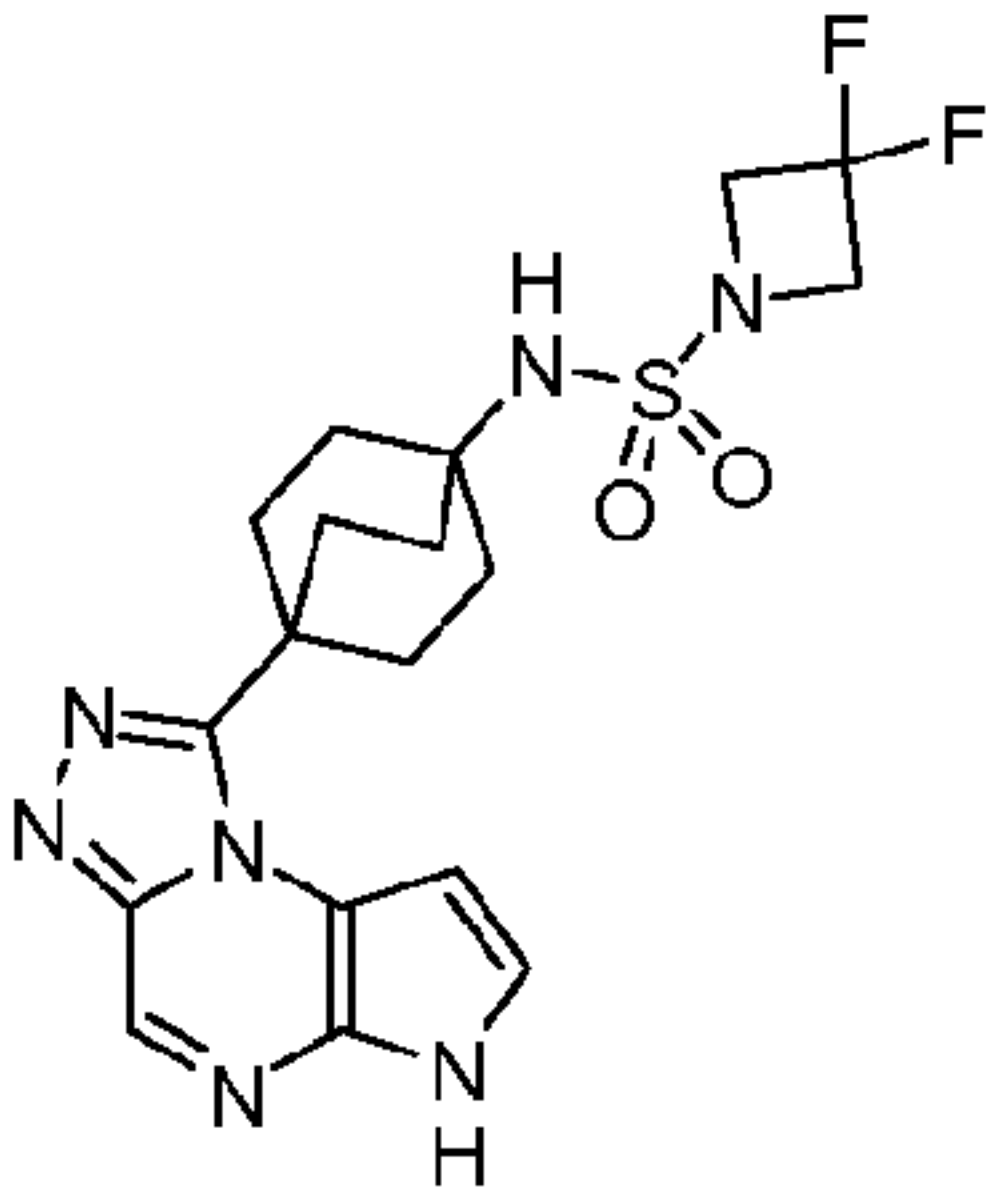
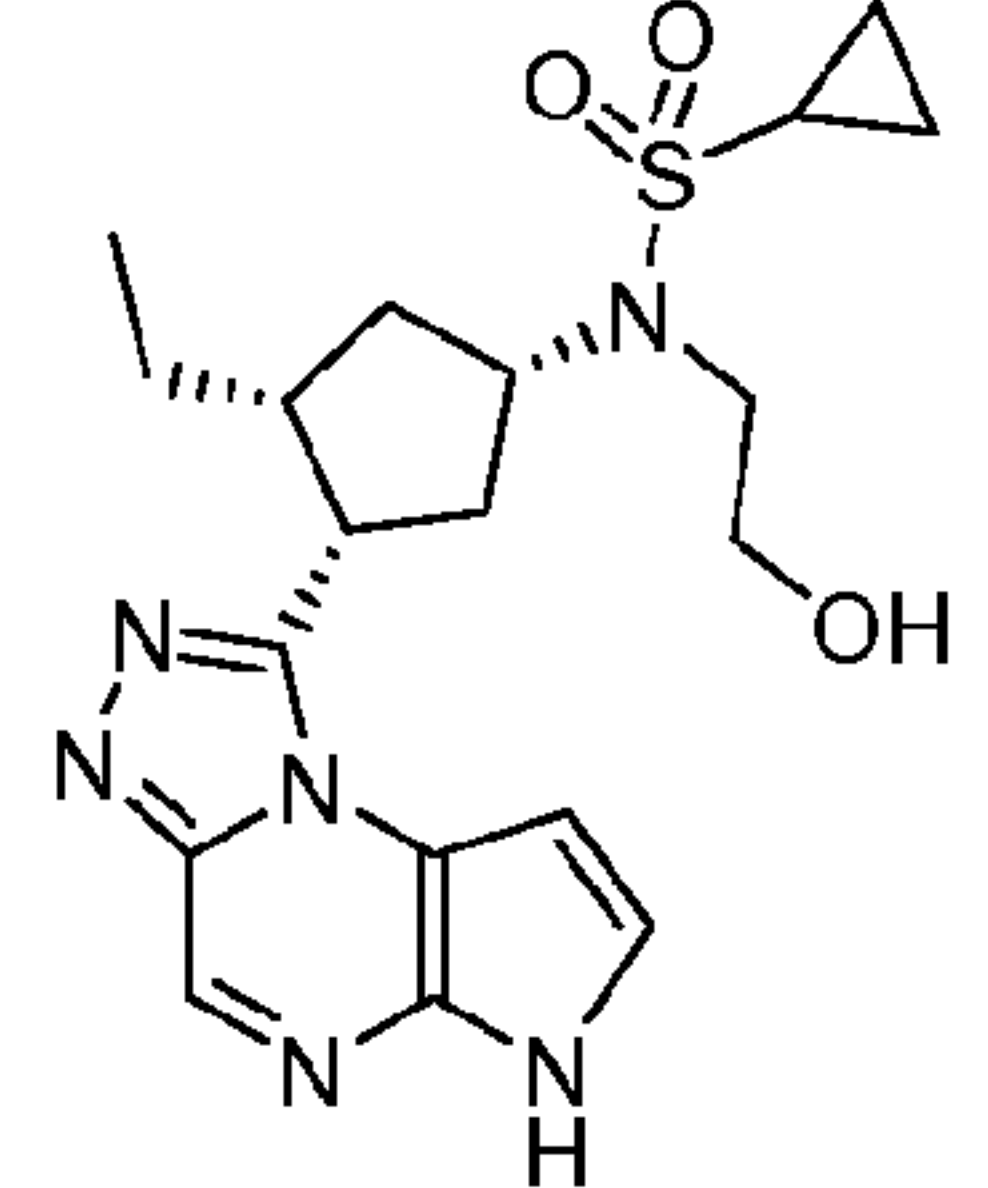
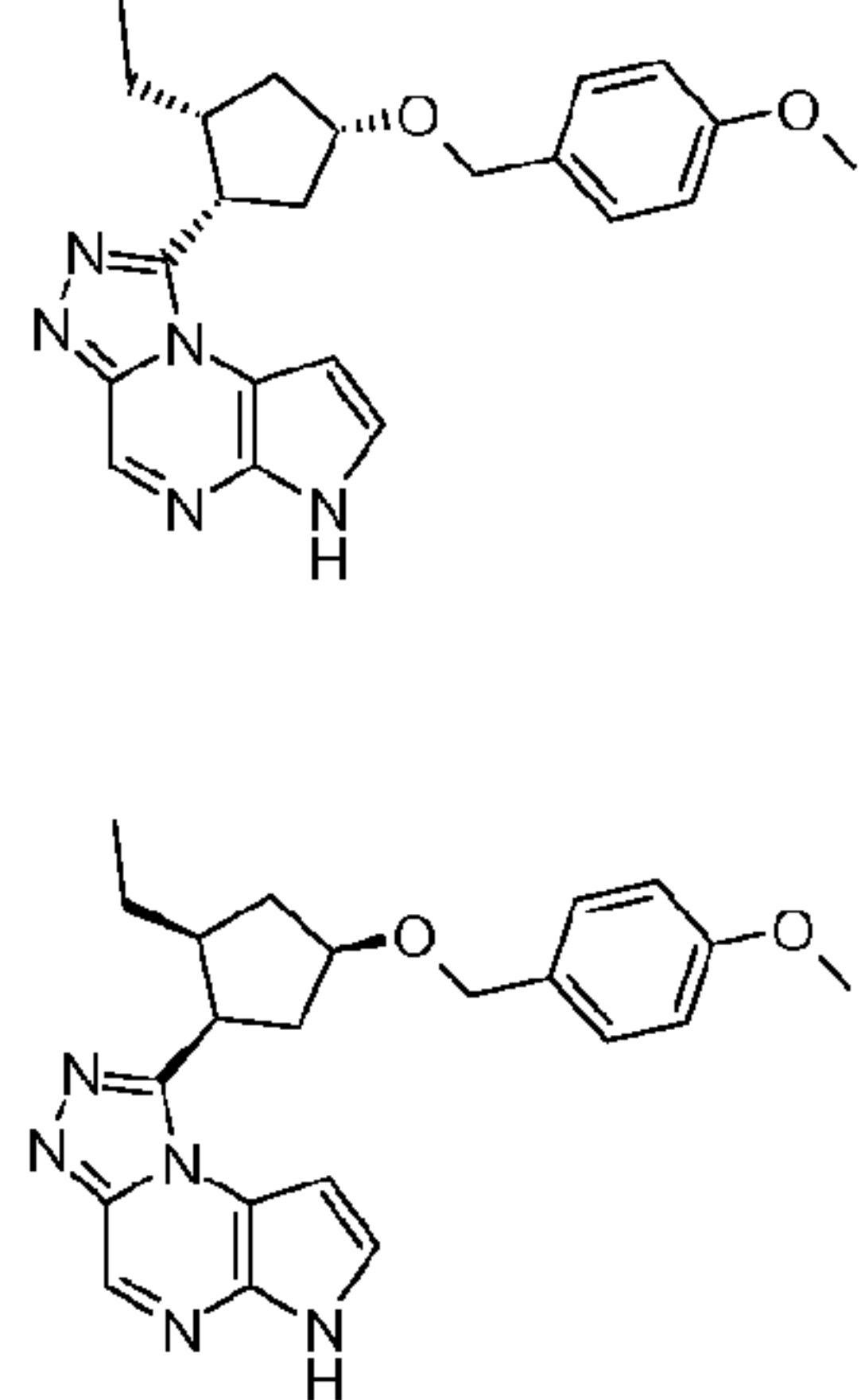
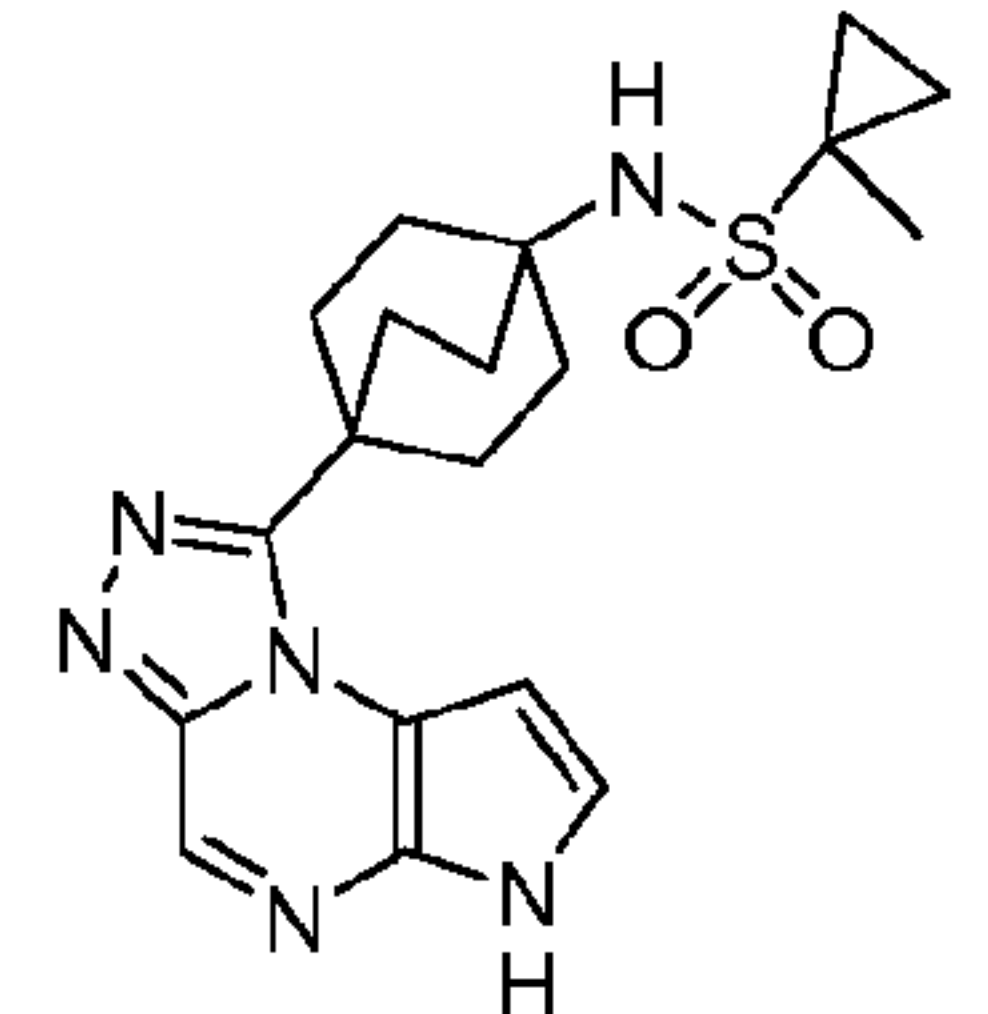
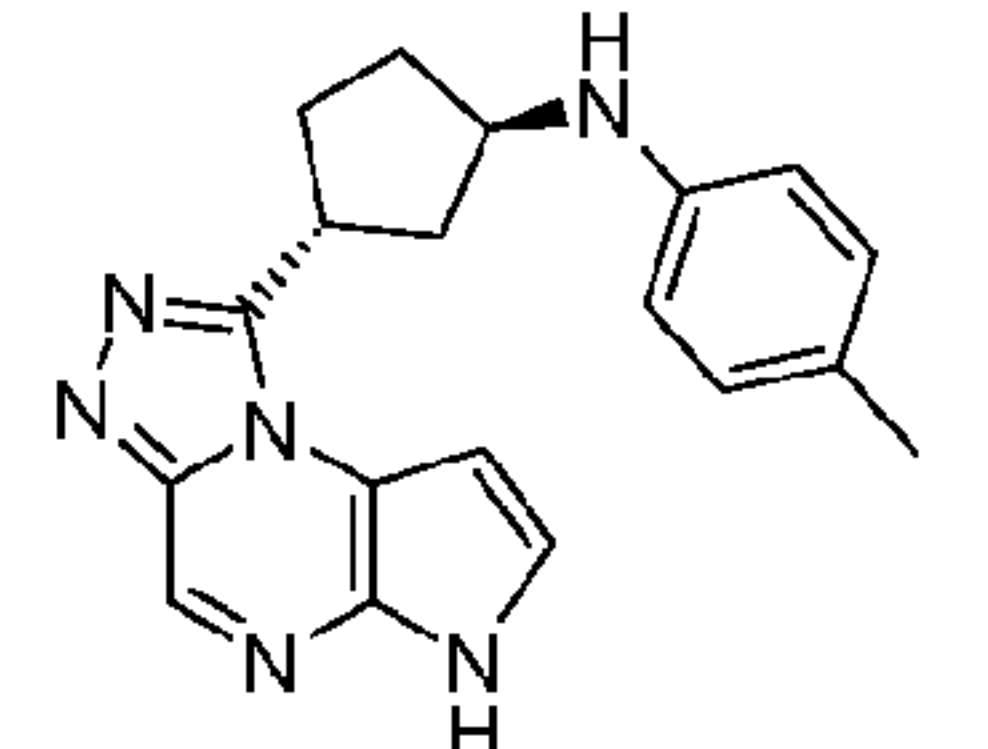
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
4-methoxy- <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)aniline (prepared using PP with Example #2 Step F, 4-methoxyphenyl boronic acid and DIEA)		D.1.8*	1.74 (a)	349
4-methoxy- <i>N</i> -(4-methoxyphenyl)- <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)aniline (prepared using PP with Example #2 Step F, 4-methoxyphenyl boronic acid and DIEA)		D.1.9*	2.30 (a)	455
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)azetidine-1-sulfonamide (Preparation #DD.1)		D.1.10*	1.81 (a)	390
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-3,3-difluoroazetidine-1-sulfonamide (prepared using DD with Example #8 Step M, 3,3-difluoroazetidine-1-sulfonyl chloride [prepared from CC with 3,3-difluoroazetidine hydrochloride [Matrix] and DIEA] and TEA)		D.1.11*	1.97 (a)	426
(<i>S</i>)- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-(trifluoromethyl)pyrrolidine-1-sulfonamide (prepared using DD with Example #8 Step M, (<i>S</i>)-2-(trifluoromethyl)pyrrolidine-1-sulfonyl chloride [prepared from CC with (<i>S</i>)-(-)-2-(trifluoromethyl)pyrrolidine and DIEA] and TEA)		D.1.12*	2.13 (a)	472

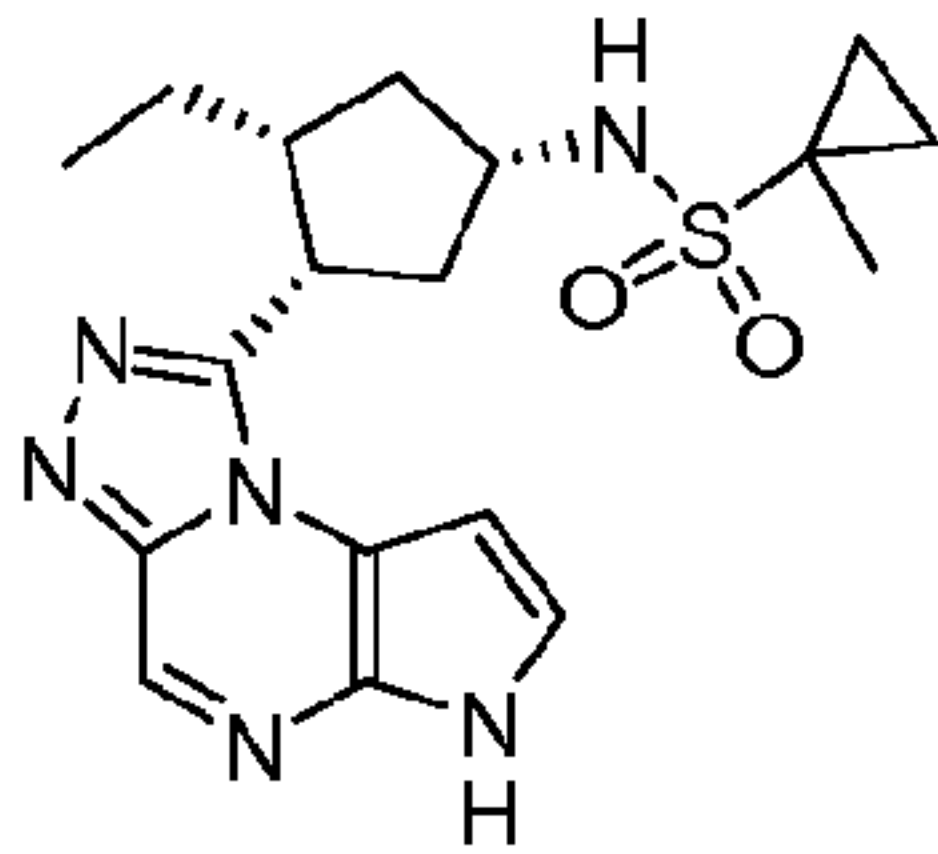
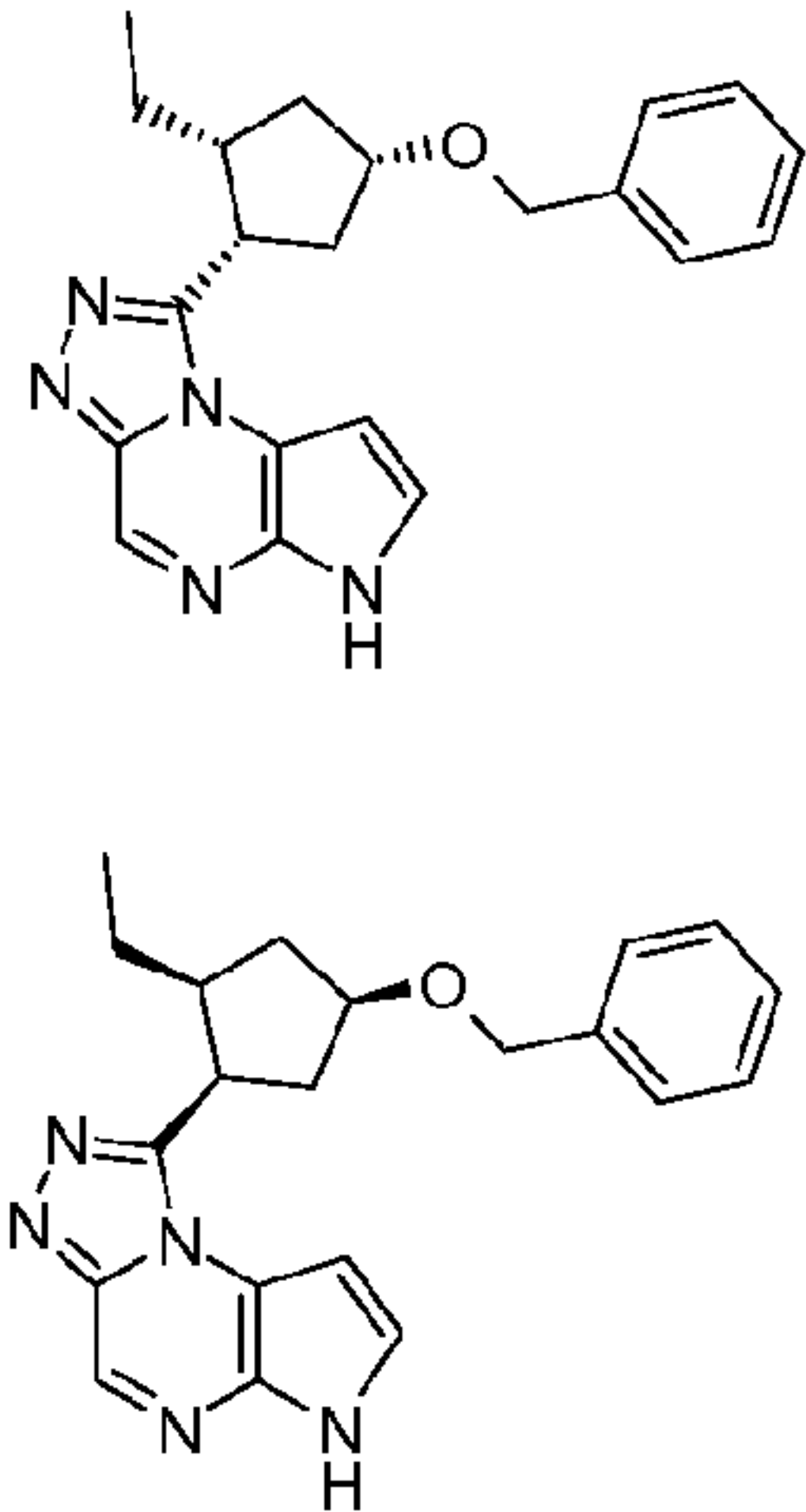
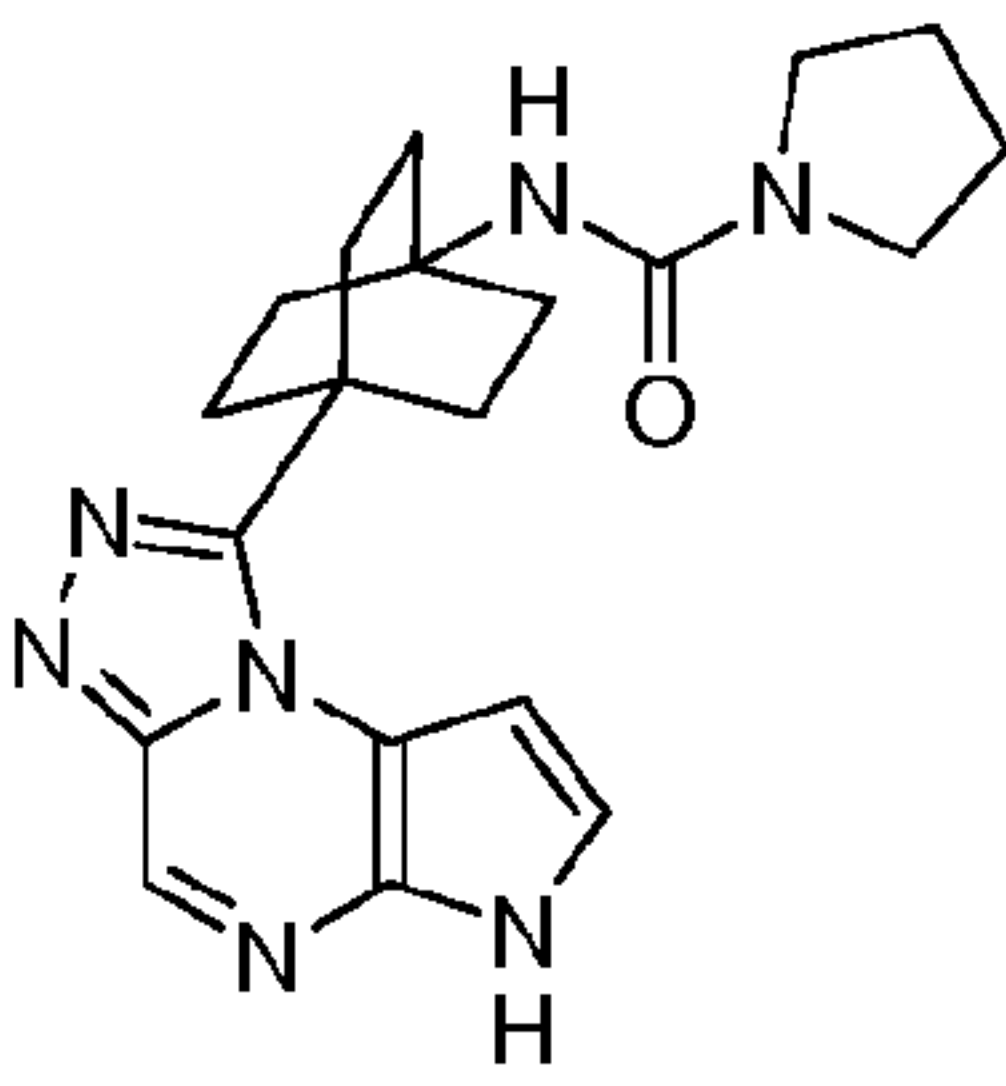
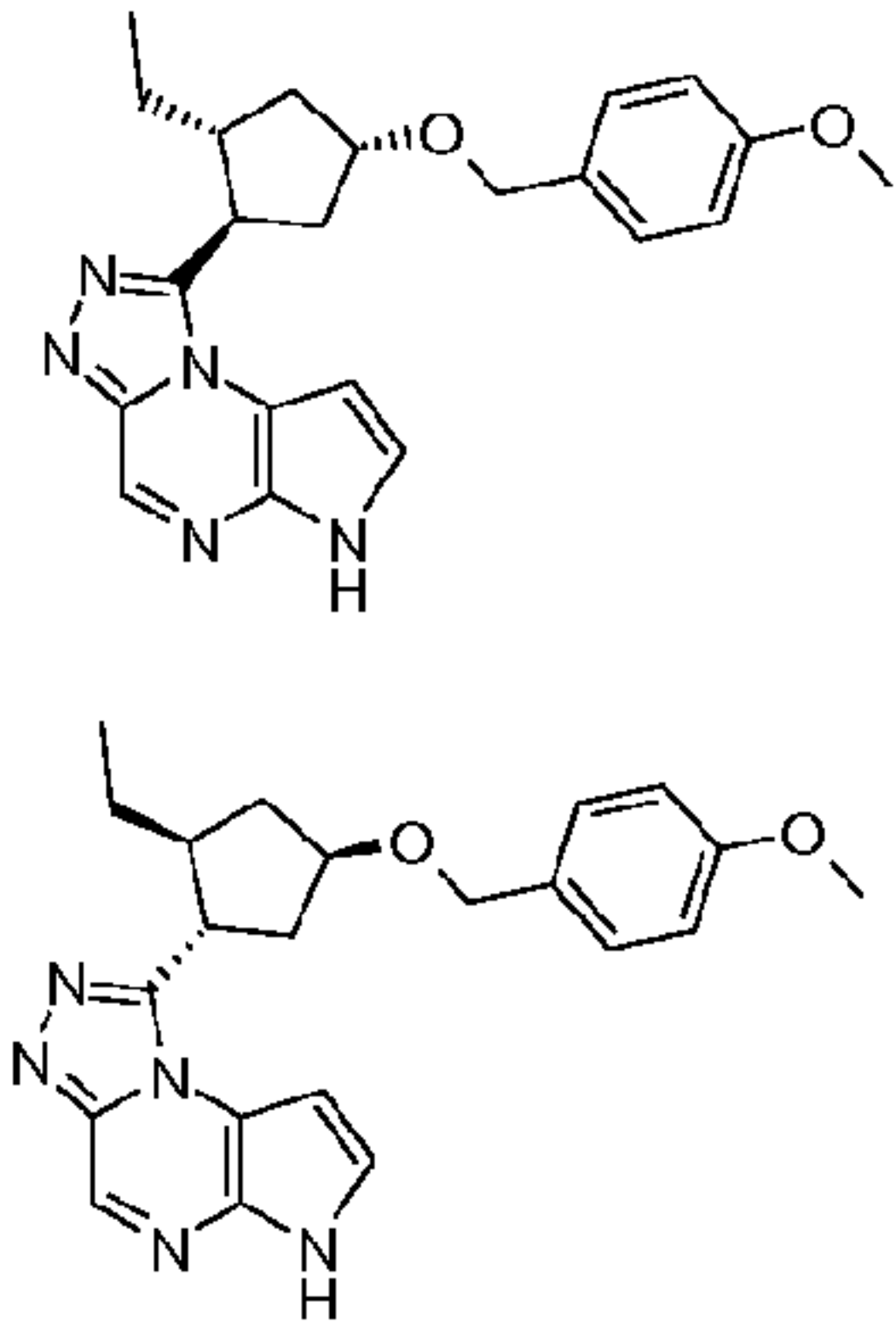
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-3,3-difluoropyrrolidine-1-sulfonamide (prepared using DD with Example #8 Step M, 3,3-difluoropyrrolidine-1-sulfonyl chloride [prepared from CC with 3,3-difluoropyrrolidine hydrochloride and DIEA] and TEA)		D.1.13*	1.98 (a)	440
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-4,4-difluoropiperidine-1-sulfonamide (prepared using DD with Example #8 Step M, 4,4-difluoropiperidine-1-sulfonyl chloride [prepared from CC with 4,4-difluoropiperidine hydrochloride and DIEA] and TEA)		D.1.14*	2.01 (a)	454
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)aniline (prepared using PP from Preparation #19.2, phenylboronic acid, and DIEA)		D.1.15*	2.01 (a)	333
4-methyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)aniline (prepared using PP from Preparation #19.2, <i>p</i> -tolylboronic acid and DIEA)		D.1.16*	2.08 (a)	347

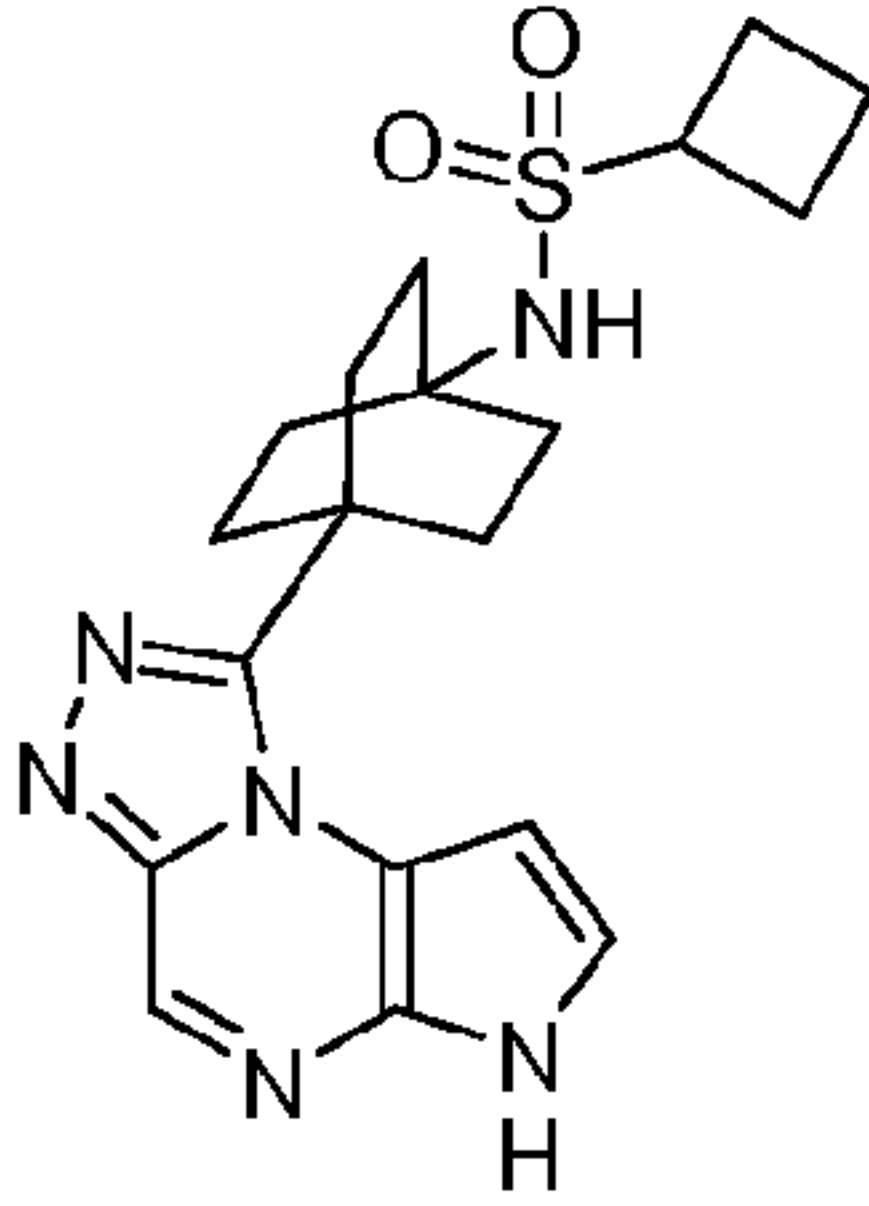
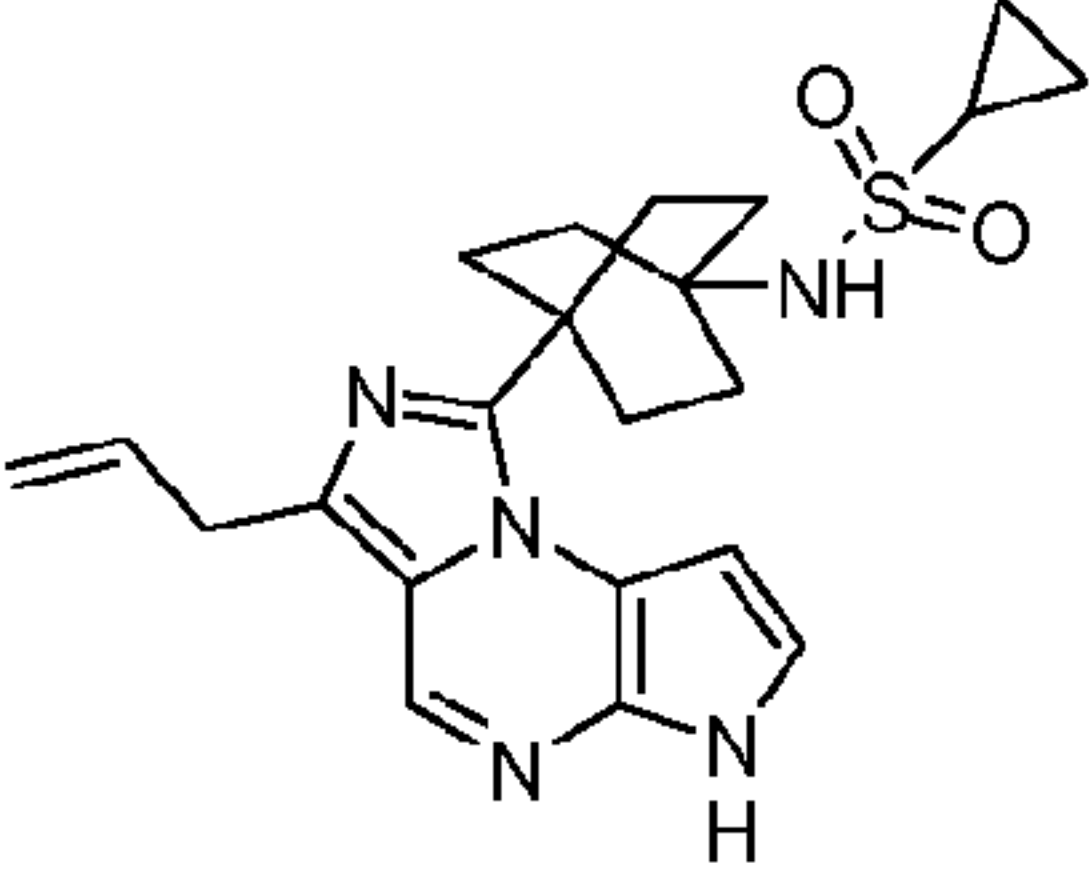
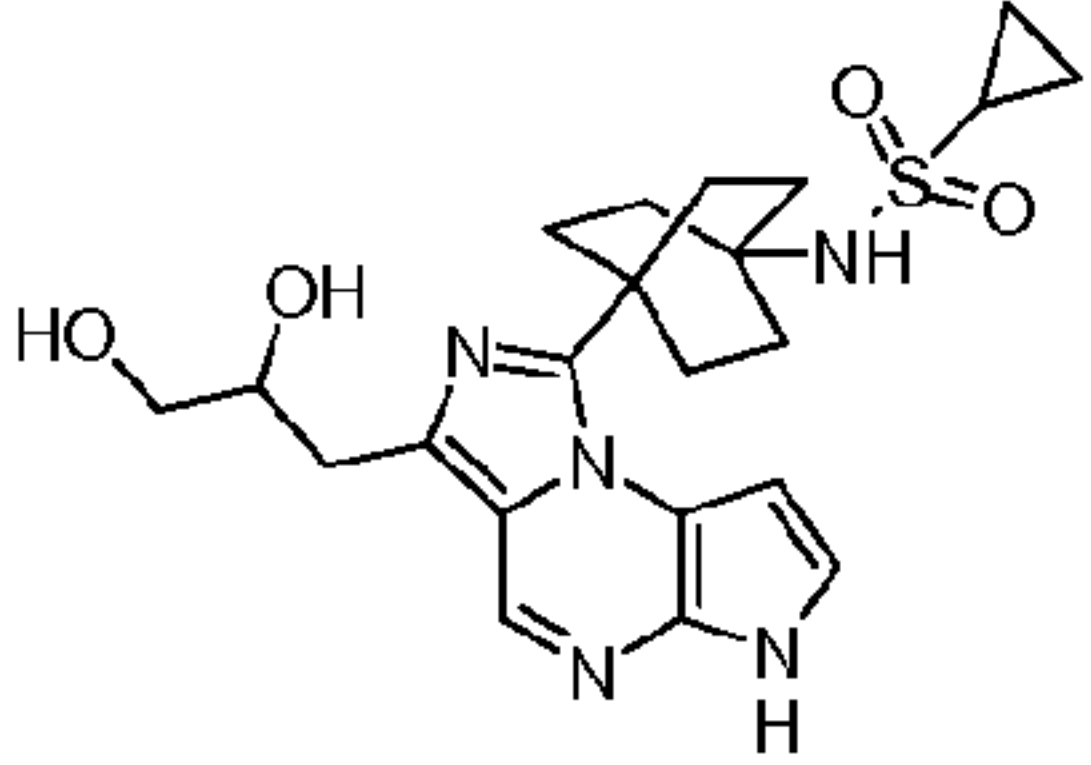
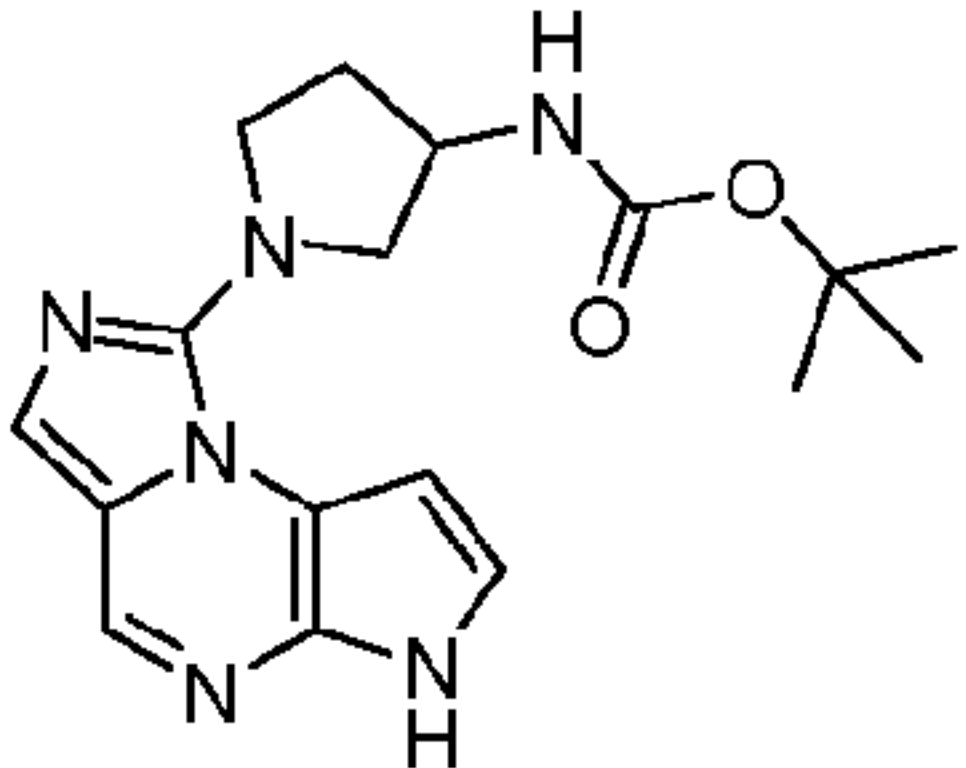
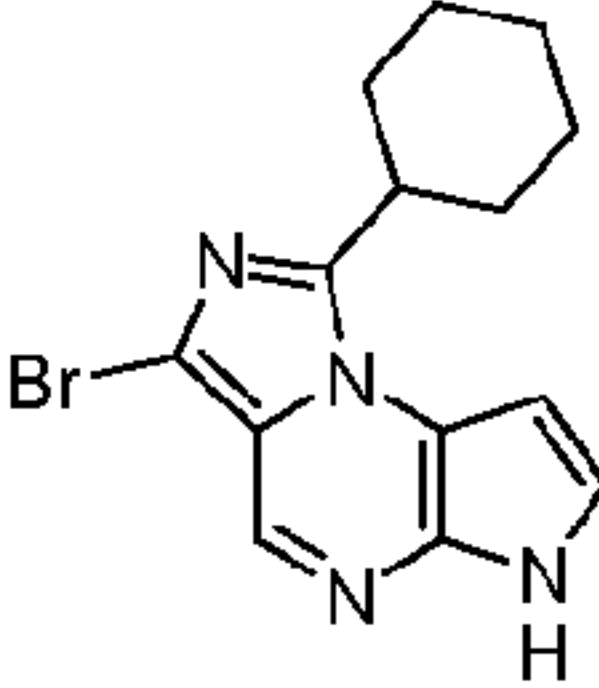
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
4-chloro- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)aniline (prepared using PP from Preparation #19.2, 4-chlorophenylboronic acid, and DIEA)		D.1.17*	2.25 (a)	367
4-fluoro- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)aniline (prepared using PP from Preparation #19.2, 4-fluorophenylboronic acid, and DIEA)		D.1.18*	2.05 (a)	351
1-(3,3-difluorocyclobutyl)-6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (prepared using H from Example #5 Step C and 3,3-difluorocyclobutanecarboxylic acid [Waterstone], HATU, and DIEA; Q with Lawesson's reagent and mercury (II) trifluoroacetate)		D.1.19	1.63 (b)	249
4-((<i>cis</i> -3-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)cyclobutoxy)methyl)benzonitrile (prepared using H from Example #5 Step C and Preparation #1 with HATU and DIEA; Q with Lawesson's reagent and mercury (II) trifluoroacetate)		D.1.20	1.81 (b)	344
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)- <i>N</i> -methylcyclopropanesulfonamide (prepared using A from Example #1 Step D and Preparation #Z.1 with HATU and TEA, B with TEA, S with iodomethane and NaH)		D.1.21*	1.75 (a)	389

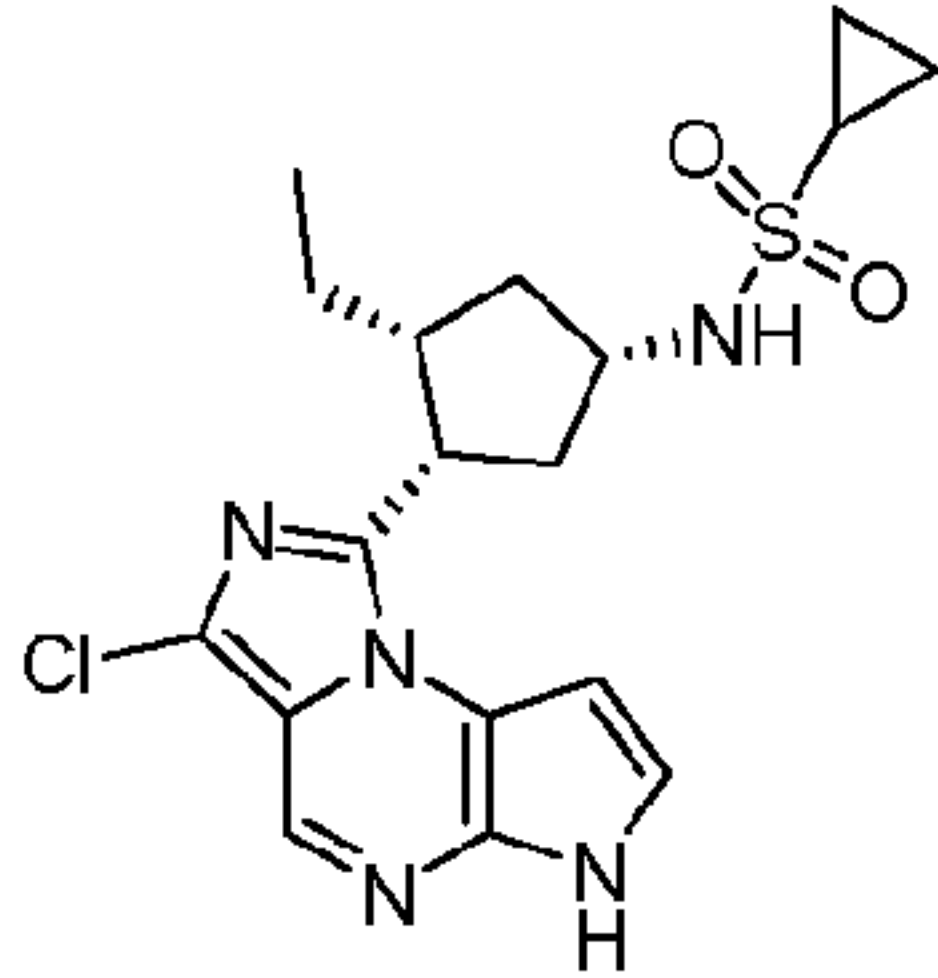
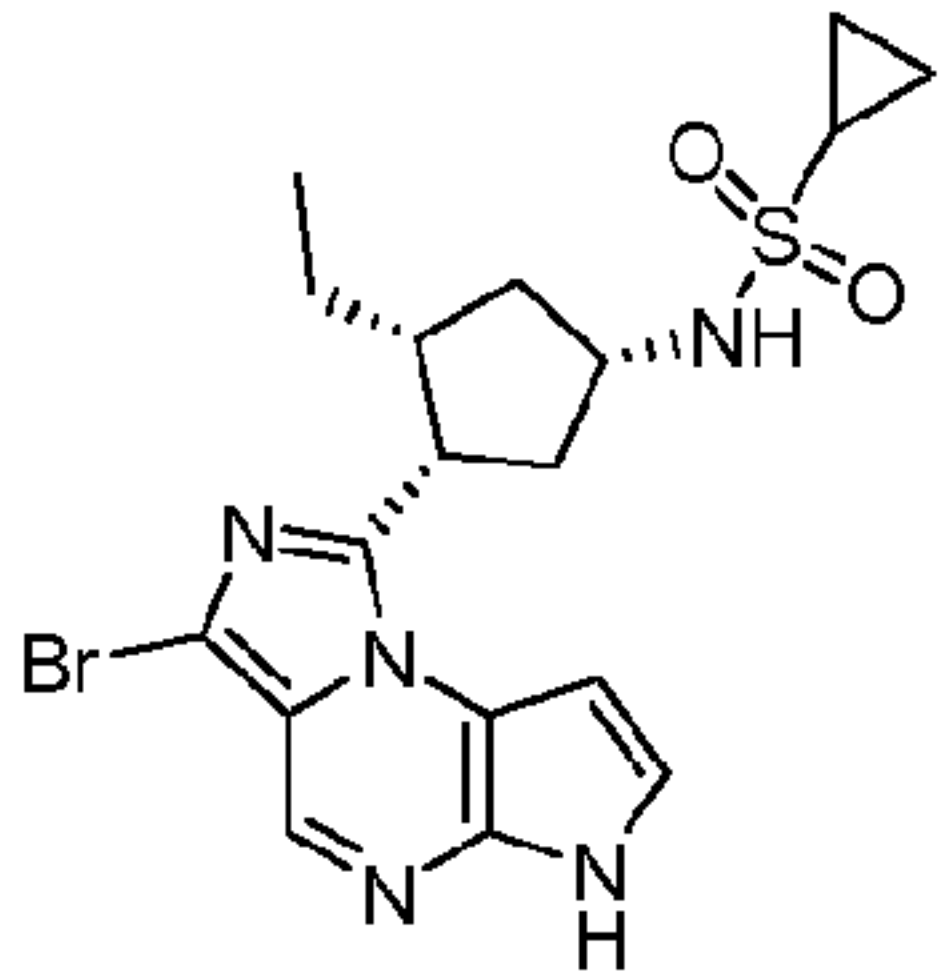
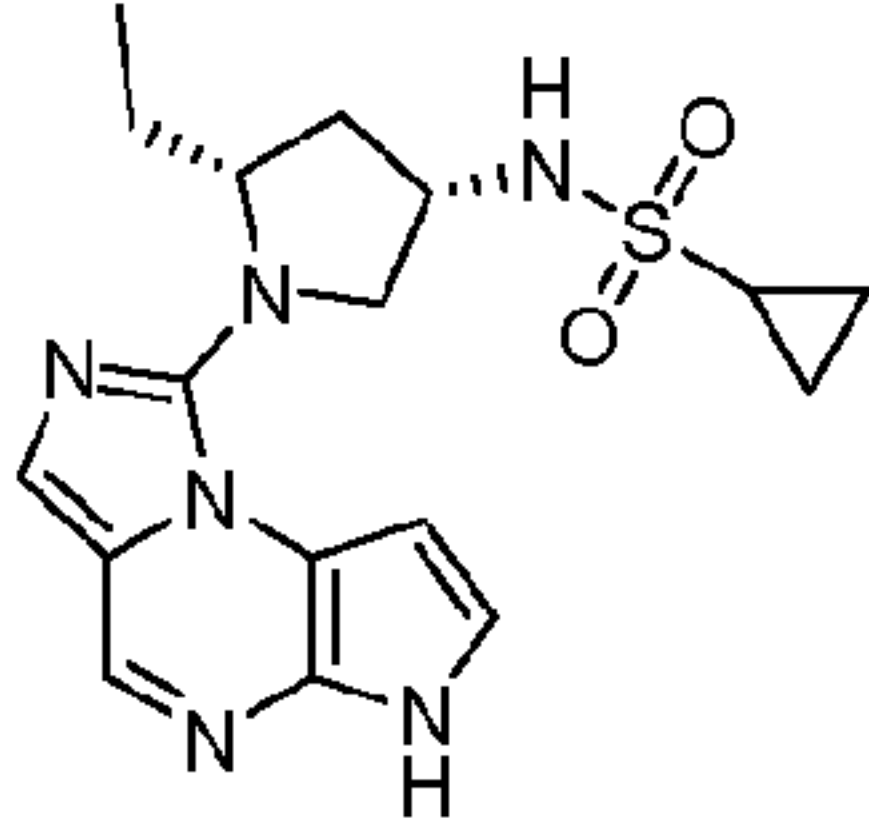
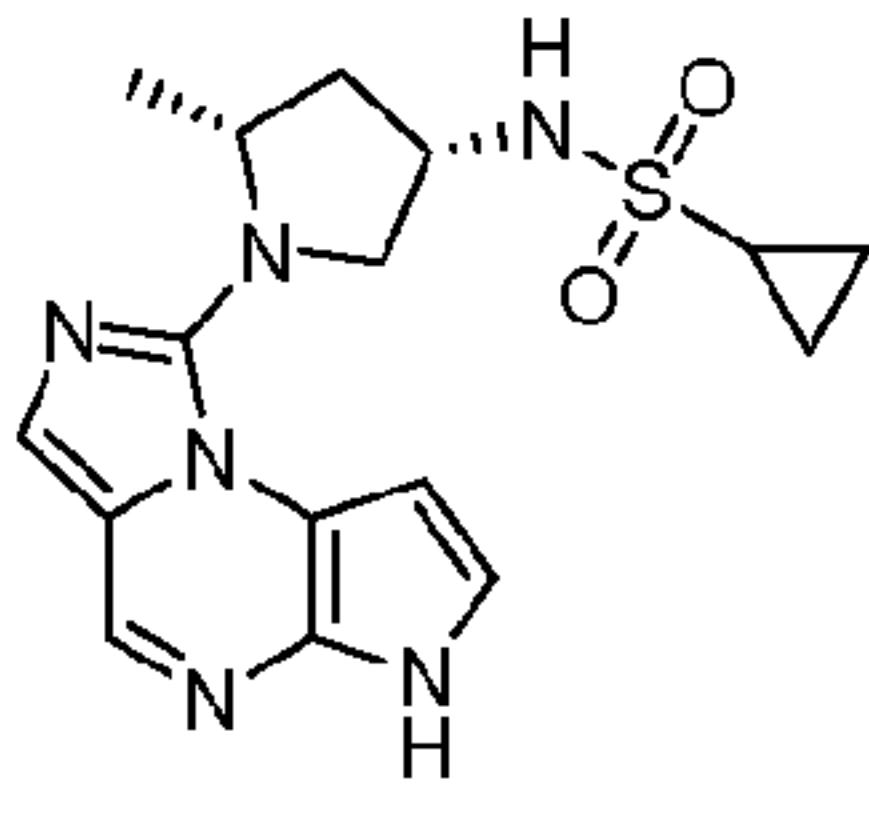
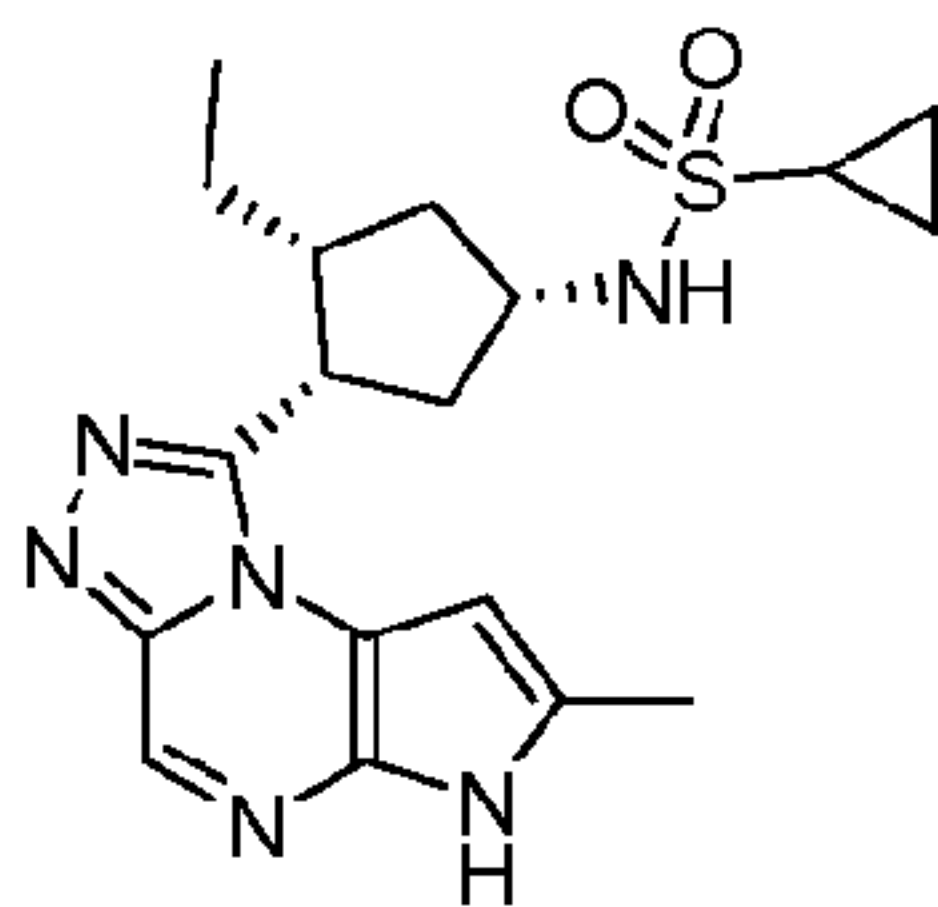
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -(cyclopropylmethyl)- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamide (prepared using A from Example #1 Step D and Preparation #Z.1 with HATU and TEA, B with TEA, S with (bromomethyl)-cyclopropane and NaH)		D.1.22*	1.98 (a)	429
1-methyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1 <i>H</i> -pyrazole-4-sulfonamide (prepared using K from Preparation #19.2, 1-methyl-1 <i>H</i> -pyrazole-4-sulfonyl chloride [Oakwood] and DIEA)		D.1.23*	1.60 (a)	401
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-3,3,3-trifluoropropane-1-sulfonamide (prepared using K from Example #8 Step M and 3,3,3-trifluoropropane-1-sulfonyl chloride [Matrix] and DIEA)		D.1.24*	2.05 (a)	431
<i>N</i> -((3 <i>S</i> ,5 <i>R</i>)-5-ethyl-1-(3-tosyl-3 <i>H</i> -imidazo[1,2- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-8-yl)pyrrolidin-3-yl)cyclopropanesulfonamide (prepared using S from Example #3 Step E and <i>tert</i> -butyl bromoacetate, E with HCl, H with Preparation #E.1, OO)		D.1.25*	1.60 (a)	375

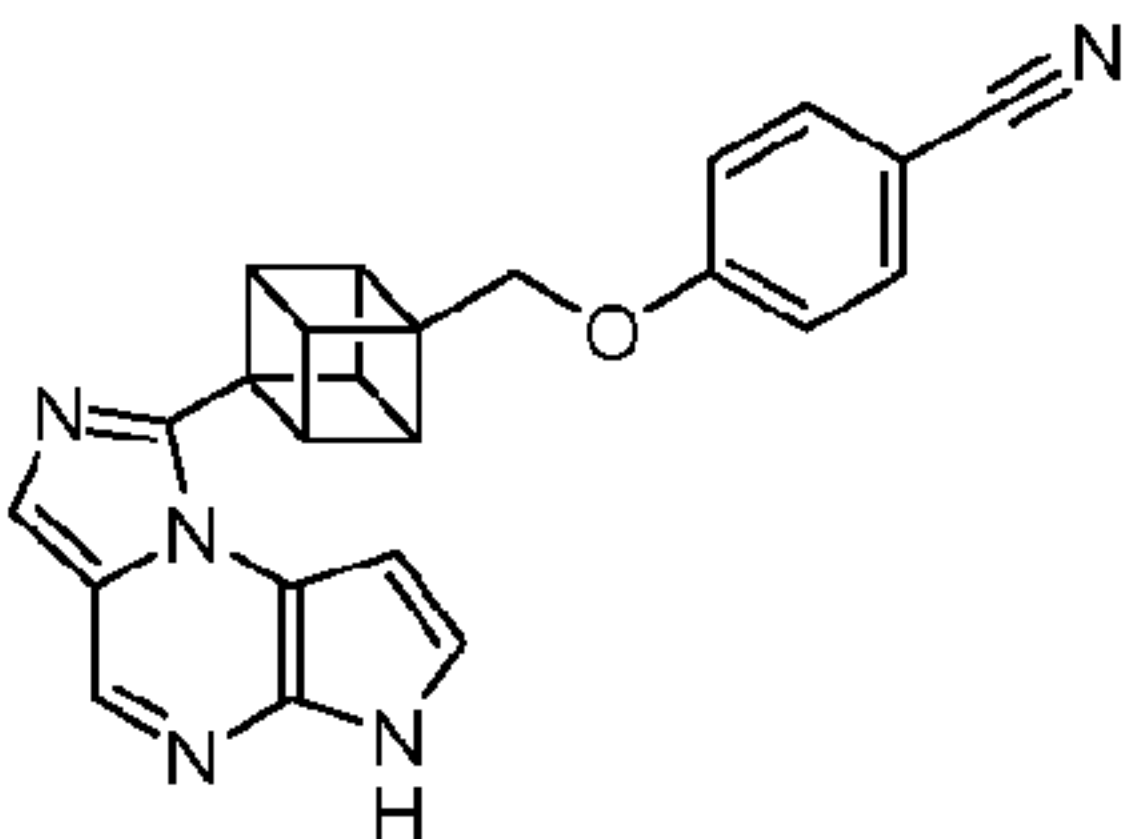
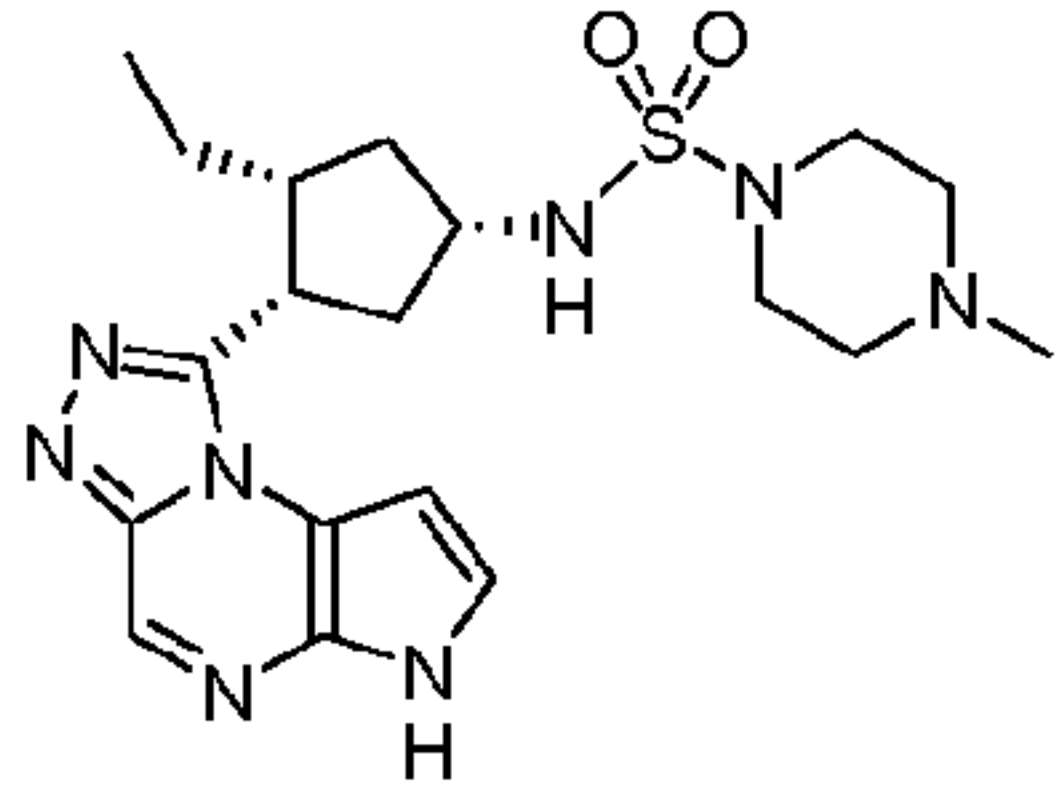
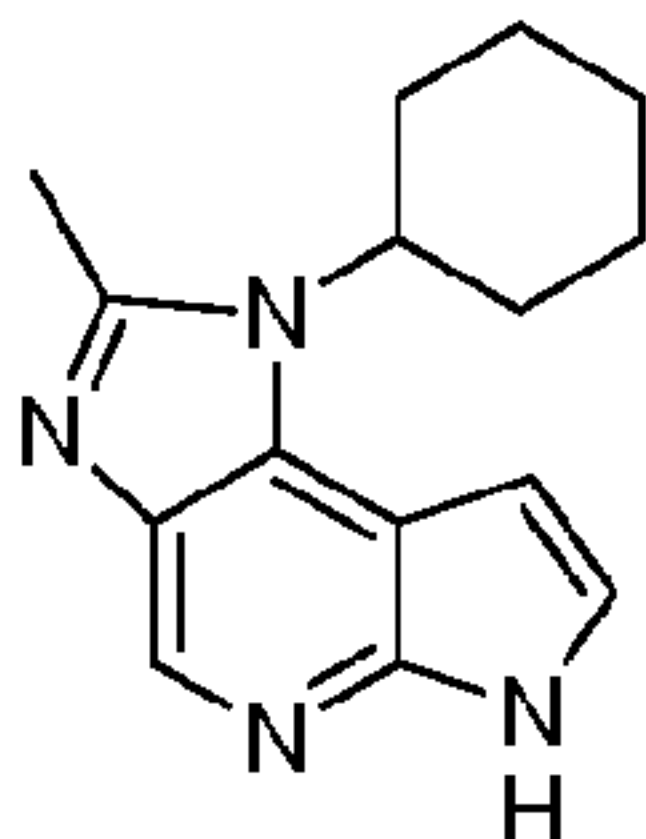
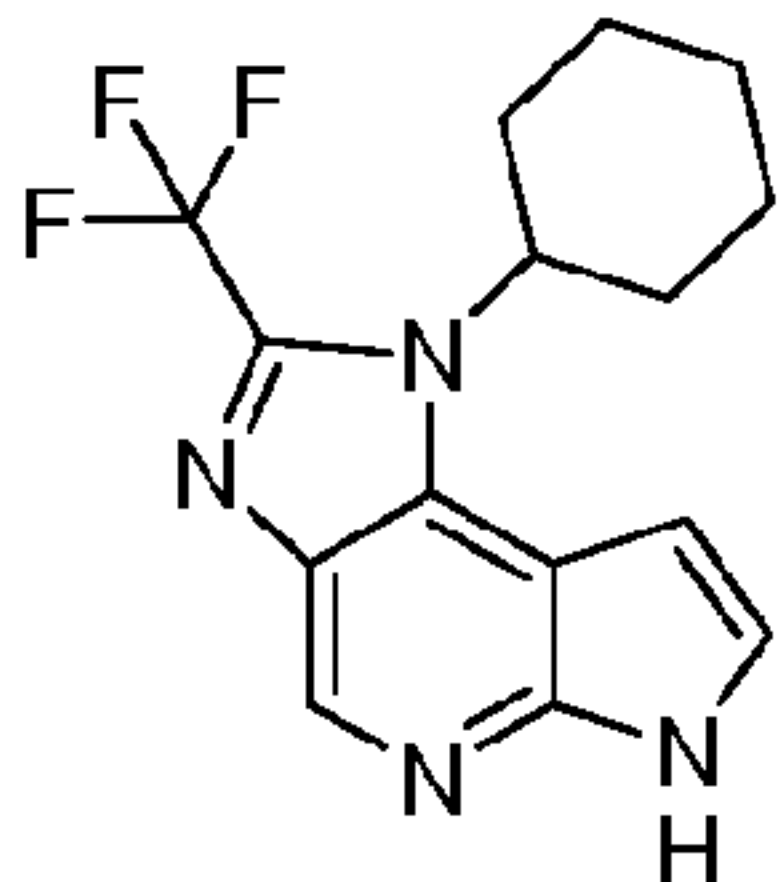
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>R</i> ,3 <i>S</i> ,4 <i>R</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)cyclopentanesulfonamide and <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)cyclopentanesulfonamide (prepared using K from Preparation #Y.1 and cyclopentanesulfonyl chloride, Z with NaOH, A with Example #1 Step D, HATU, and TEA, B with TEA)		D.1.26	1.77 (a)	403
(1 <i>S</i> ,3 <i>R</i>)-1-[3-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)-isothiazolidin-2-yl]-1,1-dioxide]cyclopentane (Preparation #2)		D.1.27*	1.47 (a)	347
1-((1 <i>R</i> ,3 <i>S</i>)-3-(1 <i>H</i> -pyrrol-1-yl)cyclopentyl)-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazine (Preparation #3)		D.1.28*	1.82 (a)	293
<i>N</i> -(4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)azetidine-1-sulfonamide (prepared using DD with Example #9, Step F and Preparation #CC.1)		D.1.29	1.44 (a)	402

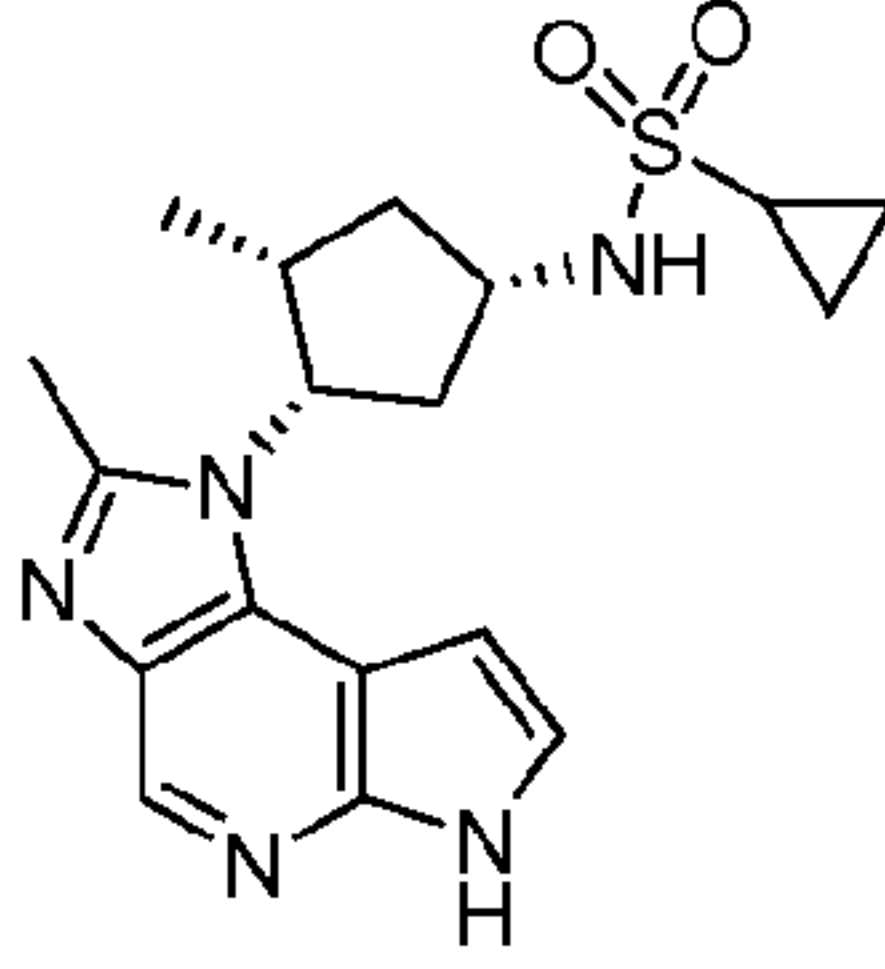
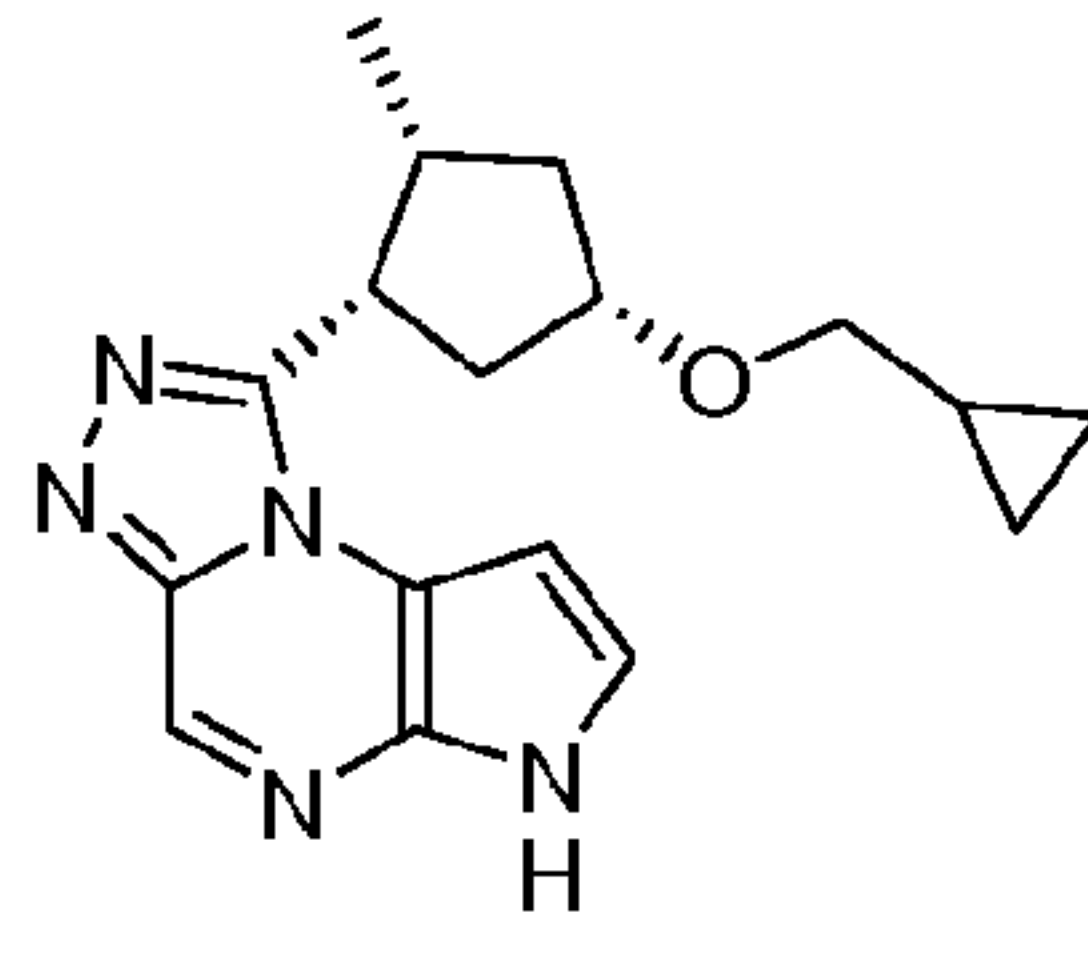
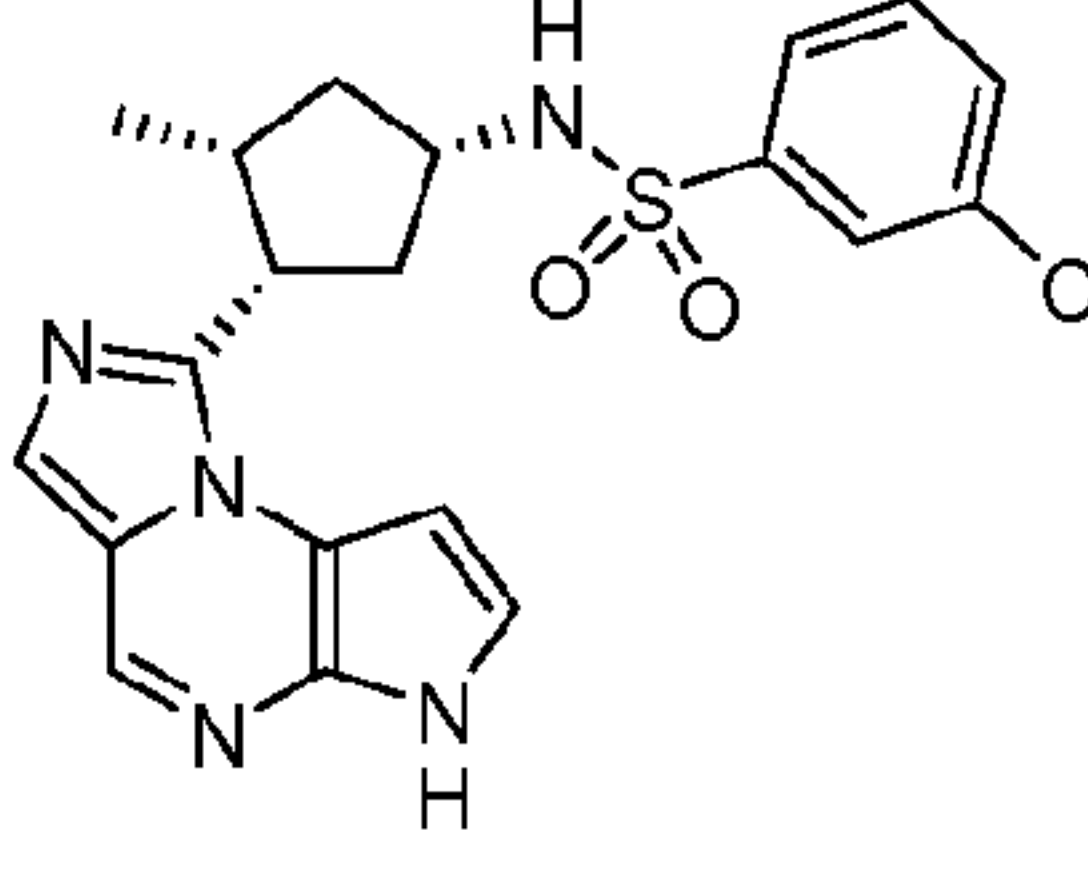
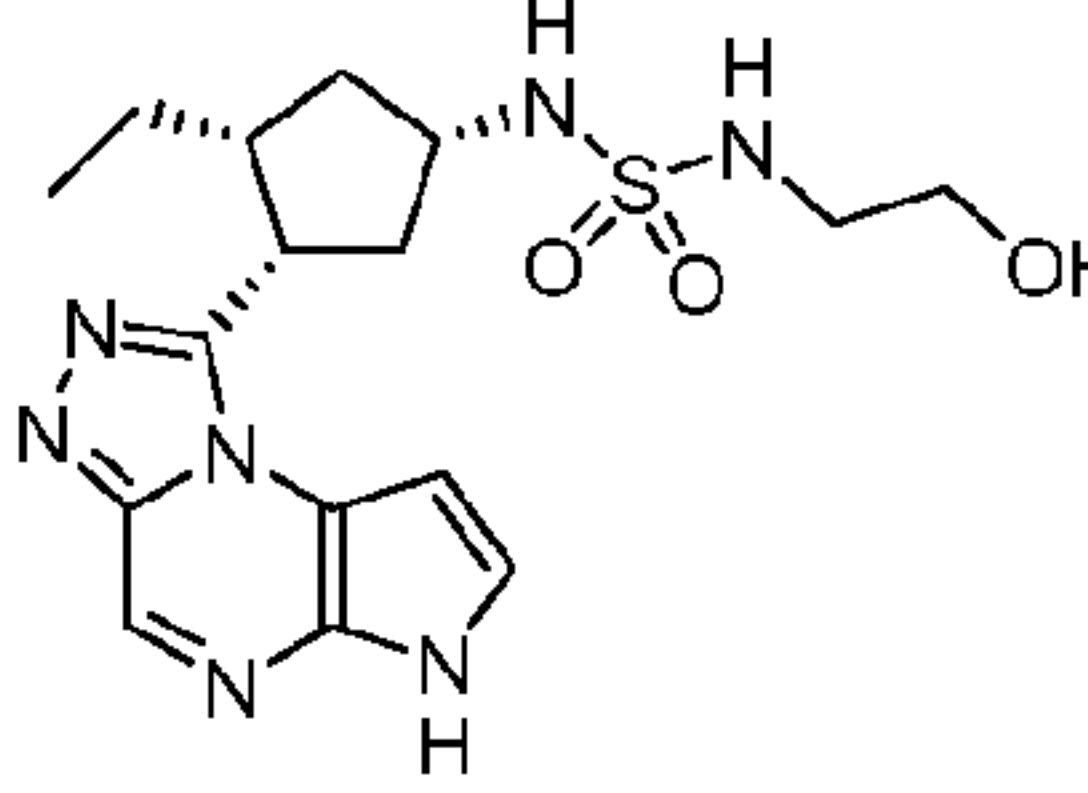
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
3,3-difluoro- <i>N</i> -(4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)azetidine-1-sulfonamide (Preparation #5)		D.1.30	1.61 (a)	438
2-(<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)cyclopropanesulfonamido)ethyl acetate (prepared using A from Preparation #Z.1, Example #1, Step D, HATU, and TEA, B with TEA, S with 2-bromoethyl acetate)		D.1.31*	1.54 (a)	419
1-((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-2-ethyl-4-(4-methoxybenzyloxy)cyclopentyl)-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazine and 1-((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-2-ethyl-4-(4-methoxybenzyloxy)cyclopentyl)-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazine (prepared using Z from Preparation #EE.1, A from Example #1, Step D, HATU, and TEA, B with DIEA)		D.1.32	2.02 (b)	392
1-methyl- <i>N</i> -(4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropane-1-sulfonamide (prepared using K from Preparation #C.1 and Preparation #6)		D.1.33	1.48 (a)	401
4-methyl- <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)aniline (prepared using PP from Example #2, Step F and <i>p</i> -tolylboronic acid)		D.1.34*	1.89 (b)	333

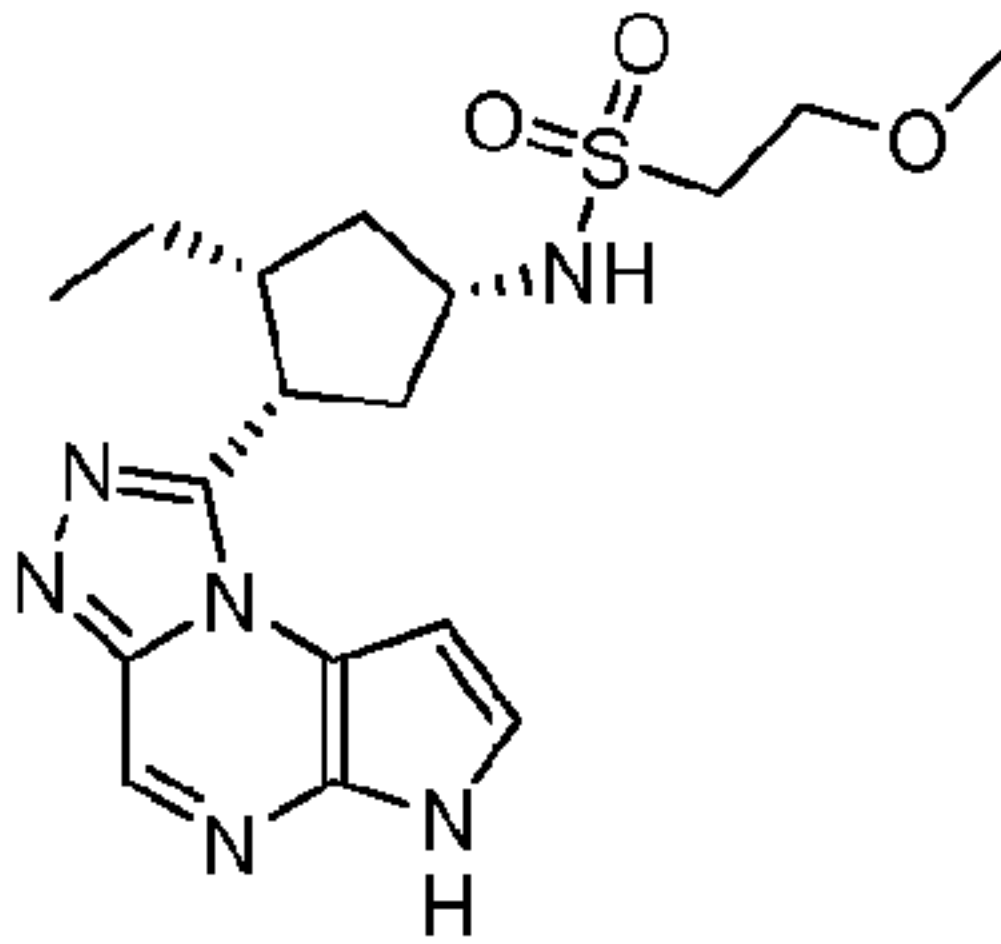
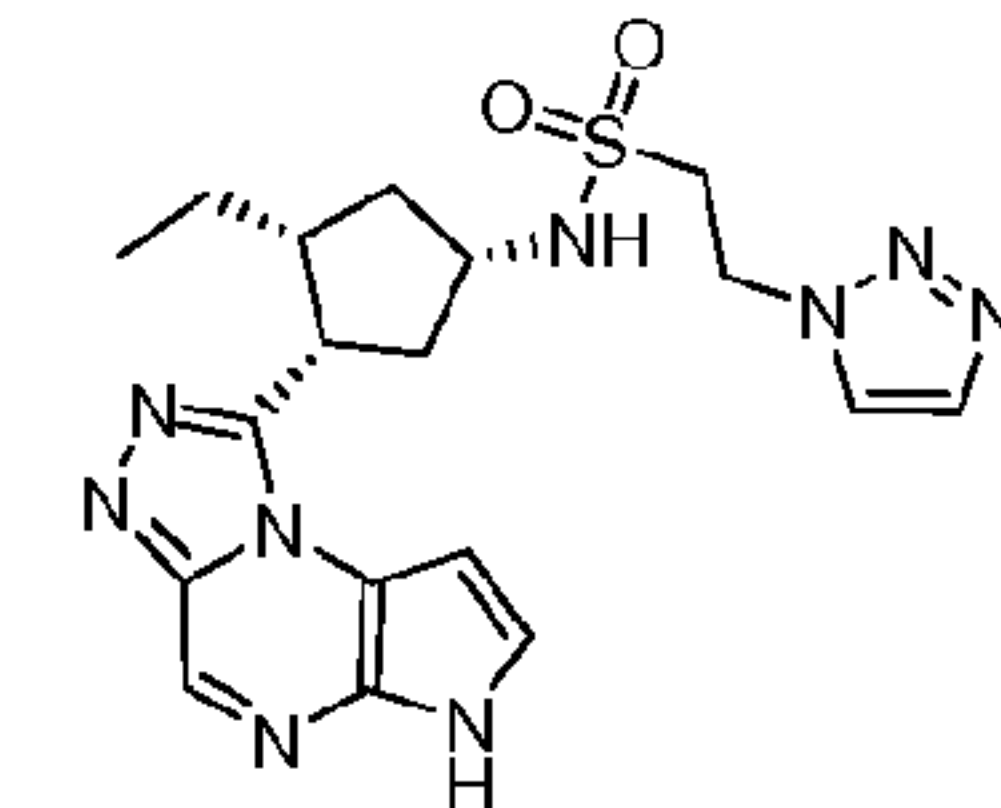
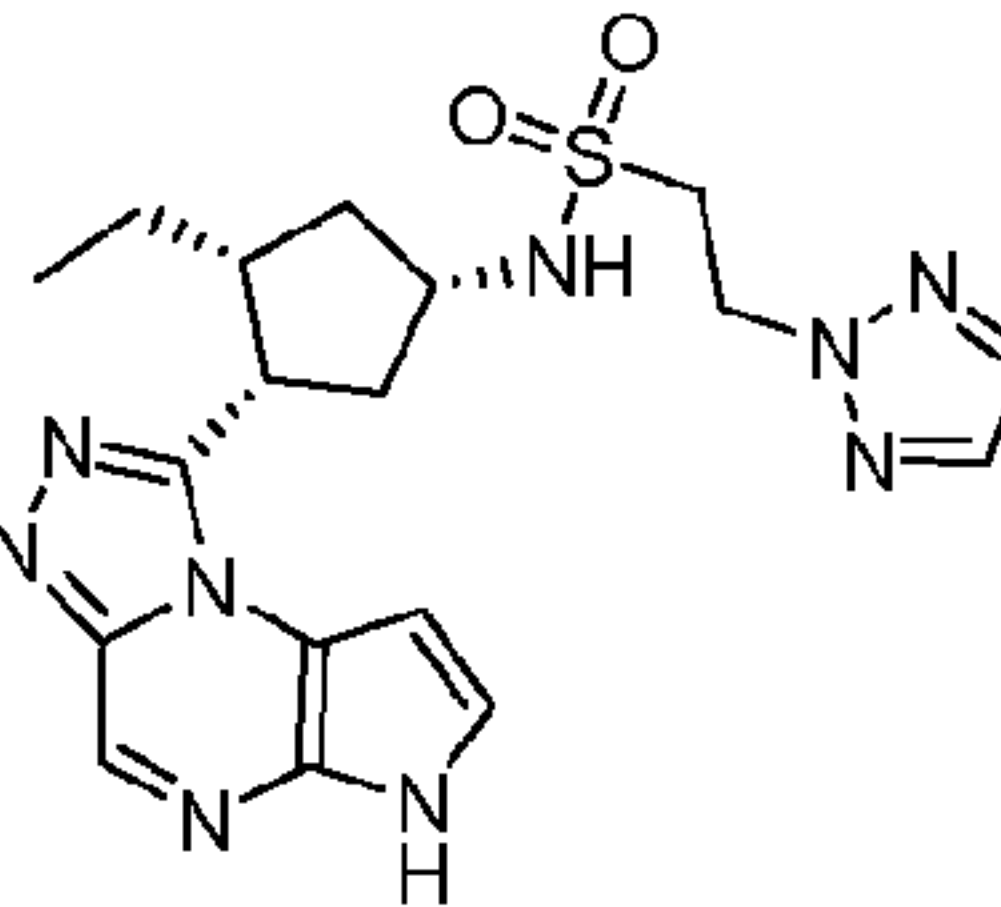
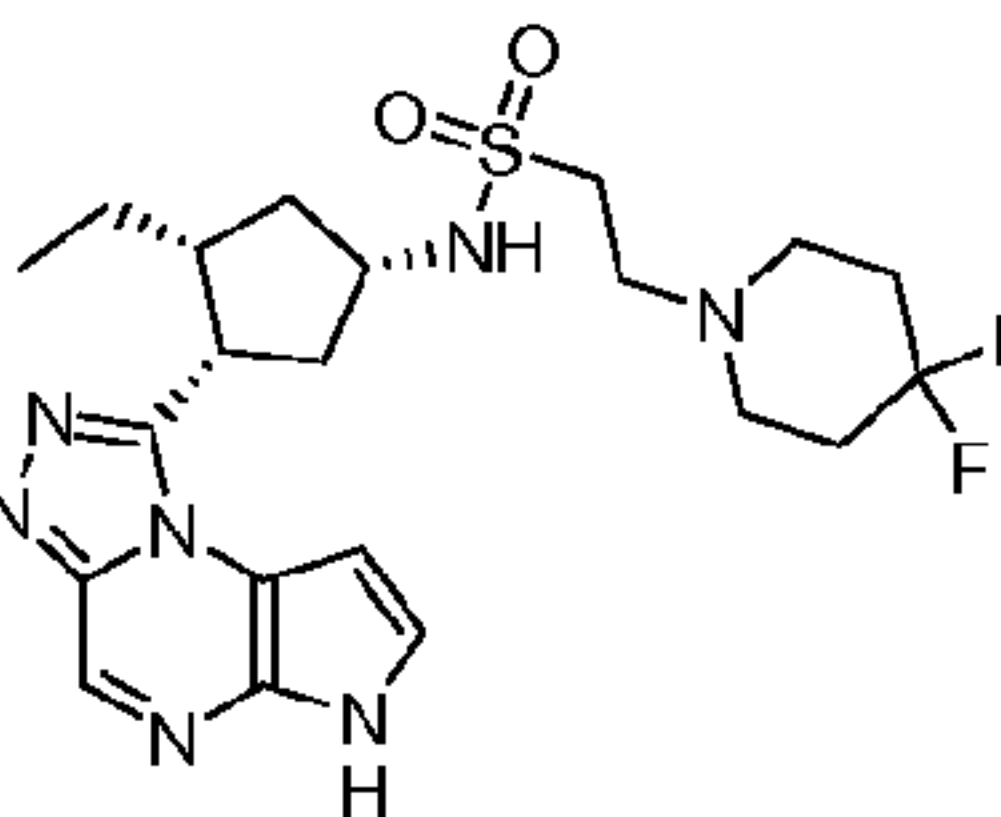
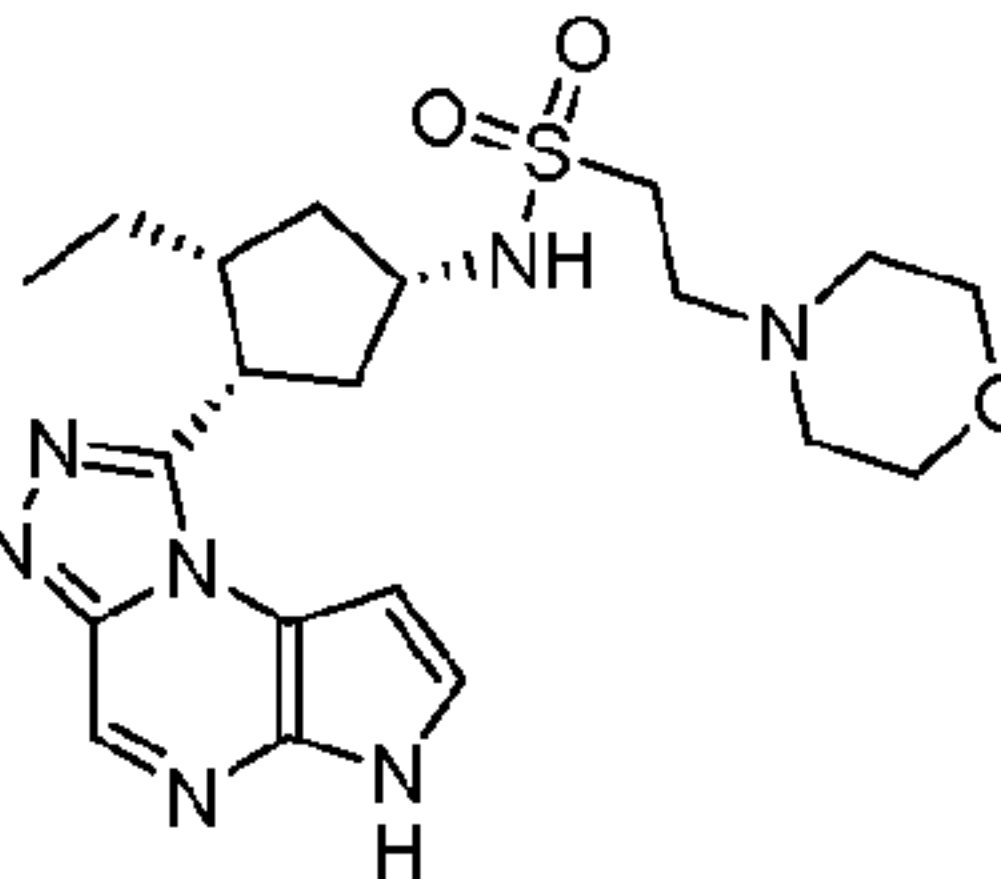
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1-methylcyclopropane-1-sulfonamide (prepared using K from Example #8, Step M and Preparation #6)		D.1.35*	1.66 (a)	389
1-((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-(benzyloxy)-2-ethylcyclopentyl)-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazine and 1-((1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)-4-(benzyloxy)-2-ethylcyclopentyl)-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazine (prepared using EE from benzyl 2,2,2-trichloroacetimidate and Preparation #FF.1)		D.1.36	2.15(b)	362
<i>N</i> -(4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)pyrrolidine-1-carboxamide (prepared using I from methyl 4-aminobicyclo[2.2.2]octane-1-carboxylate hydrochloride [Prime Organics], pyrrolidine-1-carbonyl chloride and TEA, Z with NaOH, A from Example #1, Step D, HATU and TEA, B with TEA))		D.1.37	1.65 (a)	380
1-((1 <i>R</i> ,2 <i>R</i> ,4 <i>S</i>)-2-ethyl-4-(4-methoxybenzyloxy)cyclopentyl)-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazine and 1-((1 <i>S</i> ,2 <i>S</i> ,4 <i>R</i>)-2-ethyl-4-(4-methoxybenzyloxy)cyclopentyl)-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazine (prepared using Z from Preparation #EE.1, A from Example #1, Step D, HATU, and TEA, B with DIEA)		D.1.38	2.14 (b)	392

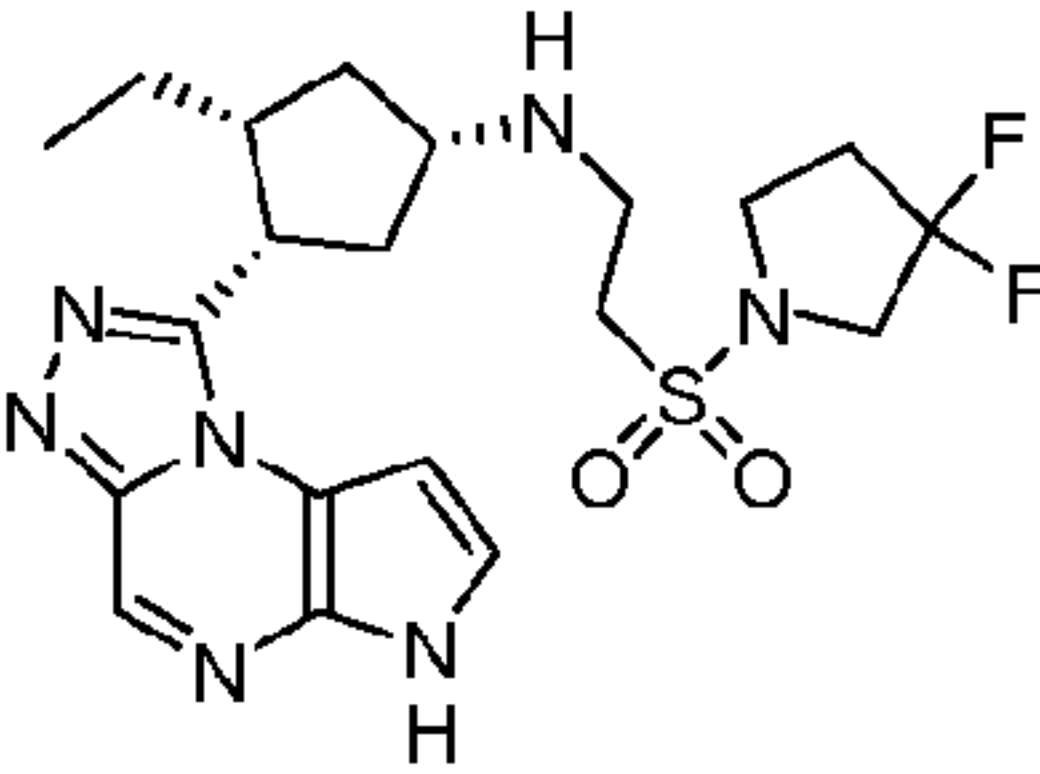
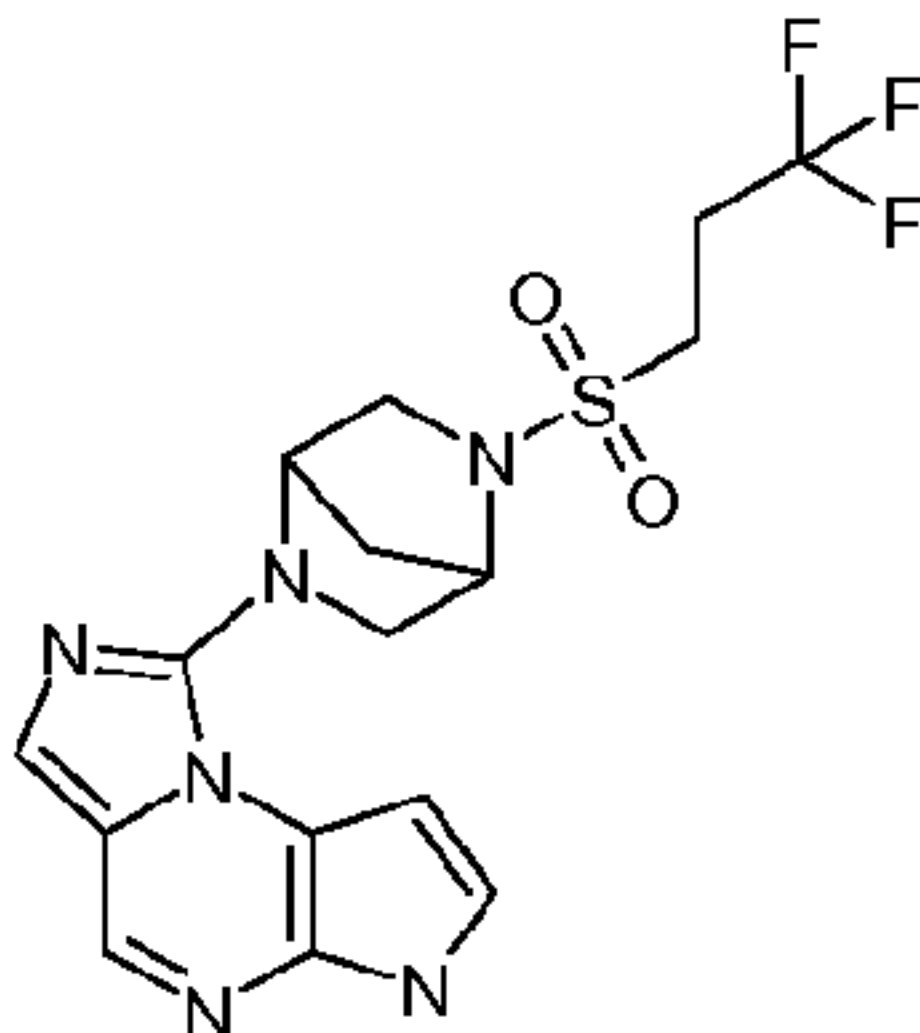
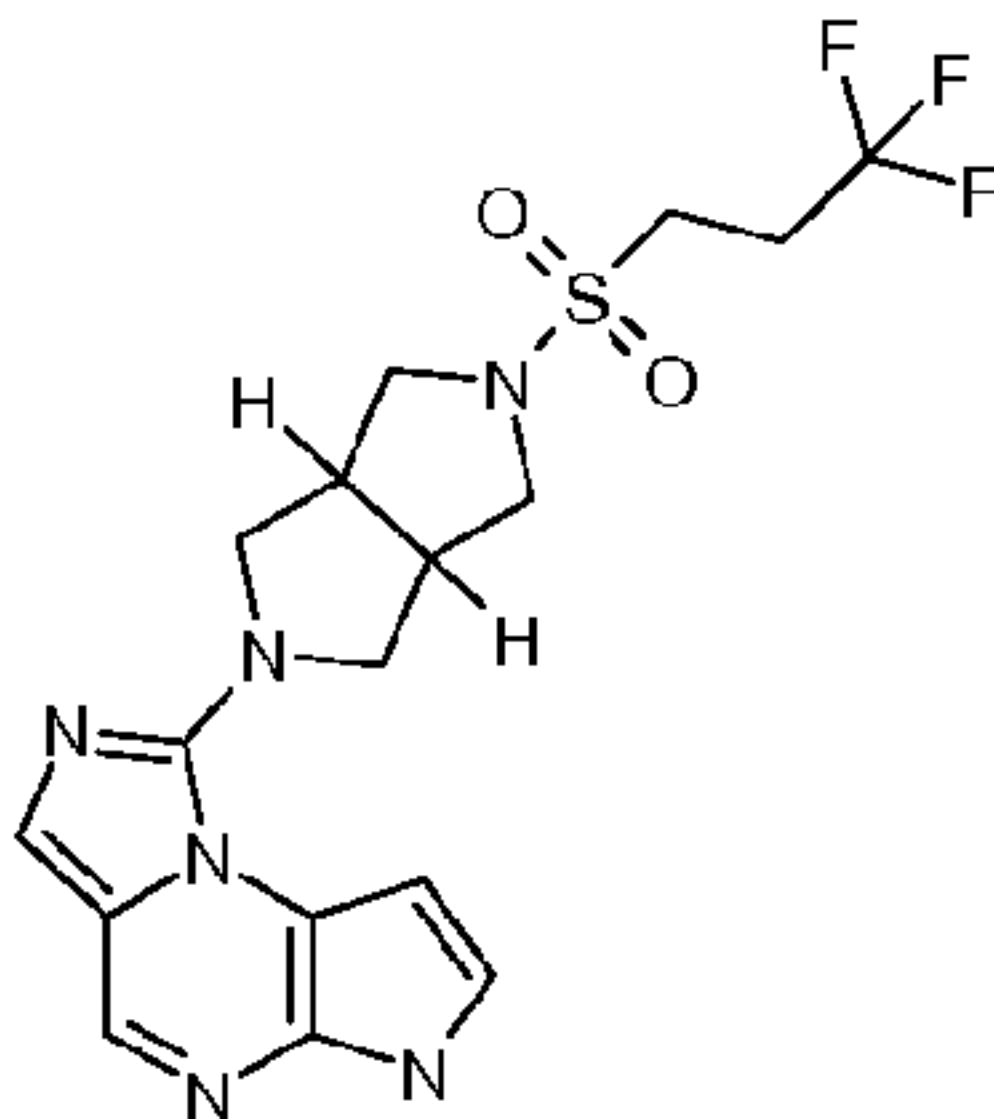
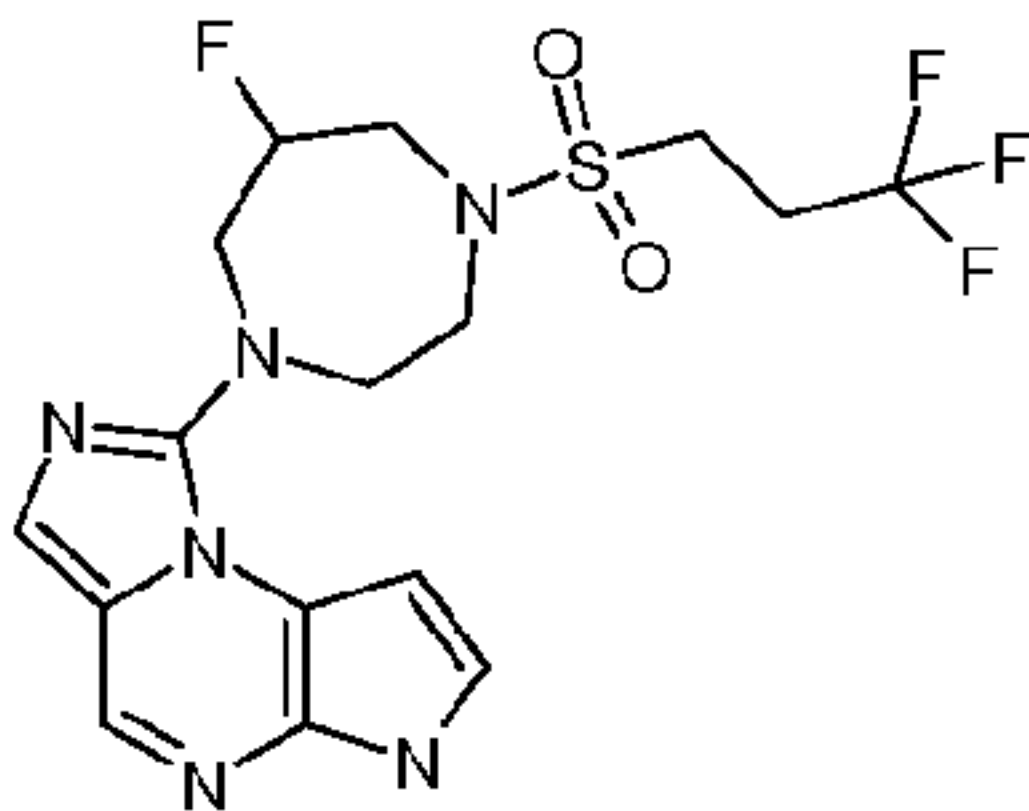
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -(4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclobutanesulfonamide (prepared using K from methyl 4-aminobicyclo[2.2.2]octane-1-carboxylate hydrobromide [Prime Organics], cyclobutanesulfonyl chloride [Hande] and TEA, Z with NaOH, A from Example #1, Step D, HATU and TEA, B with TEA))		D.1.39	1.71 (a)	401
<i>N</i> -(4-(3-allyl-6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide (prepared using E with 4-(<i>tert</i> -butoxycarbonylamino)-bicyclo[2.2.2]octane-1-carboxylic acid [Prime Organics], K with cyclopropylsulfonyl chloride, H from Preparation #12, HATU and DIEA, Q with Lawesson's reagent and mercury (II) trifluoroacetate)		D.1.40	1.89 (a)	426
<i>N</i> -(4-(3-(2,3-dihydroxypropyl)-6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide (Preparation #17)		D.1.41	1.37 (a)	460
<i>tert</i> -butyl 1-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)pyrrolidin-3-ylcarbamate (Preparation #16)		D.1.42	1.78 (a)	343
3-bromo-1-cyclohexyl-6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (Preparation #MM.1)		D.1.43	2.38 (a)	319, 321 (1:1)

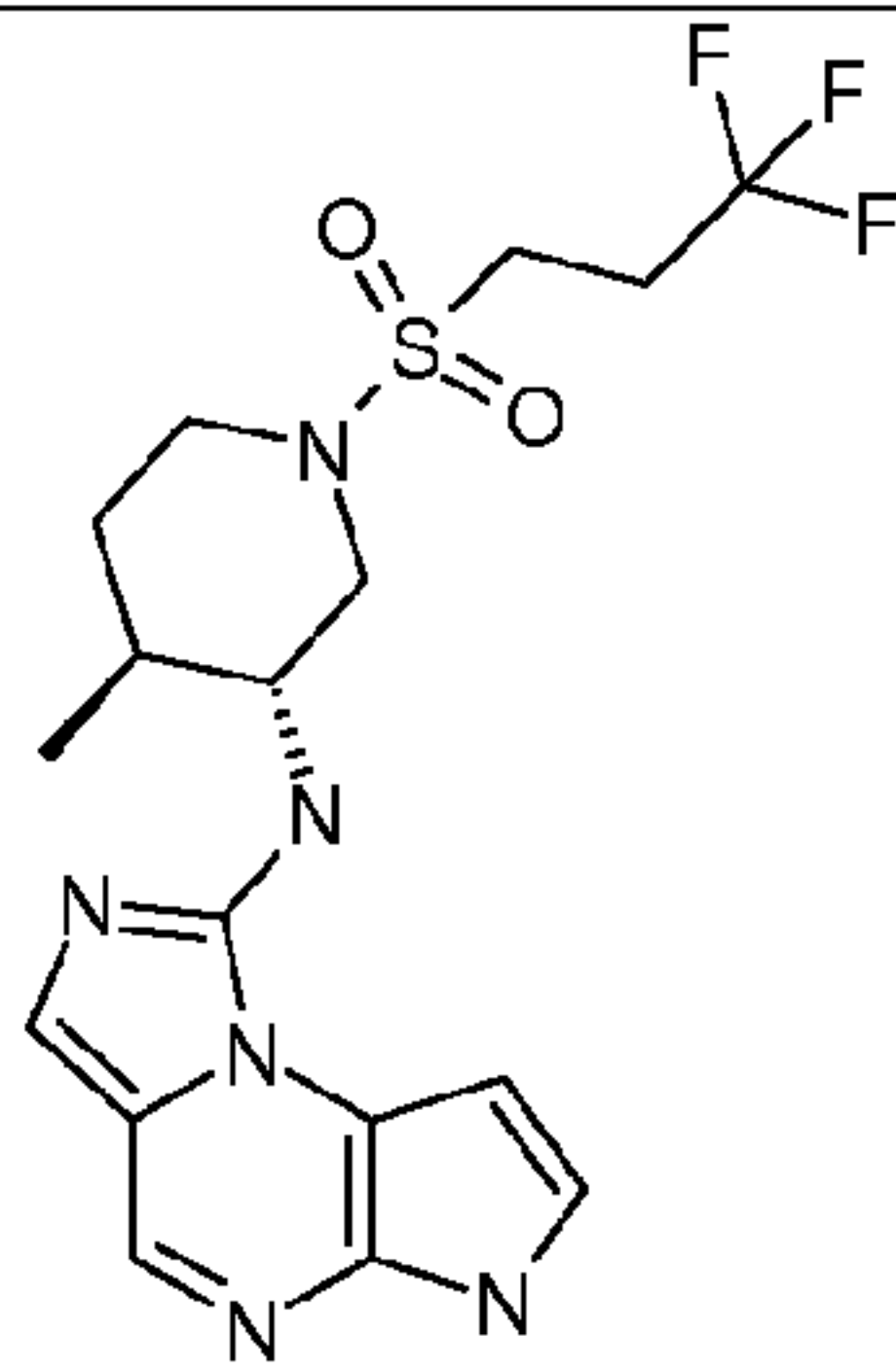
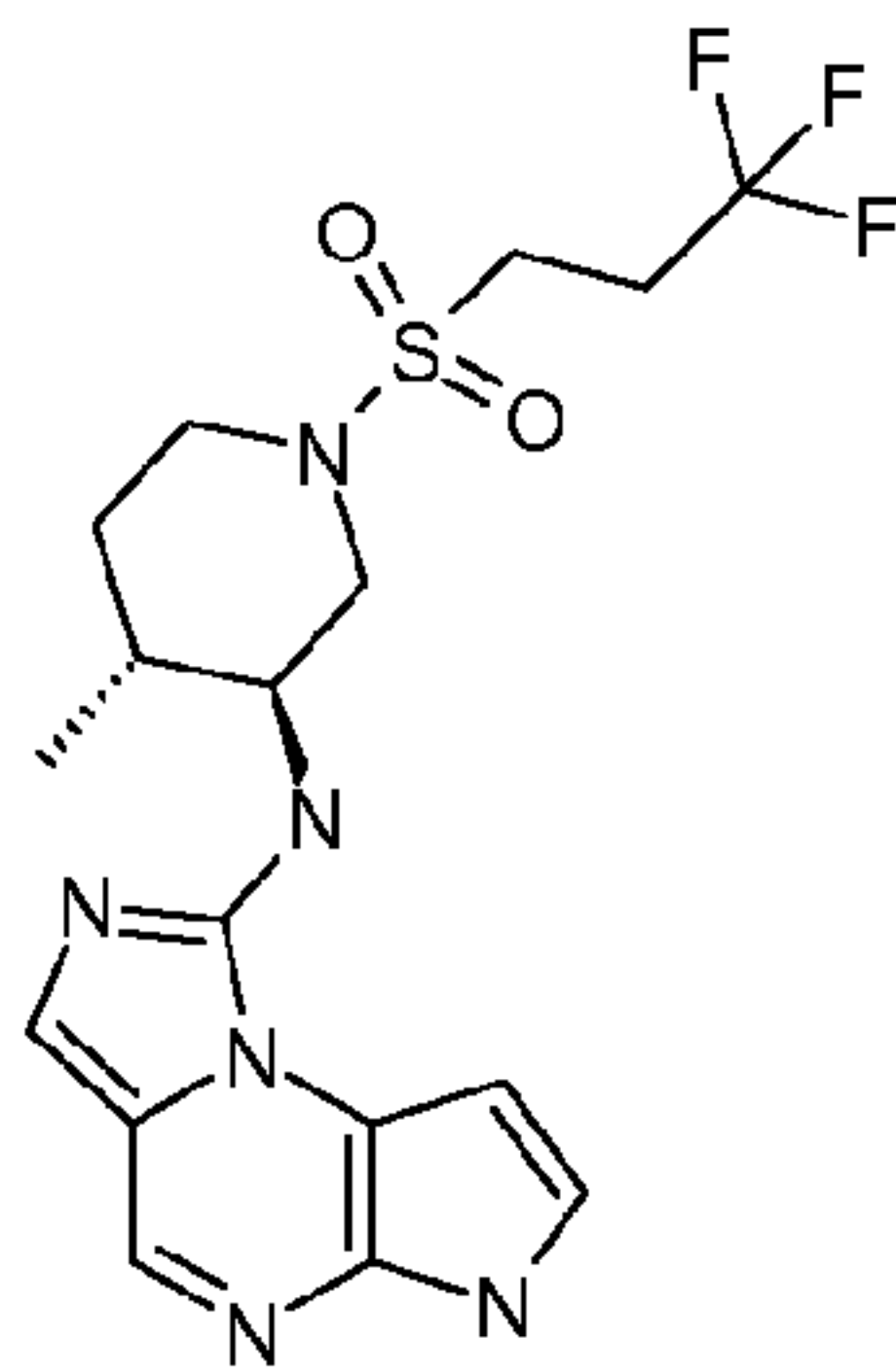
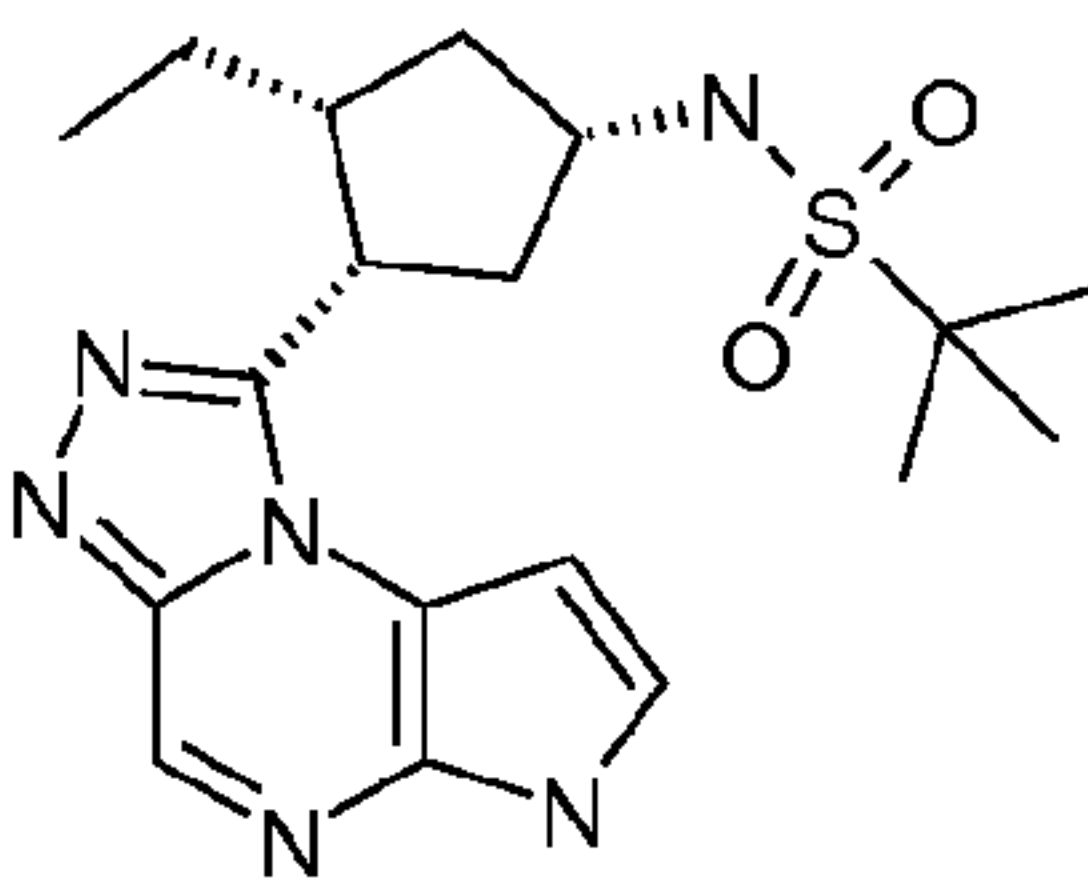
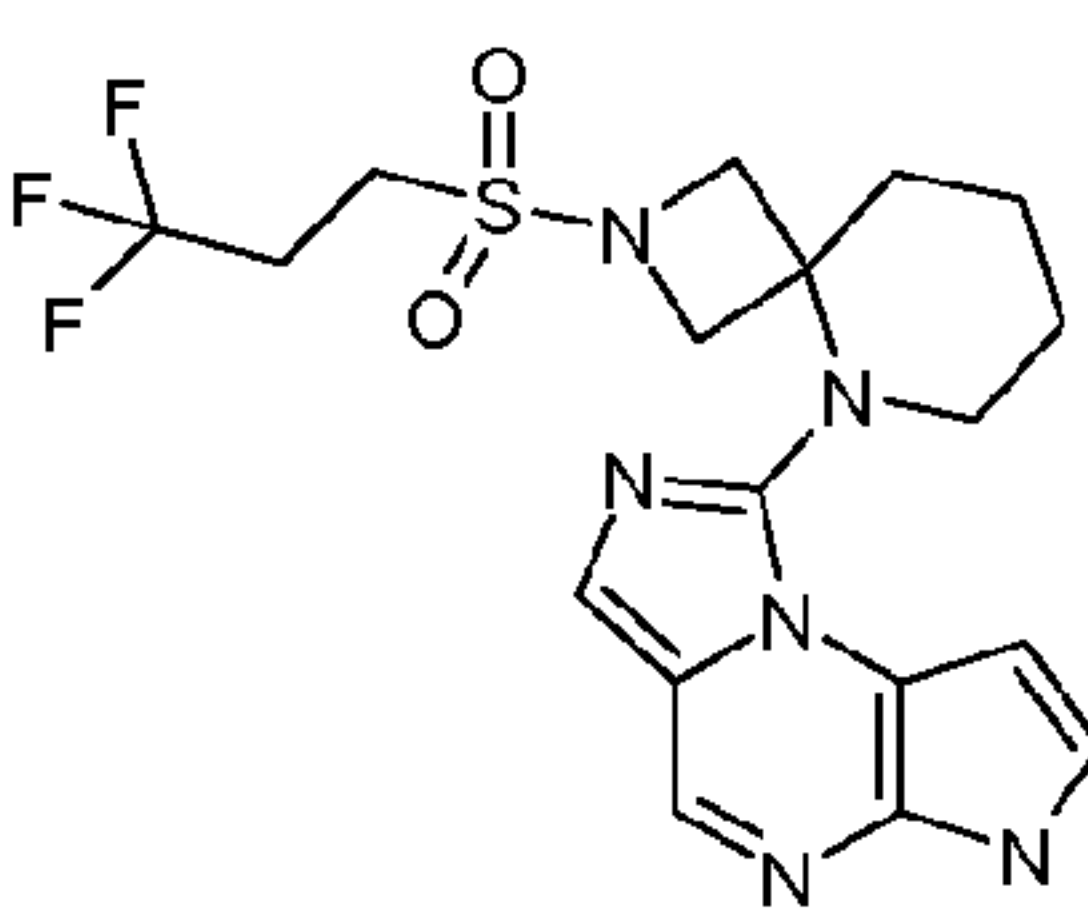
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>S</i> ,4 <i>R</i>)-3-(3-chloro-6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)-4-ethylcyclopentyl)-cyclopropanesulfonamide (prepared using H from Example #5, Step C and Preparation #Z.1, HATU and DIEA, Q with Lawesson's reagent and mercury (II) trifluoroacetate, MM with NCS)		D.1.44*	2.01 (a)	408
<i>N</i> -((1 <i>S</i> ,3 <i>S</i> ,4 <i>R</i>)-3-(3-bromo-6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)-4-ethylcyclopentyl)-cyclopropanesulfonamide (prepared using H from Example #5, Step C and Preparation #Z.1, HATU and DIEA, Q with Lawesson's reagent and mercury (II) trifluoroacetate, MM with NBS)		D.1.45*	2.05 (a)	452, 454 (1:1)
<i>N</i> -((3 <i>S</i> ,5 <i>R</i>)-5-ethyl-1-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide, (prepared using E from Preparation #15, J from Example #5, Step C with CDI, OO)		D.1.46*	1.63 (a)	375
<i>N</i> -((3 <i>S</i> ,5 <i>R</i>)-5-methyl-1-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide, (prepared using E from Preparation #14, J from Example #5, Step C with CDI, OO)		D.1.47*	1.31 (a)	359
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(7-methyl-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-cyclopropanesulfonamide (prepared using A with Preparation #18 and Preparation #Z.1, B with thionyl chloride and TEA)		D.1.48*	1.74 (a)	389

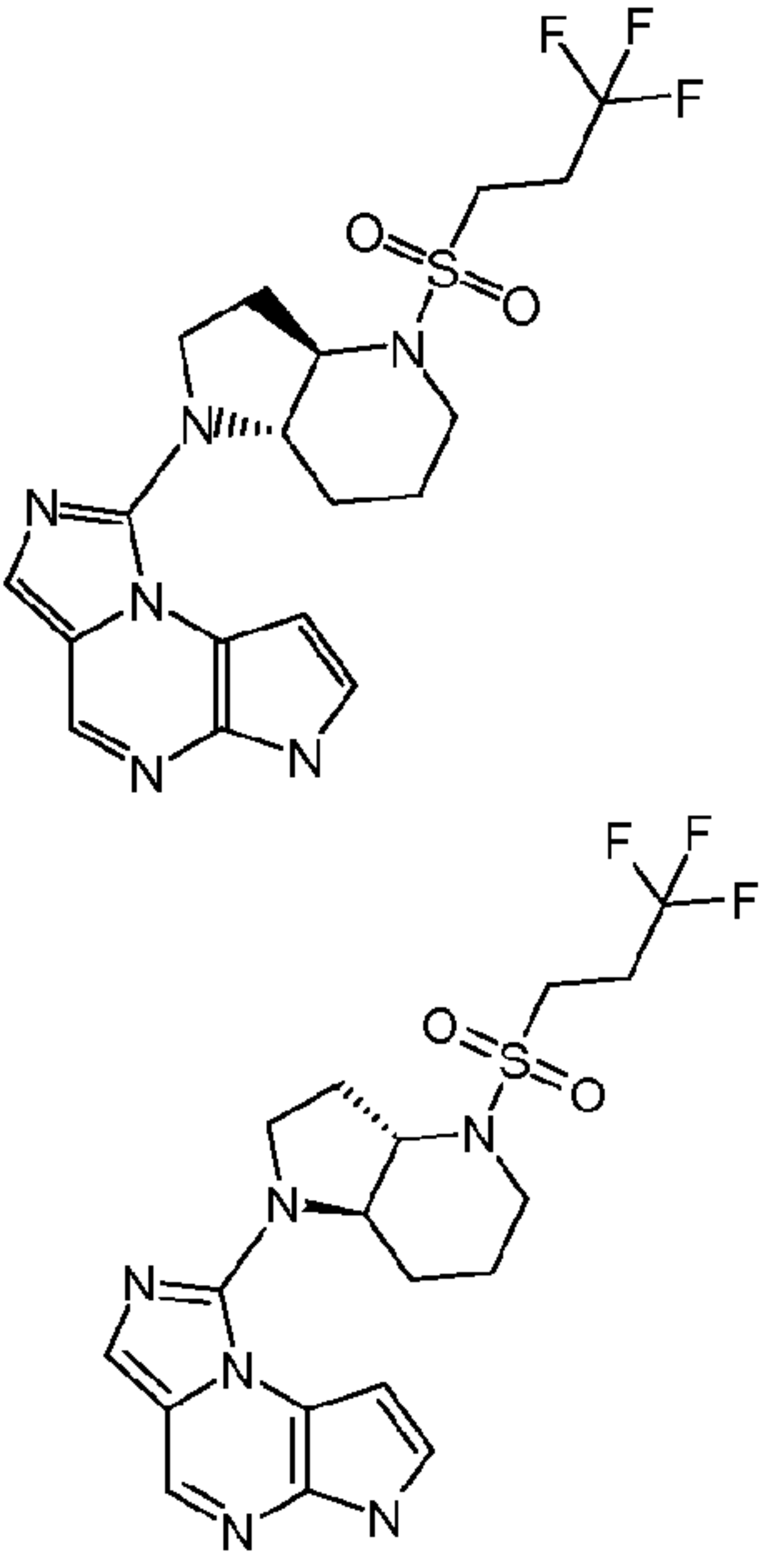
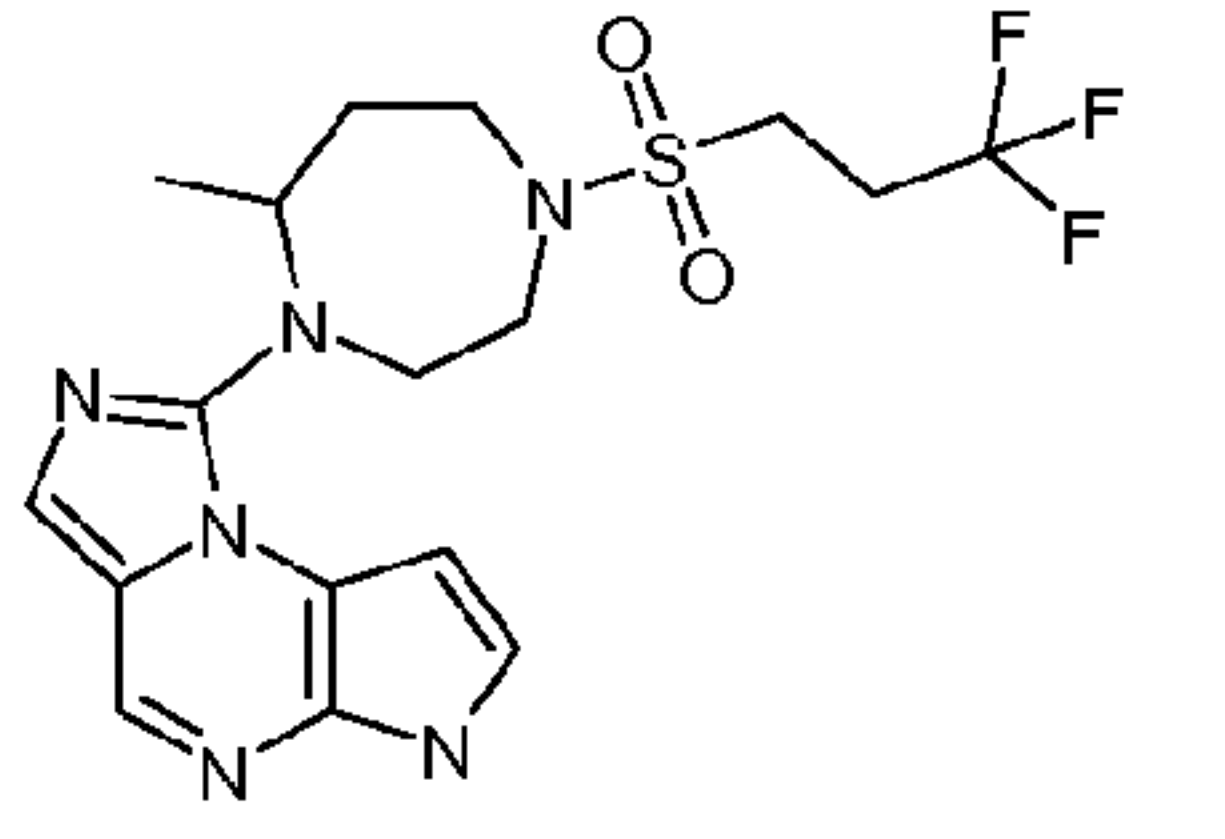
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
4-((4-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)cubanyl)methoxy)benzonitrile (prepared using H from (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) and 4-methoxycarbonylcubane carboxylic acid [Boron Molecular] with EDC•HCl and DIEA; P with DIBAL-H; II with 4-hydroxybenzonitrile, triphenylphosphine and DIAD; Q with Lawesson's reagent and mercury (II) trifluoroacetate)		D.1.49	2.05 (b)	392
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-4-methylpiperazine-1-sulfonamide (prepared using ZZ from Preparation BB.1, AAA with 1-methylpiperazine)		D.1.50*	1.32 (a)	433
1-cyclohexyl-2-methyl-6-tosyl-1,6-dihydroimidazo[4,5- <i>d</i>]pyrrolo[2,3- <i>b</i>]pyridine (prepared using K.1 from Example #21, Step E with 4-methylbenzene-1-sulfonyl chloride, L with cyclohexylamine, BBB , G with acetic anhydride and OO)		D.1.51	1.86 (a)	255
1-cyclohexyl-6-tosyl-2-(trifluoromethyl)-1,6-dihydroimidazo[4,5- <i>d</i>]pyrrolo[2,3- <i>b</i>]pyridine (prepared using prepared using K.1 from Example #21, Step E with 4-methylbenzene-1-sulfonyl chloride, L with cyclohexylamine, BBB , G with trifluoroacetic anhydride, DDD with 2,4,6-tripropyl-[1,3,5,2,4,6]trioxatriphosphine 2,4,6-trioxide)		D.1.52	2.37 (a)	309

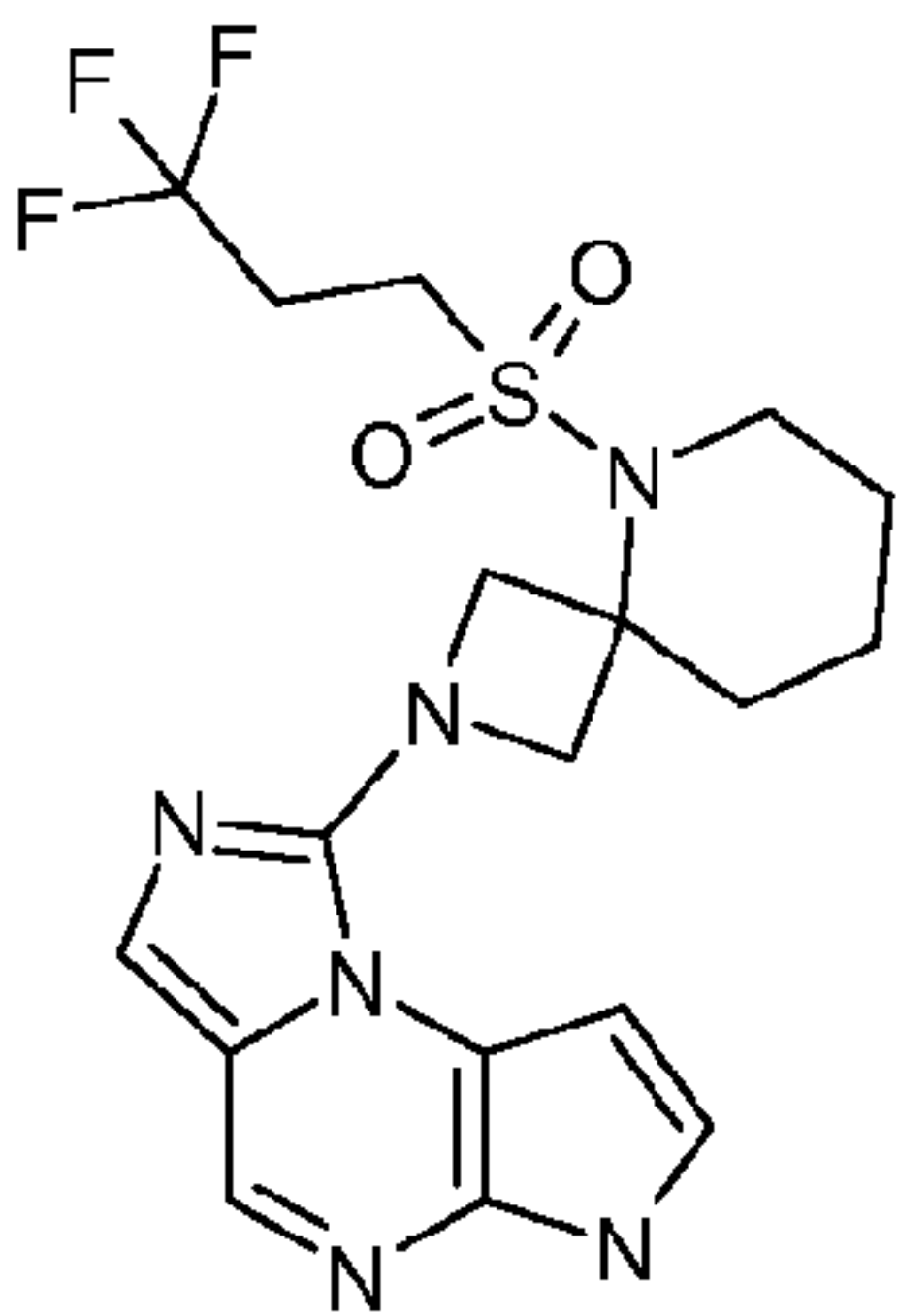
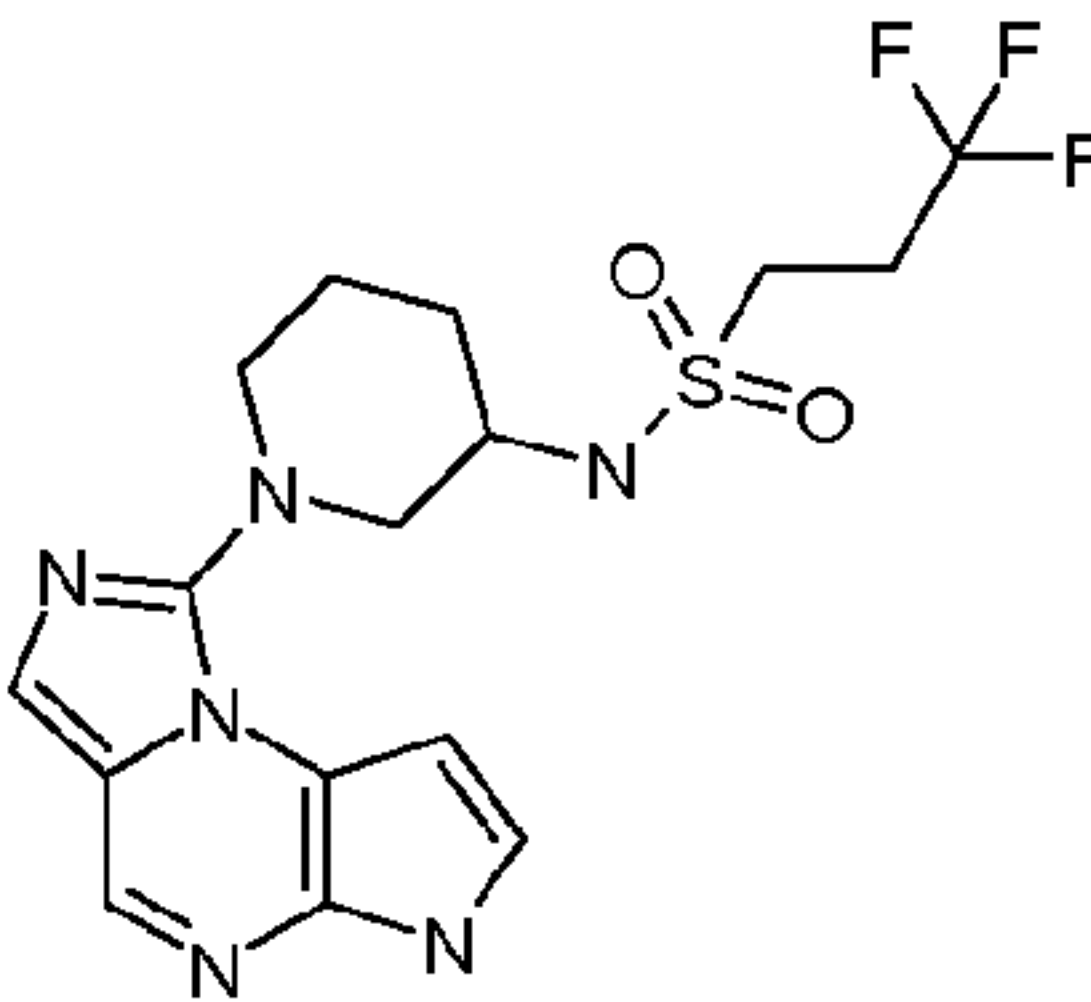
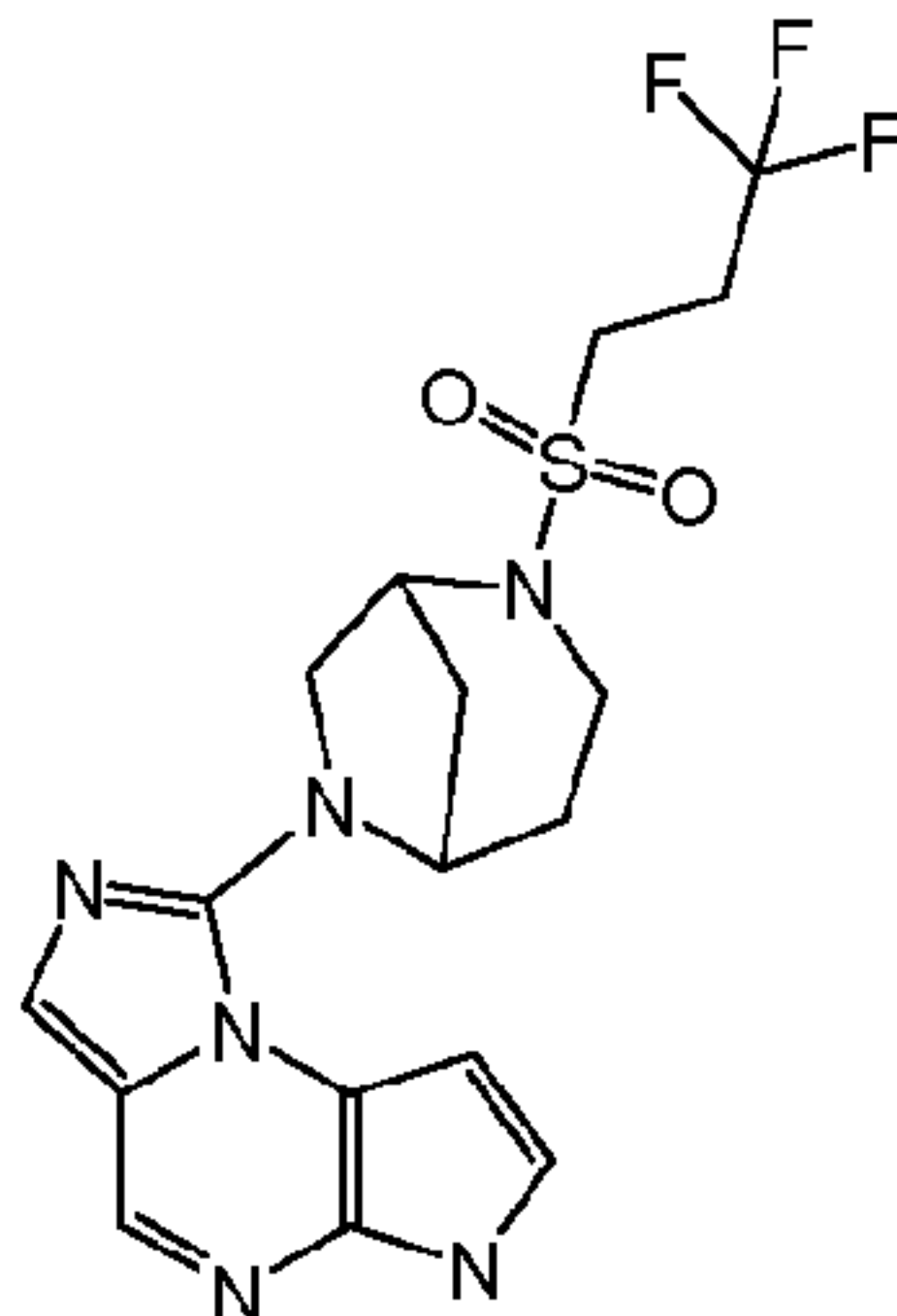
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(2-methyl-6-tosylimidazo[4,5- <i>d</i>]pyrrolo[2,3- <i>b</i>]pyridin-1(6 <i>H</i>)-yl)cyclopentyl)cyclopropanesulfonamide (prepared from Preparation #27 and Preparation #OOO.1 using L and DIEA, K.1 with TsCl and NaH, BBB , H with acetic anhydride, and DDD with POCl ₃)		D.1.53*	1.59(a)	374
1-((1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-(cyclopropylmethoxy)-2-methylcyclopentyl)-6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazine (prepared using P from Example #24 Step H and NaBH ₄ , VV , FFF with 2-cyclopropylacetaldehyde, Z with NaOH, A with Example #1 Step D, HATU and TEA, B with SOCl ₂ and DIEA)		D.1.54	1.73 (a)	312
1-methyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)cyclopentyl)cyclopropane-1-sulfonamide (prepared from 5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (WO2009152133) and (1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-acetamido-2-methylcyclopentanecarboxylic acid [prepared from ethyl 4-amino-2-methylcyclopentanecarboxylate (WO2009152133) using G , AA [Table 2, Method 3, R _t = 6.1 min, or = ND], and Z using H , OO , BB , and K with 3-chlorophenylsulfonyl chloride)		D.1.55*	2.17 (a)	430
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-hydroxyethylamino-1-sulfonamide (Preparation #ZZ.1)		D.1.56*	1.33 (a)	394

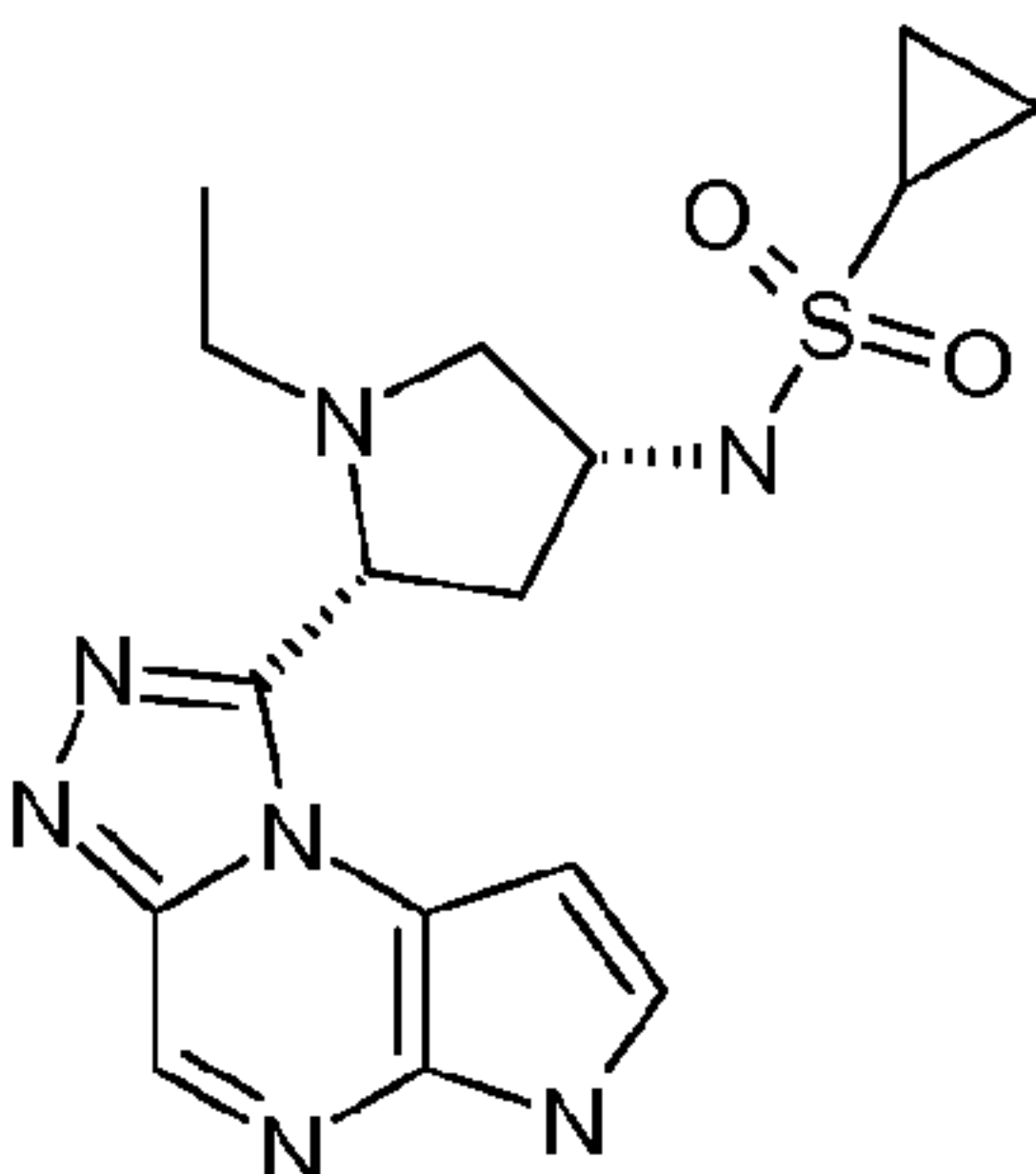
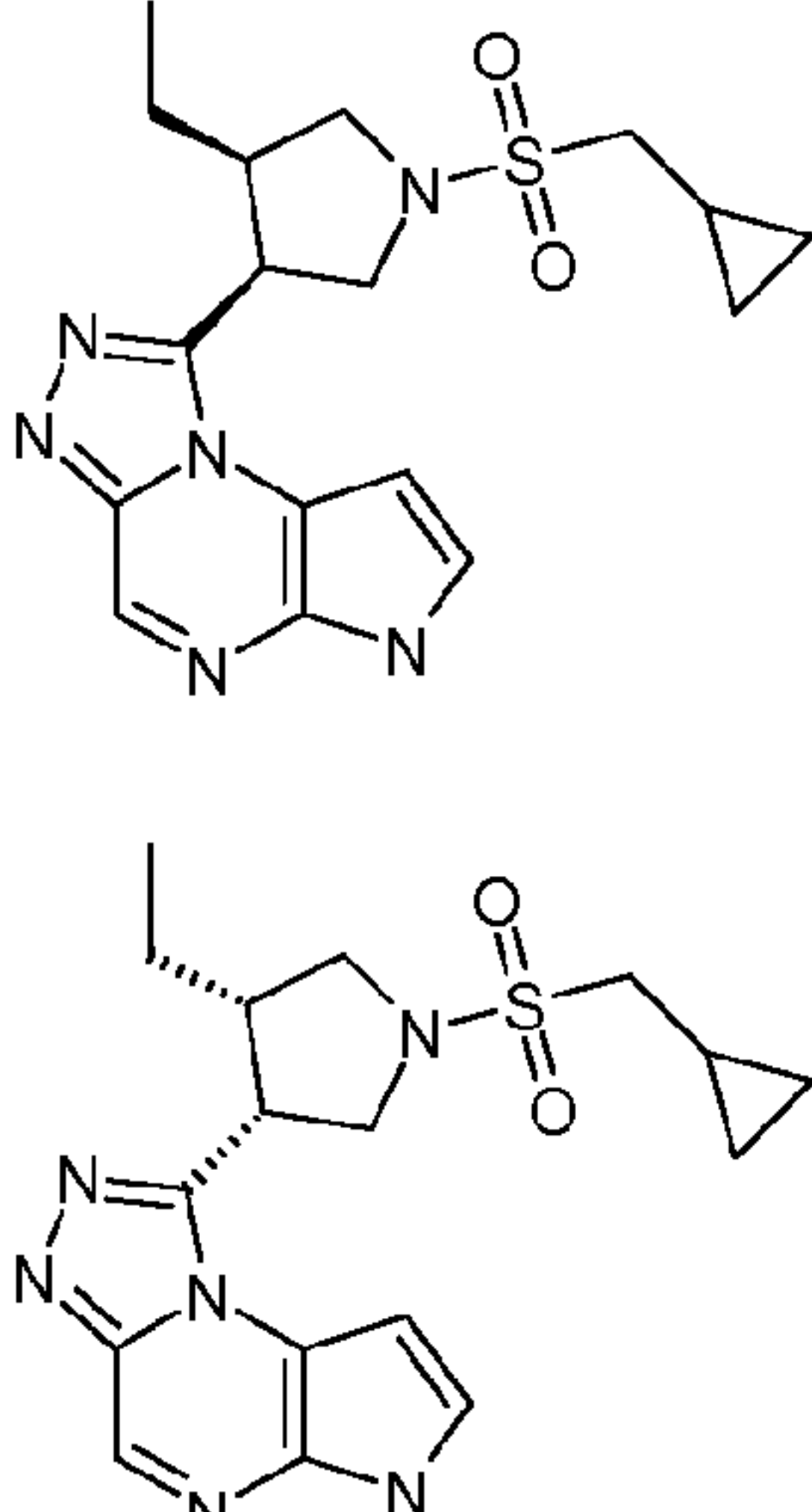
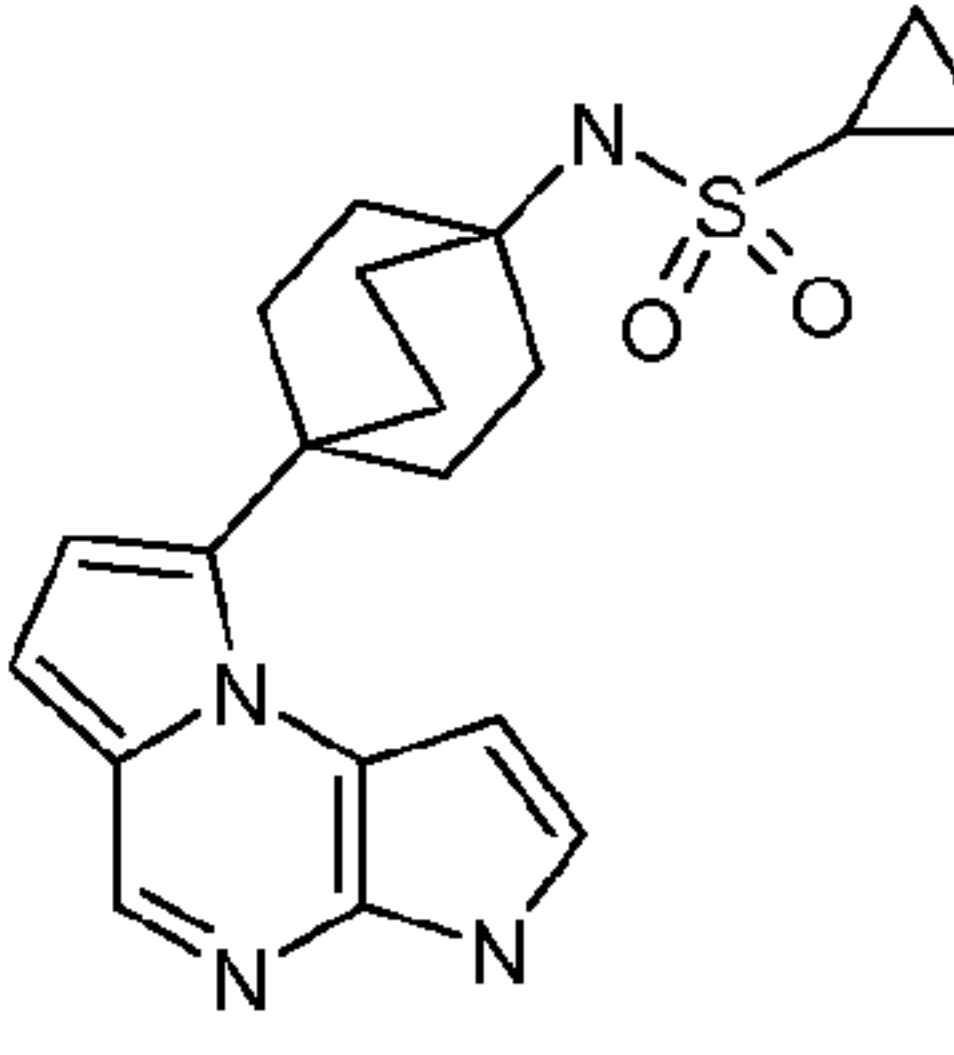
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-methoxyethanesulfonamide (prepared using K from Example #8 Step M and 2-methoxyethane-1-sulfonyl chloride [Focus Synthesis] with TEA)		D.1.57*	1.53 (b)	393
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-(1 <i>H</i> -1,2,3-triazol-1-yl)ethanesulfonamide (prepared using K.1 from Example #8 Step M and 2-chloroethanesulfonyl chloride with TEA, YY with 1 <i>H</i> -1,2,3-triazole and DIEA)		D.1.58*	1.45 (b)	430
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-(2 <i>H</i> -1,2,3-triazol-2-yl)ethanesulfonamide (prepared using K.1 from Example #8 Step M and 2-chloroethanesulfonyl chloride with TEA, YY with 1 <i>H</i> -1,2,3-triazole and DIEA)		D.1.59*	1.58 (b)	430
2-(4,4-difluoropiperidin-1-yl)- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)ethanesulfonamide (prepared using K.1 from Example #8 Step M and 2-chloroethanesulfonyl chloride with TEA, YY with 4,4-difluoropiperidine hydrochloride and DIEA)		D.1.60*	1.76 (b)	482
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-morpholinoethanesulfonamide (prepared using K.1 from Example #8 Step M and 2-chloroethanesulfonyl chloride with TEA, YY with morpholine)		D.1.61*	1.35 (b)	448

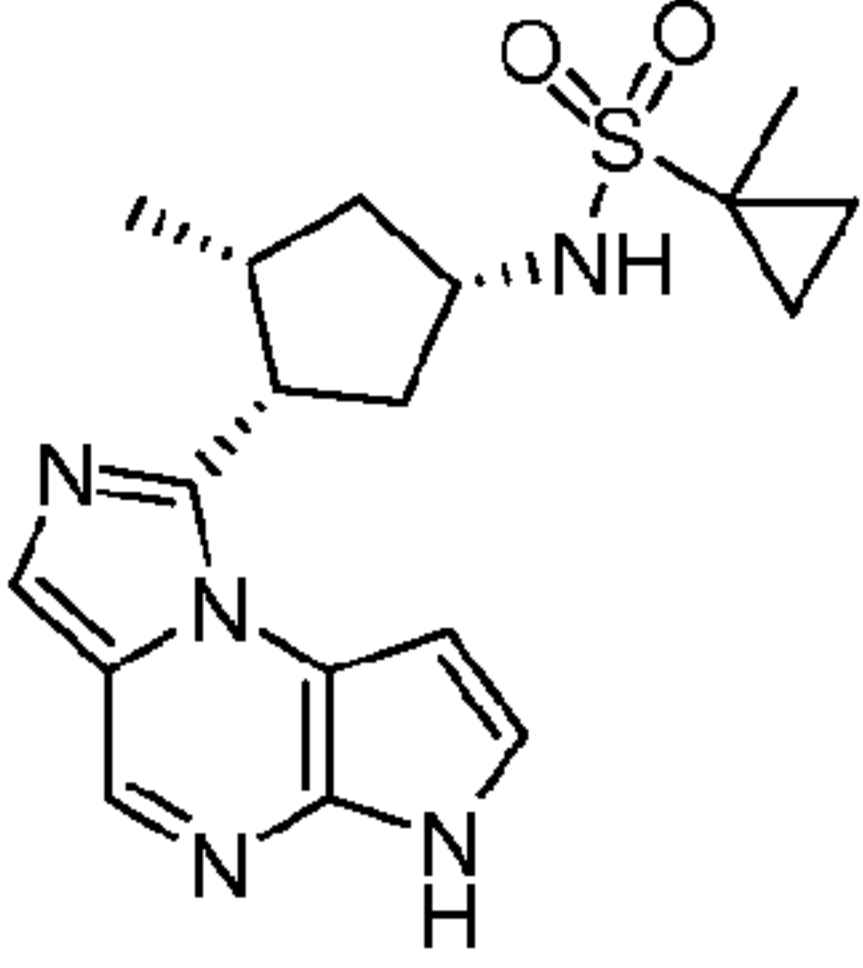
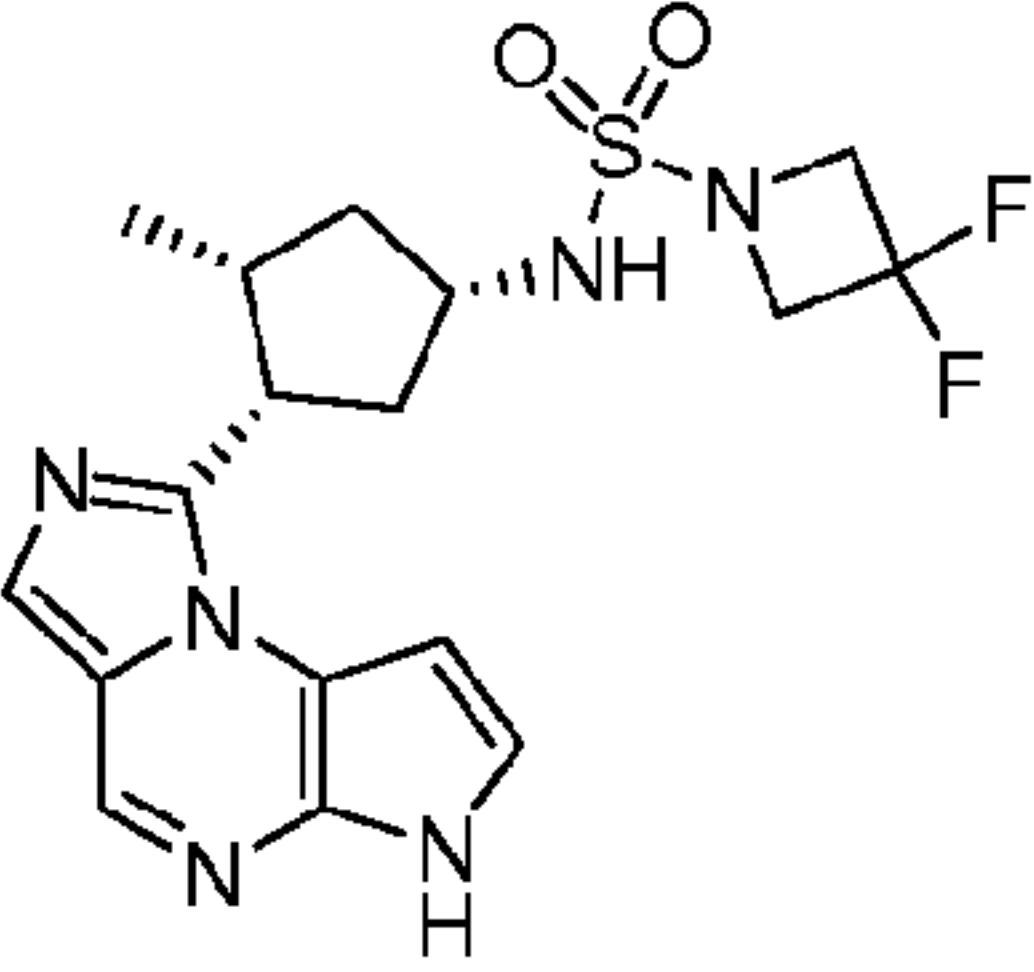
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
(1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)- <i>N</i> -(2-(3,3-difluoropyrrolidin-1-ylsulfonyl)ethyl)-3-ethyl-4-(6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentanamine (prepared using YY from Preparation #26 and Example #8 Step M with DIEA)		D.1.62*	1.53 (b)	468
(<i>cis</i>)-6-tosyl-1-(5-(3,3,3-trifluoropropylsulfonyl)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (prepared using K from (<i>cis</i>)-tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (US2003/225268) and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), E with HCl, J with CDI and (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).		D.1.63	1.85	415
(<i>cis</i>)-6-tosyl-1-(5-(3,3,3-trifluoropropylsulfonyl)hexahydropyrrolo[3,4- <i>c</i>]pyrrol-2(1 <i>H</i>)-yl)-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (prepared using K from (<i>cis</i>)-tert-butyl hexahydropyrrolo[3,4- <i>c</i>]pyrrole-2(1 <i>H</i>)-carboxylate and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), E with HCl, J with CDI and (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).		D.1.64	1.80	429
1-(6-fluoro-4-(3,3,3-trifluoropropylsulfonyl)-1,4-diazepan-1-yl)-6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (prepared using K from tert-butyl 6-fluoro-1,4-diazepane-1-carboxylate (WO2007/126935) and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), E with HCl, J with CDI and (5-tosyl-5 <i>H</i> -		D.1.65	1.86	435

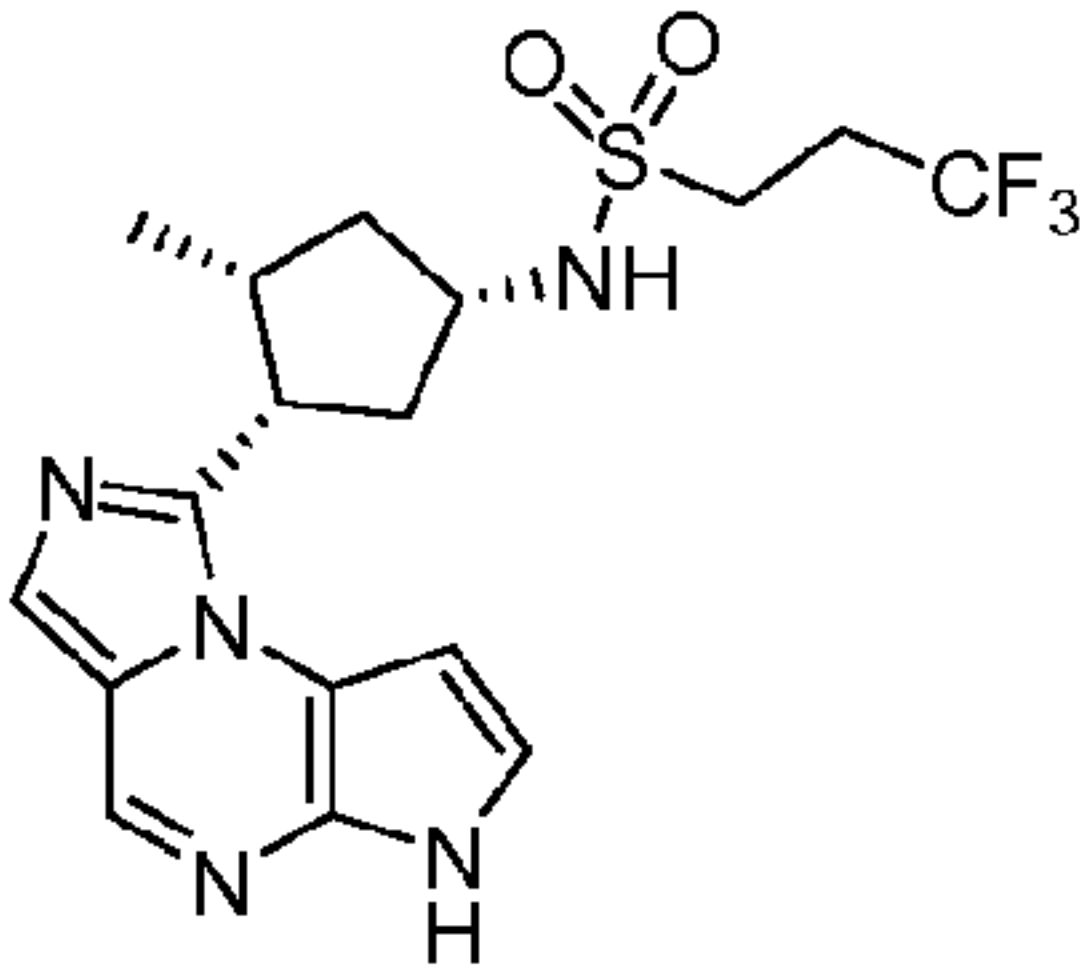
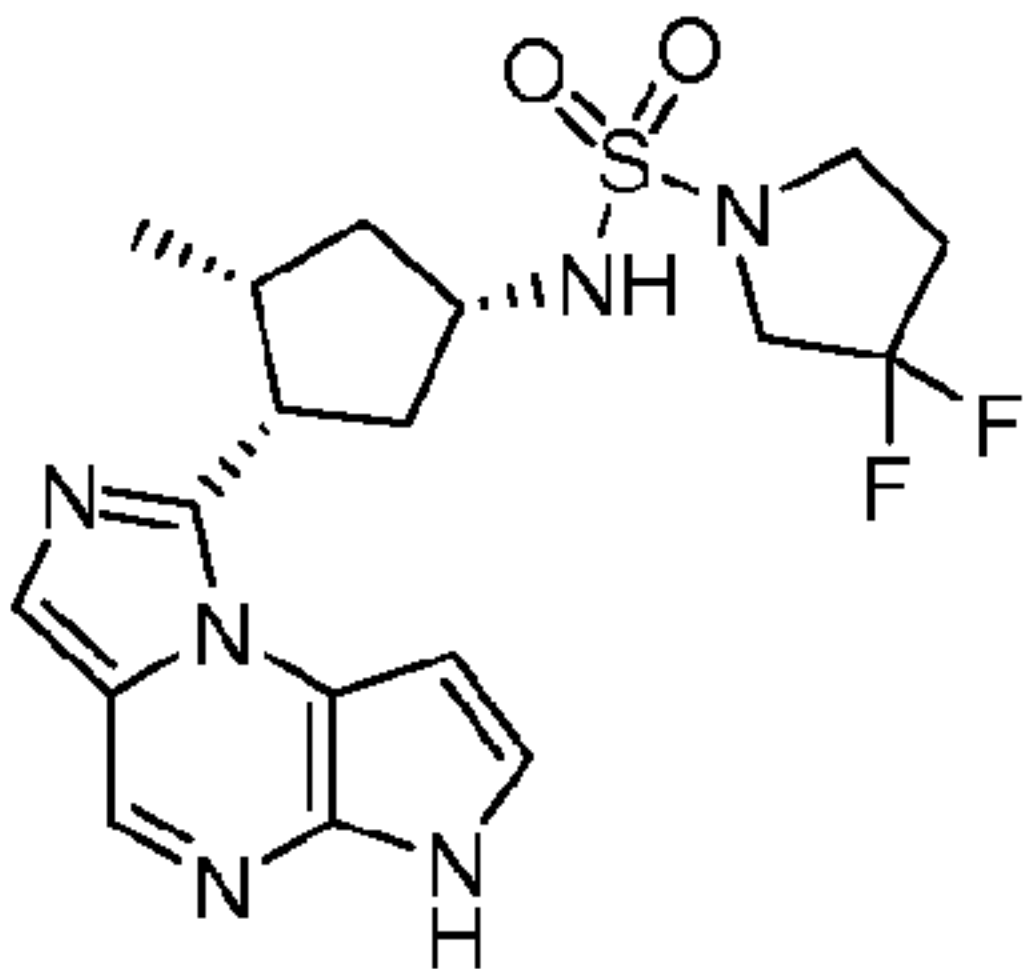
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).				
<i>trans</i> - <i>N</i> -(4-methyl-1-(3,3,3-trifluoropropylsulfonyl)piperidin-3-yl)-6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-amine (prepared using K from <i>trans</i> -tert-butyl 4-methylpiperidin-3-ylcarbamate (WO2009/140320) and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), E with HCl, J with CDI and (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).	 	D.1.66	1.89	431
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-methylpropane-2-sulfonamide (Preparation #28)		D.1.67*	1.76	391
6-tosyl-1-(2-(3,3,3-trifluoropropylsulfonyl)-2,5-diazaspiro[3.5]nonan-5-yl)-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (prepared using K from 5-benzyl-2,5-diazaspiro[3.5]nonane (WO2008/60767) and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), Y with Pd(OH) ₂ , J with CDI and (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).		D.1.68	2.07	443

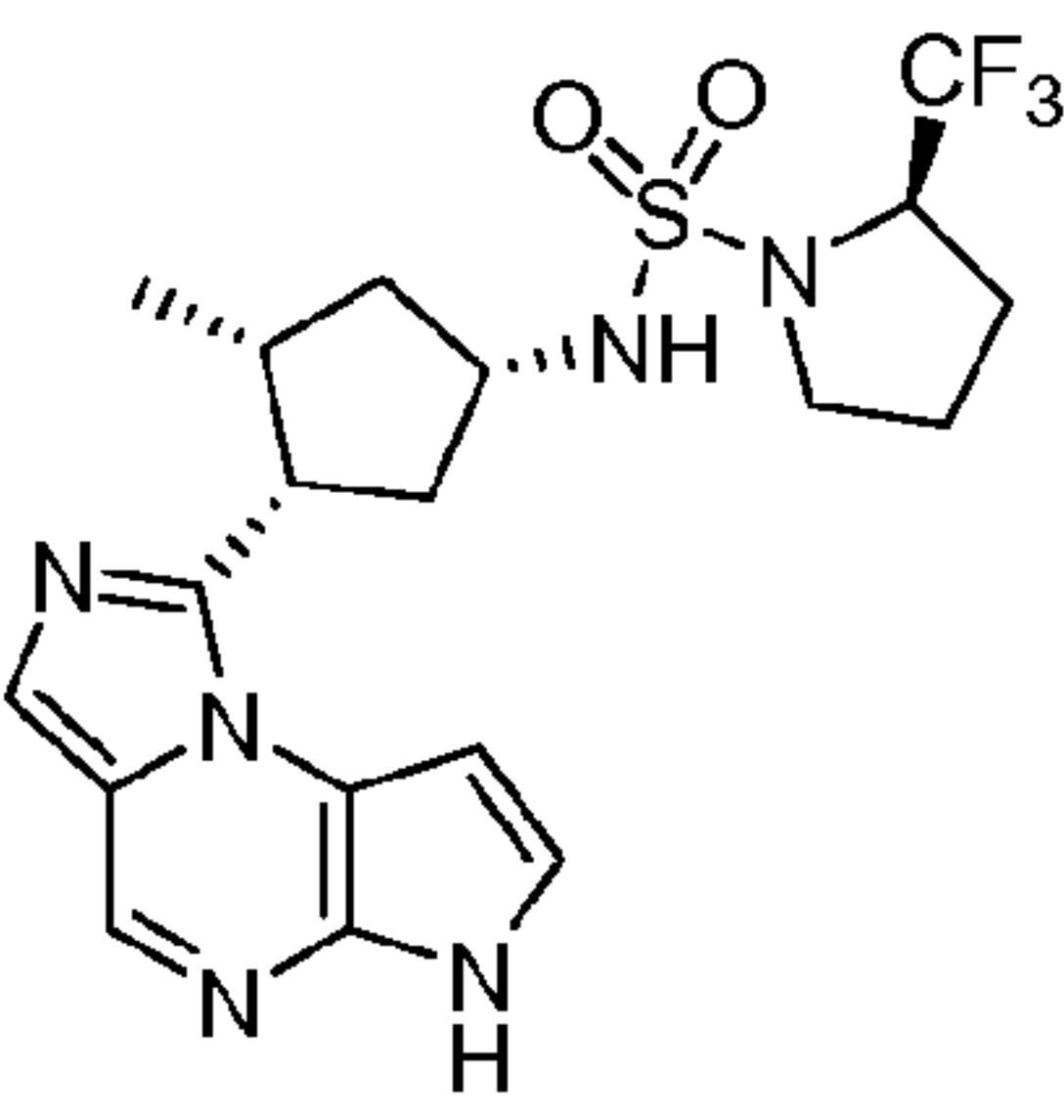
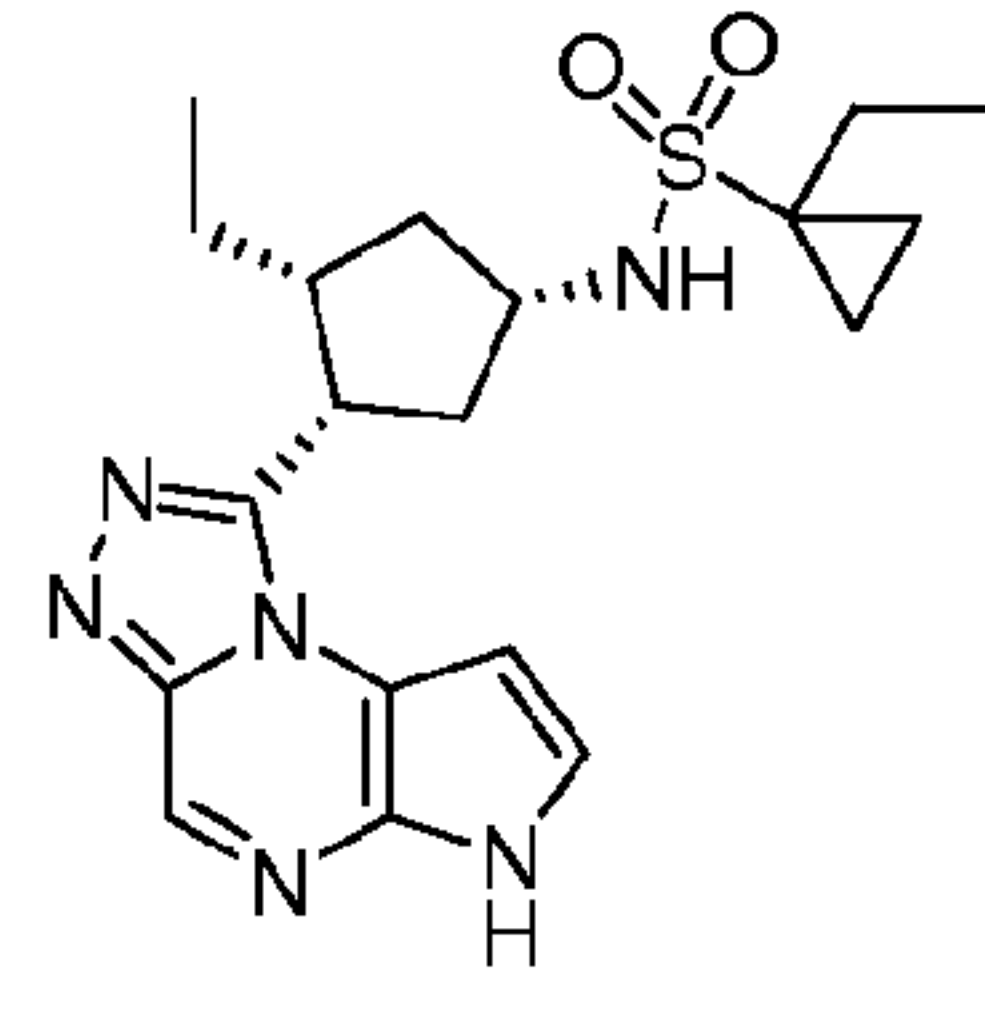
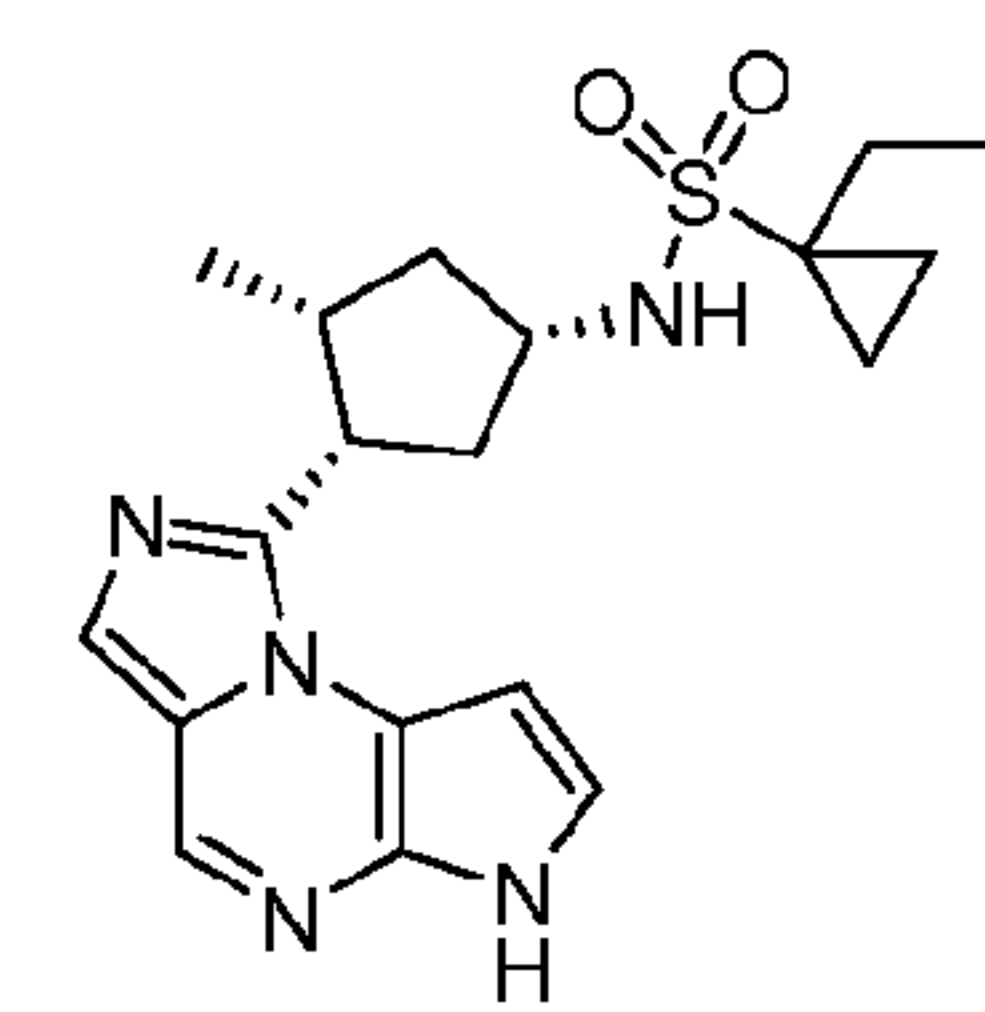
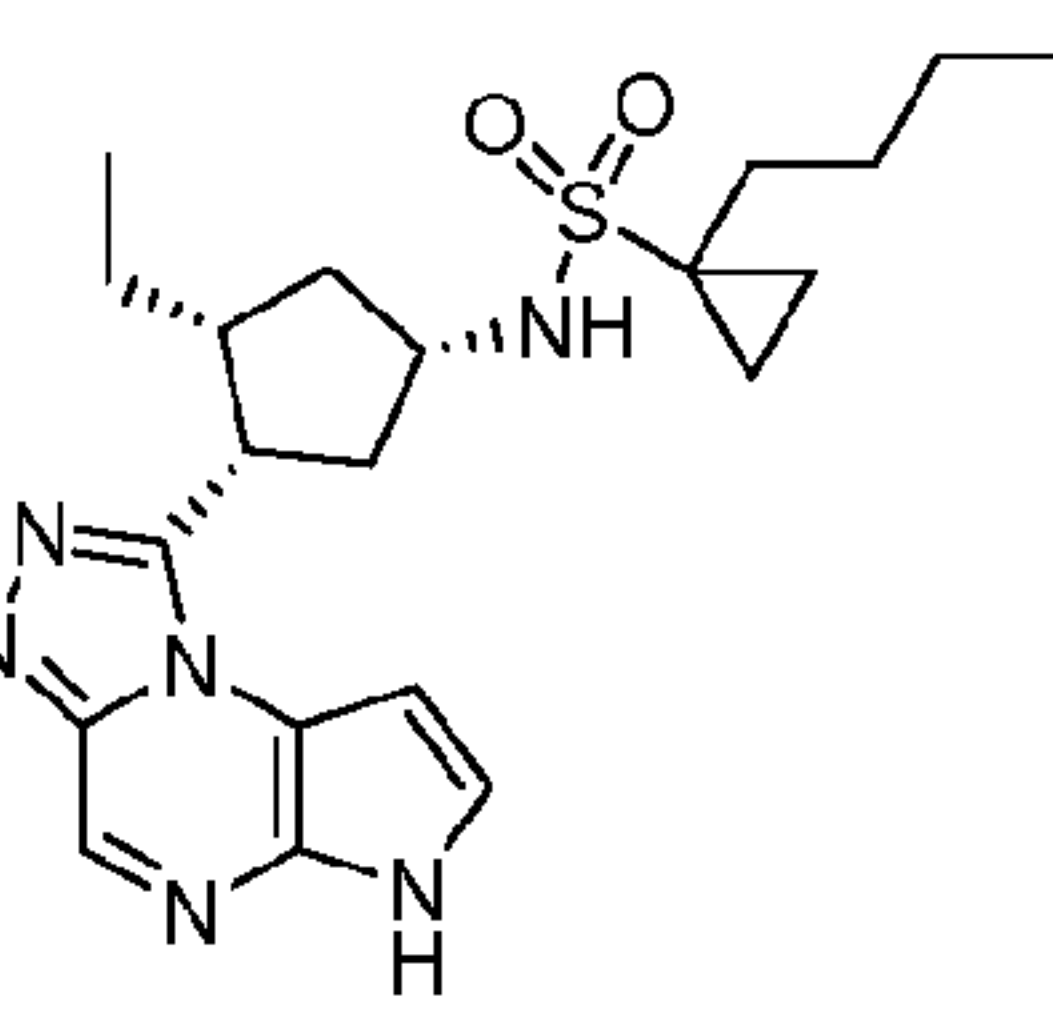
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
6-tosyl-1-((<i>trans</i>)-4-(3,3,3-trifluoropropylsulfonyl)octahydro-1 <i>H</i> -pyrrolo[3,2- <i>b</i>]pyridin-1-yl)-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (prepared using K from (<i>trans</i>)-tert-butyl octahydro-1 <i>H</i> -pyrrolo[3,2- <i>b</i>]pyridine-1-carboxylate (WO2009/140320) and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), E with HCl, J with CDI and (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).		D.1.69	1.94	443
1-(7-methyl-4-(3,3,3-trifluoropropylsulfonyl)-1,4-diazepan-1-yl)-6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (prepared using K from benzyl 7-methyl-1,4-diazepane-1-carboxylate, Hydrochloric Acid (Wlodarczyk, N.; Gilleron, P.; Millet, R.; Houssin, R.; Henichart, J.-P. <i>Tet. Let.</i> , 2007 , vol. 48, # 14 p. 2583 - 2586) and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), Y with Pd(OH) ₂ , J with CDI and (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).		D.1.70	1.97	431

Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
6-tosyl-1-(5-(3,3,3-trifluoropropylsulfonyl)-2,5-diazaspiro[3.5]nonan-2-yl)-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (prepared using K from <i>tert</i> -butyl 2,5-diazaspiro[3.5]nonane-2-carboxylate (WO2008/60767) and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), E with HCl, J with CDI and (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).		D.1.71	2.03	443
3,3,3-trifluoro-N-(1-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)piperidin-3-yl)propane-1-sulfonamide (prepared using K <i>tert</i> -butyl 3-aminopiperidine-1-carboxylate (3B-Scientific Corp.) and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), E with HCl, J with CDI and (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).		D.1.72	1.76	417
6-tosyl-1-(2-(3,3,3-trifluoropropylsulfonyl)-2,6-diazabicyclo[3.2.1]octan-6-yl)-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazine (prepared using K from benzyl 2,6-diazabicyclo[3.2.1]octane-6-carboxylate (Pharmabridge) and 3,3,3-trifluoropropane-1-sulfonyl chloride (Matrix), Y with Pd(OH) ₂ , J with CDI and (5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (Example #5, Step C) with DIEA, OO).		D.1.73	1.91	429

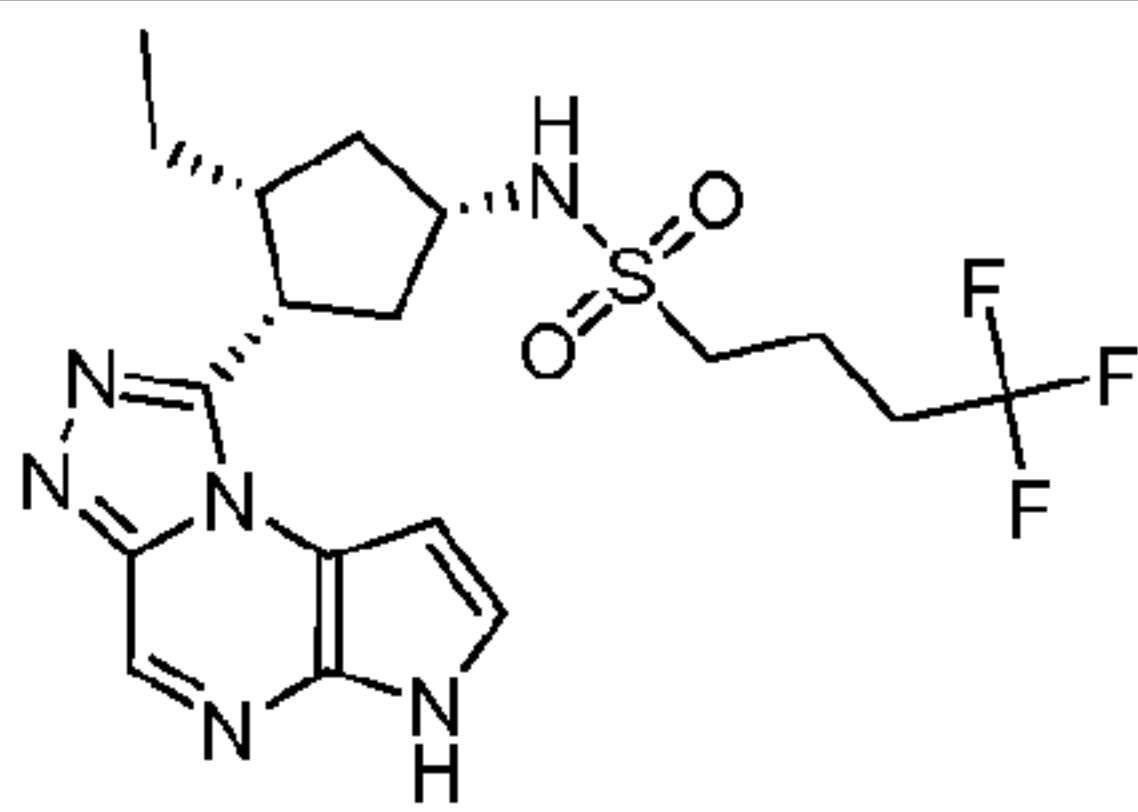
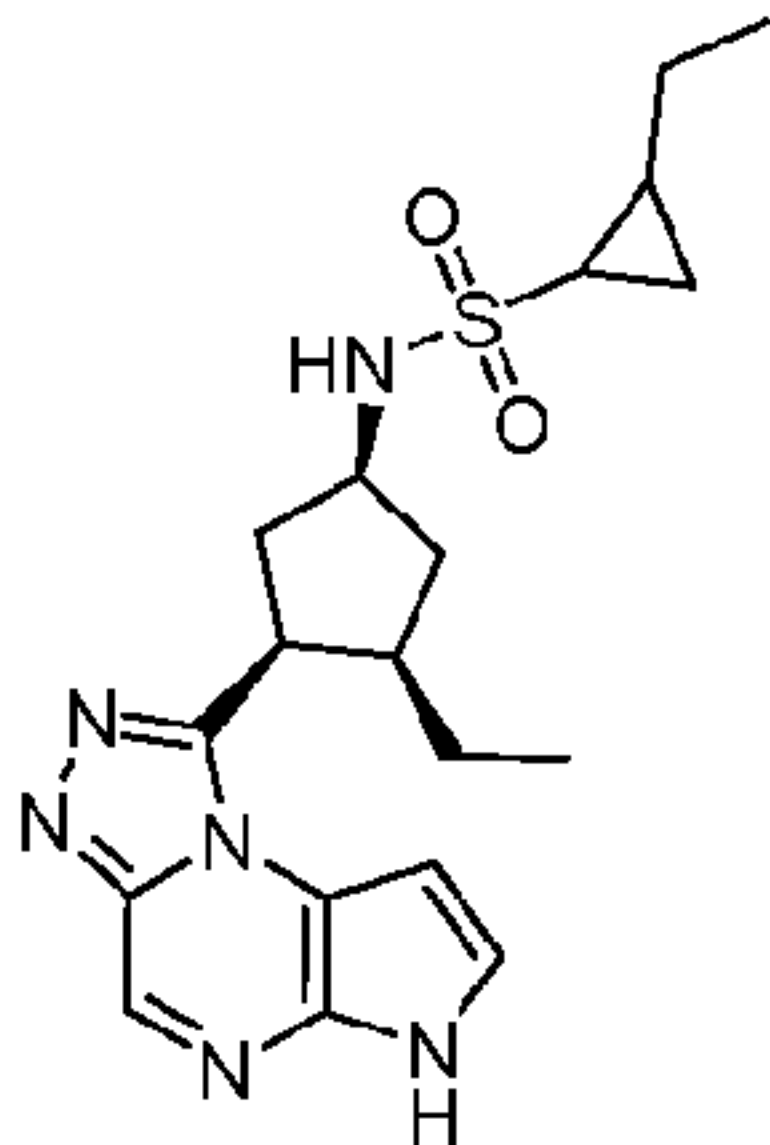
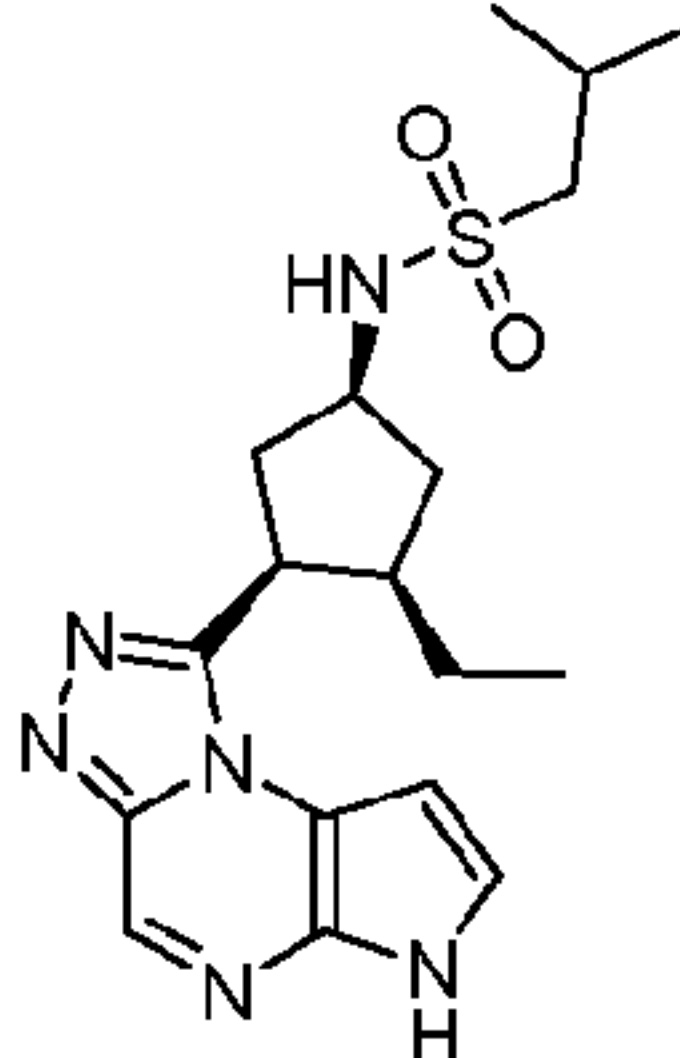
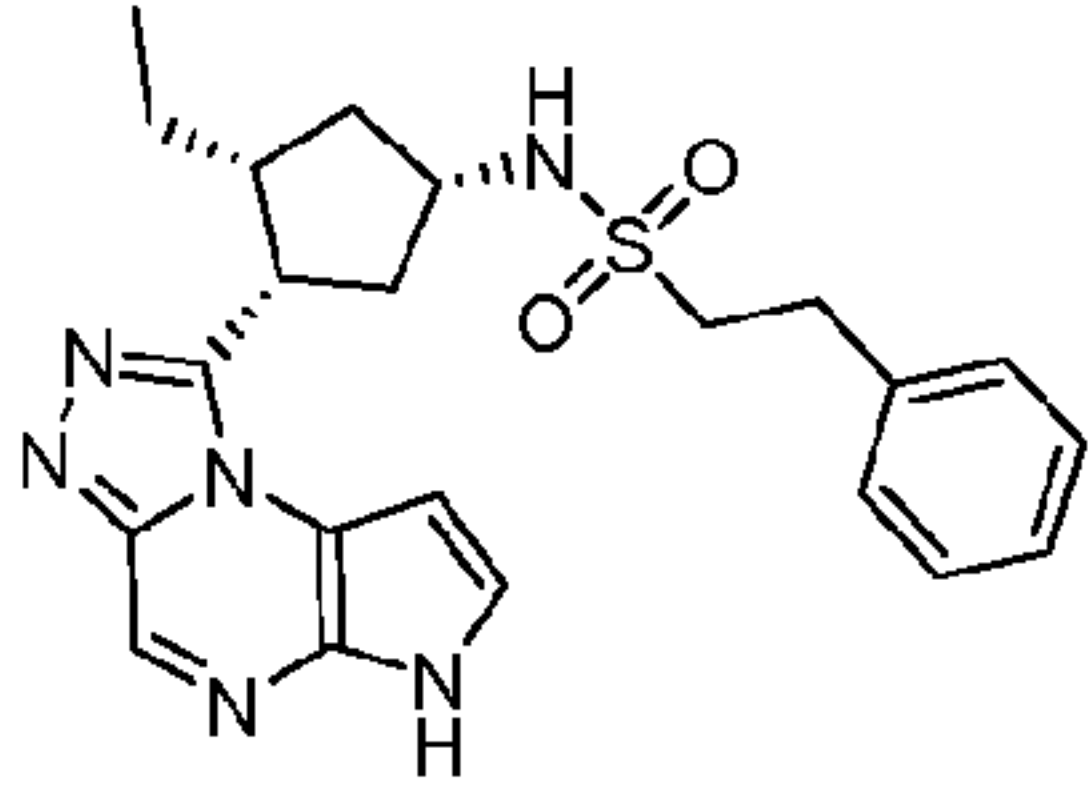
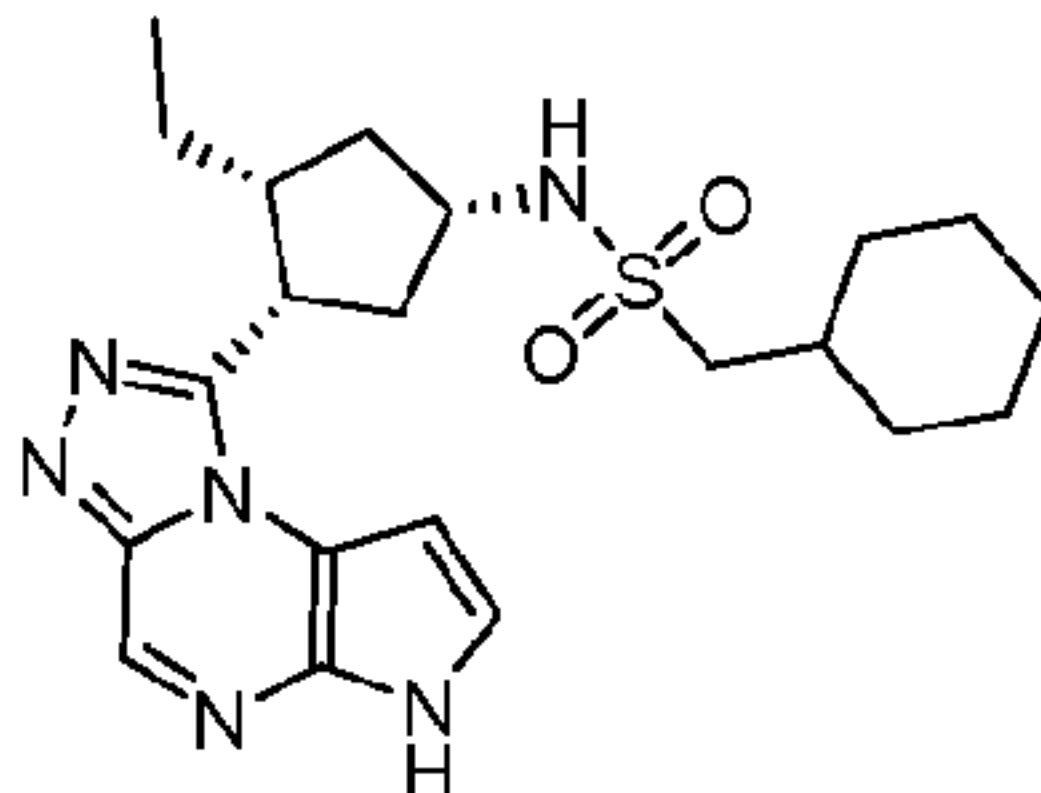
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((3 <i>R</i> ,5 <i>R</i>)-1-ethyl-5-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)pyrrolidin-3-yl)cyclopropanesulfonamide (prepared using K with (2 <i>R</i> ,4 <i>R</i>)-1- <i>tert</i> -butyl 2-methyl 4-aminopyrrolidine-1,2-dicarboxylate Hydrochloric Acid (Accsys Pharmatech Corp) and cyclopropylsulfonylchloride and TEA, Z with NaOH, A with Example #8 Step M, B , E with HCl, X with acetaldehyde.		D.1.74*	1.32	376
(<i>cis</i>)- <i>tert</i> -butyl 3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)pyrrolidine-1-carboxylate (prepared using SSS from <i>N</i> -benzyl-1-methoxy- <i>N</i> -((trimethylsilyl)methyl)methanamine and (<i>Z</i>)-ethyl pent-2-enoate (Lee, R. D.; Kassahun, K.; Abbott, F. S. J. of Pharm. Sci., 1989 , vol. 78, # 8 p. 667 – 671), TT , Y , M , A , B , E and K with cyclopropylmethanesulfonyl chloride and TEA		D.1.75	1.66	375
<i>N</i> -(4-(3-tosyl-3 <i>H</i> -dipyrrolo[1,2- <i>a</i> :2',3'- <i>e</i>]pyrazin-8-yl)bicyclo[2.2.2]octan-1-yl)cyclopropanesulfonamide (prepared using III from 5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazine-2-carbaldehyde (Preparation #12: step B) and diethyl 2-(4-(cyclopropanesulfonamido)bicyclo[2.2.2]octan-1-yl)-2-oxoethylphosphonate (Preparation #24), W , T with Lawesson's reagent).		D.1.76	1.97	385

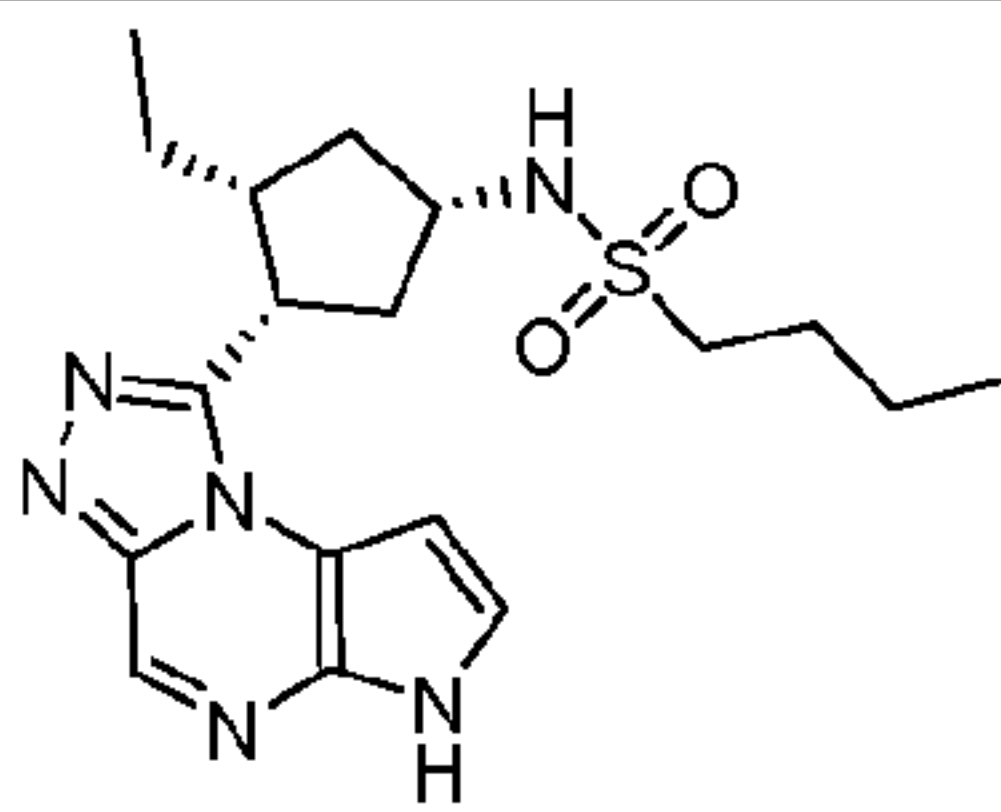
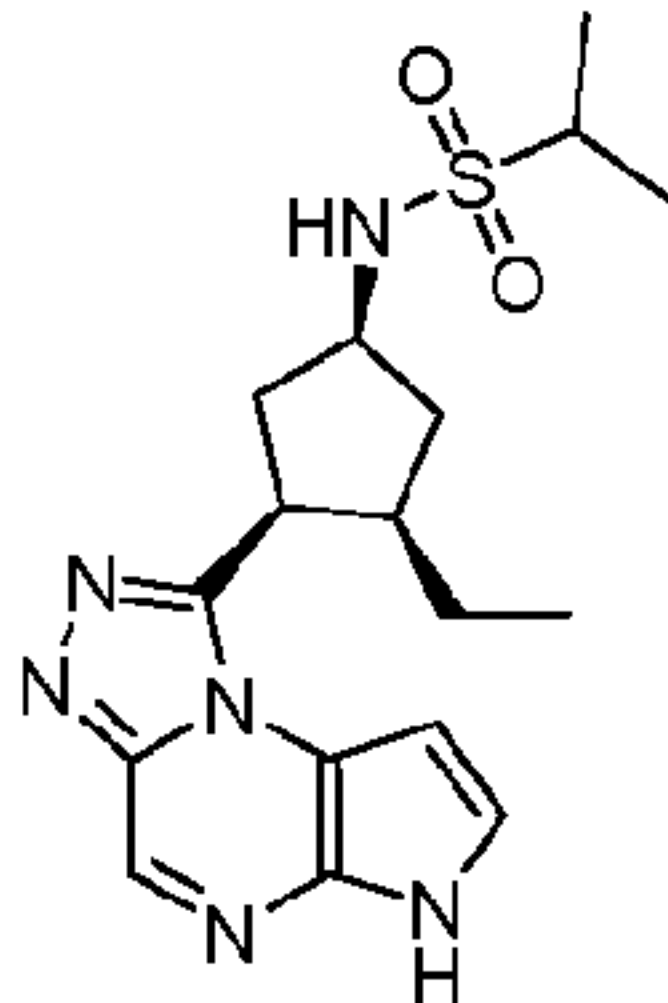
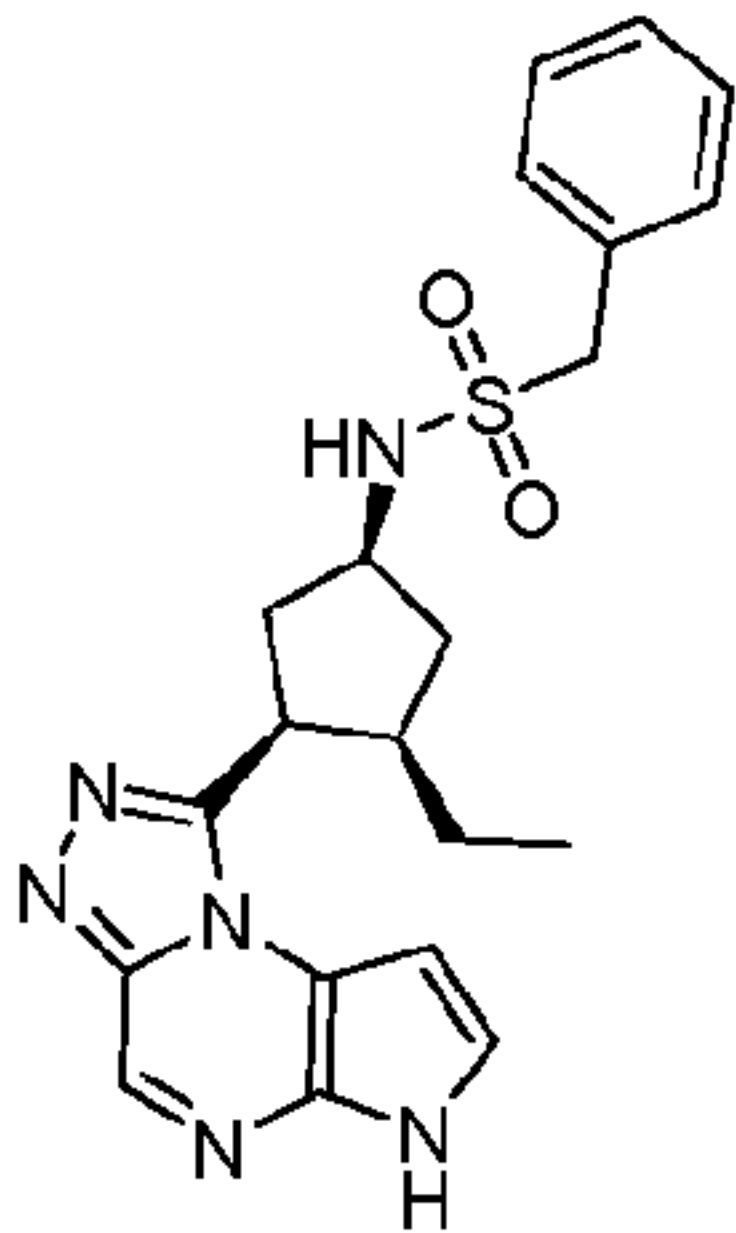
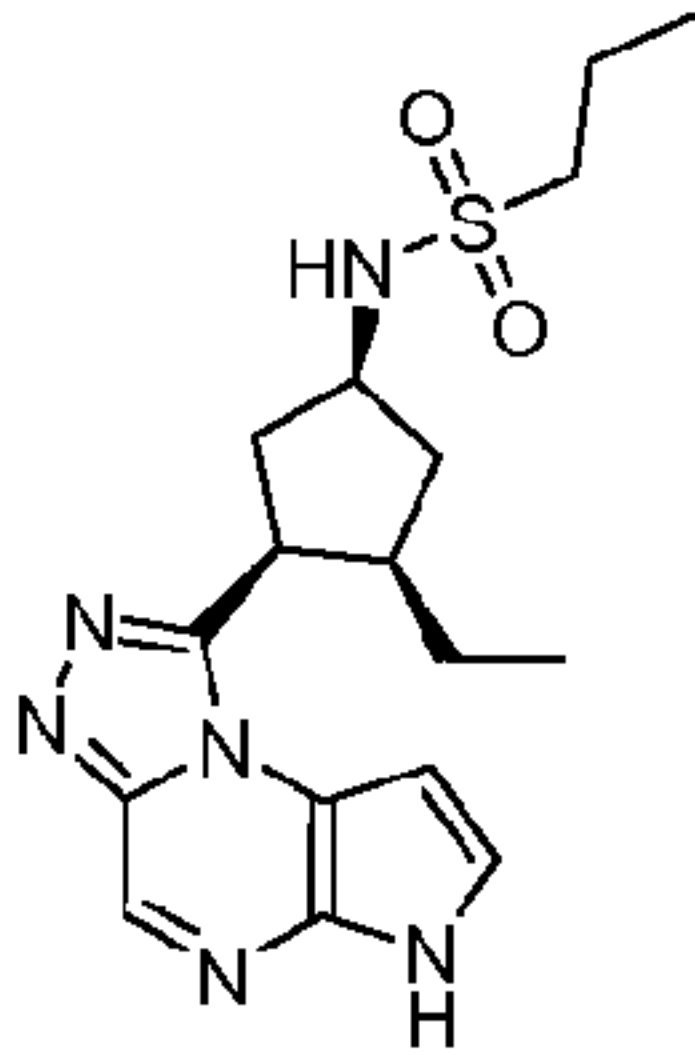
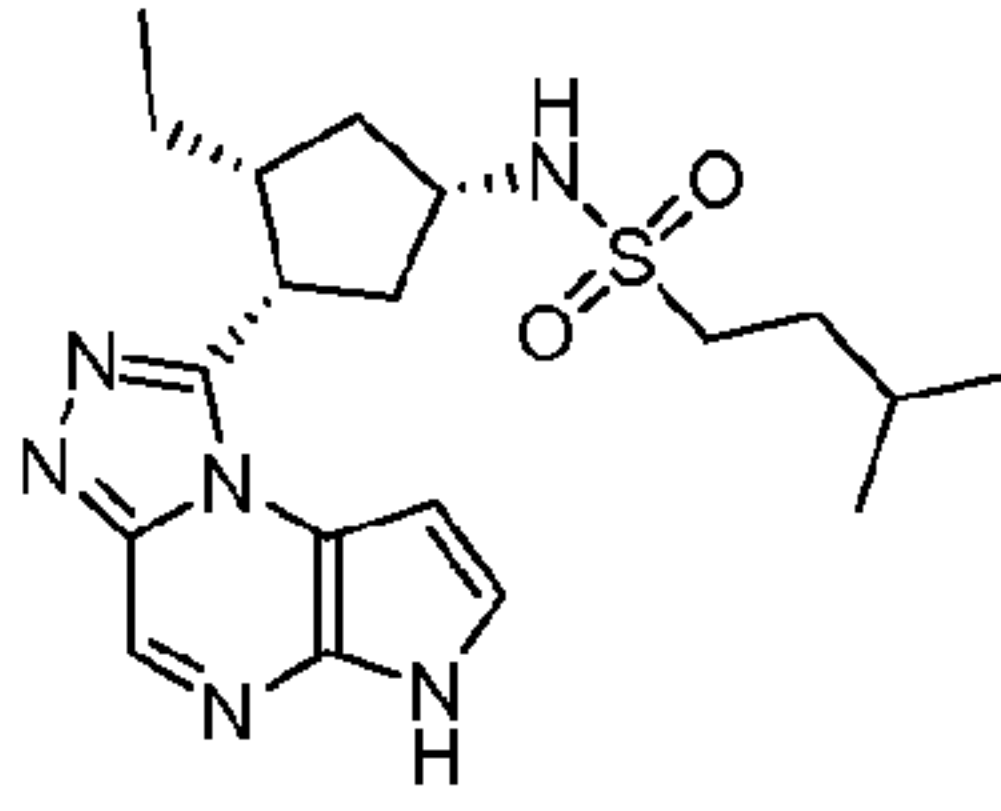
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
1-methyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)cyclopentyl)cyclopropane-1-sulfonamide (prepared from 5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (WO2009152133) and (1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-acetamido-2-methylcyclopentanecarboxylic acid [prepared from ethyl 4-amino-2-methylcyclopentanecarboxylate (WO2009152133) using G , AA [Table 2, Method 3, R _t = 6.1 min, or = ND], and Z] using H , OO , BB , and K from Preparation #6 and TEA)		D.1.77*	1.87 (a)	374
3,3-difluoro- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)cyclopentyl)azetidine-1-sulfonamide (prepared from 5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (WO2009152133) and (1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-acetamido-2-methylcyclopentanecarboxylic acid [prepared from ethyl 4-amino-2-methylcyclopentanecarboxylate (WO2009152133) using G , AA [Table 2, Method 3, R _t = 6.1 min, or = ND], and Z] using H , OO , BB , ZZ and AAA with 3,3-difluoroazetidine hydrochloride and TEA)		D.1.78*	1.99 (a)	411

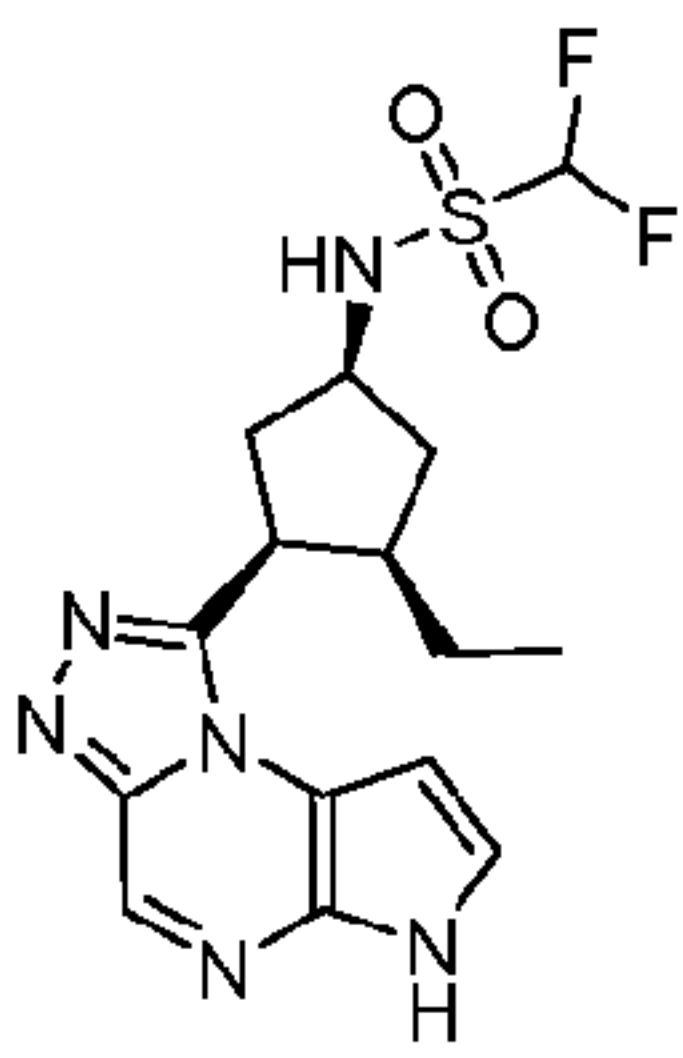
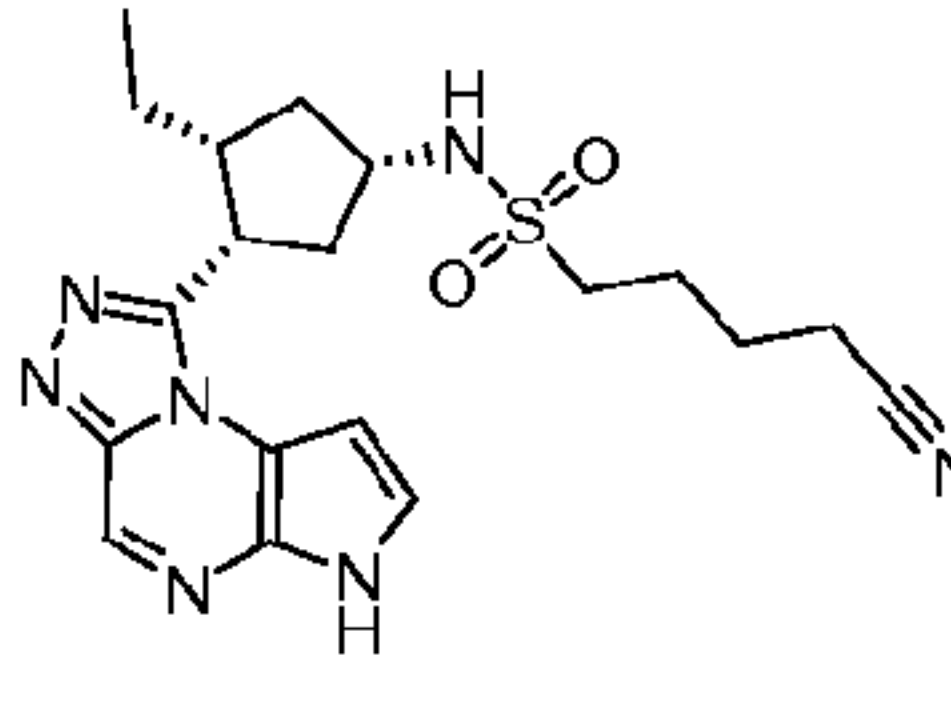
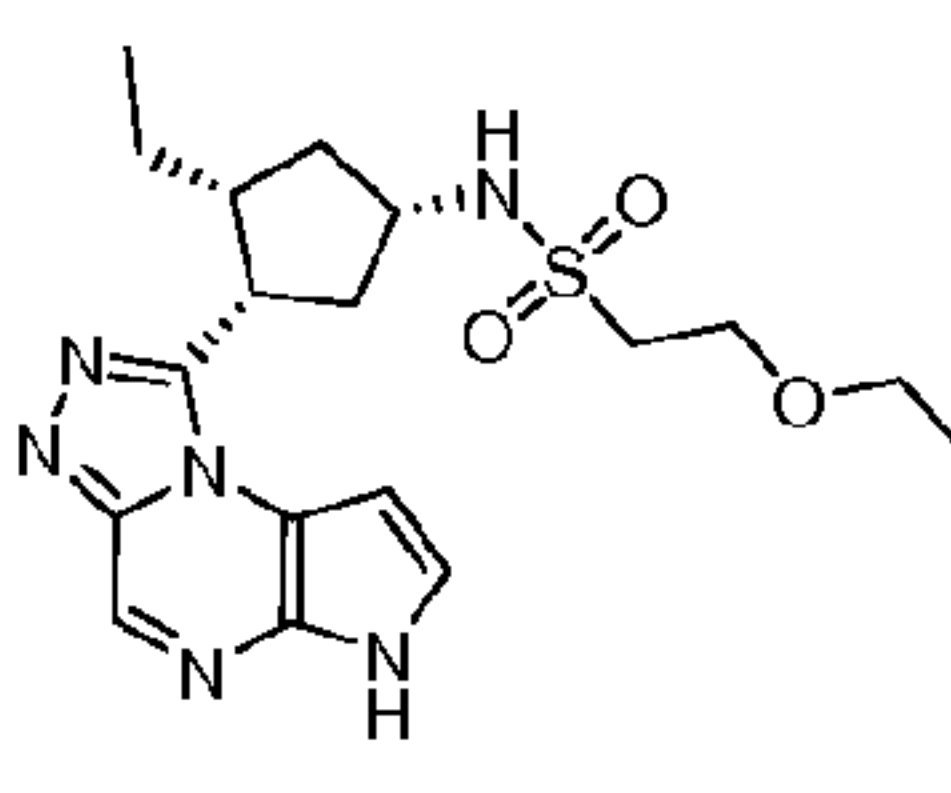
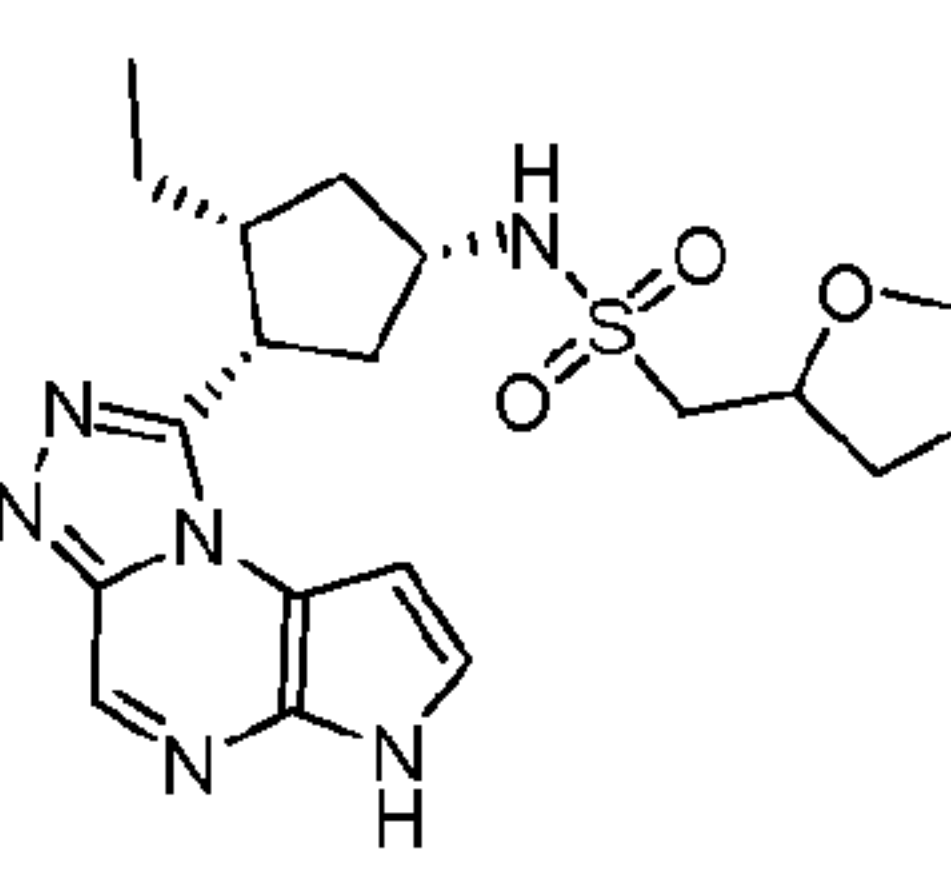
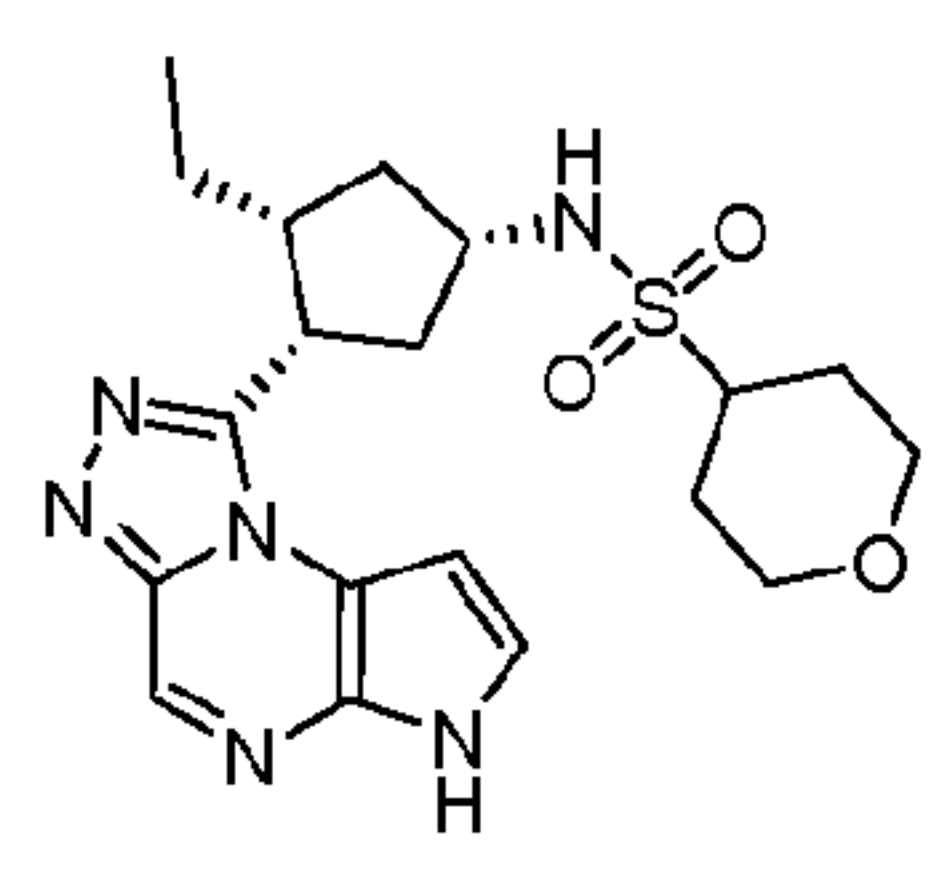
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
3,3,3-trifluoro- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide (prepared from 5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (WO2009152133) and (1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-acetamido-2-methylcyclopentanecarboxylic acid [prepared from ethyl 4-amino-2-methylcyclopentanecarboxylate (WO2009152133) using G , AA [Table 2, Method 3, R _t = 6.1 min, or = ND], and Z using H , OO , BB , and K from 3,3,3-trifluoro-propane-1-sulfonyl chloride [Matrix]and TEA)		D.1.79*	2.00 (a)	416
3,3-difluoro- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)cyclopentyl)pyrrolidine-1-sulfonamide (prepared from 5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (WO2009152133) and (1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-acetamido-2-methylcyclopentanecarboxylic acid [prepared from ethyl 4-amino-2-methylcyclopentanecarboxylate (WO2009152133) using G , AA [Table 2, Method 3, R _t = 6.1 min, or = ND], and Z] using H , OO , BB , ZZ and AAA with 3,3-difluoropyrrolidine hydrochloride and TEA)		D.1.80*	2.01 (a)	425

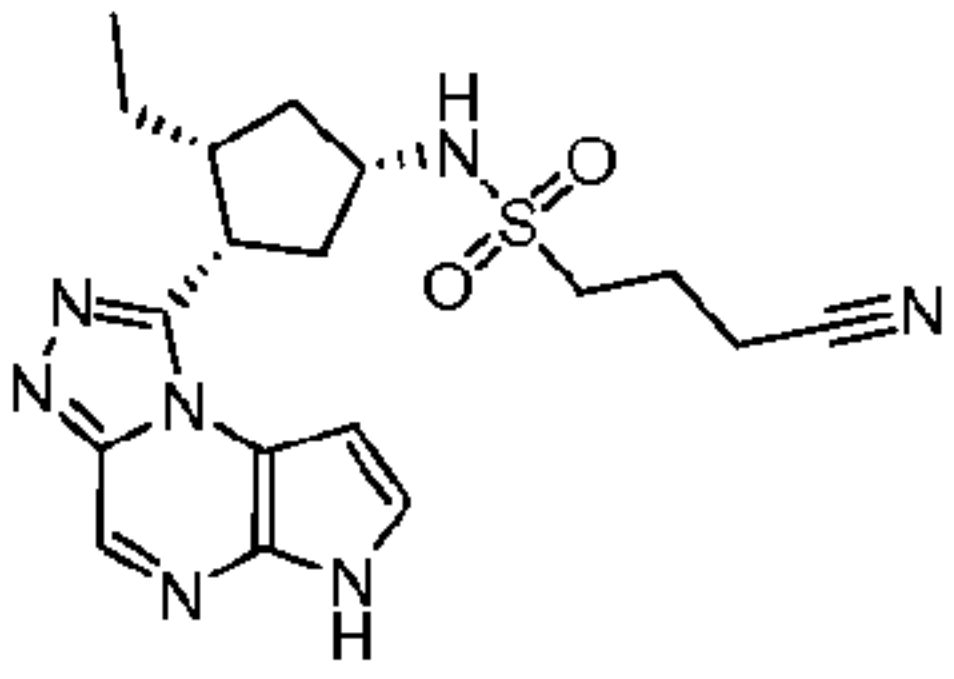
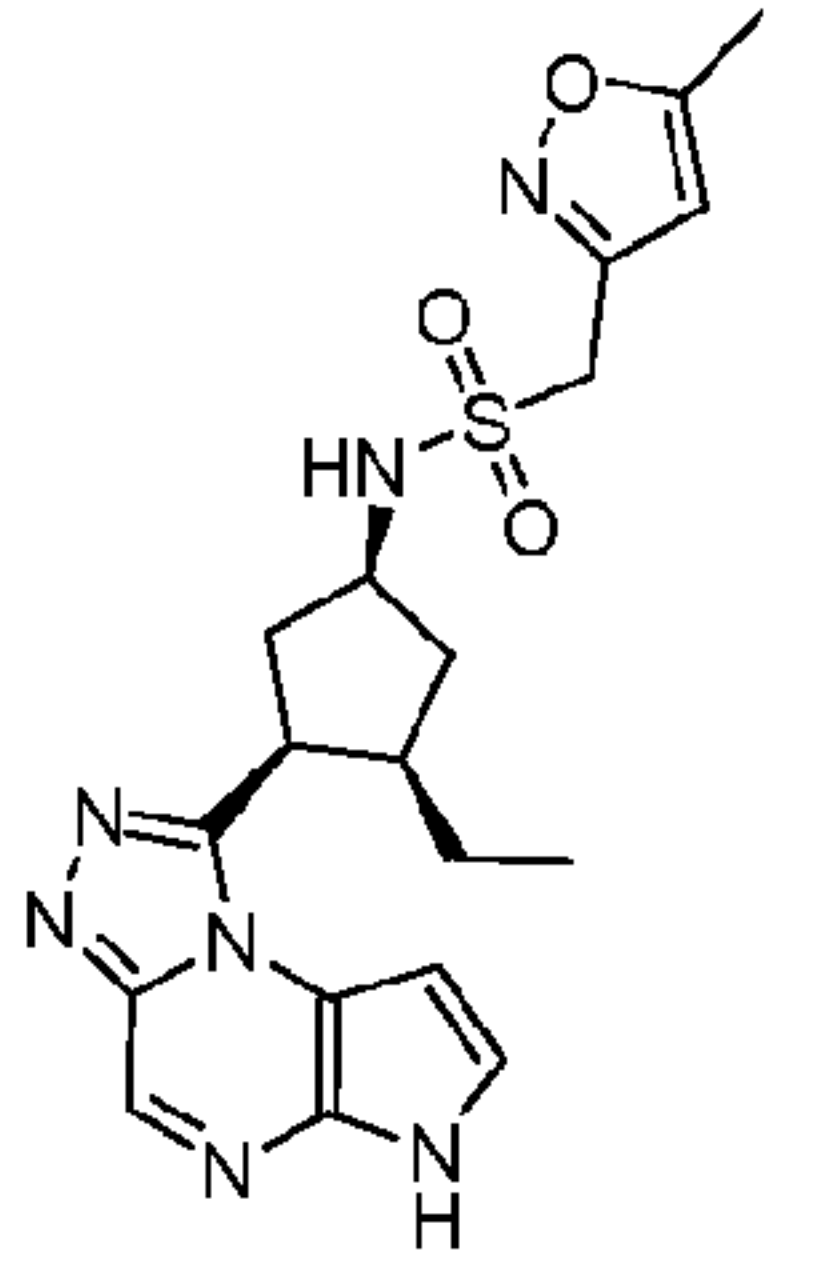
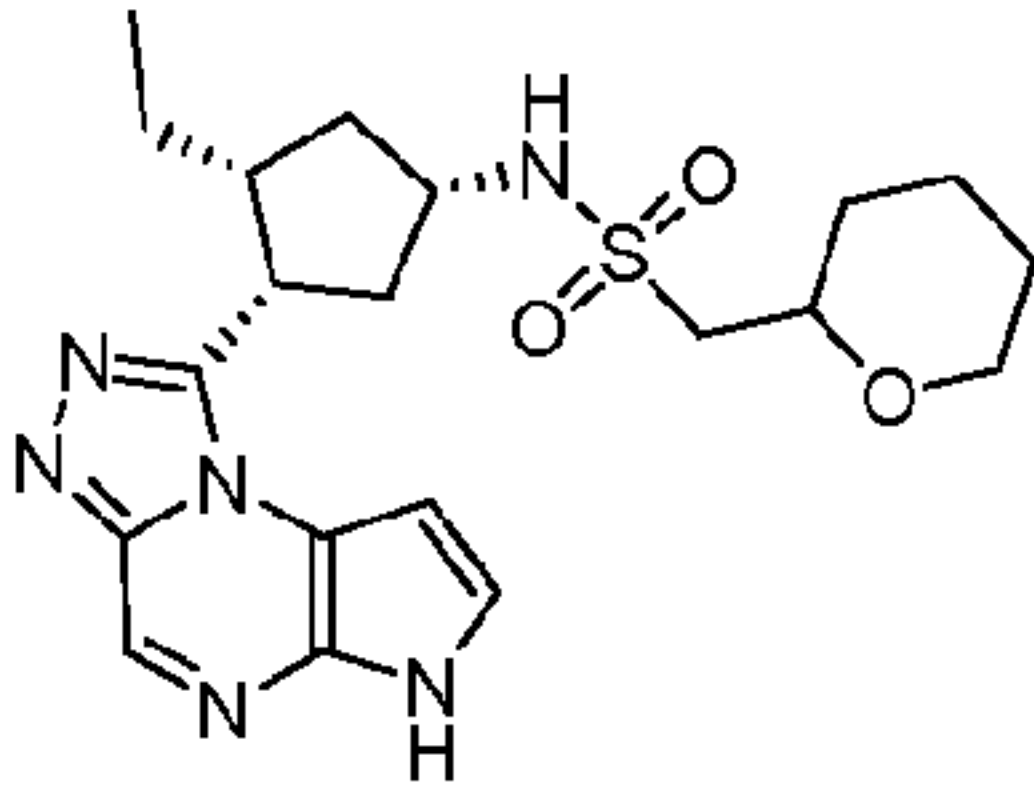
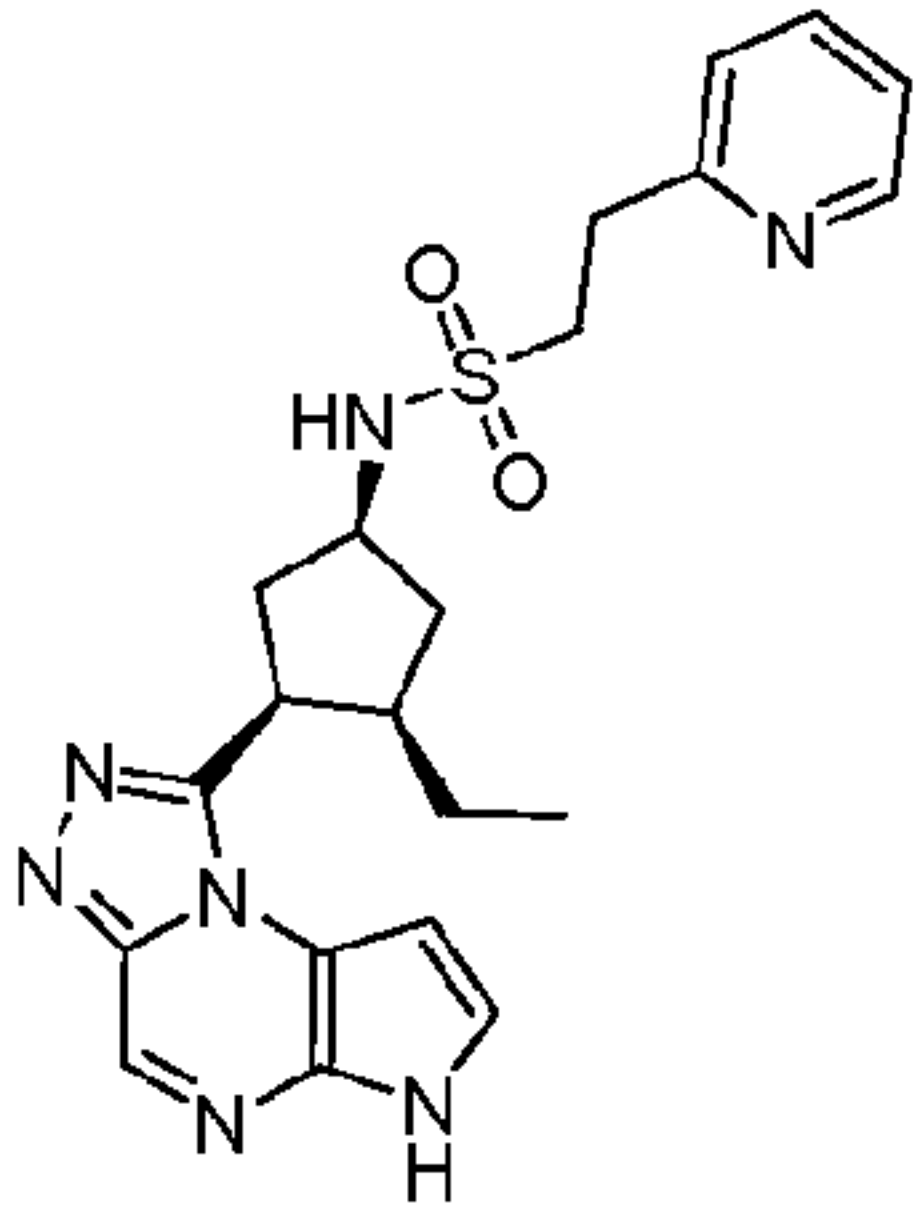
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
(<i>R</i>)- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)cyclopentyl)-2-(trifluoromethyl)pyrrolidine-1-sulfonamide sulfonamide (Preparation #AAA.1)		D.1.81*	2.16 (a)	457
1-ethyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)cyclopropane-1-sulfonamide (prepared from Example #8 Step M and Preparation #EEE.1 using K and TEA)		D.1.82*	1.90 (a)	403
1-ethyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -imidazo[1,5- <i>a</i>]pyrrolo[2,3- <i>e</i>]pyrazin-1-yl)cyclopentyl)cyclopropane-1-sulfonamide (prepared from 5-tosyl-5 <i>H</i> -pyrrolo[2,3- <i>b</i>]pyrazin-2-yl)methanamine hydrochloride (WO2009152133) and (1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)-4-acetamido-2-methylcyclopentanecarboxylic acid [prepared from ethyl 4-amino-2-methylcyclopentanecarboxylate (WO2009152133) using G , AA [Table 2, Method 3, R _t = 6.1 min, or = ND], and Z] using H , OO , BB , and K using Preparation #EEE.1 and TEA)		D.1.83*	1.96 (a)	388
1-butyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)cyclopropane-1-sulfonamide (prepared from Example #8 Step M and 1-butylcyclopropane-1-sulfonyl chloride [prepared from Preparation #6 Step A and 1,1,1-trifluoro-2-iodoethane, KHMDS using KKK , JJJ , and EEE with TEA] using K and TEA)		D.1.84*	2.13 (a)	431

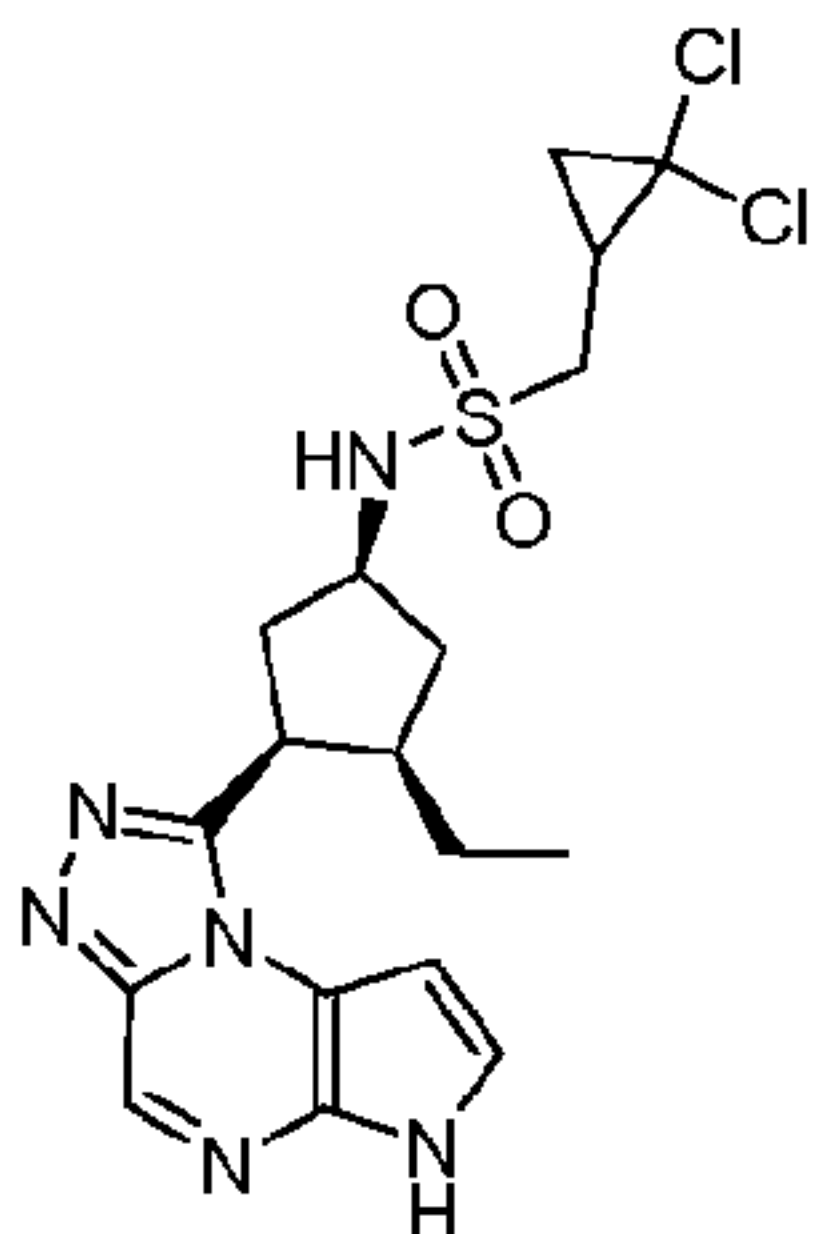
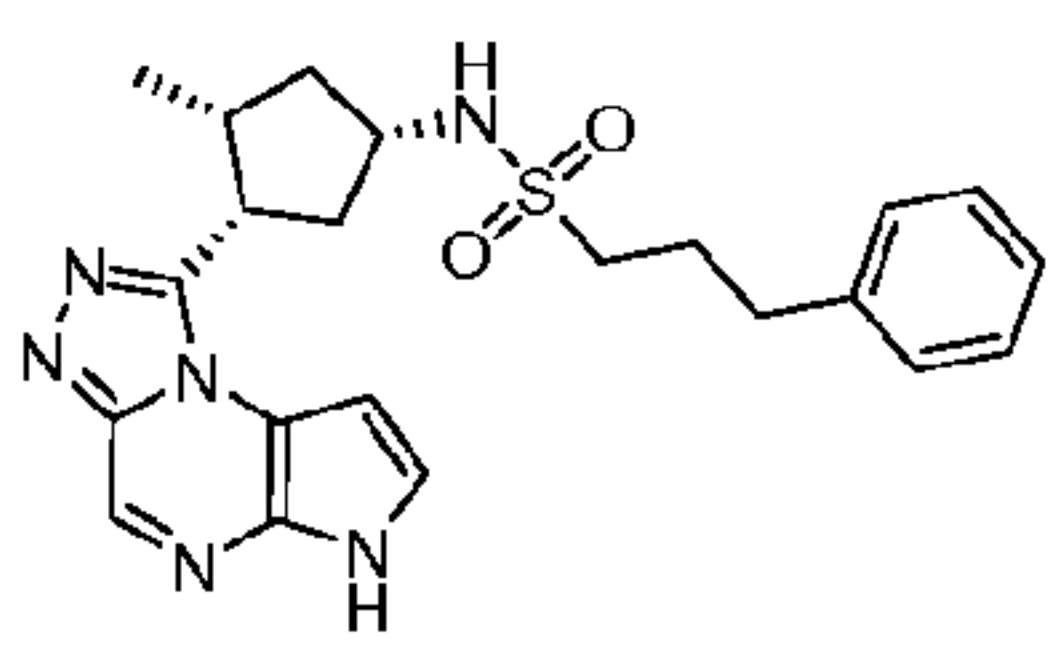
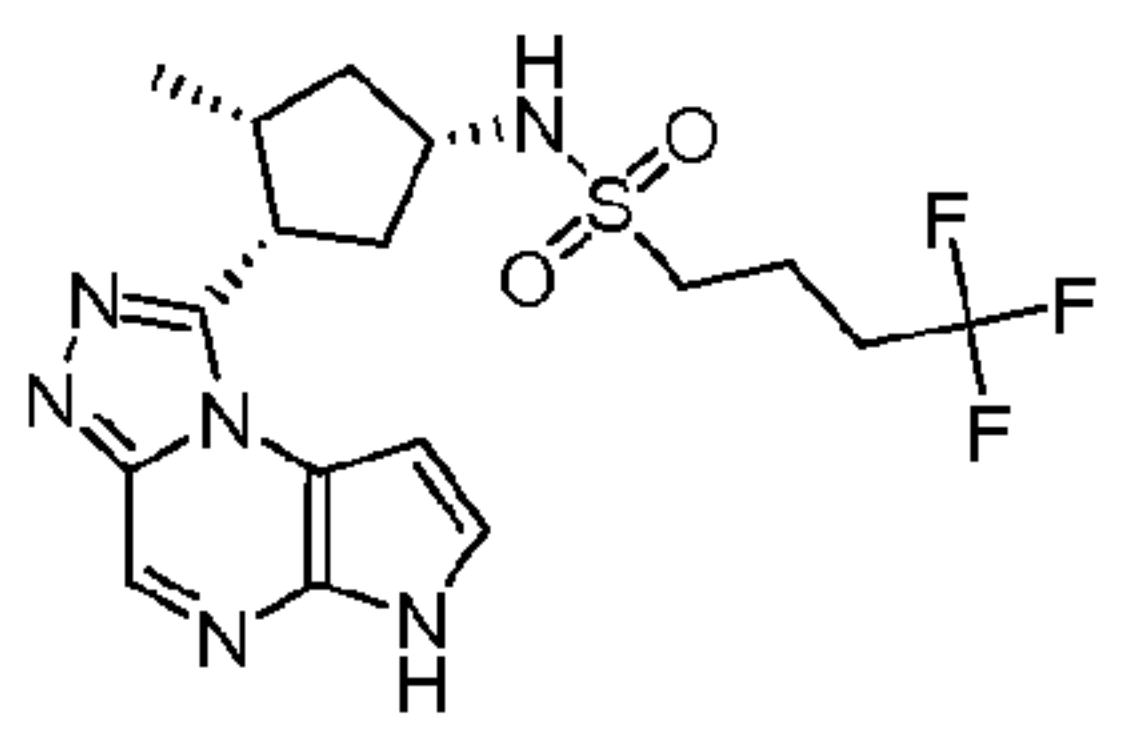
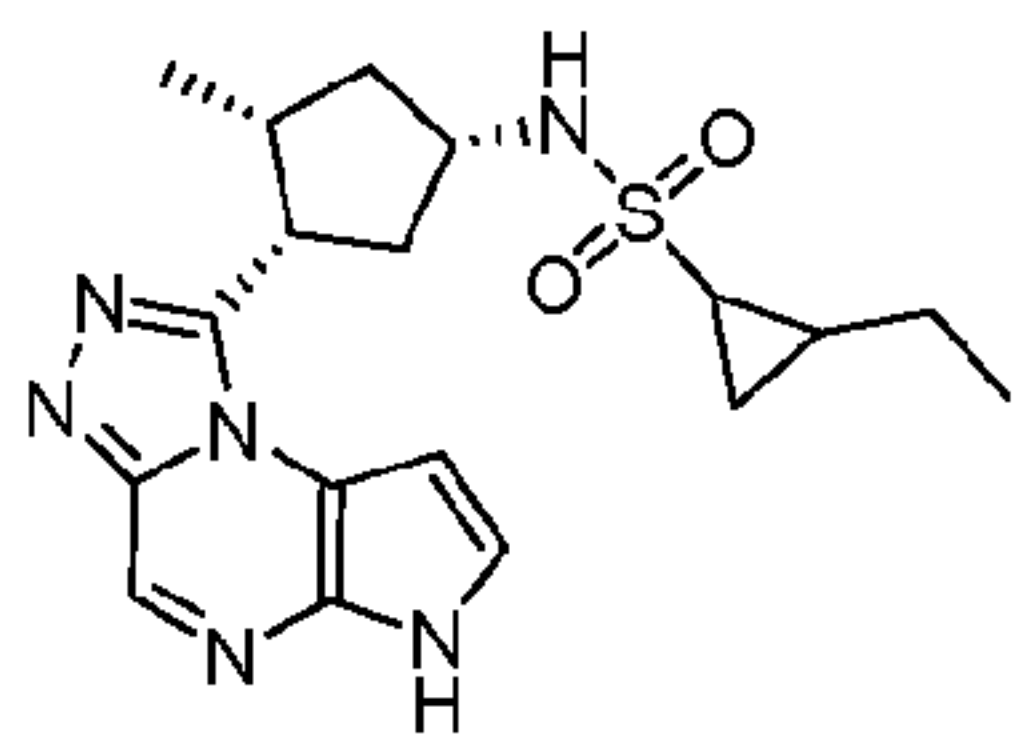
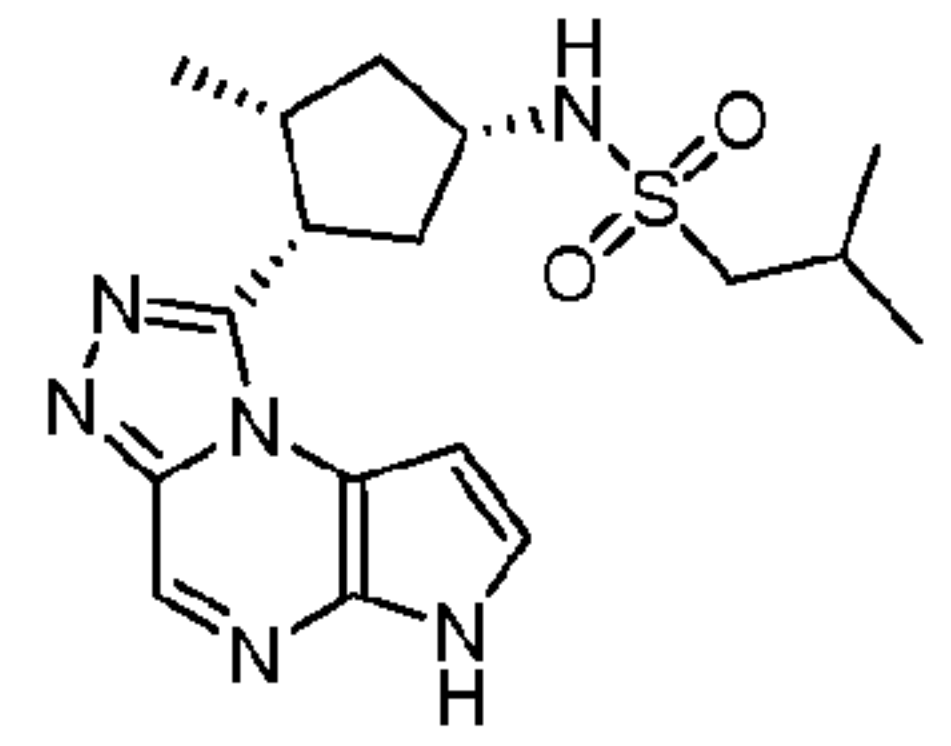
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosylimidazo[4,5- <i>d</i>]pyrrolo[2,3- <i>b</i>]pyridin-1(6 <i>H</i>)-yl)cyclopentyl)cyclopropanesulfonamide (Preparation #DDD.1)		D.1.85*	1.65 (a)	360
<i>N</i> -((1 <i>S</i> ,3 <i>S</i> ,4 <i>R</i>)-3-(2-cyclopropyl-6-tosylimidazo[4,5- <i>d</i>]pyrrolo[2,3- <i>b</i>]pyridin-1(6 <i>H</i>)-yl)-4-methylcyclopentyl)cyclopropanesulfonamide (prepared from Preparation #27 and Preparation #OOO.1 using L and DIEA, K.1 with TsCl and NaH, BBB , H with cyclopropanecarboxylic acid, HATU, and TEA, and DDD with POCl ₃)		D.1.86*	1.74 (a)	400
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosylpyrrolo[2,3- <i>b</i>][1,2,3]triazolo[4,5- <i>d</i>]pyridin-1(6 <i>H</i>)-yl)cyclopentyl)cyclopropanesulfonamide (Preparation #SSSS.1)		D.1.87*	1.82 (a)	375
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)pentane-2-sulfonamide (prepared using K from Example #8 Step M and pentane-2-sulfonyl chloride)		D.1.88	1.88 (b)	405
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-3-phenylpropane-1-sulfonamide (prepared using K from Example #8 Step M and 3-phenylpropane-1-sulfonyl chloride)		D.1.89*	1.98 (b)	453

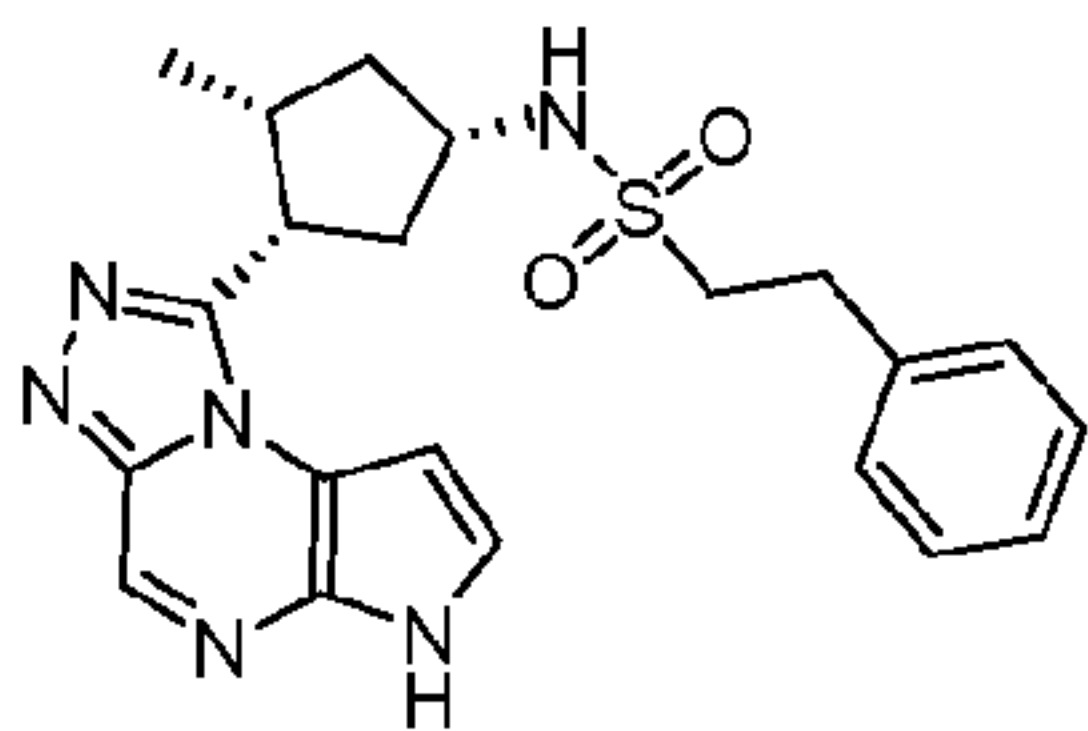
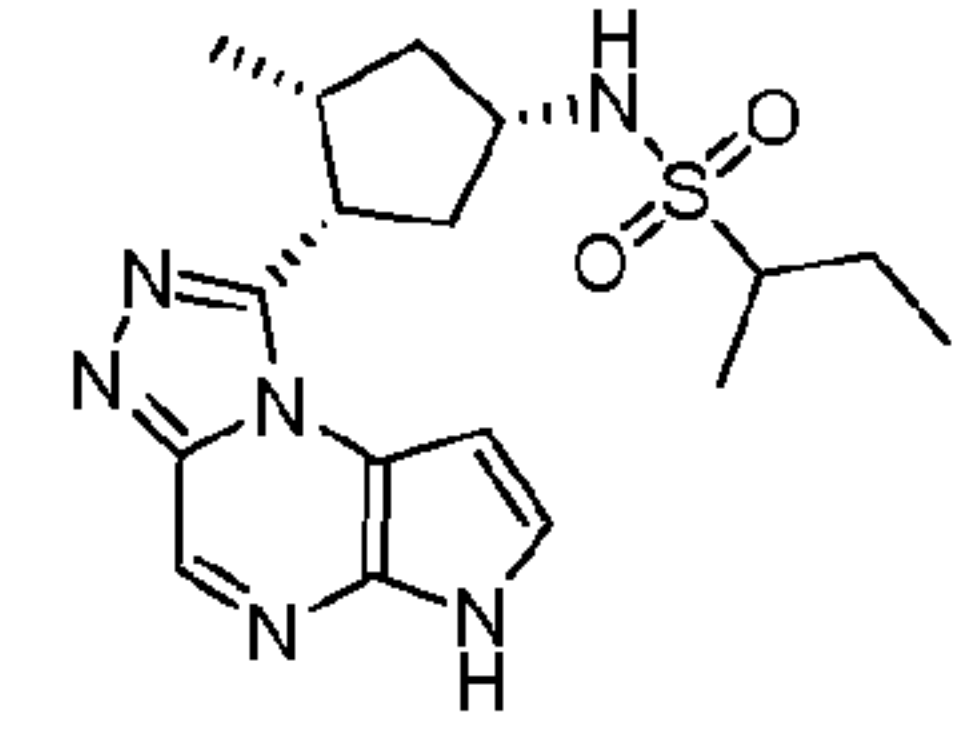
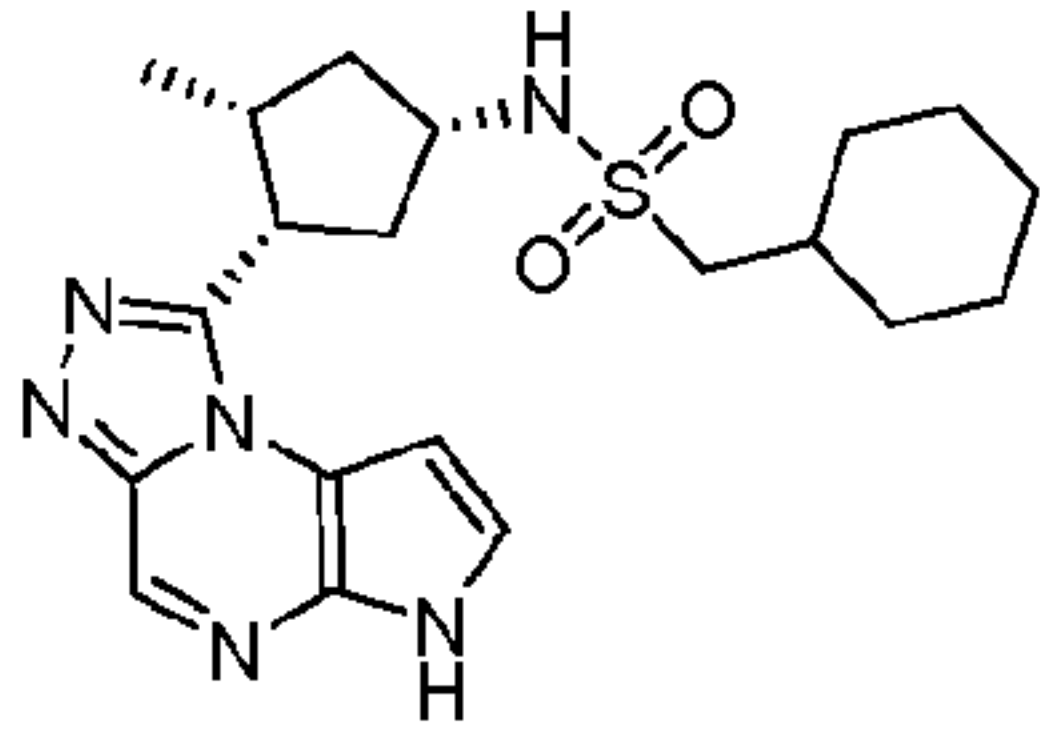
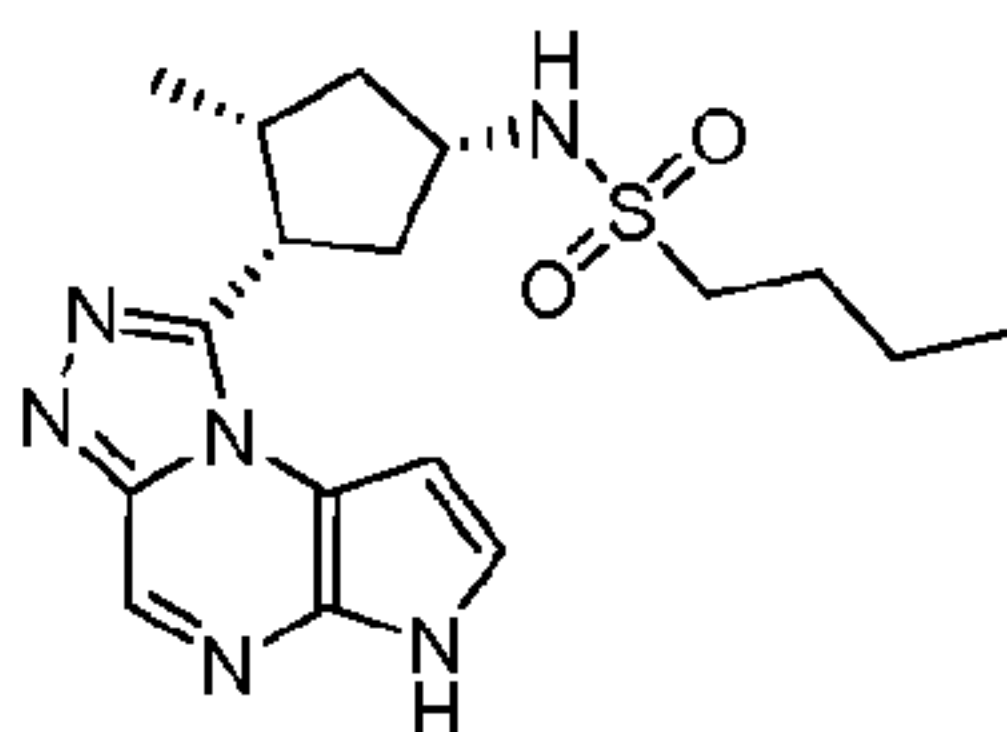
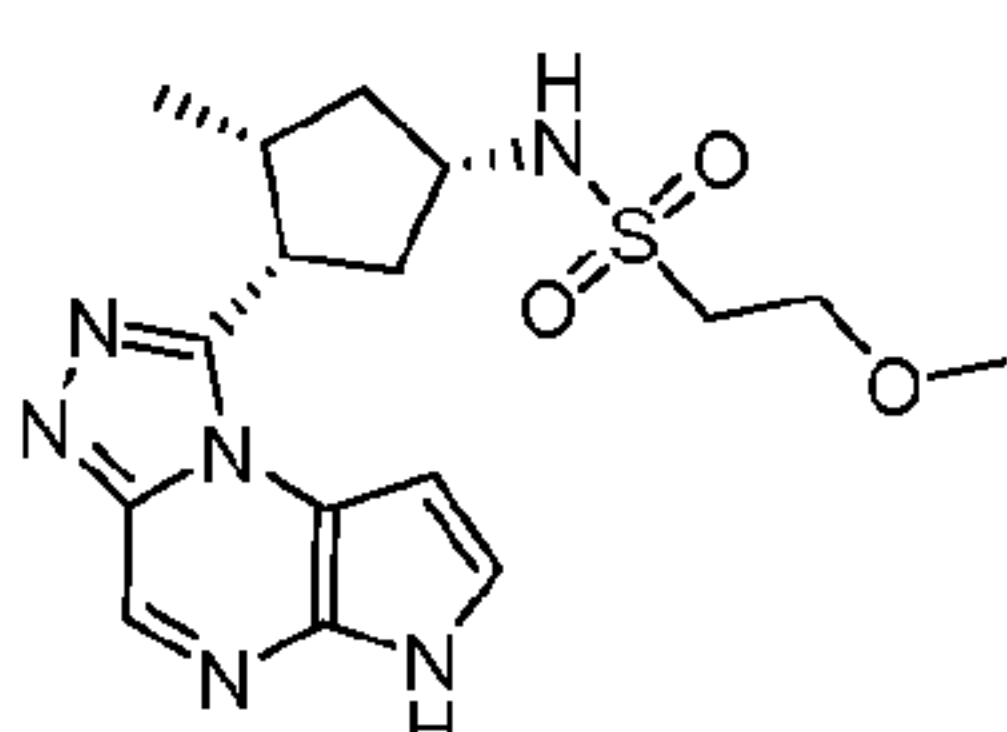
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-4,4,4-trifluorobutane-1-sulfonamide (prepared using K from Example #8 Step M and 4,4,4-trifluorobutane-1-sulfonyl chloride)		D.1.90*	1.85 (b)	445
2-ethyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)cyclopropane-1-sulfonamide (prepared using K from Example #8 Step M and 2-ethylcyclopropane-1-sulfonyl chloride)		D.1.91	1.81 (b)	403
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-methylpropane-1-sulfonamide (prepared using K from Example #8 Step M and 2-methylpropane-1-sulfonyl chloride)		D.1.92*	1.77 (b)	391
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-phenylethanesulfonamide (prepared using K from Example #8 Step M and 2-phenylethanesulfonyl chloride)		D.1.93*	1.92 (b)	439
1-cyclohexyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)methanesulfonamide (prepared using K from Example #8 Step M and cyclohexylmethanesulfonyl chloride)		D.1.94*	2.04 (b)	431

Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)butane-1-sulfonamide (prepared using K from Example #8 Step M and butane-1-sulfonyl chloride)		D.1.95*	1.78 (b)	391
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)propane-2-sulfonamide (prepared using K from Example #8 Step M and propane-2-sulfonyl chloride)		D.1.96*	1.61 (b)	377
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1-phenylmethanesulfonamide (prepared using K from Example #8 Step M and phenylmethanesulfonyl chloride)		D.1.97*	1.82 (b)	425
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide (prepared using K from Example #8 Step M and propane-1-sulfonyl chloride)		D.1.98*	1.64 (b)	377
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-3-methylbutane-1-sulfonamide (prepared using K from Example #8 Step M and 3-methylbutane-1-sulfonyl chloride)		D.1.99*	1.90 (b)	405

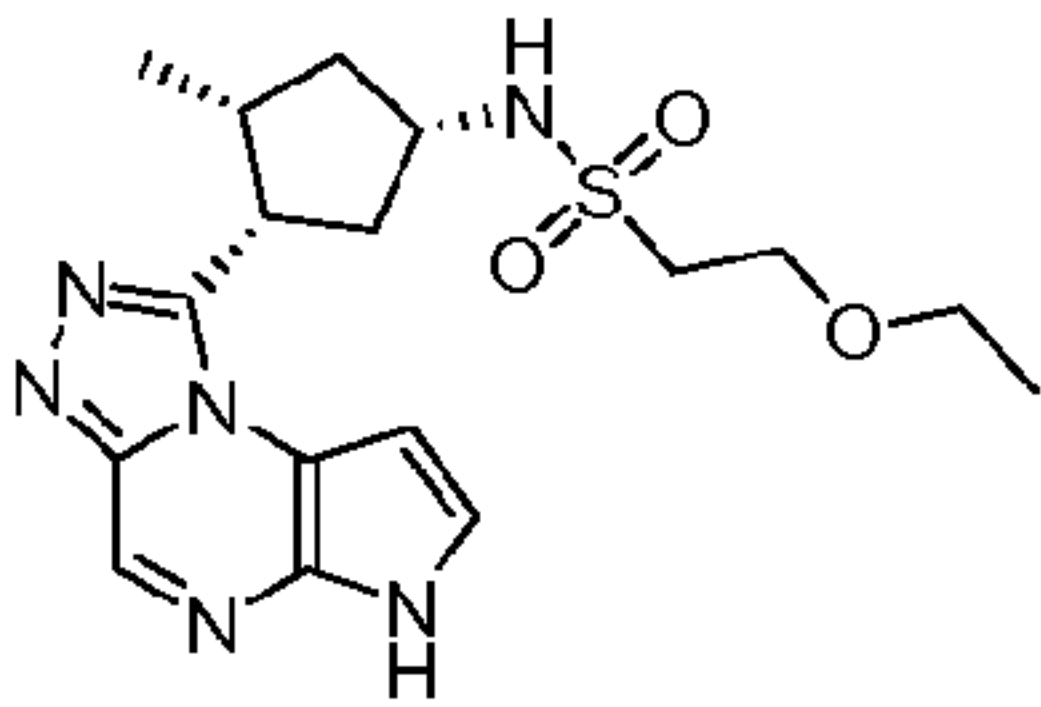
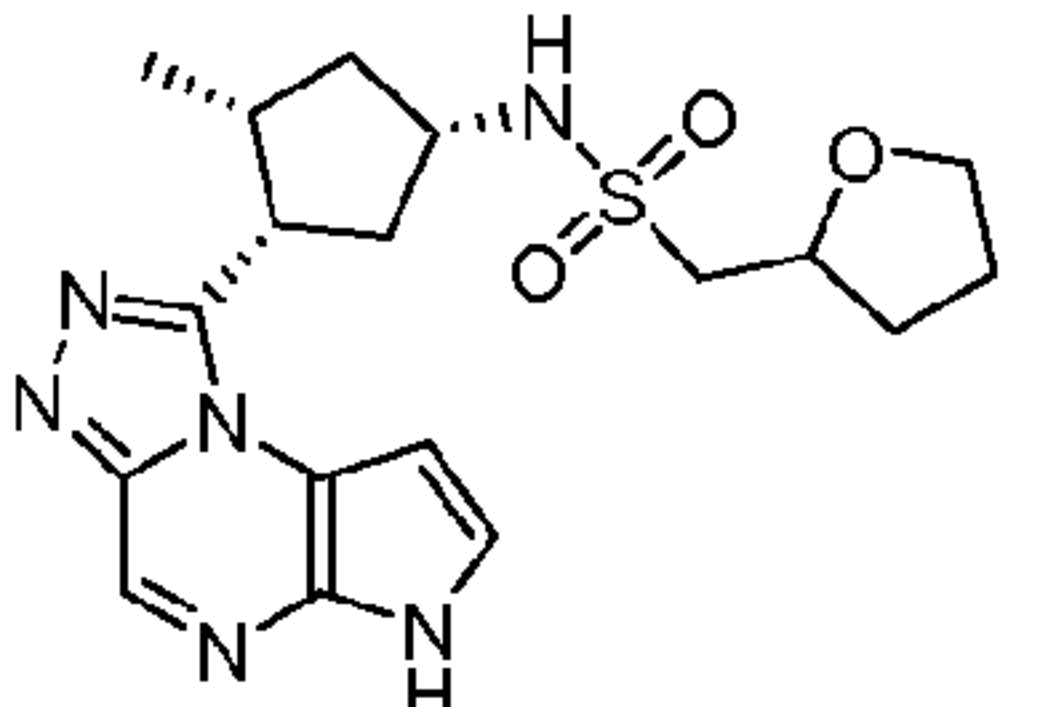
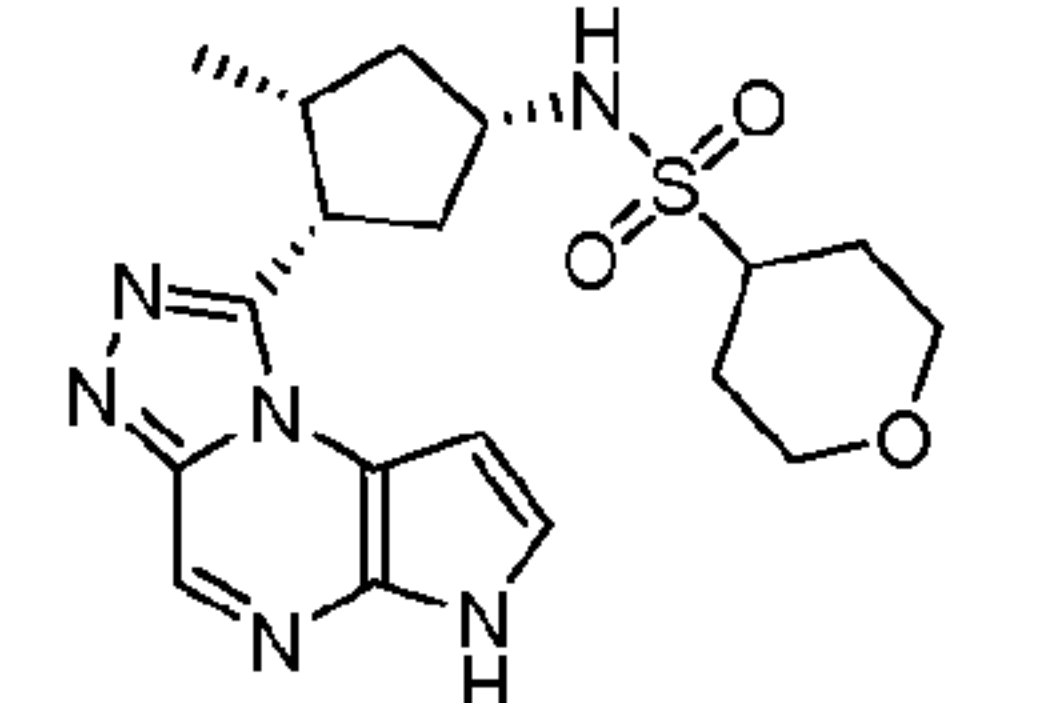
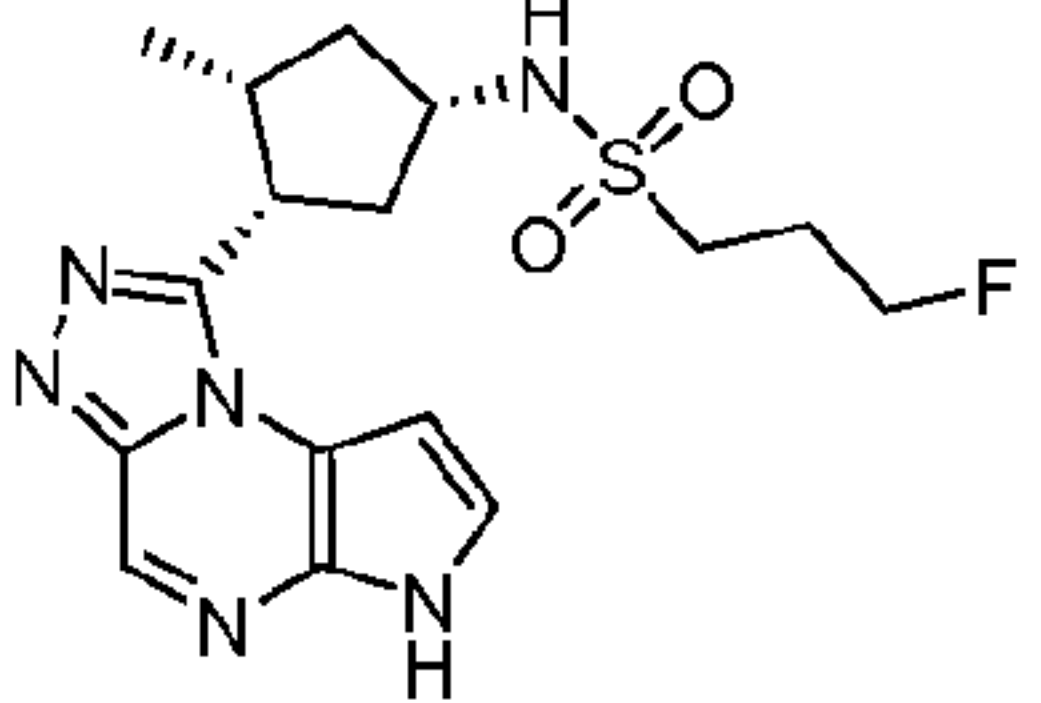
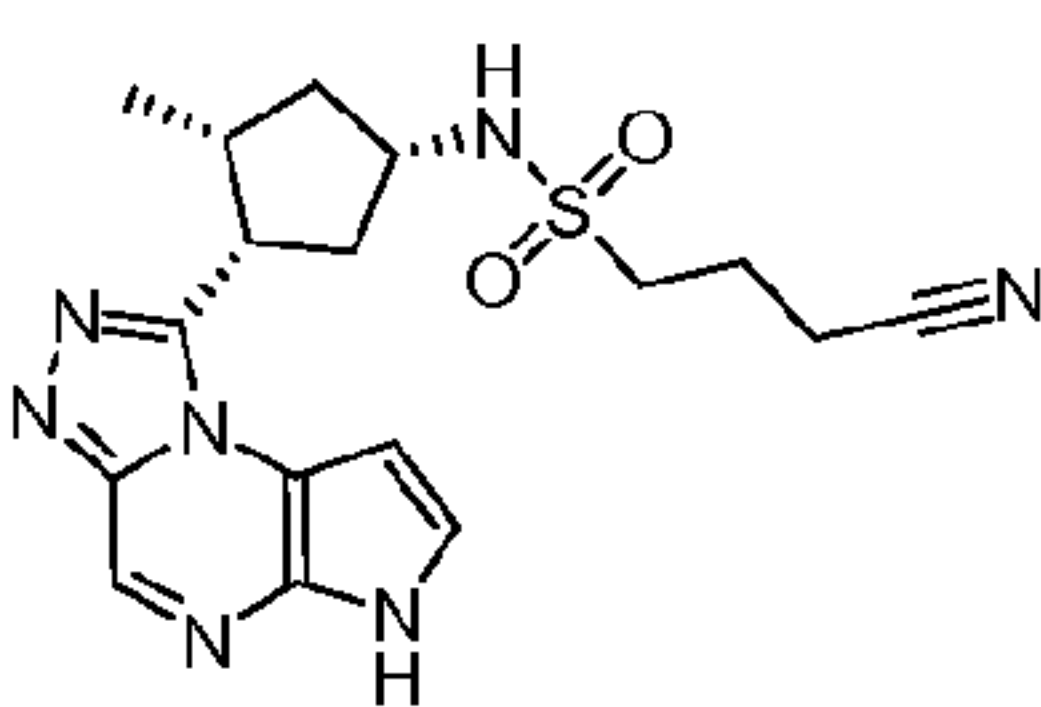
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1,1-difluoromethanesulfonamide (prepared using K from Example #8 Step M and difluoromethanesulfonyl chloride)		D.1.100*	1.75 (b)	385
4-cyano- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)butane-1-sulfonamide (prepared using K from Example #8 Step M and 4-cyanobutane-1-sulfonyl chloride)		D.1.101*	1.56 (b)	416
2-ethoxy- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)ethanesulfonamide (prepared using K from Example #8 Step M and 2-ethoxyethanesulfonyl chloride)		D.1.102*	1.62 (b)	407
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1-(tetrahydrofuran-2-yl)methanesulfonamide (prepared using K from Example #8 Step M and (tetrahydrofuran-2-yl)methanesulfonyl chloride)		D.1.103	1.58 (b)	419
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>II</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)tetrahydro-2 <i>H</i> -pyran-4-sulfonamide (prepared using K from Example #8 Step M and tetrahydro-2 <i>H</i> -pyran-4-sulfonyl chloride)		D.1.104*	1.50 (b)	419

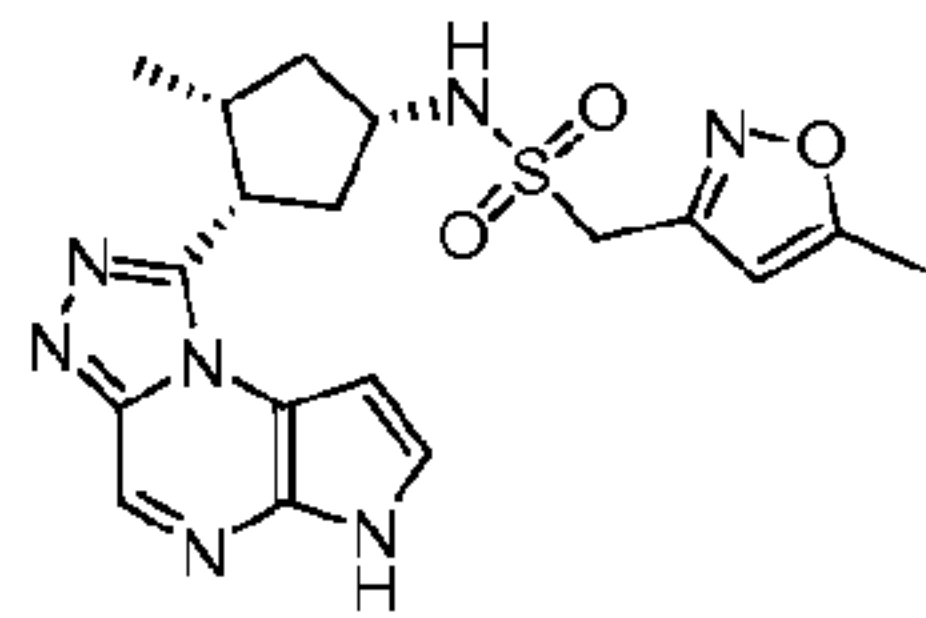
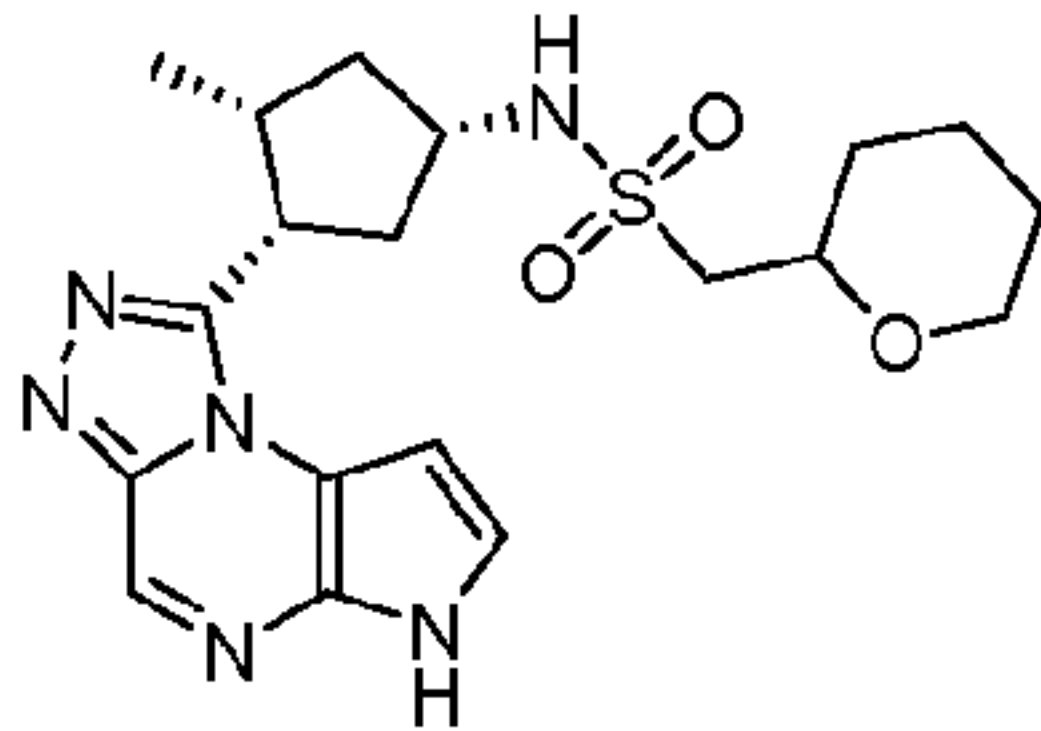
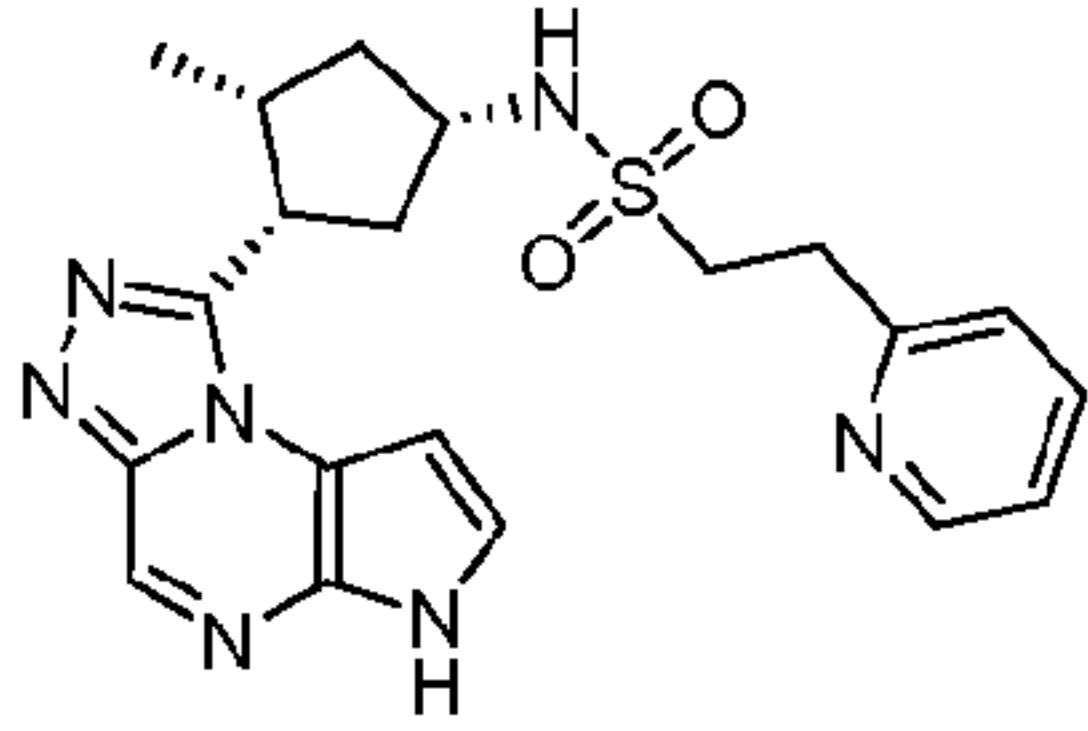
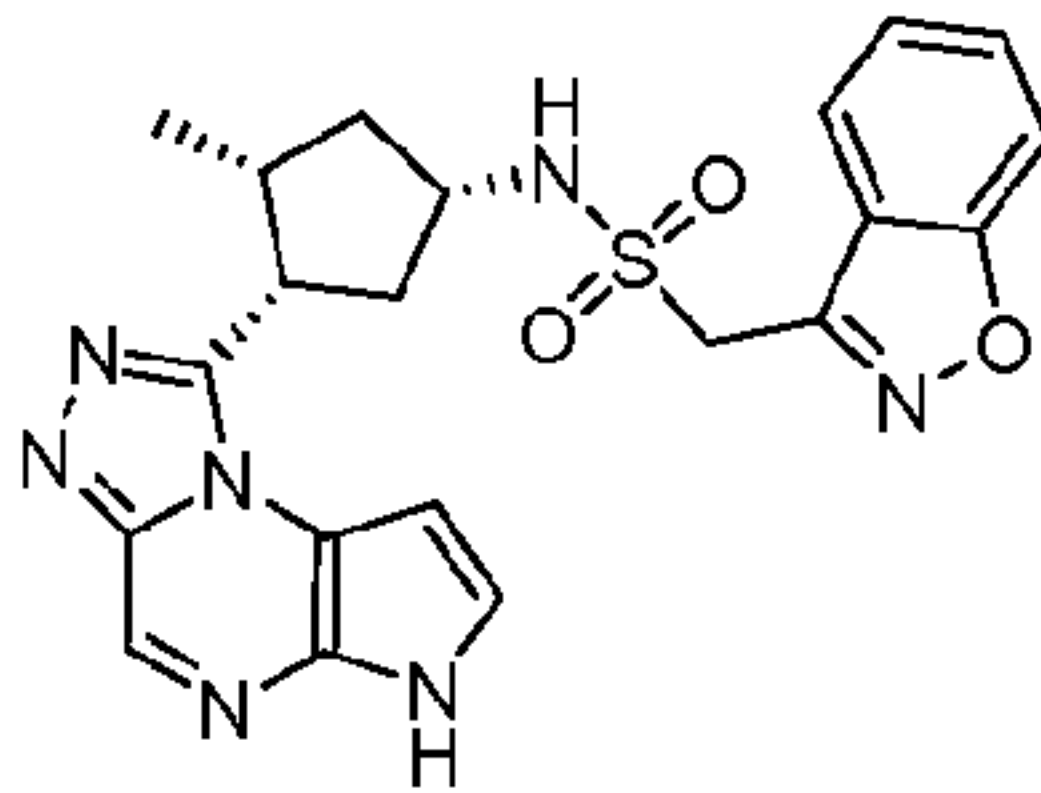
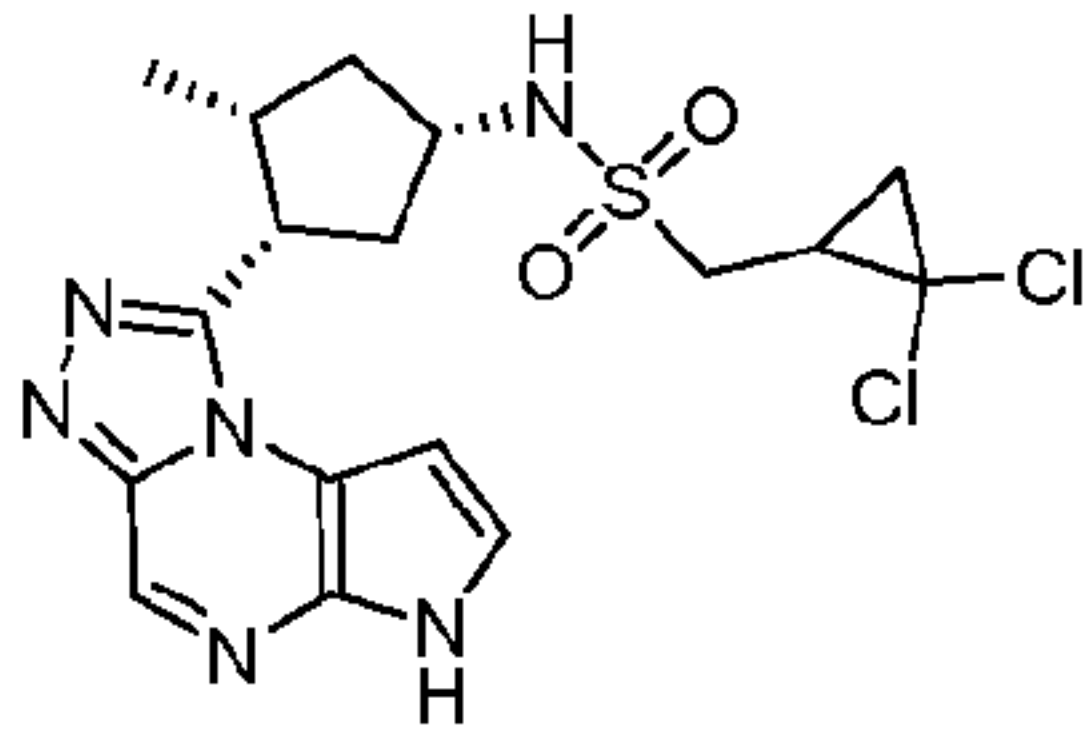
Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
3-cyano- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide (prepared using K from Example #8 Step M and 3-cyanopropane-1-sulfonyl chloride)		D.1.105*	1.51 (b)	402
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1-(5-methylisoxazol-3-yl)methanesulfonamide (prepared using K from Example #8 Step M and (5-methylisoxazol-3-yl)methanesulfonyl chloride)		D.1.106*	1.66 (b)	430
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)methanesulfonamide (prepared using K from Example #8 Step M and (tetrahydro-2 <i>H</i> -pyran-2-yl)methanesulfonyl chloride)		D.1.107	1.73 (b)	433
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-(pyridin-2-yl)ethanesulfonamide (prepared using K from Example #8 Step M and 2-(pyridin-2-yl)ethanesulfonyl chloride)		D.1.108*	1.58 (b)	440

Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
1-(2,2-dichlorocyclopropyl)-N-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-ethyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)methanesulfonamide (prepared using K from Example #8 Step M and (2,2-dichlorocyclopropyl)methane sulfonyl chloride)		D.1.109	1.91 (b)	457
N-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-3-phenylpropane-1-sulfonamide (prepared using K from Preparation #19.2 and 3-phenylpropane-1-sulfonyl chloride)		D.1.110*	1.90 (b)	439
4,4,4-trifluoro-N-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)butane-1-sulfonamide (prepared using K from Preparation #19.2 and 4,4,4-trifluorobutane-1-sulfonyl chloride)		D.1.111*	1.76 (b)	431
2-ethyl-N-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)cyclopropane-1-sulfonamide (prepared using K from Preparation #19.2 and 2-ethylcyclopropane-1-sulfonyl chloride)		D.1.112	1.70 (b)	389
2-methyl-N-((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide (prepared using K from Preparation #19.2 and 2-methylpropane-1-sulfonyl chloride)		D.1.113*	1.67 (b)	377

Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-phenylethanesulfonamide (prepared using K from Preparation #19.2 and 2-phenylethanesulfonyl chloride)		D.1.114*	1.83 (b)	425
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)butane-2-sulfonamide (prepared using K from Preparation #19.2 and 2-(methylsulfonyl)butane)		D.1.115	1.63 (b)	377
1-cyclohexyl- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)methanesulfonamide (prepared using K from Preparation #19.2 and cyclohexylmethanesulfonyl chloride)		D.1.116*	1.94 (b)	417
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)butane-1-sulfonamide (prepared using K from Preparation #19.2 and butane-1-sulfonyl chloride)		D.1.117*	1.67 (b)	377
2-methoxy- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)ethanesulfonamide (prepared using K from Preparation #19.2 and 2-methoxyethanesulfonyl chloride)		D.1.118*	1.38 (b)	379

Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)propane-2-sulfonamide (prepared using K from Preparation #19.2 and propane-2-sulfonyl chloride)		D.1.119*	1.50 (b)	363
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1-phenylmethanesulfonamide (prepared using K from Preparation #19.2 and phenylmethanesulfonyl chloride)		D.1.120*	1.72 (b)	411
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide (prepared using K from Preparation #19.2 and propane-1-sulfonyl chloride)		D.1.121*	1.53 (b)	363
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-3-methylbutane-1-sulfonamide (prepared using K from Preparation #19.2 and 3-methylbutane-1-sulfonyl chloride)		D.1.122*	1.80 (b)	391
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1,1-difluoromethanesulfonamide (prepared using K from Preparation #19.2 and difluoromethanesulfonyl chloride)		D.1.123*	1.64 (b)	371
4-cyano- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)butane-1-sulfonamide (prepared using K from Preparation #19.2 and 4-cyanobutane-1-sulfonyl chloride)		D.1.124*	1.45 (b)	402

Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
2-ethoxy- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)ethanesulfonamide (prepared using K from Preparation #19.2 and 2-ethoxyethanesulfonyl chloride)		D.1.125*	1.50 (b)	393
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1-(tetrahydrofuran-2-yl)methanesulfonamide (prepared using K from Preparation #19.2 and (tetrahydrofuran-2-yl)methanesulfonyl chloride)		D.1.126	1.46 (b)	405
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)tetrahydro-2 <i>H</i> -pyran-4-sulfonamide (prepared using K from Preparation #19.2 and tetrahydro-2 <i>H</i> -pyran-4-sulfonyl chloride)		D.1.127*	1.39 (b)	405
3-fluoro- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide (prepared using K from Preparation #19.2 and 3-fluoropropane-1-sulfonyl chloride)		D.1.128*	1.48 (b)	381
3-cyano- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)propane-1-sulfonamide (prepared using K from Preparation #19.2 and 3-cyanopropane-1-sulfonyl chloride)		D.1.129*	1.39 (b)	388

Sulfonamide	Product	Ex #	R _t min (Table 1, Method)	m/z ESI+ (M+H) ⁺
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1-(5-methylisoxazol-3-yl)methanesulfonamide (prepared using K from Preparation #19.2 and (5-methylisoxazol-3-yl)methanesulfonyl chloride)		D.1.130*	1.55 (b)	416
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-1-(tetrahydro-2 <i>H</i> -pyran-2-yl)methanesulfonamide (prepared using K from Preparation #19.2 and (tetrahydro-2 <i>H</i> -pyran-2-yl)methanesulfonyl chloride)		D.1.131	1.63 (b)	419
<i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)-2-(pyridin-2-yl)ethanesulfonamide (prepared using K from Preparation #19.2 and 2-(pyridin-2-yl)ethanesulfonyl chloride)		D.1.132*	1.47 (b)	426
1-(benzo[<i>d</i>]isoxazol-3-yl)- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)methanesulfonamide (prepared using K from Preparation #19.2 and benzo[<i>d</i>]isoxazol-3-ylmethanesulfonyl chloride)		D.1.133*	1.77 (b)	452
1-(2,2-dichlorocyclopropyl)- <i>N</i> -((1 <i>S</i> ,3 <i>R</i> ,4 <i>S</i>)-3-methyl-4-(6-tosyl-6 <i>H</i> -pyrrolo[2,3- <i>e</i>][1,2,4]triazolo[4,3- <i>a</i>]pyrazin-1-yl)cyclopentyl)methanesulfonamide (prepared using K from Preparation #19.2 and (2,2-dichlorocyclopropyl)methanesulfonyl chloride)		D.1.134	1.81 (b)	443

DEMANDES OU BREVETS VOLUMINEUX

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

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

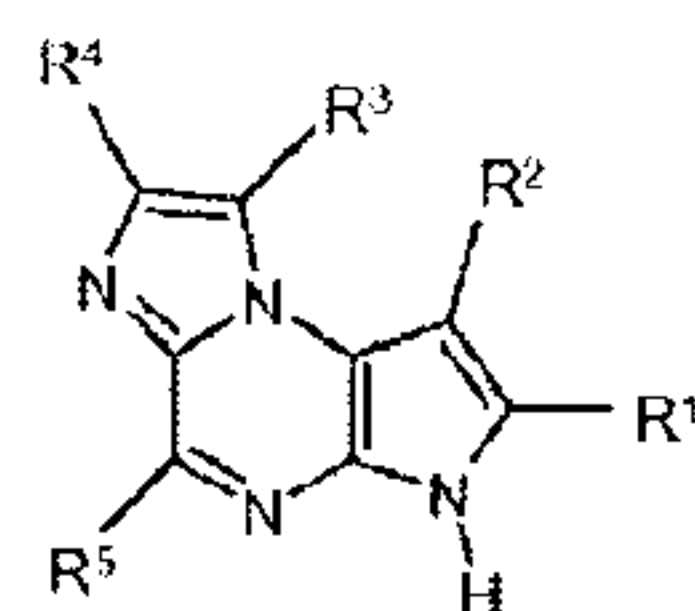
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __3__

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

What is claimed is:

1. A compound of formula Ic:



Formula (Ic)

or a pharmaceutically-acceptable salt thereof, wherein:

R¹, R², R⁴ and R⁵ are each hydrogen;

R³ is A-D-E-G, wherein A is a bond; D is an optionally substituted (C₂-C₁₀)heterocyclylene; E is a bond, R^e C(O)N(R^a)R^e-, -C(O)NHR^e-, or -R^e-N(R^a)C(O)-R^e-,; and G is -CF₃ or -C(O)N(R^a)(R^b);

R^e for each occurrence is independently a bond or an optionally substituted (C₁-C₁₀)alkylene; and

R^a and R^b are each hydrogen or an optionally substituted (C₁-C₁₀)alkyl;

wherein E is linked to either a carbon or a nitrogen atom in D; and, when G contains -N(R^a)(R^b), the nitrogen, R^a, and R^b may form a ring, such that -N(R^a)(R^b) represents an optionally substituted (C₂-C₁₀)heterocyclyl linked through a nitrogen.

2. The compound of claim 1, wherein:

G is -C(O)N(R^a)(R^b); and

R^a is hydrogen; and R^b is an optionally substituted (C₁-C₁₀)alkyl.

3. The compound of claim 2, wherein R^b is substituted by halogen or -CF₃.

4. The compound of claim 1, wherein:

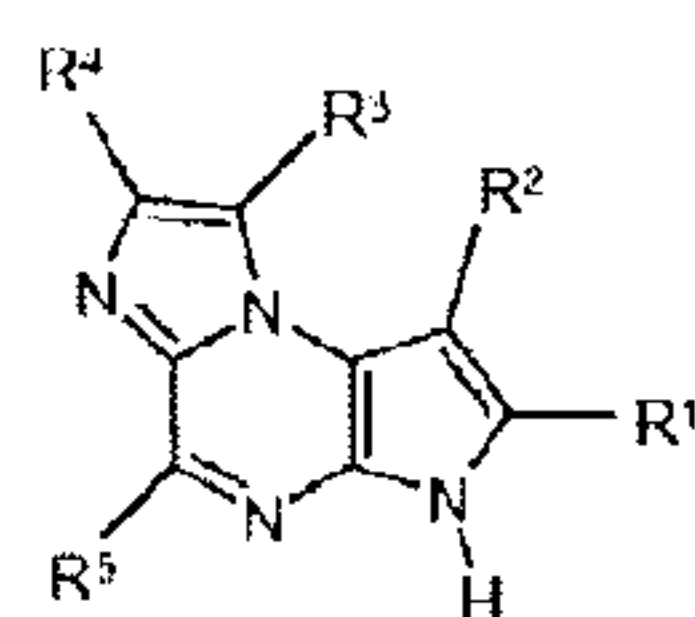
D is an optionally substituted (C₂-C₁₀)heterocyclylene; E is -R^e C(O)N(R^a)R^e-,; and G is -CF₃;

R^e for each occurrence is independently a bond or an optionally substituted (C₁-C₁₀)alkylene; and

R^a is hydrogen.

5. The compound of claim 4, wherein E is -R^e C(O)N(R^a)R^e-,.

6. The compound of any one of claims 1-5, wherein D is a saturated heterocyclylene.
7. The compound of claim 6, wherein D is optionally substituted pyrrolidinylene.
8. The compound of claim 7, wherein D is ethyl-substituted pyrrolidinylene.
9. A compound of formula I(c):

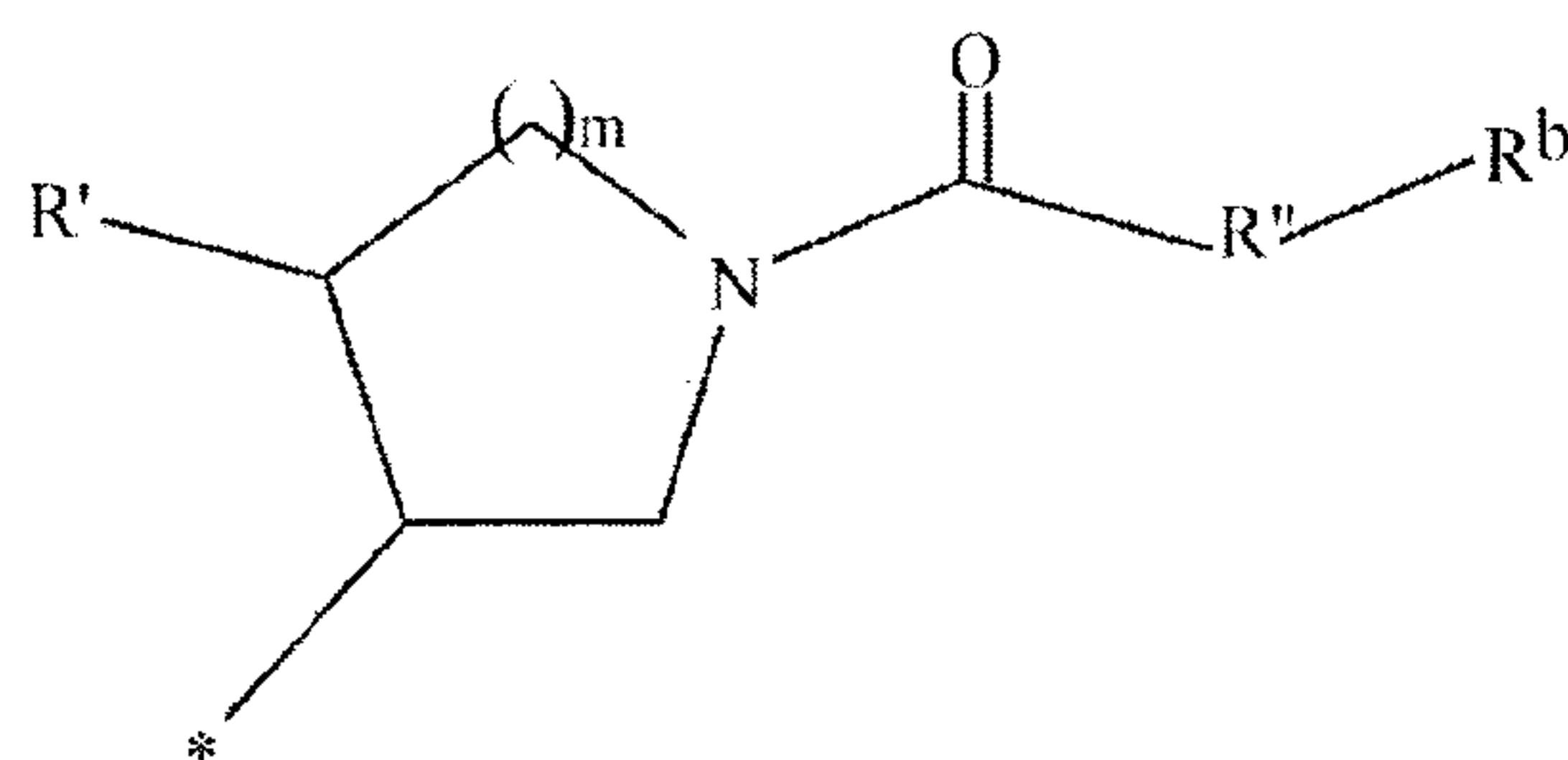


Formula I(c)

or a pharmaceutically-acceptable salt thereof, wherein:

R¹, R², R⁴ and R⁵ are each independently hydrogen; and

R³ is:



in which:

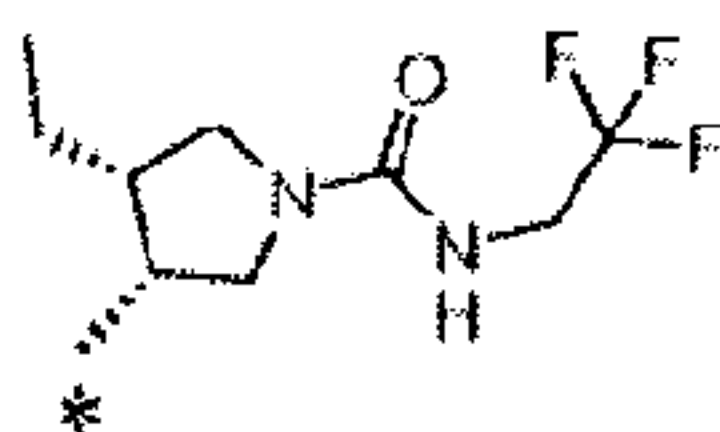
m is 0 or 1; R' is methyl or ethyl; R'' is a bond or -N(R^a)-; R^a is hydrogen, or (C₁-C₃)alkyl;

and R^b is an optionally substituted (C₁-C₃)alkyl,

wherein a line marked with an asterisk represents a bond that links R³ to a tricyclic moiety of formula I(c).

10. The compound of claim 9, wherein R'' is -NH-.
11. The compound of claim 9, wherein R^b is substituted by -CF₃.

12. The compound of claim 1, wherein R³ is



wherein a line marked with an asterisk represents a bond that links R³ to the tricyclic moiety of formula Ic.

13. The compound of claim 1, wherein:

D is methyl-substituted pyrrolidinylene;

E is a bond;

G is -C(O)NH(R^b); and

R^b is an optionally substituted (C₁-C₁₀)alkyl;

wherein G is linked to the nitrogen atom of D, and R^b is substituted by -CF₃.

14. The compound of claim 13, wherein R^b is methyl and wherein R^b is substituted by -F, -Cl, -CN, or -CF₃.

15. The compound of claim 1, wherein:

D is ethyl-substituted pyrrolidine;

E is -C(O)NHR^e;

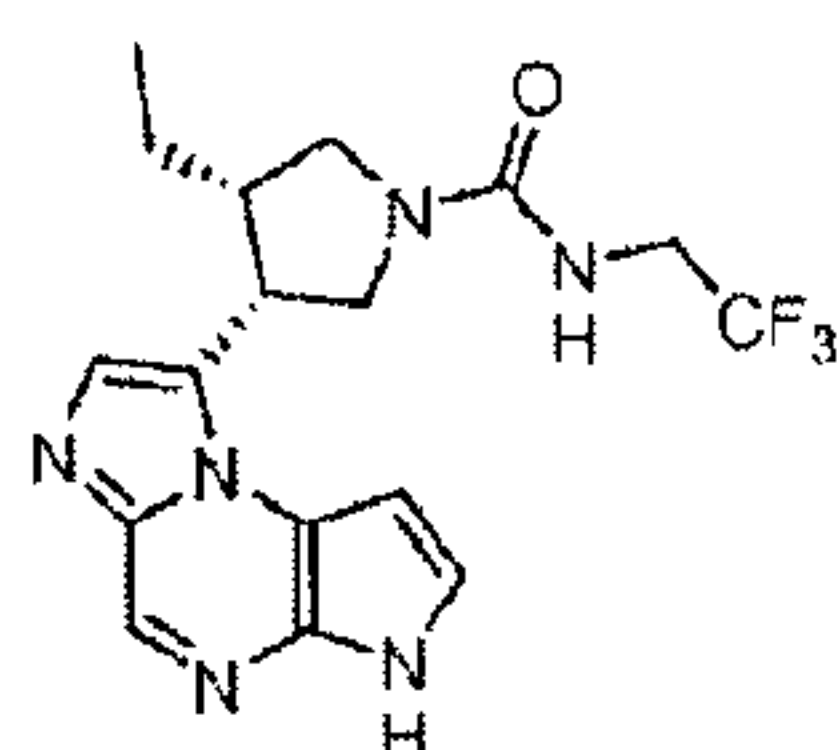
G is -CF₃; and

R^e is an optionally substituted (C₁-C₁₀)alkylene,

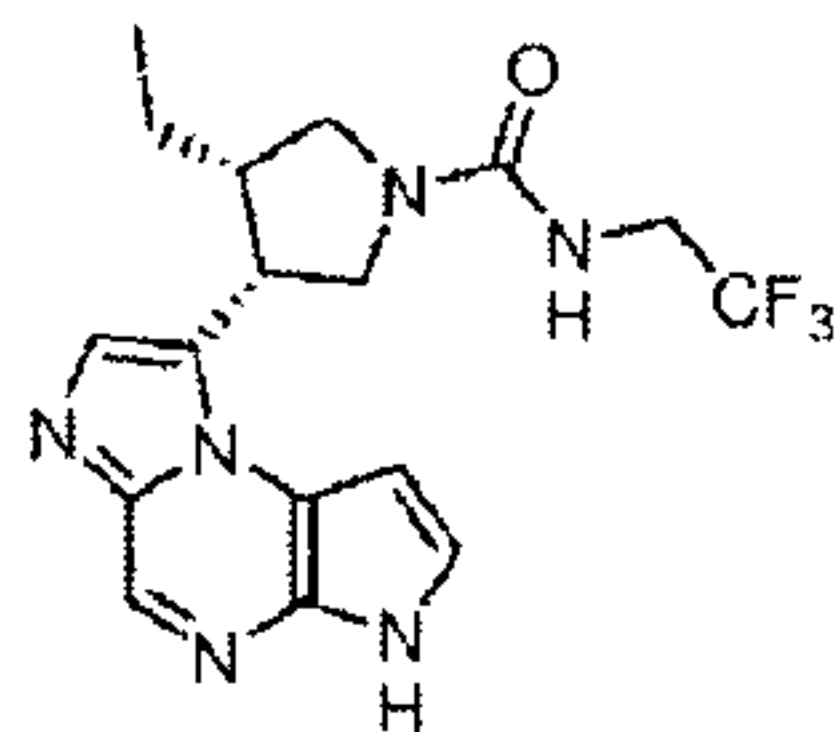
wherein E is linked to the nitrogen atom of D.

16. The compound of claim 15, wherein R^e is a methylene, ethylene, propylene, cyclopropylene, cyclobutylene, cyclopentylene, or phenylene.

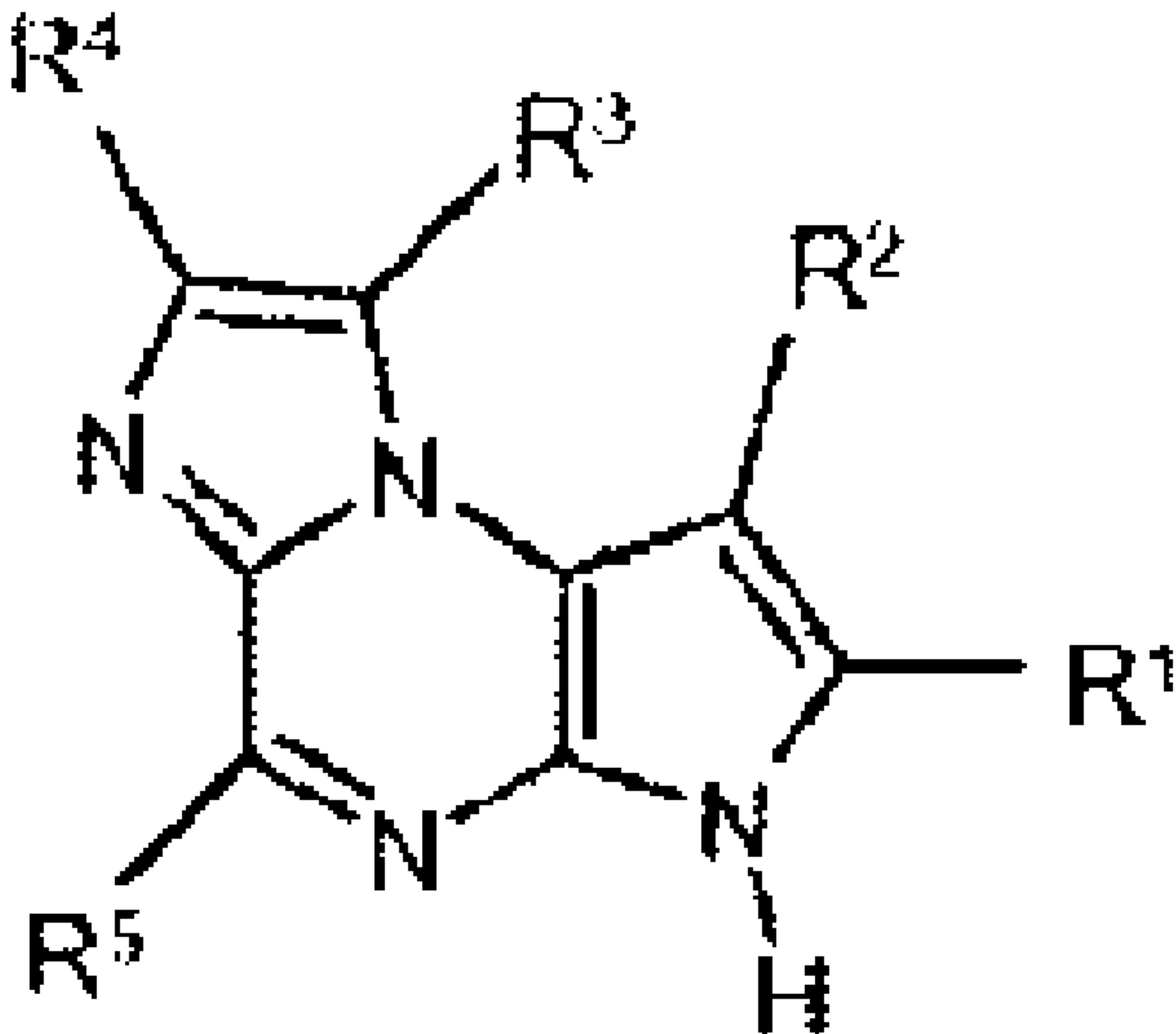
17. A compound represented by the following formula:



18. A pharmaceutically acceptable salt of a compound represented by the following formula:



19. A pharmaceutical composition comprising the compound of claim 17 or the pharmaceutically acceptable salt of the compound of claim 18, and a pharmaceutically acceptable carrier or excipient.



Formula (Ic)