Abstract: Compounds having the structures of Formula I, including pharmaceutically acceptable salts of the compounds, are CETP inhibitors, and are useful for raising HDL-cholesterol, reducing LDL-cholesterol, and for treating or preventing atherosclerosis: In the compounds of Formula I, B or R2 is a phenyl group which has an ortho aryl, heterocyclic, benzoheterocyclic or benzocycloalkyl substituent, and one other position on the 5-membered ring has an aromatic, heterocyclic, cycloalkyl, benzoheterocyclic or benzocycloalkyl substituent connected directly to the ring or attached to the ring through a -CH2-.
TITLE OF THE INVENTION
CETP INHIBITORS

FIELD OF THE INVENTION
This invention relates to a class of chemical compounds that inhibit cholesterol ester transfer protein (CETP) and therefore may have utility in the treatment and prevention of atherosclerosis.

BACKGROUND OF THE INVENTION
Atherosclerosis and its clinical consequences, coronary heart disease (CHD), stroke and peripheral vascular disease, represent a truly enormous burden to the health care systems of the industrialized world. In the United States alone, approximately 13 million patients have been diagnosed with CHD, and greater than one half million deaths are attributed to CHD each year. Further, this toll is expected to grow over the next quarter century as an epidemic in obesity and diabetes continues to grow.

It has long been recognized that in mammals, variations in circulating lipoprotein profiles correlate with the risk of atherosclerosis and CHD. The clinical success of HMG-CoA Reductase inhibitors, especially the statins, in reducing coronary events is based on the reduction of circulating Low Density Lipoprotein cholesterol (LDL-C), levels of which correlate directly with increased risk for atherosclerosis. More recently, epidemiologic studies have demonstrated an inverse relationship between High Density Lipoprotein cholesterol (HDL-C) levels and atherosclerosis, leading to the conclusion that low serum HDL-C levels are associated with an increased risk for CHD.

Metabolic control of lipoprotein levels is a complex and dynamic process involving many factors. One important metabolic control in man is the cholesteryl ester transfer protein (CETP), a plasma glycoprotein that catalyzes the movement of cholesteryl esters from HDL to the apoB containing lipoproteins, especially VLDL (see Hesler, C.B., et. al. (1987) Purification and characterization of human plasma cholesteryl ester transfer protein. J. Biol. Chem. 262(5), 2275-2282). Under physiological conditions, the net reaction is a heteroexchange in which CETP carries triglyceride to HDL from the apoB lipoproteins and transports cholesterol ester from HDL to the apoBliprotein.

In humans, CETP plays a role in reverse cholesterol transport, the process whereby cholesterol is returned to the liver from peripheral tissues. Intriguingly, many animals do not possess CETP, including animals that have high HDL levels and are known to be resistant to coronary heart disease, such as rodents (see Guyard-Dangremont, V., et. al., (1998) Phospholipid and cholesteryl ester transfer activities in plasma from 14 vertebrate species. Relation to atherogenesis susceptibility, Comp. Biochem. Physiol. B Biochem. Mol. Biol. 120(3), 517-525). Numerous epidemiologic studies correlating the effects of natural variation in CETP activity with respect to coronary heart disease risk have been performed, including studies on a small number of known human null mutations (see Hirano, K.-L., Yamashita, S. and Matsuzawa, Y. (2000) Pros and cons of inhibiting cholesteryl ester transfer protein, Curr. Opin. Lipidol. 11(6), 589-596). These studies have clearly demonstrated an inverse correlation
between plasma HDL-C concentration and CETP activity (see Inazu, A., et. al. (2000) *Cholesteryl ester transfer protein and atherosclerosis*, *Curr. Opin. Lipidol.* 11(4), 389-396), leading to the hypothesis that pharmacologic inhibition of CETP lipid transfer activity may be beneficial to humans by increasing levels of HDL-C while lowering those of LDL.

Despite the significant therapeutic advance that statins such as simvastatin (ZOCOR®) represent, statins only achieve a risk reduction of approximately one-third in the treatment and prevention of atherosclerosis and ensuing atherosclerotic disease events. Currently, few pharmacologic therapies are available that favorably raise circulating levels of HDL-C. Certain statins and some fibrates offer modest HDL-C gains. Niacin, which provides the most effective therapy for raising HDL-C that has been clinically documented, suffers from patient compliance issues, due in part to side effects such as flushing. An agent that safely and effectively raises HDL cholesterol levels can answer a significant, but as yet unmet medical need by offering a means of pharmacologic therapy that can significantly improve circulating lipid profiles through a mechanism that is complementary to existing therapies.

New classes of chemical compounds that inhibit CETP are being investigated at several pharmaceutical companies or are in clinical trials. No CETP inhibitors are currently being marketed. New compounds are needed so that one or more pharmaceutical compounds can be found that are safe and effective. The novel compounds described herein are very potent CETP inhibitors. Some structurally similar compounds are found in WO2003/032981.

**SUMMARY OF THE INVENTION**

Compounds having Formula I, including pharmaceutically acceptable salts of the compounds, are CETP inhibitors, having the utilities described below:

\[
\begin{array}{c}
B \\
(R_2)_2C \\
\text{N} \\
\text{Z} \\
\text{X} \\
\text{Y} \\
\text{C} \\
\text{R}^5 \\
\text{R}^2 \\
\end{array}
\]

In the compounds of Formula I,

Y is selected from -C(=O)- and -(CRR¹)-;

X is selected from -O-, -NH-, -N(C₁-C₅alkyl)-, and -(CRR⁶)-;

Z is selected from -C(=O)-, -S(O)₂-, and -C(=N-R⁹)-, wherein R⁹ is selected from the group consisting of H, CN, and -C₁-C₅alkyl optionally substituted with 1-11 halogens;
Each R is independently selected from the group consisting of H, -C1-C5 alkyl, and halogen, wherein -C1-C5 alkyl is optionally substituted with 1-11 halogens;

B is selected from the group consisting of A1 and A2, wherein A1 has the structure:

\[
(R^a)p \underbrace{\text{A}}_{\text{A}^3}\underbrace{\text{A}}_{\text{X}}
\]

R1 and R6 are each independently selected from H, -C1-C5 alkyl, halogen, and -(C(R)2)nA2, wherein -C1-C5 alkyl is optionally substituted with 1-11 halogens;

R2 is selected from the group consisting of H, -C1-C5 alkyl, halogen, A1, and -(C(R)2)nA2, wherein -C1-C5 alkyl is optionally substituted with 1-11 halogens;

Wherein one of B and R2 is A1; and one of B, R1, R2, and R6 is A2 or -(C(R)2)nA2; so that the compound of Formula I comprises one group A1 and one group A2;

A3 is selected from the group consisting of:

(a) an aromatic ring selected from phenyl and naphthyl;
(b) a phenyl ring fused to a 5-7 membered non-aromatic cycloalkyl ring, which optionally comprises 1-2 double bonds;
(c) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and -N(O)-, and optionally also comprising 1-3 double bonds and a carbonyl group, wherein the point of attachment of A3 to the phenyl ring to which A3 is attached is a carbon atom; and
(d) a benzoheterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and S, and optionally also having 1-2 double bonds (in addition to the double bond of the fused phenyl ring) wherein the point of attachment of A3 to the phenyl ring to which A3 is attached is a carbon atom;

A2 is selected from the group consisting of:

(a) an aromatic ring selected from phenyl and naphthyl;
(b) a phenyl ring fused to a 5-7 membered non-aromatic cycloalkyl ring, which optionally comprises 1-2 double bonds;
(c) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and -N(O)-, and optionally also comprising 1-3 double bonds and a carbonyl group;

(d) a benzo-heterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and S, and optionally also having 1-2 double bonds (in addition to the double bond of the fused phenyl ring); and

(e) a -C₃-C₈ cycloalkyl ring optionally having 1-3 double bonds;

wherein A³ and A² are each optionally substituted with 1-5 substituent groups independently selected from R⁸;

Each R⁸ is independently selected from the group consisting of -C₁-C₆ alkyl, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₃-C₈ cycloalkyl optionally having 1-3 double bonds, -OC₁-C₆alkyl, -OC₂-C₆ alkenyl, -OC₂-C₆ alkynyl, -OC₃-C₈ cycloalkyl optionally having 1-3 double bonds, -C(=O)C₁-C₆alkyl, -C(=O)C₃-C₈ cycloalkyl, -C(=O)H, -CO₂H, -CO₂C₁-C₆alkyl, -C(=O)SC₁-C₆alkyl, -OH, -NR₃R⁴, -C(=O)NR₃R⁴, -NR₃C(=O)OC₁-C₆alkyl, -NR₃C(=O)NR₃R⁴, -S(O)ₓC₁-C₆alkyl, -S(O)ₓNR₃R⁴, -NR₃S(O)ₓNR₃R⁴, halogen, -CN, -NO₂, and a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring optionally also comprising a carbonyl group and optionally also comprising 1-3 double bonds, wherein the point of attachment of said heterocyclic ring to the ring to which R⁸ is attached is a carbon atom, wherein said heterocyclic ring is optionally substituted with 1-5 substituent groups independently selected from halogen, -C₁-C₆ alkyl, and -OC₁-C₃ alkyl, wherein -C₁-C₃ alkyl and -OC₁-C₃ alkyl are optionally substituted with 1-7 halogens;

wherein for compounds in which R⁸ is selected from the group consisting of -C₁-C₆ alkyl, -C₂-C₆ alkenyl, -C₂-C₆ alkynyl, -C₃-C₈ cycloalkyl optionally having 1-3 double bonds, -OC₁-C₆alkyl, -OC₂-C₆ alkenyl, -OC₂-C₆ alkynyl, -OC₃-C₈ cycloalkyl optionally having 1-3 double bonds, -C(=O)C₁-C₆alkyl, -C(=O)C₃-C₈ cycloalkyl, -CO₂C₁-C₆alkyl, -C(=O)SC₁-C₆alkyl, -NR₃C(=O)OC₁-C₆alkyl, and -S(O)ₓC₁-C₆alkyl, R⁸ is optionally substituted with 1-15 halogens and is optionally also substituted with 1-3 substituent groups independently selected from (a) -OH, (b) -CN, (c) -NR₃R⁴, (d) -C₃-C₈ cycloalkyl optionally having 1-3 double bonds and optionally substituted with 1-15 halogens, (e) -OC₁-C₄alkyl optionally substituted with 1-9 halogens and optionally also substituted with 1-2 substituent groups independently selected from -OC₁-C₂ alkyl and phenyl, (f) -OC₃-C₈ cycloalkyl optionally having 1-3 double bonds and optionally substituted with 1-15 halogens, (g) -CO₂H, (h) -C(=O)CH₃, (i) -CO₂C₁-C₄alkyl which is optionally substituted with 1-9 halogens, and (j) phenyl which is optionally substituted with 1-3 groups independently selected from halogen, -CH₃, -CF₃, -OCH₃, and -OCF₃;

with the proviso that when B is A¹, and X and Y are -CH₂-, and Z is -C(=O)-, and R² is phenyl which has a substituent R⁸ in the 4-position, wherein R⁸ is -OC₁-C₆alkyl which is optionally
substituted as described above, then there are no other Rᵦ substituents on R² in which Rᵦ is selected from -OH, -OC₁-C₆ alkyl, -OC₂-C₆ alkenyl, -OC₂-C₆ alkynyl, and -OC₃-C₈ cycloalkyl optionally having 1-3 double bonds, all of which are optionally substituted as described above.

n is 0 or 1;

p is an integer from 0-4;

x is 0, 1, or 2;

y is 1 or 2;

R³ and R⁴ are each independently selected from H, -C₁-C₅ alkyl, -C(=O)C₁-C₅ alkyl and -S(O)ₓC₁-C₅ alkyl, wherein -C₁-C₅ alkyl in all instances is optionally substituted with 1-11 halogens; and

R⁵ is selected from the group consisting of H, -OH, -C₁-C₅ alkyl, and halogen, wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens.

In the compounds of Formula I and in subsequent compounds, alkyl, alkenyl, and alkynyl groups can be either linear or branched, unless otherwise stated.

DETAILED DESCRIPTION OF THE INVENTION

Many of compounds of this invention have a structure in accordance with Formula Ia, written below, or a pharmaceutically acceptable salt thereof:

![Diagram](attachment:image.png)

Many compounds of the invention have the structure of Formula Ib, or a pharmaceutically acceptable salt thereof:
Many other compounds have the structure of Formula Ic or a pharmaceutically acceptable salt thereof:

Still other compounds of the invention have a structure in accordance with Formula Id, or a pharmaceutically acceptable salt thereof:

In a subset of the compounds of Formula I,

Each Ra is independently selected from the group consisting of -C1-C6 alkyl, -C2-C6 alkenyl, -C2-C6 alkynyl, -C3-C8 cycloalkyl optionally having 1-3 double bonds, -OC1-C6alkyl, -OC2-C6 alkenyl, -OC2-C6 alkynyl, -OC3-C8 cycloalkyl optionally having 1-3 double bonds, -C(=O)C1-C6alkyl, -C(=O)C3-C8 cycloalkyl, -C(=O)H, -CO2H, -CO2C1-C6alkyl, -C(=O)SC1-C6alkyl, -NR3R4, -C(=O)NR3R4, -NR3C(=O)OC1-C6alkyl, -NR3C(=O)NR3R4, -S(O)xC1-C6 alkyl, -S(O)yNR3R4, -NR3S(O)yNR3R4, halogen, -CN, -NO2, and a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring optionally also comprising a carbonyl group and optionally also comprising 1-3 double bonds, wherein the point of attachment of said
heterocyclic ring to the attached ring is a carbon atom, wherein said heterocyclic ring is optionally substituted with 1-5 substituent groups independently selected from halogen, -C₁₋₃ alkyl, and -OC₁₋₃ alkyl, wherein -C₁₋₃ alkyl and -OC₁₋₃ alkyl are optionally substituted with 1-7 halogens;

wherein for compounds in which R⁸ is selected from the group consisting of -C₁₋₃ alkyl, -C₂₋₆ alkenyl, -C₂₋₆ alkylnyl, -C₃₋₈ cycloalkyl optionally having 1-3 double bonds, -OC₁₋₆ alkyl, -OC₂₋₆ alkyl, -OC₂₋₆ alkenyl, -OC₃₋₈ cycloalkyl optionally having 1-3 double bonds, -C(=O)C₁₋₆ alkyl, -C(=O)C₃₋₈ cycloalkyl, -CO₂C₁₋₆ alkyl, -C(=O)SC₁₋₆ alkyl, -NR₃C(=O)OC₁₋₆ alkyl, and -S(O)₂C₁₋₆ alkyl, then R⁸ is optionally substituted with 1-15 halogens and is optionally also substituted with 1-3 substituent groups independently selected from (a) -OH, (b) -CN, (c) -NR₃R⁴, (d) -C₃₋₈ cycloalkyl optionally having 1-3 double bonds and optionally substituted with 1-15 halogens, (e) -OC₁₋₄ alkyl optionally substituted with 1-9 halogens and optionally also substituted with 1-2 substituent groups independently selected from -OC₁₋₂ alkyl, (f) -OC₃₋₈ cycloalkyl optionally having 1-3 double bonds and optionally substituted with 1-15 halogens, (g) -CO₂H, (h) -C(=O)CH₃, and (i) -CO₂C₁₋₄ alkyl which is optionally substituted with 1-9 halogens;

with the proviso that when B is A¹, and X and Y are -CH₂-, and Z is -C(=O)-, and R² is phenyl which has a substituent R⁸ in the 4-position, wherein R⁸ is -OC₁₋₆ alkyl which is optionally substituted with 1-11 halogens, then there are no other R⁸ substituents on R² in which R⁸ is selected from -OC₁₋₆ alkyl, -OC₂₋₆ alkenyl, -OC₂₋₆ alkylnyl, and -OC₃₋₈ cycloalkyl optionally having 1-3 double bonds, all of which are optionally substituted as described above.

In many of the compounds of Formula I, Ia, Ib, Ic and Id, and pharmaceutically acceptable salts thereof,

A³ is phenyl, which is optionally substituted with 1-4 substituent groups R⁸, wherein R⁸ is independently selected from -C₁₋₅ alkyl, -OC₁₋₃ alkyl, -CO₂C₁₋₃ alkyl, -CO₂H, halogen, -NR₃R⁴, -C(=O)C₁₋₃ alkyl, -C(=O)H, -C(=O)NR₃R⁴, -SC₁₋₃ alkyl, -C₂₋₃ alkenyl, -CN, -NO₂, and 1,2,4-oxadiazolyl, wherein -C₁₋₃ alkyl and -C₁₋₅ alkyl in all occurrences is optionally substituted with 1-6 substituents independently selected from 1-5 halogens and one -OH group; and -C₂₋₃ alkenyl is optionally substituted with 1-3 halogens.

In many of the compounds of Formula I, Ia, Ib, Ic, and Id, and pharmaceutically acceptable salts thereof,

A² is selected from the group consisting of phenyl, cyclohexyl, and a heterocyclic 5-6 membered ring comprising 1-2 heteroatoms independently selected from O, N, S, and -N(O)-, and optionally also comprising 1-3 double bonds, wherein A² is optionally substituted with 1-2 substituent groups independently selected from -C₁₋₄ alkyl, -OC₁₋₃ alkyl, -NO₂, -CN, -S(O)₂C₁₋₃ alkyl, -NHS(O)(O)₂C₁₋₃ alkyl, -NR₃R⁴, -NR₃C(=O)R⁴, -C₂₋₃ alkenyl, -C(=O)NR₃R⁴, halogen, and pyridyl, wherein C₁₋₃ alkyl, C₁₋₄ alkyl, and C₂₋₃ alkenyl in all instances is optionally substituted with 1-3 halogens, with the proviso that for compounds of formula Ia, when B is A¹, and X and Y are -CH₂-,
Z is -C(=O)-, and R² is phenyl, then the number of R₈ groups on R² that are selected from -OC₁-C₃alkyl which are optionally substituted is 0 or 1.

In many of the compounds of Formula I, Ia, Ib, Ic, and Id, and pharmaceutically acceptable salts thereof, R³ and R⁴ are each independently selected from H and -C₁-C₃ alkyl.

In many of the compounds of Formula I, Ia, Ib, Ic, and Id, and pharmaceutically acceptable salts thereof, p is 0-2.

In subgroups of compounds of Formula I, including pharmaceutically acceptable salts thereof, A¹ is

Wherein R⁷ and R⁸ are each independently selected from the group consisting of H, halogen, -NR³R⁴, -C₁-C₃ alkyl, -OC₁-C₃ alkyl, -CN, -NO₂, and pyridyl, wherein C₁-C₃ alkyl in all instances is optionally substituted with 1-3 halogens.

In sub-groups of the compounds of formula I, A² is selected from the group consisting of phenyl, pyridyl, and cyclohexyl, wherein A² is optionally substituted with 1-2 substituents independently selected from -C₁-C₄ alkyl, -OC₁-C₄ alkyl, -NO₂, -CN, and halogen, wherein C₁-C₄ alkyl in all uses is optionally substituted with 1-3 halogens, with the proviso that for compounds of formula I, when B is A₁, and X and Y are CH₂, and Z is -(C=O)-, and R² is phenyl, then the number of R₈ groups on R² that are selected from -OC₁-C₄alkyl optionally substituted with 1-3 halogens is 0 or 1.

In other subgroups, A² is optionally substituted with 1-2 substituent groups independently selected from halogen, -C₁-C₄ alkyl, and -CN, wherein -C₁-C₄ alkyl is optionally substituted with 1-3 halogens.

In many embodiments of the invention, as described above, including pharmaceutically acceptable salts,

A¹ is
Wherein R⁷ is selected from H, halogen, -NR³R⁴, -C₁-C₃ alkyl, -OC₁-C₃ alkyl, -CN, -NO₂, and pyridyl, wherein C₁-C₃ alkyl in all instances is optionally substituted with 1-3 halogens; and R⁸ is selected from the group consisting of H, halogen, -CH₃, -CF₃, -OCH₃, and -OCF₃.

In many preferred embodiments of this invention, A³ is phenyl, which is substituted with 1-3 substituents independently selected from C₁-C₄ alkyl, OC₁-C₄ alkyl, -CN, Cl, F, -C(=O)CH₃, -CH=CH₂, -CO₂H, -CO₂CH₃, -S-CH₃, -S(O)CH₃, -S(O)₂CH₃, and -C(=O)NR³R⁴, wherein C₁-C₄ alkyl and -OC₁-C₄ alkyl are optionally substituted with 1-5 F substituents and optionally also substituted with one group -OH.

In other embodiments, A³ is phenyl which is optionally substituted with 1-3 substituents independently selected from the group consisting of Cl, F, -C₁-C₄ alkyl, and -OC₁-C₄ alkyl, wherein -C₁-C₄ alkyl and -OC₁-C₄ alkyl are optionally substituted with 1-5 F.

A preferred value of Y is -(CRR¹)-.

In some embodiments, R and R⁶ are each independently selected from the group consisting of H and -C₁-C₅ alkyl, wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens. In subsets of these embodiments, R¹ is selected from the group consisting of H, -C₁-C₅ alkyl, and -(C(R)₂)nA², wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens. In these, one of B and R² is A¹; and one of B, R¹, and R² is A² or -(C(R)₂)nA²; so that the compound of Formula I comprises one group A¹ and one group A².

In subgroups of compounds, A³ is selected from the group consisting of:
(a) an aromatic ring selected from phenyl and naphthyl;
(b) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and -N(O)-, and optionally also comprising 1-3 double bonds and a carbonyl group, wherein the point of attachment of A³ to the phenyl ring to which A³ is attached is a carbon atom; and
(c) a benzo heterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and -S(O)ₓ- and optionally 1-2 double bonds, wherein the point of attachment of A³ to the phenyl ring to which A³ is attached is a carbon atom.

In subgroups of compounds, A² is selected from the group consisting of:
(a) an aromatic ring selected from phenyl and naphthyl;
(b) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and -N(O)-, and optionally also comprising 1-3 double bonds and a carbonyl group;

(c) a benzo heterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and S and optionally 1-2 double bonds; and

(d) a -C3-C8 cycloalkyl ring optionally having 1-3 double bonds;

In the subgroups of A3 and A2 above, A3 and A2 are each optionally substituted with 1-4 substituent groups independently selected from R8.

A subgroup of R8 comprises substituents that are independently selected from the group consisting of -C1-C6 alkyl, -C2-C6 alkenyl, -C3-C8 cycloalkyl optionally having 1-3 double bonds, -OC1-C6alkyl, -C(=O)C1-C6alkyl, -C(=O)H, -CO2H, -CO2C1-C6alkyl, -OH, -NR3R4, -NR3C(=O)OC1-C6alkyl, -S(O)xC1-C6 alkyl, halogen, -CN, -NO2, and a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring optionally also comprising a carbonyl group and optionally also comprising 1-3 double bonds, wherein the point of attachment of said heterocyclic ring to the ring to which R8 is attached is a carbon atom, wherein said heterocyclic ring is optionally substituted with 1-5 substituent groups independently selected from halogen, -C1-C3 alkyl, and -OC1-C3 alkyl, wherein -C1-C3 alkyl and -OC1-C3 alkyl are optionally substituted with 1-7 halogens;

wherein for compounds in which R8 is selected from the group consisting of -C1-C6 alkyl, -C2-C6 alkenyl, -C3-C8 cycloalkyl optionally having 1-3 double bonds, -OC1-C6alkyl, -C(=O)C1-C6alkyl, -CO2C1-C6alkyl, -NR3C(=O)OC1-C6alkyl, and -S(O)xC1-C6 alkyl, R8 is optionally substituted with 1-15 halogens and is optionally also substituted with one substituent group selected from (a) -OH, (b) -NR3R4, (c) -OC1-C4alkyl optionally substituted with 1-9 halogens and optionally also substituted with 1-2 substituent groups independently selected from -OC1-C2 alkyl and phenyl, and (d) phenyl which is optionally substituted with 1-3 groups independently selected from halogen, -CH3, -CF3, -OCH3, and -OCF3;

with the proviso that when B is A1, and X and Y are -CH2-, and Z is -C(=O)-, and R2 is phenyl which has a substituent R3 in the 4-position, wherein R8 is -OC1-C6alkyl which is optionally substituted as described above, then there are no other R8 substituents on R2 in which R8 is -OH or -OC1-C6alkyl which is optionally substituted as described above.

In subgroups of compounds, n is an integer from 0-2. In other subgroups, n is 1 or 2.
independent subgroups, \( R^3 \) and \( R^4 \) each independently selected from H and \(-C_1-C_3 \) alkyl, or from H and \(-C_1-C_2 \) alkyl.

In subgroups of Formula I, \( Z \) is selected from the group consisting of \(-C(=O)-\), \(-S(O)_{2}-\), and \(-C(=N-R^9)-\), where \( R^9 \) is selected from the group consisting of H, -CN, and CH₃. A preferred value of \( Z \) is \(-C(=O)-\).

In independent subgroups, \( R^5 \) is selected from the group consisting of H, -OH, and \(-C_1-C_5 \) alkyl, wherein \(-C_1-C_5 \) alkyl is optionally substituted with 1-11 halogens. In other subgroups, \( R^5 \) is selected from H and \(-C_1-C_3 \) alkyl, or from H and \(-C_1-C_2 \) alkyl.

In some subgroups, each \( R \) is independently selected from the group consisting of H and \(-C_1-C_3 \) alkyl. In other groups, \( R \) is selected from H and \(-C_1-C_2 \) alkyl. In other groups, \( R \) is H or CH₃.

In some subgroups, \( R^6 \) is selected from the group consisting of H and \(-C_1-C_3 \) alkyl, wherein \(-C_1-C_3 \) alkyl is optionally substituted with 1-5 halogens. In other subgroups, \( R^6 \) is selected from H and \(-C_1-C_2 \) alkyl. In other groups, \( R^6 \) is H or CH₃.

In some subgroups, \( R^1 \) is selected from the group consisting of H, \(-C_1-C_3 \) alkyl, and \(-\{(C(R)_{2})_{n}A^2\} \), wherein \(-C_1-C_3 \) alkyl is optionally substituted with 1-5 halogens; and \( R^2 \) is selected from the group consisting of H, \(-C_1-C_3 \) alkyl, \( A^1 \), and \(-\{(C(R)_{2})_{n}A^2\} \), wherein \(-C_1-C_3 \) alkyl is optionally substituted with 1-5 halogens, and \( R^6 \) is H or alkyl. In these subgroups, one of \( B \) and \( R^2 \) is \( A^1 \); and one of \( B \), \( R^1 \), and \( R^2 \) is \( A^2 \) or \(-\{(C(R)_{2})_{n}A^2\} \); so that the compound of Formula I comprises one group \( A^1 \) and one group \( A^2 \).

In subgroups of compounds, \( A^3 \) is selected from the group consisting of:

(a) phenyl;

(b) a 5-6-membered aromatic heterocyclic ring having 1-2 heteroatoms independently selected from N, S, O, and \(-N(O)-\), wherein the point of attachment of \( A^3 \) to the phenyl ring to which \( A^3 \) is attached is a carbon atom; and

(c) a benzo-heterocyclic ring comprising a phenyl ring fused to a 5-membered aromatic heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and \(-S(O)_{2}\), wherein the point of attachment of \( A^3 \) to the phenyl ring to which \( A^3 \) is attached is a carbon atom.

In subgroups, \( A^2 \) is selected from:

(a) phenyl;

(b) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and \(-N(O)-\), and optionally also comprising 1-3 double bonds;

(c) a benzo-heterocyclic ring comprising a phenyl ring fused to a 5-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and S; and
(d) a -C₅-C₆ cycloalkyl ring.

In many compounds, A³ and A² are each optionally substituted with 1-4 substituent groups independently selected from R³. In various subgroups, A³ is optionally substituted with 1-3 substituents R³, or with 2-3 substituents R³. In various subgroups, A² is optionally substituted with 1-3 substituents R³, or with 1-2 substituents R³. Often A² is substituted with 2 substituents R³, or with 2-3 substituents R³.

In many compounds, A³ is selected from the group consisting of phenyl, thienyl, imidazolyl, pyrrolyl, pyrazolyl, pyridyl, N-oxido-pyridyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzothienyl, benzothienyl-S-oxide, and benzothienyl-S-dioxide.

In many compounds, A² is selected from the group consisting of phenyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, pyrazolyl, 1,2,4-triazolyl, tetrazolyl, benzodioxolyl, pyridyl, N-oxido-pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, cyclopentyl, cyclohexyl, and tetrahydropyranyl.

In some subsets, R³ is selected from the group consisting of -C₁-C₄ alkyl, -C₂-C₄ alkenyl, cyclopropyl, -OC₁-C₂alkyl, -C(=O)C₁-C₂alkyl, -C(=O)H, -CO₂C₁-C₄alkyl, -OH, -NR³R⁴, -NR³C(=O)OC₁-C₄ alkyl, -S(O)ₓC₁-C₂ alkyl, halogen, -CN, -NO₂, and a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from N, S, and O, wherein the point of attachment of said heterocyclic ring to the ring to which R³ is attached ring is a carbon atom, wherein said heterocyclic ring is optionally substituted with 1-5 substituent groups independently selected from halogen;

wherein for compounds in which R³ is selected from the group consisting of -C₁-C₄ alkyl, -C₂-C₄ alkenyl, -OC₁-C₂alkyl, -C(=O)C₁-C₂alkyl, -CO₂C₁-C₄alkyl, -NR³C(=O)OC₁-C₄ alkyl, and -S(O)ₓC₁-C₂ alkyl, the alkyl group of R³ is optionally substituted with 1-5 halogens and is optionally also substituted with one substituent group selected from (a) -OH, (b) -NR³R⁴, (c) -OCH₃ optionally substituted with 1-3 fluorine atoms and optionally also substituted with one phenyl group, and (d) phenyl which is optionally substituted with 1-3 groups independently selected from halogen, -CH₃, -CF₃, -OCH₃, and -OCF₃:

with the proviso that when B is A¹, and X and Y are -CH₂-, and Z is -C(=O)-, and R² is phenyl which has a substituent R³ in the 4-position, wherein R³ is -OC₁-C₂alkyl which is optionally substituted as described above, then there are no other R³ substituents on R² in which R³ is selected from -OH or -OC₁-C₂alkyl which is optionally substituted as described above.

In preferred subsets, X is selected from the group consisting of -O-, -NH-, and -N(C₁-C₃alkyl)-. X may also be selected from the group consisting of -O-, -NH-, and -N(CH₃). In highly preferred subsets, X is O.

In many subsets, Z is -C(=O)-.

A preferred subgroup of compounds has Formula Ie, including pharmaceutically acceptable salts thereof.
In compounds of formula Ie, X is selected from the group consisting of -O-, -NH-, -N(C1-C5alkyl)- and -(CH2)-;

Z is selected from the group consisting of -C(=O)-, -S(O)2-, and -C(=N-R9)-, wherein R9 is selected from the group consisting of H, -CN, and C1-C5alkyl optionally substituted with 1-11 halogens;

Each R is independently selected from the group consisting of H and -CH3;

B is selected from the group consisting of A1 and A2, wherein A1 has the structure:

R1 is selected from the group consisting of H, -C1-C5 alkyl, and -(C(R)2)nA2, wherein -C1-C5 alkyl is optionally substituted with 1-11 halogens;

R2 is selected from the group consisting of H, -C1-C5 alkyl, A1, and -(C(R)2)nA2, wherein -C1-C5alkyl is optionally substituted with 1-11 halogens;

Wherein one of B and R2 is A1; and one of B, R1, and R2 is A2 or -(C(R)2)nA2; so that the compound of Formula Ie comprises one group A1 and one group A2;

A2 is selected from the group consisting of phenyl, cyclohexyl, and pyridyl, wherein A2 is optionally substituted with 1-2 substituent groups independently selected from halogen, -C1-C4 alkyl, and -CN, wherein -C1-C4 alkyl is optionally substituted with 1-3 halogens;
Each R\(^a\) is independently selected from the group consisting of -C\(_1\)-C\(_3\) alkyl and halogen, wherein -C\(_1\)-C\(_3\) alkyl is optionally substituted with 1-3 halogens;

Each R\(^b\) is independently selected from the group consisting of Cl, F, -C\(_1\)-C\(_4\) alkyl, and -OC\(_1\)-C\(_4\) alkyl, wherein -C\(_1\)-C\(_4\) alkyl and -OC\(_1\)-C\(_4\) alkyl are optionally substituted with 1-5 F;

n is 0 or 1;
p is an integer from 0-2; and
q is an integer from 0-3.

Subsets of compounds having formula Ie include compounds of formula If, Ig, and Ih, and pharmaceutically acceptable salts thereof:
In the compounds of formula If, Ig, and Ih, R¹ and R² are each independently selected from H and -C₁-C₅ alkyl, wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens. Other groups are as defined previously.

In subsets of the compounds described above, A² may be selected from the group consisting of phenyl, cyclohexyl, and pyridyl, wherein A² is optionally substituted with 1-2 substituent groups independently selected from halogen, -CH₃, -CF₃, and -CN.

In subsets of the compounds described above, each R⁸ independently is selected from the group consisting of -CF₃ and Cl.

In subsets of the compounds described above, each Rᵇ is independently selected from the group consisting of -C₁-C₃ alkyl, -OCH₃, and F.

In subsets of the compounds described above, R¹ and R² are each independently selected from the group consisting of H and -C₁-C₂ alkyl.

In subsets of the compounds described above, X is selected from -O-, -NH-, -N(CH₃)₂, and -CH₂-.

In subsets of the compounds described above, Z is selected from the group consisting of -C(=O)-, -S(O)₂-, and -C(=N-CN)-.

In subsets of the compounds described above, p is 1.

In subsets of the compounds described above, q is 2 or 3.

A subset of compounds defined previously comprises compounds having formula li, and pharmaceutically acceptable salts thereof:

In formula li, R⁷ is selected from the group consisting of Cl and -CF₃;
R⁶ is selected from the group consisting of halogen, -CH₃, -CF₃, and -CN; and
\( t \) is an integer from 0-2. Other groups are as defined previously.
A subset of compounds defined previously comprises compounds having formula \( I_j \), or a pharmaceutically acceptable acceptable salt thereof:

\[
(R^b)^q \quad \text{Ph} \quad N \quad \begin{array}{c}
\text{O} \\
\text{O}
\end{array} \\
(R^c)^t \\
\text{Ph}
\]

\( I_j \)

In formula \( I_i \), \( R^7 \) is selected from the group consisting of \( \text{Cl} \) and \(-\text{CF}_3 \); \( R^c \) is selected from the group consisting of halogen, \(-\text{CH}_3 \), \(-\text{CF}_3 \), and \(-\text{CN} \); and \( t \) is an integer from 0-2. Other groups are as defined previously.

Definitions

"Ac" is acetyl, which is \( \text{CH}_3\text{C}(=\text{O})- \).

"Alkyl" means saturated carbon chains which may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Other groups having the prefix "alk", such as alkoxy and alkanoyl, also may be linear or branched or combinations thereof, unless the carbon chain is defined otherwise. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl, and the like.

"Alkylene" groups are alkyl groups that are difunctional rather than monofunctional. For example, methyl is an alkyl group and methylene \(-\text{CH}_2-\) is the corresponding alkylene group.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Cycloalkyl" means a saturated carbocyclic ring having from 3 to 8 carbon atoms, unless otherwise stated (e.g., cycloalkyl may be defined as having one or more double bonds). The term also includes a cycloalkyl ring fused to an aryl group. Examples of cycloalkyl include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and the like. "Cycloalkenyl" means a non-aromatic carbocyclic ring having one or more double bonds.
"Aryl" (and "arylene") when used to describe a substituent or group in a structure means a monocyclic or bicyclic compound in which the rings are aromatic and which contains only carbon ring atoms. The term "aryl" can also refer to an aryl group that is fused to a cycloalkyl or heterocycle. Preferred "aryls" are phenyl and naphthyl. Phenyl is generally the most preferred aryl group.

"EDC" is 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide.

"Heterocycl," "heterocycle," and "heterocyclic" means a fully or partially saturated or aromatic 5-6 membered ring containing 1-4 heteroatoms independently selected from N, S and O, unless otherwise stated.

"Benzoheterocycle" represents a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms, each of which is O, N, or S, where the heterocyclic ring may be saturated or unsaturated. Examples include indole, benzofuran, 2,3-dihydrobenzofuran and quinoline.

"DIPEA" is diisopropylethylamine.

"Halogen" includes fluorine, chlorine, bromine and iodine.

"HOBT" is 1-Hydroxybenzotriazole.

"IPAC" is isopropyl acetate.

"Me" represents methyl.

"Weinreb amine" is N,O-dimethylhydroxylamine.

The term "composition," as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

The substituent "tetrazole" means a 2H-tetrazol-5-yl substituent group and tautomers thereof.

**Optical Isomers - Diastereomers - Geometric Isomers - Tautomers**

Compounds of Formula I may contain one or more asymmetric centers and can thus occur as racemates, racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. The present invention is meant to include all such isomeric forms of the compounds of Formula I and all mixtures of the compounds. When structures are shown with a stereochemical representation, other stereochemical structures are also included individually and collectively, such as enantiomers, diastereoisomers (where diastereomers are possible), and mixtures of the enantiomers and/or diastereomers, including racemic mixtures.

Some of the compounds described herein may contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.
Some of the compounds described herein may exist as tautomers. An example is a ketone and its enol form, known as keto-enol tautomers. The individual tautomers as well as mixtures thereof are encompassed with compounds of Formula I.

Compounds of Formula I having one or more asymmetric centers may be separated into diastereoisomers, enantiomers, and the like by methods well known in the art.

Alternatively, enantiomers and other compounds with chiral centers may be synthesized by stereospecific synthesis using optically pure starting materials and/or reagents of known configuration.

Some of the biphenyl and biaryl compounds herein are observed as mixtures of atropisomers (rotamers) in the NMR spectra. The individual atropisomers as well as mixtures thereof are encompassed with the compounds of this invention.

Salts

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethlenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, gluclamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothentic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.
Metabolites – Prodrugs

Therapeutically active metabolites, where the metabolites themselves fall within the scope of the claimed invention, are also compounds of the current invention. Prodrugs, which are compounds that are converted to the claimed compounds as they are being administered to a patient or after they have been administered to a patient, are also compounds of this invention.

Utilities

Compounds of the current invention are potent inhibitors of CETP. They are therefore useful in treating diseases and conditions that are treated by inhibitors of CETP.

One aspect of the present invention provides a method for treating or reducing the risk of developing a disease or condition that may be treated or prevented by inhibition of CETP by administering a therapeutically effective amount of a compound of this invention to a patient in need of treatment. A patient is a human or mammal, and is most often a human. A “therapeutically effective amount” is the amount of compound that is effective in obtaining a desired clinical outcome in the treatment of a specific disease.

Diseases or conditions that may be treated with compounds of this invention, or which the patient may have a reduced risk of developing as a result of being treated with the compounds of this invention, include: atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, cardiovascular disorders, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplasty restenosis, hypertension, vascular complications of diabetes, obesity, endotoxemia, and metabolic syndrome.

The compounds of this invention are expected to be particularly effective in raising HDL-C and/or increasing the ratio of HDL-C to LDL-C. These changes in HDL-C and LDL-C may be beneficial in treating atherosclerosis, reducing or reversing the development of atherosclerosis, reducing the risk of developing atherosclerosis, or preventing atherosclerosis.

Administration and Dose Ranges

Any suitable route of administration may be employed for providing a mammal, especially a human, with an effective dose of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, creams, ointments, aerosols, and the like. Preferably compounds of Formula 1 are administered orally.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the art.
When treating the diseases for which compounds of Formula I are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.01 milligram to about 100 milligram per kilogram of animal or human body weight, preferably given as a single daily dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.5 milligram to about 500 milligrams. For a particularly potent compound, the dosage for an adult human may be as low as 0.1 mg. The dosage regimen may be adjusted within this range or even outside of this range to provide the optimal therapeutic response.

Oral administration will usually be carried out using tablets. Examples of doses in tablets are 0.5 mg, 1 mg, 2 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, 250 mg, and 500 mg. Other oral forms can also have the same dosages (e.g. capsules).

**Pharmaceutical Compositions**

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of Formula I and a pharmaceutically acceptable carrier. The pharmaceutical compositions of the present invention comprise a compound of Formula I or a pharmaceutically acceptable salt as an active ingredient, as well as a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids. A pharmaceutical composition may also comprise a prodrug, or a pharmaceutically acceptable salt thereof, if a prodrug is administered. Pharmaceutical compositions may also consist essentially of a compound of Formula I and a pharmaceutically acceptable carrier without other therapeutic ingredients.

The compositions include compositions suitable for oral, rectal, topical, parenteral (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

In practical use, the compounds of Formula I can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents
and the like in the case of oral solid preparations such as, for example, powders, hard and soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Compounds of formula I may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or suspensions and sterile powders for the extemporaneous preparation of sterile injectable solutions or suspensions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

**Combination Therapy**

Compounds of the invention (e.g. Formula I and Ia - Ij) may be used in combination with other drugs that may also be useful in the treatment or amelioration of the diseases or conditions for which compounds of Formula I are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I.
When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy also includes therapies in which the compound of Formula I and one or more other drugs are administered on different schedules.

When oral formulations are used, the drugs may be combined into a single combination tablet or other oral dosage form, or the drugs may be packaged together as separate tablets or other oral dosage forms. It is also contemplated that when used in combination with one or more other active ingredients, the compound of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

Examples of other active ingredients that may be administered in combination with a compound of this invention (e.g. Formula I), and either administered separately or in the same pharmaceutical composition, include, but are not limited to, other compounds which improve a patient’s lipid profile, such as (i) HMG-CoA reductase inhibitors, (which are generally statins, including lovastatin, simvastatin, rosvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, pitavastatin, and other statins), (ii) bile acid sequestrants (cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran, Colestid®, LoCholest®, (iii) niacin and related compounds, such as nicotinyl alcohol, nicotinamide, and nicotinic acid or a salt thereof, (iv) PPARα agonists, such as gemfibrozil and fenofibric acid derivatives (fibrates), including clofibrate, fenofibrate, bezafibrate, ciprofibrate, and etofibrate, (v) cholesterol absorption inhibitors, such as stanol esters, beta-sitosterol, sterol glycosides such as tiqueside; and azetidinones, such as ezetimibe, (vi) acyl CoA:cholesterol acyltransferase (ACAT) inhibitors, such as avasimibe and melinamide, and including selective ACAT-1 and ACAT-2 inhibitors and dual inhibitors, (vii) phenolic anti-oxidants, such as probucol, (viii) micromosomal triglyceride transfer protein (MTP)/ApoB secretion inhibitors, (ix) anti-oxidant vitamins, such as vitamins C and E and beta carotene, (x) thrombomimetics, (xi) LDL (low density lipoprotein) receptor inducers, (xii) platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin, (xiii) vitamin B12 (also known as cyanocobalamin), (xiv) folic acid or a pharmaceutically acceptable salt or ester thereof, such as the sodium salt and the methylglucamine salt, (xv) FXR and LXR ligands, including both inhibitors and agonists, (xvi) agents that enhance ABCA1 gene expression, and (xvii) ileal bile acid transporters.

Preferred classes of therapeutic compounds that can be used with the compounds of this invention for use in improving a patient’s lipid profile (i.e. raising HDL-C and lowering LDL-C) include one or both of statins and cholesterol absorption inhibitors. Particularly preferred are combinations of compounds of this invention with simvastatin, ezetimibe, or both simvastatin and ezetimibe. Also preferred are combinations of compounds of this invention with statins other than simvastatin, such as lovastatin, rosuvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, and ZD-4522.
Finally compounds of this invention can be used with compounds that are useful for treating other diseases, such as diabetes, hypertension and obesity, as well as other anti-atherosclerotic compounds. Such combinations may be used to treat one or more of such diseases as diabetes, obesity, atherosclerosis, and dyslipidemia, or more than one of the diseases associated with metabolic syndrome. The combinations may exhibit synergistic activity in treating these disease, allowing for the possibility of administering reduced doses of active ingredients, such as doses that otherwise might be sub-therapeutic.

Examples of other active ingredients that may be administered in combination with a compound of this invention include, but are not limited to, compounds that are primarily anti-diabetic compounds, including:

(a) PPAR gamma agonists and partial agonists, including glitazones and non-glitazones (e.g. pioglitazone, enalapril, MCC-555, rosiglitazone, balaglitazone, netoglitazone, T-131, LY-300512, and LY-818;

(b) biguanides such as metformin and phenformin;

(c) protein tyrosine phosphatase-1B (PTP-1B) inhibitors;

(d) dipeptidyl peptidase IV (DP-IV) inhibitors, including vildagliptin, sitagliptin, and saxagliptin;

(e) insulin or insulin mimetics, such as for example insulin lispro, insulin glargine, insulin zinc suspension, and inhaled insulin formulations;

(f) sulfonylureas, such as tolvaptam, glipizide, glimepiride, acetohexamide, chlorpropamide, glibenclamide, and related materials;

(g) α-glucosidase inhibitors (such as acarbose, adiposeine; camiglibose; emiglate; miglitol; voglibose; pradimicin-Q; and salbostatin);

(h) PPARα/γ dual agonists, such as muraclitazar, tesaglitazar, farglitazar, and naveglitazar;

(i) PPARδ agonists such as GW501516 and those disclosed in WO97/28149;

(j) glucagon receptor antagonists;

(k) GLP-1; GLP-1 derivatives; GLP-1 analogs, such as exendins, such as for example exenatide (Byetta); and non-peptidyl GLP-1 receptor agonists;

(l) GIP-1; and

(m) Non-sulfonylurea insulin secretagogues, such as the meglitinides (e.g. naeglinide and rapeglininide).

These other active ingredients that may be used in combination with the current invention also include antiobesity compounds, including 5-HT (serotonin) inhibitors, neuropeptide Y5 (NPY5) inhibitors, melanocortin 4 receptor (Mα4r) agonists, cannabinoid receptor 1 (CB-1) antagonists/inverse agonists, and β3 adrenergic receptor agonists. These are listed in more detail later in this section.
These other active ingredients also include active ingredients that are used to treat inflammatory conditions, such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and selective cyclooxygenase-2 (COX-2) inhibitors, including etoricoxib, celecoxib, rofecoxib, and Bextra.

Antihypertensive compounds may also be used advantageously in combination therapy with the compounds of this invention. Examples of antihypertensive compounds that may be used with the compounds of this invention include (1) angiotensin II antagonists, such as losartan; (2) angiotensin converting enzyme inhibitors (ACE inhibitors), such as enalapril and captopril; (3) calcium channel blockers such as nifedipine and diltiazam; and (4) endothelin antagonists.

Anti-obesity compounds may be administered in combination with the compounds of this invention, including: (1) growth hormone secretagogues and growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, and MK-0677; (2) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; (3) cannabinoid receptor ligands, such as cannabinoid CB1 receptor antagonists or inverse agonists, such as rimonabant (Sanofi Synthelabo), AMT-251, and SR-14778 and SR 141716A (Sanofi Synthelabo), SLV-319 (Solvay), BAY 65-2520 (Bayer); (4) anti-obesity serotoninergic agents, such as fenfluramine, dexfenfluramine, phentermine, and sibutramine; (5) β3-adrenoreceptor agonists, such as AD9677/TAK677 (Dainippon/Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, Trecadrine, Zeneca D7114, and SR 59119A; (6) pancreatic lipase inhibitors, such as orlistat (Xenical®), Triton WR1339, RHC80267, lipstatin, tetrahydrolipstatin, teasaponin, and diethylumbelliferyl phosphate; (7) neuropeptide Y1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, and GI-264879A; (8) neuropeptide Y5 antagonists, such as GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR226928, FR 240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104; (9) melanin-concentrating hormone (MCH) receptor antagonists; (10) melanin-concentrating hormone 1 receptor (MCH1R) antagonists, such as T-226296 (Takeda); (11) melanin-concentrating hormone 2 receptor (MCH2R) agonist/antagonists; (12) orexin-1 receptor antagonists, such as SB-334867-A; (13) melanocortin agonists, such as Melanotan II; (14) other Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, and ME-10145 (Melacure), CHIR86036 (Chiron); PT-141, and PT-14 (Palatin); (15) 5HT-2 agonists; (16) 5HT2C (serotonin receptor 2C) agonists, such as BVT933, DPCA37215, WAY161503, and R-1065; (17) galanin antagonists; (18) CCK agonists; (19) CCK-A (cholecystokinin –A) agonists, such as AR-R 15549, GI 181771, JMV-180, A- 71378, A-71623 and SR146131; (20) GLP-1 agonists; (21) corticotropin-releasing hormone agonists; (22) histamine receptor-3 (H3) modulators; (23) histamine receptor-3 (H3) antagonists/inverse agonists, such as bioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropr, iodophenpropit, imopropxifan, and GT2394 (Gliatech); (24) β-hydroxy steroid dehydrogenase-1 inhibitors (1β-HSD-1 inhibitors), such as BVT 3498 and, BVT 2733, (25) PDE (phosphodiesterase) inhibitors, such as theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide,
rolipram, and cilomilast; (26) phosphodiesterase-3B (PDE3B) inhibitors; (27) NE (norepinephrine) transport inhibitors, such as GW 320659, desipramine, talsupram, and nomifensine; (28) ghrelin receptor antagonists; (29) leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); (30) leptin derivatives; (31) BRS3 (bombesin receptor subtype 3) agonists such as [D-Phe6,beta-Ala11,Phe13,Nle14]Bn(6-14) and [D-Phe6,Phe13]Bn(6- 13)propylamide; (32) CNTF (Ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, PD170,292, and PD 149164 (Pfizer); (33) CNTF derivatives, such as axokine (Regeneron); (34) monoamine reuptake inhibitors, such as sibutramine; (35) UCP-1 (uncoupling protein-1, 2, or 3) activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro- 5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid (TTNPB), and retinoic acid; (36) thyroid hormone β agonists, such as KB-2611 (KaroBioBMS); (37) FAS (fatty acid synthase) inhibitors, such as Cerulenin and C75; (38) DGAT1 (diacylglycerol acyltransferase 1) inhibitors; (39) DGAT2 (diacylglycerol acyltransferase 2) inhibitors; (40) ACC2 (acyetyl-CoA carboxylase-2) inhibitors; (41) glucocorticoid antagonists; (42) acyl-estrogens, such as oleoyl-estrone; (43) dicarboxylate transporter inhibitors; (44) peptide YY, PYY 3-36, peptide YY analogs, derivatives, and fragments such as BIM- 43073D, BIM-43004C, (45) Neuropeptide Y2 (NPY2) receptor agonists such NPY3-36, N acetyl [Leu(28,31)] NPY 24-36, TASP-V, and cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY; (46) Neuropeptide Y4 (NPY4) agonists such as pancreatic peptide (PP); (47) Neuropeptide Y1 (NPY1) antagonists such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, and GI-264879A; (48) Opioid antagonists, such as nalmefene (Revex ® ), 3-methoxynaltrexone, naloxone, and naltrexone; (49) glucose transporter inhibitors; (50) phosphate transporter inhibitors; (51) 5-HT (serotonin) inhibitors; (52) beta-blockers; (53) Neurokinin-1 receptor antagonists (NK-1 antagonists); (54) clobenzorex; (55) cloflorex; (56) clomilorex; (57) clortermine; (58) cycloexedrine; (59) dexroamphetamine; (60) diphenmetidine, (61) N-ethylamphetamine; (62) fenbutrazate; (63) fenisorex; (64) fenproporex; (65) fluorex; (66) fluminumorex; (67) furfurylmethylethamphetamine; (68) levamfetamine; (69) levophacetoperane; (70) mefenorex; (71) metamfembrane; (72) methamphetamine; (73) norpseudoephedrine; (74) pentorex; (75) phenmetrazine; (76) phenmetrazine; (77) picilorex; (78) phytopharm 57; (79) zonisamide, (80) aminorex; (81) amphetamine; (82) amphetamine; (83) benzphetamine; (84) chlorphentermine.

The combination therapies described above which use the compounds of this invention may also be useful in the treatment of the metabolic syndrome. According to one widely used definition, a patient having metabolic syndrome is characterized as having three or more symptoms selected from the following group of five symptoms: (1) abdominal obesity; (2) hypertriglyceridemia; (3) low high-density lipoprotein cholesterol (HDL); (4) high blood pressure; and (5) elevated fasting glucose, which may be in the range characteristic of Type 2 diabetes if the patient is also diabetic. Each of these symptoms is defined clinically in the recently released Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in
Adults (Adult Treatment Panel III, or ATP III), National Institutes of Health, 2001, NIH Publication No. 01-3670. Patients with metabolic syndrome have an increased risk of developing the macrovascular and microvascular complications that are listed above, including atherosclerosis and coronary heart disease. The combinations described above may ameliorate more than one symptom of metabolic syndrome concurrently (e.g. two symptoms, three symptoms, four symptoms, or all five of the symptoms).

**CETP ASSAY**

An in vitro continuous assay for determining IC₅₀'s to identify compounds that are CETP inhibitors was performed based on a modification of the method described by Epps et al. employing BODIPY®-CE as the cholesteryl ester lipid donor. See Epps et al.(1995) *Method for measuring the activities of cholesteryl ester transfer protein (lipid transfer protein)*, *Chem. Phys. Lipids*. 77, 51-63.

Particles used in the assay were created from the following sources: Synthetic donor HDL particles containing DOPC (Dioleoyl Phosphatidyl Choline), BODIPY®-CE (Molecular Probes C-3927), triolein (a triglyceride), and apoHDL were essentially created by probe sonication as described by Epps et al., but with the addition of a non-diffusible quencher molecule, dabycyl dicetylamine, in order to reduce background fluorescence. Dabycyl dicetylamine was made by heating dabycyl n-succinimide with dicetylamine in DMF at 95°C overnight in the presence of diisopropylamine catalyst. Native lipoproteins from human blood were used as acceptor particles. Particles having a density less than 1.063 g/ml were collected by ultracentrifugation. These particles include VLDL, IDL, and LDL. Particle concentrations were expressed in terms of protein concentration as determined by BCA assay (Pierce, USA). Particles were stored at 4°C until use.

Assays were performed in Dynex Microfluor 2 U-bottom black 96-well plates (Cat #7205). An assay cocktail containing CETP, 1X CETP buffer (50 mM Tris, pH 7.4, 100 mM NaCl, 1 mM EDTA), and half the final concentration of acceptor particles was prepared, and 100 µL of the assay cocktail was added to each well of the plate. Test compounds in DMSO were added in a volume of 3 µL. The plate was mixed on a plate shaker and then incubated at 25 °C for 1 hour. A second assay cocktail containing donor particles, the remaining acceptor particles and 1X CETP buffer was prepared. 47 µL of the second assay cocktail was added to the reaction wells to start the assay. Assays were performed at 25°C in a final volume of 150 µL. Final concentrations of materials were: 5 ng/µL donor particles, 30 ng/µL acceptor particles (each expressed by protein content), 1X CETP buffer, 0.8 nM recombinant human CETP (expressed in CHO cells and partially purified), and up to 2% DMSO when testing compounds. The assay was followed in a fluorescence plate reader (Molecular Devices Spectramax GeminiXS) set for a 45 minute kinetic run at 25°C which read the samples every 45 sec at Ex = 480 nm, Em = 511 nm, with a cutoff filter at 495 nm, photomultiplier tube setting of medium, calibration on, and 6 reads/well.
Data was evaluated by obtaining an initial rate, expressed in relative fluorescence units per second, for the pseudolinear portion of the curve, often 0-500 or 1000 sec. Comparison of the rates of samples with inhibitors to an uninhibited (DMSO only) positive control yielded a percent inhibition. A plot of percent inhibition vs. log of inhibitor concentration, fit to a Sigmoidal 4 parameter equation was used to calculate IC₅₀.

EXAMPLES

The following schemes and examples are provided so that the invention will be more fully appreciated and understood. Starting materials are made using known procedures or as shown below.

The examples should not be construed as limiting the invention in any way. The scope of the invention is defined by the appended claims. Compounds of this invention have an IC₅₀ value as measured using the assay described above of less than or equal to 50µM.
SCHEME 1

Intermediates 1-2, 1-3, 1-4, 1-5 and 1-6 utilized in the present invention can be purchased or prepared as shown in Scheme 1. An appropriately substituted 2-haloaniline 1-1 wherein R^4 and p are as defined in the claims and where the halogen is preferably iodo or bromo is treated with CuCN in DMF at elevated temperature to afford the corresponding 2-cyanoaniline. Alternatively, the nitrile can be prepared by treatment of 1-1 with KCN and CuI in the presence of a palladium (II) salt or in the presence of certain copper or nickel complexes (See: Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 867 (2001) and references therein). Iodides 1-3 are prepared by treatment of 1-2 with isoamyl nitrite, n-pentyl nitrite, t-butyl nitrite or the like in the presence of diiodomethane (see for example: Smith et al., J. Org. Chem. 55, 2543, (1990) and references cited therein) either neat or in a solvent such as THF or acetonitrile. Alternatively, the iodide can be prepared first by diazonium formation using isoamyl nitrite, n-pentyl nitrite, t-butyl nitrite, sodium nitrite, nitrous acid or the like followed by heating in the presence of iodine or an iodide salt such as copper iodide, sodium iodide, potassium iodide, tetrabutylammonium iodide or the like. Reduction of 1-3 with DIBAL in dichloromethane affords aldehyde 1-4. Reduction of aldehyde 1-4 with sodium borohydride or the like in methanol or ethanol or the like gives alcohol 1-5. Treatment of 1-5 with carbon tetrabromide and triphenylphosphine in solvents such as dichloromethane, dichloroethane or the like gives benzyl bromide 1-6 (See: Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 518-519 (2001) and references therein).
Intermediates 2-2 and 2-3 of the present invention wherein R₃, p, and A³ are as defined in the claims can be prepared as shown in Scheme 2. 2-Cyaniodobenzenes 2-1 can be purchased or prepared according to the procedures outlined in Scheme 1. Compounds 2-2 are prepared via a Suzuki or Stille reaction or variation thereof employing palladium catalyzed cross coupling of iodide 2-1 with an appropriately substituted aryl- or heteroaryl-boronic acid, -boronate ester or -trialkyl tin as described in Miyaura et al., *Chem. Rev.* 95, 2457 (1995) and references cited within and as described in Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 868-869 (2001) and references cited therein. Reduction of nitrile 2-2 is accomplished with lithium aluminum hydride in diethyl ether to afford 2-aminomethyl aniline 2-3. Alternatively, the nitrile can be reduced with palladium on carbon or Raney nickel under hydrogen atmosphere in methanol, ethanol or the like. Other methods for reduction of a nitrile to an aminomethyl group can be found in Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 1204 (2001) and references therein.
Compounds 3-4 of the present invention wherein R, R^a, p, A^2, A^3 and n are as defined in the claims can be prepared according to the procedure outlined in Scheme 3. Benzyl amines 3-1 can be purchased or prepared according to the procedure outlined in Scheme 2. Reaction of 3-1 with an appropriately substituted alkyl acetate bearing a leaving group at the 2-position affords secondary amine 3-2. Alkyl acetates can be purchased or prepared using known methods. The preferred leaving group is bromide or iodide, but may also be mesylate, tosylate or the like and the solvent may be dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like. The reaction may be run with or without a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Reduction of the ester functionality of 3-2 affords amino alcohol 3-3. The preferred reducing reagent is LiAlH_4, in a solvent such as ether, tetrahydrofuran, dimethoxyethane, dioxane, or the like. Other methods for reduction of an ester can be found in "March's Advanced Organic Chemistry" 5th Ed., John Wiley and Sons, New York, pp 1551. Amino alcohol 3-3 can be cyclised to oxazolidinone 3-4 using phosgene (Y=Cl) or a phosgene equivalent such as triphosgene (Y=OCCl_3) or carbonyl-diimidazole (Y=imidazole) or the like in a solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like and a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Enantiopure products may be obtained via chiral chromatography.
SCHEME 4

Compounds of the present invention 4-3 wherein R, Rₐ, p, A², A³ and n are as defined in the claims can be prepared as shown in Scheme 4. An appropriately substituted benzylamine 4-1 can be reacted with an appropriately substituted oxirane to give amino alcohol 4-2. The oxiranes may be purchased or prepared from the corresponding aldehyde and a sulfur ylide as described in "March's Advanced Organic Chemistry" 5th Ed., John Wiley and Sons, New York, pp 1247. Alternatively the epoxide may be made from epoxidation of an olefin, cyclization of a halohydrin or 1, 2-diol, or other methods described in "March's Advanced Organic Chemistry" 5th Ed., John Wiley and Sons, New York, pp 1051. The preferred solvent for this reaction is isopropanol. Alternatively, the epoxide opening may be carried out in a solvent such as acetonitrile or the like with the aid of a Lewis Acid catalyst such as Yb(OTf)₃ or the like. Amino alcohol 4-2 can be cyclised to oxazolidinone 4-3 using phosgene (Y=Cl) or a phosgene equivalent such as triphosgene (Y=OCCl₃) or carbonyl-diimidazole (Y=imidazole) or the like in a solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like and a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Alternatively, aminoalcohol 4-2 can be converted to an appropriate carbamate by treatment with reagents such as dibenzyl dicarbonate or benzyl chloroformate in the presence of bases such as triethylamine, diisopropylethylamine or the like in solvents such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane or the like. The carbamates can then be converted into oxazolidinones 4-3 by treating with bases like lithium-, sodium- or potassium hexamethyldisilazide in solvents like tetrahydrofuran, dimethoxyethane or the like. Enantiopure products may be obtained via chiral chromatography.
Compounds of the present invention 5-5 wherein R, R\textsuperscript{a}, p, A\textsuperscript{2}, A\textsuperscript{3} and n are as defined in the claims can be prepared as shown in Scheme 5. Appropriately substituted aminoalcohol 5-1 can be prepared as shown in Scheme 4 and preferentially protected as a carbamate such as t-butyl carbamate (BOC) or benzyl carbamate (Cbz). Other carbamate and alternative protecting groups for nitrogen can be found in “Protective Groups in Organic Synthesis”, 3\textsuperscript{rd} Ed. John Wiley and Sons, New York, pp 494. Protection of the nitrogen with a BOC or Cbz group can be carried out by reaction of 5-1 with di-t-butyldicarbonate or dibenzyldicarbonate in an appropriate solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like. Alcohol 5-2 can be converted to azide 5-3 by reaction with methanesulfonyl chloride in dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like in the presence of an appropriate base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Alternatively, the alcohol may be converted to an alternative leaving group, such as tosylate, iodide, bromide, or the like. The mesylate is then displaced by an azide source, such as NaN\textsubscript{3}, LiN\textsubscript{3}, Bu\textsubscript{4}NN\textsubscript{3} or the like in an appropriate solvent, such as DMF, DMPU, or the like. Azide 5-3 can also be prepared by treatment of alcohol 5-2 with diphenylphosphoryl azide, diethylazodicarboxylate and triphenylphosphine in THF. Azide 5-3 can be reduced by hydrogenation over a metal catalyst such as PtO\textsubscript{2} or Pd/C or the like in an appropriate solvent, such as EtOAc, THF, EtOH, or the like. Following reduction and removal of the protecting group diamine 5-4 is obtained. For the BOC protecting group, TFA/CH\textsubscript{2}Cl\textsubscript{2} is the preferred method of removal; for the CBZ protecting
group, hydrogenation over a metal catalyst, such as PtO₂ or Pd/C or the like in an appropriate solvent, such as EtOAc, THF, EtOH, or the like is the preferred method of removal. Diamines 5-4 are cyclized to imidazolidinones 5-5 using phosgene (Y=Cl) or a phosgene equivalent such as triphosgene (Y=OCCl₃) or carbonyldiimidazole (Y=imidazole) or the like in a solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like and a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Enantiopure products may be obtained via chiral chromatography.

**SCHEME 6**

![Scheme 6](image).

Compounds of the present invention 6-4 wherein R, Rₐ, p, A², A³ and n are as defined in the claims can be prepared as shown in Scheme 6. Treatment of 6-1 with an appropriately substituted protected aminoaldehyde which can be purchased or prepared by known methods in the presence of a reducing agent such as sodium borohydride, sodium cyanoborohydride, sodium triacetoxyborohydride or the like in methanol, ethanol, dichloroethane, tetrahydrofuran or the like or according to methods described in Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 1187-1189 (2001) and references cited therein affords 6-2. Preferred conditions for this transformation are sodium cyanoborohydride in methanol with catalytic acetic acid. Deprotection of 6-2 affords 6-3. For the BOC protecting group, TFA/CH₂Cl₂ is the preferred method of deprotection.
Diamines 6-3 are then cyclized to imidazolidinones 6-4 using phosgene (Y=Cl) or a phosgene equivalent such as triphosgene (Y=OCCl3) or carbonyl-diimidazole (Y=imidazole) or the like in a solvent such as dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like and a base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Enantiopure products may be obtained using chiral chromatography.

Compounds of the present invention 7-5 wherein R, R', p, A², A³, and n are as defined in the claims can be prepared as shown in Scheme 7. Treatment of amine 7-1, prepared as described in Scheme 4 with an appropriate dicarbonate or chloroformate affords 7-2. 7-2 can be converted to azide 7-3 by reaction with methanesulfonyl chloride in dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane, or the like in the presence of an appropriate base such as triethylamine, diisopropylethylamine, N-methylmorpholine, or the like. Alternatively, the alcohol may be converted to an alternative leaving group, such as tosylate, iodide, bromide, or the like. The mesylate is then displaced by an azide source, such as NaN₃, LiN₃, Bu₄NN₃ or the like in an appropriate solvent, such as DMF, DMPU, or the like. Azide 7-3 can also be prepared by treatment of alcohol 5-2 with diphenylphosphoryl azide, diethylazodicarboxylate and triphenylphosphine in THF. Azide 7-3 can be reduced to amine 7-4 with H₂ over PtO₂ with THF as a solvent when R₄ is benzyl. Cyclization of 7-4 to imidazolidinones 7-5 is
accomplished through the use of an appropriate base, such as lithium diisopropylamide or lithium-, sodium-, or potassium bis(trimethylsilyl)amide or the like in an appropriate solvent, such as THF, dimethoxyethane, DMF, DMA, or the like. Enantiopure products may be obtained via chiral chromatography.

**SCHEME 8**

Compound 8-1 (prepared as described in Schemes 5, 6, and 7) wherein R, R\(^3\), A\(^2\), A\(^3\), p, and n are as defined in the claims can be converted to 8-2 by treatment with an appropriate alkylating agent such as an alkyl halide, alkyl tosylate, alkyl mesylate, or the like (for example methyl iodide) in an appropriate solvent such as THF, dimethoxyethane, DMF, DMA, or the like, in the presence of an appropriate base, such as lithium diisopropylamide or lithium-, sodium-, or potassium bis(trimethylsilyl)amide or the like.

**SCHEME 9**

Intermediates 9-3 and 9-4 wherein R\(^3\), p, and A\(^3\) are as defined in the claims utilized in the present invention can be prepared as shown in Scheme 9. An appropriately substituted benzyl nitrile 9-1 prepared as shown in Scheme 2 can be heated with a base such as sodium hydroxide or potassium
hydroxide or the like in an appropriate aqueous alcohol such as ethanol, propanol or the like to afford the appropriately substituted benzoic acid 9-2 (See: Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 1179-1180 (2001) and references therein). Benzoic acids 9-2 can be reduced to benzyl alcohols 9-3 with reducing agents such as borane in solvents such as tetrahydrofuran or the like (See: Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 1549 (2001) and references therein).

Alternatively, 9-2 can be esterified by known methods including treatment with trimethylsilyldiazomethane and the resulting ester reduced to alcohol 9-3 with LiAlH4 or the like. Intermediates 9-3 can be transformed into benzyl bromides 9-4 using reagents such as triphenylphosphine and carbon tetrabromide in solvents such as dichloromethane, dichloroethane or the like (See: Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 518-519 (2001) and references therein).

![Scheme 10](image)

Intermediates 10-4 of the present invention wherein R, R1, A2, p, and n are as defined in the claims can be prepared as shown in Scheme 10 from an appropriately substituted benzaldehyde 10-1 by condensation with a nitroalkane to afford the substituted nitroalcohol 10-2. This reaction may be catalyzed by aqueous bases such as sodium hydroxide or the like in solvents such as ethanol, methanol or the like. Nitroalcohols 10-2 can be reduced to aminoalcohols 10-3 with reductants such as Raney nickel, palladium on activated carbon or platinum oxide in the presence of hydrogen gas and aqueous acid in alcoholic solvents such as methanol, ethanol or the like (See: Langer, O., et al., Bioorg. Med. Chem., 2001, 9, 677-694). Aminoalcohols 10-3 can be cyclised to oxazolidinones 10-4 using reagents such as phosgene (Y=Cl), triphosgene (Y=OCCl3) or carbonyl diimidazole (Y=imidazole) with bases such as triethylamine, disopropylethylamine or the like in solvents like dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane or the like.
INTERMEDIATES 11-4 OF THE PRESENT INVENTION WHEREIN R, R¹, A², p AND n ARE AS DEFINED IN THE CLAIMS CAN BE PREPARED AS SHOWN IN SCHEME 11. TREATMENT OF AN N-CARBAMOYL-(N-METHOXY-N-METHYL)AMIDE OF AN AMINO ACID 11-1 WHICH CAN BE PURCHASED OR PREPARED BY KNOWN METHODS WITH A GRIGNARD OR OTHER ORGANOMETALLIC REAGENT SUCH AS AN ORGANOLITHIUM AFFORDS THE CORRESPONDING KETONE 11-2. REDUCTION OF THE KETONE WITH SODIUM BOROHYDRIDE OR ZINC BOROHYDRIDE IN ALCOHOLIC SOLVENTS OR THF OR THE LIKE OR WITH OTHER REDUCING AGENTS SUCH AS PHENYLDIMETHYL SILANE IN THF AFFORDS ALCOHOL 11-3 WHICH CAN BE CYCLIZED TO OXAZOLIDINONE 11-4 UPON TREATMENT WITH BASE SUCH AS KOH IN SOLVENTS SUCH AS MEOH, ETHOH OR THE LIKE AND THF, DIOXANE, DIMETHOXYETHANE OR THE LIKE.

SCHEME 12

COMPOUNDS OF THE PRESENT INVENTION 12-3 WHEREIN R, R¹, R³, A², A³, p AND n ARE AS DEFINED IN THE CLAIMS CAN BE PREPARED AS SHOWN IN SCHEME 12. OXAZOLIDINONES 12-2, PREPARED AS SHOWN IN SCHEMES 10 AND 11 CAN BE ALKYLATED WITH BENZYL BROMIDES 12-1 WHICH IS PREPARED AS SHOWN IN SCHEME 9 USING BASES SUCH AS SODIUM HEXAMETHYLDISILAZIDE OR SODIUM HYDRIDE IN SOLVENTS LIKE TETRAHYDROFURAN, DIMETHOXYETHANE, DIETHYL ETHER, DIMETHYLFORMAMIDE, DIMETHYLACETAMIDE, OR THE LIKE TO AFFORD PRODUCTS 12-3.

SCHEME 13
Compounds of the present invention 13-4 wherein R, R₁, R₃, A², A³, p and n are as defined in the claims can be prepared as shown in Scheme 13. Oxazolidinones 13-2, prepared as shown in Schemes 10 and 11 can be alkylated with benzyl bromides 13-1 which can be prepared as shown in Scheme 1 using bases such as sodium hexamethyldisilazide or sodium hydride in solvents like tetrahydrofuran, dimethoxyethane, diethyl ether or the like to afford products 13-3. Compounds 13-4 are then prepared via a Suzuki or Stille reaction or variation thereof employing palladium catalyzed cross coupling of iodide 13-3 with an appropriately substituted aryl- or heteroaryl-boronic acid, -boronate ester or -trialkyl tin as described in Miyaura et al., Chem. Rev. 95, 2457 (1995) and references cited within and as described in Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 868-869 (2001) and references cited therein.

SCHEME 14
Compounds 14-5 of the present invention wherein R, R³, A², A³, p and n are as defined in the claims can be prepared as shown in Scheme 14. Benzyl alcohols 14-1 can be purchased or prepared according to the procedure outline in Scheme 9. Reaction of 14-1 with the Dess-Martin periodinane affords the corresponding benzylaldehydes 14-2. Other methods for oxidizing a primary hydroxyl group to an aldehyde can also be used, for example, Swern oxidation conditions, tetrapropylammonium perruthenate, pyridinium chlorochromate, sulfur trioxide-pyridine, or the like. 2-Amino-1-phenylethanol 14-3 can be prepared from 14-2 via the corresponding silylated cyanohydrin by treatment with trimethylsilyl cyanide and catalytic zinc iodide followed by reduction with lithium aluminum hydride or the like reducing agent. Alternatively, 2-amino-1-phenylethanol 14-3 can be prepared from 14-2 via the corresponding cyanohydrin by treatment with potassium cyanide followed by reduction. 2-Amino-1-phenylethanol 14-3 can be cyclized to oxazolidinones 14-4 using reagents such as phosgene (Y=Cl), triphosgene (Y=OCCI₂) or carbonyl diimidazole (Y=imidazole) with bases such as triethylamine, diisopropylethylamine or the like in solvents like dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane or the like. Oxazolidinones 14-4 can be alkylated with alkyl, heteroalkyl, aryl, or heteroaryl bromides using bases such as sodium hexamethyldisilazide or sodium hydride in solvents like tetrahydrofuran, dimethoxyethane, diethyl ether or the like to afford products 14-5. Enantiopure products may be obtained via chiral chromatography.

SCHEME 15

- 39 -
Compounds 15-6 of the present invention wherein R, R¹, R³, A², A³, p and n are as defined in the claims can be prepared as shown in Scheme 15. Aldehydes 15-1 can be purchased or prepared according to the procedure outlined in Scheme 1. Condensation of 15-1 with a nitroalkane affords the substituted nitroalcohols 15-2. This reaction may be catalyzed by aqueous bases such as sodium hydroxide or the like in solvents such as ethanol, methanol, or the like. Nitroalcohols 15-2 can be reduced to aminoalcohols 15-3 with reductants such as Raney nickel, palladium on activated carbon, or platinum oxide in the presence of hydrogen gas and aqueous acid in alcoholic solvents such as methanol, ethanol or the like (See: Langer, O., et al., Bioorg. Med. Chem., 2001, 9, 677-694). Aminoalcohols 15-3 can be cyclized to oxazolidinones 15-4 using reagents such as phosgene (Y=Cl), triphosgene (Y=OCCl₃) or carbonyl diimidazole (Y=imidazole) with bases such as triethylamine, diisopropylethylamine or the like in solvents like dichloromethane, dichloroethane, tetrahydrofuran, dimethoxyethane or the like. Oxazolidinones 15-5 are prepared via a Suzuki or Stille reaction or variation thereof employing palladium catalyzed cross coupling of iodides 15-4 with appropriately substituted aryl- or heteroarylboronic acids, -boronate esters or -trialkyl tin compounds, as described in Miyaura et al., Chem. Rev. 95, 2457 (1995) and references cited within, and as described in Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 868-869 (2001) and references cited therein. Oxazolidinones 15-5 can be alkylated with alkyl, heteroalkyl, aryl, or heteroaryl bromides using bases such as sodium hexamethyldisilazide or sodium hydride in solvents like
tetrahydrofuran, dimethoxyethane, diethyl ether or the like to afford products 15-6. Enantiopure products may be obtained via chiral chromatography.

Compounds 16-5 of the present invention wherein R, R^1, R^2, A^2, A^3, p and n are as defined in the claims can be prepared as shown in Scheme 16. Aldehydes 16-1 can be purchased or prepared according to the procedure outline in Scheme 1. Condensation of 16-1 with chiral N-acyloxazolidinones affords the aldol adducts 16-2, as described in Evans, D.A. et al., *J. Am. Chem. Soc.*, 2002, 124, 392-3. The chiral N-acyloxazolidinones can be purchased or prepared as described in Ager, D.J.; Allen, D.A.; Schaad, D.R. *Synthesis* 1996, 1283-5. Compounds 16-2 can be hydrolyzed to the corresponding acids and then treated with diphenylphosphorazidate and a trialkylamine base to effect a Curtius rearrangement, affording chiral oxazolidinones 16-3. Oxazolidinones 16-4 are prepared via a Suzuki or Stille reaction or variation thereof employing palladium catalyzed cross coupling of iodides 16-3 with appropriately substituted aryl- or heteroaryl-boronic acids, -boronate esters or -trialkyl tin compounds, as described in Miyaura et al., *Chem. Rev.* 95, 2457 (1995) and references cited within, and as described in Smith, M. B. and March, J. “March’s Advanced Organic Chemistry”, 5th Ed., John Wiley and Sons, New York, pp. 868-869 (2001)
and references cited therein. Oxazolidinones 16-4 can be alkylated with alkyl, heteroalkyl, aryl, or heteroaryl bromides using bases such as sodium hexamethyldisilazide or sodium hydride in solvents like tetrahydrofuran, dimethoxyethane, diethyl ether or the like to afford products 16-5. Alternatively, oxazolidinones 16-3 are alkylated with the appropriate bromides to afford compounds 16-6, which are subjected to a Suzuki or Stille reaction or variation thereof with appropriately substituted aryl- or heteroaryl-boronic acids, -boronate esters or -trialkyl tin compounds to afford products 16-5.

EXAMPLE 1

\[
\begin{array}{c}
\text{F}_3\text{C} \\
\text{NH}_2 \\
\text{CN}
\end{array}
\]

2-Amino-5-(trifluoromethyl)benzonitrile
A 2-liter flask was charged with 100 g (0.348 mol) of 4-amino-3-iodobenzotrifluoride, 40 g of CuCN and 750 mL of DMF. The mixture was heated to and then maintained at reflux for 1 hour. The reaction was cooled and poured into 3 L of water containing 300 mL of concentrated ammonium hydroxide. To the mixture was added 1 L CH$_2$Cl$_2$. The mixture was then filtered through celite. The layers were separated and the aqueous layer was back extracted with CH$_2$Cl$_2$. The organic extracts were combined and the solvent removed under reduced pressure. The residue was dissolved in 1.5 L of ether and the resulting solution was washed with 1N ammonium hydroxide, aqueous sodium bisulfite, 1N aqueous HCl and brine. The solution was dried over anhydrous MgSO$_4$ and filtered through a silica gel plug containing a layer of MgSO$_4$ on top. The plug was washed with 0.5 L ether. The ether solutions were combined and concentrated to 750 mL and let stand at room temperature. After 2 days the resulting solids were collected, washed with hexanes and dried under reduced pressure to afford 2-amino-5-(trifluoromethyl)benzonitrile. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.68 (s, 1H), 7.58 (d, $J$ = 8.5 Hz, 1H), 6.81 (d, $J$ = 8.5 Hz, 1H), 4.80 (br s, 2H).

EXAMPLE 2

\[
\begin{array}{c}
\text{F}_3\text{C} \\
\text{CN}
\end{array}
\]

2-Iodo-5-(trifluoromethyl)benzonitrile
To a solution of 2-amino-5-(trifluoromethyl)benzonitrile (15.1 g) and diiodomethane (24 mL) in acetonitrile (150 mL) at 35°C was added t-butyl nitrite (21 mL) dropwise. The reaction was maintained
at 30 – 35°C during the addition. The reaction was aged for 30 min and then was heated to 60°C for 30 minutes. The reaction mixture was cooled, diluted with ether and washed 2x with water, 2x with aqueous sodium bisulfite, water and then brine. The solution was dried over anhydrous MgSO₄, filtered through a silica gel plug and then concentrated giving 100 g of a red oil. The product was purified by silica gel chromatography eluting sequentially with hexanes, 3:1 hexanes/CH₂Cl₂ and 1:1 hexanes/CH₂Cl₂ to afford 2-iodo-5-(trifluoromethyl)benzonitrile. ¹H NMR (CDCl₃, 500 MHz) δ 8.10 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 1.8 Hz, 1H), 7.52 (dd, J = 8.5, 1.8 Hz, 1H).

EXAMPLE 3

5′-Isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-carbonitrile

To a solution of 2-iodo-5-(trifluoromethyl)benzonitrile (2.0 g, 6.7 mmol) and (5-isopropyl-2-methoxyphenyl)boronic acid (1.6 g, 8.4 mmol) in dimethyl ethylene glycol (30.4 mL) was added 2M Na₂CO₃ (6.8 mL), ethanol (9.6 mL), and water (10 mL). The solution was degassed with nitrogen for 2 minutes. Pd(PPh₃)₄ (774 mg, 0.67 mmol) was added and the solution was degassed with nitrogen again for 2 minutes. The solution was divided equally into two 40 mL microwave tubes. Each tube was degassed with nitrogen for 1 minute, sealed, and placed in a microwave reactor. The wattage was set for 200 W until the temperature reached 150°C and then the temperature was held at 150°C for ten minutes. The tubes were then cooled to room temperature, combined, poured into H₂O (50 mL), and extracted with EtOAc (100 mL). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated. Purification by flash chromatography with 15% CH₂Cl₂/hexanes afforded 5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-carbonitrile as a light yellow oil. Rₜ = 0.65 (25% EtOAc/hexanes). ¹H NMR (CDCl₃, 500 MHz) δ 7.97 (s, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.31 (dd, J = 8.5, 2.0 Hz, 1H), 7.12 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H), 3.82 (s, 3H), 2.93 (m, 1H), 1.27 (d, J = 7.0 Hz, 6H).

EXAMPLE 4
1-[5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biaryl-2-yl]methanamine

5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biaryl-2-carbonitrile (996.2 mg, 3.12 mmol) was dissolved in Et₂O (33 mL) and cooled to 0°C. LAH (12.49 mL of a 1 M solution in Et₂O, 12.49 mmol) was added dropwise by syringe. After stirring at 0°C for 10 minutes, the reaction was warmed to room temperature and stirred at room temperature for 6 hours. The reaction was then quenched by slow dropwise addition of 1.5 mL of H₂O (vigorous evolution of gas), followed by 1.5 mL of 30% NaOH, followed by 3.0 mL of H₂O. The resulting gelatinous precipitate was washed with 5 x 20 mL of CH₂Cl₂; the organic washes were dried over Na₂SO₄, filtered and concentrated. Purification of the residue by flash chromatography with 2%MeOH/CH₂Cl₂ containing 0.1% Et₃N afforded 1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biaryl-2-yl]methanamine. Rₚ = 0.30 (10% MeOH/CH₂Cl₂). LCMS = 324.3 (M+1)⁺.

¹H NMR (CDCl₃, 500 MHz) δ 7.77 (s, 1H), 7.55 (d, J = 6.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.25 (dd, J = 8.3, 2.1 Hz, 1H), 7.00 (d, J = 2.1 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 3.66-3.74 (m, 5H), 2.91 (m, 1H), 1.26 (d, J = 6.9 Hz, 6H).

EXAMPLE 5

4-[3.5-bis(trifluoromethyl)phenyl]-3-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biaryl-2-yl]methyl]-1,3-oxazolidin-2-one

Step A: methyl [3.5-bis(trifluoromethyl)phenyl](hydroxy)acetate

To solution of [3.5-bis(trifluoromethyl)phenyl](hydroxy)acetic acid (510 mg, 1.77 mmol) in benzene (10 mL) was added MeOH (1.5 mL) followed by (trimethylsilyl)diazomethane (1.06 mL of a 2M solution in hexanes, 2.12 mmol). After 10 minutes, the reaction was quenched with several drops of HOAc (add until yellow color disappears). The reaction was concentrated and purified by flash chromatography with 10 to 80% EtOAc/hexanes to afford methyl [3.5-bis(trifluoromethyl)phenyl](hydroxy)acetate. ¹H NMR (CDCl₃, 500 MHz) δ 7.94 (s, 2H), 7.85 (s, 1H), 5.32 (s, 1H), 3.83 (s, 3H), 3.68 (bs, 1H).

Step B: methyl [3.5-bis(trifluoromethyl)phenyl](bromo)acetate

Methyl [3.5-bis(trifluoromethyl)phenyl](hydroxy)acetate (300 mg, 0.993 mmol) was dissolved in CH₂Cl₂ (10 mL). The solution was cooled to 0°C and CBr₄ (659 mg, 1.986 mmol) was added followed
by PPh₃ (521 mg, 1.986 mmol). After 1 hour, the reaction was warmed to room temperature and stirred at room temperature for 1 hour. The reaction was filtered through a short plug of silica gel with CH₂Cl₂. The filtrate was concentrated and the residue was purified by flash chromatography with 5% EtOAc/hexanes to afford methyl [3,5-bis(trifluoromethyl)phenyl](bromo)acetate. Rₗ = 0.24 (5% EtOAc/hexanes). ¹H NMR (CDCl₃, 500 MHz) δ 8.02 (s, 2H), 7.87 (s, 1H), 5.41 (s, 1H), 3.83 (s, 3H).

Step C: methyl[3,5-bis(trifluoromethyl)phenyl][{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino]acetate
To a flask containing methyl [3,5-bis(trifluoromethyl)phenyl](bromo)acetate (237.7 mg, 0.651 mmol) was added 1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyamine (102.1 mg, 0.316 mmol) in CH₂Cl₂ (4 mL). The reaction was stirred at room temperature for 5 hours and then diluted with EtOAc (50 mL). The organic solution was washed with water and brine (15 mL each). The organic extract was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography (5 to 15% EtOAc/hexanes) afforded methyl[3,5-bis(trifluoromethyl)phenyl][{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino]acetate. Rₗ = 0.33 (15% EtOAc/hexanes). LCMS = 608.4 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.76-7.79 (m, 3H), 7.62 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.23 (dd, J = 8.2, 1.9 Hz, 1H), 6.96 (m, 1H), 6.89 (d, J = 8.5 Hz, 1H), 4.30 (m, 1H), 3.54-3.70 (m, 8H), 2.87 (m, 1H), 1.21-1.23 (m, 6H).

Step D: 2-[3,5-bis(trifluoromethyl)phenyl]-2-{{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino}ethanol
A solution of methyl[3,5-bis(trifluoromethyl)phenyl][{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino]acetate (13.2 mg, 0.0217 mmol) was dissolved in Et₂O (1.5 mL) and cooled to 0°C. LAH (108.5 µL of a 1 M solution in LAH, 0.1085 mmol) was added dropwise by syringe. The reaction was warmed to room temperature and stirred at room temperature for 1 hour. The reaction was then quenched by addition of H₂O (100 µL) followed by 1 N NaOH (100 µL), followed by H₂O (300 µL). The gelatinous precipitate was washed several times with CH₂Cl₂. The organic washes were filtered through a plug of silica gel with 2% MeOH/CH₂Cl₂ and the filtrate was concentrated. Purification of the residue by PTLC with 25% EtOAc/hexanes afforded 2-[3,5-bis(trifluoromethyl)phenyl]-2-{{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino}ethanol. Rₗ = 0.27 (25% EtOAc/hexanes). LCMS = 580.4 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.79 (s, 1H), 7.75 (s, 2H), 7.63-7.68 (m, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.8 Hz, 1H), 7.23 (m, 1H), 6.94 (m, 1H), 6.89 (m, 1H), 3.43-3.76 (m, 9H), 2.86 (m, 1H), 1.90 (bs, 1H), 1.20 (d, J = 6.8 Hz, 6H).

Step E: 4-[3,5-bis(trifluoromethyl)phenyl]-3-{{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-1,3-oxazolidin-2-one
To a solution of phosgene (21 µL of a 20% solution in toluene, ~ 0.0535 mmol) in CH₂Cl₂ (0.5 mL) was added 2-[3,5-bis(trifluoromethyl)phenyl]-2-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}amino)ethanol (3.1 mg, 0.00535 mmol) in CH₂Cl₂ (0.5 mL), followed by DIPEA (19 µL, 0.107 mmol). After stirring for 5 minutes, the reaction was poured into water (1 mL) and the mixture was extracted with EtOAc (20 mL). The organic extract was washed with H₂O, saturated NaHCO₃, and brine (5 mL each). The organic layer was then dried over Na₂SO₄, filtered, and concentrated. The residue was purified by PTLC to afford 4-{3,5-bis(trifluoromethyl)phenyl}-3-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}-1,3-oxazolidin-2-one. R<sub>f</sub> = 0.27 (25% EtOAc/hexanes).

LCMS = 606.3 (M+1)<sup>+</sup>. <sup>1</sup>H NMR (CD₂Cl₂, 500 MHz) (Doubling of some peaks observed; atropisomers present in 1:1 ratio) δ 7.84 (s, 1H), 7.19-7.60 (m, 6H), 6.80-6.87 (m, 2H), 3.84-4.68 (m, 5H), 3.68 & 3.64 (2 singlets, 3H), 2.82 (m, 1H), 1.17-1.21 (m, 6H).

**EXAMPLE 6**

![Chemical Structure]

5-{3,5-bis(trifluoromethyl)phenyl}-3-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}-1,3-oxazolidin-2-one

**Step A: 2-[3,5-bis(trifluoromethyl)phenyl]oxirane**

In a dry flask was placed NaH (1.09 g of 60% NaH, 27.27 mmol). DMSO (90 mL) was added followed by trimethylsulfoxonium iodide (7.0 g, 31.82 mmol). The reaction was stirred for 5 minutes and then 3,5-bis(trifluoromethyl)benzaldehyde (1.5 mL, 9.09 mmol) was added as a solution in DMSO (15 mL). The reaction was stirred at room temperature for 1 hour and then poured into ice/water (300 mL). The mixture was extracted with pentanes (3 x 150 mL). The pentane extracts were combined and filtered through a short plug of silica gel with 10% EtO/Pentanes. The filtrate was concentrated and the residue was purified by flash chromatography with 10% EtO/Pentanes to give 2-[3,5-bis(trifluoromethyl)phenyl]oxirane. R<sub>f</sub> = 0.42 (10% EtO/Pentanes).<sup>1</sup>H NMR (CDCl₃, 500 MHz) 7.82 (s, 1H), 7.74 (s, 2H), 3.99 (dd, J = 3.9, 2.5 Hz, 1H), 3.23 (dd, J = 5.2, 4.1 Hz, 1H), 2.79 (dd, J = 5.5, 2.5 Hz, 1H).
Step B: 1-[3,5-bis(trifluoromethyl)phenyl]-2-({[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)ethanol

A solution of 1-[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methenamine (300 mg, 0.929 mmol) and 2-[3,5-bis(trifluoromethyl)phenyl]oxirane (297 mg, 1.161 mmol) in 2-propanol (9 mL) was heated at reflux for 15 hours and then cooled to room temperature. The solution was concentrated, and purification of the residue by flash chromatography with 10 to 80% EtOAc/hexanes afforded 1-[3,5-bis(trifluoromethyl)phenyl]-2-({[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)ethanol. Rf = 0.24 (25% EtOAc/hexanes). LCMS = 580.3 (M+1)+. 1H NMR (CDCl3, 500 MHz) δ 7.75-7.76 (m, 3H), 7.69 (s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.7 Hz, 1H), 7.25 (m, 1H), 6.98 (bs, 1H), 6.92 (d, J = 8.5 Hz, 1H), 4.62 (m, 1H), 3.65-3.82 (m, 5H), 2.89 (m, 1H), 2.79 (dd, J = 12.4, 3.0 Hz, 1H), 2.48 (m, 1H), 1.23 (d, J = 6.8 Hz, 6H).

Step C: 5-[3,5-bis(trifluoromethyl)phenyl]-3-([5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1,3-oxazolidin-2-one

To a solution of 1-[3,5-bis(trifluoromethyl)phenyl]-2-({[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)ethanol (31.9 mg, 0.0551 mmol) in CH2Cl2 (5 mL) at 0°C was added DIPEA (67 μL, 0.386 mmol), followed by triphosgene (8.2 mg, 0.0276 mmol). The reaction was stirred at 0°C for 30 minutes. The reaction was then poured into saturated NaHCO3 (15 mL) and the mixture was extracted with EtOAc (50 mL). The organic layer was washed with brine (15 mL), dried over Na2SO4, filtered, and concentrated. Purification of the residue by flash chromatography (20% EtOAc/hexanes) afforded 5-[3,5-bis(trifluoromethyl)phenyl]-3-([5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl)-1,3-oxazolidin-2-one. Rf = 0.32 (25% EtOAc/hexanes). LCMS = 606.3 (M+1)+. 1H NMR (CD2Cl2, 500 MHz) (atropisomers present in 1:1 ratio, doubling of some peaks) δ 7.90 (s, 1H), 7.77 (s, 2H), 7.57-7.62 (m, 2H), 7.37 (d, J = 8.0 Hz, 1H), 7.27 (m, 1H), 6.98 (s, 1H), 6.93 (dd, J = 8.4, 3.2 Hz, 1H), 5.42-5.53 (m, 1H), 4.15-4.59 (m, 2H), 3.72 & 3.73 (2 singlets, 3H), 3.05-3.65 (m, 2H), 2.88 (m, 1H), 1.19-1.23 (m, 6H).

The 2 enantiomers could be separated by chiral HPLC using 15% IPA/heptanes and an AD chiral column.

EXAMPLE 7
3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]-5-pyridin-2-yl-1,3-oxazolidin-2-one

Step A: 2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]amino]-1-pyridin-2-ylethanol

A solution of 1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methenamine (300 mg, 0.929 mmol) and 2-oxiran-2-ylpyridine (640 mg) [prepared by reaction of 2-pyridine carboxaldehyde with NaH and trimethylsulfoxonium iodide in DMSO] in 2-propanol (9 mL) was heated at reflux for 5 hours and then cooled to room temperature. The solution was concentrated, and the residue was purified by flash chromatography with 50 to 100% EtOAc/hexanes containing 0.5% Et3N to afford 2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]amino]-1-pyridin-2-ylethanol. Analysis by LCMS showed the desired product contaminated with several minor impurities. This material was used in the next reaction without further purification or analysis.

Step B: Benzyl (2-hydroxy-2-pyridin-2-ylethyl)[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]carbamate

A solution of (PhCH₂OCO)₂O (103 mg, 0.360 mmol) in dry CH₂Cl₂ (2 mL) was added by cannula to a stirred solution of 2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]amino]-1-pyridin-2-ylethanol (160 mg, 0.360 mmol) in dry CH₂Cl₂ (10 mL) at room temperature under N₂. The reaction was stirred for 2 h at room temperature and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 25 x 160 mm, 0-50% EtOAc in hexanes gradient) to afford benzyl (2-hydroxy-2-pyridin-2-ylethyl)[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]carbamate. Rf = 0.63 (50% EtOAc/hexanes). LCMS calc. = 579.25; found = 579.2 (M+1)+.

Step C: 3-[[5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]-5-pyridin-2-yl-1,3-oxazolidin-2-one

A solution of potassium bis(trimethylsilyl)amide (464 μL of a 0.5M solution in toluene, 0.232 mmol) was added dropwise to a stirred solution of benzyl (2-hydroxy-2-pyridin-2-ylethyl)[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]carbamate (134.3 mg, 0.232 mmol) in dry THF (10 mL) at room temperature under N₂. After stirring at room temperature for 1 h, the reaction was quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash
chromatography (Si, 25 x 160 mm, 0-70% EtOAc in hexanes gradient) to afford 3-\{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl\}-5-pyridin-2-yl-1,3-oxazolidin-2-one. R_f = 0.58 (50% EtOAc/hexanes). LCMS calc. = 471.19; found = 471.2 (M+1)^+.

EXAMPLE 8

\[
\begin{align*}
\text{MeO} & \\
\text{F}_3\text{C} & \\
\text{CO}_2\text{H} & \\
\end{align*}
\]

5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxylic acid

A solution of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbonitrile (727 mg, 2.28 mmol) and KOH (767 mg, 13.7 mmol) in H_2O (7.70 mL) and i-PrOH (11.55 mL) was subjected to microwave irradiation (300W 130°C, 4 h) in a sealed tube. The reaction mixture was concentrated in vacuo to remove the i-PrOH. The aqueous slurry obtained was diluted with water (50 mL) and extracted with EtOAc (50 mL). The organic extract was dried (Na_2SO_4) and concentrated in vacuo to afford 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxamide. The aqueous layer was acidified with concentrated HCl and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxylic acid as a colorless solid. ^1H NMR (CDCl_3, 500 MHz) δ 8.01 (s, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.14 (d, J = 8.1 Hz, 1H), 7.04 (s, 1H), 6.77 (d, J = 8.1, 1H), 3.68 (s, 3H), 2.84 (septet, J = 6.7 Hz, 1H), 1.19 (d, J = 6.7 Hz, 6H).

EXAMPLE 9

\[
\begin{align*}
\text{MeO} & \\
\text{F}_3\text{C} & \\
\text{OH} & \\
\end{align*}
\]

[5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol

A solution of borane in THF (1 M, 859 μL, 0.859 mmol) was added dropwise to a stirred solution of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxylic acid and 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carboxamide (3:1, 96.8 mg, 0.286 mmol) in dry THF at room temperature under N_2. The reaction was stirred at room temperature for 3 h and carefully quenched with water (10 mL). The mixture was extracted with EtOAc (3 x 20 mL) and the combined extracts were washed with
brine, dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 125 x 160 mm, 0-30% EtOAc in hexanes gradient) to afford [5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol as a colorless oil. Rᵣ = 0.27 (10% EtOAc/hexanes). ¹H NMR (CDCl₃, 500 MHz) δ 7.89 (br s, 1H), 7.62 (dd, J = 8.0, 1.3 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.29 (dd, J = 8.5, 2.3 Hz, 1H), 7.03 (d, J = 2.3 Hz, 1H), 6.96 (d, J = 8.5, 1H), 4.51 (m, 2H), 3.74 (s, 3H), 2.93 (septet, J = 7.0 Hz, 1H), 2.51 (s, 1H), 1.29 (d, J = 7.0 Hz, 6H).

EXAMPLE 10

2-(Bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl
CBr₄ (112 mg, 0.211 mmol) and Ph₃P (55 mg, 0.211 mmol) were added successively to a stirred solution of [5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol (57.1 mg, 0.176 mmol) in dry CH₂Cl₂ (1 mL) at 0°C under N₂. The solution was stirred at room temperature for 1 h and the reaction mixture was concentrated in vacuo to afford the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-20% EtOAc in hexanes gradient) to give 2-(bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl as a colorless oil. Rᵣ = 0.95 (20% EtOAc/hexanes). LCMS calc. = 387.05; found = 387.0 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.83 (br s, 1H), 7.60 (dd, J = 8.0, 1.3 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.29 (dd, J = 8.5, 2.3 Hz, 1H), 7.14 (d, J = 2.3 Hz, 1H), 6.95 (d, J = 8.5, 1H), 4.45 (d, J = 10.6 Hz, 1H), 4.33 (d, J = 10.6 Hz, 1H), 3.76 (s, 3H), 2.94 (septet, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H).

EXAMPLE 11

1-(4-Methylphenyl)-2-nitroethanol

- 50 -
A stirred solution of 4-methylbenzaldehyde (325 mg, 3.19 mL, 2.71 mmol) and nitromethane (531 µL, 9.89 mmol) in absolute EtOH (20 mL) at 0°C was treated with 10% aq. NaOH (m/v) (1.14 mL, 2.84 mmol), stirred for 1 h and treated with 2% aq. acetic acid (m/v) (8.54 mL, 2.84 mmol). The reaction was stirred for 1 h at room temperature then partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed with saturated NaHCO3 (50 mL) and brine (50 mL), dried (Na2SO4) and concentrated in vacuo to afford 1-(4-methylphenyl)-2-nitroethanol as a colorless oil. 1H NMR (CDCl3, 500 MHz) δ 7.28 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 8.1 Hz, 2H), 5.42 (dt, J = 9.6, 3.3 Hz, 1H), 4.60 (dd, J = 13.3, 9.7 Hz, 1H), 4.49 (dd, J = 13.3, 3.1 Hz, 1H), 2.79 (d, J = 3.7, 1H), 2.36 (s, 3H).

EXAMPLE 12

2-Amino-1-(4-methylphenyl)ethanol
A suspension of 10% Pd/C (24 mg) in a solution of 1-(4-methylphenyl)-2-nitroethanol (50 mg, 0.276 mmol) in absolute EtOH (1 mL) was stirred overnight at room temperature under 15 psi of H2. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo to afford 2-amino-1-(4-methylphenyl)ethanol as an oil. LCMS calc. = 152.10; found = 152 (M+1)+. 1H NMR (CDCl3, 500 MHz) δ 7.20 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 4.57 (dd, J = 7.9, 3.9 Hz, 1H), 2.86 (dd, J = 12.7, 3.9 Hz, 1H), 2.76 (dd, J = 12.7, 7.9 Hz, 1H), 2.33 (s, 3H).

EXAMPLE 13

5-(4-Methylphenyl)-1,3-oxazolidin-2-one
Diisopropylethylamine (181 mg, 244 µL, 1.40 mmol) and triphosgene (138 mg, 0.466 mmol) were added successively to a stirred solution of 2-amino-1-(4-methylphenyl)ethanol (35.2 mg, 0.233 mmol) in dry CH2Cl2 (22 mL) at 0°C under N2. The reaction was stirred at 0°C for 1 h then concentrated in vacuo to a volume of about 5 mL. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na2SO4) and concentrated in vacuo to give the crude
product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-80% EtOAc in hexanes gradient) to afford 5-(4-methylphenyl)-1,3-oxazolidin-2-one. $R_f = 0.41$ (50% EtOAc/hexanes). LCMS calc. = 178.08; found = 178.1 (M+1)$^+$. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.25 (d, $J = 7.4$ Hz, 2H), 7.19 (d, $J = 7.4$ Hz, 2H), 6.69 (br s, 1H), 5.55 (t, $J = 7.8$ Hz, 1H), 3.93 (t, $J = 8.6$ Hz, 1H), 3.52 (t, $J = 8.1$ Hz, 1H), 2.35 (s, 3H).

**EXAMPLE 14**

![Example 14 Diagram](image)

3-[[5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl[methyl]-5-(4-methylphenyl)-1,3-oxazolidin-2-one

Sodium hydride (6.4 mg of a 60% dispersion in mineral oil, 0.161 mmol) was added to a stirred solution of 5-(4-methylphenyl)-1,3-oxazolidin-2-one (37.7 mg, 0.0973 mmol) in dry THF (1 mL) at room temperature under N$_2$. The reaction was stirred for 30 min and a solution of 2-(bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl (19.0 mg, 0.107 mmol) in dry THF (2 mL) was added by cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated NH$_4$Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-80% EtOAc in hexanes gradient) to afford 3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl[methyl]-5-(4-methylphenyl)-1,3-oxazolidin-2-one as a colorless oil. $R_f = 0.37$ (20% EtOAc/hexanes). LCMS calc. = 484.21; found = 484.2 (M+1)$^+$. $^1$H NMR (benzene-$d_6$, 500 MHz, 1:1 mixture of atropisomers) $\delta$ 7.76 (s, 0.5H), 7.65 (s, 0.5H), 7.31 (d, $J = 7.7$ Hz, 1H), 7.08 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.05 (br d, $J = 7.8$ Hz, 1H), 6.95-6.86 (m, 5H), 6.58 (t, $J = 7.7$ Hz, 1H), 4.74 (t, $J = 8.0$ Hz, 0.5H), 4.70 (t, $J = 8.0$ Hz, 0.5H), 4.50 (d, $J = 15.7$ Hz, 0.5H), 4.42 (d, $J = 15.7$ Hz, 0.5H), 4.25 (d, $J = 15.7$ Hz, 0.5H), 4.11 (d, $J = 15.7$ Hz, 0.5H), 3.26 (s, 1.5H), 3.21 (s, 1.5H), 2.81 (t, $J = 8.6$ Hz, 0.5H), 2.76 (septet, $J = 7.0$ Hz, 1H), 2.68 (t, $J = 8.6$ Hz, 0.5H), 2.55 (t, $J = 8.6$ Hz, 0.5H), 2.53 (t, $J = 8.6$ Hz, 0.5H), 2.04 (s, 3H), 1.20 (t, $J = 7.0$ Hz, 3H), 1.19 (t, $J = 7.0$ Hz, 3H).
EXAMPLE 15

![Chemical Structure](image)

1-[3,5-Bis(trifluoromethyl)phenyl]-2-nitropropan-1-ol

A stirred solution of 3,5-bis(trifluoromethyl)benzaldehyde (1.00 g, 4.13 mmol) and nitroethane (1.13 g, 1.08 mL, 15.1 mmol) in absolute EtOH (20 mL) at 0°C was treated with 10% aq. NaOH (m/v) (1.73 mL, 4.34 mmol), stirred for 1 h and treated with 2% aq. acetic acid (m/v) (13.0 mL, 4.32 mmol). The reaction was stirred for 1 h at room temperature then partitioned between water (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL) and the combined organic extracts were washed with saturated NaHCO₃ (50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated in vacuo to afford a 1.5:1 mixture of threo- and erythro- 1-[3,5-bis(trifluoromethyl)phenyl]-2-nitropropan-1-ol as a colorless oil. ¹H NMR (CDCl₃, 500 MHz) threo-diastereoisomer: δ 7.88 (br s, 1H), 7.86 (br s, 2H), 5.22 (d, J = 8.4 Hz, 1H), 4.77 (dq, J = 8.4, 6.9 Hz, 1H), 3.03 (br s 1H), 1.42 (d, J = 6.9 Hz, 3H), erythro-diastereoisomer: δ 7.90 (br s, 1H), 7.86 (br s, 2H), 5.59 (d, J = 3.2 Hz, 1H), 4.72 (dq, J = 3.2, 6.9 Hz, 1H), 3.03 (br s 1H), 1.50 (d, J = 6.9 Hz, 3H).

EXAMPLE 16

![Chemical Structure](image)

2-Amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol

A suspension of Raney Nickel (50 mg) in a solution of a 1.5:1 mixture of threo- and erythro- 1-[3,5-bis(trifluoromethyl)phenyl]-2-nitropropan-1-ol (50 mg, 0.158 mmol) in 30% (v/v) aqueous HCO₂H (0.75 mL) and MeOH (10 mL) was stirred overnight at room temperature under 15 psi of H₂. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo to remove the
MeOH. The aqueous slurry was adjusted to pH 9-10 with 28% aq NH$_4$OH, diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated in vacuo to afford a mixture of threo- and erythro- 2-amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol as colorless solid. LCMS calc. = 288.08; found = 288.1 (M+1)$^+$. $^1$H NMR (CDCl$_3$, 500 MHz) threo-diastereoisomer: $\delta$ 7.79 (br s, 3H), 4.35 (br s, 1H), 3.25 (br s, 1H), 2.59 (br s, 3H), 0.86 (d, $J = 6.1$ Hz, 3H), erythro-diastereoisomer: $\delta$ 7.79 (br s, 3H), 4.71 (br s, 1H), 3.00 (br s, 1H), 2.59 (br s, 3H), 1.06 (d, $J = 5.0$ Hz, 3H).

**EXAMPLE 17**

![Chemical Structure]

5-[3,5-Bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

Diallylpropylethylamine (106 mg, 142 µL, 0.817 mmol) and triplosgene (20.2 mg, 0.068 mmol) were added successively to a stirred solution of 2-Amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol (39.1 mg, 0.136 mmol) in dry CH$_2$Cl$_2$ (10 mL) at 0°C under N$_2$. The reaction was stirred at 0°C for 1 h then concentrated in vacuo to a volume of about 5 mL. The mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-70% EtOAc in hexanes gradient) to afford threo-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (17.5 mg) and erythro-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (14.4 mg) as colorless solids. threo-diastereoisomer: $R_f$ = 0.63 (50% EtOAc/hexanes). LCMS calc. = 314.06; found = 314.1 (M+1)$^+$. $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 7.90 (br s, 1H), 7.83 (br s, 2H), 6.71 (br s, 1H), 5.17 (d, $J = 7.0$ Hz, 1H), 3.86 (br pentet, $J = 6.2$ Hz, 1H), 1.48 (d, $J = 6.2$ Hz, 1H). This compound was separated into its enantiomers (4R, 5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and (4S, 5S)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one using chiral HPLC (AS column, 20 x 250 mm, 20% i-PrOH in heptane). erythro-diastereoisomer: $R_f$ = 0.38 (50% EtOAc/hexanes). LCMS calc. = 314.06; found = 314.1 (M+1)$^+$. $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 7.90 (br s, 1H), 7.79 (br s, 2H), 5.83 (d, $J = 8.0$ Hz, 1H), 5.34 (br s, 1H), 4.31 (br pentet, $J = 7.0$ Hz, 1H), 0.84 (d, $J = 6.6$ Hz, 1H). This compound was separated into its two enantiomers (4S, 5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and (4R, 5S)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one using chiral HPLC (AS column, 20 x 250 mm, 15% i-PrOH in heptane).
Chiral Synthesis of (4S,5R)-5-[3,5-Bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

This intermediate can be made directly from the chiral starting material CBZ-L-alanine by the 3-step route shown below. The compound (4R,5S)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one can be made by an analogous route starting from CBZ-D-alanine.

**Step 1**

\[
\begin{align*}
\text{HO} &\quad \text{NHBZ} \\
\text{O} &\quad \text{NHBZ} \\
1. \text{HOBt-H₂O, EDC-HCl} &\quad \text{O} \\
\text{DIPEA, Me(OEt)₂} &\quad \text{NHBZ} \\
2. \text{HCl/IPAC} &\quad \text{NHBZ} \\
3. \text{Heptane Crystallization} &\quad \text{NHBZ}
\end{align*}
\]

CBZ-L-Alanine (6.5 kg, 28.5 mol), HOBt-hydrate (4.8 kg, 34.8 mol), Weinreb amine-HCl salt (3.4 kg, 36.2 mol) and THF (32 L) are charged to a clean flask under nitrogen. The mixture is cooled to 0-10°C and then DIPEA (12.4L) is slowly added at a temperature less than 25°C. EDC-HCl (7Kg, 36.2 mol) is then added slowly with cooling at 15°-25°C. The slurry is aged overnight at 20°-25°C. The mixture is then cooled to 0°-10°C and 3 N HCl (12L) is added slowly. Then IPAC (32 L) is added and the layers are separated. The organic layer is washed once with HCl (13L) and twice with 8% NaHCO₃ (13L) (CAUTION: FOAMING). The organic layer is then concentrated under vacuum to about 15L at 50°C. The clear solution is cooled slowly to room temperature, allowing the product to crystallize. Heptane (~70L) is then added slowly. The slurry is filtered, washed with heptane (18L), and dried at room temperature on the filter pot. Product is obtained with >99.9% ee measured by chiral HPLC.

**Step 2**

\[
\begin{align*}
\text{F₃C} &\quad \text{NHBZ} \\
\text{Br} &\quad \text{NHBZ} \\
\text{F₃C} &\quad \text{NHBZ} \\
\text{F₃C} &\quad \text{NHBZ}
\end{align*}
\]

The Weinreb amide from Step 1 (6kg, 22.5 mol) and 3,5-bis(trifluoromethyl)bromobenzene (4.85L, 28.1 mol) are dissolved in anhydrous THF (24L). The solution is purged with nitrogen to remove oxygen. The water content should be <500ppm at this point. Atmospheric distillation can be carried out to azetropically remove water if necessary. The solution is cooled to -10°C and iso-PrMgCl in THF (56.4 mol) is slowly added (2 hours) to the reaction via addition funnel, maintaining a reaction temperature ≤ -5°C. The solution is allowed to warm to 20°C and aged overnight at 20°C, until the amide is <0.5 LCAP. The reaction is then cooled to -10°C under nitrogen and is quenched slowly over 2 hours into 5N HCl (14L) that is maintained at 0-5°C. MTBE (12L) is added and the biphasic mixture is agitated for 5 min. After warming to 20°-25°C, it is allowed to settle for 30 min, and then the layers are separated. The organic layer is washed with water twice (12L).
The organic layer is vacuum transferred through a 1-micron in-line PTFE filter into a distillation flask and is then concentrated to ~12L under vacuum (internal temperature <40°C) to a minimum agitated volume. The solution is then azeotropically dried with toluene and taken to a minimum agitated volume again. The solution is used directly in the next step.

If a solid product is desired, heptane is added to the organic layer after it has been concentrated to a minimum agitated volume. The distillation is continued under vacuum at 40°-55°C until the final volume is 40L. The solution is cooled to 35°-37°C, seeded (~0.5%, 30gms) and then aged for 30min to allow for a full seed bed to grow. The slurry is cooled to 10°C over 2-3 hrs. The slurry is then filtered, washed with 5°C heptane (18L), and allowed to dry fully on the filter pot using a vacuum/nitrogen sweep overnight. The dried solid is obtained with >99.9ee%. The amide can be recrystallized from straight heptane if the optical purity is not sufficient.

**Step 3**

\[
\begin{align*}
\text{TFA (9L) is added to a 100 L Buchi reactor under an inert atmosphere and is cooled to -5°C. The ketone product from Step 2 (5.50 kg, 13.1 mol) is added as a solid followed by a TFA rinse (2 L). The solution is cooled to -5°C and is stirred until all the solid dissolves. The silane (2.18 kg, 15.7 mol) is added slowly over ~1 h (in two portions) while keeping the temperature at <0°C. The reaction is aged at ~2 to -6°C for 15-20 h, at which time LC reveals <2% of the ketone remains. A 50w/w% KOH solution is prepared by adding 13.6kg of KOH pellets (87w%) slowly to 10 L water while keeping the highly exothermic dissolution at <30 °C. The solution is stored in a refrigerator.}

The reaction is quenched with ~2 L of the 50w/w% KOH solution with vigorous stirring and cooling, keeping temp at ~20 °C. Cold THF (16.5L, previously stored in freezer) is added, followed by slow addition of the remainder of the KOH solution (~13.7 L), followed by a 2 L water rinse while keeping temp <20 °C. After complete addition of KOH, the reaction is aged at room temperature. The reaction is quenched after 3 h with 27.5 L IPAC and 20 L 20%w/v aq NaCl.

The aqueous and organic layers are separated. The organic layer is washed with 26 L of 20%w/v aq NaCl, then with 36 L water, then with 31 L 0.5 N HCl, and finally with 32 L of water. The organic layer is concentrated to ~10 L. Heptane (20 L) is added, yielding crystals. The organic layer is concentrated to ~10 L. Heptane (20L) is added again, and the organic layer is concentrated to ~10 L. Heptane (22 L) is added and the slurry is aged at rt. The solid is filtered and washed with 24 L heptane.

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A solid product is obtained (98.8% purity, >99.95% ee, by LC). The solid is then re-dissolved in 12.5 L MeOH (endothermic). At rt, 3 L water is added, and the mixture is aged to initiate crystallization. Water (9.5 L) is added over ~60 min at rt. After aging for 60 min, the slurry is filtered and the solid is washed with 5 L MeOH/water (1/1.5), 5 L MeOH/water (1/4) and then 4 L water. The solid product is dried at 50° C under vacuum (99.9% pure by LC, >99.95% ee).

The reaction in Step 3 can also be carried out using Al(O-i-Pr)₃ as the reducing agent. For example, the ketone (6 kg) is heated at 50°C with 0.3 eq of Al(O-i-Pr)₃ (790 g) in 12 L IPA and 18 L of toluene for 15.5 hours. The solution is cooled to ambient temperature, and solid KOH pellets (1.35 kg) are added slowly with vigorous stirring, while keeping the temperature at < 25 °C. After about 2 hours, when HPLC shows > 99.5% cyclization, 33 L of 1N HCl solution is added to quench the reaction, which is kept at < 25 °C. If a rag layer of solids forms, it should be filtered off to upgrade the enantiomeric excess. The organic layer is then washed first with 36 L of 0.5N HCl, then with 6 L IPA combined with 45 L water, and finally with 6 L IPA combined with 36 L water. The organic layer is transferred via an inline filter. The solvent is switched to heptane (target volume is ~42 L) at ~40 °C until <2 v% toluene is left. Aging at rt for 2 h gives the solid product.

**HPLC Method for assays used in Step 3:**
Ace-C8 column 250 x 4.6 mm  A: MeCN;  B: 0.1% H₃PO₄ in H₂O;
Gradient:  5A:95B at 0 min to 95A:5B at 9 min; hold 95A:5B until 13 min; return to 5A:95B 13-15 min.
Conditions:  35 °C, 1.5 mL/min, 210 nm

**EXAMPLE 18**

![Chemical Structure](image)

**erythro-5-{3,5-Bis(trifluoromethyl)phenyl}-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one**
Sodium bis(trimethylsilyl)amide (172 μL of a 1M solution in THF, 0.172 mmol) was added to a stirred solution of **erythro- 5-{3,5-bis(trifluoromethyl)phenyl}-4-methyl-1,3-oxazolidin-2-one** (50 mg, 0.129 mmol) in dry THF (1 mL) at room temperature under N₂. The reaction was stirred for 15 min and a solution of 2-(bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl (27.0 mg, 0.0861...
mmol) in dry THF (2 mL) was added by cannula. The reaction was stirred at room temperature for 3 days. The reaction was quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-40% EtOAc in hexanes gradient) to afford erythro-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one as a colorless oil. \( R_f = 0.64 \) (20% EtOAc/hexanes). LCMS calc. = 620.18; found = 620.2 (M+1)⁺. \( \textsuperscript{1}H \) NMR (benzene-\( d_6 \), 600 MHz, 1:1 mixture of atropisomers) δ 7.74 (s, 0.5H), 7.72 (s, 0.5H), 7.64 (s, 0.5H), 7.63 (s, 0.5H), 7.39-7.34 (m, 3H), 7.12-7.04 (m, 2H), 6.95 (d, \( J = 2.1 \) Hz, 0.5H), 6.86 (d, \( J = 1.7 \) Hz, 0.5H), 6.64 (d, \( J = 8.5 \) Hz, 0.5H), 6.56 (d, \( J = 8.5 \) Hz, 0.5H), 4.99 (d, \( J = 15.9 \) Hz, 0.5H), 4.93 (d, \( J = 15.9 \) Hz, 0.5H), 4.73 (d, \( J = 7.9 \) Hz, 0.5H), 4.61 (d, \( J = 7.9 \) Hz, 0.5H), 3.88 (d, \( J = 15.9 \) Hz, 0.5H), 3.82 (d, \( J = 15.9 \) Hz, 0.5H), 3.35 (s, 1.5H), 3.24 (s, 1.5H), 3.05 (septet, \( J = 6.9 \) Hz, 0.5H), 3.01 (septet, \( J = 6.9 \) Hz, 0.5H), 2.75 (m, 1H), 1.19 (dd, \( J = 6.9, 2.7 \) Hz, 3H), 1.17 (dd, \( J = 10.9, 6.9 \) Hz, 3H), -0.18 (d, \( J = 6.4 \) Hz, 1.5H), -0.33 (t, \( J = 6.4 \) Hz, 1.5H). This compound was separated into its two enantiomers (4R,5S)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one and (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one using chiral HPLC (AD column, 20 x 250 mm, 3% i-PrOH in heptane).

**EXAMPLE 19**

\[
\begin{align*}
\text{MeO} & \\
\text{F_3C} & \\
\text{O} & \\
\text{N} & \\
\text{HN} & \\
\text{F_3C} & \\
\text{CF_3} & \\
\end{align*}
\]

4-[3,5-bis(trifluoromethyl)phenyl]-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]imidazolidin-2-one.

**Step A:** tert-butyl[2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxyethyl][[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate

To a solution of 1-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino)ethanol (Example 6 Step B, 325.0 mg, 0.561 mmol) in CH₂Cl₂ (15 mL) was added BOC₂O (122 mg, 0.561 mmol) and DIPEA (98 µL, 0.561 mmol). The reaction was stirred at room temperature. After 5 hours, additional BOC₂O (50 mg, 0.229 mmol) and
DIPEA (50 µL, 0.287 mmol) were added. The reaction was stirred at room temperature for 48 hours. The reaction was then concentrated to ~ 2 mL, diluted with hexanes (8 mL) and purified by flash chromatography with 10 to 20% EtOAc/hexanes to afford tert-butyl[2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxyethyl]{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate. $R_f = 0.38$ (25% EtOAc/hexanes). LCMS = 580.3 (M+1-BOC)$^+$. $^1$H NMR (CD$_2$Cl$_2$, 500 MHz) $\delta$ 7.78 (s, 1H), 7.54-7.67 (m, 4H), 7.23-7.33 (m, 2H), 6.90-6.95 (m, 2H), 3.15-3.82 (m, 9H), 2.87 (m, 1H), 1.19-1.43 (m, 15 H).

**Step B:** 1-[3,5-bis(trifluoromethyl)phenyl]-2-((tert-butoxycarbonyl){[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)ethyl methanesulfonate

To a solution of tert-butyl[2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxyethyl]{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate (350.1 mg, 0.516 mmol) in CH$_2$Cl$_2$ (15 mL) was added DIPEA (450 µL, 2.58 mmol). The solution was cooled to 0°C and MsCl (100 µL, 1.29 mmol) was added. After 45 minutes of stirring at 0°C, the reaction was diluted with EtOAc (100 mL) and washed with saturated NaHCO$_3$ (25 mL), brine (25 mL), 1N HCl (25 mL), and brine (2 x 25 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was put through a short plug of silica gel with 25% EtOAc/hexanes and concentrated. The product, 1-[3,5-bis(trifluoromethyl)phenyl]-2-((tert-butoxycarbonyl){[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)ethyl methanesulfonate, was used immediately in the next reaction without further characterization. $R_f = 0.33$ (25% EtOAc/hexanes).

**Step C:** tert-butyl[2-azido-2-[3,5-bis(trifluoromethyl)phenyl]ethyl]{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate

The 1-[3,5-bis(trifluoromethyl)phenyl]-2-((tert-butoxycarbonyl){[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}amino)ethyl methanesulfonate from the previous reaction was dissolved in DMPU (15 mL) and treated with NaN$_3$ (140 mg, 2.15 mmol). The reaction was stirred at room temperature for 15 hours and then diluted with EtOAc (75 mL). The solution was washed with H$_2$O (5 x 40 mL) and brine (40 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated. The residue was purified with 20% EtOAc/hexanes to afford tert-butyl[2-azido-2-[3,5-bis(trifluoromethyl)phenyl]ethyl]{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate. $R_f = 0.52$ (15% EtOAc/hexanes). LCMS = 605.3 (M+1-BOC)$^+$. $^1$H NMR (CD$_3$D$_6$, 500 MHz, 70°C) $\delta$ 7.80 (s, 1H), 7.67 (s, 1H), 7.48 (s, 2H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.01-7.11 (m, 2H), 6.89 (m, 1H), 6.64 (d, $J = 8.6$ Hz, 1H), 4.22-4.69 (m, 3H), 3.28 (s, 3H), 2.61-3.16 (m, 3H), 1.34 (s, 9H), 1.13-1.18 (m, 6H).

**Step D:** mixture of tert-butyl [2-amino-2-[3,5-bis(trifluoromethyl)phenyl]ethyl]{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}carbamate and tert-butyl [1-[3,5-
bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yll methyl]amino]ethyl]carbamate

To a solution of tert-butyl [2-azido-2-[3,5-bis(trifluoromethyl)phenyl]ethyl] [[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate (300 mg, 0.426 mmol) in EtOAc (15 mL) was added 10% Pd on C (100 mg). The reaction was placed under H₂ and stirred at room temperature for 5 hours. At this time the reaction was complete to give a mixture of two products, tert-butyl [2-amino-2-[3,5-bis(trifluoromethyl)phenyl]ethyl] [[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate and tert-butyl [1-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino]ethyl]carbamate. The catalyst was filtered off and the filtrate was concentrated to afford the product mixture. LCMS = 679.3 (M+1)⁺. The products were used in the next reaction without further purification or characterization.

Step E: 1-[3,5-bis(trifluoromethyl)phenyl]-N₂-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]ethane-1,2-diamine

To a solution of 283.5 mg (0.418 mmol) of the mixture of tert-butyl [2-amino-2-[3,5-bis(trifluoromethyl)phenyl]ethyl] [[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate and tert-butyl [1-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino]ethyl]carbamate in CH₂Cl₂ (15 mL) was added TFA (1.5 mL). The reaction was stirred at room temperature for 5 hours and then poured into 1 N NaOH (50 mL). The mixture was extracted with CH₂Cl₂ (3 x 50 mL) and the organic extracts were combined, dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 5 to 10% MeOH/CH₂Cl₂ gave 1-[3,5-bis(trifluoromethyl)phenyl]-N₂-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]ethane-1,2-diamine. Rf = 0.46 (10% MeOH/CH₂Cl₂). LCMS = 579.2 (M+1)⁺. 1H NMR (CD₂Cl₂, 500 MHz) δ 7.83 (s, 2H), 7.77 (s, 2H), 7.55 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.24 (dd, J = 8.4, 2.3 Hz, 1H), 6.99 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.5 Hz, 1H), 4.06 (m, 1H), 3.59-3.76 (m, 2H), 3.69 (s, 3H), 2.88 (m, 1H), 2.67 (dd, J = 11.9, 4.3 Hz, 1H), 2.51 (m, 1H), 1.22 (d, J = 6.9 Hz, 6H).

Step F: 4-[3,5-bis(trifluoromethyl)phenyl]-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]imidazolidin-2-one

A solution of 1-[3,5-bis(trifluoromethyl)phenyl]-N₂-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]ethane-1,2-diamine (125.2 mg, 0.217 mmol) in CH₂Cl₂ (30 mL) was cooled to 0°C and DIPEA (227 μL, 1.30 mmol) was added. Next, triphosgene (32.2 mg, 0.109 mmol) was added. The reaction was stirred at 0°C for 45 minutes and then poured into saturated NaHCO₃ (20 mL). The mixture was extracted with EtOAc (100 mL) and the organic layer was washed with brine (25 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash chromatography with 40% EtOAc/hexanes to afford 4-[3,5-bis(trifluoromethyl)phenyl]-1-[[5'-isopropyl-
2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]imidazolidin-2-one. $R_f = 0.22$ (40% EtOAc/hexane). LCMS = 605.2 (M+1)$^*$. $^1$H NMR (CDCl$_3$, 500 MHz) (atroposimers present in 1:1 ratio; doubling of some peaks observed) $\delta$ 7.83 (s, 1H), 7.78 (s, 2H), 7.55-7.62 (m, 2H), 7.32 (d, $J = 7.8$ Hz, 1H), 7.22 (m, 1H), 6.94 (s, 1H), 6.88 (d, $J = 8.3$ Hz, 1H), 5.33 & 5.24 (2 singlets, 1H), 4.80-4.88 (m, 1H), 4.00-4.61 (m, 2H), 3.72 & 3.70 (2 singlets, 3H), 3.55-3.59 (m, 1H), 2.83-2.93 (m, 2H), 1.17-1.23 (m, 6H).

The two enantiomers of this compound could be separated using an AD chiral column with 5% IPA/heptanes.

EXAMPLE 20

\[
\begin{align*}
\text{MeO} & \\
\text{F}_3\text{C} & \\
\text{N} & \\
\text{HNN} & \\
\end{align*}
\]

(4R)-1-[(S)-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-phenylimidazolidin-2-one

**Step A: tert-butyl [(1R)-2-hydroxy-1-phenylethyl]carbamate**

To a solution of (2R)-2-amino-2-phenylethanol (400 mg, 2.91 mmol) in CH$_2$Cl$_2$ (15 mL) was added BOC$_2$O (636 mg, 2.91 mmol) and DIPEA (507 $\mu$L, 2.91 mmol). The reaction was stirred at room temperature for 18 hours, diluted with EtOAc (75 mL) and washed with H$_2$O, brine, 1N HCl, brine, saturated NaHCO$_3$, and brine (25 mL each). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated. Purification of the residue by flash chromatography with 50% EtOAc/hexanes afforded tert-butyl [(1R)-2-hydroxy-1-phenylethyl]carbamate. $R_f = 0.23$ (40% EtOAc/hexane). $^1$H NMR (CDCl$_3$, 600 MHz) $\delta$ 7.27-7.37 (m, 5H), 5.27 (bs, 1H), 4.78 (bs, 1H), 3.83 (bs, 2H), 2.46 (bs, 1H), 1.44 (bs, 9H).

**Step B: tert-butyl [(1R)-2-oxo-1-phenylethyl]carbamate**

To a solution of tert-butyl [(1R)-2-hydroxy-1-phenylethyl]carbamate (200 mg, 0.844 mmol) in CH$_2$Cl$_2$ (20 mL) at 0°C was added Dess-Martin periodinane (447 mg, 1.05 mmol). The reaction was stirred at 0°C for 15 minutes and then at room temperature for 30 minutes. The reaction was then diluted with EtOAc (75 mL) and washed rapidly with 10% K$_2$CO$_3$ (2 x 30 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated. Purification of the residue on a short column of silica gel with 50%
EtOAc/hexanes gave tert-butyl [(1R)-2-oxo-1-phenylethyl]carbamate. \( ^1H \) NMR (CDCl\(_3\), 600 MHz) (a major and a minor conformer observed). Data for major conformer given) \( \delta \) 9.53 (s, 1H), 7.29-7.40 (m, 5H), 5.80 (bs, 1H), 5.31 (m, 1H), 1.42 (s, 9H). This material was used immediately in the following reaction.

**Step C: tert-butyl[(1R)-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino]-1-phenylethyl]carbamate**

To a solution of tert-butyl(1R)-2-oxo-1-phenylethyl]carbamate (113.8 mg, 0.484 mmol) in MeOH (7 mL) was added 1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methenamine (98 mg, 0.303 mmol), followed by NaCNBH\(_3\) (30 mg, 0.477 mmol) and HOAc (2 drops). The reaction was stirred overnight at room temperature, diluted with EtOAc (75 mL), and washed with 1 N NaOH (25 mL) and brine (25 mL). The organic layer was dried over Na\(_2\)SO\(_4\), filtered, and concentrated. Purification of the residue by flash chromatography with 5 to 25% EtOAc/hexanes gave tert-butyl[(1R)-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino]-1-phenylethyl]carbamate. \( R_f \) = 0.30 (25% EtOAc/hexane). LCMS = 543.4 (M+1)+.

**Step D: (1R)\(-\)-N\(^2\)-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1-phenylethane-1,2-diamine**

To a solution of tert-butyl(1R)-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino]-1-phenylethyl]carbamate (150 mg, 0.277 mmol) containing minor impurities in CH\(_2\)Cl\(_2\) (10 mL) was added TFA (1 mL). The reaction was stirred at room temperature for 2 hours and then poured into 1 N NaOH (25 mL). The mixture was extracted with CH\(_2\)Cl\(_2\) (3 x 25 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered, and concentrated. Purification of the resulting residue by flash chromatography with 0 to 10% MeOH/CH\(_2\)Cl\(_2\) afforded (1R)-\(\text{N}^2\)-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1-phenylethane-1,2-diamine. \( R_f \) = 0.27 (10% MeOH/CH\(_2\)Cl\(_2\)). LCMS = 443.4 (M+1)+.

**Step E: (4R)-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-phenylimidazolidin-2-one**

A solution of (1R)-\(\text{N}^2\)-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1-phenylethane-1,2-diamine (96.0 mg, 0.22 mmol) in CH\(_2\)Cl\(_2\) (15 mL) was cooled to 0°C and DIPEA (230 µL, 1.32 mmol) was added followed by triphosgene (32.6 mg, 0.11 mmol). After 45 minutes, the reaction was poured into saturated NaHCO\(_3\) (25 mL). The mixture was extracted with EtOAc (75 mL). The organic layer was washed with brine, dried over Na\(_2\)SO\(_4\), filtered, and concentrated. Purification of the residue by flash chromatography with 10 to 60% EtOAc/hexanes afforded (4R)-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-phenylimidazolidin-2-one. The minor enantiomer was removed by chiral HPLC using an AD chiral column and 15% IPA/heptanes to afford
enantiomerically pure product. R_f = 0.16 (40% EtOAc/hexanes). LCMS = 469.3 (M+1)^+. 1H NMR (CDCl_3, 500 MHz) (atropisomers present in 1:1 ratio, doubling of some peaks observed) δ 7.65 (m, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.21-7.36 (m, 7H), 6.87-6.94 (m, 2H), 4.65-4.77 (m, 2H), 4.10-4.49 (m, 2H), 3.71 & 3.72 (2 singlets, 3H), 3.49-3.53 (m, 1H), 2.94-2.97 (m, 1H), 2.87 (m, 1H), 1.19-1.24 (m, 6H).

EXAMPLE 21

![](image)

4-(4-chlorophenyl)-1-[[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]imidazolidin-2-one

**Step A: 1-(4-chlorophenyl)-2-[[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino]ethanol**

A solution of 1-[5′-isopropyl-2′-methoxy-5-(trifluoromethyl)biphenyl-2-yl]methanamine (300 mg, 1.1 mmol) and 2-(4-chlorophenyl)oxirane (143 μL, 1.2 mmol) in isopropyl alcohol (10.5 mL) was heated to reflux for 24 hours. The reaction was concentrated and purified by flash chromatography with 5% to 80% EtOAc/hexanes to afford 1-(4-chlorophenyl)-2-[[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino]ethanol. R_f = 0.37 (50% EtOAc/hexanes). LCMS = 478.1 (M+1)^+. 1H NMR (CDCl_3, 500 MHz) δ 7.70 (s, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.33-7.19 (m, 6H), 6.97 (s, 1H), 6.90 (d, J = 8.5 Hz, 1H), 4.52 (m, 1H), 3.77-3.62 (m, 5H), 2.89 (m, 1H), 2.71 (m, 1H), 2.51 (m, 1H), 1.24 (d, J = 7.0 Hz, 6H).

**Step B: benzyl [2-(4-chlorophenyl)-2-hydroxyethyl][[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate**

To a solution of 1-(4-chlorophenyl)-2-[[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino]ethanol (40 mg, 0.08 mmol) in CH_2Cl_2 (2 mL) was added dibenzyl dicarbonate (24 mg, 0.08 mmol). The reaction was stirred at room temperature for 24 hours and then poured into H_2O (15 mL). The resultant mixture was extracted with EtOAc (50 mL) and the organic layer was washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. Purification of the residue by flash chromatography with 5% to 60% EtOAc/hexanes afforded benzyl [2-(4-chlorophenyl)-2-hydroxyethyl][[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate. R_f = 0.20
(25% EtOAc/hexanes). LCMS = 612.2 (M+1)⁺. ¹H NMR (CD₂D₆, 600 MHz, peaks broadened and/or doubled; rotamers and/or atropisomers present) δ 7.98-6.45 (m, 15H), 5.00-3.46 (m, 6H), 3.20-2.96 (m, 5H), 2.72 (m, 1H), 1.20-1.15 (m, 6H).

Step C: benzyl [2-azido-2-(4-chlorophenyl)ethyl][15'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate

A solution of benzyl [2-(4-chlorophenyl)-2-hydroxyethyl][15'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate. (44 mg, 0.07 mmol) in CH₂Cl₂ (6 mL) was cooled to 0°C and N,N diisopropylethylamine (63 µL, 0.36 mmol) was added followed by methanesulfonfyl chloride (14 µL, 0.18 mmol). The reaction was stirred at 0°C for 30 minutes and then poured into saturated NaHCO₃ (15 mL). The result mixture was extracted with EtOAc (50 mL) and the organic layer was washed with brine (15 mL), dried over Na₂SO₄, filtered through a short plug of silica gel, and concentrated. The residue was redissolved in DMPU (6 mL) and sodium azide (12 mg, 0.18 mmol) was added. The reaction was stirred at room temperature for 24 hours and then poured into H₂O (15 mL). The result mixture was extracted with EtOAc (50 mL) and the organic layer was washed with H₂O (2 x 15 mL) and brine (15 mL), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 25% EtOAc/hexanes afforded benzyl [2-azido-2-(4-chlorophenyl)ethyl][15'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate. Rf = 0.66 (25% EtOAc/hexanes). LCMS = 637.3 (M+1)⁺. ¹H NMR (CD₂D₆, 600 MHz, peaks broadened; rotamers and/or atropisomers present) δ 8.03-6.52 (m, 15 H), 5.00-5.08 (m, 2H), 4.76-4.12 (m, 3H), 3.28-2.86 (m, 5H), 2.77 (m, 1H), 1.23-1.18 (m, 6H).

Step D: benzyl [2-amino-2-(4-chlorophenyl)ethyl][15'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate

To a solution of benzyl [2-azido-2-(4-chlorophenyl)ethyl][15'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate (30 mg, 0.05 mmol) in THF (1 mL) was added PtO₂ (8 mg) and the reaction was stirred at room temperature under hydrogen for 1 hour. The catalyst was removed by filtration through a plug of Celite with 100% EtOAc and the filtrate was concentrated to afford crude benzyl [2-amino-2-(4-chlorophenyl)ethyl][15'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate. Rf = 0.66 (25% EtOAc/hexanes). LCMS = 611.3 (M+1)⁺.

Step E: 4-(4-chlorophenyl)-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]imidazolidin-2-one

To a solution of benzyl [2-amino-2-(4-chlorophenyl)ethyl][15'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]carbamate (30 mg, 0.05 mmol) in THF (2 mL) was added potassium bis(trimethylsilyl)amide (295 µL of a 0.5M solution in toluene, 0.147 mmol) The reaction was
stirred at room temperature for 30 minutes and then quenched with saturated NH₄Cl (15 mL). The resultant mixture was extracted with EtOAc (25 mL) and the organic layer was washed with H₂O (15 mL) and brine (15 mL), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 5% to 60% EtOAc/hexanes afforded 4-(4-chlorophenyl)-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]imidazolidin-2-one. Rₚ = 0.46 (5% MeOH/CH₂Cl₂). LCMS = 503.1 (M+1)+. ¹H NMR (CD₆D₆, 600 MHz, atropisomers observed; doubling of peaks) δ 7.90 – 7.03 (m, 6H), 6.89-6.20 (m, 4H), 4.69-3.88 (m, 3H), 3.16 (s, 3H), 2.88-2.30 (m, 3H), 1.18-1.13 (m, 6H).

**EXAMPLE 22**

![Chemical Structure](image)

(4R)-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-3-methyl-4-phenylimidazolidin-2-one

To a solution of (4R)-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-phenylimidazolidin-2-one (12.6 mg, 0.0269 mmol) in THF (1.5 mL) was added MeI (10 µL, 0.162 mmol), followed by KHMDS (162 µL of a 0.5 M solution in toluene, 0.081 mmol). The reaction was stirred at room temperature for 10 minutes, and then poured into water (10 mL). The mixture was extracted with EtOAc (30 mL) and the organic layer was washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 50% EtOAc/hexanes afforded (4R)-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-3-methyl-4-phenylimidazolidin-2-one. Rₚ = 0.26 (40% EtOAc/hexanes). LCMS = 483.2 (M+1)+. ¹H NMR (CDCl₃, 500 MHz, atropisomers observed; doubling of peaks) δ 7.68 – 7.53 (m, 2H), 7.21-7.36 (m, 7H), 6.87-6.94 (m, 2H), 4.08-4.56 (m, 3H), 3.72 & 3.71 (2 singlets, 3H), 3.34-3.38 (m, 1H), 2.77-2.89 (m, 2H), 2.67 & 2.63 (2 singlets, 3H), 1.18-1.26 (m, 6H).

Following the procedures outlined in EXAMPLES 1-22 the compounds listed in Table 1 were prepared:

**Table 1**

- 65 -
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**EXAMPLE 50**

- 68 -
4-[3,5-bis(trifluoromethyl)phenyl]-2-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,2,5-thiadiazolidine 1,1-dioxide

A solution of 1-[3,5-bis(trifluoromethyl)phenyl]-N-[2-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]ethane-1,2-diamine (8.0 mg, 0.014 mmol) and sulfaamide (2.0 mg, 0.021 mmol) in pyridine (300 µL) was heated to 120°C in a sealed tube. After 3 hours, the reaction was cooled to room temperature and diluted with 25 mL of EtOAc. The organic solution was washed with 1 N HCl (2 x 5 mL) and brine (1 x 5 mL), dried over Na2SO4, filtered, and concentrated. Purification of the residue by PTLC with 25% EtOAc/hexanes afforded 4-[3,5-bis(trifluoromethyl)phenyl]-2-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,2,5-thiadiazolidine 1,1-dioxide. Rf = 0.29 (25% EtOAc/hexanes). LCMS = 641.1 (M+1)⁺. 1H NMR (CDCl3, 500 MHz; atropisomers present) δ 7.58-7.85 (m, 5H), 7.35-6.86 (m, 4H), 4.82-4.94 (m, 2H), 3.54-4.42 (m, 6H), 2.71-2.91 (m, 2H), 1.11-1.26 (m, 6H).

EXAMPLE 51

5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one

Step A: [5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol

To a solution of 1.08 g of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbonitrile (EXAMPLE 3) in 25 mL of n-PrOH, was added 0.97 g of KOH. The mixture was heated to reflux and stirred at this temperature for 36 h, then cooled and concentrated to a clear oil. This oil was partitioned between 15 mL of water and 10 mL of Et2O. The aqueous phase was extracted with 10 mL of Et2O. The combined organics were washed with brine (15 mL), dried over Na2SO4, and concentrated. The residue was purified by flash chromatography on a Biotage Horizon 40S column, eluting with 1 CV of 95% hexanes-5% of a mixture of 5% formic acid in acetone, followed by a linear gradient of the acetone mixture in hexanes from 5 to 100% over 10 CV. The resulting white solid was dissolved in 10 mL of 9:1
benzene-MeOH and excess TMSCH₂N₂ was added. The mixture was stirred for 10 min at room temperature, then quenched with trifluoroacetic acid and concentrated. The residue was dissolved in 15 mL of Et₂O and cooled to 0°C. A 1-M solution of LiAlH₄ in Et₂O (5.4 mL) was added dropwise via addition funnel. The cooling bath was removed once the addition was complete, and the mixture was stirred 2 h at room temperature, then recooled to 0°C and quenched by dropwise addition of 0.2 mL of water, 0.2 mL of 15% aqueous NaOH, and 0.5 mL of water. The cooling bath was removed once the addition was complete, and the mixture was stirred 30 min at room temperature, filtered (washing the solids liberally with Et₂O), and concentrated. Flash chromatography on a Biotage Horizon, 40S column, eluting with 1 CV of 4% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 4 to 100% over 10 CV provided the title compound. Mass spectrum (ESI) 307.2 (M-17). ¹H NMR (500 MHz, CDCl₃): δ 7.85 (s, 1H), 7.60 (d, J=8 Hz, 1H), 7.33 (d, J=8 Hz, 1H), 7.25 (dd, J=2 Hz, 9 Hz, 1H), 6.99 (d, J=2.5 Hz, 1H), 6.93 (d, J=8.5 Hz, 1H), 4.49 (m, 2H), 3.74 (s, 3H), 2.90 (septet, J=7 Hz, 1H), 1.25 (d, J=7 Hz, 6H).

**Step B: S'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde**

To a solution of 0.725 g of [S'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol in 10 mL of CH₂Cl₂ was added 1.14 g of Dess-Martin periodinane. The mixture was stirred at room temperature for 30 min, then filtered and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 40S column, eluting with 1 CV of 1% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 1 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 323.2 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 9.81 (s, 1H), 8.28 (s, 1H), 7.88 (dd, J=1.5 Hz, 8 Hz, 1H), 7.54 (d, J=8 Hz, 1H), 7.33 (dd, J=2 Hz, 8 Hz, 1H), 7.16 (d, J=2.5 Hz, 1H), 6.95 (d, J=8.5 Hz, 1H), 3.74 (s, 3H), 2.95 (septet, J=7 Hz, 1H), 1.29 (d, J=7 Hz, 6H).

**Step C: 2-amino-1-[S'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]ethanol**

To a solution of 0.679 g of [S'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde in 1.5 mL of CH₂Cl₂ was added ca. 5 mg of ZnI₂, then 0.23 g of trimethylsilyl cyanide. The mixture was stirred at room temperature for 3 h, and then partitioned between 15 mL of water and 10 mL of Et₂O. The aqueous phase was extracted with 2 x 10 mL of Et₂O. The combined organics were dried over Na₂SO₄ and concentrated. The residue was dissolved in 15 mL of Et₂O and cooled to 0°C. A 1-M solution of LiAlH₄ in Et₂O (4.2 mL) was added dropwise via addition funnel. The cooling bath was removed once the addition was complete, and the mixture was stirred overnight at room temperature, then recooled to 0°C and quenched by dropwise addition of 0.15 mL of water, 0.15 mL of 15% aqueous NaOH, and 0.4 mL of water. The cooling bath was removed once the addition was complete, and the mixture was stirred 30 min at room temperature, filtered (washing the solids liberally with Et₂O), and concentrated to provide the title compound, which was used without further purification. Mass spectrum (ESI) 354.2 (M+1). Some ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.88 (s, 1H), 7.55 (app t, J=7.5 Hz, 1H), 7.22-7.28 (m, 2H), 6.99, 6.95 (d, J=2.5 Hz,
1H), 6.92, 6.90 (sm 1H), 4.52 (m, 1H), 3.70 (s, 3H), 2.90 (septet, J=7 Hz, 1H), 2.81 (m, 1H), 2.60-2.70 (m, 2H), 1.23-1.28 (m, 6H).

**Step D: 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one**

To a 0°C solution of 0.44 g of 2-amino-1-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]ethanol in 15 mL of CH₂Cl₂ was added 0.241 g of disopropylethylamine, then 0.185 g of triphosgene. The mixture was stirred at 0°C for 30 min, and then diluted with 30 mL of EtOAc and 20 mL of saturated NaHCO₃. The phases were separated and the organic phase was washed with 20 mL of brine, dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 40S column, eluting with 1 CV of 5% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 5 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 380.2 (M+1). ¹H NMR signals are doubled because of atropoisomerism ¹H NMR (500 MHz, CDCl₃): δ 7.90, 7.86 (s, 1H), 7.66 (d, J=8 Hz, 1H), 7.35 (d, J=8 Hz, 1H), 7.27 (dd, J=2.5 Hz, 8.5 Hz 1H), 7.03 (d, J=2.5 Hz, 0.5H), 6.87-6.93 (m, 1.5H), 5.65, 5.50 (t, J=8 Hz,1H), 5.23, 5.09 (s, 1H), 3.75 (s, 1.5H), 3.69 (s, 1.5H), 3.68, 3.51 (t, J=9 Hz, 1H), 3.31, 3.19 (t, J=8.5 Hz, 0.5H), 2.90 (septet, J=7 Hz, 1H), 1.25, 1.24 (d, J=7 Hz, 6H).

Further purification by HPLC on Chiralpak AD 2 x 25 cm, eluting with 10% isopropanol in heptane at 9 mL/min, provided two enantiomers: enantiomer A, tr=15.1 min; enantiomer B, tr=17.4 min.

**EXAMPLE 52**

3-Benzyl-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one

To a 0°C solution of 44 mg of 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one in 1 mL of DMF was added 10 mg of sodium hydride. The mixture was stirred 10 min at room temperature, and then 24 mg of benzyl bromide was added. The mixture was stirred overnight at room temperature, then diluted with 15 mL of EtOAc and 5 mL of water. The phases were separated and the organic phase was washed with 5 mL each of water and brine, dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of hexanes, followed by a linear gradient of EtOAc in hexanes from 0 to 50% over 10 CV to provide the title compound. Mass spectrum (ESI) 470.1 (M+1). ¹H NMR (500 MHz, CDCl₃): δ 7.86, 7.76 (s, 1H), 7.62 (d, J=8 Hz, 1H), 7.14-7.40 (m, 7H), 7.01, 6.77 (d, J=2.5 Hz, 1H), 6.87, 6.83 (d, J= 8.5 Hz, 1H), 5.45, 5.04.
5.53 (m, 1H), 4.30-4.53 (m, 2H), 3.73, 3.55 (s, 3H), 3.48, 3.30 (m, 1H), 3.10, 2.96 (t, J=8.5 Hz, 1H), 2.89, 2.82 (septet, J=7 Hz, 1H), 1.24, 1.16 (m, 6H).

EXAMPLE 53

3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one (racemic)
Following the procedure described in EXAMPLE 50, 43 mg of 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one and 43 mg of 3,5-bis(trifluoromethyl)benzyl bromide gave the title compound. Mass spectrum (ESI) 606.1 (M+1). 1H NMR signals are doubled because of atropoisomerism. 1H NMR (500 MHz, CDCl3): δ 7.58-7.88 (m, 5H), 7.34 (d, J=8 Hz, 1H), 7.23 (m, 1H), 7.02, 6.79 (d, J=2 Hz, 1H), 6.88, 6.85 (d, J= 8.5 Hz, 1H), 5.45, 5.42 (m, 1H), 4.52-4.64 (m, 1.5H), 4.36 (d, J=15.5 Hz, 0.5 H), 3.74, 3.57 (s, 3H), 3.49, 3.34 (m, 1H), 3.09, 2.99 (t, J=8.5 Hz, 1H), 2.89, 2.81 (septet, J=7 Hz, 1H), 1.24, 1.12 (m, 6H).

EXAMPLE 54

3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one (enantiomer A)
Following the procedure described in EXAMPLE 50, 43 mg of 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1,3-oxazolidin-2-one, enantiomer A, and 43 mg of 3,5-bis(trifluoromethyl)benzyl bromide gave the title compound. Analytical HPLC on Chiralpak AS 4.6 x 250 mm, eluting with 5% isopropanol in heptane at 0.5 mL/min: tR=9.9 min
EXAMPLE 55

3-(3,5-bis(trifluoromethyl)benzyl)-5-(5'-isopropyl-2-methoxy-4-(trifluoromethyl)biphenyl-2-yl)-1,3-oxazolidin-2-one (enantiomer B)

Following the procedure described in EXAMPLE 50, 44 mg of 5-(5'-isopropyl-2-methoxy-4-(trifluoromethyl)biphenyl-2-yl)-1,3-oxazolidin-2-one, enantiomer B, and 43 mg of 3,5-bis(trifluoromethyl)benzyl bromide gave the title compound. Analytical HPLC on Chiralpak AS 4.6 x 250 mm, eluting with 5% isopropanol in heptane at 0.5 mL/min: t_R=11.0 min

EXAMPLE 56

1-(4-Fluorphenyl)-1-hydroxyacetone

A suspension of ground LaCl_3 (26 mg, 0.104 mmol) in dry THF (7.8 mL) under N_2 was cooled to -78°C and stirred for 15 min. A solution of n-BuLi (1.6 M in hexanes, 195 µL, 0.312 mmol) was added and stirring was continued for 15 min. The reaction was warmed to 0°C and stirred for 30 min. Trimethylsilyl cyanide (31 mg, 42 µL, 0.312 mmol) was added and the reaction was stirred for 30 min at 0°C and warmed to room temperature over 30 min. A solution of acetyltrimethylsilane (Cunico, R. F., Kuan, C. P., J. Org. Chem., 1985, 50, 5410-5413) (121 mg, 1.04 mmol) and 4-fluorobenzaldehyde (142 mg, 1.14 mmol) in dry THF (19 mL) was added by cannula and the reaction was stirred at room temperature for 2 h. After this time 1N HCl (24 mL) was added and the reaction was stirred for 1 h. Et_2O (25 mL) was added and the organic layer was separated and washed with H_2O (2 x 25 mL). The combined aqueous layers were extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried (MgSO_4) and concentrated in vacuo to give the crude product. This was purified by flash
chromatography (Si, 25 x 160 mm, 0-50% EtOAc in hexanes gradient) to give 1-(4-fluorophenyl)-1-hydroxyacetone as a colorless solid. Rf = 0.31 (20% EtOAc/hexanes). 1H NMR (CDCl₃, 500 MHz) δ 7.29 (m, 2H), 7.08-7.04 (m, 2H), 5.06 (d, J = 3.6 Hz, 1H), 4.35 (t, J = 6.5 Hz, 1H), 2.05 (s, 3H).
**EXAMPLE 57**

![Chemical Structure](image)

**erythro- and threo-1-(4-Fluorophenyl)-2-((5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl)amino)propan-1-ol**

NaCNBH₃ (19 mg, 0.306 mmol) was added to a solution of ((5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl)amine (67 mg, 0.204 mmol) and 1-(3,5-dichlorophenyl)-1-hydroxyacetone (45 mg, 0.204 mmol) in MeOH at room temperature followed by acetic acid (2 drops). The reaction was stirred for 5 h at room temperature. The reaction mixture was diluted with EtOAc (20 mL), H₂O (20 mL) and brine (5 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-50% EtOAc in hexanes gradient) to give the two possible diastereoisomers, **erythro-1-(4-fluorophenyl)-2-((5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl)amino)propan-1-ol** (68.4 mg) and **threo-1-(4-fluorophenyl)-2-((5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl)amino)propan-1-ol** (48.9 mg) as colorless oils. **erythro-diastereoisomer:** Rₚ = 0.40 (20% EtOAc/hexanes). LCMS calc. = 476.22; found = 476.2 (M+1)⁺. **threo-diastereoisomer:** Rₚ = 0.20 (20% EtOAc/hexanes). LCMS calc. = 476.22; found = 476.2 (M+1)⁺.

**¹H NMR (500 MHz, CDCl₃)** δ 7.72 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.36 (m, 1H), 7.27 (dd, J = 8.5, 2.3 Hz, 1H), 7.19 (m, 2H), 7.04-6.92 (m, 4H), 4.63-4.56 (m, 1H), 3.85-3.65 (m, 7H), 2.92 (m, 1H), 2.72 (m, 1H), 1.26 (t, J = 8.0 Hz, 6H), 0.64 (t, J = 5.4 Hz, 3H).
EXAMPLE 58

\[ \text{erythro-5-(4-Fluorophenyl)-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one} \]

As for EXAMPLE 7 Step 3. \( R_f = 0.38 \) (20% EtOAc/hexanes). LCMS calc. = 502.20; found = 502.2 (M+1)^+. \( ^1\text{H NMR} \) (500 MHz, benzene-d\(_6\), 1:1 mixture of atropisomers) \( \delta \): 7.96 (s, 0.5H), 7.75 (s, 0.5H), 7.35 (d, \( J = 7.7 \text{ Hz} \), 1H), 7.10-7.06 (m, 2H), 6.94 (d, \( J = 2.1 \text{ Hz} \), 0.5H), 6.88 (d, \( J = 2.1 \text{ Hz} \), 0.5H), 6.69-6.62 (m, 4.5H), 6.55 (d, \( J = 8.4 \text{ Hz} \), 0.5H), 4.95 (d, \( J = 15.9 \text{ Hz} \), 0.5H), 4.86 (d, \( J = 15.8 \text{ Hz} \), 0.5H), 4.80 (d, \( J = 7.9 \text{ Hz} \), 0.5H), 4.70 (d, \( J = 7.8 \text{ Hz} \), 0.5H), 4.04 (d, \( J = 15.8 \text{ Hz} \), 0.5H), 3.93 (d, \( J = 15.9 \text{ Hz} \), 0.5H), 3.36 (s, 1.5H), 3.22 (s, 1.5H), 3.14 (m, 0.5H), 3.05 (m, 0.5H), 2.79-2.71 (m, 1H), 1.18 (m, 6H), 0.02 (d, \( J = 6.5 \text{ Hz} \), 1.5H), -0.04 (d, \( J = 6.5 \text{ Hz} \), 1.5H). This compound was separated into its two enantiomers \((4R,5S)-5-(4-Fluorophenyl)-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one\) and \((4S,5R)-5-(4-Fluorophenyl)-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one\) using chiral HPLC (AD column, 20 x 250 mm, 3% EtOH in heptane).

Following the procedures outlined in EXAMPLE 58 the compounds listed in Table 2 were prepared:

### Table 2

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EXAMPLE 64

1-[[5'-Isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-phenylpyrroolidin-2-one
Sodium bis(trimethylsilyl)amide (114 μL of a 1M solution in THF, 0.114 mmol) was added to a stirred solution of 4-phenylpyrroolidin-2-one (Winans, C. F., Adkins, H., J. Am. Chem. Soc., 1933, 55, 4167-4176) (17 mg, 0.103 mmol) in dry THF (1 mL) at room temperature under N₂. The reaction was stirred for 5 min and a solution of 2-(bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl (20 mg, 0.0516 mmol) in dry THF (2 mL) was added by cannula. The reaction was stirred at room
temperature for 3 days. The reaction was quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-90% EtOAc in hexanes gradient) to afford 1-[[5′-isopropyl-2′-methoxy-4-(trifluoromethyl) biphenyl-2-yl]methyl]-4-phenylpyrrolidin-2-one as a colorless oil. R₇ = 0.11 (20% EtOAc/hexanes). LCMS calc. = 468.22; found = 468.2 (M+1)⁺. ¹H NMR (600 MHz, benzene-d₆, 1:1 mixture of atropisomers) δ 7.79 (s, 0.5H), 7.73 (s, 0.5H), 7.33 (d, J = 7.7 Hz, 1H), 7.08-7.04 (m, 4H), 6.99 (m, 1H), 6.92 (s, 0.5H), 6.88 (s, 0.5H), 6.76 (dd, J = 16.0, 7.4 Hz, 2H), 6.60 (dd, J = 8.5, 3.1 Hz, 1H), 4.58 (d, J = 15.4 Hz, 1H), 4.38 (t, J = 13.9 Hz, 1H), 3.29 (s, 1.5H), 3.26 (s, 1.5H), 2.85-2.73 (m, 3H), 2.63-2.57 (m, 1H), 2.38-2.28 (m, 1H), 2.21-2.11 (m, 1H), 1.20-1.16 (m, 6H).

EXAMPLE 65

![Image](image)

4-(3,4-Difluorophenyl)-1-[[5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]pyrrolidin-2-one

 Prepared by a similar method as EXAMPLE 64 starting with 4-(3,4-difluorophenyl)pyrrolidin-2-one (prepared by a similar method as in Marivet, M. C., Bourguignon, J.-J.; Lugnier, C., Mann, A., Stoclet, J.-C., Wermuth, C. -G. J. Med. Chem., 1989, 32, 1450-1457). LCMS calc. = 504.20; found = 504.2 (M+1)⁺.
EXAMPLE 66

5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]1,3-oxazolidin-2-one

A stirred suspension of sodium hydride (60% in oil, 167 mg, 4.18 mmol) in THF (5 mL) was treated at
0°C with 5-[3,5-bis(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one (500 mg, 1.67 mmol) dissolved in THF
(1 mL), under an atmosphere of N₂. The reaction was stirred for 20 min and a solution of 2-
bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (610 mg, 1.67 mmol) in THF (1 mL) was added
dropwise. The reaction was stirred at room temperature for 18 h. The reaction was quenched with H₂O
(1 mL) and partitioned between EtOAc (80 mL) and H₂O (25 mL). The aqueous phase was re-extracted
with EtOAc (2 x 20 mL) and the combined organic extracts were washed with brine (30 mL), dried
(MgSO₄) and concentrated in vacuo to give the crude product. This was purified by flash silica-gel
chromatography (0-30% EtOAc in hexanes gradient) to afford 5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-
iodo-5-(trifluoromethyl)benzyl]1,3-oxazolidin-2-one. R₁ = 0.55 (515% EtOAc/hexanes). LCMS 584
(M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 8.05 (d, J = 8.2 Hz, 1H), 7.95 (br s, 1H), 7.85 (br s, 2H), 7.51 (br
s, 1H), 7.32 (m, 1H), 5.72 (t, J = 8.0 Hz, 1 H), 4.74 (d, J = 15.5 Hz, 1H), 4.64 (d, J = 15.3 Hz), 4.14 (t, J =
7.1 Hz, 1H), 3.47 (dd, J = 7.1, 1.6 Hz).

EXAMPLE 67

(4S)-4-benzyl-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-
one.
Step A: (4S)-4-benzyl-3-[2-iodo-5-(trifluoromethyl)benzyl]1,3-oxazolidin-2-one

A stirred suspension of sodium hydride (60% in oil, 27 mg, 0.68 mmol) in THF (3 mL) was treated at 0°C with (S)-4-benzyl-2-oxazolidinone (49 mg, 0.27 mmol) dissolved in THF (1 mL), under an atmosphere of N₂. The reaction was stirred for 20 min and a solution of 2-(bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (100 mg, 0.27 mmol) in THF (1 mL) was added dropwise. The reaction was stirred at room temperature for 18 h. The reaction was quenched with H₂O (1 mL) and partitioned between EtOAc (80 mL) and H₂O (25 mL). The aqueous phase was re-extracted with EtOAc (2 x 20 mL) and the combined organic extracts were washed with brine (30 mL), dried (MgSO₄) and concentrated in vacuo to give the crude product. This was purified by flash silica-gel chromatography (0-30% EtOAc in hexanes gradient) to afford (4S)-4-benzyl-3-[2-iodo-5-(trifluoromethyl)benzyl]1,3-oxazolidin-2-one. R₂ = 0.45 (15% EtOAc/hexanes). LCMS 462 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 8.04 (d, J = 8.2 Hz, 1H), 7.54 (br s, 1H), 7.33-7.27 (m, 5H), 7.11-7.10 (m, 2H), 7.32 (m, 1H), 4.80 (d, J = 16.0 Hz, 1H), 4.49 (d, J = 16.1 Hz), 4.28 (t, J = 8.7 Hz, 1H), 4.25 (t, J = 9.1, 4.8 Hz, 1H), 3.94 (m, 1H), 3.16 (dd, J = 13.5, 4.8 Hz, 1H), 2.73 (dd, J = 9.1, 4.4 Hz, 1H).

Step B: (4S)-4-benzyl-3-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one.

A stirred suspension of (4S)-4-benzyl-3-[2-iodo-5-(trifluoromethyl)benzyl]1,3-oxazolidin-2-one (63 mg, 0.137 mmol), 2-methoxy-5-isopropylphenyl boronic acid (52 mg, 0.274 mmol), K₂CO₃ (47 mg, 0.34 mmol) and Pd(OAc)₂ (9.2 mg, 0.0137 mmol) in acetone:H₂O (5:1) (6 mL) was heated at reflux for 1 h. The reaction mixture was concentrated in vacuo, diluted with H₂O (15 mL) and extracted with EtOAC (3 x 30 mL). The combined organic extracts were washed with brine (30 mL), dried (MgSO₄), filtered and concentrated. The crude product was purified by silica-gel flash chromatography (0-20% EtOAc in hexanes gradient) to (4S)-4-benzyl-3-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2- yl]methyl]-1,3-oxazolidin-2-one. R₂ = 0.35 (15% EtOAc/hexanes). LCMS 484 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) (atropisomers present; doubling of some peaks observed in ¹H NMR) δ 7.72 (br s 1H), 7.65 (br s, 1H), 7.42 (m, 1H), 7.32-7.22 (m, 3H), 7.08 (d, J = 2.3 Hz, 1H), 6.90-6.84 (m, 3H), 4.80 (d, J = 15.8 Hz, 1H), 4.35 (d, J = 15.8 Hz), 4.28 (t, J = 8.7 Hz, 1H), 3.96-3.92 (m, 3H), 3.78 (s, 3H), 3.62-3.52 (m, 1H), 2.94-2.86 (m, 1H), 2.82 (dd, J = 9.4, 3.9 Hz, 1H), 2.42 (dd, J = 9.6, 3.9 Hz, 1.26 (s, 3H), 1.10 (s, 3H).
EXAMPLE 68

![Chemical structure](image)

2-Iodo-5-(trifluoromethyl)benzoic acid

Potassium hydroxide (3.78 g; 0.0673 mol) was added to a stirred solution of 2-iodo-5-(trifluoromethyl)benzonitrile (EXAMPLE 2; 4 g; 0.0135 mol) in a 1:1 isopropanol:H₂O solution (60 mL). The reaction was heated at reflux for 14 h and then partitioned between H₂O (50 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (50 mL) and acidified to pH 5 with 6N HCl. The aqueous layer was further extracted with EtOAc (4 x 50 mL) and the combined extracts were washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated in vacuo to afford 2-iodo-5-(trifluoromethyl)benzoic acid as a yellow solid. LCMS = 317.0 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 8.27 (d, J = 1.6 Hz, 1 H), 8.25 (d, J = 8.2 Hz, 1 H), 7.47 (dd, J = 8.2, 1.8 Hz, 1 H).

EXAMPLE 69

![Chemical structure](image)

[2-Iodo-5-(trifluoromethyl)phenyl]methanol

Borane-THF (1.0M solution in THF; 94 mL; 94 mmol) was added to a stirred solution of 2-iodo-5-(trifluoromethyl)benzoic acid (2.97g; 9.4 mmol) in THF (300 mL) at 0°C under N₂. The reaction was heated at reflux for 90 min and then carefully quenched with 6N HCl until no further gas evolution. The reaction was diluted with H₂O (250 mL) and extracted with EtOAc (3 x 250 mL). The combined extracts were washed with brine (300 mL), dried over MgSO₄, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (0-25% EtOAc/hexanes gradient) to afford [2-iodo-5-(trifluoromethyl)phenyl]methanol as a white solid. LCMS = 285.0 (M-17)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 7.97 (d, J = 8.3 Hz, 1 H), 7.79 (s, 1 H), 7.28 (d, J = 8.4 Hz, 1 H), 4.75 (s, 2 H).

An alternative procedure is as follows: To a solution of 2-iodo-5-(trifluoromethyl)benzaldehyde (EXAMPLE 80, Step A, 9g) in THF (100 mL) and water (10 mL) at 0°C was added NaBH₄ (0.5 g). The reaction was stirred 30 minutes. To the reaction mixture was added dilute aqueous HCl (cautiously). The mixture was extracted with ether and the ether layer was washed with water, then brine. The ether layer was then dried over anhydrous MgSO₄, filtered and concentrated. The material is chromatographed
on SiO$_2$ using a step gradient of 1:3 CH$_2$Cl$_2$/hexanes, then 1:1 CH$_2$Cl$_2$/hexanes, then 100% CH$_2$Cl$_2$ to afford [2-iodo-5-(trifluoromethyl)phenyl]methanol as a white solid.

EXAMPLE 70

![Chemical structure](image)

2-(Bromoethyl)-1-iodo-4-(trifluoromethyl)benzene

Carbon tetrabromide (1.86 g; 5.6 mmol) and triphenylphosphine (1.47 g; 5.6 mmol) were added successively to a stirred solution of [2-iodo-5-(trifluoromethyl)phenyl]methanol (1.13 g; 3.74 mmol) in CH$_2$Cl$_2$ (25 mL) at 0°C under N$_2$. The reaction was stirred at room temperature for 48 h. A second equivalent of carbon tetrabromide (1.2 g; 3.74 mmol) and triphenylphosphine (0.98 g; 3.74 mmol) was added and the reaction was stirred an additional 14 h. The solvent was removed in vacuo and the residue was purified by flash chromatography (0-25% EtOAc/hexanes gradient) to afford 2-(bromoethyl)-1-iodo-4-(trifluoromethyl)benzene as a clear oil. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 8.02 (d, $J = 8.2$ Hz, 1 H), 7.73 (d, $J = 1.8$ Hz, 1 H), 7.26 (dd, $J = 8.3$, 1.8 Hz, 1 H), 4.64 (s, 2 H).

EXAMPLE 71

![Chemical structure](image)

5-[3,5-bis(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 13, 5.46 g of 2-amino-1-[3,5-bis(trifluoromethyl)phenyl]ethanol yielded 5-[3,5-bis(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one as an off-white solid. LCMS = 300.1 (M+1)$^+$. $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.94 (s, 1 H), 7.89 (s, 2 H), 5.81-5.77 (m, 1 H), 5.29 (s, 1 H), 4.17-4.12 (m, 1 H), 3.59-3.55 (m, 1 H).
EXAMPLE 72

![Chemical Structure Image]

5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one

A mixture of 5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one (60 mg; 0.103 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (27 mg; 0.129 mmol), palladium acetate (7 mg; 0.0103 mmol), and potassium carbonate (36 mg; 0.257 mmol) in 5:1 acetone/water (6 mL) was heated at reflux for 1 h. Acetone was removed in vacuo and the residue was diluted with H2O (10 mL) and extracted with CH2Cl2 (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (0-25% EtOAc/hexanes gradient) to afford 5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one as a clear glass. LCMS = 624.2 (M+1)⁺. ¹H NMR (benzene-d6, 500 MHz, 1:1 mixture of atropisomers): δ 7.60 (s, 1.5 H), 7.45 (s, 0.5 H), 7.31-7.25 (m, 3 H), 6.98-6.94 (m, 1 H), 6.87-6.82 (m, 1 H), 6.43-6.37 (m, 1 H), 4.54 (d, J = 15.6 Hz, 0.5 H), 4.40-4.36 (m, 1 H), 4.47 (d, J = 15.6 Hz, 0.5 H), 3.96 (d, J = 15.5 Hz, 0.5 H), 3.80 (d, J = 15.8 Hz, 0.5 H), 3.24-3.15 (m, 1 H), 3.02 (s, 3 H), 2.62-2.58 (m, 0.5 H), 2.53-2.48 (m, 0.5 H), 2.12-2.07 (m, 0.5 H), 2.04-2.00 (m, 0.5 H) 1.22-1.11 (m, 6 H).

The racemic material was separated by chiral HPLC using 15% IPA/heptane and an OD column into its two enantiomers.

(5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one: LCMS = 624.2 (M+1)⁺. ¹H NMR (benzene-d6, 500 MHz, 1:1 mixture of atropisomers): δ 7.62 (s, 1.5 H), 7.47 (s, 0.5 H), 7.34-7.27 (m, 3 H), 6.99-6.95 (m, 1 H), 6.88-6.83 (m, 1 H), 6.44-6.39 (m, 1 H), 4.54 (d, J = 15.5 Hz, 0.5 H), 4.47-4.41 (m, 1 H), 4.33 (d, J = 15.6 Hz, 0.5 H), 3.98 (d, J = 15.7 Hz, 0.5 H), 3.82 (d, J = 15.8 Hz, 0.5 H), 3.24-3.15 (m, 1 H), 3.05 (s, 3 H), 2.67-2.62 (m, 0.5 H), 2.57-2.52 (m, 0.5 H), 2.16-2.11 (m, 0.5 H), 2.09-2.04 (m, 0.5 H) 1.22-1.11 (m, 6 H).
(5S)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one: LCMS = 624.2 (M+1)+. 1H NMR (benzene-d6, 500 MHz, 1:1 mixture of atropisomers): δ 7.63 (s, 1.5 H), 7.48 (s, 0.5 H), 7.35-7.27 (m, 3 H), 7.00-6.95 (m, 1 H), 6.88-6.83 (m, 1 H), 6.44-6.38 (m, 1 H), 4.54 (d, J = 15.8 Hz, 0.5 H), 4.48-4.42 (m, 1 H), 4.34 (d, J = 15.8 Hz, 0.5 H), 3.99 (d, J = 15.8 Hz, 0.5 H), 3.83 (d, J = 15.8 Hz, 0.5 H), 3.25-3.15 (m, 1 H), 3.05 (s, 3 H), 2.68-2.63 (m, 0.5 H), 2.58-2.53 (m, 0.5 H), 2.18-2.12 (m, 0.5 H), 2.10-2.05 (m, 0.5 H) 1.23-1.11 (m, 6 H).

**EXAMPLE 73**

![Chemical Structure](image)

**Step 1: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one**

To a stirred suspension of sodium hydride (60% dispersion in mineral oil; 1.3 g; 0.0325 mol) in THF (60 mL) at 0 °C under N2 was added dropwise a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (Example 17) (4.077 g; 0.013 mol) in THF (50 mL). Gas evolution was observed. The resultant mixture stirred at 0 °C for 30 min prior to addition of a solution of 2-(bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (4.754 g; 0.013 mol) in THF (20 mL). The reaction was allowed to warm to room temperature and stirred for 14 h. The reaction was carefully quenched with H2O (15 mL) and partitioned between EtOAc (250 mL) and H2O (75 mL). The aqueous layer was extracted with EtOAc (3 x 100 mL). Combined organic layers were washed with brine (100 mL), dried (MgSO4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (0-20% EtOAc/hexanes gradient) to afford 6.4 g (82.5%) of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one as a white solid. LCMS = 598.1 (M+1)+. 1H NMR (CDCl3, 500 MHz): δ 8.03 (d, J = 8.2 Hz, 1 H), 7.90 (s, 1 H), 7.79 (s, 2 H), 7.58 (s, 1H), 7.30 (dd, J = 8.2 Hz, J = 2.0 Hz, 1 H), 5.76 (d, J = 8 Hz, 1 H), 4.88 (d, J = 15.8 Hz, 1 H), 4.37 (d, J = 15.8 Hz, 1 H), 4.09-4.02 (m, 1 H), 0.8 (d, J = 6.6 Hz, 3 H).

**Step 2: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one**

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A stirred mixture of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (4.29 g; 7.19 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (Example 78) (4.57 g; 21.57 mmol), tetraakis(triphenylphosphine)palladium (0) (1.0 g; 0.86 mmol), and sodium carbonate (6.35 g) in C6H6/EtOH/H2O (120 mL/17 mL/51 mL) was heated at reflux (100°C) under N2 for 14 h. The reaction was partitioned between EtOAc (200 mL) and H2O (100 mL). The aqueous phase was extracted with EtOAc (3 x 200 mL). The combined organic phases were washed with brine (100 mL), dried (MgSO4), filtered and concentrated in vacuo. The residue was purified by silica-gel flash chromatography (0-25% EtOAc/hexanes gradient) to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl][methyl]-4-methyl-1,3-oxazolidin-2-one as a yellow solid. To remove the yellow impurity, 2.7 g were dissolved in 165 mL EtOH and 275 mg decolorizing charcoal was added (activated carbon, Darco, G-60, 100 mesh powder, Aldrich). The mixture was stirred at room temperature for 40 min, filtered, and concentrated in vacuo. Trituration with ca. 25 mL hexanes afforded 2.46 g of the title compound as a white solid. 1H NMR indicated trace impurities which were removed by silica gel flash chromatography (0-15% EtOAc/hexanes gradient). Residual solvent was removed by lyophilization from acetonitrile.

LCMS = 638.3 (M+1)⁺. 1H NMR (benzene-d6, 500 MHz, 1:1 mixture of atropisomers): δ 7.82 (s, 0.5 H), 7.60 (s, 0.5 H), 7.57 (s, 1 H), 7.33 (d, J = 8 Hz, 1H), 7.27 (d, J = 9.9 Hz, 2 H), 7.02-6.98 (m, 1 H), 6.89 (d, J = 8.5 Hz, 0.5 H), 6.82 (d, J = 8.5 Hz, 0.5 H), 6.45 (d, J = 12.1 Hz, 0.5 H), 6.35 (d, J = 11.9 Hz, 0.5 H), 4.94 (d, J = 16.0 Hz, 0.5 H), 4.87 (d, J = 15.8 Hz, 0.5 H), 4.54 (d, J = 8.0 Hz, 0.5 H), 4.50 (d, J = 7.8 Hz, 0.5 H), 3.74-3.66 (m, 1 H), 3.23-3.15 (m, 1 H), 3.12 (s, 1.5 H), 2.99 (s, 1.5 H), 2.97-2.92 (m, 0.5 H), 2.89-2.84 (m, 0.5 H), 1.21-1.09 (m, 6 H), -0.27 (d, J = 6.7 Hz, 1.5 H), -0.40 (d, J = 6.7 Hz, 1.5 H).

Alternate procedure for making (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl][methyl]-4-methyl-1,3-oxazolidin-2-one:
A mixture of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (50 mg; 0.084 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (EXAMPLE 78, 22 mg; 0.105 mmol), palladium acetate (6 mg; 0.0103 mmol), and potassium carbonate (29 mg; 0.257 mmol) in 5:1 acetone/water (6 mL) was heated at reflux for 1 h. Acetone was removed in vacuo and the residue was diluted with H2O (10 mL) and extracted with CH2Cl2 (3 x 10 mL). The combined extracts were washed with brine (10 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (0-25% EtOAc/hexanes gradient) to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl][methyl]-4-methyl-1,3-oxazolidin-2-one as a clear glass. This product can also be made by the method provided in Example 372.

EXAMPLE 74
(4R,5S)-4-[3,5-bis(trifluoromethyl)phenyl]-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-methylimidazolidin-2-one.

**Step A:** (4S,5S)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one.

((4S,5S)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one) (46.2 mg, 0.148 mmol) was placed in a dry flask and DMA (3 mL) was added. NaHMDS (296 μL of a 1M solution in THF, 0.296 mmol) was added and the reaction was stirred for 5 min. At this time, 2'-(bromomethyl)-5-isopropyl-4'- (trifluoromethyl)biphenyl-2-yl methyl ether (80.0 mg, 0.207 mmol) was added by cannula in DMA (2 mL). After 30 min, the reaction was quenched with saturated NH₄Cl (2 mL). The mixture was diluted with EtOAc (40 mL). The organic layer was washed with water (15 mL), and brine (15 mL), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 25% EtOAc/hexanes afforded (4S,5S)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one. Rₜ = 0.27 (25% EtOAc/hexanes). LCMS = 620.2 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz; atropisomers present) δ 6.90-7.88 (m, 9H), 4.04-5.05 (m, 3H), 3.25-3.74 (m, 4H), 2.88 (m, 1H), 1.19-1.24 (m, 6H), 0.99-1.07 (m, 3H).

**Step B:** (1S,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino)propan-1-ol.

To a solution of (4S,5S)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one (147.7 mg, 0.239 mmol) in EtOH (7.5 mL) was added H₂O (1.5 mL) and KOH (150 mg, 2.67 mmol). The solution was heated to 75°C for 30 h and then cooled to room temperature. EtOAc (75 mL) was added and the organic layer was washed with H₂O (15 mL) and brine (2 x 15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography to afford (1S,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]amino)propan-1-ol. Rₜ = 0.44 (40% EtOAc/hexanes). LCMS = 594.2 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 6.93-7.78 (m, 9H), 3.51-4.20 (m, 6H), 2.91 (m, 1H), 2.49 (m, 1H), 1.22-1.26 (m, 6H), 0.79-0.81 (m, 3H).

**Step C:** tert-butyl(1S,2S)-2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-1-methyllethyl][5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl] carbamate.
To a solution of (1S,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-2-[(5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]amino)propan-1-ol (135.5 mg, 0.228 mmol) in CH$_2$Cl$_2$ (5 mL) was added BOC$_2$O (49.7 mg, 0.228 mmol). The reaction was stirred at room temperature for 2 days; during this time, 2 additional portions of BOC$_2$O (25 mg each) were added. After 2 days, the reaction was concentrated, and the residue was purified by flash chromatography with 20% EtOAc/hexanes to afford tert-butyl[(1S,2S)-2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-1-methylethyl]{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}carbamate. R$_f$ = 0.41 (40% EtOAc/hexanes). LCMS = 594.2 (M+1-BOC)$^+$.  

**Step D:** tert-butyl[(1S,2R)-2-azido-2-[3,5-bis(trifluoromethyl)phenyl]-1-methylethyl]{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}carbamate.

A dry flask was charged with THF (1 mL) diethyl azodicarboxylate (DEAD) (11 µL, 0.0698 mmol) and diphenylphosphoryl azide (DPPA) (15 µL, 0.0698 mmol). tert-butyl[(1S,2S)-2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-1-methylethyl]{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}carbamate (20.7 mg, 0.0698 mmol) was added by cannula in THF (1 mL). Next Ph$_3$P (18.3 mg, 0.0698 mmol) was added. The reaction was stirred at room temperature for 30 min, and then additional DEAD (11 µL, 0.0698 mmol), DPPA (15 µL, 0.0698 mmol), and Ph$_3$P (18.3 mg, 0.0698 mmol) were added. After an additional 30 min, the reaction was diluted with EtOAc (40 mL) and washed with water and brine (15 mL each). The organic layer was dried over Na$_2$SO$_4$, filtered, and concentrated. Purification of the residue by flash chromatography with 15% EtOAc/hexanes afforded tert-butyl[(1S,2R)-2-azido-2-[3,5-bis(trifluoromethyl)phenyl]-1-methylethyl]{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}carbamate. R$_f$ = 0.60 (25% EtOAc/hexanes). LCMS = 619.3 (M+1-BOC)$^+$.  

**Step E:** (1R, 2S)-1-azido-1-[3,5-bis(trifluoromethyl)phenyl]-N-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}propan-2-amine.

To a solution of tert-butyl[(1S,2R)-2-azido-2-[3,5-bis(trifluoromethyl)phenyl]-1-methylethyl]{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}carbamate (21.7 mg, 0.030 mmol) in CH$_2$Cl$_2$ (2 mL) was added TFA (200 µL). The reaction was stirred at room temperature for 1 hour and then diluted with CH$_2$Cl$_2$ (25 mL). The CH$_2$Cl$_2$ solution was washed with 1 N NaOH (15 mL) and the aqueous phase was re-extracted with CH$_2$Cl$_2$ (25 mL). The organic extracts were combined, washed with brine (20 mL), dried over Na$_2$SO$_4$, filtered, and concentrated. Purification of the residue by flash chromatography with 15% EtOAc/hexanes afforded (1R, 2S)-1-azido-1-[3,5-bis(trifluoromethyl)phenyl]-N-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}propan-2-amine. R$_f$ = 0.45 (15% EtOAc/hexanes). LCMS = 619.2 (M+1)$^+$.  

**Step F:** (1R, 2S)-1-[3,5-bis(trifluoromethyl)phenyl]-N-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}propane-1,2-diamine.

To a solution of (1R, 2S)-1-[3,5-bis(trifluoromethyl)phenyl]-N-{{5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}propan-2-amine (17.8 mg, 0.0288 mmol) in THF (3 mL) was
added PtO₂ (12 mg, 0.053 mmol). The reaction was placed under hydrogen balloon atmosphere and stirred at room temperature for 3 h. The catalyst was removed by filtration and the filtrate was concentrated. The residue was put through a short plug of silica gel with 0-10% MeOH/CH₂Cl₂ to give (1R,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-N²-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]propane-1,2-diamine. LCMS = 619.2 (M+1)⁺.

**Step G:** (4R,5S)-4-[3,5-bis(trifluoromethyl)phenyl]-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-methylimidazolidin-2-one.

A solution of (1R,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-N²-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]propane-1,2-diamine (8.0 mg, 0.0135 mmol) in CH₂Cl₂ (2 mL) was cooled to 0°C and DIPEA (14 µL, 0.081 mmol) was added followed by triphosgene (2 mg, 0.00657 mmol). The reaction was stirred at 0°C for 30 min and then diluted with EtOAc (30 mL). The reaction was washed with saturated NaHCO₃ (10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 40% EtOAc/hexanes afforded (4R,5S)-4-[3,5-bis(trifluoromethyl)phenyl]-1-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-methylimidazolidin-2-one. Rᵣ = 0.24 (40% EtOAc/hexanes). LCMS = 619.2 (M+1)⁺. ¹H NMR (CD₂Cl₂, 600 MHz; atropisomers present) δ 6.91-7.84 (m, 9H), 3.84-4.94 (m, 4H), 3.64-3.80 (m, 4H), 2.88 (m, 1H), 1.18-1.26 (m, 6H), 0.27-0.42 (m, 3H).

**EXAMPLE 75**

![Example 75](image)

(3S,4R)-4-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-3-methyl-1,2,5-thiadiazolidine 1,1-dioxide.

A glass reaction tube was charged with (1R,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-N²-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]propane-1,2-diamine (15.9 mg, 0.0269 mmol), sulfamide (4 mg, 0.0403 mmol), and pyridine (600 µL). The tube was flushed with N₂, sealed, and heated at 120°C for 2 h. The reaction was then cooled to room temperature, diluted with EtOAc (40 mL) and washed with H₂O, 1N HCl, and brine (10 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography with 25% EtOAc/hexanes afforded (3S,4R)-4-[3,5-bis(trifluoromethyl)phenyl]-2-[[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-3-methyl-1,2,5-thiadiazolidine 1,1-dioxide. Rᵣ = 0.27 (25%
EtOAc/hexanes). LCMS = 655.2 (M+1)+. 1H NMR (CD6D, 500 MHz; atropisomers present) δ 6.51-8.19 (m, 9H), 3.64-4.53 (m, 4H), 3.00-3.18 (m, 4H), 2.73 (m, 1H), 1.13-1.20 (m, 6H), -0.03-0.09 (m, 3H).

EXAMPLE 76

2-fluoro-1-isopropenyl-4-methoxybenzene

Step A: 2-(2-fluoro-4-methoxyphenyl)propan-2-ol

To a solution of 2'-fluoro-4'-methoxyacetophenone (4.45 g, 26.5 mmol) in THF (50 ml) at 0°C, a solution of 2.4 M MeMgBr (11.6 mmol, 27.8 mmol) was added. The mixture was stirred at 0°C and then room temperature for 4 h. The reaction was quenched with saturated ammonium chloride solution. The organic was extracted with ethyl acetate (3 x 50 ml). The combined ethyl acetate layers were washed with brine and dried over sodium sulfate. The resulting alcohol was obtained as an oil after flash column using EtOAc:hexane = 2:8 as the elute.

Step B: 2-fluoro-1-isopropenyl-4-methoxybenzene

To a solution of 2-(2-fluoro-4-methoxyphenyl)propan-2-ol from Step A (3.89 g, 21.14 mmol) in methylene chloride (50 ml) at 0°C, MsCl (1.95 ml, 25.4 mmol) and triethylamine (6.52 ml, 46.5 mmol) were added. The solution was stirred at 0°C and then room temperature for 2 h. The solution was diluted with methylene chloride (100 ml), washed with water, and dried over sodium sulfate. The title compound was obtained as an oil after flash column using EtOAc:hexane = 1:9 as the elute. 1H NMR (CDCl3, 500 MHz) δ 7.25 (t, J = 9.0 Hz, 1H), 6.68 (dd, J = 8.5, 2.5 Hz, 1H), 6.63 (dd, J = 13, 2.5 Hz, 1H), 5.20 (d, J = 17.0 Hz, 2H), 3.82 (s, 3H), 2.18 (s, 3H).

Alternate route to make 2-fluoro-1-isopropenyl-4-methoxybenzene:

A solution of sodium bis(trimethylsilyl)-amide, 1.0M in tetrahydrofuran (714ml, 0.714m) was added to a suspension of methyltriphenylphosphonium bromide (255g, 0.714m) in THF (2.50L) cooled with an ice bath. The resultant yellow colored suspension was stirred for 30 minutes at ice bath temperature and then cooled to -78°C. A total of 2-fluoro-4-methoxyacetophenone (100g, 0.595m) in THF (200ml) was added dropwise and stirred at -78°C for 1.5 hours. Reaction mixture was allowed to warm to room temperature for one hour, quenched with acetic acid (~80ml) where color change was observed from yellow to off white and stirred for 30 minutes (pH~7)(slight exotherm noted). The mixture was concentrated to a slush, diluted with 7:2 hexane:ethyl acetate, and was allowed to sit overnight. Solids were removed by filtration and the filtrate was concentrated to yellow oil. The title compound was obtained after flash column using 9:1 hexane:ethyl as the eluant.
EXAMPLE 77

![Chemical structure](image)

1-fluoro-4-iodo-2-isopropyl-5-methoxybenzene
A solution of the 2-fluoro-1-isopropenyl-4-methoxybenzene (Example 76, 1.96 g, 11.81 mmol) in MeOH (30 ml) was charged with hydrogen at 1 atm with catalytic amount of Pd/C. The mixture was stirred at room temperature for 1 h. The mixture was filtered through Celite. The filtrate was then added to a mixture of silver sulfate (3.68 g, 11.81 mmol) and Iodine (3.00 g, 11.81 mmol) in MeOH (10 ml). The mixture was stirred at room temperature for 3 h until the color of solution became light yellow. The mixture was filtered and the filtrate was concentrated. The title compound was obtained after flash column using EtOAc:hexane 5:95 as the elute. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.61 (d, \(J = 8.0\) Hz, 1H), 6.56 (d, \(J = 12.5\) Hz, 1H), 3.90 (s, 3H), 3.18 (m, 1H), 1.28 (m, 6H).

EXAMPLE 78

![Chemical structure](image)

(4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid
To a solution of 1-fluoro-4-iodo-2-isopropyl-5-methoxybenzene (Example 77, 2.61 g, 8.88 mmol) in THF at -78°C, n-BuLi (4.26 ml, 10.65 mmol, 2.5 M) was added dropwise. The solution was stirred at -78°C for 30 min. Trimethyl borate (2.98 ml, 26.6 mmol) was added. The solution was then stirred at -78°C for 3 h. The reaction was quenched at -78°C with saturated ammonium chloride and the mixture was warmed to room temperature. The organic was extracted with ethyl acetate (3 x 50 ml). The combined ethyl acetate layers were washed with brine and dried over sodium sulfate. The title compound was obtained as a solid pure enough for next step. Further purification with silica gel caused decomposition of product. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 7.74 (d, \(J = 10.0\) Hz, 1H), 6.62 (d, \(J = 12.5\) Hz, 1H), 5.65 (br s, 2H), 3.92 (s, 3H), 3.20 (m, 1H), 1.22 (m, 6H).

The boronic acid intermediate can also be made by the following 4-step process:
Conversion of 1 to 2:

THF (24 L) was added to a 100L cylindrical vessel at room temperature. To this was added 2.75 kg of CeCl₃. The resultant slurry was aged at room temperature for 1.5 hours. A sample was then examined under a microscope to confirm that the desired form change had occurred. The slurry was cooled to 9°C and MeMgCl was added. The rate of addition was adjusted to maintain internal temperature below 19°C. The mixture was cooled to -11°C, and a solution of acetophenone 1 (4.0kg diluted to 10L with THF) was added dropwise, maintaining the internal temperature below 0°C. The reaction mixture was then aged at a temperature below 0°C for an hour. The reaction was quenched with 5.7L of 3N HCl in a dropwise fashion, maintaining the internal temperature below 15°C. The quenched reaction mixture was then aged at 5-10°C for 1.5 hours and was filtered through a plug of Solka Floc.

Hydrogenation of 2 to 3:

The THF solution of 2 was solvent switched into ethanol (~18L volume), and 1.9L HCl was added, followed by 190gm of 10% Pd/C (50% water). The mixture was placed under 15 psi hydrogen at 40°C until the reaction was complete based on HPLC analysis. The mixture was cooled to room temperature. The catalyst was removed by filtration using Solka-Flok as a filter aid. The anisole product in ethanol was then solvent switched into acetonitrile for the next step.

Bromination of 3 to 4:

Anisole 3 is diluted in acetonitrile (1.72 L, 4mL MeCN/ mMol 3). This mixture is warmed to 35°C, and NBS (1.1 eq, 84 g) is added in a single solid addition. The reaction is complete in 2-4 hours. The solution is concentrated to 400 mL total volume and diluted with 1L of toluene. The solution is then washed with sodium thiosulfate and water to remove the succinimide by-product. The organic layer is then concentrated and solvent switched to toluene.

Conversion of Aryl Bromide 4 to Boronic Acid 5:

A 75 L glass reaction vessel was charged with 1.87 kg of aryl bromide 4 (7.6 Mol), which was added as 6.4 kg of a 29.1 wt% solution of 4 in toluene. This solution was diluted with 5.6 L of THF. The vessel was flushed with nitrogen, and tri-isopropylborate (1.35 eq, 2.35 L, 10.3 Mol) was added.
The mixture was cooled to < -70 °C. Then 5.9 L of 1.6 M n-BuLi in hexanes (9.5 Mol) was added slowly over 4 hours, maintaining a temperature of < -55 °C. Thirty minutes after completion of the n-BuLi addition, the reaction was complete by LC analysis. The reaction was warmed to -35 °C and quenched into 3.0 M H$_2$SO$_4$ solution (5.6 L). The aqueous phase after the quench should be acidic (pH ~ 2). MTBE (7.5 L) was added to the mixture to dilute the organic layer. The mixture was stirred (15 min) and the aqueous layer was cut away. The organic layer was washed with another 5.6 L of a 3.0 M H$_2$SO$_4$ solution (15 min). After separating layers again, the organic MTBE/Toluene layer was extracted twice with 1 M KOH (15.1 L first and then 7.6 L). The two KOH extractions were combined, diluted with 2-propanol (6.4 L), and cooled to 15°C. Then the solution was slowly acidified to pH ~ 2 using 3.0 M sulphuric acid (∼ 7.6 L) while maintaining temperature at 15-20 °C. The resulting slurry was stirred for 1h and then filtered. The filter cake was washed with water (2 x 6 L) and dried under an air flow for 1 day. The filtered solid was placed in an oven under vacuum at 50°C for 2-3 days to decompose a diaryl impurity and to dry the solid. The off-white crystalline solid was isolated to yield 1.59 kg of boronic acid 5.

EXAMPLE 79

![Chemical Structure](image)

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4-chloro-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

Step A: 1-bromo-2-(bromomethyl)-4-chlorobenzene

A mixture of 2-bromo-5-chloro-toluene (2.00 g, 9.75 mmol), NBS (2.08 g, 11.7 mmol) and catalytic amount of AIBN in carbon tetrachloride (50 ml) was stirred under refluxing conditions for 4 h. TLC (EtOAc:hexane = 5:95) showed no starting material. The mixture was filtered and the filtrate was concentrated. The title compound was obtained as a white solid after flash column using EtOAc:hexane = 5:95 as the elute. $^1$H NMR (CDCl$_3$, 500 MHz) δ 7.53 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 2.5 Hz, 1H), 7.18 (dd, J = 8.5, 2.5 Hz, 1H), 4.60 (s, 2H).

Step B. (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-bromo-5-chlorobenzyl)-4-methyl-1,3-oxazolidin-2-one
To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl) phenyl]-4-methyl-1,3-oxazolidin-2-one (0.050 g, 0.16 mmol) in THF (1 ml) at 0°C, NaH (7.6 mg, 0.19 mmol, 60%) was added. The mixture was stirred at 0°C for 30 min. The title compound from Step A (0.059 g, 0.21 mmol) was added. The whole mixture was stirred at 0°C for 1 h and warmed to room temperature for 4 h. The reaction was quenched with saturated ammonium chloride. The organic was extracted with ethyl acetate (3 x 15 ml). The combined ethyl acetate layers were washed with brine and dried over sodium sulfate. The title compound was obtained after preparative TLC purification using EtOAc:hexane = 2:8 as the elute. 1H NMR (CDCl3, 500 MHz) δ 7.92 (s, 1H), 7.82 (s, 2H), 7.55 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 2.5 Hz, 1H), 7.23 (dd, J = 8.5, 2.5 Hz, 1H), 5.77 (d, J = 8.0 Hz, 1H), 4.86 (d, J = 16.0 Hz, 1H), 4.36 (d, J = 16.0 Hz, 1H), 4.11 (m, 1H), 0.82 (d, J = 6.5 Hz, 3H).

**Step C. (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4-chloro-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2'-yl)methyl]-4-methyl-1,3-oxazolidin-2-one**

A mixture of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(2-bromo-5-chlorobenzyl)-4-methyl-1,3-oxazolidin-2-one (44 mg, 0.085 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (Example 78, 23 mg, 0.11 mmol), potassium carbonate (25 mg, 0.18 mmol) and catalytic amount of PdOAc in a 4:1 mixture of acetone/water was heated to reflux for 1 h. Acetone was removed and water was added. The organic was extracted with methylene chloride (3 x 15 ml). The combined methylene chloride layers were washed with brine and dried over sodium sulfate. The title compound was obtained as a solid after preparative reverse phase HPLC. 1H NMR (CDCl3, 500 MHz) a 1:1 mixture of rotamer δ7.90 (s, 1H), 7.73 (s, 2H), 7.49 (m, 1H), 7.40 (m, 1H), 7.20 (m, 1H), 7.00 (m, 1H), 6.68 (dd, J = 12.0, 3.0 Hz, 1H), 5.63 (d, J = 8.0 Hz, ½ H), 5.44 (d, J = 8.0 Hz, ½ H), 4.85 (d, J = 10.0 Hz, ½ H), 4.82 (d, J = 10.0 Hz, ½ H), 4.03 (d, J = 16.0 Hz, ½ H), 3.84 (m, 11/2 H), 3.80 (s, 3H), 3.20 (m, 1H), 1.20 (m, 6H), 0.56 (d, J = 6.5 Hz, 3/2 H), 0.38 (d, J = 6.5H, 3/2 H). LC-MS (M+1): 604.3, 4.61 min.

**EXAMPLE 80**

![Chemical Structure](image)

5-[2-iodo-5-(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one

**Step A: 2-iodo-5-(trifluoromethyl)benzaldehyde**

To a solution of 2-iodo-5-(trifluoromethyl)benzonitrile (EXAMPLE 2, 42 g) in CH2Cl2 (300 mL) at -78°C was added a solution of DIBAL in CH2Cl2 (175 mL, 1M) over 30 minutes. A precipitate formed. The reaction was warmed to 0°C. An additional 25 mL of the DIBAL solution was added dropwise over 30 minutes. The reaction was poured into 200 mL 2N aqueous HCl, diluted with ether and stirred 1 hour. TLC analysis indicates imine still present and an additional 100 mL 2N aqueous was added and the
reaction stirred overnight. Imine was still present by TLC analysis and 200 mL 2N aqueous HCl was added and the mixture stirred 2 hours. The layers were separated and the aqueous layer back extracted with ether. The ether extracts were combined, washed with brine, dried over anhydrous MgSO₄, filtered and concentrated. The product was purified by silica gel chromatography eluting with 95:5 hexanes/EtOAc to give 2-Iodo-5-(trifluoromethyl)benzaldehyde as a white solid. 1H NMR (500 MHz, CDCl₃): δ 10.00 (s, 1H), 8.12 (s, 1H), 8.11 (d, J=8 Hz, 1H), 7.53 (dd, J=2 Hz, 8 Hz, 1H).

Step B: 5-[2-iodo-5-(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one
To a 0°C solution of 0.2 g of 2-ido-5-(trifluoromethyl)benzaldehyde in 3 mL of EtOH was added 0.13 mL of nitromethane, then 0.28 mL of a 2.5 N solution of NaOH. The mixture was stirred at 0°C for 3 h, and then neutralized by addition of 2.1 mL of a 0.33 N aqueous solution of AcOH. The mixture was partitioned between 10 mL of water and 10 mL of EtOAc. The aqueous phase was extracted with 2 x 5 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na₂SO₄, and concentrated. The residue was dissolved in 4 mL of MeOH and 0.5 mL of 88% aqueous formic acid was added. Approximately 200 mg of a Raney nickel slurry was added and the mixture was flushed with H₂, and stirred under an H₂ balloon for 4 h. The mixture was filtered through a pad of Celite, washing with MeOH, and the filtrate was concentrated. The residue was partitioned between 10 mL of 10% aqueous NH₄OH and 20 mL of EtOAc. The aqueous phase was extracted with 2 x 10 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na₂SO₄, and concentrated. The residue was dissolved in 2 mL of CH₂Cl₂. To the solution was added 0.114 mL of diisopropylethylamine, then 0.065 g of triphosgene. The mixture was stirred at 0°C for 30 min, then diluted with 10 mL of EtOAc and 10 mL of saturated NaHCO₃. The aqueous phase was extracted with 2 x 10 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of 4% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 4 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 350.0 (M+1). 1H NMR (500 MHz, CDCl₃): δ 8.00 (d, J=8 Hz, 1H), 7.74 (br s, 1H), 7.33 (br d, J=8 Hz, 1H), 5.80 (dd, J=7 Hz, 9 Hz 1H), 5.05-5.50 (br, 1H), 4.28 (t, J=9 Hz, 1.5H), 3.36 (dd, J= 7 Hz, 9 Hz, 1H).

EXAMPLE 81

![Structure Image](image_url)

5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl) biphenyl-2-yl]-1,3-oxazolidin-2-one
To a solution of 65 mg of 5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl) biphenyl-2-yl]-1,3-oxazolidin-2-one, 45 mg of (5-isopropyl-2-methoxyphenyl)boronic acid, and 66 mg of potassium carbonate in 6 mL of
acetone and 1.5 mL of water was added ca. 5 mg of palladium acetate. The mixture was heated to reflux and stirred at this temperature for 1.5 h. Acetone was removed by rotary evaporation and the residue was diluted with 10 mL of EtOAc and 10 mL of water. The aqueous phase was extracted with 10 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of 10% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 10 to 100% over 10 CV to provide the title compound. Spectral data are provided in EXAMPLE 49.

Following the procedures outlined in EXAMPLE 52 the compounds listed in Table 2 were prepared:

Table 3

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**EXAMPLE 90**

![Chemical Structure](image5)

**5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one**

Following the procedure described in EXAMPLE 80 and using nitroethane, 0.2 g of 2-iodo-5-(trifluoromethyl)benzaldehyde provided 0.102 g of the desired product, which was separated into the cis and trans diastereomers by flash chromatography Biotage Horizon, 25S column, eluting with 1 CV of 10% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 10 to 100% over 10 CV.

**trans-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one**: Mass spectrum (ESI) 372.1 (M+1). \(^1\)H NMR (500 MHz, CDCl3): δ 8.02 (d, J=8 Hz, 1H), 7.61 (d, J=1.5 Hz, 1H), 7.32 (dd, J=2 Hz, 8 Hz, 1H), 6.16 (s, 1H), 5.39 (d, J=4 Hz, 1H), 3.76 (dq, J= 6 Hz, 4.5 Hz, 1H), 1.62 (d, J=6 Hz, 3H).

**cis-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one**: Mass spectrum (ESI) 372.1 (M+1). \(^1\)H NMR (500 MHz, CDCl3): δ 7.98 (d, J=8 Hz, 1H), 7.60 (br s, 1H), 7.33 (dd, J=1.5 Hz, 8 Hz, 1H), 6.25 (s, 1H), 5.85 (d, J=8 Hz, 1H), 3.76 (dq, J= 8 Hz, 7 Hz, 1H), 0.81 (d, J=7 Hz, 3H).

- 96 -
EXAMPLE 91

\[
\text{MeO} \\
\begin{array}{c}
\text{F}_3\text{C} \\
\text{O} \\
\text{N} \\
\end{array}
\]

trans-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (racemic)

To a solution of 0.036 g of trans-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one, 0.024 g of (5-isopropyl-2-methoxyphenyl)boronic acid, and 0.04 g of potassium carbonate in 2 mL of acetone and 0.5 mL of water was added ca. 2 mg of palladium acetate. The mixture was heated to reflux and stirred at this temperature for 1.5 h. Acetone was removed by rotary evaporation and the residue was diluted with 10 mL of EtOAc and 10 mL of water. The aqueous phase was extracted with 10 mL of EtOAc. The combined organics were washed with 10 mL of brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of 10% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 10 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 394.2 (M+1). ¹H NMR signals are doubled because of atropoisomerism. ¹H NMR (500 MHz, CDCl₃): δ 7.80, 7.78 (s, 1H), 7.64, 7.63 (d, J=8 Hz, 1H), 7.35 (d, J=7.5 Hz, 1H), 7.27, 7.26 (d, J=8 Hz 1H), 7.00, 6.95 (d, J=2.5 Hz, 1H), 6.93, 6.92 (d, J=8 Hz, 1H), 5.87, 5.81 (s, 1H), 5.16, 5.10 (d, J=5 Hz, 1H), 3.70-3.78 (m, 3.5H), 3.49 (m, 0.5H), 2.89 (m, 1H), 1.24 (m, 6H), 0.90, 0.70 (d, J=6.5 Hz, 3H).

EXAMPLE 92

\[
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\begin{array}{c}
\text{F}_3\text{C} \\
\text{O} \\
\text{N} \\
\end{array}
\]

cis-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (racemic)

Following the procedure described in EXAMPLE 91, 0.046 g of cis-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one provided the desired product. Mass spectrum
trans-3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (racemic)

To a 0°C solution of 30 mg of trans-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one in 1 mL of DMP was added 8 mg of sodium hydride. The mixture was stirred 10 min at room temperature, and then 32 mg of 3,5-bis(trifluoromethyl)benzyl bromide was added. The mixture was stirred overnight at room temperature, then diluted with 10 mL of EtOAc and 10 mL of water. The phases were separated and the aqueous phase was extracted with 5 mL of EtOAc. The combined organics were washed with 5 mL of brine, dried (Na$_2$SO$_4$), and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of 4% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 4 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 620.2 (M+1). $^1$H NMR signals are doubled because of atropoisomerism. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53-7.80 (m, 5H), 7.33 (d, J=8 Hz, 1H), 7.21-7.29 (m, 1H), 7.00, 6.76 (d, J=2.5 Hz, 1H), 6.91, 6.86 (d, J= 8.5 Hz, 0.4H), 5.15, 5.10 (d, J=4.5 Hz, 1H), 4.80, 4.74 (d, J=16 Hz, 1H), 4.25, 4.21 (d, 16 Hz, 1H), 3.76 (s, 2H), 3.49 (s, 1H), 3.43 (m, 0.4H), 3.18 (m, 0.5H), 2.77-2.98 (m, 1H), 1.24 (m, 3H), 1.16 (m, 3H), 0.78, 0.61 (d, J=6.5 Hz, 3H).
cis-3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (racemic)

Following the procedure described in EXAMPLE 93, 40 mg of cis-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one and 42 mg of 3,5-bis(trifluoromethyl)benzyl bromide gave the title compound. Mass spectrum (ESI) 620.2 (M+1). 1H NMR signals are doubled because of atropoisomerism. 1H NMR (500 MHz, CDCl₃): δ 7.82-7.94 (m, 2H), 7.62-7.74 (m, 3H), 7.39, 7.37 (d, J=8.5 Hz, 1H), 7.25, 7.17 (br s, J=8.5 Hz, 1H), 7.00, 6.78 (s, 1H), 6.87, 6.84 (d, J=8.5 Hz, 1H), 5.59, 5.56 (d, J=4.5 Hz, 1H), 4.96 (d, J=16 Hz, 1H), 4.22, 4.11 (d, J=16 Hz, 1H), 3.76 (s, 2H), 3.58 (s, 1H), 3.40 (m, 0.4H), 2.85-3.00 (m, 1H), 2.78 (m, 0.5H), 1.23 (d, J=7 Hz, 3H), 1.06 (m, 3H), 0.88, 0.69 (d, J=6.5 Hz, 3H).

EXAMPLE 95

(4R,5R)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

Step A: (4S)-4-benzyl-3-[(2R,3S)-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]-2-methylpropanoyl]-1,3-oxazolidin-2-one
A mixture of 1.8 g of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde (EXAMPLE 80, Step A), 1.16 g of (4S)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one, 0.048 g of magnesium chloride, 1.40 mL of triethylamine, and 0.91 mL of chlorotrimethylsilane in 10 mL of EtOAc was stirred at r.t. for 24 h, then filtered through a 10 x 10 cm plug of silica gel, eluting with 400 mL of Et2O. The filtrate was concentrated, and 10 mL of MeOH was added along with 2 drops of trifluoroacetic acid. This solution was stirred at r.t. for 30 min and concentrated to a pale yellow oil. The residue was purified by flash chromatography on a Biotage Horizon, 65i column, eluting with 15 CV of 10% acetone in hexanes to provide the title compound. Mass spectrum (ESI) 516.2 (M-OH). 1H NMR (500 MHz, CDCl3): δ 8.00 (d, J=8.5 Hz, 1H), 7.76 (d, J=2 Hz, 1H), 7.22-7.32 (m, 4H), 7.07 (br d, J=6.5 Hz, 2H), 5.18 (dd, J=6.5 Hz, 7.5 Hz, 1H), 4.67 (m, 1H), 4.46 (dq, J= 6.5 Hz, 7.5 Hz, 1H), 4.17 (t, J=9 Hz, 1H), 4.11 (dd, J=3 Hz, 9 Hz, 1H), 3.97 (d, J=8 Hz, 1H), 3.19 (dd, J=7 Hz, 13.5 Hz, 1H), 2.57 (dd, J=9.5 Hz, 13.5 Hz, 1H), 1.34 (d, J=7.5 Hz, 3H).

Step B: (4R,5R)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

To a 0°C solution of 0.65 g of (4S)-4-benzyl-3-[(2R,3S)-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]-2-methylpropanoyl]-1,3-oxazolidin-2-one in 6 mL of 3:1 tetrahydrofuran-water was added 0.102 g of lithium hydroxide in 1.5 mL of water, then 0.554 mL of a 30% aqueous solution of hydrogen peroxide. The solution was stirred 1 h at 0°C, at which point LC/MS analysis showed no starting material. A 1.5 M solution of sodium sulfite (3.7 mL) was added to the cold solution, which was then poured into a separatory funnel and extracted with 2 x 10 mL of CH2Cl2. The combined CH2Cl2 extracts were back-extracted with 20 mL of 3:1 water-saturated aqueous NaHCO3. The combined aqueous layers were acidified (pH <1) with 6 N HCl and extracted with 4 x 10 mL of EtOAc. The combined EtOAc extracts were washed with 10 mL of brine, dried over Na2SO4, and concentrated. The residue was dissolved in 10 mL of toluene. Diphenylphosphoryl azide (0.315 mL) and 0.24 mL of triethylamine were added and the mixture was stirred overnight at 100°C, then cooled and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 40S column, eluting with 1 CV of 5% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 5 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 372.1 (M+1). 1H NMR (500 MHz, CDCl3): δ 8.02 (d, J=8 Hz, 1H), 7.61 (d, J=1.5 Hz, 1H), 7.32 (dd, J=2 Hz, 8 Hz, 1H), 6.16 (s, 1H), 5.39 (d, J=4 Hz, 1H), 3.76 (dq, J= 6 Hz, 4.5 Hz, 1H), 1.62 (d, J=6 Hz, 3H). Analytical HPLC on Chiralpak AD 4.6 x 250 mm, eluting with 4% ethanol in heptane at 0.75 mL/min (rR=21.56 min for R,R; rR=18.00 min for S,S) showed 98% e.e.

EXAMPLE 96
(4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

To a 0°C solution of 95 mg of (4R,5R)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one in 1 mL of DMF was added 20 mg of sodium hydride. The mixture was stirred 10 min at 0°C; then 94 mg of 3,5-bis(trifluoromethyl)benzyl bromide was added. The mixture was stirred 10 min at 0°C, then diluted with 10 mL of EtOAc and 10 mL of water. The phases were separated and the aqueous phase was extracted with 10 mL of EtOAc. The combined organic phases were washed with 10 mL of brine, dried over Na₂SO₄, and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25M column, eluting with 1 CV of 2% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 2 to 100% over 10 CV to provide the title compound. Mass spectrum (ESI) 598.1 (M+1). ¹H NMR (500 MHz, CDCl₃): 8 8.00 (d, J=8.5 Hz, 1H), 7.77 (s, 1H), 7.58 (br s, 3H), 7.34 (dd, J=1.5 Hz, 8 Hz, 1H), 5.36 (d, J=4 Hz, 1H), 4.89 (d, J=16 Hz, 1H), 4.31 (d, J=16 Hz, 1H), 4.48 (dq, J= 6 Hz, 4 Hz, 1H), 1.55 (d, J=6.5 Hz, 3H).

EXAMPLE 97
(4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 81, 41 mg of (4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and 17 mg of (5-isopropyl-2-methoxyphenyl)boronic acid gave the title compound. Mass spectrum (ESI) 620.4 (M+1). 1H NMR signals are doubled because of atropoisomerism. 1H NMR (500 MHz, CDCl3): δ 7.53-7.80 (m, 5H), 7.33 (d, J=8 Hz, 1H), 7.21-7.29 (m, 1H), 7.00, 6.76 (d, J=2.5 Hz, 1H), 6.91, 6.86 (d, J= 8.5 Hz, 0.4H), 5.15, 5.10 (d, J=4.5 Hz, 1H), 4.80, 4.74 (d, J=16 Hz, 1H), 4.25, 4.21 (d, 16 Hz, 1H), 3.76 (s, 2H), 3.49 (s, 1H), 3.43 (m, 0.4H), 3.18 (m, 0.5H), 2.77-2.98 (m, 1H), 1.24 (m, 3H), 1.16 (m, 3H), 0.78, 0.61 (d, J=6.5 Hz, 3 Hz).

EXAMPLE 98

(4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 81, 38.5 mg of (4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and 18 mg of (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (EXAMPLE 78) gave the title compound. Mass spectrum (ESI) 638.3 (M+1). 1H NMR signals are doubled because of atropoisomerism. 1H NMR (500 MHz, CDCl3): δ 7.55-7.80 (m, 5H), 7.29 (d, J=8 Hz, 1H), 7.00, 6.77 (d, J= 8.5 Hz, 1H), 6.68, 6.63 (d, J=12 Hz, 1H), 5.08, 5.04 (d, J=5 Hz, 1H), 4.81, 4.75 (d, J=16 Hz, 1H), 4.26, 4.23 (d, 15.5 Hz, 1H), 3.75 (s, 2H), 3.50 (s, 1H), 3.43 (m, 0.5H), 3.12-3.24 (m, 1.5H), 1.24, 1.22 (d, J=5 Hz, 3H), 1.17, 1.06 (d, J=7 Hz, 3H), 0.84, 0.70 (d, J=6 Hz, 3H).

EXAMPLE 99
(4S,5S)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

Step A: (4R)-4-benzyl-3-[(2S,3R)-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]-2-methylpropanoyl]-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 95, Step A, 0.72 g of 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde (EXAMPLE 80, Step A), 0.466 g of (4R)-4-benzyl-3-propionyl-1,3-oxazolidin-2-one, 0.02 g of magnesium chloride, 0.56 mL of triethylamine, and 0.38 mL of chlorotrimethylsilane provided the title compound. Mass spectrum (ESI) 516.2 (M-OH). 1H NMR (500 MHz, CDCl3): δ 8.00 (d, J=8.5 Hz, 1H), 7.76 (d, J=2 Hz, 1H), 7.22-7.32 (m, 4H), 7.07 (br d, J=6.5 Hz, 2H), 5.18 (dd, J=6.5 Hz, 7.5 Hz, 1H), 4.67 (m, 1H), 4.46 (dq, J= 6.5 Hz, 7.5 Hz, 1H), 4.17 (t, J=9 Hz, 1H), 4.11 (dd, J=3 Hz, 9 Hz, 1H), 3.97 (d, J=8 Hz, 1H), 3.19 (dd, J=7 Hz, 13.5 Hz, 1H), 2.57 (dd, J=9.5 Hz, 13.5 Hz, 1H), 1.34 (d, J=7.5 Hz, 3H).

Step B: (4S,5S)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 95, Step B, 0.214 g of (4R)-4-benzyl-3-[(2S,3R)-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]-2-methylpropanoyl]-1,3-oxazolidin-2-one, 0.034 g of lithium hydroxide, 0.16 mL of a 30% aqueous solution of hydrogen peroxide, 0.1 mL of diphenylphosphoryl azide, and 0.072 mL of triethylamine provide the title compound. Mass spectrum (ESI) 372.1 (M+). 1H NMR (500 MHz, CDCl3): δ 8.02 (d, J=8 Hz, 1H), 7.61 (d, J=1.5 Hz, 1H), 7.32 (dd, J=2 Hz, 8 Hz, 1H), 6.16 (s, 1H), 5.39 (d, J=4 Hz, 1H), 3.76 (dq, J= 6 Hz, 4.5 Hz, 1H), 1.62 (d, J=6 Hz, 3H). Analytical HPLC on Chiralpak AD 4.6 x 250 mm, eluting with 4% ethanol in heptane at 0.75 mL/min (trR=21.56 min for R,R; trS=18.00 min for S,S) showed 99% e.e.

EXAMPLE 100
(4S,5S)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 96, 0.108 g of (4S,5S)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one, 23 mg of sodium hydride, and 107 mg of 3,5-bis(trifluoromethyl)benzyl bromide provided the title compound. Mass spectrum (ESI) 598.1 (M+1). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.00 (d, J=8.5 Hz, 1H), 7.77 (s, 1H), 7.58 (br s, 3H), 7.34 (dd, J=1.5 Hz, 8 Hz, 1H), 5.36 (d, J=4 Hz, 1H), 4.89 (d, J=16 Hz, 1H), 4.31 (d, J=16 Hz, 1H), 4.48 (dq, J= 6 Hz, 4 Hz, 1H), 1.55 (d, J=6.5 Hz, 3H).

EXAMPLE 101

(4S,5S)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 81, 40 mg of (4S,5S)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and 17 mg of (5-isopropyl-2-methoxyphenyl)boronic acid gave the title compound. Mass spectrum (ESI) 620.4 (M+1). $^1$H NMR signals are doubled because of atropoisomerism. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53-7.80 (m, 5H), 7.33 (d, J=8 Hz, 1H), 7.21-7.29 (m, 1H), 7.00, 6.76 (d, J=2.5 Hz, 1H), 6.91, 6.86 (d, J= 8.5
Hz, 0.4H), 5.15, 5.10 (d, J=4.5 Hz, 1H), 4.80, 4.74 (d, J=16 Hz, 1H), 4.25, 4.21 (d, 16 Hz, 1H), 3.76 (s, 2H), 3.49 (s, 1H), 3.43 (m, 0.4H), 3.18 (m, 0.5H), 2.77-2.98 (m, 1H), 1.24 (m, 3H), 1.16 (m, 3H), 0.78, 0.61 (d, J=6.5 Hz, 3 Hz).

EXAMPLE 102

(4R,5R)-5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 81, 240 mg of (4R,5R)-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one and 171 mg of (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (EXAMPLE 78) gave the title compound. Mass spectrum (ESI) 412.3 (M+1). $^1$H NMR signals are doubled because of atropoisomerism. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.79, 7.77 (s, 1H), 7.64, 7.62 (dd, J=2.5 Hz, 8 Hz, 1H), 7.32, 7.31 (d, J=8 Hz, 1H), 7.00, 6.95 (d, J=8.5 Hz, 1H), 6.70, 6.67 (d, J= 12 Hz, 1H), 6.47, 6.43 (s, 1H), 5.08, 5.04 (d, J=5 Hz, 0.1H), 3.68-3.80 (m, 3.5H), 3.53 (m, 0.5H), 3.21 (m, 1H), 1.19-1.30 (m, 6H), 0.95, 0.77 (d, J=6 Hz, 3H).

Following the procedures outlined in EXAMPLE 96 the compounds listed in Table 4 were prepared from (4R,5R)-5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one:
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((4R,5S)-4-[3,5-bis(trifluoromethyl)phenyl]-1-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-methylimidazolidin-2-ylidene)cyanamide.

To a solution of (1R,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-N-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}propane-1,2-diamine (25.1 mg, 0.0424 mmol) in dichloroethane (1.5 mL) was added triethylamine (15 µL, 0.105 mmol) and diphenyl cyanocarbonimidate (13 mg, 0.053 mmol). The reaction was heated at 60°C overnight, cooled to room temperature, filtered, and loaded directly onto a silica gel column for purification by flash chromatography with 10 to 40% EtOAc/hexanes to afford ((4R,5S)-4-[3,5-bis(trifluoromethyl)phenyl]-1-{[5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-methylimidazolidin-2-ylidene)cyanamide. Rf = 0.20 (25% EtOAc/hexanes). LCMS = 643.3 (M+1)+. 1H NMR (CDCl3, 500 MHz; atropisomers present, doubling of some peaks) δ 6.53-8.83 (m, 10H), 3.61-4.91 (m, 3H), 3.28-2.70 (m, 5H), 1.14-1.25 (m, 6H), -0.39-0.26 (m, 3H).

Following the general procedures outlined above, the compounds in Table 5 were prepared:
Table 5

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<th>Compound</th>
<th>$A^3$</th>
<th>$A^2$</th>
<th>Z</th>
<th>LCMS (M+1)</th>
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<td><img src="image2.png" alt="Image" /></td>
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<td><img src="image12.png" alt="Image" /></td>
<td>SO$_2$</td>
<td>673.3</td>
</tr>
</tbody>
</table>

INTERMEDIATE 1

![Image](image13.png)
(4S,5R)-5-(3,5-difluorophenyl)-4-methyl-1,3-oxazolidin-2-one
Step A: benzyl [(1S)-2-(3,5-difluorophenyl)-1-methyl-2-oxoethyl]carbamate
To a -15 °C solution of benzyl [(1S)-2-[methoxy(methyl)amino]-1-methyl-2-oxoethyl]carbamate (1.96 g, 7.36 mmol) in THF (9.4 mL) was added i-propyl magnesium chloride (3.6 mL of a 2M solution in Et₂O, 7.2 mmol). The reaction was stirred at -15 °C for 15 minutes and then 3,5-difluorophenylmagnesium bromide (29.44 mL of a 0.5 M solution in THF, 14.72 mmol) was added. The reaction was warmed to room temperature and stirred for 24 hours. The reaction was then poured into saturated NH₄Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The organic extracts were washed with water and brine (100 mL each), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (15% EtOAc/hexanes) afforded benzyl [(1S)-2-(3,5-difluorophenyl)-1-methyl-2-oxoethyl]carbamate. Rᶠ = 0.34 (15% EtOAc/hexanes). LCMS = 342.3 (M+Na⁺).
Step B: benzyl [(1S,2S)-2-(3,5-difluorophenyl)-2-hydroxy-1-methylethyl]carbamate
To a -78 °C solution of benzyl [(1S)-2-(3,5-difluorophenyl)-1-methyl-2-oxoethyl]carbamate. (1.35 g, 4.23 mmol) in THF (75 mL) was added L-Selectride (6.35 mL of a 1M solution in THF, 6.35 mmol). After stirring at -78 °C for 1 hour, the reaction was poured into 1N HCl (50 mL). The mixture was extracted with EtOAc (2 x 100 mL). The organic extracts were washed with water and brine (50 mL each), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (5 to 40% EtOAc/hexanes) afforded benzyl [(1S,2S)-2-(3,5-difluorophenyl)-2-hydroxy-1-methylethyl]carbamate (major product). LCMS = 322.3 (M+1⁺).
Step C: (4S,5R)-5-(3,5-difluorophenyl)-4-methyl-1,3-oxazolidin-2-one
To a solution of [(1S,2S)-2-(3,5-difluorophenyl)-2-hydroxy-1-methylethyl]carbamate (900 mg, 2.80 mmol) in THF (28.6 mL) was added MeOH (14.3 mL) and 7.5 N KOH (7.2 mL). The reaction was stirred at room temperature for 4 hours and then extracted with EtOAc (2 x 75 mL). The organic extracts were washed with water and brine (50 mL each), dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (10 to 75% EtOAc/hexanes) afforded (4S,5S)-5-(3,5-difluorophenyl)-4-methyl-1,3-oxazolidin-2-one. Rᶠ = 0.07 (25% EtOAc/hexanes). LCMS = 214.3 (M+1⁺). ¹H NMR (CDCl₃, 500 MHz) δ 6.89-6.93 (m, 2H), 6.82 (m, 1H), 6.24 (bs, 1H), 5.01 (d, J = 6.8 Hz, 1H), 3.79 (m, 1H), 1.42 (d, J = 6.2 Hz, 3H).

INTERMEDIATE 2

[Chemical structure image]

- 109 -
6-chloro-5-fluoro-2-iodopyridin-3-ol
To a solution of 6-chloro-5-fluoropyridin-3-ol (307.8 mg, 2.08 mmol) in water (11 mL) was added Na₂CO₃ (441 mg, 4.16 mmol) and I₂ (549 mg, 2.08 mmol). After 2 hours, the reaction mixture was acidified with 1 N HCl to pH 3, diluted with EtOAc (100 mL), and washed with aq. NaHSO₃ and brine (50 mL each). The organic layer was dried over Na₂SO₄, filtered and concentrated to afford 6-chloro-5-fluoro-2-iodopyridin-3-ol. LCMS = 273.9 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.11 (d, J = 8.5 Hz, 1H), 5.47 (d, J = 1.4 Hz, 1H).

INTERMEDIATE 3

2-bromo-6-isopropenyl-3-methoxypyridine
In a tube were placed 2-bromo-6-iodo-3-methoxypyridine (700 mg, 2.236 mmol), isopropenylboronic acid (212 mg, 2.460 mmol), DME (7.5 mL), EtOH (2.8 mL), and 1M aq. Na₂CO₃ (5.6 mL). The mixture was degassed with N₂. Next, Pd(PPh₃)₄ (206 mg, 0.179 mmol) was added and the mixture was degassed again with N₂. The tube was sealed and heated at 80 °C for 16 hours. The reaction was then cooled to room temperature, diluted with EtOAc (100 mL), and washed with saturated NaHCO₃ and brine (50 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (0 to 15% EtOAc/hexanes) afforded 2-bromo-6-isopropenyl-3-methoxypyridine. Rf = 0.38 (25% EtOAc/hexanes). LCMS = 230.0 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.36 (d, J = 8.5 Hz, 1H), 7.07 (d, J = 9.4 Hz, 1H), 5.81 (s, 1H), 5.21 (s, 1H), 3.92 (s, 3H), 2.16 (s, 3H).

INTERMEDIATE 4

2-iodo-3-methoxypyridine
To a solution of 2-iodopyridin-3-ol (45.3 mg, 0.205 mmol) in DMF (3 mL) was added Cs₂CO₃ (334 mg, 1.030 mmol) and MeI (25 µL, 0.410 mmol). After 1 hour, the reaction was poured into water (10 mL), diluted with EtOAc (20 mL), washed with water (3 x 10 mL) and brine (10 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated to afford 2-iodo-3-
methoxypyridine. LCMS = 236.1 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 8.00 (dd, J = 1.4, 4.6 Hz, 1H), 7.20 (dd, J = 4.6, 8.0 Hz, 1H), 7.00 (dd, J = 1.4, 8.3 Hz, 1H), 3.90 (s, 3H).

INTERMEDIATE 5

2-bromo-6-iodopyridin-3-ol
To a solution of 2-bromopyridin-3-ol (1.00 g, 5.80 mmol) in water (30 mL) was added Na₂CO₃ (1.23 g, 11.60 mmol) and I₂ (1.53 g, 5.80 mmol). After 1 hour, the reaction was quenched with 1 N HCl (20 mL), extracted with EtOAc (2 x 100 mL), and washed with aq. NaHSO₃ and brine (50 mL each). The organic layer was dried over Na₂SO₄, filtered and concentrated. Purification of the residue by flash chromatography on silica gel (20 to 40% EtOAc/hexanes) afforded 2-bromo-6-iodopyridin-3-ol. Rₓ = 0.44 (25% EtOAc/hexanes). LCMS = 301.9 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.56 (d, J = 8.3 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 5.65 (s, 1H).

INTERMEDIATE 6

1-(2-bromo-1,3-thiazol-5-yl)ethanol
To a 0 °C solution of 2-bromo-5-formylthiazole (100.6 mg, 0.524 mmol) in THF (5 mL) was added MeMgBr (175 µL of a 3M solution in Et₂O, 0.524 mmol). After 30 minutes, additional MeMgBr (50 µL of a 3M solution in Et₂O, 0.150 mmol) was added. After 30 more minutes, the reaction was quenched by pouring into saturated NH₄Cl (20 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (25 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography (0 to 80% EtOAc/hexanes) afforded 1-(2-bromo-1,3-thiazol-5-yl)ethanol. Rₓ = 0.13 (25% EtOAc/hexanes). LCMS = 210.0 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.40 (s, 1H), 5.12 (q, J = 6.4 Hz, 1H), 1.59 (d, J = 6.4 Hz, 3H).

INTERMEDIATE 7
4-((\{\text{tert-buty}l(dimethyl)silyl\}oxy)methyl)-2-iodo-1,3-thiazole.

Step A: 4-((\{\text{tert-buty}l(dimethyl)silyl\}oxy)methyl)-1,3-thiazole

To a solution of 1,3-thiazol-4-ylmethanol (311.4 mg, 2.7 mmol) in CH₂Cl₂ (15 mL) was added Et₃N (1.9 mL, 13.6 mmol). The solution was cooled to -78 °C and TBSOTf (776 µL, 3.38 mmol) was added. The reaction was warmed to room temperature and stirred for 1 hour. Next, the reaction was diluted with EtOAc (75 mL) and washed with saturated NaHCO₃, brine, 1N HCl, and brine (20 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (0 to 15% EtOAc/hexanes) to afford 4-(((tert-buty1(dimethyl)silyl)oxy)methyl)-1,3-thiazole. Rf = 0.28 (15% EtOAc/hexanes). LCMS = 230.1 (M+1)+. ¹H NMR (CDCl₃, 600 MHz) δ 8.77 (d, J = 2.0 Hz, 1H), 7.25 (m, 1H), 4.93 (d, J = 1.1 Hz, 2H), 0.95 (s, 9H), 0.12 (s, 6H).

Step B: 4-(((tert-buty1(dimethyl)silyl)oxy)methyl)-2-iodo-1,3-thiazole.

To a -78 °C solution of 4-(((tert-buty1(dimethyl)silyl)oxy)methyl)-1,3-thiazole (106.4 mg, 0.465 mmol) in THF (5 mL) was added dropwise a solution of n-BuLi (465 µL of a 1.6M solution in hexanes, 0.744 mmol). The reaction was stirred at -78 °C for 30 minutes, and then a solution of iodine (295 mg, 1.16 mmol) in THF (5mL) was added by cannula. The reaction was warmed to room temperature for 15 minutes and then quenched by pouring into aq. NaHSO₃ (20 mL). The mixture was extracted with EtOAc (60 mL) and the organic layer was washed with brine, saturated NaHCO₃, and brine (20 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography (15% EtOAc/hexanes) afforded 4-(((tert-buty1(dimethyl)silyl)oxy)methyl)-2-iodo-1,3-thiazole. Rf = 0.55 (15% EtOAc/hexanes). LCMS = 356.0 (M+1)+. ¹H NMR (CDCl₃, 600 MHz) δ 7.16 (s, 1H), 4.86 (s, 2H), 0.93 (s, 9H), 0.10 (s, 6H).

INTERMEDIATE 8

- 112 -
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (975 mg, 1.633 mmol) in DMSO (16 mL) were added bis(pinacolato)diboron (1.24 g, 4.899 mmol), [1,1’-Bis(diphenylphosphino)-ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (133 mg, 0.1633 mmol), and KOAc (320 mg, 3.266 mmol). The mixture was degassed with N₂, and then heated at 80 °C for 16 hours. The reaction was then cooled to room temperature, diluted with EtOAc (200 mL), and washed with saturated NaHCO₃ and brine (80 mL each). The organic layer was dried over Na₂SO₄, filtered through a plug of silica, and concentrated. Purification of the residue by reverse-phase chromatography (C-18, 10 to 95% MeCN/water with 0.1% TFAA) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one. LCMS = 598.1 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.98 (d, J = 7.8 Hz, 1H), 7.88 (s, 1H), 7.78 (s, 2H), 7.67 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 5.68 (d, J = 7.5 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 4.76 (d, J = 15.5 Hz, 1H), 3.98-3.93 (m, 1H), 1.35 (d, J = 6.9 Hz, 12H), 0.77 (d, J = 6.7 Hz, 3 H).

**EXAMPLE 118**

![Chemical Structure](image)

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[3'-isopropyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

In a tube were placed (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (52.5 mg, 0.0879 mmol), 3-isopropylbenzeneboronic acid (17.3 mg, 0.106 mmol), DME (370 μL), EtOH (120 μL), and 1M aqueous Na₂CO₃ (264 μL, 0.264 mmol). The mixture was degassed with N₂. Next, Pd(PPh₃)₄ (10.2 mg, 8.8 x 10⁻³ mmol) was added and the mixture was degassed again with N₂. The tube was sealed and heated at 100 °C for two hours. The reaction was then cooled to room temperature.
temperature, diluted with EtOAc (50 mL), and washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (0 to 15% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-3'-isopropenyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one. R₇ = 0.29 (15% EtOAc/hexanes). LCMS = 590.1 (M+1)+. ¹H NMR (CDCl₃, 500 MHz) δ 7.85 (s, 1H), 7.72 (s, 1H), 7.68 (s, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.29 (d, J = 7.8 Hz, 1H), 7.15 (bs, 1H), 7.11 (bd, J = 7.5 Hz, 1H), 5.46 (d, J = 8.0 Hz, 1H), 4.91 (d, J = 15.7 Hz, 1H), 4.21 (d, J = 15.8 Hz, 1H), 3.69 (m, 1H), 2.96 (m, 1H), 1.26-1.28 (m, 6H), 0.38 (d, J = 6.4 Hz, 3H).

**EXAMPLE 119**

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-3'-isopropenyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one.

In a tube was placed (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[3'-chloro-4'-fluoro-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one (Example 146) (30.2 mg, 0.0504 mmol), isopropenylboronic acid (27 mg, 0.31 mmol), 1,1-bis(di-t-butylphosphino)ferrocene palladium chloride (5.5 mg, 8.4 x 10⁻³ mmol), THF (350 μL) and 1 M aq. K₂CO₃ (350 μL). The tube was degassed with nitrogen, sealed, and heated at 100 °C for 5 hours. The reaction was then cooled to room temperature, diluted with EtOAc (50 mL) and washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (0 to 15% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-3'-isopropenyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one. R₇ = 0.29 (15% EtOAc/hexanes). LCMS = 606.2 (M+1)+. ¹H NMR (CDCl₃, 500 MHz) δ 7.86 (s, 1H), 7.70 (s, 3H), 7.64 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.23 (dd, J = 7.8, 2.0 Hz, 1H), 7.12-7.17 (m, 2H), 5.54 (d, J = 8.0 Hz, 1H), 5.28 (s, 1H), 5.26 (s, 1H), 4.90 (d, J = 15.8 Hz, 1H), 4.18 (d, J = 15.8 Hz, 1H), 3.78 (m, 1H), 2.16 (s, 3H), 0.47 (d, J = 6.7 Hz, 3H).
EXAMPLE 120

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-(1H-pyrrol-3-yl)-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one

To a 0 °C solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[5-(trifluoromethyl)-2-[1-(triisopropylsilyl)-1H-pyrrol-3-yl]benzyl]-1,3-oxazolidin-2-one (Example 149) (22.6 mg, 0.0326 mmol) in THF (2 mL) was added TBAF (65 μL of a 1M solution in THF, 0.065 mmol). After 30 minutes, the reaction was quenched with saturated NH₄Cl (5 mL). The mixture was extracted with EtOAc (35 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (25 to 60% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-(1H-pyrrol-3-yl)-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one. Rₓ = 0.11 (25% EtOAc/hexanes). LCMS = 537.1 (M+1)+. ¹H NMR (CDCl₃, 600 MHz) δ 8.49 (s, 1H), 7.85 (s, 1H), 7.71 (s, 2H), 7.64 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 6.88-6.91 (m, 2H), 6.33 (d, J = 1.6 Hz, 1H), 5.53 (d, J = 8.0 Hz, 1H), 5.02 (d, J = 15.7 Hz, 1H), 4.46 (d, J = 15.6 Hz, 1H), 3.80 (m, 1H), 0.49 (d, J = 6.6 Hz, 3H).

EXAMPLE 121
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2-(1-isopropyl-1 H-pyrrol-3-yl)-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-(1 H-pyrrol-3-yl)-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one (6.8 mg, 0.0127 mmol) (Example 120) in DMSO (300 µL) was added powdered KOH (3.6 mg, 0.0643 mmol). After stirring for 15 minutes, 2-iodopropane (3.2 µL, 0.032 mmol) was added. After 1.5 hours of stirring at room temperature, water (5 mL) was added, and the mixture was extracted, first with CH₂Cl₂ (2 x 15 mL) and then with EtOAc (2 x 15 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by PTLC (25% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(1-isopropyl-1 H-pyrrol-3-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one. Rₚ = 0.33 (25% EtOAc/hexanes). LCMS = 579.2 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.85 (s, 1H), 7.71 (s, 2H), 7.61 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 6.83 (t, J = 2.1 Hz, 1H), 6.79 (t, J = 2.5 Hz, 1H), 6.24 (t, J = 2.3 Hz, 1H), 5.49 (d, J = 8.0 Hz, 1H), 5.04 (d, J = 15.5 Hz, 1H), 4.48 (d, J = 15.6 Hz, 1H), 4.27 (m, 1H), 3.76 (m, 1H), 1.48 (d, J = 6.6 Hz, 6H), 0.49 (d, J = 6.6 Hz, 3H).

EXAMPLE 122

![Chemical Structure](image)

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-methoxy-5'-nitro-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one (example 143) (159.4 mg, 0.276 mmol) in HOAc (5 mL) was added HNO₃ (1.5 mL). After 45 minutes, additional HNO₃ (1.5 mL) was added. 45 minutes later, the reaction was quenched by pouring into ice water (30 mL). The mixture was extracted with EtOAc (75 mL), and the organic layer was washed with 1 N NaOH, saturated NaHCO₃, and brine (25 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (8 to 40% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-
bis(trifluoromethyl)phenyl)-3-{{2'-methoxy-5'-nitro-4-(trifluoromethyl)biphenyl-2-yl}methyl}-4-methyl-1,3-oxazolidin-2-one. \( R_f = 0.11 \) (25% EtOAc/hexanes). LCMS = 623.1 (M+1)^+.

\(^1\)H NMR (CDCl\(_3\), 500 MHz, rotamers present) \( \delta \) 8.34 (m, 1H), 8.10 (m, 1H), 7.85 (d, \( J = 6.9 \) Hz, 1H), 7.61-7.71 (m, 4H), 7.40 (m, 1H), 7.11 (m, 1H), 5.66 (d, \( J = 8.0 \) Hz), 5.28 (d, \( J = 8.2 \) Hz), 4.89-4.94 (m, 1H), 3.74-4.09 (m, 5H), 0.61 (d, \( J = 6.6 \) Hz), 0.47 (d, \( J = 6.5 \) Hz).

EXAMPLE 123

\[(4S,5R)-3-\{5'-amino-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl\}methyl\}-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one\]

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{{2'-methoxy-5'-nitro-4-(trifluoromethyl)biphenyl-2-yl}methyl}-4-methyl-1,3-oxazolidin-2-one (example 122) (48.2 mg, 0.077 mmol) in EtOAc (4 mL) was added \( \text{PtO}_2 \) (12 mg) and the reaction was placed under an atmosphere of hydrogen (balloon) and stirred vigorously. After 45 minutes, the catalyst was removed by filtration through a plug of silica gel with 100% EtOAc. The filtrate was concentrated to afford (4S,5R)-3-\{5'-amino-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl\}methyl\}-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one. \( R_f = 0.20 \) (40% EtOAc/hexanes). LCMS = 593.2 (M+1)^+.

\(^1\)H NMR (CDCl\(_3\), 500 MHz, rotamers present) \( \delta \) 7.85 (s, 1H), 7.60-7.70 (m, 4H), 7.36 (d, \( J = 7.8 \) Hz, 1H), 6.74-6.84 (m, 2H), 6.56 (s, 1H), 5.45-5.54 (m, 1H), 4.82-4.87 (m, 1H), 3.64-4.17 (m, 2H), 3.70 (s, 3H), 0.43-0.53 (m, 3H).

EXAMPLE 124
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-methoxy-5'-(methylthio)-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-3-[[5'-amino-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (Example 123) (40 mg, 0.0676 mmol) in CHCl₃ (1 mL) that had been degassed with N₂ was added methyl disulfide (10 µL, 0.101 mmol) and t-butyl nitrite (16 µL, 0.135 mmol). The reaction was stirred at room temperature for 30 minutes and then heated to reflux for 2 hours. The reaction was then cooled to room temperature and diluted with hexanes (3 mL). The solution was loaded directly onto a silica gel column and eluted with 25% EtOAc/hexanes. Fractions containing the desired product were combined and repurified by silica gel chromatography with 5 to 25% EtOAc/hexanes to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-methoxy-5'-(methylthio)-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one. Rₛ = 0.52 (40% EtOAc/hexanes). LCMS = 624.1 (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz, rotamers present) δ 6.94-7.85 (m, 9H), 5.58 (d, J = 8.1 Hz), 5.25 (d, J = 7.8 Hz), 4.94 (d, J = 15.8 Hz), 4.85 (d, J = 15.7 Hz), 3.65-4.12 (m, 5H), 2.47 (s), 2.44 (s), 0.54 (d, J = 6.6 Hz), 0.40 (d, J = 6.6 Hz).

EXAMPLE 125
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2'-methoxy-5'- (methylsulfonyl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one

To a -60 °C solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2'-methoxy-5'-(methylthio)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one (example 124) (32.5 mg, 0.0522 mmol) in CH₂Cl₂ (5 mL) was added m-CPBA (14.6 mg, 77% purity, 0.0652 mmol). The reaction was warmed slowly to -20 °C and then diluted with EtOAc (35 mL), washed withaq. NaHSO₃, brine, saturated NaHCO₃, and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (20 to 100% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2'-methoxy-5'-(methylsulfonyl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one. Rₜ = 0.10 (75% EtOAc/hexanes). LCMS = 640.1 (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz) δ 7.10-7.86 (m, 9H), 4.87-5.59 (m, 2H), 3.56-4.14 (m, 5H), 2.79 (s), 2.75 (s), 2.73 (s), 0.61 (d, J = 6.5 Hz), 0.57 (d, J = 6.4 Hz), 0.46 (d, J = 6.4 Hz), 0.43 (d, J = 6.5 Hz).

EXAMPLE 126

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2'-methoxy-5'-(methylsulfonyl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one

To a 0 °C solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2'-methoxy-5'- (methylthio)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one (example 124) (7.8 mg, 0.013 mmol) in CH₂Cl₂ (1 mL) was added m-CPBA (14 mg, 77% purity, 0.063 mmol). The reaction was stirred at room temperature for 30 minutes and then diluted with EtOAc (35 mL), washed withaq. NaHSO₃, brine, saturated NaHCO₃, and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by PTLC (50% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[2'-methoxy-5'-(methylsulfonyl)-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one. Rₜ = 0.11 (40% EtOAc/hexanes). LCMS = 656.2 (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz, rotamers
present) δ 7.99-8.02 (m, 1H), 7.84-7.86 (m, 1H), 7.75-7.78 (m, 1H), 7.58-7.72 (m, 4H), 7.38-7.42 (m, 1H), 7.15-7.18 (m, 1H), 5.55 (d, J = 8.0 Hz), 5.26 (d, J = 8.1 Hz), 4.91-4.97 (m, 1H), 3.63-4.03 (m, 5H), 3.12 (s), 3.10 (s), 0.62 (d, J = 6.6 Hz), 0.48 (d, J = 6.6 Hz).

EXAMPLE 127

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(6-isopropenylpyridin-2-yl)]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

Step A: 2-bromo-6-isopropenylpyridine

In a tube were placed 2,6-dibromopyridine (100 mg, 0.422 mmol), isopropenylboronic acid (40 mg, 0.464 mmol), DME (1.5 mL), EtOH (500 μL), and 1M aqueous Na₂CO₃ (1 mL, 1.0 mmol). The mixture was degassed with N₂. Next, Pd(PPh₃)₄ (37 mg, 0.032 mmol) was added and the mixture was degassed again with N₂. The tube was sealed and heated at 100 °C for 1 hour. The reaction was then cooled to room temperature, diluted with EtOAc (50 mL), and washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (5% EtOAc/hexanes) afforded 2-bromo-6-isopropenylpyridine. R_f = 0.45 (15% EtOAc/hexanes). LCMS = 200.0 (M+1)^+.

1H NMR (CDCl₃, 500 MHz) δ 7.49 (t, J = 7.8 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 5.93 (s, 1H), 5.32 (m, 1H), 2.17 (s, 3H).

Step B: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(6-isopropenylpyridin-2-yl)]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

In a tube were placed 2-bromo-6-isopropenylpyridine (17.5 mg, 0.0878 mmol), (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)]-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one (26.2 mg, 0.0439 mmol), DME (190 μL), EtOH (62 μL), and 1M aqueous Na₂CO₃ (100 μL, 0.1 mmol). The mixture was degassed with N₂. Next, Pd(PPh₃)₄ (9 mg, 7.8 x 10⁻³ mmol) was added and the mixture was degassed again with N₂. The tube was sealed and heated at 100 °C for 2 hours. The reaction was then cooled to room temperature, diluted with EtOAc (50 mL), and washed with water and brine (15 mL each). The
organic layer was dried over Na2SO4, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (5 to 25% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(6-isopropenylpyridin-2-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one. Rf = 0.15 (15% EtOAc/hexanes). LCMS = 589.1 (M+1)+. 1H NMR (CDCl3, 500 MHz) δ 7.81-7.85 (m, 2H), 7.74 (s, 1H), 7.69-7.69 (m, 3H), 7.58 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 7.7 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 5.94 (s, 1H), 5.48 (d, J = 7.7 Hz, 1H), 5.36 (s, 1H), 5.06 (d, J = 16.0 Hz, 1H), 4.47 (d, J = 16.1 Hz, 1H), 3.91 (m, 1H), 2.23 (s, 3H), 0.50 (d, J = 6.6 Hz, 3H).

EXAMPLE 128

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(3-methoxy-6-methyl-1-oxidopyridin-2-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a 0 ºC solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(3-methoxy-6-methylpyridin-2-yl)-5-(trifluoromethyl) benzyl]-4-methyl-1,3-oxazolidin-2-one (Example 174) (7.6 mg, 0.0128 mmol) in CH2Cl2 (1.3 mL) was added m-CPBA (5.8 mg, 77% purity, 0.0256 mmol). The reaction was stirred at room temperature for 1 hour and then diluted with CH2Cl2 (10 mL), washed with aq. NaHSO3, saturated K2CO3, and brine (5 mL each). The organic layer was dried over Na2SO4, filtered, and concentrated. Purification of the residue by PTLC (50% Et2O/CH2Cl2) afforded the title compound. Rf = 0.23 (50% Et2O/CH2Cl2). LCMS = 609.2 (M+1)+. 1H NMR (CDCl3, 500 MHz) δ 7.85 (s, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.70 (s, 2H), 7.62 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.9 Hz, 1H), 7.04 (d, J = 9.2 Hz, 1H), 5.74 (d, J = 8.3 Hz, 1H), 4.88 (d, J = 14.8 Hz, 1H), 4.11-3.96 (m, 1H), 3.88 (d, J = 14.9 Hz, 1H), 3.86 (s, 3H), 2.49 (s, 3H), 0.65 (d, J = 6.6 Hz, 3H).

EXAMPLE 129
(4S,5R)-3-[2-(3-amino-6-isopropylpyridin-2-yl)-5-(trifluoromethyl)benzyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(6-isopropenyl-3-nitropyridin-2-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (example 177) (19.3 mg, 0.0305 mmol) in EtOH (300 μL) was added 10% Pd/C (5 mg). The reaction was placed under a H₂ atmosphere (balloon) and stirred vigorously. After 90 minutes, the mixture was loaded on to a PTLC plate and purified (30% EtOAc/hexanes, developed twice), affording (4S,5R)-3-[2-(3-amino-6-isopropylpyridin-2-yl)-5-(trifluoromethyl)benzyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one. Rf = 0.63 (30% EtOAc/hexanes, developed twice). LCMS = 606.2 (M+1)+. ¹H NMR (CDCl₃, 500 MHz) δ 7.84 (s, 1H), 7.78 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.69 (s, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.09-7.05 (m, 2H), 5.53-5.52 (m, 1H), 4.92 (d, J = 5.5 Hz, 1H), 4.15-4.10 (m, 1H), 3.89-3.78 (m, 1H), 3.48 (s, 2H), 3.00-2.95 (m, 1H), 1.26-1.23 (m, 6H), 0.44 (d, J = 5.1 Hz, 3H).

EXAMPLE 130

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(3-chloro-6-isopropylpyridin-2-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of CuCl₂ (9.3 mg) and t-butyl nitrite (6.6 μL, 0.0559 mmol) in MeCN (300 μL) was added (4S,5R)-3-[2-(3-amino-6-isopropylpyridin-2-yl)-5-(trifluoromethyl)benzyl]-5-[3,5-
bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (Example 129) (16.9 mg, 0.0279 mmol) in MeCN (300 µL) via cannula. The reaction was heated at 60 °C for 1 hour and then cooled to room temperature, diluted with EtOAc (20 mL) and washed with water and brine (8 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by PTLC (30% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(3-chloro-6-isopropylpyridin-2-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one. R_f = 0.56 (30% EtOAc/hexanes). LCMS = 625.1 (M+1)^+. ^1H NMR (CDCl₃, 500 MHz) δ 7.85 (s, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.73-7.71 (m, 2H), 7.68 (s, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 8.2 Hz, 1H), 5.55 (d, J = 7.7 Hz, 1H), 5.05 (d, J = 15.4 Hz, 1H), 3.97 (d, J = 15.4 Hz, 1H), 3.88-3.82 (m, 1H), 3.17-3.08 (m, 1H), 1.30-1.32 (m, 6H), 0.53 (d, J = 6.7 Hz, 3H).

EXAMPLE 131

![Chemical structure image]

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(2-isopropenyl-1,3-thiazol-4-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

Step A: 4-bromo-2-isopropenyl-1,3-thiazole

In a tube were placed 2,4-dibromothiazole (100 mg, 0.411 mmol), isopropenylboronic acid (39 mg, 0.452 mmol), DME (1.625 mL), EtOH (563 µL), and 1M aqueous Na₂CO₃ (1.03 mL, 1.03 mmol). The mixture was degassed with N₂. Next, Pd(PPh₃)₄ (24 mg, 0.0206 mmol) was added and the mixture was degassed again with N₂. The tube was sealed and heated at 100 °C for 2 hours. The reaction was then cooled to room temperature, diluted with EtOAc (50 mL), and washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (0 to 15% EtOAc/hexanes) afforded 4-bromo-2-isopropenyl-1,3-thiazole; NMR showed an impurity present that was not removed. R_f = 0.53 (15% EtOAc/hexanes). LCMS = 206.0 (M+1)^+. ^1H NMR (CDCl₃, 500 MHz) δ 7.13 (s, 1H), 5.87 (s, 1H), 5.33 (d, J = 1.3 Hz, 1H), 2.21 (s, 3H).

Step B: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(2-isopropenyl-1,3-thiazol-4-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one
In a tube were placed 4-bromo-2-isopropenyl-1,3-thiazole (20 mg, 0.097 mmol), (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one (29.4 mg, 0.0492 mmol), THF (340 μL), 1M aqueous K₂CO₃ (340 μL), and 1,1-bis(di-i-butylphosphino)ferrocene palladium chloride (3.2 mg, 4.9 x 10⁻³ mmol). The mixture was degassed with N₂. The tube was sealed and heated at 100 °C for 1.5 hours. The reaction was then cooled to room temperature, diluted with EtOAc (50 mL), and washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (5 to 25% EtOAc/hexanes) and then by PTLC (90% CH₂Cl₂/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(2-isopropenyl-1,3-thiazol-4-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one. Rₜ = 0.16 (15% EtOAc/hexanes). LCMS = 595.1 (M+1)⁺. ¹H NMR (CD₂Cl₂, 500 MHz) δ 7.90 (s, 1H), 7.64-7.76 (m, 5H), 7.38 (s, 1H), 5.89 (s, 1H), 5.60 (d, J = 8.1 Hz, 1H), 5.37 (d, J = 1.2 Hz, 1H), 4.99 (d, J = 16.0 Hz, 1H), 4.66 (d, J = 16.0 Hz, 1H), 3.94 (m, 1H), 2.25 (s, 3H), 0.59 (d, J = 6.4 Hz, 3H).

**EXAMPLE 132**

![Chemical Structure](image)

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a 0 °C solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[4-(4-hydroxymethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (Example 178) (54.0 mg, 0.0774 mmol) in THF (10 mL) was added TBAF (194 μL of a 1M solution in THF, 0.194 mmol). The reaction was stirred at 0 °C for 30 minutes and then quenched by pouring into saturated NH₄Cl (15 mL). The mixture was extracted with EtOAc (60 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (60% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[4-(hydroxymethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one. Rₜ = 0.11 (40% EtOAc/hexanes).
LCMS = 585.1 (M+1)+. 1H NMR (CDCl3, 500 MHz) δ 7.85 (s, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.70-7.73 (m, 4H), 7.36 (s, 1H), 5.52 (d, J = 8.0 Hz, 1H), 5.39 (d, J = 15.3 Hz, 1H), 4.81 (s, 2H), 4.55 (d, J = 15.3 Hz, 1H), 3.87 (m, 1H), 0.69 (d, J = 6.7 Hz, 3H).

EXAMPLE 133

2-[2-(((4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-2-oxo-1,3-oxazolidin-3-yl)methyl]-4-(trifluoromethyl)phenyl]-1,3-thiazole-4-carbaldehyde

To a 0 ºC solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[4-(hydroxymethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (Example 132) (40.9 mg, 0.070 mmol) in CH3Cl2 (5 mL) was added DMP (59.4 mg, 0.140 mmol). The reaction was warmed to room temperature and stirred for 45 minutes. Next the reaction was diluted with EtOAc (40 mL) and washed with 1N NaOH (2 x 15 mL) and brine (2 x 15 mL). The organic layer was dried over Na2SO4, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (50% EtOAc/hexanes) afforded 2-[2-(((4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-2-oxo-1,3-oxazolidin-3-yl)methyl]-4-(trifluoromethyl)phenyl]-1,3-thiazole-4-carbaldehyde. Rf = 0.24 (40% EtOAc/hexanes). LCMS = 583.1 (M+1)+. 1H NMR (CDCl3, 500 MHz) δ 10.09 (s, 1H), 8.33 (s, 1H), 7.87 (s, 2H), 7.82 (d, J = 8.2 Hz, 1H), 7.79 (s, 2H), 7.72, (d, J = 8.1 Hz, 1H), 5.70 (d, J = 8.0 Hz, 1H), 5.13 (d, J = 16.0 Hz, 1H), 4.83 (d, J = 16.0 Hz, 1H), 4.23 (m, 1H), 0.75 (d, J = 6.6 Hz, 3H).

EXAMPLE 134
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a -40 °C solution of 2-[2-(((4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-2-oxo-1,3-oxazolidin-3-yl)methyl]-4-(trifluoromethyl)phenyl]-1,3-thiazole-4-carbaldehyde (Example 133) (43.9 mg, 0.075 mmol) in Et₂O (7.5 mL) was added MeMgBr (30 µL of a 3M solution in Et₂O, 0.10 mmol). The reaction was monitored closely by TLC and additional MeMgBr was added dropwise until nearly all starting aldehyde was consumed. At this point, the reaction was quenched by pouring it into saturated NH₄Cl (15 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (5 to 50% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one. Rᵢ = 0.17 (40% EtOAc/hexanes). LCMS = 599.1 (M+1)+. ¹H NMR (CDCl₃, 500 MHz) δ 7.70-7.86 (m, 6H), 7.31-7.32 (m, 1H), 5.33-5.55 (m, 1H), 5.35-5.41 (m, 1H), 5.06 (m, 1H), 4.57-4.62 (m, 1H), 3.88 (m, 1H), 1.61-1.63 (m, 3H), 0.69 (d, J = 6.7 Hz, 3H).

EXAMPLE 135

(4S,5R)-3-[2-(4-acetyl-1,3-thiazol-2-yl)-5-(trifluoromethyl)benzyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one
To a 0 °C solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[4-(1-hydroxyethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (Example 134) (31.0 mg, 0.052 mmol) in CH₂Cl₂ (6 mL) was added DMP (55 mg, 0.130 mmol). The reaction was warmed to room temperature and stirred for 45 minutes. Next, the reaction was diluted with EtOAc (40 mL) and washed with 1N NaOH (2 x 15 mL) and brine (2 x 15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (40% EtOAc/hexanes) afforded (4S,5R)-3-[2-(4-acetyl-1,3-thiazol-2-yl)-5-(trifluoromethyl)benzyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one. Rᵣ = 0.26 (40% EtOAc/hexanes). LCMS = 597.1 (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz) δ 8.27 (s, 1H), 7.89 (s, 1H), 7.77-7.82 (m, 4H), 7.71 (d, J = 7.9 Hz, 1H), 5.68 (d, J = 7.9 Hz, 1H), 5.22 (d, J = 16.3 Hz, 1H), 4.85 (d, J = 16.4 Hz, 1H), 4.08 (m, 1H), 2.70 (s, 3H), 0.71 (d, J = 6.6 Hz, 3H).

EXAMPLE 136

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[4-(1-hydroxy-1-methylethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a -40 °C solution of (4S,5R)-3-[2-(4-acetyl-1,3-thiazol-2-yl)-5-(trifluoromethyl)benzyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (Example 135) (38.1 mg, 0.064 mmol) in THF/heptanes (1:1, 8 mL) was added MeMgBr (21 µL of a 3M solution in Et₂O, 0.07 mmol). The temperature was maintained between -40 °C and -20 °C and the reaction was monitored closely by TLC; additional MeMgBr was added dropwise until nearly all starting ketone was consumed. At this point, the reaction was quenched by pouring it into saturated NH₄Cl (15 mL). The mixture was extracted with EtOAc (50 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (10 to 60% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[4-(1-hydroxy-1-methylethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one. Rᵣ = 0.20 (40% EtOAc/hexanes). LCMS = 613 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.90 (s, 1H),
7.85 (d, J = 8.0 Hz, 1H), 7.77 (s, 3H), 7.71 (d, J = 8.3 Hz, 1H), 7.32 (s, 1H), 5.59 (d, J = 8.0 Hz, 1H), 5.28 (d, J = 15.8 Hz, 1H), 4.74 (d, J = 15.8 Hz, 1H), 3.89 (m, 1H), 3.01 (bs, 1H), 1.63 (s, 3H), 1.62 (s, 3H), 0.64 (d, J = 6.5 Hz, 3H).

**EXAMPLE 137**

![Chemical structure](image)

**(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(4-isopropenyl-1,3-thiazol-2-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one**

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[4-(1-hydroxy-1-methylethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (example 136) (9.5 mg, 0.015 mmol) in toluene (4 mL) was added p-toluenesulfonic acid monohydrate (20 mg, 0.105 mmol). The reaction was heated to 80 °C for 30 minutes and then cooled to room temperature, diluted with EtOAc (35 mL), and washed with saturated NaHCO₃ and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (25% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(4-isopropenyl-1,3-thiazol-2-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one. Rf = 0.55 (40% EtOAc/hexanes). LCMS = 595.1 (M+1)⁺. ¹H NMR (CD₂Cl₂, 500 MHz) δ 7.91 (s, 1H), 7.78-7.83 (m, 4H), 7.68 (d, J = 8.5 Hz, 1H), 7.33 (s, 1H), 5.95 (d, J = 0.9 Hz, 1H), 5.66 (d, J = 8.0 Hz, 1H), 5.24 (m, 1H), 5.07 (d, J = 16.4 Hz, 1H), 5.00 (d, J = 16.3 Hz, 1H), 4.03 (m, 1H), 2.17 (s, 3H), 0.63 (d, J = 6.4 Hz, 3H).

**EXAMPLE 138**
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-3'-isopropyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-3'-isopropenyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one (Example 119) (18.8 mg, 0.031 mmol) in EtOH (4.5 mL) was added 10% Pd/C (15 mg). The reaction was placed under a H₂ atmosphere (balloon) and stirred vigorously. After 45 minutes, the catalyst was removed by filtration. The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel with 15% EtOAc/hexanes. Further purification by PTLC with 75% CH₂Cl₂/hexanes afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-3'-isopropyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one. R_f = 0.35 (15% EtOAc/hexanes). LCMS = 608.2 (M+)^+. ¹H NMR (CDCl₃, 500 MHz) δ 7.86 (s, 1H), 7.71 (s, 1H), 7.70 (s, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.15 (m, 1H), 7.08-7.12 (m, 2H), 5.52 (d, J = 8.0 Hz, 1H), 4.89 (d, J = 15.7 Hz, 1H), 4.18 (d, J = 15.8 Hz, 1H), 3.76 (m, 1H), 3.28 (m, 1H), 1.25-1.29 (m, 6H), 0.42 (d, J = 6.4 Hz, 3H).

EXAMPLE 139

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[5-(1-methoxyethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one
To a 0 °C solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[5-(1-hydroxyethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (Example 154) (13.2 mg, 0.0221 mmol) in THF (1 mL) was added NaHMDS (26.5 µL of a 1M solution in THF, 0.0265 mmol) followed by MeI (1 drop). After 1.5 hours, additional NaHMDS (15 µL of a 1M solution in THF, 0.015 mmol) and MeI (1 drop) were added to the reaction. The reaction was warmed to room temperature for 20 minutes and then quenched by pouring into saturated NH₄Cl (10 mL). The mixture was extracted with EtOAc (35 mL) and the organic layer was washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (15 to 75% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-[5-(1-methoxyethyl)-1,3-thiazol-2-yl]-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one. Rf = 0.37 (40% EtOAc/hexanes). LCMS = 613.0 (M+H)+. ¹H NMR (CDCl₃, 500 MHz) δ 7.87 (s, 1H), 7.74-7.82 (m, 5H), 7.67 (d, J = 8.0 Hz, 1H), 6.63-5.66 (m, 1H), 5.08-5.14 (m, 1H), 4.83-4.88 (m, 1H), 4.64-4.68 (m, 1H), 4.01-4.08 (m, 1H), 3.34 (m, 3H), 1.60 (d, J = 6.4 Hz, 3H), 0.69 (d, J = 6.7 Hz, 3H).

EXAMPLES 140 and 141

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-(1-oxido-1-benzothien-2-yl)-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one and (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(1,1-dioxido-1-benzothien-2-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-3-[2-(1-benzothien-2-yl)-5-(trifluoromethyl)benzyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (Example 150) (14.5 mg, 0.024 mmol) in CH₂Cl₂ (2 mL) was added m-CPBA (16 mg, 77% purity, 0.071 mmol). The reaction was stirred at room temperature for 3 hours, and then diluted with EtOAc (40 mL) and washed with aq. NaHSO₃ (15 mL), saturated NaHCO₃ (15 mL) and brine (15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by PTLC (25% EtOAc/hexanes, 2 elutions) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(1,1-
dioxido-1-benzothien-2-yl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one and 2.2 mg (15%) of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-(1-oxido-1-benzothien-2-yl)-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one. Data for 141: R_f = 0.09 (25% EtOAc/hexanes). LCMS = 636.2 (M+H)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.96 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.68-7.77 (m, 5H), 7.63 (m, 1H), 7.57 (m, 1H), 7.50 (d, J = 7.6 Hz, 1H), 7.28 (s, 1H), 5.75 (d, J = 8.0 Hz, 1H), 5.21 (d, J = 15.8 Hz, 1H), 4.21 (d, J = 15.8 Hz, 1H), 4.01 (m, 1H), 0.70 (d, J = 6.7 Hz, 3H). Data for 140: R_f = 0.06 (25% EtOAc/hexanes). LCMS = 620.2 (M+H)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.15-7.95 (m, 11H), 5.72-5.75 (m, 1H), 5.36 (d, J = 15.6 Hz), 5.07 (d, J = 15.8 Hz), 4.41 (d, J = 16.0 Hz), 4.22 (d, J = 15.8 Hz), 3.88-4.08 (m, 1H), 0.68 (d, J = 6.6 Hz), 0.61(d, J = 6.6 Hz).

EXAMPLE 142

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4′-fluoro-5′-isopropyl-2′-methoxy-4-(trifluoromethoxy)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

Step A: 2-(bromomethyl)-1-nitro-4-(trifluoromethoxy)benzene

Fuming nitric acid (5 mL) was cooled to 0°C and 3-(trifluoromethoxy)benzyl bromide (1 mL, 6.16 mmol) was added. After 15 minutes, the reaction was poured into ice water (100 mL) and extracted with EtOAc (200 mL). The organic layer was washed with water, saturated NaHCO₃, and brine (75 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (0 to 15% EtOAc/hexanes) afforded 2-(bromomethyl)-1-nitro-4-(trifluoromethoxy)benzene R_f = 0.54 (15% EtOAc/hexanes). ¹H NMR (CDCl₃, 500 MHz) δ 8.14 (d, J = 8.9 Hz, 1H), 7.43 (m, 1H), 7.31 (m, 1H), 4.82 (s, 2H).

Step B: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-nitro-5-(trifluoromethoxy)benzyl]-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (840 mg, 2.68 mmol) in DMA (25 mL) was added NaHMDS (2.68 mL of a 1M solution in THF, 2.68 mmol). The reaction was stirred at room temperature for 5 minutes, and then 2-(bromomethyl)-1-nitro-4-(trifluoromethoxy)benzene (967 mg, 3.22 mmol) was added by cannula in DMA (5
mL). After 15 minutes, the reaction was poured into saturated NH₄Cl (50 mL). The mixture was extracted with EtOAc (150 mL) and the organic layer was washed with water and brine (40 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (5 to 25% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-nitro-5-(trifluoromethoxy)benzyl]-1,3-oxazolidin-2-one. R₂ = 0.10 (15% EtOAc/hexanes). LCMS = 533.2 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 8.16 (d, J = 8.9 Hz, 1H), 7.92 (s, 1H), 7.80 (s, 2H), 7.44 (s, 1H), 7.33 (d, J = 8.9 Hz, 1H), 5.78 (d, J = 7.8 Hz, 1H), 4.94 (d, J = 17.0 Hz, 1H), 4.79 (d, J = 16.9 Hz, 1H), 4.25 (m, 1H), 0.81 (d, J = 6.7 Hz, 3H).

**Step C:** (4S,5R)-3-[2-amino-5-(trifluoromethoxy)benzyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-3-[2-nitro-5-(trifluoromethoxy)benzyl]-1,3-oxazolidin-2-one (1.07 g, 2.01 mmol) in EtOAc (30 mL) was added PtO₂ (100 mg, 0.44 mmol). The reaction was placed under a H₂ atmosphere (balloon) and stirred vigorously. After 1 hour, the catalyst was removed by filtration, and the filtrate was concentrated. Purification of the residue by flash chromatography (5 to 40% EtOAc/hexanes) afforded (4S,5R)-3-[2-amino-5-(trifluoromethoxy)benzyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one. R₂ = 0.45 (40% EtOAc/hexanes). LCMS = 503.2 (M+1)⁺. ¹H NMR (CDCl₃, 600 MHz) δ 7.89 (s, 1H), 7.75 (s, 2H), 7.03 (dd, J = 8.7, 2.0 Hz, 1H), 6.90 (d, J = 2.1 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 5.67 (d, J = 8.5 Hz, 1H), 4.73 (d, J = 15.4 Hz, 1H), 4.35 (bs, 2H), 4.09 (d, J = 15.4 Hz, 1H), 4.04 (m, 1H), 0.78 (d, J = 6.6 Hz, 3H).

**Step D:** (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-ido-5-(trifluoromethoxy)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-3-[2-amino-5-(trifluoromethoxy)benzyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (582 mg, 1.16 mmol) in CHCl₃ (35 mL) was added t-butyl nitrite (275 µL, 2.32 mmol). After 10 minutes, I₂ (736 mg, 2.9 mmol) was added. The reaction was stirred at room temperature for 30 minutes, and then heated to 65 °C for 2 hours. The reaction was then cooled to room temperature, diluted with EtOAc (150 mL) and washed with aqueous NaHSO₃, water, brine, saturated NaHCO₃, and brine (50 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (2 to 15% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-ido-5-(trifluoromethoxy)benzyl]-4-methyl-1,3-oxazolidin-2-one. R₂ = 0.30 (15% EtOAc/hexanes). LCMS = 614.1 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.89-7.91 (m, 2H), 7.79 (s, 2H), 7.23 (m, 1H), 6.95 (m, 1H), 5.75 (d, J = 8.0 Hz, 1H), 4.81 (d, J = 15.8 Hz, 1H), 4.32 (d, J = 15.8 Hz, 1H), 4.07 (m, 1H), 0.78 (d, J = 6.6 Hz, 3H).

**Step E:** (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[14'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethoxy)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one
In a microwave tube were placed (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethoxy)benzyl]-4-methyl-1,3-oxazolidin-2-one (41.6 mg, 0.0679 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (18 mg, 0.085 mmol), DME (305 μL), EtOH (100 μL), and 1M aqueous Na2CO₃ (140 μL, 0.140 mmol). The mixture was degassed with N₂. Next, Pd(PPh₃)₄ (4 mg, 3.4 x 10⁻³ mmol) was added and the mixture was degassed again with N₂. The tube was sealed and irradiated in a microwave for 10 minutes at 150 °C and 200 W. The reaction was then cooled to room temperature, diluted with EtOAc (40 mL), and washed with water and brine (15 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (2 to 15% EtOAc/hexanes) afforded (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethoxy)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one. Rf = 0.24 (15% EtOAc/hexanes). LCMS = 654.3 (M+1)+. 1H NMR (CDCl₃, 500 MHz, rotamers present) δ 7.85 (s, 1H), 7.69 (s, 2H), 7.21-7.30 (m, 4H), 6.95-7.00 (m, 1H), 6.65-6.68 (m, 1H), 5.59 (d, J = 8.0 Hz), 5.41 (d, J = 8.0 Hz), 4.74-4.81 (m, 1H), 3.75-4.09 (m, 5H), 3.19 (m, 1H), 1.16-1.27 (m, 6H), 0.51 (d, J = 6.7 Hz), 0.36 (d, J = 6.6 Hz).

Following the general procedures outlined above, the compounds in Table 6 were prepared:

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Following the general procedures outlined above, the compounds in Table 7 were prepared:

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INTERMEDIATE 9

\[
\begin{array}{c}
\text{MeO} \\
\text{F} \\
\text{F}_3\text{C} \\
\text{OH}
\end{array}
\]

\[\text{4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol}\]

A mixture of [2-iodo-5-(trifluoromethyl)phenyl]methanol (EXAMPLE 69) (3.09 g, 10.2 mmol), (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (4.34 g, 20.5 mmol), (Ph\(_3\)P)\(_4\)Pd (1.42 g, 1.23 mmol) and Na\(_2\)CO\(_3\) (9.11 g, 85.9 mmol) in benzene/EtOH/H\(_2\)O (7:1:3, 250 mL) was heated at reflux for 24 h under N\(_2\). After cooling to room temperature, the aqueous phase was separated and extracted with CH\(_2\)Cl\(_2\) (3 x 50 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 65 x 200 mm, 0-20% EtOAc in hexanes gradient) to afford 4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol. R\(_f\) = 0.50 (20% EtOAc in hexanes). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.86 (s, 1 H), 7.59 (d, \(J = 6.7\) Hz, 1H), 7.30 (d, \(J = 7.9\) Hz, 1H), 6.99 (d, \(J = 8.6\) Hz, 1H), 6.68 (d, \(J = 12.0\) Hz, 1H), 4.52 (br s, 1H), 4.46 (br s, 1H), 3.73 (s, 3H), 3.25-3.17 (m, 1H), 1.82 (br s, 1H), 1.24 (d, \(J = 6.8\) Hz, 6H).

INTERMEDIATE 10
2'-(bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'- (trifluoromethyl)biphenyl

A solution of triphenylphosphine (3.11 g, 11.8 mmol) in dry CH₂Cl₂ (7 mL) was added by cannula to a stirred solution of carbon tetrabromide (3.93 g, 11.8 mmol) and 4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methanol (3.38 g, 9.87 mmol) in dry CH₂Cl₂ (56 mL) at 0 ºC under N₂. The reaction was allowed to warm to room temperature. After 2 h, the reaction mixture was concentrated *in vacuo* to give the crude product. This was purified by flash chromatography (Si, 65 x 200 mm, 0-20% EtOAc in hexanes gradient) to afford 2'- (bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'- (trifluoromethyl)biphenyl. ¹H NMR (500 MHz, CDCl₃) δ 7.83 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.15 (d, J = 8.6 Hz, 1H), 6.72 (d, J = 12.0 Hz, 1H), 4.43 (br d, J = 10.0 Hz, 1H), 4.30 (br d, J = 10.2 Hz, 1H), 3.76 (s, 3H), 3.30-3.22 (m, 1H), 1.29 (d, J = 6.9 Hz, 6H).

INTERMEDIATE 11

5-[3,5-bis(trifluoromethyl)phenyl]-3-[4'-fluoro-5'-isopropyl-2'-methoxy-4- (trifluoromethyl)biphenyl-2-yl]methyl]-4,4-dimethyl-1,3-oxazolidin-2-one

Step A: benzyl [2-[methoxy(methyl)amino]-1,1-dimethyl-2-oxoethyl]carbamate

N-Methylmorpholine (682 mg, 741 µL, 6.74 mmol) and isobutyric anhydride (460 mg, 441 µL, 3.37 mmol) were added successively to a stirred solution of N-carbobenzyloxy-2-methylalanine (0.64 g, 2.69 mmol) in dry CH₂Cl₂ at 0 ºC under N₂. The resulting cloudy mixture was stirred at 0 ºC for 90 min. N,O-Dimethylhydroxylamine hydrochloride (316 mg, 3.24 mmol) was added portionwise and the mixture was warmed to room temperature and stirred for 3 h. The mixture was poured into 1N HCl (30 mL) and extracted with CH₂Cl₂ (3 x 40 mL). The combined extracts were washed with 1N HCl (30 mL), dried (Na₂SO₄) and concentrated *in vacuo* to give the crude product. This was purified by flash chromatography (Si, 40 x 160 mm, 0-80% EtOAc in hexanes gradient) to afford benzyl [2-[methoxy(methyl)amino]-1,1-dimethyl-2-
oxoethyl]carbamate. \( R_f = 0.47 \) (50% EtOAc in hexanes). LCMS calc. = 303.1; found = 303.2 (M+Na)\(^+\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.37-7.29 (m, 5H), 5.82 (s, 1H), 5.09 (s, 2H), 3.60 (s, 3H), 3.18 (s, 3H), 1.60 (s, 6H).

**Step B: benzyl (1,1-dimethyl-2-oxoethyl)carbamate**

Diisobutylaluminum hydride (1.77 mL, 1M solution in toluene, 0.708 mmol) was added to a stirred solution of benzyl [2-[methoxy(methyl)amino]-1,1-dimethyl-2-oxoethyl]carbamate (198.5 mg, 0.708 mmol) in dry THF (7.1 mL) at -78 °C under N\(_2\). The reaction was stirred at -78 °C for 4 h. MeOH (100 \( \mu \)L) and 1N HCl (250 \( \mu \)L) were added and the reaction was allowed to warm to room temperature. The mixture was diluted with Et\(_2\)O (50 mL) and washed with 1N HCl (2 x 50 mL), 50% saturated NaHCO\(_3\) (50 mL) and water (50 mL), then dried (MgSO\(_4\)) and concentrated in vacuo to give benzyl (1,1-dimethyl-2-oxoethyl)carbamate. \( R_f = 0.40 \) (20% EtOAc in hexanes). LCMS calc. = 244.1; found = 244.1 (M+Na)\(^+\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 9.43 (s, 1H), 7.38-7.30 (m, 5H), 5.34 (s, 1H), 5.09 (s, 2H), 1.37 (s, 6H).

**Step C: benzyl [2-[(3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-1,1-dimethylethyl]carbamate**

Ethylmagnesium bromide (1.63 mL, 1M in THF, 1.63 mmol) was added dropwise to a stirred solution of 1-iodo-3,5-bis(trifluoromethyl)benzene (608 mg, 317 \( \mu \)L, 1.79 mmol) in dry THF (1 mL) at room temperature under N\(_2\) and the reaction was stirred for 30 min. The resulting solution was added to a stirred solution of benzyl (1,1-dimethyl-2-oxoethyl)carbamate (163.5 mg, 0.739 mmol) in dry THF (1 mL) at -20 °C and the reaction was allowed to warm to room temperature over 3 h. Saturated NH\(_4\)Cl (10 mL) and water (10 mL) were added and the mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 25 x 160 mm, 0-40% EtOAc in hexanes gradient) to afford benzyl [2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-1,1-dimethylethyl]carbamate. \( R_f = 0.40 \) (20% EtOAc in hexanes). LCMS calc. = 436.1; found = 436.0 (M+1)\(^+\). \(^1\)H NMR (600 MHz, CDCl\(_3\)) \( \delta \) 7.80 (s, 1H), 7.77 (s, 2H), 7.39-7.33 (m, 5H), 5.12-5.08 (m, 2H), 1.36 (s, 1H), 4.90 (d, \( J = 4.4 \) Hz, 1H), 4.81 (s, 1H), 1.36 (s, 3H), 1.23 (s, 3H).

**INTERMEDIATE 12**

\[
\text{benzyl [(1S)-2-[(4-chloropyridin-2-yl)-1-methyl-2-oxoethyl]carbamate}
\]

A solution of 2-(dimethylamino)ethanol (471 mg, 531 mL, 5.28 mmol) in dry hexanes (3.3 mL) was cooled to -5 °C and n-butyllithium (1.6 M in hexanes, 6.60 mL, 10.6 mmol) was added.
dropwise under N₂. After 30 min at 0 °C, the solution was cooled to -78 °C and a solution of 4-chloropyridine (obtained by washing a solution of the corresponding HCl salt (264 mg, 1.76 mmol) in CH₂Cl₂ (20 mL) with saturated K₂CO₃ (10 mL), then back extracting with CH₂Cl₂ (2 x 20 mL), combining the organic layers, drying (Na₂SO₄) and concentrating in vacuo) in hexanes (3.3 mL) was added dropwise by cannula. The solution became dark red in color and after 1 h at -78 °C, a solution of the electrophile (prepared by adding isopropylmagnesium chloride (2M in THF, 1.29 mL, 2.59 mmol) to a solution of benzyl [(1S)-2-[methoxy(methyl)amino]-1-methyl-2-oxoethyl]carbamate (702 mg, 2.64 mmol) in dry THF (3.5 mL) at -15 °C under N₂ and stirring for 15 min) was added by cannula. The reaction was allowed to warm slowly to room temperature overnight. Water (25 mL) and saturated NH₄Cl (50 mL) were added and the mixture was extracted with EtOAc (3 x 50 mL). The combined extracts were dried (MgSO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 40 x 160 mm, 0-30% EtOAc in hexanes gradient) to afford benzyl [(1S)-2-(4-chloropyridin-2-yl)-1-methyl-2-oxoethyl]carbamate. R₇ = 0.46 (20% EtOAc in hexanes). LCMS calc. = 319.1; found = 319.3 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 8.58 (d, J = 5.0 Hz, 1H), 8.04 (s, 1H), 7.47 (dd, J = 5.2, 2.0 Hz, 1H), 7.35-7.30 (m, 5H), 5.78 (s, 1H), 5.72 (m, 1H), 5.11 (m, 2H), 1.47 (d, J = 7.0 Hz, 3H).

INTERMEDIATE 13

benzyl [(1S)-1-methyl-2-oxo-2-(1,3-thiazol-2-yl)ethyl]carbamate

n-Butyllithium (1.6M in hexanes, 1.76 mL, 2.83 mmol) was added dropwise to a stirred solution of 2-bromothiazole (462 mg, 251 µL, 2.82 mmol) in dry THF (13 mL) at -78 °C under N₂ and the reaction was stirred at -78 °C for 45 min. Separately, isopropylmagnesium chloride (2M in THF, 0.94 mL, 1.99 mmol) was added to a stirred solution of benzyl [(1S)-2-[methoxy(methyl)amino]-1-methyl-2-oxoethyl]carbamate (500 mg, 1.88 mmol) in dry THF (4 mL) at -15 °C under N₂. This solution was stirred for 15 min at -15 °C and was added dropwise to the above 2-lithiothiazole solution at -78 °C. The reaction was allowed to warm to room temperature overnight and saturated NH₄Cl (20 mL) and water (10 mL) were added and the mixture was extracted with EtOAc (3 x 30 mL). The combined extracts were washed with brine, dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 25 x 160 mm, 0-50% EtOAc in hexanes gradient) to afford benzyl [(1S)-1-methyl-2-oxo-2-(1,3-thiazol-2-yl)ethyl]carbamate. R₇ = 0.28 (20% EtOAc in hexanes). LCMS
calc. = 291.1; found = 291.3 (M+1)⁺. ¹H NMR (600 MHz, CDCl₃) δ 8.03 (s, 1H), 7.70 (d, J = 3.1 Hz, 1H), 7.34-7.29 (m, 5H), 5.79 (d, J = 6.6 Hz, 1H), 5.53-5.49 (m, 1H), 5.14-5.08 (m, 2H), 1.55 (d, J = 6.4 Hz, 3H).

INTERMEDIATE 14

**Benzyl [((1S)-1-methyl-2-(1-methyl-1H-imidazol-4-yl)-2-oxoethyl]carbamate**

A solution of benzyl ((1S)-2-[methoxy(methyl)amino]-1-methyl-2-oxoethyl]carbamate (64 mg, 0.24 mmol) in CH₂Cl₂ (1 mL) was cooled to -20 °C under N₂, and isopropylmagnesium chloride (120 µL of a 2.0 M solution in THF) was added dropwise. The mixture was stirred at -20 °C for 20 min. In a separate flask ethylmagnesium bromide (480 µL of a 2.0 M solution in Et₂O) was added to a solution of 4-iodo-1-methyl-1H-imidazole (109 mg, 0.48 mmol) in dry CH₂Cl₂ (1.5 mL) at room temperature. The resulting mixture was stirred for 20 min and then added by cannula to the solution above slowly. The resulting solution was left to stir overnight. Saturated NH₄Cl was added to the reaction solution. The mixture was diluted with water and the aqueous phase was extracted with CH₂Cl₂ (2 x 25 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated in vacuo. Flash chromatography of the residue yielded benzyl [(1S)-1-methyl-2-(1-methyl-1H-imidazol-4-yl)-2-oxoethyl]carbamate. LCMS calc. = 288.14; found = 288.3 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 7.65 (s, 1H); 7.47 (s, 1H); 7.35-7.28 (m, 5H); 5.93 (d, J = 6.9 Hz, 1H); 5.29-5.25 (m, 1H); 5.13 (s, 2H); 3.73 (s, 3H); 1.26 (d, J=7.1 Hz, 3H).

INTERMEDIATE 15

**Benzyl [((1S)-2-[1-[(benzyloxy)methyl]-1H-imidazol-2-yl]-1-methyl-2-oxoethyl]carbamate**

**Step A: 1-[(benzyloxy)methyl]-1H-imidazole**

A mixture of chloromethylether (4.3 mL, 29 mmol) and imidazole (6 g, 58 mmol) in acetonitrile (200 mL) was heated at reflux for 3.5 h. The solvent was removed in vacuo. The resulting oily residue was partitioned between CH₂Cl₂ (300 mL) and water (150 mL). Then the organic extract was washed with water (2 x 150 mL), dried (Na₂SO₄) and concentrated in vacuo to yield 1-
[(benzyloxy)methyl]-1H-imidazole used without further purification. LCMS calc. = 189.10; found = 189.1 (M+1)+. 1H NMR (500 MHz, CDCl3) δ 7.63 (s, 1 H); 7.40-7.30 (m, 5 H); 7.16 (t, J = 6.5 Hz, 1 H); 7.09 (t, J = 10.6 Hz, 1 H); 5.34 (s, 2 H); 4.45 (s, 2 H).

Step B: benzyl (1S)-2-{1-[(benzyloxy)methyl]-1H-imidazol-2-yl}-1-methyl-2-oxoethyl)carbamate
To a solution of 1-[(benzyloxy)methyl]-1H-imidazole (706 mg, 3.75 mmol) in THF (4 mL) at -78 ºC under N2, was added n-Butyllithium (2.3 mL of a 1.6 M solution in hexanes ). The mixture was stirred at -78 ºC for 30 min. To a solution of benzyl (1S)-2-[methoxy(methyl)amino]-1-methyl-2-oxoethyl)carbamate (200 mg, 0.75 mmol) in THF (2 mL) under N2 at -15 ºC, was added isopropylmagnesium chloride (375 µL of a 2.0 M solution in THF). The resulting mixture was stirred at -15 ºC for 15 min. This mixture was then added, by cannula to the solution above at -78 ºC. The mixture stirred at -78 ºC for about 3 h, then warmed up gradually to room temperature and stirred overnight. The mixture was quenched with saturated NH4Cl. The aqueous layer was extracted with CH2Cl2 (3 x 25 mL). The organic layers were combined, dried (Na2SO4) and concentrated in vacuo. The residue was purified by flash chromatography to afford benzyl (1S)-2-{1-[(benzyloxy)methyl]-1H-imidazol-2-yl}-1-methyl-2-oxoethyl)carbamate contaminated with about 30% of the unreacted starting material benzyl (1S)-2-[methoxy(methyl)amino]-1-methyl-2-oxoethyl)carbamate. The mixture was carried forward to the next step without further purification. LCMS calc. = 394.18; found = 394.2 (M+1)+.

INTERMEDIATE 16

2-bromo-4,5-dichloro-1-methyl-1H-imidazole
A mixture of 2-bromo-4,5-dichlorimidazole (1 g, 4.6 mmol), methyl iodide (346 µL, 5.56 mmol), potassium carbonate (1.27 g, 9.2 mmol) and tetrabutylammonium bromide (148 mg, 0.46 mmol) in acetonitrile (2 mL) was stirred vigorously at 70-80 ºC for 1.0 h. After cooling to room temperature, the inorganic salts were filtered off and washed with acetonitrile. The filtrate was evaporated and the residue was purified by flash chromatography (Si) to afford 2-bromo-4,5-dichloro-1-methyl-1H-imidazole as a white solid. LCMS calc. = 230.89; found = 230.9 (M+1)+. 1H NMR (500 MHz, CDCl3) δ 3.61 (s, 3 H).

INTERMEDIATE 17
4-iodo-1-methyl-1H-pyrazole
To a solution of 18-crown-6 (132 mg, 0.5 mmol) in Et₂O (8 mL) under N₂, was added potassium tert-butoxide (616 mg, 5.5 mmol). The mixture was stirred while 4-iodopyrazole (1 g, 5 mmol) was introduced in a single portion at room temperature. The reaction was cooled to 0 ⁰C and a solution of iodomethane (342 µL, 5.5 mmol) in Et₂O (2 mL) was added dropwise at 0 ⁰C. The resulting mixture was warmed to room temperature and stirred overnight. The reaction was then diluted with water and extracted with Et₂O (2 x 50 mL). The combined organic layers were washed with brine (45 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. Flash chromatography gave 4-iodo-1-methyl-1H-pyrazole. LCMS calc. = 208.96; found = 209.0 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 7.52 (s, 1 H); 7.43 (s, 1 H); 3.95 (s, 3 H).

INTERMEDIATE 18

3-iodo-1-methyl-1H-pyrazole
1-methyl-1H-pyrazole-3-amine (250 mg, 2.57 mmol) was heated at reflux for 3 h with tert-butyl nitrite (336 µL, 2.83 mmol) in diiodomethane (5 mL). The solvent and volatile material was removed in vacuo and the resulting residue was purified by flash chromatography (Si) to yield 3-iodo-1-methyl-1H-pyrazole. LCMS calc. = 208.96; found = 209.0 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 7.21 (d, J = 2.1 Hz, 1 H); 6.42 (d, J = 2.2 Hz, 1 H); 3.94 (s, 3 H).

INTERMEDIATES 19, 20

(4S,5S)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-5-(1-methyl-1H-tetrazol-5-yl)-1,3-oxazolidin-2-one and (4S,5S)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-5-(2-methyl-2H-tetrazol-5-yl)-1,3-oxazolidin-2-one
Step A: benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(1H-tetrazol-5-yl)ethyl]carbamate and benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(2H-tetrazol-5-yl)ethyl]carbamate

A mixture of benzyl ((1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-2-cyano-1-methylethyl]carbamate (106.6 mg, 0.306 mmol), triethylamine hydrochloride (211 mg, 1.53 mmol) and sodium azide (99.4 mg, 1.56 mmol) in dry toluene (6 mL) was heated at reflux under N₂ for 20 h and at room temperature for 2 days. The reaction was diluted with 1N HCl (20 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to afford the crude product. This was carried forward with no further purification. LCMS calc. = 392.2; found = 392.1 (M+1)⁺.

Step B: benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(1-methyl-1H-tetrazol-5-yl)ethyl]carbamate and benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(2H-tetrazol-5-yl)ethyl]carbamate

(Trimethylsilyl)diazomethane (2M in hexanes, 459 µL, 0.918 mmol) was added dropwise to a solution of the crude benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(1H-tetrazol-5-yl)ethyl]carbamate and benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(2H-tetrazol-5-yl)ethyl]carbamate in CH₂Cl₂/MeOH (3:2, 5 mL) at room temperature under N₂. After 15 min and gas evolution had ceased, the reaction mixture was concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-70% EtOAc in hexanes gradient) to afford benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(1-methyl-1H-tetrazol-5-yl)ethyl]carbamate and benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(2-methyl-2H-tetrazol-5-yl)ethyl]carbamate, as a 2:1 mixture of regioisomers. LCMS calc. = 406.2; found = 406.2 (M+1)⁺.

Step C: benzyl [(1S,2S)-2-hydroxy-1-methyl-2-(1-methyl-1H-tetrazol-5-yl)ethyl]carbamate and benzyl [(1S,2S)-2-hydroxy-1-methyl-2-(2-methyl-2H-tetrazol-5-yl)ethyl]carbamate

Tetrabutylammonium fluoride (1M, in THF, 177 µL, 0.177 mmol) was added dropwise to a stirred solution of benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(1-methyl-1H-tetrazol-5-yl)ethyl]carbamate and benzyl [(1S,2S)-2-[(tert-butyl(dimethyl)silyloxy)-1-methyl-2-(2-methyl-2H-tetrazol-5-yl)ethyl]carbamate (2:1 mixture of regioisomers, 65.2 mg, 0.161 mmol) in THF (2 mL) at 0 °C. The reaction was stirred for 2 h at 0 °C, diluted with saturated NH₄Cl (10 mL) and extracted with EtOAc (3 x 30 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-80% EtOAc in hexanes gradient) to afford benzyl [(1S,2S)-2-hydroxy-1-methyl-2-(2-methyl-2H-tetrazol-5-yl)ethyl]carbamate and benzyl [(1S,2S)-2-hydroxy-1-methyl-2-(1-methyl-1H-tetrazol-5-yl)ethyl]carbamate. 2-methyl isomer (INTERMEDIATE 20): LCMS calc. = 292.1; found = 292.1 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.29 (m, 5H), 5.59 (d, J = 8.5 Hz, 1H), 5.09-5.00 (m, 5H), 4.49 (m, 1H), 4.26 (s, 3H), 1.07 (d, J = 6.9 Hz, 3H). 1-
methyl isomer (INTERMEDIATE 19): LCMS calc. = 292.1; found = 292.1 (M+1)\(^+\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.29 (m, 5H), 5.72 (s, 1H), 5.07 (m, 3H), 4.99 (m, 2H), 4.18 (m, 1H), 4.10 (s, 3H), 1.24 (d, \(J = 6.7\) Hz, 3H).

EXAMPLE 196

![Chemical structure](image)

(4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-([trifluoromethyl]biphenyl-2-yl)methyl]-4-methyl-5-pyridin-4-yl-1,3-oxazolidin-2-one

Step A: benzyl [(1S)-1-methyl-2-oxo-2-pyridin-4-ylethyl]carbamate
A solution of isopropylmagnesium chloride (1.6 mL, 1M in THF, 3.23 mmol) was added dropwise to a stirred solution of benzyl [(1S)-2-[methoxy(methyl)amino]-1-methyl-2-oxoethyl]carbamate (EXAMPLE 17, Step 1) (879 mg, 3.30 mmol) in dry THF (4.2 mL) at -15 °C under N\(_2\). The reaction was stirred at -15 °C for 30 min then a suspension of 4-pyridylmagnesium bromide in dry THF (prepared by adding ethyl magnesium bromide (6mL, 2M in THF, 6.00 mmol) to a stirred solution of 4-iodopyridine (1.35 g, 6.60 mmol) in dry THF (45 mL) at room temperature under N\(_2\) and stirring for 30 min) was added dropwise by cannula. The reaction was allowed to warm to room temperature and was stirred for 5 h. 1N HCl (15 mL) was added to quench the reaction and the mixture was adjusted to basic pH with saturated NaHCO\(_3\). The mixture was extracted with EtOAc (2 x 50 mL) and CH\(_2\)Cl\(_2\) (3 x 50 mL). The EtOAc and CH\(_2\)Cl\(_2\) extracted were washed with brine separately, dried (Na\(_2\)SO\(_4\)), combined and concentrated \textit{in vacuo} to give the crude product. This was purified by flash chromatography (Si, 40 x 160 mm, 0-100% EtOAc in hexanes gradient) to afford benzyl [(2R)-1-methyl-2-oxo-2-pyridin-4-ylethyl]carbamate, as a colorless solid. \(R_f = 0.33\) (50% EtOAc/hexanes). LCMS calc. = 285.1; found = 285.3 (M+1)\(^+\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.85 (d, \(J = 3.3\) Hz, 2H), 7.76 (d, \(J = 5.5\) Hz, 2H), 7.36-7.32 (m, 5H), 5.70 (d, \(J = 6.8\) Hz, 1H), 5.31-5.25 (m, 1H), 5.13 (s, 2H), 1.43 (s, 3H).

Step B: benzyl [(1S,2R)-2-hydroxy-1-methyl-2-pyridin-4-ylethyl]carbamate

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Lithium tri-tert-butoxylum metal hydride (964 mg, 3.79 mmol) was added to a solution of benzyl [(2R)-1-methyl-2-oxo-2-pyridin-4-yl]carbamate (539.1 mg, 1.90 mmol) in dry EtOH (40 mL) at -78 °C under N₂. The reaction was stirred at -78 °C for 2 h. 2% Aqueous acetic acid was added to quench the reaction and the mixture was adjusted to basic pH with saturated NaHCO₃ (~50 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the combined extracts were washed with brine (50 mL), dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 40 x 160 mm, 0-100% EtOAc in hexanes gradient) to afford benzyl [(1S,2R)-2-hydroxy-1-methyl-2-pyridin-4-yl]carbamate as a colorless solid. Rf = 0.49 (EtOAc). LCMS calc. = 287.1; found = 287.3 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 8.41 (d, J = 5.7 Hz, 2H), 7.36-7.32 (m, 7H), 5.27 (d, J = 7.4 Hz, 1H), 5.10 (s, 2H), 4.89 (s, 1H), 4.02 (br s, 1H), 0.96 (d, J = 6.7 Hz, 3H).

**Step C: (4S,5R)-3-[[4’-fluoro-5’-isopropyl-2’-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-pyridin-4-yl-1,3-oxazolidin-2-one**

Sodium hydride (52.4 mg, 60% dispersion in mineral oil, 1.31 mmol) was added to a solution of benzyl [(1S,2R)-2-hydroxy-1-methyl-2-pyridin-4-yl]carbamate (150 mg, 0.524 mmol) in dry THF (6 mL) at room temperature under N₂. After stirring for 30 min at room temperature a solution of 2-(bromomethyl)-5’-isopropyl-2’-methoxy-4-(trifluoromethyl)biphenyl (255 mg, 0.629 mmol) in dry THF (3 mL) was added by cannula. The reaction mixture was stirred overnight at room temperature. Saturated NH₄Cl (10 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 25 x 160 mm, 0-70% EtOAc in hexanes gradient) to afford (4S,5R)-3-[[4’-fluoro-5’-isopropyl-2’-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-pyridin-4-yl-1,3-oxazolidin-2-one as a colorless oil. Rf = 0.49 (EtOAc). LCMS calc. = 503.2; found = 503.3 (M+1)⁺. ¹H NMR (600 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 8.61 (d, J = 4.1 Hz, 2H), 7.68 (s, 0.5H), 7.61 (s, 1H), 7.60 (s, 0.5H), 7.33 (dd, J = 7.4, 3.8, Hz 1H), 7.16 (br s, 2H), 6.97 (dd, J = 17.8, 8.4 Hz, 1H), 6.67 (dd, J = 12.0, 3.4 Hz, 1H), 5.44 (d, J = 8.2 Hz, 0.5H), 5.28 (d, J = 8.0 Hz, 0.5H), 4.79 (d, J = 15.8 Hz, 0.5H), 4.76 (d, J = 15.8 Hz, 0.5H), 4.15-4.09 (m, 1H), 3.88 (d, J = 15.8 Hz, 0.5H), 3.79-3.70 (m, 0.5H), 3.74 (s, 3H), 3.23-3.17 (m, 1H), 1.26-1.16 (m, 6H), 0.52 (d, J = 6.5 Hz, 1.5H), 0.38 (d, J = 6.5 Hz, 1.5H).

**EXAMPLE 197**
(4S,5S)-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-5-(4-methyl-1,3-thiazol-2-yl)-1,3-oxazolidin-2-one

**Step A: benzyl [(1S)-1-methyl-2-oxoethyl]carbamate**

Dimethylsulfoxide (1.01 g, 918 µL, 12.9 mmol) was added dropwise to a stirred solution of oxalyl chloride (790 mg, 543 µL, 6.23 mmol) in dry CH₂Cl₂ (12.6 mL) at -78 °C under N₂ and the reaction was stirred for 15 min. A solution of benzyl [(1S)-2-hydroxy-1-methylethyl]carbamate (965 mg, 4.61 mmol) in dry CH₂Cl₂ (12.6 mL) was added dropwise by cannula and the mixture was stirred at -78 °C for 30 min. Triethylamine (1.34 g, 1.85 mL, 13.2 mmol) was added and the reaction was allowed to warm to room temperature and was stirred for 2 h. Water (15 mL) was added and the aqueous phase was separated and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic extracts were washed with saturated NaHCO₃ and brine, then dried (MgSO₄) and concentrated in vacuo to afford benzyl [(1S)-1-methyl-2-oxoethyl]carbamate as a colorless oil. Rₓ = 0.75 (50% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃) δ 9.58 (s, 1H), 7.39-7.35 (m, 5H), 5.39 (br s, 1H), 5.15 (s, 2H), 4.33 (m, 1H), 1.40 (d, J = 7.1 Hz, 3H).

**Step B: benzyl [(1S)-2-cyano-2-hydroxy-1-methylethyl]carbamate**

Diethylaluminum cyanide (4.53 mL, 1M in toluene, 4.53 mmol) was added dropwise to a stirred solution of benzyl [(1S)-1-methyl-2-oxoethyl]carbamate (0.853 g, 4.12 mmol) in dry toluene (33 mL) at -78 °C under N₂. The mixture was stirred at -78 °C for 6 h and then allowed to warm to room temperature overnight. Saturated NH₄Cl (20 mL) and water (10 mL) were added then the mixture was extracted with EtOAc (3 x 50 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to afford the crude product. This was purified by flash chromatography (Si, 40 x 160 mm, 0-40% EtOAc in hexanes gradient) to afford benzyl [(1S)-2-cyano-2-hydroxy-1-methylethyl]carbamate as a 3:1 mixture of diastereoisomers. Rₓ = 0.63 (50% EtOAc in hexanes). LCMS calc. = 257.1; found = 257.1 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) major diastereoisomer: δ 7.39-7.31 (m, 5H), 5.11 (m, 2H), 4.60 br (s, 1H), 3.96 (m, 1H), 1.34 (d, J =
6.7 Hz, 3H), minor diastereoisomer: δ 7.39-7.31 (m, 5H), 5.14 (m, 2H), 4.50 br (s, 1H), 4.10 (m, 1H), 1.30 (d, J = 7.0 Hz, 3H).

Step C: benzyl (1S,2S)-2-[[tert-butyl(dimethyl)silyl]oxy]-2-cyano-1-methylethyl)carbamate tert-Butyldimethylsilyl chloride (471 mg, 3.12 mmol) and imidazole (483 mg, 7.10 mmol) were added successively to a stirred solution of benzyl [(1S)-2-cyano-2-hydroxy-1-methylethyl]carbamate (665 mg, 2.84 mmol) in dry CH₂Cl₂ (13 mL) at room temperature under N₂ and the mixture was stirred overnight. Water (30 mL) was added and the mixture was extracted with Et₂O (3 x 30 mL). The combined extracts were dried (MgSO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 40 x 160 mm, 0-15% EtOAc in hexanes gradient) to afford benzyl (1S,2R)-2-[[terti-butyl(dimethyl)silyl]oxy]-2-cyano-1-methylethyl)carbamate and benzyl (1S,2S)-2-[[t-tert-butyl(dimethyl)silyl]oxy]-2-cyano-1-methylethyl)carbamate. (1S,2R)-diastereoisomer: R₇ = 0.29 (10% EtOAc in hexanes). LCMS calc. = 349.2; found = 349.1 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 7.39-7.33 (m, 5H), 5.16 (d, J = 12.1 Hz, 1H), 5.07 (d, J = 12.1 Hz, 1H), 4.89 (br d, J = 6.6 Hz, 1H), 4.68 (br, d, J = 3.6 Hz, 1H), 3.92 (m, 1H), 1.31 (d, J = 6.7 Hz, 3H), 0.91 (s, 9H), 0.21 (s, 3H), 0.17 (s, 3H). (1S,2S)-diastereoisomer: R₇ = 0.24 (10% EtOAc in hexanes). LCMS calc. = 349.2; found = 349.1 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.32 (m, 5H), 5.10 (s, 2H), 4.76 (br d, J = 6.9 Hz, 1H), 4.63 (br s, 1H), 4.00 (m, 1H), 1.31 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 2.9 Hz, 9H), 0.17 (s, 3H), 0.08 (s, 3H).

Step D: benzyl (1S,2S)-3-amino-2-[[t-tert-butyl(dimethyl)silyl]oxy]-1-methyl-3-thioxopropyl)carbamate

A mixture of benzyl (1S,2S)-2-[[t-tert-butyl(dimethyl)silyl]oxy]-2-cyano-1-methylethyl)carbamate (115.6 mg, 0.287 mmol), diethylidithiophosphate (1 mL) and water (3 drops) was stirred overnight at room temperature. The reaction mixture was partitioned between saturated NaHCO₃ (40 mL) and EtOAc (40 mL). The aqueous layer was separated and extracted with EtOAc (2 x 40 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-40% EtOAc in hexanes gradient) to afford benzyl (1S,2S)-3-amino-2-[[t-tert-butyl(dimethyl)silyl]oxy]-1-methyl-3-thioxopropyl)carbamate as a colorless oil. R₇ = 0.30 (20% EtOAc in hexanes). LCMS calc. = 383.2; found = 383.1 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃) δ 8.36 (s, 1H), 7.87 (s, 1H), 7.37-7.29 (m, 5H), 5.13 (m, 2H), 4.85 (d, J = 8.2 Hz, 1H), 4.72 (s, 1H), 4.47 (m, 1H), 1.05 (d, J = 6.7 Hz, 3H), 0.96 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).

Step E: benzyl (1S,2S)-2-hydroxy-1-methyl-2-(4-methyl-1,3-thiazol-2-yl)ethyl)carbamate

A solution of benzyl (1S,2S)-3-amino-2-[[t-tert-butyl(dimethyl)silyl]oxy]-1-methyl-3-thioxopropyl)carbamate (96.8 mg, 0.253 mmol) and chloroacetone (117 mg, 101 µL, 1.27 mmol) in dry EtOH (5 mL) was heated at reflux under N₂ for 20 h, then stirred at room temperature for 2 days. The reaction mixture was concentrated in vacuo to give the crude product. This was
purified by flash chromatography (Si, 12 x 160 mm, 0-100% EtOAc in hexanes gradient) to afford benzyl [(1S,2S)-2-hydroxy-1-methyl-2-(4-methyl-1,3-thiazol-2-yl)ethyl]carbamate. \( R_f = 0.44 \) (50% EtOAc in hexanes). LCMS calc. = 307.1; found = 307.1 (M+1)+. \(^1\)H NMR (500 MHz, CDCl$_3$) \( \delta \) 7.31 (m, 5H), 6.80 (s, 1H), 5.49 (br s, 1H), 5.06 (m, 3H), 4.26-4.18 (m, 1H), 2.38 (s, 3H), 1.09 (d, \( J = 6.5 \) Hz, 3H).

**Step F:** (4S,5S)-4-methyl-5-(4-methyl-1,3-thiazol-2-yl)-1,3-oxazolidin-2-one

A solution of benzyl [(1S,2S)-2-hydroxy-1-methyl-2-(4-methyl-1,3-thiazol-2-yl)ethyl]carbamate (53.4 mg, 0.174 mmol) in 7.5 N aqueous KOH (1 mL), MeOH (2 mL) and THF (4 mL) was stirred at room temperature overnight. The reaction mixture was acidified with 3N HCl and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with brine, dried (Na$_2$SO$_4$) and concentrated in vacuo to afford the product. LCMS calc. = 199.1; found = 199.1 (M+1)+. \(^1\)H NMR (500 MHz, CDCl$_3$) \( \delta \) 6.92 (s, 1H), 6.82 (s, 1H), 5.91 (d, \( J = 8.2 \) Hz, 1H), 4.39-4.35 (m, 1H), 2.44 (s, 3H), 0.95 (d, \( J = 6.4 \) Hz, 3H).

**Step G:** (4S,5S)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-(4-methyl-1,3-thiazol-2-yl)-1,3-oxazolidin-2-one

Sodium hydride (60% dispersion in mineral oil, 8.1 mg, 0.202 mmol) was added to a stirred solution of (4S,5S)-4-methyl-5-(4-methyl-1,3-thiazol-2-yl)-1,3-oxazolidin-2-one (33.4 mg, 0.168 mmol) in dry THF (1 mL) at room temperature under N$_2$. The reaction was stirred for 15 min then a solution of 2'-(bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)biphenyl (81.0 mg, 0.202 mmol) in dry THF (2 mL) was added by cannula. The reaction was stirred at room temperature overnight. Saturated NH$_4$Cl (10 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 25 x 160 mm, 0-70% EtOAc in hexanes gradient) and chiral HPLC (IA column, 20 x 250 mm, 5% i-ProH in heptane) to afford (4S,5S)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-(4-methyl-1,3-thiazol-2-yl)-1,3-oxazolidin-2-one. \( R_f = 0.18 \) (20% EtOAc in hexanes). LCMS calc. = 523.2; found = 523.1 (M+1)+. \(^1\)H NMR (500 MHz, CDCl$_3$, 1:1 mixture of atropisomers) \( \delta \) 7.68 (s, 0.5H), 7.63 (s, 0.5H), 7.59 (d, \( J = 8.0 \) Hz, 1H), 7.32 (d, \( J = 7.9 \) Hz, 1H), 6.99 (d, \( J = 8.5 \) Hz, 0.5H), 6.95 (d, \( J = 8.5 \) Hz, 0.5H), 6.88 (s, 1H), 6.68 (d, \( J = 5.0 \) Hz, 0.5H), 6.66 (d, \( J = 4.9 \) Hz, 0.5H), 5.70 (d, \( J = 8.3 \) Hz, 0.5H), 5.55 (d, \( J = 8.2 \) Hz, 0.5H), 4.72 (d, \( J = 15.9 \) Hz, 0.5H), 4.64 (d, \( J = 15.9 \) Hz, 0.5H), 4.20 (d, \( J = 15.9 \) Hz, 0.5H), 3.95 (d, \( J = 15.9 \) Hz, 0.5H), 3.91-3.83 (m, 1H), 3.75 (s, 1.5H), 3.74 (s, 1.5H), 3.23-3.15 (m, 1H), 2.40 (s, 3H), 1.26-1.18 (m, 6H), 0.65 (d, \( J = 6.5 \) Hz, 1.5H), 0.55 (d, \( J = 6.5 \) Hz, 1.5H).

Following the general procedures outlined above, the compounds in Table 8 were prepared. Example 198 was made as a reference compound.
Table 8

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**EXAMPLE 253, 254**
(4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-[3-(methylsulfinyl)phenyl]-1,3-oxazolidin-2-one (EXAMPLE 253)

(4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-[3-(methylsulfonyl)phenyl]-1,3-oxazolidin-2-one (EXAMPLE 254)

To a solution of (4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-[3-(methylthio)phenyl]-1,3-oxazolidin-2-one (EXAMPLE 208) (25 mg, 0.0457 mmol) in dry dichloromethane (1.5 mL) under N₂ at 0 °C, was added dropwise a solution of 3-chloroperoxybenzoic acid (77%, 26 mg, 0.114 mmol) in CH₂Cl₂ (0.5 mL). After addition the mixture was left to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with saturated Na₂SO₃ (15 mL). The aqueous layer was extracted with Et₂O (3 x 20 mL). The combined organic extracts were washed with saturated NaHCO₃, dried (Na₂SO₄) and concentrated in vacuo. The crude material was purified by flash chromatography (Si, 12 x 160 mm, 0-60% EtOAc in hexanes gradient) to afford (4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-[3-(methylsulfinyl)phenyl]-1,3-oxazolidin-2-one and (4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-[3-(methylsulfonyl)phenyl]-1,3-oxazolidin-2-one. EXAMPLE 253: LCMS calc. = 564.19; found = 564.3 (M+1)+. ¹H NMR (500 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 7.73 (s, 0.5 H); 7.66-7.52 (m, 4.5 H); 7.42 (s, 0.5 H); 7.40 (s, 0.5 H); 7.37 (d, J = 3.4 Hz, 0.5 H); 7.36 (d, J = 3.5 Hz, 0.5 H); 7.02 (d, J = 8.4 Hz, 0.5 H); 6.99 (d, J = 8.4 Hz, 0.5 H); 6.71 (d, J = 3.1 Hz, 0.5 H); 6.69 (d, J = 2.9 Hz, 0.5 H); 5.59 (d, J = 5.9 Hz, 0.5 H); 5.57 (d, J = 5.9 Hz, 0.5 H); 5.42 (t, J = 8.4 Hz, 1 H); 4.85 (d, J = 3.4 Hz, 0.5 H); 4.82 (d, J = 3.4 Hz, 0.5 H); 4.80 (d, J = 7.8 Hz, 0.5 H); 4.77 (d, J = 7.7 Hz, 0.5 H); 4.16 (d, J = 15.8 Hz, 0.5 H); 3.92 (d, J = 15.8 Hz, 0.5 H); 3.76 (s, 3 H); 3.85-3.72 (m, 1 H); 3.26-3.19 (m, 1 H); 2.73 (d, J = 4.7 Hz, 3 H); 1.30-1.26 (m, 4.5 H); 1.20 (d, J = 6.9 Hz, 1.5 H); 0.55 (d, J = 6.7 Hz, 0.75 H); 0.52 (d, J = 6.7 Hz, 0.75 H); 0.41 (d, J = 4.0 Hz, 0.75 H); 0.39 (d, J = 4.1 Hz, 0.75 H).

EXAMPLE 254: LCMS calc. = 580.17; found = 580.3 (M+1)+. ¹H NMR (500 MHz, CDCl₃, 1:1
mixture of atropisomers) δ 7.95 (s, 0.5 H); 7.94 (s, 0.5 H); 7.81 (s, 0.5 H); 7.80 (s, 0.5 H); 7.73 (s, 0.5 H); 7.65-7.58 (m, 3 H); 7.57 (s, 0.5 H); 7.38 (d, J = 3.5 Hz, 0.5 H); 7.36 (d, J = 3.8 Hz, 0.5 H); 7.02 (d, J = 8.4 Hz, 0.5 H); 6.99 (d, J = 8.4 Hz, 0.5 H); 6.72 (s, 0.5 H); 6.69 (s, 0.5 H); 5.58 (d, J = 8.1 Hz, 0.5 H); 5.42 (d, J = 8.0 Hz, 0.5 H); 4.86 (d, J = 15.9 Hz, 0.5 H); 4.81 (d, J = 15.9 Hz, 0.5 H); 4.17 (d, J = 15.8 Hz, 0.5 H); 3.91 (d, J = 15.8 Hz, 0.5 H); 3.81-3.75 (m, 1 H); 3.78 (s, 3H); 3.27-3.19 (m, 1 H); 3.07 (s, 3 H); 1.30-1.26 (m, 4.5 H); 1.21 (t, J = 8.7 Hz, 1.5 H); 0.53 (d, J = 6.5 Hz, 1.5 H); 0.39 (d, J = 6.5 Hz, 1.5 H).

**EXAMPLE 255**

![Chemical Structure](image)

3-((4S,5R)-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-ethyl-2-oxo-1,3-oxazolidin-5-yl)benzaldehyde

The solution of (4S,5R)-5-[3-(1,3-dioxan-2-yl)phenyl]-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one (EXAMPLE 210) (380 mg, 0.647 mmol) in THF and 1N HCl (3:1) (4 mL) was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc and washed with NaHCO₃ and brine. The organic layer was dried and concentrated in vacuo. The crude material was purified by flash chromatography (Si) to provide 3-((4S,5R)-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-2-oxo-1,3-oxazolidin-5-yl)benzaldehyde. LCMS calc. = 530.19; found = 530.4 (M+1)+. 1H NMR (500 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 10.03 (s, 1 H); 7.88 (s, 0.5 H); 7.87 (s, 0.5 H); 7.77-7.52 (m, 5 H); 7.37 (d, J = 3.5 Hz, 0.5 H); 7.36 (d, J = 3.4 Hz, 0.5 H); 7.02 (d, J = 8.4 Hz, 0.5 H); 6.99 (d, J = 8.4 Hz, 0.5 H); 6.71 (d, J = 3.5 Hz, 0.5 H); 6.69 (d, J = 3.4 Hz, 0.5 H); 4.17 (d, J = 15.8 Hz, 0.5 H); 6.98 (d, J = 15.8 Hz, 0.5 H); 3.78 (s, 3 H); 3.85-3.71 (m, 1 H); 3.26-3.19 (m, 1 H); 1.30-1.26 (m, 4.5 H); 1.19 (d, J = 6.9 Hz, 1.5 H); 0.53 (d, J = 6.6 Hz, 1.5 H); 0.40 (d, J = 6.6 Hz, 1.5 H).

**EXAMPLE 256**
(4S, 5R)-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-[3-(hydroxy)-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-[3-(hydroxy] to a solution of 3-{[4S,5R]-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-2-oxo-1,3-oxazolidin-5-yl}benzaldehyde (12 mg, 0.023 mmol) in anhydrous EtOH (1 mL) at 0 °C under N₂, was added NaBH₄ (4.5 mg, 0.119 mmol) as a powder. The solution was warmed to room temperature and stirred for 1 h. The mixture was quenched with 2% HOAc and diluted with water. The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with saturated NaHCO₃ (12 mL) and brine (12 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude material was purified by flash chromatography to yield (4S, 5R)-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-[3-(hydroxy)-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl}-5-[3-(hydroxy]. LCMS calc. = 532.0; found = 532.4 (M+H)⁺. ¹H NMR (500 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 7.73 (s, 0.5 H); 7.67 (s, 0.5 H); 7.64 (s, 0.5 H); 7.62 (s, 0.5 H); 7.42-7.32 (m, 3 H); 7.24 (s, 1 H); 7.15 (s, 0.5 H); 7.14 (s, 0.5 H); 7.01 (d, J = 8.4 Hz, 0.5 H); 6.98 (d, J = 8.5 Hz, 0.5 H); 6.71 (s, 0.5 H); 6.68 (s, 0.5 H); 5.51 (d, J = 8.1 Hz, 0.5 H); 5.37 (d, J = 8.0 Hz, 0.5 H); 4.81 (d, J = 15.9 Hz, 0.5 H); 4.74 (d, J = 16 Hz, 0.5 H); 4.73 (s, 2 H); 4.15 (d, J = 15.9 Hz, 1 H); 3.92 (d, J = 15.9 Hz, 1 H); 3.77 (s, 3.0 H); 3.79-3.74 (m, 0.5 H); 3.74-3.68 (m, 0.5 H); 3.25-3.18 (m, 1 H); 1.29-1.25 (m, 4.5 H); 1.19 (d, J = 6.9 Hz, 1.5 H); 0.53 (d, J = 6.4 Hz, 1.5 H); 0.40 (d, J = 6.4 Hz, 1.5 H).

EXAMPLE 257
(4S, 5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-[3-(1-hydro)-xyethyl]phenyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of 3-((4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-2-oxo-1,3-oxazolidin-5-yl)benzaldehyde (11 mg, 0.021 mmol) in THF (1 mL) at -78 °C under N₂, was added methylmagnesium bromide (30 μL of a 3.0 M solution in Et₂O). The mixture was stirred at -78 °C for 2 h. The mixture was quenched with saturated NH₄Cl (10 mL). The aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si) to afford (4S, 5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-[3-(1-hydro)-xyethyl]phenyl]-4-methyl-1,3-oxazolidin-2-one. LCMS calc. = 546.22; found = 546.4 (M+1)+.

¹H NMR (500 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 7.74 (s, 0.5 H); 7.67 (s, 0.5 H); 7.64 (s, 0.5 H); 7.63 (s, 0.5 H); 7.36 (m, 3 H); 7.24 (s, 1 H); 7.15 (s, 0.5 H); 7.14 (s, 0.5 H); 7.01 (d, J = 8.5 Hz, 0.5 H); 6.99 (d, J = 8.5 Hz, 0.5 H); 6.71 (s, 0.5 H); 6.68 (s, 0.5 H); 5.52 (d, J = 8.0 Hz, 0.5 H); 5.36 (d, J = 7.9 Hz, 0.5 H); 4.92 (q, J = 6.4 Hz, 1 H); 4.83 (d, J = 15.7, 0.5 H); 4.77 (d, J = 16.0, 0.5 H); 4.16 (d, J = 15.5 Hz, 0.5H); 3.92 (d, J = 15.5 Hz, 0.5 H); 3.77 (d, J = 7.1 Hz, 3 H); 3.81-3.68 (m, 1 H); 3.25-3.18 (m, 1 H); 1.64 (br, s, 1 H); 1.49 (d, J = 6.4 Hz, 3 H); 1.30-1.26 (m, 4.5 H); 1.19 (d, J = 6.9 Hz, 1.5 H); 0.53 (d, J = 6.5 Hz, 1.5 H); 0.40 (d, J = 6.5 Hz, 1.5 H).

Following the general procedures outlined above, the compounds in Table 9 were prepared:

<table>
<thead>
<tr>
<th>Table 9</th>
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<td>258</td>
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<td>259</td>
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**EXAMPLE 260**

(4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl) biphenyl-2-yl]methyl]-4-methyl-5-[[3-[(methylamino)methyl]phenyl]-1,3-oxazolidin-2-one

To a solution of 3-[(4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-2-oxo-1,3-oxazolidin-5-yl]benzaldehyde (15 mg, 0.028 mmol) in 1,2-dichloroethane (1 mL) was added methylamine (1 mL of a 2.0 M solution in THF). The resulting mixture was treated with sodium triacetoxyborohydride (34.8 mg, 0.16 mmol) and AcOH (0.05 mL). The mixture was stirred under N₂ at room temperature for 5 days. The reaction mixture was quenched with 1N NaOH and the aqueous layer was extracted with ether (3 x 15 mL). The ether extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography (Si) to afford (4S, 5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-[[3-[(methylamino)methyl]phenyl]-1,3-
oxazolidin-2-one. LCMS calc. = 545.23; found = 545.4 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 7.74 (s, 0.5 H); 7.67 (s, 0.5 H); 7.64 (s, 0.5 H); 7.62 (s, 0.5 H); 7.33 (m, 3 H); 7.20 (s, 1 H); 7.13 (s, 0.5 H); 7.12 (s, 0.5 H); 7.01 (d, J = 8.4 Hz, 0.5 H); 6.98 (d, J = 8.5 Hz, 0.5 H); 6.71 (d, J = 2.9 Hz, 0.5 H); 6.68 (d, J = 2.8 Hz, 0.5 H); 5.51 (d, J = 8.1 Hz, 0.5 H); 5.37 (d, J = 8.0 Hz, 0.5 H); 4.82 (d, J = 15.9 Hz, 0.5 H); 4.75 (d, J = 15.9 Hz, 0.5 H); 4.16 (d, J = 15.9 Hz, 0.5 H); 3.92 (d, J = 15.9 Hz, 0.5 H); 3.77 (m, 5.5 H); 3.70 (t, J = 6.6 Hz, 0.5 H); 3.25-3.18 (m, 1 H); 2.45 (s, 3 H); 1.93 (br, s, 1 H); 1.27 (m, 4.5 H); 1.19 (d, J = 6.9 Hz, 1.5 H); 0.53 (d, J = 6.5 Hz, 1.5 H); 0.40 (d, J = 6.5 Hz, 1.5 H).

EXAMPLE 261

\[
\text{(4S, 5R)-5-[(3-[(dimethylamino)methyl]phenyl)-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one}
\]

To a solution of 3-((4S,5R)-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-2-oxo-1,3-oxazolidin-5-yl)benzaldehyde (15 mg, 0.028 mmol) in EtOH (1 mL) was added dimethylamine (140 µL of a 2.0 M solution in MeOH) and titanium isopropoxide (79 µL, 0.28 mmol). The resulting white suspension was stirred overnight. Sodium borohydride (7.1 mg, 0.188 mmol) was added and the mixture was stirred overnight. The reaction was quenched by pouring the mixture into 2N aqueous ammonia (2 mL). The resulting inorganic precipitate was filtered and washed with dichloromethane. The combined filtrates were extracted with dichloromethane (2 x 15 mL). The extracts were dried (Na₂SO₄) and concentrated \textit{in vacuo}. The residue was purified by flash chromatography (Si) to give (4S, 5R)-5-[(3-[(dimethylamino)methyl]phenyl)-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one. LCMS calc. = 559.25; found = 559.4 (M+1)⁺. ¹H NMR (500 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 7.74 (s, 0.5 H); 7.67 (s, 0.5 H); 7.64 (s, 0.5 H); 7.62 (s, 0.5 H); 7.37-7.29 (m, 3 H); 7.18 (s, 1 H); 7.16 (s, 0.5 H); 7.13 (s, 0.5 H); 7.01 (d, J = 8.4 Hz, 0.5 H); 6.99 (d, J = 8.5 Hz, 0.5 H); 6.71 (d, J = 3.0
Hz, 0.5 H); 6.68 (d, J = 2.9 Hz, 0.5 H); 5.52 (d, J = 8.1 Hz, 0.5 H); 5.37 (d, J = 8.0 Hz, 0.5 H); 4.82 (d, J = 15.9 Hz, 0.5 H); 4.77 (d, J = 16.0 Hz, 0.5 H); 4.15 (d, J = 16.0 Hz, 0.5 H); 3.91 (d, J = 15.9 Hz, 0.5 H); 3.76 (s, 3 H); 3.80-3.73 (m, 0.5 H); 3.72-3.68 (m, 0.5 H); 3.43 (s, 2 H); 3.25-3.18 (m, 1 H); 2.23 (s, 6 H); 1.27 (m, 4.5 H); 1.19 (d, J = 6.9 Hz, 1.5 H); 0.53 (d, J = 6.5 Hz, 1.5 H); 0.39 (d, J = 6.6 Hz, 1.5 H).

**EXAMPLE 262**

![Chemical Structure](image)

(4S, 5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl) biphenyl-2-yl]methyl]-5-(1H-imidazol-2-yl)-4-methyl-1,3-oxazolidin-2-one

A mixture of (4S,5S)-5-[[1-[(benzyloxy)methyl]-1H-imidazol-2-yl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one (EXAMPLE 244) (16.9 mg, 0.028 mmol), 20% palladium hydroxide on carbon (8.3 mg) and 1N HCl (28 uL) in MeOH (1 mL) was stirred under hydrogen (balloon) overnight, after which time it was filtered through Celite and concentrated *in vacuo*. The crude material was purified by flash chromatography to afford (4S, 5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-(1H-imidazol-2-yl)-4-methyl-1,3-oxazolidin-2-one.

LCMS calc. = 492.18; found = 492.2 (M+1)+. 1H NMR (500 MHz, CDCl3, 1:1 mixture of atropisomers) δ 7.71 (s, 0.5 H); 7.67 (s, 0.5 H); 7.65 (s, 0.5 H); 7.64 (s, 0.5 H); 7.37 (d, J = 3.2 Hz, 0.5 H); 7.35 (d, J = 3.3 Hz, 0.5 H); 7.09 (d, J = 3.3 Hz, 0.5 H); 7.02 (d, J = 8.4 Hz, 0.5 H); 6.99 (d, J = 8.5 Hz, 0.5 H); 6.72 (d, J = 4.3 Hz, 0.5 H); 6.69 (d, J = 4.2 Hz, 0.5 H); 5.76 (d, J = 8.3 Hz, 0.5 H); 5.64 (d, J = 8.7 Hz, 0.5 H); 4.72 (d, J = 15.8 Hz, 0.5 H); 4.68 (d, J = 15.8 Hz, 0.5 H); 4.20 (d, J = 15.7 Hz, 0.5 H); 4.01 (d, J = 15.7 Hz, 0.5 H); 3.90 (br, s, 1 H); 3.79-3.72 (m, 4H); 3.25-3.18 (m, 1 H); 1.28-1.22 (m, 6 H); 0.67 (d, J = 6.5 Hz, 1.5 H); 0.59 (d, J = 6.5 Hz, 1.5 H).

**EXAMPLE 263**
(4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-(1-oxidopyridin-4-yl)-1,3-oxazolidin-2-one

m-Chlorobenzoic acid (77%, 47.9 mg, 0.214 mmol) was added to a solution of (4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-pyridin-4-yl-1,3-oxazolidin-2-one (53.7, 0.107 mmol) in dry CH₂Cl₂ (10.8 mL) at 0 °C. After 15 min at 0 °C, the reaction was stirred at room temperature for 3 h. The reaction was diluted with CH₂Cl₂ (40 mL) and washed with saturated Na₂SO₃ (20 mL) and saturated K₂CO₃ (2 x 20 mL). The organic layer was dried (Na₂SO₄) and concentrated in vacuo to afford (4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-(1-oxidopyridin-4-yl)-1,3-oxazolidin-2-one as an oil. LCMS calc. = 519.2; found = 519.3 (M+1)⁺.

EXAMPLE 264

4-((4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-2-oxo-1,3-oxazolidin-5-yl)pyridine-2-carbonitrile
Trimethylsilyl cyanide (39.9 mg, 54 µL, 0.402 mmol) was added to a stirred solution of (4S,5R)-3-[[4’-fluoro-5’-isopropyl-2’-methoxy-4-[(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-(1-oxidopyridin-4-yl)-1,3-oxazolidin-2-one (37.9 mg, 0.0732 mmol) in dry CH₂Cl₂ (2 mL) at room temperature under N₂. The reaction was stirred for 5 min and benzoyl chloride (20.5 mg, 17 µL, 0.146 mmol) was added. The reaction was stirred at room temperature overnight. 50% Saturated K₂CO₃ (10 mL) was added and the mixture was diluted with CH₂Cl₂ (20 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 10 mL). The combined organic extracts were dried (K₂CO₃) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-70% EtOAc in hexanes gradient) to afford the product (11.6 mg, 30%), as a colorless oil. This was resolved into its enantiomers by chiral HPLC (AD column, 20 x 250 mm, 10% i-PrOH in heptane) to give 4-(((4S,5R)-3-[[4’-fluoro-5’-isopropyl-2’-methoxy-4-[(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-2-oxo-1,3-oxazolidin-5-yl]pyridine-2-carbonitrile and 4-(((4R,5S)-3-[[4’-fluoro-5’-isopropyl-2’-methoxy-4-[(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-2-oxo-1,3-oxazolidin-5-yl]pyridine-2-carbonitrile. R₉ = 0.72 (50% EtOAc in hexanes). LCMS calc. = 528.2; found = 528.3 (M+1)+. ¹H NMR (500 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 8.73 (s, 1H), 7.67-7.59 (m, 2H), 7.55 (d, J = 3.3 Hz, 1H), 7.40 (d, J = 4.2 Hz, 1H), 7.35 (dd, J = 7.8, 3.3 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 6.69 (d, J = 3.1 Hz, 1H), 6.67 (d, J = 3.1 Hz, 1H), 5.47 (d, J = 8.1 Hz, 0.5H), 5.30 (d, J = 8.1 Hz, 0.5H), 4.81 (t, J = 15.1 Hz, 1H), 4.11 (d, J = 15.8 Hz, 0.5H), 3.89 (d, J = 15.8 Hz, 0.5H), 3.83-3.73 (m, 1H), 3.76 (s, 3H), 3.24-3.16 (m, 1H), 1.27-1.17 (m, 6H), 0.54 (d, J = 6.5 Hz, 1.5H), 0.39 (d, J = 6.5 Hz, 1.5H).

EXAMPLE 265

![Chemical structure](image)

(4S,5R)-5-(2-chloropyridin-4-yl)-3-[[4’-fluoro-5’-isopropyl-2’-methoxy-4-[(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

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A solution of \((4S,5R)-3-\{4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl\}methyl\}-4-methyl-5-(1-oxidopyridin-4-yl)-1,3-oxazolidin-2-one (53.7 mg, 0.104 mmol) in phosphorous oxychloride (4 mL) was heated at reflux under \(N_2\) for 2 h. The reaction mixture was cooled to room temperature, concentrated \textit{in vacuo}, diluted with EtOAc (20 mL) and water (5 mL), then washed with saturated NaHCO\(_3\) (10 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)) and concentrated \textit{in vacuo} to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-70% EtOAc in hexanes gradient) to afford the product as a colorless oil. This was resolved into its enantiomers by chiral HPLC (AD column, 20 x 250 mm, 5% i-PrOH in heptane) to afford \((4S,5R)-5-(2-chloropyridin-4-yl)-3-\{4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl\}methyl\}-4-methyl-1,3-oxazolidin-2-one. \(R_f = 0.17\) (20% EtOAc in hexanes). LCMS calc. = 537.2; found = 537.3 (M+1)\(^+\). \(^1\)H NMR (500 MHz, CDCl\(_3\), 1:1 mixture of atropisomers) \(\delta 8.40\) (br s, 1H), 7.70 (s, 0.5H), 7.63 (s, 1.5H), 7.37 (m, 1H), 7.24 (br s, 1H), 7.10 (br s, 1H), 7.01 (d, \(J = 8.2\) Hz, 0.5H), 6.98 (d, \(J = 8.2\) Hz, 0.5H), 6.72-6.68 (m, 1H), 5.44 (d, \(J = 8.1\) Hz, 0.5H), 5.29 (d, \(J = 8.1\) Hz, 0.5H), 4.81 (t, \(J = 16.9\) Hz, 1H), 4.14 (d, \(J = 15.9\) Hz, 0.5H), 3.91 (d, \(J = 15.9\) Hz, 0.5H), 3.81-3.71 (m, 1H), 3.76 (s, 3H), 3.27-3.19 (m, 1H), 1.29-1.19 (m, 6H), 0.58 (d, \(J = 6.5\) Hz, 1.5H), 0.44 (d, \(J = 6.5\) Hz, 1.5H).

**EXAMPLE 266**

![Chemical Structure](image)

\((4S,5R)-3-\{4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl\}methyl\}-4-methyl-5-(2-methylpyridin-4-yl)-1,3-oxazolidin-2-one

A solution of \((4S,5R)-5-(2-chloropyridin-4-yl)-3-\{4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl\}methyl\}-4-methyl-1,3-oxazolidin-2-one (20.9 mg, 0.0389 mmol), trimethylboroxine (14.7 mg, 16 \(\mu\)L, 0.116 mmol), Cs\(_2\)CO\(_3\) (38.0 mg, 0.117 mmol) and (Ph\(_3\))\(_4\)Pd (9.0 mg, 0.00778 mmol) in dry 1,4-dioxane (1 mL) was heated at reflux overnight. The reaction mixture was filtered through a plug of Celite and washed with EtOAc. The filtrate was
concentrated in vacuo to afford the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-70% EtOAc in hexanes gradient) to afford the product as a colorless oil. This was resolved into its enantiomers by chiral HPLC (AD column, 20 x 250 mm, 10% i-PrOH in heptane) to afford (4S,5R)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-(2-methylpyridin-4-yl)-1,3-oxazolidin-2-one and (4R,5S)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-5-(2-methylpyridin-4-yl)-1,3-oxazolidin-2-one. Rf = 0.22 (50% EtOAc in hexanes). LCMS calc. = 517.2; found = 517.1 (M+1)^+. ¹H NMR (500 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 8.48 (d, J = 4.9 Hz, 1H), 7.69 (s, 0.5H), 7.61 (s, 1H), 7.60 (s, 0.5H), 7.33 (m, 1H), 7.05 (s, 1H), 6.99-6.93 (m, 2H), 6.69 (d, J = 3.2 Hz, 1H), 6.66 (d, J = 3.2 Hz, 1H), 5.40 (d, J = 8.1 Hz, 0.5H), 5.24 (d, J = 8.1 Hz, 0.5H), 4.79 (d, J = 15.9 Hz, 0.5H), 4.74 (d, J = 15.9 Hz, 0.5H), 4.13 (d, J = 15.9 Hz, 0.5H), 3.89 (d, J = 15.9 Hz, 0.5H), 3.78-3.66 (m, 1H), 3.73 (s, 3H), 3.23-3.17 (m, 1H), 2.56 (s, 3H), 1.25-1.17 (m, 6H), 0.53 (d, J = 6.5 Hz, 1.5H), 0.39 (d, J = 6.5 Hz, 1.5H).

Following the general procedures outlined above, the compounds in Table 10 were prepared:

Table 10

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Following the general procedures outlined above, the compounds in Table 11 were prepared:

Table 11

- 169 -
Following the general procedures outlined above, the compounds in Table 12 were prepared:

Table 12

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**EXAMPLE 281**
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-2'-hydroxy-5'-isopropyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

**Step A: 4-fluoro-2’-(iodomethyl)-5-isopropyl-4’-(trifluoromethyl)biphenyl-2-ol**

A solution of [4’-fluoro-5’-isopropyl-2’-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methanol (71.5 mg, 0.209 mmol) and iodine (610 mg, 2.40 mmol) in phenyltrimethylsilane (877 µL) was heated at 110 °C in a sealed tube overnight. The reaction was cooled to room temperature, diluted with 1N HCl (10 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were washed with 10% Na₂S₂O₅ (20 mL), dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-20% EtOAc in hexanes gradient) to afford 4-fluoro-2’-(iodomethyl)-5-isopropyl-4’-(trifluoromethyl)biphenyl-2-ol. R_f = 0.65 (20% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃) δ 7.81 (s, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 11.1 Hz, 1H), 4.82 (s, 1H), 4.41 (d, J = 9.4 Hz, 1H), 4.23 (d, J = 9.3 Hz, 1H), 3.27-3.19 (m, 1H), 1.27 (br s, 6H).

**Step B: 2-[[4-fluoro-2’-(iodomethyl)-5-isopropyl-4’-(trifluoromethyl)biphenyl-2-yl]oxy]tetrahydro-2H-pyran**

p-Toluensulfonic acid (2.8 mg, 0.0145 mmol) was added to a solution of 4-fluoro-2’-(iodomethyl)-5-isopropyl-4’-(trifluoromethyl)biphenyl-2-ol (63.4 mg, 0.145 mmol) and 3,4-dihydro-2H-pyran (60.8 mg, 66 µL, 0.723 mmol) in dry CH₂Cl₂ (7.2 mL) at room temperature under N₂ and the reaction was stirred for 3 days. The reaction mixture was diluted with saturated NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-20% EtOAc in hexanes gradient) to afford 2-[[4-fluoro-2’-(iodomethyl)-5-isopropyl-4’-(trifluoromethyl)biphenyl-2-yl]oxy]tetrahydro-2H-pyran. R_f = 0.74 (10% EtOAc in hexanes). ¹H NMR (500 MHz, CDCl₃) δ 7.75 (s, 1H), 7.62 (d, J = 8.3 Hz, 0.5H), 7.59 (d, J = 8.3 Hz, 0.5H), 7.53 (t, J = 7.3 Hz, 0.5H), 7.41 (s, 0.5H), 7.32 (d, J = 7.9 Hz, 0.5H), 7.25 (d, J = 7.9 Hz, 0.5H), 7.15 (t, J = 9.4 Hz, 0.5H), 6.99 (d, J = 12.2 Hz, 0.5H), 6.94 (d,
$J = 12.2$ Hz, 0.5H), 6.69 (d, $J = 11.0$ Hz, 0.5H), 5.37 (s, 0.5H), 5.23 (s, 0.5H), 5.13 (s, 1H), 4.45 (d, $J = 9.6$ Hz, 0.5H), 4.40 (d, $J = 9.6$ Hz, 0.5H), 4.31 (d, $J = 9.6$ Hz, 0.5H), 4.23 (d, $J = 9.6$ Hz, 0.5H) 3.76 (m, 0.5H), 3.66-3.54 (m, 1.5H), 3.29-3.21 (m, 1H), 1.68-1.44 (m, 4H) 1.32-1.26 (m, 6H).

Step C: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-2'-hydroxy-5'-isopropyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

Sodium hydride (60% dispersion in mineral oil, 1.9 mg, 0.0485 mmol) was added to a stirred solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one in dry DMF (1 mL) and the reaction was stirred for 30 min. A solution of 2-[[4-fluoro-2'-(iodomethyl)-5-isopropyl-4'-(trifluoromethyl)biphenyl-2-yl]oxy]tetrahydro-2H-pyan (16.9 mg, 0.324 mmol) in dry DMF (1 mL) was added by cannula and the reaction was stirred at room temperature overnight. The reaction was diluted with saturated NH$_4$Cl (10 mL) and water (5 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na$_2$SO$_4$) and concentrated in vacuo to give the crude product. A solution of the crude product and p-toluenesulfonylic acid (0.6 mg, 0.00324 mmol) in MeOH (5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-35% EtOAc in hexanes gradient) to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-2'-hydroxy-5'-isopropyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one. R$_f$ = 0.33 (20% EtOAc in hexanes). LCMS calc. = 624.2; found = 624.3 (M+1)$^+$. $^1$H NMR (500 MHz, CDCl$_3$, 1:1 mixture of atropisomers) δ 7.86 (s, 1H), 7.67 (m, 4H), 7.42 (d, $J = 7.1$ Hz, 0.5H), 7.41 (d, $J = 7.1$ Hz, 0.5H), 6.95 (d, $J = 7.3$ Hz, 0.5H), 6.94 (d, $J = 7.3$ Hz, 0.5H), 6.70 (d, $J = 5.6$ Hz, 0.5H), 6.68 (d, $J = 5.6$ Hz, 0.5H), 5.66 (d, $J = 8.0$ Hz, 0.5H), 5.36 (d, $J = 8.1$ Hz, 0.5H), 4.93 (d, $J = 15.8$ Hz, 0.5H), 4.88 (d, $J = 15.8$ Hz, 0.5H), 4.18 (d, $J = 15.8$ Hz, 0.5H), 4.00 (d, $J = 15.8$ Hz, 0.5H), 3.87-3.83 (m, 0.5H), 3.77-3.71 (m, 0.5H), 3.22-3.14 (m, 1H), 1.77 (br s, 1H), 1.27-1.17 (m, 6H), 0.57 (d, $J = 6.5$ Hz, 1.5H), 0.45 (d, $J = 6.5$ Hz, 1.5H).

Following the general procedures outlined above, the compounds in Table 13 were prepared:

<table>
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<tr>
<th>Example</th>
<th>R</th>
<th>LCMS (M+1)$^+$</th>
</tr>
</thead>
</table>

- 173 -
(4S,5R)-5-[[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-3'-hydroxy-5'-isopropyl-2'-methoxy-4- (trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

Step A: tert-butyl[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2- yl]methoxy]dimethylsilane

tert-Butyldimethylsilyl chloride (0.48 g, 3.21 mmol) and imidazole (0.50 g, 7.30 mmol) were added successively to a stirred solution of [4'-fluoro-5'-isopropyl-2'-methoxy-4- (trifluoromethyl)biphenyl-2-yl]methanol (1.00 g, 2.93 mmol) in dry CH₂Cl₂ (13.4 mL) at room temperature under N₂ and the reaction was stirred overnight. Water (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined extracts were dried (MgSO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 25 x 160 mm, 1% EtOAc in hexanes) to afford tert-butyl[[4'-fluoro-5'-isopropyl-2'-methoxy-4- (trifluoromethyl)biphenyl-2-yl]methoxy]dimethylsilane as a colorless oil. R_f = 0.16 (1% EtOAc
in hexanes). LCMS calc. = 457.2; found = 457.2 (M+1)+. 1H NMR (500 MHz, CDCl3) δ 7.94 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 6.69 (d, J = 12.1 Hz, 1H), 4.63 (br s, 1H), 4.50 (br s, 1H), 3.75 (s, 3H), 3.29-3.21 (m, 1H), 1.28 (d, J = 6.9 Hz, 6H), 0.93 (s, 9H), 0.03 (s, 6H).

Step B: 2'-([(tert-butyldimethylsilyloxy)methyl]-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)bibenyl-3-ol)

n-Butyllithium (1.6M in hexanes, 261 μL, 0.417 mmol) was added dropwise over 30-45 min with a syringe pump to a stirred solution of tert-butyl{[4'-fluoro-5'-isopropyl-2'-methoxy-4'-(trifluoromethyl)bibenyl-2-yl]methoxy}dimethylsilane (200 mg, 0.438 mmol) in dry THF (0.5 mL) at -78 °C under N2. The reaction was stirred for a further 2 h at -78 °C after the addition to give a violet colored solution. Trimethyl borate (43.4 mg, 47 μL, 0.417 mmol) was added dropwise and the reaction was stirred at -78 °C for 3 h. The reaction mixture was warmed to 0 °C and acetic acid (25.1 mg, 24 μL, 0.626 mmol) was added quickly followed by 30% aqueous hydrogen peroxide (52 μL, 0.459 mmol) dropwise. The reaction was stirred at room temperature overnight, diluted with water (10 mL) and extracted with Et2O (3 x 20 mL). The combined extracts were washed with 50% saturated FeSO4 (20 mL), dried (Na2SO4) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-100% EtOAc in hexanes gradient) to afford 2'-([(tert-butyldimethylsilyloxy)methyl]-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)bibenyl-3-ol. Rf = 0.32 (10% EtOAc in hexanes). LCMS calc. = 473.1; found = 473.2 (M+1)+. 1H NMR (600 MHz, CDCl3) δ 7.95 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.9 Hz, 1H), 6.53 (d, J = 7.8 Hz, 1H), 5.65 (s, 1H), 4.68 (br s, 1H), 4.54 (br s, 1H), 3.42 (s, 3H), 3.26-3.20 (m, 1H), 1.25 (d, J = 6.9 Hz, 6H), 0.90 (s, 9H), 0.02 (s, 6H).

Step C: 4-fluoro-2'-(hydroxymethyl)-5-isopropyl-2-methoxy-4'-(trifluoromethyl)bibenyl-3-ol
tert-Butylammonium fluoride (1M in THF, 179 μL, 0.179 mmol) was added dropwise to a stirred solution of 2'-([(tert-butyldimethylsilyloxy)methyl]-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)bibenyl-3-ol (76.8 mg, 0.163 mmol) in THF (2 mL) at 0 °C and the reaction was allowed to warm to room temperature overnight. Saturated NH4Cl (10 ml) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na2SO4) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-40% EtOAc in hexanes gradient) to afford 4-fluoro-2'-(hydroxymethyl)-5-isopropyl-2-methoxy-4'-(trifluoromethyl)bibenyl-3-ol. Rf = 0.26 (20% EtOAc in hexanes). 1H NMR (600 MHz, CDCl3) δ 7.85 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.53 (d, J = 7.7 Hz, 1H), 4.50 (br s, 1H), 4.47 (s, 1H), 3.42 (s, 3H), 3.25-3.19 (m, 1H), 1.24 (br s, 6H).

Step D: 2'-(bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)bibenyl-3-ol
A solution of triphenylphosphine (102.8 mg, 0.392 mmol) in dry CH2Cl2 (2 mL) was added by cannula to a stirred solution of carbon tetrabromide (130 mg, 0.392 mmol) and 4-fluoro-2'
(hydroxymethyl)-5-isopropyl-2-methoxy-4'-((trifluoromethyl)biphenyl-3-ol (58.5 mg, 0.163 mmol) in dry CH₂Cl₂ (2 mL) at 0 °C under N₂ and the reaction was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-40% EtOAc in hexanes gradient) to afford 2'-(bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-((trifluoromethyl)biphenyl-3-ol. R_f = 0.55 (20% EtOAc in hexanes). ¹H NMR (600 MHz, CDCl₃) δ 7.84 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 5.59 (s, 1H), 4.50 (d, J = 9.6 Hz, 1H), 4.39 (d, J = 9.7 Hz, 1H), 3.47 (s, 3H), 3.29-3.23 (m, 1H), 1.27 (d, J = 6.9 Hz, 6H).

Step E: 2-[(2'-bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-((trifluoromethyl)biphenyl-3-yl)oxy]tetrahydro-2H-pyran

3,4-Dihydro-2H-pyran (51.9 mg, 56 µL, 0.617 mmol) was added to a stirred solution of p-toluenesulfonic acid (2.3 mg, 0.0123 mmol) and 2'-(bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-((trifluoromethyl)biphenyl-3-ol (52.0 mg, 0.123 mmol) in dry CH₂Cl₂ (6.1 mL) at room temperature under N₂ and the reaction was stirred overnight. The reaction mixture was diluted with CH₂Cl₂ (45 mL) and washed with saturated NaHCO₃ (5 mL) and 30% saturated Na₂SO₃ (5 mL), dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-40% EtOAc in hexanes gradient) to afford 2-[(2'-bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-((trifluoromethyl)biphenyl-3-yl)oxy]tetrahydro-2H-pyran. R_f = 0.59 (20% EtOAc in hexanes). ¹H NMR (600 MHz, CDCl₃) δ 7.82 (s, 1H), 7.60 (d, J = 7.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 5.77 (s, 1H), 4.97 (dd, J = 4.9, 2.9 Hz, 1H), 4.49 (d, J = 9.8 Hz, 1H), 4.37 (d, J = 9.8 Hz, 1H), 3.89-3.87 (m, 1H), 3.61-3.49 (m, 1H), 3.46 (s, 3H), 3.27-3.21 (m, 1H), 1.89-1.83 (m, 1H), 1.78-1.70 (m, 1H), 1.64-1.48 (m, 1H), 1.26 (d, J = 6.8 Hz, 6H).

Step F: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4'-fluoro-3'-hydroxy-5'-isopropyl-2'-methoxy-4'-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

Sodium hydride (60% dispersion in mineral oil, 14.7 mg, 0.368 mmol) was added to a stirred solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (57.7 mg, 0.184 mmol) in dry THF (2 mL) at room temperature. After 30 min a solution of 2'-(bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)biphenyl-3-ol (62.0 mg, 0.123 mmol) in dry THF (2 mL) was added by cannula and the reaction mixture was stirred overnight. Saturated NH₄Cl (10 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by flash chromatography (Si, 12 x 160 mm, 0-40% EtOAc in hexanes gradient) to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4'-fluoro-3'-hydroxy-5'-isopropyl-2'-methoxy-4'-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one. R_f = 0.25 (20% EtOAc in hexanes). LCMS calc. = 654.2; found = 654.2 (M+1)++. ¹H NMR (500 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 7.86 (m, 1H), 7.73-7.63 (m, 4H) 7.44 (m, 1H), 6.55
(d, J = 7.6 Hz, 0.5H), 6.52 (d, J = 7.7 Hz, 0.5H), 5.71 (br s, 1H), 5.60 (d, J = 8.0 Hz, 0.5H), 5.54 (d, J = 8.0 Hz, 0.5H), 4.87 (d, J = 16.0 Hz, 0.5H), 4.72 (d, J = 16.1 Hz, 0.5H), 4.23 (d, J = 16.1 Hz, 0.5H), 3.98 (d, J = 15.9 Hz, 0.5H), 3.93-3.85 (m, 0.5H), 3.77-3.71 (m, 0.5H), 3.51 (s, 1.5H), 3.47 (s, 1.5H), 3.25-3.17 (m, 1H), 1.26-1.18 (m, 6H), 0.58 (d, J = 6.5 Hz, 1.5H), 0.38 (d, J = 6.6 Hz, 1.5H).

EXAMPLE 284

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-2',3'-dihydroxy-5'-isopropyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

Boron tribromide (17.4 mg, 6.6 µL, 0.0692 mmol) was added to a stirred solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-3'-hydroxy-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one (22.6 mg, 0.0346 mmol) in dry CH₂Cl₂ (1 mL) at -78 ℃ at room temperature under N₂ and the reaction was stirred for 8 h. The reaction was diluted with water (5 mL) and extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give the crude product. This was purified by chiral HPLC (IA column, 20 x 250 mm, 15% i-PrOH in heptane) to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-2',3'-dihydroxy-5'-isopropyl-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one. Rᶠ = 0.24 (20% EtOAc in hexanes). LCMS calc. = 640.2; found = 640.2 (M+1)⁺. ¹H NMR (600 MHz, CDCl₃, 1:1 mixture of atropisomers) δ 7.85 (s, 1H), 7.70-7.62 (m, 4H), 7.41 (m, 1H), 6.52 (s, 0.5H), 6.51 (s, 0.5H), 6.20 (br s, 2H), 5.65 (d, J = 7.9 Hz, 0.5H), 5.38 (d, J = 8.0 Hz, 0.5H), 5.00 (d, J = 15.5 Hz, 0.5H), 4.92 (d, J = 15.6 Hz, 0.5H), 4.15 (d, J = 15.5 Hz, 0.5H), 4.02 (d, J = 15.6 Hz, 0.5H), 3.88 (t, J = 6.7 Hz, 0.5H), 3.77 (t, J = 6.7 Hz, 0.5H), 3.19-3.13 (m, 1H), 1.26-1.17 (m, 6H), 0.59 (d, J = 6.1 Hz, 1.5H), 0.48 (d, J = 6.2 Hz, 1.5H).
INTERMEDIATE 20

\[
\text{\begin{center}
\includegraphics[width=0.2\textwidth]{image}
\end{center}}
\]

**Step A: 2-(2-fluoro-3,4-dimethoxyphenyl)propan-2-ol**

A solution of methylmagnesium chloride (3M in THF, 1.74 mL, 5.22 mmol) was added dropwise to a stirred solution of 1-(2-fluoro-3,4-dimethoxyphenyl)ethanone (J. Chem. Soc. Perkin Trans. 2 1994, 547-555) (646 mg, 3.26 mmol) in heptane (3.1 mL) and THF (1.4 mL) at -20 °C under N₂. The reaction was allowed to warm to room temperature and was stirred for 4 h. 50% Saturated NH₄Cl (20 mL) was added and the mixture was extracted with EtOAc (3 x 20 mL). The combined extracts were dried (Na₂SO₄) and concentrated in vacuo to give 2-(2-fluoro-3,4-dimethoxyphenyl)propan-2-ol as a colorless oil. LCMS calc. = 197.1; found = 197.1 (M-OH)⁺.

\(^1\)H NMR (600 MHz, CDCl₃) δ 7.14 (t, J = 8.8 Hz, 1H), 6.61 (dd, J = 8.8, 1.4 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.56-2.25 (br s, 1H), 1.58 (s, 6H).

**Step B: 2-fluoro-1-isopropyl-3,4-dimethoxybenzene**

A suspension of 10% palladium on carbon (69.8 mg) in a solution of 2-(2-fluoro-3,4-dimethoxyphenyl)propan-2-ol (698 mg, 3.26 mmol) in 5N HCl (0.7 mL) and EtOH (5.6 mL) was stirred at room temperature under H₂ (15 psi) overnight. The mixture was filtered through a plug of Celite and washed with EtOAc (~75 mL). The filtrate was washed with 50% saturated brine (10 mL), dried (MgSO₄) and concentrated in vacuo to afford 2-fluoro-1-isopropyl-3,4-dimethoxybenzene.

\(^1\)H NMR (500 MHz, CDCl₃) δ 6.86 (t, J = 8.3 Hz, 1H), 6.63 (dd, J = 8.7, 1.5 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.19-3.11 (m, 1H), 1.22 (d, J = 6.8 Hz, 6H).

**Step C: 1-bromo-3-fluoro-2-isopropyl-4,5-dimethoxybenzene**

Bromine (80.6 mg, 26 µL, 0.504 mmol) was added to a solution of 2-fluoro-1-isopropyl-3,4-dimethoxybenzene (50.0 mg, 0.252 mmol) and potassium acetate (49.5 mg, 0.504 mmol) in acetic acid (1 mL) at room temperature and the reaction was stirred overnight. The reaction was diluted with water (10 mL) and saturated Na₂SO₃ (10 mL), then extracted with EtOAc (3 x 20 mL). The combined extracts were washed with saturated NaHCO₃ (2 x 10 mL), dried (MgSO₄) and concentrated in vacuo to afford 1-bromo-3-fluoro-2-isopropyl-4,5-dimethoxybenzene.

\(^1\)H NMR (600 MHz, CDCl₃) δ 6.86 (d, J = 2.0 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.43-3.34 (m, 1H), 1.31-1.29 (dd, J = 7.1, 1.4 Hz, 6H).

Following the general procedures outlined above, the compounds in Table 14 were prepared:
Table 14

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EXAMPLE 289
5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5'- (difluoromethyl)-2'-methoxy-4- (trifluoromethyl)biphenyl-2-yl)methyl]-1,3-oxazolidin-2-one

Step A: 2'-(5-[3,5-bis(trifluoromethyl)phenyl]-2-oxo-1,3-oxazolidin-3-yl)methyl)-6-methoxy-4'-(trifluoromethyl)biphenyl-3-carbaldehyde

A mixture of 5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one (Example 66, 50 mg; 0.0858 mmol), 5-formyl-2-methoxyphenyl boronic acid (46 mg; 0.257 mmol), tetrakis(triphenylphosphine)palladium (0) (12 mg; 0.0103 mmol), and sodium carbonate (74 mg) in benzene/ethanol/water (2.8/0.4/1.2 mL) was heated at reflux for 60 h. The reaction was diluted with EtOAc (30 mL) and washed successively with H2O (10 mL) and brine (10 mL), dried over MgSO4, filtered, and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (0-50% EtOAc/hexanes gradient) to afford 2'-(5-[3,5-bis(trifluoromethyl)phenyl]-2-oxo-1,3-oxazolidin-3-yl)methyl)-6-methoxy-4'-(trifluoromethyl)biphenyl-3-carbaldehyde as a yellow oil. LCMS = 592.1 (M+1)+. 1H NMR (CDCl3, 500 MHz, mixture of atropisomers): δ 9.98 (s, 1 H), 7.99-7.96 (m, 1 H), 7.90 (s, 1 H), 7.75 (s, 2 H), 7.69-7.64 (m, 2 Hz), 7.53 (s, 1 H), 7.41-7.38 (m, 1 H), 7.17-7.14 (m, 1 H), 5.37 (t, J = 8.2 Hz, 1 H), 4.59 (d, J = 15.3 Hz, 1 H), 4.37 (d, J = 15.6 Hz, 1 H), 3.92 (s, 3 H), 3.67-3.64 (m, 1 H), 3.19-3.16 (m, 1 H).

Step B: 5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5'-(difluoromethyl)-2'-methoxy-4- (trifluoromethyl)biphenyl-2-yl)methyl]-1,3-oxazolidin-2-one

Diethylaminosulfur trifluoride (22 μL, 0.1675 mmol) was added dropwise to a stirred solution of 2'-(5-[3,5-bis(trifluoromethyl)phenyl]-2-oxo-1,3-oxazolidin-3-yl)methyl)-6-methoxy-4'-(trifluoromethyl)biphenyl-3-carbaldehyde (Step A, 50 mg, 0.0838 mmol) in CH2Cl2 (1 mL) at 0°C. The reaction stirred at room temperature for 14 h. The reaction was quenched with H2O at 0°C, diluted with CH2Cl2 (10 mL), washed with H2O (10 mL) and brine (10 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (0-25% EtOAc/hexanes gradient) to afford 5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5'-(difluoromethyl)-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-1,3-oxazolidin-2-one as a clear glass. LCMS = 594.2 (M - 19)+. 1H NMR (benzene-d6, 500 MHz, mixture of
atropisomers): δ 7.64 (s, 1 H), 7.38-7.36 (m, 2 H), 7.30-7.26 (m, 2 H), 7.14-7.11 (m, 2 H), 6.85 (d, J = 8 Hz, 1 H), 6.45 (d, J = 8.5 Hz, 1 H), 6.37-6.13 (m, 1 H), 4.46-4.38 (m, 2 H), 3.79-3.76 (m, 1 H), 3.21 (s, 3 H), 2.36 (t, J = 8.7 Hz, 1 H), 2.05 (t, J = 8.4 Hz, 1 H).

This compound was separated into its enantiomers (5S)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5’-(difluoromethyl)-2’-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one and (5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[5’-(difluoromethyl)-2’-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one using chiral HPLC (15% IPA/heptane, AS column).

EXAMPLE 290

5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2’-methoxy-4,5’-bis(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one

Step A: 2-iodo-1-methoxy-4-(trifluoromethyl)benzene

To a stirred solution of 2-methoxy-5-(trifluoromethyl)aniline (500 mg, 2.62 mmol) in CH₂Cl₂ (10 mL) was added r-butyl nitrite (467 µL, 3.93 mmol). The reaction was stirred for 5 min prior to addition of iodine (1.3 g, 5.24 mmol), and then heated at 70°C for 2 h. The reaction was cooled, diluted with CH₂Cl₂ (10 mL), washed with sat. Na₂SO₄ (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (hexanes) to afford 2-iodo-1-methoxy-4-(trifluoromethyl)benzene as a light yellow solid. ¹H NMR (CDCl₃, 500 MHz): δ 8.05 (d, J = 2 Hz, 1 H), 7.61 (dd, J = 8.7, 1.8 Hz, 1 H), 6.89 (d, J = 8.7 Hz, 1 H), 3.97 (s, 3 H).

Step B: [2-methoxy-5-(trifluoromethyl)phenyl]boronic acid

n-Butyl lithium (1.6M in hexanes, 456 µL, 0.729 mmol) was added dropwise to a stirred solution of 2-iodo-1-methoxy-4-(trifluoromethyl)benzene (Step A, 200 mg, 0.662 mmol) in THF (1.5 mL) at -78°C under an atmosphere of nitrogen. The reaction stirred at -78°C for 30 min prior to the addition of triisopropyl borate (458 µL, 1.986 mmol). The reaction stirred an additional 2 h at -78°C and was quenched with sat. NH₄Cl. The mixture was extracted with CH₂Cl₂ and the
organic phase was washed with NaHCO₃ (15 mL) and brine (15 mL), dried (Na₂SO₄), filtered, conc. in vacuo to afford [2-methoxy-5-(trifluoromethyl)phenyl] boronic acid which was carried on without purification.

Step C: 5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-methoxy-4,5'-bis(trifluoromethyl)-biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one

5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-1,3-oxazolidin-2-one (Example 66, 100 mg; 0.171 mmol) was treated with [2-methoxy-5-(trifluoromethyl)phenyl] boronic acid (Step B, 113 mg; 0.514 mmol), tetrakis(triphenylphosphine)palladium (0) (24 mg; 0.0206 mmol), and sodium carbonate (148 mg) as described in Example 291 to afford 5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-methoxy-4,5'-bis(trifluoromethyl)-biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one as a clear glass. LCMS = 612.1 (M-19)⁺. ¹H NMR (benzene-d₆, 500 MHz, mixture of atropisomers): δ 7.61 (s, 1H), 7.40-7.36 (m, 1H), 7.31 (s, 1 H), 7.27-7.23 (m, 4 H), 6.74-6.72 (m, 1 H), 6.35 (d, J = 8.7 Hz, 1 H), 4.42-4.32 (m, 2 H), 3.70 (d, J = 15.8 Hz, 1 H), 3.14 (s, 3 H), 2.28 (t, J = 8.7 Hz, 1 H), 1.98 (t, J = 8.2 Hz, 1 H). This compound was separated into its enantiomers (5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-methoxy-4,5'-bis(trifluoromethyl)-biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one and (5S)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-methoxy-4,5'-bis(trifluoromethyl)-biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one using chiral HPLC (5% EtOH/heptane, AS column).

![Intermediate 21](image-url)

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (400 mg, 1.28 mmol) was treated with NaH (60% in oil, 128 mg, 3.2 mmol) and 2-(bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (Example 70, 466 mg, 1.28 mmol) as described in Example 66 to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one as a white solid. LCMS = 598.0 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz): δ 8.06 (d, J = 8.2 Hz, 1 H), 7.93 (s, 1 H), 7.82 (s, 2 H), 7.61 (s, 1 H), 7.33 (dd, J = 8.2, 1.4 Hz, 1
H), 5.79 (d, J = 7.8 Hz, 1 H), 4.91 (d, J = 16 Hz, 1 H), 4.40 (d, J = 16 Hz, 1 H), 4.16-4.06 (m, 1 H), 0.83 (d, J = 6.4 Hz, 3 H).

EXAMPLE 291

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(2-methoxy-5-methyl-3-thienyl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

Step A: 3,5-dibromo-2-methoxythiophene

To a stirred solution of 2-methoxythiophene (1 g, 8.76 mmol) in CH₂Cl₂ (18 mL) at 0°C was added N-bromosuccinimide (3.12 g, 17.52 mmol) slowly. The reaction was allowed to warm to room temperature and stirred for 14 h. The reaction was cooled in an ice bath and filtered. The filtrate was washed with sat. NaHCO₃ (2 x 25 mL). The aqueous layer was neutralized with 1N HCl and extracted with CHCl₃ (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried (Na₂SO₄), filtered and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (hexanes) to afford 3,5-dibromo-2-methoxythiophene as a pale pink oil. LCMS = 272.9 (M+)⁺.

Step B: 3-bromo-2-methoxy-5-methylthiophene

n-Butyl lithium (2.0M in pentane, 0.97 mL, 1.93 mmol) was added to a stirred solution of 3,5-dibromo-2-methoxythiophene (Step A, 500 mg, 1.84 mmol) in THF (5 mL) at -78°C under an atmosphere of N₂. The reaction stirred at -78°C for 1 h prior to addition of methyl iodide (114 µL, 1.84 mmol). The reaction was allowed to warm to room temperature and stirred for 20 h. The solvent was removed under reduced pressure and the residue was partitioned between EtOAc (15 mL) and H₂O (15 mL). The aqueous layer was re-extracted with ether (2 x 15 mL) and the combined organic layers were washed with H₂O (15 mL) and brine (15 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (hexanes) to afford 3-bromo-2-methoxy-5-methylthiophene as a yellow oil. ¹H NMR (CDCl₃, 500 MHz): δ 6.44 (s, 1 H), 3.95 (s, 3 H), 2.41 (s, 3 H).

Step C: (2-methoxy-5-methyl-3-thienyl)boronic acid
A stirred mixture of 3-bromo-2-methoxy-5-methylthiophene (Step B, 296 mg, 1.43 mmol) and triisopropyl borate (396 µL, 2.15 mmol) in toluene/THF (2.3/0.6 mL) was cooled to -70°C under an atmosphere of N₂. n-Butyl lithium (2.0M in pentane, 1.07 mL, 2.15 mmol) was added dropwise via a syringe pump over 1 h. The reaction stirred at -70°C for 40 min more and was quenched with 2N HCl (2 mL) at -20°C. The reaction was partitioned between EtOAc (15 mL) and H₂O (15 mL). The aqueous layer was extracted with EtOAc (10 mL); the combined organic layers were washed with brine (15 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo to afford (2-methoxy-5-methyl-3-thienyl)boronic acid as a yellow oil. This material was used without further purification.

Step D: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(2-methoxy-5-methyl-3-thienyl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (Intermediate 21, 13 mg; 0.0219 mmol) was treated with (2-methoxy-5-methyl-3-thienyl)boronic acid (Step C, 10.4 mg; 0.0657 mmol), tetrakis(triphenylphosphine)palladium (0) (3 mg; 0.0026 mmol), and sodium carbonate (20 mg) as described in Example 291 to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-(2-methoxy-5-methyl-3-thienyl)-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one as a yellow glass. LCMS = 598.2 (M+1)+. ¹H NMR (benzene-d₆, 500 MHz): δ 7.75 (s, 1 H), 7.57 (s, 1 H), 7.31-29 (m, 1H), 7.24 (s, 2 H), 7.12-7.10 (m, 1 H), 6.14 (s, 1 H), 4.96 (d, J = 16 Hz, 1 H), 4.57 (d, J = 8 Hz, 1 H), 3.99 (d, J = 15.8 Hz, 1 H), 3.30 (s, 3 H), 2.95-2.92 (m, 1 H), 2.05 (s, 3 H), -0.28 (d, J = 6.7 Hz, 3 H).

Following the general procedures outlined above, the compounds in Table 15 were prepared:

Table 15

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<td>608.1 (M-19)+</td>
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EXAMPLE 298

(4S,5R)-5-[(3,5-bis(trifluoromethyl)phenyl)-3-[(4'-fluoro-2'-methoxy-5'-(2-methyl-1,3-dioxolan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4,1,3-oxazolidin-2-one

A mixture of (4S,5R)-5-[(3,5-bis(trifluoromethyl)phenyl)-3-[(2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one (Intermediate 21, 7.34 g, 12.29 mol), [4-fluoro-2-methoxy-5-(2-methyl-1,3-dioxolan-2-yl)phenyl]boronic acid (5.5 g, 21.48 mol), tetrakis(triphenylphosphine)palladium (0) (1.7 g; 1.47 mol), and sodium carbonate (10 g) in
benzene/EtOH/H₂O (203/29/86 mL) was heated at reflux for 14 h. The reaction was quenched with H₂O and partitioned between EtOAc (250 mL) and H₂O (75 mL). The aqueous layer was re-extracted with EtOAc (3 x 200 mL). The combined extracts were washed with brine (100 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (0-25% EtOAc/hexanes gradient) to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{{4'-fluoro-2'-methoxy-5'-(2-methyl-1,3-dioxolan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl}methyl}-4,1,3-oxazolidin-2-one as an amorphous solid. LCMS = 682.2 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz, mixture of atropisomers): δ 7.86 (s, 1 H), 7.71 (S, 3 H), 7.65-7.61 (m, 1 H), 7.37-7.34 (m, 1 H), 7.32-7.28 (m, 1 H), 6.75 (dd, J = 12.4, 3.6 Hz, 1H), 5.58 (d, J = 8.1 Hz, 1 H), 4.89 (d, J = 15.8 Hz, 1 H), 4.08-4.04 (m, 2 H), 3.91-3.76 (m, 7 H), 1.73 (d, J = 10.5 Hz, 3 H), 0.4 (d, J = 6.5 Hz, 3 H).

EXAMPLE 299

![Chemical Structure](attachment:image)

(4S,5R)-3-{{5'-acetyl-4'-fluoro-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

To a stirred solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{{4'-fluoro-2'-methoxy-5'-(2-methyl-1,3-dioxolan-2-yl)-4-(trifluoromethyl)biphenyl-2-yl}methyl}-4,1,3-oxazolidin-2-one (8 g, 0.0118 mol) in acetone (400 mL) was added p-toluenesulfonic acid acid monohydrate (670 mg, 0.0035 mol). The reaction stirred at room temperature for 14 h. The reaction was partitioned between EtOAc (250 mL) and sat. NaHCO₃ (250 mL). The aqueous layer was re-extracted with EtOAc (3 x 250 mL) and the combined organic layers were washed with brine (200 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (0-25% EtOAc/hexanes gradient) to afford (4S,5R)-3-{{5'-acetyl-4'-fluoro-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl}methyl}-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one as a yellow solid. LCMS = 638.2 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz, mixture of atropisomers): δ 7.87 (s, 1 H), 7.81-7.79 (m, 1 H), 7.74 (s, 1 H), 7.70 (s, 2 H), 7.59 (s, 1 H), 7.39 (d, J = 8 Hz, 1 H), 6.80 (d, J = 12.8 Hz, 1 H),
5.27 (d, J = 8.2 Hz, 1 H), 4.97 (d, J = 15.3 Hz, 1 H), 4.04 (d, J = 15.5 Hz, 1 H), 3.94 (s, 3 H),
3.72-3.66 (m, 1 H), 2.67-2.64 (m, 3 H), 0.62 (d, J = 6.4 Hz, 3 H).

**EXAMPLE 300**

![Chemical Structure](image_url)

**(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropenyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one**

Methyl magnesium iodide (29 µL, 0.085 mmol) was added dropwise to a solution of (4S,5R)-3-
[[5'-acetyl-4'-fluoro-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-[3,5-
bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (30 mg, 0.047 mmol) in diethyl ether
(2 mL) at room temperature. The reaction was carefully heated at reflux 4 h. Additional methyl
magnesium iodide (63 µL, 0.19 mmol) and ether (1 mL) was added and the reaction was refluxed
for 3 h. The reaction was quenched with sat. NH₄Cl and extracted with EtOAc (3 x 25 mL). The
combined extracts were washed with brine (25 mL), dried (Na₂SO₄), filtered, and concentrated in
vacuo. The crude product was purified by flash silica gel chromatography (0-25%
EtOAc/hexanes gradient) to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'
isopropenyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-
one as a clear glass. L CMS = 636.3 (M+1). ¹H NMR (benzene-d₆, 500 MHz, mixture of
atropisomers): δ 7.59 (s, 1 H), 7.55 (s, 1 H), 7.35 (d, J = 8 Hz, 1 H), 7.30-7.27 (m, 2 H), 6.99-
6.96 (m, 2 H), 6.45 (d, J = 12.9 Hz, 1 H), 5.32 (d, J = 16.9 Hz, 1 H), 5.16-5.15 (m, 1 H), 4.90 (d,
J = 16.3 Hz, 1 H), 4.48 (d, J = 7.7 Hz, 1 H), 3.70 (d, J = 6.4 Hz, 1 H), 3.16 (s, 3 H), 2.85-2.79
(m, 1 H), 2.12 (s, 3 H), -0.025 (d, J = 6.5 Hz, 3 H).

**EXAMPLE 301**
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4'-fluoro-2'-hydroxy-5'-isopropenyl-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a stirred solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4'-fluoro-5'-isopropenyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one (Example 300, 50 mg, 0.078 mmol) in DMF (450 µL) was added lithium chloride (13.4 mg, 0.315 mmol). The vial was sealed and the reaction was heated at 160°C for 14 h. 10% NaOH (10 mL) was added and the resultant solution was extracted with ether (3 x 10 mL). The aqueous layer was acidified to pH~3 with 3N HCl and was re-extracted with ether (3 x 25 mL). The combined organic extracts were washed with brine (25 mL), dried (MgSO₄), filtered, and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (0-25% EtOAc/hexanes gradient) to afford (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4'-fluoro-2'-hydroxy-5'-isopropenyl-4-(trifluoromethyl)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one as a clear glass. LCMS = 622.1 (M+1)+. 1H NMR (CDCl₃, 500 MHz, mixture of atropisomers): δ 7.90 (s, 1 H), 7.76-7.70 (m, 4 H), 7.48-7.45 (m, 1 H), 7.11-7.07 (m, 1 H), 6.75 (d, J = 11.7 Hz, 1 H), 5.71 (d, J = 7.8 Hz, 1 H), 5.59-5.56 (m, 1 H), 5.25-5.21 (m, 2 H), 4.81 (d, J = 15.4 Hz, 1 H), 4.04 (d, J = 15.6 Hz, 1 H), 3.97-3.92 (m, 1 H), 2.13 (s, 3 H), 0.58 (d, J = 6.6 Hz, 3 H).

EXAMPLE 302
(4S)-4-benzyl-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one.

A stirred suspension of sodium hydride (60% in oil, 37 mg, 0.926 mmol) in THF (1 mL) was treated at 0°C with (S)-4-benzyl-2-oxazolidinone (33 mg, 0.185 mmol) dissolved in THF (1 mL), under an atmosphere of N₂. The reaction was stirred for 20 min and a solution of 2'- (bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)biphenyl (Intermediate 10, 50 mg, 0.124 mmol) in THF (1 mL) was added dropwise. The reaction was stirred at room temperature for 60 h. The reaction was quenched with H₂O (1 mL) and partitioned between EtOAc (25 mL) and H₂O (10 mL). The aqueous phase was re-extracted with EtOAc (3 x 15 mL) and the combined organic extracts were washed with brine (25 mL), dried (MgSO₄) and concentrated in vacuo to give the crude product. This was purified by flash silica-gel chromatography (0-25% EtOAc/hexanes gradient) to afford (4S)-4-benzyl-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-1,3-oxazolidin-2-one as a clear glass. LCMS = 502.3 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz, mixture of atropisomers) δ 7.69-7.64 (m, 1H), 7.58 (s, 1H), 7.39-7.36 (m, 1H), 7.29-7.24 (m, 3H), 7.06 (d, J = 8.5 Hz, 1H), 6.97-6.91 (m, 2H), 6.73 (d, J = 11.7, 1H), 4.79 (d, J = 15.8 Hz, 1H), 4.30 (d, J = 15.8 Hz, 1H), 4.08-4.05 (m, 1H), 3.99-3.97 (m, 1H), 3.76 (s, 3H), 3.65-3.58 (m, 1H), 3.27-3.17 (m, 1H), 2.81 (dd, J = 13.5, 4.1 Hz, 1H), 2.45-2.40 (m, 1H), 1.30-1.4 (m, 6H).

**EXAMPLE 303**

![Chemical Structure](image)

(4S)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-(4-methylbenzyl)-1,3-oxazolidin-2-one

Step A: (2S)-2-amino-3-(4-methylphenyl)propan-1-ol

A mixture of lithium aluminum hydride (254 mg, 6.696 mmol) in THF (20 mL) was heated at reflux for 1 h, then cooled in an ice bath. (S)-4-Methylphenylalanine (500 mg, 2.79 mmol) was added portionwise and the resultant mixture was heated at reflux for 14 h. The excess lithium aluminum hydride was decomposed by successive addition of H₂O (1 mL), 10% aq NaOH (10 mL) and H₂O (2.5 mL). The mixture was filtered and the solid was washed with THF. The filtrate was concentrated in vacuo and the residue was dissolved in CHCl₃ (50 mL), washed with
5% aq. NaOH (25 mL), H₂O (25 mL) and brine (25 mL), dried (MgSO₄), filtered, and concentrated in vacuo to afford (2S)-2-amino-3-(4-methylphenyl)propan-1-ol as an off-white solid. ¹H NMR (CD₃OD, 500 MHz) δ 7.13-7.09 (m, 4H), 3.52 (dd, J = 10.7, 4.6 Hz, 1H), 3.36 (dd, J = 10.7, 6.9 Hz, 1H), 3.04-2.99 (m, 1 H), 2.73 (dd, J = 13.5, 6.2 Hz, 1H), 2.53 (dd, J = 13.5, 7.7 Hz, 1H), 2.30 (s, 3 H).

Step B: (4S)-4-(4-methylbenzyl)-1,3-oxazolidin-2-one
A stirred solution of (2S)-2-amino-3-(4-methylphenyl)propan-1-ol (Step A, 460 mg, 2.79 mmol) in CH₂Cl₂ (20 mL) at 0°C was treated with diisopropylethylamine (2.92 mL, 16.74 mmol) and triphosgene (414 mg, 1.39 mmol) under an atmosphere of N₂. The reaction stirred at 0°C for 3 h. The reaction was quenched with sat. NaHCO₃ (10 mL) and extracted with EtOAc (4 x 20 mL). The combined organic layers were washed with brine (25 mL), dried (MgSO₄), filtered and concentrated in vacuo. The crude product was purified by flash silica gel chromatography (0-70% EtOAc/hexanes gradient) to afford (4S)-4-(4-methylbenzyl)-1,3-oxazolidin-2-one as a white solid. LCMS = 192.2 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.17 (d, J = 8 Hz, 2 H), 7.09 (d, J = 7.7 Hz, 2 H), 5.39 (br s, 1 H), 4.48 (t, J = 8.4 Hz, 1 H), 4.37 (dd, J = 8.6, 5.6 Hz, 1 H), 4.11-4.06 (m, 1 H), 3.86 (d, J = 7.1 Hz, 2 H), 2.36 (s, 3 H).

Step C: (4S)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl[methyl]-4-(4-methylbenzyl)-1,3-oxazolidin-2-one
(4S)-4-(4-methylbenzyl)-1,3-oxazolidin-2-one (Step B, 14 mg, 0.074 mmol) was treated with sodium hydride (60% in oil, 6.2 mg, 0.154 mmol) and 2'-(bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)biphenyl (Intermediate 10, 25 mg, 0.062 mmol) as described in Example 305 to afford (4S)-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl[methyl]-4-(4-methylbenzyl)-1,3-oxazolidin-2-one as clear gum. LCMS = 516.4 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz, mixture of atropisomers) δ 7.65-7.60 (m, 1 H), 7.53 (s, 1 H), 7.35-7.32 (m, 1 H), 7.06-7.20 (m, 2 H), 6.82-6.75 (m, 2 H), 6.69 (d, J = 11.7 Hz, 1 H), 4.67 (d, J = 15.8 Hz, 1 H), 4.06 (d, J = 15.8 Hz, 1 H), 3.96-3.93 (m, 1 H), 3.73 (s, 3 H), 3.55-3.48 (m, 1 H), 3.23-3.15 (m, 1 H), 2.63 (dd, J = 13.5, 3.6 Hz, 1 H), 2.35 (d, J = 13.5 Hz, 1 H), 2.29 (s, 3 H), 1.25-1.13 (m, 6 H).

Following the general procedures outlined above, the compounds in Table 16 were prepared:

Table 16
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(4S,5S)-4-benzyl-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl) biphenyl-2-yl]methyl]-5-methyl-1,3-oxazolidin-2-one

**Step A: tert-butyl[(S)-1-benzyl-2-oxopropyl]carbamate**

A stirred solution of \(N\)-(tert-butoxycarbonyl)-\(N\)-methoxy-\(N\)-methyl-L-phenylalaninamide (500 mg, 1.62 mmol) in THF (3 mL) at -15°C was treated with methyl magnesium bromide (540μL, 1.62 mmol) under an atmosphere of N₂. The reaction stirred at -15°C for 15 min prior to dropwise addition of methyl magnesium bromide (1.08 mL, 3.24 mmol). The reaction stirred for
14 h at room temperature and was quenched with 1N HCl (5 mL). The mixture was partitioned between H$_2$O (15 mL) and EtOAc (20 mL) and the aqueous layer was re-extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with H$_2$O (20 mL) and brine (20 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by flash silica gel chromatography to afford tert-butyl[1(S)-1-benzyl-2-oxopropyl]carbamate as a white solid. LCMS = 164.2 (M-BOC)$^+$. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.34-7.26 (m, 3H), 7.18 (d, $J = 7.1$ Hz, 2H), 5.15 (br s, 1H), 4.59-4.56 (m, 1H), 3.14-2.99 (m, 2H), 2.16 (s, 3H), 1.44 (s, 9H).

**Step B: tert-butyl[1(S)-1-benzyl-2-hydroxypropyl]carbamate**

A stirred solution of tert-butyl[1(S)-1-benzyl-2-oxopropyl]carbamate (Step A, 150 mg, 0.57 mmol) in dry MeOH (5 mL) at -20°C was treated with sodium borohydride (44.2 mg, 1.169 mmol). The reaction stirred at -20°C for 1 h and was quenched with H$_2$O (1 mL) and concentrated in vacuo. The residue was dissolved in EtOAc (25 mL) and washed sequentially with H$_2$O (15 mL) and brine (15 mL), dried (Na$_2$SO$_4$), filtered and concentrated in vacuo. The crude product was purified by preparatory thin-layer chromatography, eluting with 15% acetone/hexanes to afford tert-butyl[(1S,2R)-1-benzyl-2-hydroxypropyl]carbamate (45 mg) and tert-butyl[(1S,2S)-1-benzyl-2-hydroxypropyl]carbamate as white solids. tert-butyl[(1S,2R)-1-benzyl-2-hydroxypropyl]carbamate: LCMS = 166.2 (M-BOC)$^+$. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.34-7.31 (m, 2H), 7.26-7.23 (m, 3H), 4.81 (br s, 1H), 3.83 (dq, $J = 6.4$, 2.7 Hz, 1H), 3.71-3.69 (m, 1H), 2.90 (d, $J = 7.3$ Hz, 2H), 1.43 (s, 9H), 1.22 (d, $J = 6.5$ Hz, 3H). tert-butyl[(1S,2S)-1-benzyl-2-hydroxypropyl]carbamate: LCMS = 166.2 (M-BOC)$^+$. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 7.34-7.31 (m, 2H), 7.26-7.23 (m, 3H), 4.58 (br s, 1H), 3.393-3.85 (m, 2H), 2.90 (dd, $J = 14.2$, 5 Hz, 1H), 2.82-2.73 (m, 1H), 1.40 (s, 9H), 1.25 (d, $J = 6.4$ Hz, 3H).

**Step C: (4S,5S)-4-benzyl-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-5-methyl-1,3-oxazolidin-2-one**

tert-butyl[(1S,2R)-1-benzyl-2-hydroxypropyl]carbamate (Step B, 39 mg, 0.148 mmol) was treated with sodium hydride (60% in oil, 12 mg, 0.309 mmol) and 2'-bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)biphenyl (Intermediate 10, 50 mg, 0.123 mmol) as described in Example 305 to afford (4S,5S)-4-benzyl-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-5-methyl-1,3-oxazolidin-2-one as a clear glass. LCMS = 516.4 (M+1)$^+$. $^1$H NMR (CDCl$_3$, 500 MHz, mixture of atropisomers) $\delta$ 7.68 (d, $J = 11.5$ Hz, 1H), 7.66-7.63 (m, 1H), 7.39-7.36 (m, 1H), 7.28-7.23 (m, 3H), 7.07 (d, $J = 8.5$ Hz, 1H), 6.94 (d, $J = 6.9$ Hz, 2H), 6.73 (d, $J = 4.8$ Hz, 1H), 4.81 (d, $J = 16$ Hz, 1H) 4.38 (d, $J = 16.1$ Hz, 1H), 4.28-4.23 (m, 1H), 3.78 (s, 3H), 3.29-3.17 (m, 2H), 2.81 (dd, $J = 13.3$, 3.9 Hz, 1H), 2.38-2.28 (m, 1H), 1.29-1.13 (m, 6H), 0.98 (d, $J = 6.2$ Hz, 3H).

**EXAMPLE 318**
(4S,5R)-4-benzyl-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-5-methyl-1,3-oxazolidin-2-one

tert-butyl[(1S,2S)-1-benzyl-2-hydroxypropyl]carbamate (Example 317, Step B, 39 mg, 0.148 mmol) was treated with sodium hydride (60% in oil, 12 mg, 0.309 mmol) and 2'-(bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-(trifluoromethyl)biphenyl (Intermediate 10, 50 mg, 0.123 mmol) as described in Example 305 to afford (4S,5R)-4-benzyl-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4'-(trifluoromethyl)biphenyl-2-yl)methyl]-5-methyl-1,3-oxazolidin-2-one as a clear glass. LCMS = 516.4 (M+). 1H NMR (CDCl3, 500 MHz, mixture of atropisomers) δ 7.64-759 (m, 2 H), 7.33-7.30 (m, 1 H), 7.28-7.21 (m, 2 H), 7.16 (s, 1 H), 7.00-6.91 (m, 3 H), 6.67 (d, J = 3 Hz, 1 H), 4.70 (d, J = 2.7 Hz, 1 H), 4.52-4.47 (m, 1 H), 3.95 (d, J = 15.8 Hz, 1 H), 3.70 (s, 3 H), 3.68-3.62 (m, 1 H), 3.24-3.18 (m, 1 H), 2.72-2.53 (m, 2 H), 1.28-1.21 (m, 6H), 1.19 (d, J = 6.8 Hz, 3 H).

EXAMPLE 319

(4R)-4-benzyl-3-[(5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)methyl]-1,3-oxazolidin-2-one.

The title compound was prepared according to the procedure described in Example 67 starting from (R)-4-benzyl-2-oxazolidinone (49 mg, 0.27 mmol) and 2-(bromomethyl)-1-iodo-4-(trifluoromethyl)benzene (100 mg, 0.27 mmol) to afford the title compound as a colorless oil. Rf = 0.35 (15% EtOAc/hexanes). LCMS 484 (M+). 1H NMR (CDCl3, 500 MHz) (atropisomers present) δ 7.72 (br s 1H), 7.65 (br s, 1H), 7.42 (m, 1H), 7.32-7.22 (m, 3H), 7.08 (m, 1H), 6.90-
6.84 (m, 3H), 4.81 (d, J = 15.8 Hz, 1H), 4.35 (d, J = 15.8 Hz), 4.28 (t, J = 8.7 Hz, 1H), 3.96-3.92 (m, 3H), 3.78 (s, 3H), 3.62-3.52 (m, 1H), 2.94-2.86 (m, 1H), 2.82 (dd, J = 9.4, 3.9 Hz, 1H), 2.42 (dd, J = 9.6, 3.9 Hz), 1.26 (s, 3H), 1.10 (s, 3H).

EXAMPLE 320

Example 322 was prepared according to the procedure described in Example 14 starting from (S)-4-benzyl-5,5-dimethyl-2-oxazolidinone (10 mg, 0.05 mmol) and 2-(bromomethyl)-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl (20 mg, 0.05 mmol) to afford the title compound as a colorless oil. LCMS 512 (M+1)^+. 1H NMR (CDCl3, 500 MHz) (atropisomers present) δ 7.72 (br s 1H), 7.31 (br s, 1H), 7.12-7.02 (m, 2H), 6.85-6.82 (m, 3H), 6.45-6.35 (m, 4H), 4.61 (d, J = 15.8 Hz, 1H), 4.21 (d, J = 15.8 Hz), 3.21 (s, 2H), 3.16 (s, 3H), 2.62-2.52 (m, 1H), 2.42-2.18 (m, 1H), 1.98 (m, 2H), 1.22 (d, J = 7.1 Hz), 1.05 (d, J = 7.1 Hz), 0.98 (s, 3H), 0.88 (s, 3H).

EXAMPLE 321

(4R, 5S)-4-[3,5-bis(trifluoromethyl)phenyl]-1-[4'-fluoro-5'-isopropyl]-2'-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]-5-methyl-pyrolidin-2-one

Step A: ethyl 3-[3,5-bis(trifluoromethyl)phenyllacrylate

To a suspension of NaH (60% suspension in oil, 168 mg, 4.96 mmol) in THF (3 mL) was added a solution of triethyl phosphonoacetate (0.5 mL, 2.52 mmol) at 0°C, under an atmosphere of
nitrogen. The reaction was allowed to stir for 30 min at 0°C and 3,5-
bis(trifluoromethyl)benzaldehyde (609 mg, 2.52 mmol) was added. The reaction was allowed to warm to ambient temperature, stirred for an additional 2 h and then concentrated in vacuo. The residue was diluted with EtOAc (20 mL), washed with H₂O, brine, dried over MgSO₄, concentrated and purified by flash chromatography with 10% EtOAc/hexanes to afford the title compound as a white solid. LCMS 313 (M+1)⁺.

Step B. methyl 3-[3,5-bis(trifluoromethyl)phenyl]-4-nitropentanoate
Ethyl 3-[3,5-bis(trifluoromethyl)phenyl]acrylate (170 mg, 0.54 mmol) and nitromethane (736 uL, 10.29 mmol) were treated with a solution of tetrabutylammonium hydroxide (1.0 M solution in MeOH, 1.5 mL) and the mixture heated to reflux for 3 h, diluted with 10% aqueous ammonium chloride (10 mL) and extracted with EtOAC (4 x 30 mL). The combined organic extracts were washed with 10% ammonium chloride (20 mL), dried over MgSO₄, concentrated in vacuo to give the crude product. This was purified by flash chromatography using 10% EtOAC/hexanes to afford methyl 3-[3,5-bis(trifluoromethyl)phenyl]-4-nitropentanoate as a colorless oil. 1H NMR (CDCl₃, 500 MHz) 8 7.82 (br s 1H), 7.64 (br s, 2H), 4.91 (m, 1H), 3.91 (m, 1H), 3.61 (s, 3H), 2.82 (m, 2H), 1.42 (d, J = 6.7 Hz, 3H).

Step C: 4-[3,5-bis(trifluoromethyl)phenyl]-5-methylpyrrolidin-2-one
A suspension of Raney Nickel (50% w/v slurry in H₂O, 200 mg) was added to a solution of methyl 3-[3,5-bis(trifluoromethyl)phenyl]-4-nitropentanoate in absolute EtOH (5 mL) and the resultant mixture was stirred at room temperature overnight under a balloon atmosphere of H₂. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo to remove the EtOH. The residue was purified by flash chromatography using 75% EtOAC/hexanes to afford threo-4-[3,5-bis(trifluoromethyl)phenyl]-5-methylpyrrolidin-2-one and erythro-4-[3,5-bis(trifluoromethyl)phenyl]-5-methylpyrrolidin-2-one as white solids. erythro-diastereomer: LCMS 353 (M+1)⁺. 1H NMR (CDCl₃, 500 MHz) 8 7.82 (br s 1H), 7.64 (br s, 2H), 5.72 (br s, 1H), 3.85 (m, 1H), 3.31 (dd, J = 8.9, 8.2 Hz, 1H), 2.61 (dd, J = 8.9, 8.2 Hz, 1H), 1.34 (d, J = 6.1 Hz, 3H). erythro-diastereomer: LCMS 353 (M+1)⁺. 1H NMR (CDCl₃, 500 MHz) 8 7.82 (br s 1H), 7.64 (br s, 2H), 5.76 (br s, 1H), 4.20 (m, 1H), 3.90 (m, 1H), 2.81 (dd, J = 8.5, 8.2 Hz, 1H), 2.73 (dd, J = 8.5, 8.2 Hz, 1H), 0.88 (d, J = 6.7 Hz, 3H).

Step D: (4R,5S)-4-[3,5-bis(trifluoromethyl)phenyl]-1-{4'-fluoro-5'-isopropyl}-2'-methoxy-4-(trifluoromethyl)bibhphenyl-2-vlmethyl]-5-methyl-pyrrolidin-2-one
To a stirred suspension of NaH (60% in oil, 4.4 mg, 0.11 mmol) in THF (3 mL), was added a solution of erythro-4-[3,5-bis(trifluoromethyl)phenyl]-5-methylpyrrolidin-2-one (16 mg, 0.051 mmol) in THF (1 mL) at 0°C under an atmosphere of nitrogen. The resultant mixture was allowed to stir for 30 min at 0°C before the addition of 2'-bromomethyl)-4-fluoro-5-isopropyl-2-methoxy-4'-{trifluoromethyl}bibhphenyl (16 mg, 0.051 mmol). After 3 h, the reaction was diluted with 15 mL EtOAc and 5 mL H₂O. The phases were separated and the organic phase was
washed with H₂O, brine, dried (MgSO₄), and concentrated. The residue was purified by flash chromatography using 10% EtOAC/hexanes to afford the title compound as a colorless oil. LCMS 636 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) (atropisomers present) ¹H NMR δ 7.82 (br s 1H), 7.80 (br s, 1H), 7.45-7.36 (m, 3H), 7.32-7.22 (m, 3H), 7.08 (d, J = 10.1 Hz, 1H), 6.60 (m, 1H), 5.05 (m, 1H), 4.01 (d, J = 15.5 Hz), 3.78 (s, 3H), 3.71-3.52 (m, 2H), 3.24 (m, 1H), 1.32-1.20 (m, 6H), 0.56 (d, J= 6.4 Hz, 3H). This compound was separated into its two enantiomers (4R, 5S)-4-[3,5-bis(trifluoromethyl)phenyl]-1-[[4'-fluoro-5'-isopropyl]-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-methyl-pyridin-2-one and (4S, 5R)-4-[3,5-bis(trifluoromethyl)phenyl]-1-[[4'-fluoro-5'-isopropyl]-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-5-methyl-pyridin-2-one using chiral HPLC (IA column, 20 x 250 mm, 3% i-PrOH in heptane).

Following the general procedures outlined above, the compounds in Table 17 were prepared:

<table>
<thead>
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<th>Example</th>
<th>R</th>
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</tr>
<tr>
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<td>534.2</td>
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<td>568.1</td>
</tr>
</tbody>
</table>

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(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-{[4′-fluoro-5′-isopropyl]-2′-methoxy-6-methyl-4-(trifluoromethyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one

**Step A:** 2,6-dimethyl-4-(trifluoromethyl)phenylamine
A mixture of 2,6-dibromo-4-trifluoromethyl aniline (1.00 g, 3.14 mmol), trimethylboroxine (1.16 ml, 1.04 g, 8.33 mmol), potassium carbonate (1.15 g, 8.33 mmol) and catalytic amount (10%) Pd(PPh₃)₄ in DMF (5 ml) was heated to 90°C for 14 h. Water (10 ml) was added. The mixture was extracted with ethyl acetate (3 x 20 ml). The combined EtOAc layers were washed with brine and dried over sodium sulfate. The titled compound was obtained as a colorless oil after a flash column using EtOAc:hexane (1:9) as the elute. ¹H NMR (CDCl₃, 500 MHz): δ 7.28 (s, 1H), 7.22 (s, 1H), 3.88 (br s, 2H), 2.21 (s, 6H).

**Step B:** 2-iodo-1,3-dimethyl-5-(trifluoromethyl)benzene
A mixture of the titled compound from Step A (0.27 g, 1.43 mmol), n-pentyl nitrite (0.50 g, 2.86 mmol) and I₂ (0.72 g, 2.86 mmol) in chloroform (10 ml) was refluxed for 1 h. The mixture was diluted with methylene chloride (20 ml) and washed with saturated sodium thiosulfate solution, and brine. The organic layer was dried over sodium sulfate. The titled compound was obtained as a light yellow liquid after flash column using hexane as the elute. ¹H NMR (CDCl₃, 500 MHz) δ 7.31 (s, 2H), 2.58 (s, 6H).

**Step C:** 1-(bromomethyl)-2-iodo-3-methyl-5-(trifluoromethyl)benzene
A mixture of the titled compound from Step B (0.26 g, 0.87 mmol), NBS (0.154 g, 0.87 mmol) and catalytic amount of AIBN in CCl₄ was refluxed for 6 h. TLC (hexane) showed a mixture of starting material and a new spot. Upon addition of more AIBN the reaction was allowed to reflux for another 2 h. No change was observed. The reaction mixture was cooled to room temperature and the solvent was removed. The titled compound was obtained as a white solid along with the starting material after preparative TLC purification using hexane as the elute. ¹H NMR (CDCl₃, 500 MHz): δ 7.54 (s, 1H), 7.42(s, 1H), 4.67(s, 2H), 2.60 (s, 3H).

Step D: (4S,5R)-5-[3.5-bis(trifluoromethyl)phenyl]-3-[2-iodo-3-methyl-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of oxazalidone from Example xx, step xx, (0.058 g, 0.186 mmol) in THF (5 ml) at 0°C, NaH was added. The mixture was stirred for 30 min at 0°C. A solution of benzyl bromide from Step C (0.064 g, 0.169 mmol) in THF (5 ml) was added via syringe. The mixture was then allowed to stirred at room temperature for 12 h. The reaction was quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl acetate (3 x 15 ml). The combined EtOAc layers were washed with brine and dried over sodium sulfate. The titled compound was obtained after a preparative TLC plate using EtOAc:hexane=1:9 as the elute. ¹H NMR (CDCl₃, 500 MHz): δ 7.92 (s, 1H), 7.82 (s, 2H), 7.49 (s, 1H), 7.38 (s, 1H), 5.77 (d, J = 8 Hz, 1H), 4.93 (d, J = 16 Hz, 1H), 4.45 (d, J = 16 Hz, 1H), 4.05 (m, 1H), 2.60 (s, 3H), 0.81 (d, J = 6.5 Hz, 3H).

Step E: (4S,5R)-5-[3.5-bis(trifluoromethyl)phenyl]-3-[4'-fluoro-5'-isopropyl-2'-methoxy-6-methyl-4-(trifluoromethyl) biphenyl-2-y]methyl]-4-methyl-1,3-oxazolidin-2-one

A mixture of the titled compound from Step D (0.07 g, 0.11 mmol), 2-methoxy-4-fluoro-5-isopropyl phenyl boronic acid (0.036 g, 0.17 mmol), sodium carbonate (0.024 g, 0.23 mmol) and catalytic amount of Pd(PPh₃)₄ in a mixture of 2:1:4 EtOH/H₂O/toluene was heated to reflux for 3 h. The solvents were removed and the aqueous was extracted with methylene chloride (3 x 20 ml). The combined methylene chloride layers were washed with brine, and dried over sodium sulfate. The titled compound was obtained after a preparative TLC plate using EtOAc:hexane = 1:9 as the elute. Two diastereomeric atropisomers of the titled compound were separated by a chiral OD column using EtOH/n-Heptane as the elute. Isomer A (faster elute): ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (s, 1H), 7.75 (s, 2H), 7.52 (s, 2H), 6.85 (d, J = 8.5 Hz, 1H), 6.71 (d, J = 12 Hz, 1H), 5.63 (d, J = 8 Hz, 1H), 4.71 (d, J = 16 Hz, 1H), 3.93 (m, 1H), 3.87 (d, J = 16 Hz, 1H), 3.72 (s, 3H), 3.22 (m, 1H), 2.09 (s, 3H), 1.26 (m, 6H), 0.53 (d, J = 6.5 Hz, 3H); LC-MS (M+1): 652.3.

Isomer B (slower elute): ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (s, 1H), 7.73 (s, 2H), 7.53 (s, 2H), 6.90 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 12 Hz, 1H), 5.60 (d, J = 8 Hz, 1H), 4.69 (d, J = 15.5 Hz, 1H), 3.88 (m, 1H), 3.86 (d, J = 15.5 Hz, 1H), 3.76 (s, 3H), 3.22 (m, 1H), 2.11 (s, 3H), 1.23 (m, 6H), 0.48 (d, J = 6.5 Hz, 3H); LC-MS (M+1): 652.3.
EXAMPLE 328

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[6-chloro-4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

Step A: [2-chloro-6-methyl-4-(trifluoromethyl)phenyl]amine
A mixture of 2-bromo-6-chloro-4-trifluoromethyl aniline (1.00 g, 3.64 mmol), trimethylboroxine (0.66 ml, 0.59 g, 4.47 mmol), potassium carbonate (1.00 g, 7.30 mmol) and catalytic amount (10%) Pd(PPh₃)₄ in DMF (5 ml) was heated to 90°C for 14 h. Water (20 ml) was added. The mixture was extracted with ethyl acetate (3 x 50 ml). The combined EtOAc layers were washed with brine and dried over sodium sulfate. The titled compound was obtained as a colorless oil after a flash column using EtOAc:hexane (1:9) as the elute. ¹H NMR (CDCl₃, 500 MHz): δ 7.43 (s, 1H), 7.24 (s, 1H), 4.38 (br s, 2H), 2.22 (s, 3H).

Step B: [2-chloro-6-(iodomethyl)-4-(trifluoromethyl)phenyl]amine
A mixture of the titled compound from Step A (0.67 g, 3.20 mmol), n-pentyl nitrite (0.75 g, 6.41 mmol) and I₂ (1.05 g, 4.17 mmol) in chloroform (10 ml) was refluxed for 1 h. The mixture was diluted with methylene chloride (20 ml) and washed with saturated sodium thiosulfate solution, and brine. The organic layer was dried over sodium sulfate. 2-Iodo-3-chloro-4-trifluoromethyl benzyl iodide were obtained as after flash column using hexane as the elute. ¹H NMR (CDCl₃, 500 MHz): δ 7.60 (s, 2H), 4.65 (s, 2H).

Step C: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[3-chloro-2-iodo-5-(trifluoromethyl)benzyl]-4-methyl-1,3-oxazolidin-2-one
To a solution of oxazolidone from Example xx, step xx, (0.058 g, 0.186 mmol) in THF (5 ml) at 0°C, NaH was added. The mixture was stirred for 30 min at 0°C. A solution of 2-iodo-3-chloro-4-trifluoromethyl benzyl iodide from Step B (0.226 g, 0.51 mmol) in THF (5 ml) was added via syringe. The mixture was then allowed to stir at room temperature for 3 h. The reaction was quenched with saturated ammonium chloride solution. The mixture was extracted with ethyl
acetate (3 x 20 ml). The combined EtOAc layers were washed with brine and dried over sodium sulfate. The titled compound was obtained after a flash column using EtOAc:hexane=1:9 as the elute. LC-MS (M+1): 432.0.

Step D: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[6-chloro-4'-fluoro-5'-isopropyl-2'-methoxy-4-[(trifluoromethyl)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

A mixture of the titled compound from Step C (0.10 g, 0.16 mmol), 2-methoxy-4-fluoro-5-isopropyl phenyl boronic acid (0.067 g, 0.32 mmol), sodium carbonate (0.034 g, 0.32 mmol) and catalytic amount of Pd(PPh3)4 in a mixture of 2:1:4 EtOH/H2O/toluene was heated to reflux for 4 h. The solvents were removed and the aqueous was extracted with methylene chloride (3 x 15 ml). The combined methylene chloride layers were washed with brine, and dried over sodium sulfate. The titled compound was obtained after a preparative TLC plate using EtOAc:hexane = 1:9 as the elute. Two diastereomeric atropisomers of the titled compound were separated by a chiral AD column using i-PrOH/n-Heptane as the elute. Isomer A (faster elute): 1H NMR (CDCl3, 500 MHz): δ 7.91 (s, 1H), 7.75 (s, 3H), 7.61 (s, 1H), 6.92 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 12 Hz, 1H), 5.64 (d, J = 8 Hz, 1H), 4.72 (d, J = 16 Hz, 1H), 3.95 (d, J = 16 Hz, 1H), 3.93 (m, 1H), 3.78 (s, 3H), 3.22 (m, 1H), 1.23 (m, 6H), 0.55 (d, J = 7 Hz, 3H); LC-MS (M+1): 672.1. Isomer B (slower elute): 1H NMR (CDCl3, 500 MHz): δ 7.89 (s, 1H), 7.75 (s, 1H), 7.73 (s, 2H), 7.62 (s, 1H), 6.98 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 12 Hz, 1H), 5.61 (d, J = 8.5 Hz, 1H), 4.72 (d, J = 16 Hz, 1H), 3.91 (d, J = 16 Hz, 1H), 3.87 (m, 1H), 3.79 (s, 3H), 3.22 (m, 1H), 1.22 (m, 6H), 0.48 (d, J = 6.5 Hz, 3H); LC-MS (M+1): 672.1.

INTERMEDIATE 22

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-bromo-5-fluorobenzyl)-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl) phenyl] – 4-methyl-1,3-oxazolidin-2-one (2.0g, 6.39 mmol) in THF (40 mL) at 0 ºC, NaH (285 mg, 60 w/w % in mineral oil, 7.13 mmol, 1.1 eq.) was added in one portion. The resulting foaming mixture was stirred in an ice bath. Additional THF (50 mL) was added into the reaction. The mixture was stirred at 0 ºC for 30
min. A solution of 2-bromo-5-fluorobenzyl bromide (1.712 g, 6.39 mmol) in THF (20 mL) was added. The resulting mixture was stirred cold for 30 min and then allowed to warm to ambient. The reaction was completed in 3 h, monitored by LC-MS. The reaction was quenched with saturated aq. NH₄Cl (80 mL). Volatiles were removed in vacuo. Crude mixture was extracted with EtOAc, and dried over Na₂SO₄. The resulting clear gel was purified by SiO₂ (Biotage 40+M cartridge, EtOAc/hexane, gradient). The titled compound was obtained as a clear oil. LC-MS: 500.09 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.88 (s, 1H), 7.79 (s, 2H), 7.55 (dd, J = 8.8, 5.2 Hz, 1H), 7.17 (dd, J = 8.7, 4.5 Hz, 1H), 6.95 (m, 1H), 5.74 (d, J = 8.0 Hz, 1H), 4.83 (d, J = 15.8, 1H), 4.54 (d, J = 16.0 Hz, 1H), 4.11 (m, 1H), 0.80 (d, J = 6.6 Hz, 3H).

EXAMPLE 329

![Chemical structure diagram](image)

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4,4'-difluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-bromo-5-fluorobenzyl)-4-methyl-1,3-oxazolidin-2-one (1.0 g, 2.0 mmol) in 1, 4-dioxane (6 mL) was added (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (509 mg, 2.4 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (82 mg, 5 mol%) and aq. potassium hydroxide (1.3 mL, 3M, 2 eq.). The reaction mixture was purged with nitrogen and then sealed in a microwave vessel. The reaction vessel was subject to microwave irradiation at 150 °C for 40 min. Crude mixture was worked up with water. Volatiles were evaporated. The resulting mixture was extracted with EtOAc. The combined extracts were dried over Na₂SO₄. The resulting purple residue was purified by SiO₂ (Biotage 40+M cartridge, eluted by EtOAc/hexane, gradient; 5% to 25%). The titled compound was obtained as clear solid. LC-MS: 588.23 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) a 6:4 mixture of rotamers δ 7.85 (s, 1H), 7.69 (s, 2H), 7.16–7.21 (m, 1.5 H), 7.04–7.13 (m, 1.5 H), 6.96 (dd, J = 14.3, 8.80 Hz, 1H), 6.65 (d, J = 10.0 Hz, 1H), 5.59 (d, J = 8.0 Hz, 0.6H), 5.43 (d, J = 8.0 Hz, 0.4H), 4.85 (d, J = 15.8 Hz, 0.6H), 4.82 (d, J = 15.8 Hz, 0.4H), 4.02
(d, J = 15.8 Hz, 0.6 H), 3.85 (m, 0.6 H), 3.76-3.81 (m, 0.8 H), 3.75 (s, 1.8H), 3.73 (s, 1.2H), 3.19 (m, 1H), 1.14-1.26 (m, 6 H), 0.56 (d, J = 6.6 Hz, 1.2 H), 0.38 (d, J = 6.6 Hz, 1.8 H).

INTERMEDIATE 23

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-chloro-4-fluorobenzyl)-4-methyl-1,3-oxazolidin-2-one
To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl) phenyl] – 4-methyl-1,3-oxazolidin-2-one (1.0 g, 3.19 mmol)/THF (40 mL) at 0 °C, was added NaH (153 mg, 60 w/w % in mineral oil, 3.83 mmol, 1.2 eq.) in one portion. The resulting foaming mixture was stirred in an ice bath for 30 min, followed by addition of 2-chloro-4-fluorobenzyl chloride (572 mg, 3.19 mmol). The resulting mixture was stirred at 0 °C for 30 min then warmed to ambient overnight. The reaction failed to proceed at room temperature and it was warmed in a 60 °C oil bath for 20 h. An aliquot indicated that the reaction was over. It was quenched with aq. NH₄Cl (50 mL). Volatiles were evaporated. The resulting mixture was extracted with EtOAc. The combined extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to a yellow oil. The oil was purified by SiO₂ (Biotage 40+M cartridge, eluted by EtOAc/hexanes, gradient; 5% to 40%). The titled compound was obtained as a colorless glassy material. LC-MS: 456.12 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.89 (s, 1H), 7.77 (s, 2H), 7.46 (dd, J = 8.7, 6.0 Hz, 1H), 7.17 (dd, J = 8.4, 2.5 Hz, 1H), 7.03 (m, 1H), 5.68 (d, J = 8.2 Hz, 1H), 4.83 (d, J = 15.6, 1H), 4.36 (d, J = 15.3 Hz, 1H), 4.06 (m, 1H), 0.79 (d, J = 6.4 Hz, 3H).

EXAMPLE 330
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-([4′,5-difluoro-5′-isopropyl-2′-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-chloro-4-fluorobenzyl)-4-methyl-1,3-oxazolidin-2-one (100 mg, 0.22 mmol) in 1, 4-dioxane (1 mL) was added (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (55.8 mg, 0.26 mmol), palladium(II) acetate (10 mg, 20 mol %), potassium hydroxide aqueous solution (147 μL, 3M, 2 eq.) and tri-tert-butylphosphine (13.4 mg, 0.066 mmol, 30 mol % as a 10% w/w hexane solution). The resulting reaction mixture was N₂ purged and sealed in a microwave vessel. The vessel was subject to microwave irradiation at 140 °C for 40 min. LC-MS indicated the formation of desired product. It was quenched with water (50 mL). Volatiles were evaporated. The resulting mixture was extracted with EtOAc. The combined extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to an oil. The titled compound was obtained after two purifications with silica gel and one reversed phase prep-HPLC. LC-MS: 588.25 (M+1)⁺.

INTERMEDIATE 24

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-chloro-6-fluorobenzyl)-4-methyl-1,3-oxazolidin-2-one
To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl) phenyl]-4-methyl-1,3-oxazolidin-2-one (1.0 g, 3.19 mmol) in THF (40 mL) at 0 °C, was added NaH (153 mg, 60 w/w % in mineral oil, 3.83 mmol, 1.2 eq.) in one portion. The resulting foaming mixture was stirred in an ice bath for 30 min followed by addition of benzyl chloride (572 mg, 3.19 mmol). The resulting mixture was stirred at 0 °C for 30 min then warmed to 60 °C for 30 hr. An aliquot indicated about 10 % of starting (4S,5R)-5-[3,5-bis(trifluoromethyl) phenyl]-4-methyl-1,3-oxazolidin-2-one left. The reaction was cooled and quenched with saturated NH₄Cl (50 mL). Volatiles were evaporated. The resulting mixture was extracted with EtOAc. The combined extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to a yellow oil. The titled compound was obtained as a colorless glassy material after purification by SiO₂ (Biotage 40+M, eluted by EtOAc/hex, gradient; 5% to 40%). LC-MS: 456.11 (M+1)^+. ¹H NMR (CDCl₃, 500 MHz) δ 7.77 (s, 1H), 7.22-7.34 (m, 2H), 7.01-7.09 (m, 1H), 5.62 (d, J = 8.2 Hz, 1H), 5.01 (dd, J = 14.8, 2.0 Hz, 1H), 4.45 (d, J = 14.6 Hz, 1H), 3.91 (m, 1H), 0.81 (d, J = 6.4 Hz, 3H).

EXAMPLE 331

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(3,4′-difluoro-5′-isopropyl-2′-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-chloro-6-fluorobenzyl)-4-methyl-1,3-oxazolidin-2-one (327 mg, 0.72 mmol) in 1, 4-dioxane (4 mL) was added (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (228 mg, 1.08 mmol), Palladium(II) acetate (33 mg, 20 mol %), potassium hydroxide (588 μL, 3M, 2.5 eq.) and tri-tert-butylphosphine (44 mg, 0.22 mmol, 30 mol % as a 10% w/w hexane solution). The resulting reaction mixture was purged with nitrogen and sealed in a microwave vessel. The vessel was subject to microwave irradiation at 135 °C for 50 min. LC-MS indicated the starting material/product ratio was about 55:45. The reaction mixture was re-submitted to reaction conditions (µw at 135 °C for 50 min). The LC-MS trace indicated that no progress was made from the 2nd irradiation. More palladium(II) acetate (33 mg, 20 mol %) and tri-tert-butylphosphine (44 mg, 0.22 mmol, 30 mol % as a 10% w/w
hexane solution) were added into reaction mixture. The mixture was resubmitted to reaction conditions (µw at 135 °C, 1 hr). Again, the LC-MS indicated no significant progress. The reaction mixture was quenched with H₂O. The volatiles were removed under reduced pressure. The resulting mixture was extracted with EtOAc. The combined extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to a yellow oil. The oil was dissolved in DMSO and purified twice by a reversed phase prep-HPLC (column: Kromasil, 100-5C18, 100 x 21.1 mm) eluted by 10% to 90% H₂O (0.1% TFA, v/v) / MeCN (0.1% TFA, v/v). The resulting glassy material was then purified on a prep-TLC plate by 100% dichloromethane to afford the titled compound. LC-MS: 588.21 (M+H)⁺. ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 7.83 (s, 1 H), 7.67 (s, 1 H) 7.65 (s, 1 H), 7.32 – 7.41 (m, 1H), 7.09 – 7.16 (m, 1H), 6.96 – 7.06 (m, 1H), 6.64 – 6.70 (m, 1H), 5.47 (d, J = 8.0 Hz, 0.5 H), 5.19 (d, J = 7.8 Hz, 0.5 H), 4.96 (d, J = 14.9 Hz, 0.5 H), 4.80 (d, J = 15.1 Hz, 0.5 H), 4.31 (d, J = 15.1 Hz, 0.5 H), 3.91 (d, J = 15.1 Hz, 0.5 H), 3.78 (s, 1.5 H), 3.75 (s, 1.5 H), 3.62-3.69 (m, 1 H), 3.15-3.26 (m, 1 H), 1.14-1.25 (m, 6 H), 0.54 (d, J = 6.6 Hz, 1.5 H), 0.33 (d, J = 6.4 Hz, 1.5 H).

EXAMPLE 332

![Chemical Structure](image)

Step A: 2-bromo-5-nitrophenyl)methanol
Methyl 2-bromo-5-nitrobenzoate (10g, 38.46 mmol) was dissolved in THF (100 mL) and cooled to internal temperature = -15 ~ -10 °C. To this mixture was added diisobutylaluminum hydride solution (1.0 M in toluene, 57 mL, 57 mmol) slowly while maintaining internal temperature < 0 °C. The resulting mixture was stirred at ambient for 1 hour then quenched with aq. NH₄Cl (150 mL). The crude mixture was diluted with EtOAc (100 mL) and then filtered. Volatiles were removed under reduced pressure. The resulting residue was extracted with EtOAc (200 mL x 2). The combined extracts were dried over Na₂SO₄, filtered and evaporated to an oil. The resulting oil was purified by SiO₂ (Biotage 65i, EtOAc/hexanes, gradient; 10% to 15%). The titled compound was obtained as a yellow crystalline solid. ¹H NMR (CDCl₃, 500 MHz) δ 8.44 (d, J = 2.74 Hz 1H), 8.02 (dd, J = 8.7, 2.8 Hz, 1 H), 7.72 (d, J = 8.7, 1H), 4.83 (s, 3 H).
Step B: 1-bromo-2-(bromomethyl)-4-nitrobenzene

To a solution of 2-bromo-5-nitrophenyl)methanol (4.746 g, 20.45 mmol) in anhydrous dichloromethane (150 mL), was added triphenylphosphine (6.43 g, 24.5 mmol) and carbon tetrabromide (8.15g, 24.5 mmol). The mixture was stirred at 0 °C for 30 min then at 20 °C for 1h. TLC showed complete consumption of starting material. Volatiles were removed under reduced pressure. The resulting oil was purified by SiO₂ (Biotage 40M, eluted by EtOAc/hexanes, gradient) to afford the titled compound as a colorless solid. ⁱH NMR (CDCl₃, 500 MHz) δ 8.33 (d, J = 2.74 Hz, 1H), 8.03 (dd, J = 8.7, 2.5 Hz, 1H), 7.78 (d, J = 8.7, 1H), 4.63 (s, 3H).

Step C: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-bromo-5-nitrobenzyl)-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl) phenyl] - 4-methyl-1,3-oxazolidin-2-one (5.3g, 16.95 mmol) in THF (100 mL) at 0 °C, NaH (746 mg, 60 w/w % in mineral oil, 18.65 mmol, 1.1 eq.) was added in one portion. The resulting foaming mixture was stirred in an ice bath. Additional THF (100 mL) was added into the reaction. The mixture was stirred at 0 °C for 30 min. A solution of 1-bromo-2-(bromomethyl)-4-nitrobenzene (5.0 g, 16.95 mmol) in THF (25 mL) was added. The resulting mixture was stirred cold for 30 min and then allowed to warm to ambient. The reaction was completed in 1.5 h. The reaction was quenched with sat. aqueous NH₄Cl (100 mL). Crude mixture was extracted with EtOAc, and dried over Na₂SO₄. The resulting clear gel was purified by SiO₂ (Biotage 40M cartridge, EtOAc/hexane, gradient, 25% to 45%). The titled compound was obtained as a crystalline solid. LC-MS: 529.11 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 8.24 (d, J = 2.5 Hz, 1H), 8.07 (dd, J = 8.7, 2.8 Hz, 1H), 7.91 (s, 1H), 7.79 – 7.83 (m, 3H), 5.82 (d, J = 7.8 Hz, 1H), 4.82 (d, J = 16.2 Hz, 1H), 4.44 (d, J = 16.3, 1H), 4.11 – 4.20 (m, 1H), 0.84 (d, J = 6.6 Hz, 3H).

Step D: (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[4′-fluoro-5′-isopropyl-2′-methoxy-4-nitrophenyl]-2-yl)methyl-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-bromo-5-nitrobenzyl)-4-methyl-1,3-oxazolidin-2-one (3.877g, 7.35 mmol) in a toluene (24 mL): ethanol (12 mL): water (6 mL) mixture was added (4-fluoro-5-isopropyl-2-methoxyphenyl)borationic acid (2.337g, 11.03 mmol), tetrakis (triphenylphosphine) palladium(0) (425 mg, 5 mol %) and sodium carbonate (1.56 g, 14.72 mmol). The resulting mixture was bubbled with nitrogen and then heated in a 90 °C oil bath for 10 h. An aliquot showed complete consumption of the starting material. The reaction was quenched with brine. The resulting mixture was extracted with EtOAc and dried over Na₂SO₄. The resulting glassy mixture was purified by SiO₂ (Biotage 40S cartridge, EtOAc/hexane, gradient). The titled compound was obtained as a crystalline solid. LC-MS: 615.26 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 8.31 (s, 1 H), 8.20 – 8.26 (m, 1 H), 7.86 (s, 1 H), 7.70 (s, 2 H), 7.39 – 7.43 (m, 1 H), 6.96 – 7.01 (m, 1H), 6.67 – 6.72
(m, 1H), 5.64 (d, J = 8.0 Hz, 0.5H), 5.48 (d, J = 8.0 Hz, 0.5H), 4.90 (d, J = 16.3 Hz, 0.5H), 4.86 (d, J = 16.3 Hz, 0.5H), 4.10 – 4.16 (m, 0.5 H), 3.84-3.94 (m, 1.5 H), 3.77 (s, 1.5H), 3.75 (s, 1.5H), 3.15 – 3.26 (m, 1H), 1.15-1.29 (m, 6 H), 0.57 (d, J = 6.6 Hz, 1.5 H), 0.40 (d, J = 6.6 Hz, 1.5 H).

EXAMPLE 333

(4S,5R)-3-[(4-amino-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

A solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-nitrobiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one (1.94 g, 3.16 mmol) in methanol (20 mL) was subject to H₂ (40 psi., Parr shaker) at 20 °C for 1.5 h. LCMS indicated the presence of trace starting material. The crude mixture was filtered through a bed of Celite (521). The filtrate was evaporated in vacuo to afford a glass as the product. LC-MS: 585.32 (M+1)+

¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 7.83 (s, 1 H), 7.67 (s, 2 H), 6.93 – 7.06 (m, 2 H), 6.87 (s, 0.5H), 6.72 – 6.82 (m, 1.5H), 5.57 (d, J = 8.0 Hz, 0.5H), 5.36 (d, J = 8.0 Hz, 0.5H), 4.77 (d, J = 5.5 Hz, 0.5H), 4.74 (d, J = 6.5 Hz, 0.5 H), 3.95 (d, J = 15.5 Hz, 0.5 H), 3.75-3.86 (m, 1.5 H), 3.73 (s, 3 H), 3.12 – 3.24 (m, 1H), 1.11-1.29 (m, 6 H), 0.47 (d, J = 6.5 Hz, 1.5 H), 0.29 (d, J = 6 Hz, 1.5 H).

EXAMPLE 334
(4S,5R)-5-[(3,5-bis(trifluoromethyl)phenyl)-3-[(4-bromo-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution (4S,5R)-3-[(4-amino-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (526 mg, 0.90 mmol) in bromoform (2.5 mL) was added tert-butyl nitrite (186 mg, 1.80 mmol). The resulting mixture was stirred at 80 °C for 20 min. An aliquot indicated completion of the reaction. The reaction crude was purified silica gel to afford the title compound as a yellow glass. LC-MS: 650.09 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 7.85 (s, 1 H), 7.69 (s, 2 H), 7.60 (s, 0.5 H), 7.48 – 7.53 (m, 1.5H), 7.07 – 7.11 (m, 1 H), 6.93 – 6.99 (m, 1 H), 6.62 – 6.67 (m, 1H), 5.59 (d, J = 8.0 Hz, 0.5H), 5.39 (d, J = 7.0 Hz, 0.5H), 4.82 (d, J = 6.5 Hz, 0.5H), 4.75 (d, J = 6.5 Hz, 0.5 H), 3.98 (d, J = 16.0 Hz, 0.5 H), 3.76-3.85 (m, 1.5 H), 3.75 (s, 1.5 H), 3.74(s, 1.5 H), 3.13 – 3.23 (m, 1H), 1.13-1.29 (m, 6 H), 0.52 (d, J = 6.5 Hz, 1.5 H), 0.34 (d, J = 7.0 Hz, 1.5 H).

EXAMPLE 335

(4S,5R)-5-[(3,5-bis(trifluoromethyl)phenyl)-3-[(4-cyclopropyl-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one
To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one (100 mg, 0.15 mmol) in 1, 4-dioxane (0.5 mL) was added cyclopropylboronic acid (10 mg, 0.19 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) (82 mg, 8 mol %), bis(tri-tert-butylphosphine)palladium (0) (10 mg, 13 mol %) and aqueous potassium hydroxide (78 μL, 3M, 1.5 eq.). The reaction mixture was purged with nitrogen and then sealed in a microwave vessel. The reaction vessel was subject to microwave irradiation at 150 °C for 30 min. An aliquot indicated complete consumption of starting material. Reaction crude was worked up with water. The resulting mixture was extracted with EtOAc and dried over Na₂SO₄. The titled compound was obtained as a glassy material after two preparative TLC plates using respectively 20% EtOAc in hexanes and 5% EtOAc in dichloromethane as the eluent. LC-MS: 610.26 (M+H)⁺. 

1H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 7.84 (s, 1 H), 7.65 – 7.70 (m, 2 H), 7.21 (s, 0.5 H), 7.08 – 7.14 (m, 1.5 H), 6.95 – 7.04 (m, 2 H), 6.61 – 6.67 (m, 1 H), 5.52 (d, J = 8.5 Hz, 0.5H), 5.27 (d, J = 8.0 Hz, 0.5H), 4.85 (d, J = 15.5 Hz, 0.5H), 4.81 (d, J = 15.5 Hz, 0.5 H), 4.00 (d, J = 15.5 Hz, 0.5 H), 3.69-3.81 (m, 4.5 H), 3.13 – 3.24 (m, 1H), 1.90 -1.99 (m, 1 H), 1.12-1.30 (m, 6 H), 0.98 – 1.15 (m, 2 H), 0.71 – 0.77 (m, 2 H), 0.48 (d, J = 6.5 Hz, 1.5 H), 0.29 (d, J = 6.5 Hz, 1.5 H).

**EXAMPLE 336**

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(methylthio)biphenyl-2-yl]methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution (4S,5R)-3-[[4-amino-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl]methyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (200 mg, 0.34 mmol) in methyl disulfide (2 mL) was added tert-butyl nitrite (70 mg, 0.68 mmol). The resulting mixture was stirred at 80 °C for 30 min. An aliquot indicated completion of the reaction. The titled compound was obtained as a glassy material after two preparative TLC plates using respectively 20% EtOAc in hexanes and 10% EtOAc in dichloromethane as the eluent. LC-MS: 616.21
(M+1)+. 1H NMR (CDCl3, 500 MHz) a 1:1 mixture of rotamers δ 7.84 (s, 1 H), 7.67 (s, 2 H), 7.35 (s, 0.5 H), 7.22 – 7.28 (m, 1.5 H), 7.12 – 7.19 (m, 1 H), 6.94 – 7.02 (m, 1 H), 6.61 – 6.68 (m, 1 H), 5.55 (d, J = 8.0 Hz, 0.5H), 5.31 (d, J = 9.5 Hz, 0.5H), 4.85 (d, J = 16.0 Hz, 0.5H), 4.83 (d, J = 15.5 Hz, 0.5 H), 3.99 (d, J = 15.5 Hz, 0.5 H), 3.69-3.81 (m, 4.5 H), 3.12 – 3.24 (m, 1H), 2.54, (s, 1.5 H), 2.53 (s, 1.5 H), 1.11-1.27 (m, 6 H), 0.50 (d, J = 6.5 Hz, 1.5 H), 0.31 (d, J = 7.0 Hz, 1.5 H).

EXAMPLE 337

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(4S,5R)-5-[[3,5-bis(trifluoromethyl)phenyl]-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-(methylsulfonyl)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one
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To a solution of (4S,5R)-5-[[3,5-bis(trifluoromethyl)phenyl]-3-{[4'-fluoro-5'-isopropyl-2'-methoxy-4-(methylthio)biphenyl-2-yl]methyl}-4-methyl-1,3-oxazolidin-2-one (156 mg, 0.25 mmol) in dichloromethane (3 mL) was added 3-chloroperbenzoic acid (175 mg, 1.01 mmol). The resulting mixture was stirred at 20 °C for 1 h. An aliquot indicated completion of the reaction. Reaction crude was partitioned between water and dichloromethane. The organic layer was separated and dried over Na2SO4. The titled compound was obtained as a glassy material after three preparative TLC plates using respectively 50% EtOAc in hexanes, 20% EtOAc in dichloromethane and dichloromethane as the eluent. LC-MS: 648.29 (M+1)+. 1H NMR (CDCl3, 500 MHz) a 1:1 mixture of rotamers δ 7.99 (s, 0.5 H), 7.92 – 7.96 (m, 1.5 H), 7.86 (s, 1 H), 7.70 (s, 2 H), 7.42 – 7.46 (m, 1 H), 6.96 – 7.00 (m, 1 H), 6.69 (d, J = 12 Hz, 1 H), 5.64 (d, J = 8.0 Hz, 0.5H), 5.45 (d, J = 8.0 Hz, 0.5H), 4.93 (d, J = 6.0 Hz, 0.5H), 4.90 (d, J = 6.5 Hz, 0.5 H), 4.09 (d, J = 16 Hz, 0.5 H), 3.88 (d, J = 16 Hz, 0.5 H), 3.80 - 3.88 (m, 1 H), 3.78 (s, 1.5 H), 3.75 (s, 1.5 H), 3.16 – 3.25 (m, 1H), 3.14 (s, 1.5 H), 3.13 (s, 1.5 H), 1.22 – 1.28 (m, 6 H), 0.57 (d, J = 6.5 Hz, 1.5 H), 0.38 (d, J = 6.5 Hz, 1.5 H).

EXAMPLE 338

- 211 -
2-(((4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-2-oxo-1,3-oxazolidin-3-yl)methyl)-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-4-carbonitrile

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4-bromo-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one (100 mg, 0.15 mmol) in N,N-dimethylformamide (1.5 mL) was added copper(II) cyanide (17 mg, 0.19 mmol). The resulting reaction mixture was N₂ purged and sealed in a microwave vessel. The vessel was subject to microwave irradiation at 150 °C for 30 min. LC-MS indicated only the starting bromide was present. Added tetrakis(triphenylphosphine)palladium(0) (10 mg, 6 mol %) into the reaction mixture. Repeated microwave irradiation at 150 °C for 30 min. An aliquot indicated the desired product was formed and all starting bromide was consumed. Reaction crude was partitioned between water and hexanes. The aqueous phase was back extracted with diethyl ether. The combined extracts were dried over Na₂SO₄. The titled compound was obtained as a glassy material after two preparative TLC plates developed respectively by 20 % EtOAc in hexanes and 4 % EtOAc in dichloromethane. LC-MS: 595.03 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 7.86 (s, 1 H), 7.61 (S, 0.5 H), 7.67 – 7.71 (m, 2.5 H), 7.64 – 7.68 (m, 1 H), 7.32 – 7.36 (m, 1 H), 6.98 (d, J = 8.5 Hz, 0.5 H), 6.95 (d, J = 8.5 Hz, 0.5 H), 6.68 (d, J = 12 Hz, 1 H), 5.62 (d, J = 8.0 Hz, 0.5H), 5.46 (d, J = 8.0 Hz, 0.5H), 4.85 (d, J = 16.0 Hz, 0.5H), 4.80 (d, J = 16.0 Hz, 0.5H), 4.06 (d, J = 16 Hz, 0.5 H), 3.79 – 3.86 (m, 1 H), 3.70 – 3.78 (m, 3.5 H), 3.16 – 3.24 (m, 1 H), 3.75 (s, 1.5 H), 3.16 – 3.25 (m, 1H), 3.14 (s, 1.5 H), 3.13 (s, 1.5 H), 1.15 – 1.27 (m, 6 H), 0.54 (d, J = 7.0 Hz, 1.5 H), 0.37 (d, J = 6.5 Hz, 1.5 H).

EXAMPLE 339
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4'-fluoro-5'-isopropyl-2'-methoxy-4-methylbiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4-bromo-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one (82.5 mg, 0.13 mmol) in 1,4-dioxane (1 mL) was added trimethylboroxine (39 mg, 0.31 mmol), Pd(PPh₃)₄ (15 mg, 10 mol %) and potassium carbonate (35 mg, 0.25 mmol). The resulting reaction mixture was purged with nitrogen and sealed in a microwave vessel. The vessel was subject to microwave irradiation at 130 °C for 15 min. The crude mixture was diluted with brine and extracted with EtOAc. The combined organic extracts were dried over Na₂SO₄. The titled compound was obtained as a glassy material after two preparative TLC plates developed respectively by 20 % EtOAc in hexanes and dichloromethane. LC-MS: 584.08 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 7.84 (s, 1 H), 7.65 -7.70 (m, 2 H), 7.29 (s, 0.5 ), 7.18 – 7.22 (m, 1.5 H), 7.10 – 7.15 (m, 1 H), 7.01 (d, J = 8.0 Hz, 0.5 H), 6.98 (d, J = 8.5 Hz, 0.5 H), 6.66 (d, J = 5.0 Hz, 0.5 H), 6.64 (d, J = 5.5 Hz, 0.5 H), 5.54 (d, J = 8.5 Hz, 0.5H), 5.31 (d, J = 8.0 Hz, 0.5H), 4.82 (d, J = 15.5 Hz, 1 H), 4.02 (d, J = 15 Hz, 0.5 H), 3.71 – 3.82 (m, 5 H), 3.15 – 3.24 (m, 1 H), 2.42 (s, 1.5 H), 2.41 (s, 1.5 H), 1.13 – 1.27 (m, 6 H), 0.48 (d, J = 6.5 Hz, 1.5 H), 0.31 (d, J = 6.5 Hz, 1.5 H).

EXAMPLE 340
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4'-fluoro-4-isopropenyl-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4-bromo-4'-fluoro-5'-isopropyl-2'-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one (38 mg, 0.059 mmol) in 1, 4-dioxane (5 mL) was added (2-chloro-5-isopropylphenyl)boronic acid (10 mg, 0.12 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (2.4 mg, 5 mol %) and aqueous potassium hydroxide (40 µL, 3M, 2 eq.). The reaction mixture was purged with nitrogen and then sealed in a microwave vessel. The reaction vessel was subjected to microwave irradiation at 140 °C for 20 min. Crude mixture was worked up with water and EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo to give the crude product. This was purified by preparative TLC plate eluted by 20% EtOAc in hexanes to give the titled compound. LC-MS: 610.04 (M⁺). ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 7.84 (s, 1 H), 7.64 - 7.70 (m, 2 H), 7.56 (s, 0.5), 7.45 - 7.50 (m, 1.5 H), 7.18 - 7.23 (m, 1 H), 7.02 (d, J = 9.0 Hz, 0.5 H), 6.99 (d, J = 8.5 Hz, 0.5 H), 6.67 (d, J = 7.0 Hz, 0.5 H), 6.64 (d, J = 5.5 Hz, 0.5 H), 5.52 (d, J = 8.0 Hz, 0.5H), 5.43 (d, J = 8.5 Hz, 1 H), 5.26 (d, J = 8.0 Hz, 0.5 H), 5.13 - 5.17 (m, 1 H), 4.91 (d, J = 15.0 Hz, 0.5 H), 4.86 (d, J = 15.5 Hz, 0.5 H), 4.04 (d, J = 15.5 Hz, 0.5 H), 3.83 (d, J = 15.5, 0.5 H), 3.70 - 3.78 (m, 3 H), 3.14 - 3.25 (m, 1 H), 2.18 - 2.22 (m, 3 H), 1.14 - 1.29 (m, 6 H), 0.50 (d, J = 6.5 Hz, 1.5 H), 0.31 (d, J = 6.5 Hz, 1.5 H).

EXAMPLE 341
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4′-fluoro-4,5′-diisopropyl-2′-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

A solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4′-fluoro-4-isopropenyl-5′-isopropyl-2′-methoxybiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one (15 mg, 0.025 mmol) in methanol (1 mL) was subject to H₂ (balloon atmosphere) at 20 °C overnight. The crude mixture was filtered through a syringe filter. The filtrate was evaporated in vacuo and purified by preparative TLC plates developed by 20 % EtOAc in hexanes to give the titled compound. LC-MS: 612 (M+H)⁺. ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 7.84 (s, 1 H), 7.64 - 7.68 (m, 2 H), 7.30 (s, 0.5 ), 7.20 – 7.27 (m, 1.5 H), 7.13 – 7.17 (m, 1 H), 7.02 (d, J = 8.5 Hz, 0.5 H), 6.99 (d, J = 8.0 Hz, 0.5 H), 6.65 (d, J = 6.0 Hz, 0.5 H), 6.63 (d, J = 6.0 Hz, 0.5 H), 5.52 (d, J = 8.0 Hz, 0.5H), 5.25 (d, J = 8.0 Hz, 1 H), 4.87 (d, J = 15.5 Hz, 0.5 H), 4.82 (d, J = 15.5 Hz, 0.5 H), 4.03 (d, J = 15.0 Hz, 0.5 H), 3.81 (d, J = 15.0 Hz, 0.5 H), 3.69 – 3.77 (m, 4 H), 3.14 – 3.24 (m, 1 H), 2.92 – 3.02 (m, 1 H), 1.14 – 1.33 (m, 12 H), 0.48 (d, J = 6.5 Hz, 1.5 H), 0.30 (d, J = 7.0 Hz, 1.5 H).

INTERMEDIATE 25

(4S,5R)-3-(5-amino-2-bromobenzyl)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one
A mixture of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-bromo-5-nitrobenzyl)-4-methyl-1,3-oxazolidin-2-one (614 mg, 1.17 mmol), tin(II) chloride dehydrate (1.314 g, 5.823 mmol) and ethanol (3 mL) was stirred at 20 °C for 36h. Reaction crude was worked up with water. The resulting mixture was extracted with EtOAc and dried over Na₂SO₄. The titled compound was obtained as a glassy material after SiO₂ purification (Biotage 40+M, gradient, 0% to 35% EtOAc in hexanes). LC-MS: 499.05 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) δ 7.88 (s, 1H), 7.77 (s, 2H), 7.31 (d, J = 8.5, 1H), 6.77 (d, J = 2.7, 1H), 6.54 (dd, J = 8.5, 2.7 Hz, 1H), 5.69 (d, J = 8.0 Hz, 1H), 4.77 (d, J = 15.3, 1H), 4.29 (d, J = 15.3 Hz, 1H), 4.05 – 4.12 (m, 1H), 0.79 (d, J = 6.4 Hz, 3H).

INTERMEDIATE 26

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[2-bromo-5-(methylthio)benzyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-3-(5-amino-2-bromobenzyl)-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (457 mg, 0.92 mmol) in methyl disulfide (4 mL) was added tert-butyl nitrite (182 µL, d = 0.867, 1.38 mmol). The resulting mixture was stirred at 80 °C for 1 h. An aliquot indicated completion of the reaction. The titled compound was obtained as a glassy material after preparative TLC plates eluted by 25 % EtOAc in hexanes. LC-MS: 529.71 (M+1)⁺.

EXAMPLE 342
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-chloro-4'-fluoro-5'-isopropyl-4-(methylthio)biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[2'-bromo-5-(methylthio)benzyl]-4-methyl-1,3-oxazolidin-2-one (60 mg, 0.114 mmol) in 1, 4-dioxane (1 mL) was added (2-chloro-4-fluoro-5-isopropylphenyl)boronic acid (10 mg, 0.12 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (28 mg, 30 mol %) and aqueous potassium hydroxide (95 μL, 3M, 2 eq.). The reaction mixture was purged with nitrogen and then sealed in a microwave vessel. The reaction vessel was subject to microwave irradiation at 150 °C for 30 min. Crude mixture was worked up with water and EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo to give the crude product. This was purified by preparative TLC plate to afford the titled compound. LC-MS: 619.95 (M+1)+. ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 7.83 – 7.88 (m, 1 H), 7.72 (s, 1 H) 7.68 (s, 1 H), 7.30 – 7.35 (m, 1 H), 7.24 – 7.29 (m, 1H), 7.11 – 7.19 (m, 2.5H), 7.04 – 7.07 (m, 0.5 H), 5.62 (d, J = 8.2 Hz, 0.5 H), 5.24 (d, J = 8.0 Hz, 0.5 H), 4.87 (d, J = 15.3 Hz, 0.5 H), 4.70 (d, J = 15.8 Hz, 0.5 H), 3.79 – 3.98 (m, 2 H), 3.18 (m, 1 H), 2.55 (s, 1.5 H), 2.54 (s, 1.5 H), 1.20-1.29 (m, 6 H), 0.53 (d, J = 6.4 Hz, 1.5 H), 0.47 (d, J = 6.6 Hz, 1.5 H).

EXAMPLE 343
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(2'-chloro-5'-isopropyl-4-nitro biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-(2-bromo-5-nitrobenzyl)-4-methyl-1,3-oxazolidin-2-one (950 mg, 1.80 mmol) in a toluene (5.2 mL): ethanol (2.6 mL): water (1.3 mL) mixture was added (2-chloro-5-isopropylphenyl) boronic acid (325 mg, 1.64 mmol), tetrakis(triphenylphosphine)palladium(0) (188 mg, 10 mol %) and sodium carbonate (346 mg, 3.26 mmol). The resulting mixture was heated in an 80 °C oil bath for 12 h. The reaction crude was evaporated into dryness. The resulting residue was taken up by a mixture of water and EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo to give the crude product, which was purified by SiO₂ (Biotage 40+S cartridge, EtOAc/hexane, gradient) to afford the titled compound. LC-MS: 601.19 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) a 1:1 mixture of rotamers δ 8.31 – 8.30 (m, 1 H), 8.24 – 8.28 (m, 1 H), 7.85 – 7.89 (m, 1 H), 7.68-7.76 (m, 2 H), 7.42 – 7.48 (m, 2 H), 7.26 – 7.30 (m, 1 H), 7.04 – 7.11 (m, 1 H), 5.74 (d, J = 7.8 Hz, 0.5 H), 5.58 (d, J = 8.0 Hz, 0.5 H), 4.92 (d, J = 15.8 Hz, 0.5H), 4.76 (d, J = 16.2 Hz, 0.5H), 3.97 – 4.04 (m, 1.5 H), 3.82 (dt, J = 8.0, 6.6 Hz, 0.5H), 2.89 – 2.99 (m, 1H) 1.22 - 1.29 (m, 6 H), 0.60 (d, J = 6.4 Hz, 1.5 H), 0.52 (d, J = 6.6 Hz, 1.5 H).

EXAMPLE 344

![Chemical structure](image)

(4S,5R)-3-[(4-amino-2'-chloro-5'-isopropylbiphenyl-2-yl)methyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one

A solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(2'-chloro-5'-isopropyl-4-nitro biphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one (425 mg, 0.71 mmol) in methanol (10 mL) was subject to H₂ (40 psi., Parr shaker) at 20 °C for 6 h. The crude mixture was filtered through a bed of Celite (521). The filtrate was evaporated in vacuo to afford a glass. The titled compound was obtained after a preparative TLC plate developed by 20% EtOAc in hexanes. LC-MS: 571.22 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) a 6:4 mixture of rotamers δ 7.82 – 7.86
(m, 1 H), 7.65 – 7.71 (m, 2 H), 7.34 – 7.38 (m, 1 H), 7.11-7.17 (m, 2 H), 7.02 – 7.06 (m, 1 H), 6.76 – 6.82 (m, 1 H), 6.68 – 6.74 (m, 1 H), 5.58 (d, J = 8.0 Hz, 0.4 H), 5.51 (d, J = 8.2 Hz, 0.6 H), 4.82 (d, J = 15.3 Hz, 0.6H), 4.70 (d, J = 15.6 Hz, 0.4H), 3.69 - 4.00 (m, 4 H), 2.84 – 2.94 (m, 1 H), 1.19 - 1.28 (m, 6 H), 0.45 (d, J = 6.6 Hz, 1.2 H), 0.40 (d, J = 6.6 Hz, 1.8 H).

EXAMPLE 345

(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4-bromo-2'-chloro-5'-isopropylbiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one
To a solution of (4S,5R)-3-[(4-amino-2'-chloro-5'-isopropylbiphenyl-2-yl)methyl]-5-[3,5-bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (100 mg, 0.175 mmol) in bromoform (0.5 mL) and dichloromethane (1 mL) was added t-butyl nitrite (23 µL, d = 0.867, 90 % pure, 0.193 mmol). The resulting mixture was stirred at 50 °C for 1 h. An aliquot indicated completion of the reaction. The reaction crude was deposited on 2 prep-TLC plates eluted by dichloromethane to afford the title compound. LC-MS: 635.80 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) a 6:4 mixture of rotamers δ 7.84 – 7.88 (m, 1 H), 7.67 – 7.74 (m, 2 H), 7.60 – 7.63 (m, 1 H), 7.51-7.57 (m, 1 H), 7.38 – 7.42 (m, 1 H), 7.19 – 7.23 (m, 1 H), 7.11 – 7.16 (m, 1 H), 7.09 (d, J = 2.3 Hz, 0.6 H), 7.03 (d, J = 2.3 Hz, 0.4 H), 5.66 (d, J = 8.0 Hz, 0.4 H), 5.55 (d, J = 8.0 Hz, 0.6 H), 4.86 (d, J = 15.6 Hz, 0.6H), 4.70 (d, J = 15.6 Hz, 0.4H), 3.77-4.00 (m, 2 H), 2.87 – 2.95 (m, 1 H), 1.20 - 1.28 (m, 6 H), 0.53 (d, J = 6.6 Hz, 1.2 H), 0.45 (d, J = 6.4 Hz, 1.8 H).

EXAMPLE 346
(4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(2'-chloro-4-cyclopropyl-5'-isopropylbiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one

To a solution of (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(4-bromo-2'-chloro-5'-isopropylbiphenyl-2-yl)methyl]-4-methyl-1,3-oxazolidin-2-one (27 mg, 0.043 mmol) in 1, 4-dioxane (1 mL) was added cyclopropylboronic acid (9 mg, 0.10 mmol), [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) (10.4 mg, 30 mol %) and aqueous potassium hydroxide (42 μL, 3M, 3 eq.). The reaction mixture was purged with nitrogen and then sealed in a microwave vessel. The reaction vessel was subject to microwave irradiation at 120 °C for 20 min. Crude mixture was worked up with water and EtOAc. The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo to give the crude product. This was purified by preparative TLC plate eluted by 20 % EtOAc in hexanes to afford the titled compound. LC-MS: 595.99 (M+1)⁺. ¹H NMR (CDCl₃, 500 MHz) a 6:4 mixture of rotamers δ 7.82 – 7.86 (m, 1 H), 7.66 – 7.72 (m, 2 H), 7.36-7.40 (m, 1 H), 7.21 – 7.23 (m, 0.5 H), 7.11 – 7.19 (m, 3 H), 7.01 – 7.08 (m, 1.5 H), 5.58 (d, J = 8.0 Hz, 0.4 H), 5.50 (d, J = 8.0 Hz, 0.6 H), 4.88 (d, J = 15.1 Hz, 0.6H), 4.71 (d, J = 15.6 Hz, 0.4H), 3.76-3.95 (m, 2 H), 2.84 – 2.95 (m, 1 H), 1.92 – 2.00 (m, 1 H), 1.18 - 1.29 (m, 6 H), 1.00 – 1.07 (m, 2 H), 0.71 – 0.82 (m, 2 H), 0.47 (d, J = 6.6 Hz, 1.2 H), 0.42 (d, J = 6.6 Hz, 1.8 H).

Following the procedures outlined in EXAMPLE 96 the compounds listed in Table 18 were prepared from (4R,5R)-5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)-biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one:

Table 18

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**EXAMPLE 360**
(4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[5'-isopropyl-2'-(trifluoromethoxy)-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

To a solution of 80 mg of (4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one in 2mL of benzene, 1 mL of water, and 0.5 mL ethanol was added 100 mg of 5-isopropyl-2-(trifluoromethoxy)phenyl boronic acid, 0.15 mL of 2M aqueous sodium carbonate, and 21 mg of Pd(PPh$_3$)$_4$. A reflux condenser was attached, and the mixture was heated to 100°C for 24 hours, and then was diluted with 10 mL of EtOAc and 10 mL of water. The phases were separated and the aqueous phase was extracted with 10 mL of EtOAc. The combined organic phases were washed with 10 mL of brine, dried over Na$_2$SO$_4$, and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25M column, eluting with 1 CV of 2% EtOAc in hexanes, followed by a linear gradient of EtOAc in hexanes from 2 to 100% over 10 CV. The product was repurified using the same conditions to provide the title compound. Mass spectrum (ESI) 674.4 (M+1).

Following the general procedures described above the compounds listed in Table 19 were prepared.

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(4R,5R)-4-ethyl-5-[2-iodo-5-(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one

**Step A: (4S)-4-benzyl-3-butyryl-1,3-oxazolidin-2-one**

To a -78°C solution of S-benzyl-oxazolidinone in 15 mL of THF was added n-BuLi over ca. 1 min, and then butyryl chloride. The mixture was stirred for 30 min at -78°C, and then allowed to warm to r.t. over ca. 30 min. Excess acid chloride was quenched by addition of 3 mL of saturated aqueous NH₄Cl, and then the bulk of the solvent was removed by rotary evaporation. The residue was diluted with 17 mL of saturated aqueous NH₄Cl and 30 mL of CH₂Cl₂. The phases were separated and the aqueous phase was extracted with 20 mL of CH₂Cl₂. The combined organic extracts were washed with 20 mL of 1 N NaOH solution and 20 mL of brine, dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 40M column, eluting with 1 CV of 2% EtOAc in hexanes followed by a linear gradient of 2\(\rightarrow\) 100% EtOAc in hexanes over 10 CV. The residue was stored in the freezer overnight, where it crystallized. The resulting solid was triturated with hexanes, filtered, and dried under high vacuum. Mass spectrum (ESI) 178.2 (M-C₃H₇CO).

**Step B: (4S)-4-benzyl-3-([2R]-2-[(S)-hydroxy[2-iodo-5-trifluoromethyl]phenyl[methyl]butanoyl]-1,3-oxazolidin-2-one**

Following the procedure described in EXAMPLE 95, Step A, the title compound was prepared from 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde (EXAMPLE 80, Step A) and (4S)-4-benzyl-3-butyryl-1,3-oxazolidin-2-one. Mass spectrum (ESI) 530.1 (M-OH).

**Step C: (4R,5R)-4-ethyl-5-[2-iodo-5-(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one**
Following the procedure described in EXAMPLE 95, Step B, the title compound was prepared from (4S)-4-benzyl-3-((2R)-2-{(S)-hydroxy[2-iodo-5-(trifluoromethyl)phenyl]methyl}butanoyl)-1,3-oxazolidin-2-one. Mass spectrum (ESI) 386.2 (M+1).

INTERMEDIATE 28

(4R,5R)-4-benzyl-5-[2-iodo-5-(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one

Step A: (4S)-4-benzyl-3-[(3-phenylpropanoyl)-1,3-oxazolidin-2-one

Following the procedure described in INTERMEDIATE 27, Step A, the title compound was prepared from S-benzyl-oxazolidinone and hydrocinnamoyl chloride. Mass spectrum (ESI) 178.2 (M-PhC2H4CO),

Step B: (4S)-4-benzyl-3-{(2R,3S)-2-benzyl-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]propanoyl]-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 95, Step A, the title compound was prepared from 5'-isopropyl-2'-methoxy-4-(trifluoromethyl)benzhydryl-2-carbaldehyde (EXAMPLE 80, Step A) and (4S)-4-benzyl-3-(3-phenylpropanoyl)-1,3-oxazolidin-2-one. Mass spectrum (ESI) 592.3 (M-OH).

Step C: (4R,5R)-4-benzyl-5-[2-iodo-5-(trifluoromethyl)phenyl]-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 95, Step B, the title compound was prepared from (4S)-4-benzyl-3-{(2R,3S)-2-benzyl-3-hydroxy-3-[2-iodo-5-(trifluoromethyl)phenyl]propanoyl}-1,3-oxazolidin-2-one. Mass spectrum (ESI) 448.2 (M+1).

Following the general procedures outlined above, the compounds in Table 20 were prepared:

Table 20
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**EXAMPLE 372**

Alternate procedure for making (4S,5R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-y]methyl]-4-methyl-1,3-oxazolidin-2-one (Example 73)

The compound of Example 73 can be made by the procedure shown below:
Step 1: Suzuki Coupling Reaction of Boronic Acid 1 and aryl chloride 2:
A 3 M K₂CO₃ solution is prepared by adding 4.71 kg of solid K₂CO₃ to 10.3 L water. Cooling is applied to keep the solution at 20–25 °C. THF (12 L), aryl chloride 2 (2.69 kg), and the boronic acid 1 that was made in Example 78 (2.74kg) are added to the K₂CO₃ followed by a 1 L THF rinse. HPLC analysis is used to confirm the 1.00/1.00 ratio of 1/2. The solution is degassed by sparging with nitrogen gas for 70 min. The catalyst, 1,1 bis(di-tert-butylphosphino)ferrocene palladium dichloride (42g) is added as a solid and is followed by a degassed THF rinse (1.5 L). The organic layer turns dark brown immediately. The biphasic mixture is aged at 36°–40°C with vigorous stirring. After HPLC reveals complete conversion (15-18 h), the mixture is cooled to rt and the aqueous layer is removed. To the organic layer is added heptane (25.6L) and water (25.6 L) and the layers are cut. The organic layer is washed with water (19L). The organic layer is treated with 680 g Darco KB-B at rt for 60 min and filtered through solka-floc with a 10%THF/Heptane rinse (~15 L). The solvent is switched to heptane (~35 L) at ~45–50 °C until <0.5% of THF is left. More heptane is added to bring the total volume to ~45–50 L. The solution is seeded with crystals obtained from earlier runs if no seed bed forms. The slurry is slowly cooled to rt and then to ~15 °C. After aging at ~15 °C for 1–2 h, after LC of the supernatant shows ~2g/l loss of the product in the supernatant, the slurry is filtered and the product is washed with cold heptane (~25 L), providing compound 3.

Step 2: Chlorination of 3 to 4:
To a solution of biaryl 3 (3.4 kg) in DMF (17L) which was maintained at 10°C was added thionyl chloride (940ml), and then the mixture was warmed to room temperature. The mixture was aged until >99.8% conversion was measured by HPLC. Water (3.4 L) was then added. Seed crystals (1wt%) were added, and the mixture was aged for 30 min more before slowly adding 5.1 L of additional water over ~1hr. The solid was filtered and washed with first 20 L 1:1 DMF:water and then 3x 20L water. The solid product 4 was dried at 20°C until <0.1wt% water remained.
Step 3: Alkylation of the product of Example 17 with compound 4 to yield the product of Example 73:
The chiral intermediate (4S,5R)-5-[3,5-Bis(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one which
was made in Example 17 is dissolved in DMF (2.8 kg in 32.7 L) and cooled to -15°C. 2.0 M NaHMD
(3.92 L, 1.05 eq) was then added over 1.5 hr, followed by addition of the biaryl chloride 4 (2.8 kg) in
DMF. The mixture was warmed to +12°C and was aged until complete conversion took place. Then 5N
HCl (3.4 L) was added, followed by 16 L of 10% IPAC/Heptane and 34 L of water, keeping the
temperature between 10°C and 20°C throughout. The layers were cut and the organic layer was washed
twice with 14 L of 1:1 DMF:water followed by two 14 L water washes. The organic layer was assayed for
yield and was then filtered through 2.4 kg of silica gel to remove the excess oxazolidinone to <0.5%. The
silica was washed with 5% IPAC/Heptane. The combined organic solutions were distilled to remove
IPAC to <1%. The warm heptane solution was then transferred slowly into a 20°C heptane solution
containing 10 wt% seed. The slurry was then cooled to -20°C and filtered. The filter cake was washed
with cold heptane and was then dried, yielding the compound that was originally made in Example 73.

(4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-ido-3-nitro-5-(trifluoromethyl)phenyl]-4-
methyl-1,3-oxazolidin-2-one

(4R,5R)-3-[3,5-Bis(trifluoromethyl)benzyl]-5-[2-ido-5-(trifluoromethyl)phenyl]-4-methyl-1,3-
oxazolidin-2-one was added in portions to 2 mL of fuming nitric acid at 0°C. The reaction
mixture was stirred overnight at r.t., and then heated to 75°C for 4 h. The reaction mixture was
cooled and then added dropwise to a rapidly stirred mixture of 10 mL of water and 10 mL of
EtOAc. The phases were separated and the organic phase was washed with 10 mL each of
saturated NaHCO₃ and brine, dried (Na₂SO₄), and concentrated. The residue was purified by
flash chromatography on a Biotage Horizon, 25S column, eluting with 1 CV of 5% EtOAc in
hexanes followed by a linear gradient of 5→100% EtOAc in hexanes over 10 CV, to provide the
title compound. Mass spectrum (ESI) 643 (M+1).
EXAMPLE 373

(4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[4'-fluoro-5'-isopropyl-2'-methoxy-6-nitro-4-
(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one

Following the procedure described in EXAMPLE 81, 48 mg of (4R,5R)-3-[3,5-
bis(trifluoromethyl)benzyl]-5-[2-iodo-3-nitro-5-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one
and 48 mg of (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (EXAMPLE 78) provided two
atropoisomers, which were separable by flash chromatography on a Biotage Horizon, 25S column,
eluting with 1 CV of 5% EtOAc in hexanes followed by a linear gradient of 5→ 100% EtOAc in hexanes
over 10 CV, providing atropoisomer A [mass spectrum (ESI) 683.4 (M+1)] and atropoisomer B [mass
spectrum (ESI) 683.3 (M+1)].

EXAMPLE 374

(4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[4'-fluoro-5'-isopropyl-2'-methoxy-6-iodo-4-
(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (atropoisomer A)
To a solution of 17 mg of (4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[4'-fluoro-5'-isopropyl-2'-methoxy-6-nitro-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one, atropoisomer A (EXAMPLE 373), in 1 mL EtOAc was added 5 mg of PdO (Adam’s catalyst). The reaction mixture was flushed with H₂, and then stirred under an H₂ balloon for 2 h, at which point LC/MS analysis showed mostly the nitroso product. The reaction mixture was filtered through Celite, washing liberally with EtOAc, and the filtrate was concentrated and resubmitted to reaction conditions overnight. The reaction mixture was filtered through Celite, washing liberally with EtOAc, and the filtrate was concentrated. The residue was dissolved in 0.5 mL of CH₂Cl₂ and 6 μL of t-butyl nitrite was added. The reaction mixture was stirred for 1.5 h at 80°C. The reaction mixture was purified by preparative thin-layer chromatography on a 1000 μM plate, eluting with 20% EtOAc in hexanes, to provide the title compound. Mass spectrum (ESI) 764.3 (M+1).

EXAMPLE 375

(4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[4'-fluoro-5'-isopropyl-2'-methoxy-6-iodo-4-(trifluoromethyl)biphenyl-2-yl]-4-methyl-1,3-oxazolidin-2-one (atropoisomer B)

To a solution of 70 mg of (4R,5R)-3-[3,5-bis(trifluoromethyl)benzyl]-5-[2-iodo-3-nitro-4-(trifluoromethyl)phenyl]-4-methyl-1,3-oxazolidin-2-one (intermediate 30) in 1 mL EtOH was added 124 mg of SnCl₂. The reaction mixture was stirred overnight at r.t.; then another 60 mg of SnCl₂ was added and the mixture was heated to 80°C and stirred overnight. The reaction mixture was concentrated and the residue was partitioned between 10 mL of CH₂Cl₂ and 10 mL of 1 N NaOH. The aqueous phase was extracted with 2 x 10 mL of CH₂Cl₂ and the combined organics were dried (Na₂SO₄), and concentrated. Following the procedure described in EXAMPLE 81, the residue from the reduction and 70 mg of (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (EXAMPLE 78) provided the corresponding biphenyl compound as a mixture of atropoisomers. This mixture was dissolved in 0.5 mL of CH₂Cl₂ and 14 μL of t-butyl nitrite was added. The reaction mixture was stirred for 1.5 h at 80°C and then cooled and added directly to two 1000-μM thin-layer chromatography plates, eluting with 20% EtOAc in hexanes to
provide approximately equal amounts of atropoisomer A and B of the title compound. Mass spectrum (ESI) 764.2 (M+1).

INTERMEDIATE 31

4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde
Following the procedure described in EXAMPLE 81, 200 mg of 2-iodo-5-(trifluoromethyl)benzaldehyde (EXAMPLE 80, Step A) and 170 mg of (4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (EXAMPLE 78) gave the title compound. Mass spectrum (ESI) 341.3 (M+1).

INTERMEDIATE 32

5-(4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl)-1-(4-methoxybenzyl)imidazolidin-2-one
Step A: [4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl][[4-
methoxybenzyl]aminolacetonitrile
To a solution of 203 mg of 4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-carbaldehyde (INTERMEDIATE 31) in 2 mL of CH₂Cl₂ was added 100 µL of TMSCN, and then 1 mg of ZnH₂. The mixture was stirred for 30 min at r.t. p-Methoxybenzylamine (157 µL) in 2 mL of MeOH was added and the mixture was heated to reflux for 1.5 h. The reaction mixture was cooled and concentrated. The residue was purified by flash chromatography on a Biotage Horizon, 25M column, eluting with 1 CV of 2% EtOAc in hexanes followed by a linear gradient of 2 → 100% EtOAc in hexanes over 10 CV to provide the title compound. Mass spectrum (ESI) 487.2 (M+1).
Step B: 5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1-(4-
methoxybenzyl)imidazolidin-2-one
To a 0°C solution of 100 mg of [4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl][((4-
methoxybenzyl)amine)acetonitrile in 4 mL of THF was added 620 µL of a 1 M solution of LiAlH₄ in
Et₂O. The cooling bath was removed and the mixture was stirred for 45 min at r.t. The mixture was
recycled to 0°C and carefully quenched by dropwise addition of 24 µL of water, 24 µL of 15% aqueous
NaOH solution, and 60 µL of water. The solids were filtered, washing liberally with Et₂O, and the
filtrate was concentrated. The residue was dissolved in 2 mL of CH₂Cl₂ and cooled to 0°C. Triethylamine
(55 µL) and then triphosgene (32 mg) were added. The mixture was stirred for 45 min at 0°C. The
reaction mixture was partitioned between 10 mL of EtOAc and 10 mL of water. The aqueous was
extracted with 10 mL of EtOAc and the combined organics were washed with 10 mL of brine, dried
(Na₂SO₄), and concentrated. The residue was purified by flash chromatography on a Biotage Horizon,
25S column, eluting with 1 CV of 15% EtOAc in hexanes followed by a linear gradient of 15→ 100%
EtOAc in hexanes over 10 CV to provide the title compound. Mass spectrum (ESI) 517.3 (M+1).

EXAMPLE 376

![Chemical Structure](image)

1-[3,5-bis(trifluoromethyl)benzyl]-4-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-
yl]imidazolidin-2-one

Step A: 1-[3,5-bis(trifluoromethyl)benzyl]-4-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-3-(4-methoxybenzyl)imidazolidin-2-one

To a 0°C solution of 19 mg of 5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2-yl]-1-
(4-methoxybenzyl)imidazolidin-2-one (INTERMEDIATE 32) in 1 mL of DMF was added 3 mg of NaH
(60% dispersion in oil). The solution was stirred for 10 min at 0°C and then 8 µL of 3,5-
bistrifluoromethylbenzyl bromide was added and the mixture was stirred for 3 h at 0°C. The reaction
mixture was quenched with a drop of water and then filtered and purified by reverse-phase HPLC
[Waters XTerra C8 19 x 50 mm column, eluting at 20 mL/min with 90% water (0.1% TFA) to 100%
acetonitrile (0.1% TFA) over 5.15 min, hold for 1.45 min, then back to 90% water over 0.5 min] to
provide the title compound. Mass spectrum (ESI) 743.2 (M+1).
Step B: 1-[3,5-bis(trifluoromethyl)benzyl]-4-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)]biphenyl-2-yl]imidazolidin-2-one

A solution of 15 mg of 1-[3,5-bis(trifluoromethyl)benzyl]-4-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)]biphenyl-2-yl]-3-(4-methoxybenzyl)imidazolidin-2-one in 0.5 mL of TFA was stirred overnight at r.t. The reaction mixture was concentrated and then purified by reverse-phase HPLC (Waters X Terra C8 19 x 25 mm column, eluting at 20 mL/min with 90% water (0.1% TFA) to 100% acetonitrile (0.1% TFA) over 5.15 min, hold for 1.45 min, then back to 90% water over 0.5 min) to provide the title compound. Mass spectrum (ESI) 623.4 (M+1).

**EXAMPLE 377**

![Chemical Structure](image)

1-benzyl-4-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)]biphenyl-2-yl]imidazolidin-2-one

**Step A: 1-benzyl-4-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)]biphenyl-2-yl]-3-(4-methoxybenzyl)imidazolidin-2-one**

Following the procedure described in EXAMPLE 379, Step A, 31 mg of 5-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)]biphenyl-2-yl]-1-(4-methoxybenzyl)imidazolidin-2-one (INTERMEDIATE 32) and 9 µL of benzyl bromide gave the title compound. Mass spectrum (ESI) 607.5 (M+1).

**Step B: 1-benzyl-4-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)]biphenyl-2-yl]imidazolidin-2-one**

Following the procedure described in EXAMPLE 379, Step B, 5 mg of 1-benzyl-4-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)]biphenyl-2-yl]-3-(4-methoxybenzyl)imidazolidin-2-one gave the title compound. Mass spectrum (ESI) 487.4 (M+1).
WHAT IS CLAIMED IS:

1. A compound having Formula I, or a pharmaceutically acceptable salt thereof,

\[
\begin{array}{c}
\text{B} \\
\text{(R)}_2\text{C} \\
\text{N} \\
\text{Z} \\
\text{X} \\
\text{Y} \\
\text{---C---R}^5 \\
\text{R}^2 \\
\text{I}
\end{array}
\]

Y is selected from the group consisting of -C(=O)- and -(CRR^1)-;

X is selected from the group consisting of -O-, -NH-, -N(C_1-C_5 alkyl)-, and -(CRR^6)-;

Z is selected from the group consisting of -C(=O)-, -S(O)_{2-}, and -C(=N-R^9)-, wherein

R^9 is selected from the group consisting of H, -CN, and C_1-C_5 alkyl optionally substituted with 1-11 halogens;

Each R is independently selected from the group consisting of H, -C_1-C_5 alkyl, and halogen, wherein -C_1-C_5 alkyl is optionally substituted with 1-11 halogens;

B is selected from the group consisting of A^1 and A^2, wherein A^1 has the structure:

\[
\begin{array}{c}
\text{(R^a)}_p \text{A}^3 \\
\end{array}
\]

R^1 and R^6 are each selected from the group consisting of H, -C_1-C_5 alkyl, halogen, and -(C(R^2)_nA^2, wherein -C_1-C_5 alkyl is optionally substituted with 1-11 halogens;

R^2 is selected from the group consisting of H, -C_1-C_5 alkyl, halogen, A^1, and -(C(R^2)_nA^2, wherein -C_1-C_5 alkyl is optionally substituted with 1-11 halogens;

Wherein one of B and R^2 is A^1; and one of B, R^1, R^2, and R^6 is A^2 or -(C(R^2)_nA^2; so that the compound of Formula I comprises one group A^1 and one group A^2;

A^3 is selected from the group consisting of:

(a) an aromatic ring selected from phenyl and naphthyl;
(b) a phenyl ring fused to a 5-7 membered non-aromatic cycloalkyl ring, which optionally comprises 1-2 double bonds;
(c) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and \(-\text{N(O)}\), and optionally also comprising 1-3 double bonds and a carbonyl group, wherein the point of attachment of A\(^3\) to the phenyl ring to which A\(^3\) is attached is a carbon atom; and
(d) a benzo heterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and \(-\text{S(O)}X\) and optionally 1-2 double bonds, wherein the point of attachment of A\(^3\) to the phenyl ring to which A\(^3\) is attached is a carbon atom;

A\(^2\) is selected from the group consisting of:
(a) an aromatic ring selected from phenyl and naphthyl;
(b) a phenyl ring fused to a 5-7 membered non-aromatic cycloalkyl ring, which optionally comprises 1-2 double bonds;
(c) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and \(-\text{N(O)}\), and optionally also comprising 1-3 double bonds and a carbonyl group;
(d) a benzo heterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and S and optionally 1-2 double bonds; and
(e) a -C\(_3\)-C\(_8\) cycloalkyl ring optionally having 1-3 double bonds;

wherein A\(^3\) and A\(^2\) are each optionally substituted with 1-5 substituent groups independently selected from R\(^a\);

Each R\(^a\) is independently selected from the group consisting of -C\(_1\)-C\(_6\) alkyl, -C\(_2\)-C\(_6\) alkenyl, -C\(_2\)-C\(_6\) alkynyl, -C\(_3\)-C\(_8\) cycloalkyl optionally having 1-3 double bonds, -OC\(_1\)-C\(_6\) alkyl, -OC\(_2\)-C\(_6\) alkenyl, -OC\(_2\)-C\(_6\) alkynyl, -OC\(_3\)-C\(_8\) cycloalkyl optionally having 1-3 double bonds, -C(=O)C\(_1\)-C\(_6\) alkyl, -C(=O)C\(_3\)-C\(_8\) cycloalkyl, -C(=O)H, -CO\(_2\)H, -CO\(_2\)C\(_1\)-C\(_6\) alkyl, -C(=O)SC\(_1\)-C\(_6\) alkyl, -OH, -NR\(^3\)R\(^4\), -C(=O)NR\(^3\)R\(^4\), -NR\(^3\)C(=O)OC\(_1\)-C\(_6\) alkyl, -NR\(^3\)C(=O)NR\(^3\)R\(^4\), -S(O)\(_x\)C\(_1\)-C\(_6\) alkyl, -S(O)\(_y\)NR\(^3\)R\(^4\), -NR\(^3\)S(O)\(_x\)NR\(^3\)R\(^4\), halogen, -CN, -NO\(_2\), and a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring optionally also comprising a carbonyl group and optionally also comprising 1-3 double bonds, wherein the point of attachment of said heterocyclic ring to the ring to which R\(^a\) is attached is a carbon atom, wherein said heterocyclic ring is optionally substituted with 1-5 substituent groups independently selected from halogen, -C\(_1\)-C\(_3\) alkyl, and -OC\(_1\)-C\(_3\) alkyl, wherein -C\(_1\)-C\(_3\) alkyl and -OC\(_1\)-C\(_3\) alkyl are optionally substituted with 1-7 halogens;
wherein for compounds in which $R^a$ is selected from the group consisting of $-C_1-C_6$ alkyl, $-C_2-C_6$ alkenyl, $-C_2-C_6$ alkynyl, $-C_3-C_8$ cycloalkyl optionally having 1-3 double bonds, $-OC_1-C_6$ alkyl, $-OC_2-C_6$ alkenyl, $-OC_2-C_6$ alkynyl, $-OC_3-C_8$ cycloalkyl optionally having 1-3 double bonds, $-C(=O)C_1-C_6$ alkyl, $-C(=O)C_3-C_8$ cycloalkyl, $-CO_2C_1-C_6$ alkyl, $-C(=O)SC_1-C_6$ alkyl, $-NR^3C(=O)OC_1-C_6$ alkyl, and $-S(O)_xC_1-C_6$ alkyl, then $R^a$ is optionally substituted with 1-15 halogens and is optionally also substituted with 1-3 substituent groups independently selected from (a) $-OH$, (b) $-CN$, (c) $-NR^3R^4$, (d) $-C_3-C_8$ cycloalkyl optionally having 1-3 double bonds and optionally substituted with 1-15 halogens, (e) $-OC_1-C_4$ alkyl optionally substituted with 1-9 halogens and optionally also substituted with 1-2 substituent groups independently selected from $-OC_1-C_2$ alkyl and phenyl, (f) $-OC_3-C_8$ cycloalkyl optionally having 1-3 double bonds and optionally substituted with 1-15 halogens, (g) $-CO_2H$, (h) $-C(=O)CH_3$, (i) $-CO_2C_1-C_4$ alkyl which is optionally substituted with 1-9 halogens, and (j) phenyl which is optionally substituted with 1-3 substituent groups independently selected from halogen, $-CH_3$, $-CF_3$, $-OCH_3$, and $-OCF_3$;

with the proviso that when $B$ is $A^1$, and $X$ and $Y$ are $-CH_2-$, and $Z$ is $-C(=O)-$, and $R^2$ is phenyl which has a substituent $R^a$ in the 4-position, wherein $R^a$ is $-OC_1-C_6$ alkyl which is optionally substituted as described above, then there are no other $R^a$ substituents on $R^2$ in which $R^a$ is selected from $-OH$, $-OC_1-C_6$ alkyl, $-OC_2-C_6$ alkenyl, $-OC_2-C_6$ alkynyl, and $-OC_3-C_8$ cycloalkyl optionally having 1-3 double bonds, optionally substituted as described above.

$n$ is 0 or 1;
$p$ is an integer from 0-4;
$x$ is 0, 1, or 2;
y is 1 or 2;

$R^3$ and $R^4$ are each independently selected from $H$, $-C_1-C_5$ alkyl, $-C(=O)C_1-C_5$ alkyl and $-S(O)_xC_1-C_5$ alkyl, wherein $-C_1-C_5$ alkyl in all instances is optionally substituted with 1-11 halogens; and

$R^5$ is selected from the group consisting of $H$, $-OH$, $-C_1-C_5$ alkyl, and halogen, wherein $-C_1-C_5$ alkyl is optionally substituted with 1-11 halogens.

2. The compound of Claim 1, which is selected from the group consisting of compounds having Formula Ia, Ib, and Id, or a pharmaceutically acceptable salt thereof:
3. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Y is -(CRR₁)-;

R and R⁶ are each independently selected from the group consisting of H and -C₁-C₅ alkyl, wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens;

R¹ is selected from the group consisting of H, -C₁-C₅ alkyl, and -(C(R)₂)ₙA², wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens;
Wherein one of B and R² is A¹; and one of B, R¹, and R² is A² or -\{(R)\}_nA²; so that the compound of Formula I comprises one group A¹ and one group A²;

A³ is selected from the group consisting of:
(a) an aromatic ring selected from phenyl and naphthyl;
(b) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and \(-\text{N(O)}\)-, and optionally also comprising 1-3 double bonds and a carbonyl group, wherein the point of attachment of A³ to the phenyl ring to which A³ is attached is a carbon atom; and
(c) a benzo heterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and \(-\text{S(O)}_X\)- and optionally 1-2 double bonds, wherein the point of attachment of A³ to the phenyl ring to which A³ is attached is a carbon atom;

A² is selected from the group consisting of:
(a) an aromatic ring selected from phenyl and naphthyl;
(b) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and \(-\text{N(O)}\)-, and optionally also comprising 1-3 double bonds and a carbonyl group;
(c) a benzo heterocyclic ring comprising a phenyl ring fused to a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and S and optionally 1-2 double bonds; and
(d) a \(-\text{C}_3\text{-C}_8\) cycloalkyl ring optionally having 1-3 double bonds;

wherein A³ and A² are each optionally substituted with 1-4 substituent groups independently selected from R³;

Each R³ is independently selected from the group consisting of \(-\text{C}_1\text{-C}_6\) alkyl, \(-\text{C}_2\text{-C}_6\) alkenyl, \(-\text{C}_3\text{-C}_8\) cycloalkyl optionally having 1-3 double bonds, \(-\text{OC}_1\text{-C}_6\) alkyl, \(-\text{C}(=\text{O})\text{_C}_1\text{-C}_6\) alkyl, \(-\text{C}(=\text{O})\text{_H}\), \(-\text{CO}_2\text{H}\), \(-\text{CO}_2\text{C}_1\text{-C}_6\) alkyl, \(-\text{OH}\), \(-\text{NR}_3\text{R}_4\), \(-\text{NR}_3\text{C}(=\text{O})\text{OC}_1\text{-C}_6\) alkyl, \(-\text{S(O)}_3\text{C}_1\text{-C}_6\) alkyl, halogen, \(-\text{CN}\), \(-\text{NO}_2\), and a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, and O, said heterocyclic ring optionally also comprising a carbonyl group and optionally also comprising 1-3 double bonds, wherein the point of attachment of said heterocyclic ring to the ring to which R³ is attached is a carbon atom, wherein said heterocyclic ring is optionally substituted with 1-5 substituent groups independently selected from halogen, \(-\text{C}_1\text{-C}_3\) alkyl, and \(-\text{OC}_1\text{-C}_3\) alkyl, wherein \(-\text{C}_1\text{-C}_3\) alkyl and \(-\text{OC}_1\text{-C}_3\) alkyl are optionally substituted with 1-7 halogens;

wherein for compounds in which R³ is selected from the group consisting of \(-\text{C}_1\text{-C}_6\) alkyl, \(-\text{C}_2\text{-C}_6\) alkenyl, \(-\text{C}_3\text{-C}_8\) cycloalkyl optionally having 1-3 double bonds, \(-\text{OC}_1\text{-C}_6\) alkyl, \(-\text{C}(=\text{O})\text{_C}_1\) - 239 -
C₆alkyl, -CO₂C₁-C₆alkyl, -NR₃C(=O)OC₁-C₆alkyl, and -S(O)ₓC₁-C₆alkyl, R⁸ is optionally substituted with 1-15 halogens and is optionally also substituted with one substituent group selected from (a) -OH, (b) -NR³R⁴, (c) -OC₁-C₄alkyl optionally substituted with 1-9 halogens and optionally also substituted with 1-2 substituent groups independently selected from -OC₁-C₂ alkyl and phenyl, and (d) phenyl which is optionally substituted with 1-3 groups independently selected from halogen, -CH₃, -CF₃, -OCH₃, and -OCF₃;

with the proviso that when B is A¹, and X and Y are -CH₂-, and Z is -C(=O)-, and R² is phenyl which has a substituent R⁸ in the 4-position, wherein R⁸ is -OC₁-C₆alkyl which is optionally substituted as described above, then there are no other R⁸ substituents on R² in which R⁸ is -OH or -OC₁-C₆alkyl which is optionally substituted as described above;

p is an integer from 0-2;

R³ and R⁴ are each independently selected from H and -C₁-C₅ alkyl, wherein -C₁-C₅ alkyl in all instances is optionally substituted with 1-11 halogens; and

R⁵ is selected from the group consisting of H, -OH, and -C₁-C₅ alkyl, wherein -C₁-C₅ alkyl is optionally substituted with 1-11 halogens.

4. The compound of Claim 1, or a pharmaceutically acceptable salt thereof,

wherein:

Y is -(CRR¹)⁻;

Z is selected from the group consisting of -C(=O)-, -S(O)₂-, and -C(=N-R⁹)-, wherein R⁹ is selected from the group consisting of H, -CN, and CH₃;

Each R is independently selected from the group consisting of H and C₁-C₂ alkyl;

R⁶ is selected from the group consisting of H and -C₁-C₃ alkyl, wherein C₁-C₃ alkyl is optionally substituted with 1-5 halogens;

R¹ is selected from the group consisting of H, -C₁-C₃ alkyl, and -(C(R)₂)ₙA², wherein -C₁-C₃ alkyl is optionally substituted with 1-5 halogens;

R² is selected from the group consisting of H, -C₁-C₃ alkyl, A¹, and -(C(R)₂)ₙA², wherein -C₁-C₃ alkyl is optionally substituted with 1-5 halogens;
Wherein one of B and R² is A¹; and one of B, R¹, and R² is A² or -(R²)ₙA²; so that the compound of Formula I comprises one group A¹ and one group A²;

A³ is selected from the group consisting of:
(a) phenyl;
(b) a 5-6-membered aromatic heterocyclic ring having 1-2 heteroatoms independently selected from N, S, O, and -N(O)-, wherein the point of attachment of A³ to the phenyl ring to which A³ is attached is a carbon atom; and
(c) a benzoheterocyclic ring comprising a phenyl ring fused to a 5-membered aromatic heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and -S(O)ₓ, wherein the point of attachment of A³ to the phenyl ring to which A³ is attached is a carbon atom;

A² is selected from the group consisting of:
(a) phenyl;
(b) a 5-6-membered heterocyclic ring having 1-4 heteroatoms independently selected from N, S, O, and -N(O)-, and optionally also comprising 1-3 double bonds;
(c) a benzoheterocyclic ring comprising a phenyl ring fused to a 5-membered heterocyclic ring having 1-2 heteroatoms independently selected from O, N, and S; and
(d) a -C₅-C₆ cycloalkyl ring;

wherein A³ and A² are each optionally substituted with 1-4 substituent groups independently selected from R³;

Each R³ is independently selected from the group consisting of -C₁-C₄ alkyl, -C₂-C₄ alkenyl, cyclopropyl, -OC₁-C₂alkyl, -C(=O)C₁-C₂alkyl, -C(=O)H, -CO₂C₁-C₄alkyl, -OH, -NR³R⁴, -NR³C(=O)OC₁-C₄alkyl, -S(O)ₓC₁-C₂ alkyl, halogen, -CN, -NO₂, and a 5-6-membered heterocyclic ring having 1-2 heteroatoms independently selected from N, S, and O, wherein the point of attachment of said heterocyclic ring to the ring to which R³ is attached ring is a carbon atom, wherein said heterocyclic ring is optionally substituted with 1-5 substituent groups independently selected from halogen;

wherein for compounds in which R³ is selected from the group consisting of -C₁-C₄ alkyl, -C₂-C₄ alkenyl, -OC₁-C₂alkyl, -C(=O)C₁-C₂alkyl, -CO₂C₁-C₄alkyl, -NR³C(=O)OC₁-C₄alkyl, and -S(O)ₓC₁-C₂ alkyl, the alky group of R³ is optionally substituted with 1-5 halogens and is optionally also substituted with one substituent group selected from (a) -OH, (b) -NR³R⁴, (c) -OCH₃ optionally substituted with 1-3 fluorine atoms and optionally also substituted with one phenyl group, and (d) phenyl which is optionally substituted with 1-3 groups independently selected from halogen, -CH₃, -CF₃, -OCH₃, and -OCF₃;

with the proviso that when B is A¹, and X and Y are -CH₂-, and Z is -(=O)-, and R² is phenyl which has a substituent R³ in the 4-position, wherein R³ is -OC₁-C₂alkyl which is optionally
substituted as described above, then there are no other Ra substitutents on R² in which Ra is selected from -OH or -OC₁₋₃alkyl which is optionally substituted as described above;

p is an integer from 0-2; and

R³, R⁴, and R⁵ are each independently selected from H and -C₁₋₃ alkyl.

5. The compound of Claim 4, or a pharmaceutically acceptable salt thereof,

wherein

A³ is selected from the group consisting of phenyl, thienyl, imidazolyl, pyrrolyl, pyrazolyl, pyridyl, N-oxido-pyridyl, thiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, benzothienyl, benzothienyl-S-oxide, and benzothienyl-S-dioxide; and

A² is selected from the group consisting of phenyl, thienyl, imidazolyl, thiazolyl, pyrrolyl, pyrazolyl, 1,2,4-triazolyl, tetrazolyl, benzodioxolyl, pyridyl, N-oxido-pyridyl, pyrazinyl, pyrimidinyl, pyrazinyl, cyclopentyl, cyclohexyl, and tetrahydropyranyl.

6. The compound of Claim 5, or a pharmaceutically acceptable salt thereof,

wherein

X is selected from the group consisting of -O-, -NH-, and -N(C₁₋₃alkyl)⁻; and

Z is -C(=O)⁻.

7. The compound of Claim 4, or a pharmaceutically acceptable salt thereof,

wherein A² and A³ are both phenyl; and

Rᵃ is selected from the group consisting of -C₁₋₃alkyl which is optionally substituted with 1-5 fluorine atoms and is optionally also substituted with one group selected from -OH and -OCH₃; -OC₁₋₃alkyl, which is optionally substituted with 1-3 fluorine atoms; -C₂₋₄ alkenyl; -C₁₋₃ alkyl which is substituted with one group -NR³R⁴; -C₁₋₃ alkyl-O-C₁₋₃ alkyl-phenyl; cyclopropyl; -C(=O)H; -OH; -NR³R⁴; -S(O)ₓC₁₋₃ alkyl; halogen; -CN; -NO₂; and a 5-6-membered heterocyclic ring comprising 1-2 oxygen atoms which is optionally substituted with C₁₋₃alkyl;

subject to the same proviso as in Claim 4.

8. The compound of Claim 7 having Formula II, or a pharmaceutically acceptable salt thereof, wherein:
R⁷ is selected from the group consisting of Cl and -CF₃;
Each Rᵇ is independently selected from the group consisting of -C₁-C₃ alkyl, -OCH₃,
and F;

R¹ is selected from the group consisting of H and -C₁-C₂ alkyl;
Rᶜ is selected from the group consisting of halogen, -CH₃ -CF₃, and -CN;
q is 2 or 3; and
t is an integer from 0-2.

9. The compound of Claim 7 having Formula Ij, or a pharmaceutically acceptable
acceptable salt thereof, wherein:

R⁷ is selected from the group consisting of Cl and -CF₃;
Each Rᵇ is independently selected from the group consisting of -C₁-C₃ alkyl, -OCH₃,
and F;

R¹ is selected from the group consisting of H and -C₁-C₂ alkyl;
Rᶜ is selected from the group consisting of halogen, -CH₃ -CF₃, and -CN;
q is 2 or 3; and
t is an integer from 0-2.
10. The compound of Claim 1, or a pharmaceutically acceptable salt thereof, wherein

A³ is phenyl, which is optionally substituted with 1-4 substituent groups R⁸, wherein R⁸ is independently selected from -C₁-C₅ alkyl, -OC₁-C₃ alkyl, -CO₂C₁-C₃ alkyl, -CO₂H, halogen, -NR³R⁴, -C(=O)C₁-C₃ alkyl, -C(=O)H, -C(=O)NR³R⁴, -SC₁-C₃ alkyl, -C₂-C₃ alkenyl, -CN, -NO₂, and 1,2,4-oxadiazoxy, wherein -C₁-C₃ alkyl and -C₁-C₅ alkyl in all occurrences is optionally substituted with 1-6 substituents independently selected from 1-5 halogens and one -OH group; and -C₂-C₃ alkenyl is optionally substituted with 1-3 halogens;

A² is selected from the group consisting of phenyl, cyclohexyl, and a heterocyclic 5-6 membered ring comprising 1-2 heteroatoms independently selected from O, N, S, and -N(O)- and optionally also comprising 1-3 double bonds, wherein A² is optionally substituted with 1-2 substituent groups independently selected from -C₁-C₄ alkyl, -OC₁-C₃ alkyl, -NO₂, -CN, -S(O)₂C₁-C₃ alkyl, -NHS(O)₂C₁-C₃ alkyl, -NR³R⁴, -NR³C(=O)R⁴, -C₂-C₃ alkenyl, -C(=O)NR³R⁴, halogen, and pyridyl, wherein C₁-C₃ alkyl, C₁-C₄ alkyl, and C₂-C₃ alkenyl in all instances is optionally substituted with 1-3 halogens, with the proviso that when B is A¹, and X and Y are -CH₂-, and Z is -C(=O)-, and R² is phenyl which has a substituent R⁸ in the 4-position in which R⁸ is -OC₁-C₃ alkyl which is optionally substituted as described above, then there are no other Ra substituents on R² in which R⁸ is -OC₁-C₃ alkyl optionally substituted as described above;

R³ and R⁴ are each independently selected from H and -C₁-C₃ alkyl; and

p is 0-2.

11. The compound of Claim 10, or a pharmaceutically acceptable salt thereof, wherein A¹ is

![Diagram]

R⁷ and R⁸ are each independently selected from the group consisting of H, halogen, -NR³R⁴, -C₁-C₃ alkyl, -OC₁-C₃ alkyl, -CN, -NO₂, and pyridyl, wherein C₁-C₃ alkyl in all instances is optionally substituted with 1-3 halogens; and
A² is selected from the group consisting of phenyl, pyridyl, and cyclohexyl, wherein A² is optionally substituted with 1-2 substituents independently selected from -C₁₋₄ alkyl, -OC₁₋₃ alkyl, -NO₂, -CN, and halogen, wherein C₁₋₄ alkyl and C₁₋₃ alkyl in all uses is optionally substituted with 1-3 halogens, with the proviso that when B is A¹, and X and Y are -CH₂-, and Z is -C(=O)-, and R² is phenyl which has a substituent R³ in the 4-position, wherein R³ is -OC₁₋₃ alkyl which is optionally substituted with 1-3 halogens, then there are no other Ra substituents on R² in which R³ is selected from -OC₁₋₃ alkyl which is optionally substituted with 1-3 halogens.

12. The compound of Claim 11, or a pharmaceutically acceptable salt thereof, wherein A¹ is

R⁷ is selected from the group consisting of H, halogen, -NR³R⁴, -C₁₋₃ alkyl, -OC₁₋₃ alkyl, -CN, -NO₂, and pyridyl, wherein C₁₋₃ alkyl in all instances is optionally substituted with 1-3 halogens; and

R⁸ is selected from the group consisting of H, halogen, -CH₃, -CF₃, -OCH₃, and -OCF₃.

13. A pharmaceutical composition comprising the compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

14. The compound of Claim 4, which is selected from the group consisting of the following compounds, or a pharmaceutically acceptable salt thereof:
15. The compound of Claim 4, which is selected from the group consisting of compounds with the formula (a) to (c), or a pharmaceutically acceptable salt thereof:

(a) 

wherein R is selected from the group consisting of
wherein R is selected from the group consisting of

- $\text{F}$
- $\text{Cl}$
- $\text{NC}$
- $\text{Cyl}$
- $\text{Ph}$
and (c)

wherein R is selected from the group consisting of

- [Diagram of structures]

- [Diagram of structures]

- [Diagram of structures]

- [Diagram of structures]

- [Diagram of structures]

and

- [Diagram of structures]

- [Diagram of structures]
16. The compound of Claim 4, which is selected from the group consisting of the following compounds, or a pharmaceutically acceptable salt thereof:
17. The compound of Claim 4, selected from the group consisting of compounds having the formula (a) to (k), or a pharmaceutically acceptable salt thereof:

(a)  

wherein \( A^3, A^2, \) and \( Z \) for the compounds (1) to (6) are selected from the group consisting of:

<table>
<thead>
<tr>
<th></th>
<th>( A^3 )</th>
<th>( A^2 )</th>
<th>( Z )</th>
</tr>
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<tbody>
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<td>( x^d )( F )</td>
<td>CO</td>
</tr>
<tr>
<td>(2)</td>
<td>( O )( \text{F} )</td>
<td>( x^d )( F )</td>
<td>CO</td>
</tr>
<tr>
<td>(3)</td>
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<td>( x^d )( CF_3 )</td>
<td>CO</td>
</tr>
<tr>
<td>(4)</td>
<td>![Chemical Structure]</td>
<td>![Chemical Structure]</td>
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<td>----</td>
</tr>
<tr>
<td>(5)</td>
<td>![Chemical Structure]</td>
<td>![Chemical Structure]</td>
<td>CO and</td>
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<tr>
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<td>![Chemical Structure]</td>
<td>SO₂</td>
</tr>
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</table>

(b)

wherein \(A^3\) is selected from the group consisting of:

- ![Chemical Structure]
- ![Chemical Structure]
- ![Chemical Structure]
- ![Chemical Structure]
- ![Chemical Structure]
wherein A3 and A2 for the compounds (1) to (6) are selected from the group consisting of:
<table>
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<tr>
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<th>A²</th>
</tr>
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<tr>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
<td><img src="Image5" alt="Chemical Structure" /></td>
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<tr>
<td>4</td>
<td><img src="Image7" alt="Chemical Structure" /></td>
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</tr>
<tr>
<td>5</td>
<td><img src="Image9" alt="Chemical Structure" /></td>
<td><img src="Image10" alt="Chemical Structure" /> and</td>
</tr>
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<td>6</td>
<td><img src="Image11" alt="Chemical Structure" /></td>
<td><img src="Image12" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>
wherein R is selected from the group consisting of

![Diagram of chemical structures](image-url)
and
wherein R is Et or n-Pr;

wherein R and A3 for the compounds (1) to (4) are selected from the group consisting of

<table>
<thead>
<tr>
<th></th>
<th>R</th>
<th>A3</th>
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<tr>
<td>(1)</td>
<td><img src="image" alt="Chemical Structure" /></td>
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<tr>
<td>(3)</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td><img src="image" alt="Chemical Structure" /> and</td>
</tr>
</tbody>
</table>
wherein R is selected from the group consisting of:
wherein $A^2$ is selected from the group consisting of

- $\text{F}$
- $\text{OMe}$
- $\text{Cl}$
- with and
wherein R is selected from the group consisting of

- Chlorine
- Fluorine
- Ether
- Methoxy
- Tetrafluoromethyl
- Cbz
- Pyridine
wherein $A^3$ is selected from the group consisting of:

\begin{align*}
&\text{F} \quad &\text{Cl} \\
&\text{Cl} \quad &\text{Cl} \\
&\text{F} \quad &\text{Cl} \\
&\text{CF}_3 \quad &\text{CF}_3 \\
&\text{F}_3\text{C} \quad &\text{Cl} \\
&\text{F}_3\text{C} \quad &\text{Cl} \\
\end{align*}

and

\begin{align*}
&\text{F}_3\text{CO} \quad &\text{Cl} \\
\end{align*}
wherein A³, R² and R³ for the compounds (1) to (3) are selected from the group consisting of:

<table>
<thead>
<tr>
<th>A³</th>
<th>R²</th>
<th>R³</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Et</td>
</tr>
<tr>
<td>(2)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Et</td>
</tr>
<tr>
<td>(3)</td>
<td><img src="image5.png" alt="Image" /></td>
<td>Et</td>
</tr>
</tbody>
</table>

18. A method of treating atherosclerosis in a patient in need of treatment comprising the administration of a therapeutically effective amount of the compound of Claim 1 to said patient, or a pharmaceutically acceptable salt thereof.

19. A method of raising HDL-C in a patient in need of treatment comprising the administration of a therapeutically effective amount of the compound of Claim 1 to said patient, or a pharmaceutically acceptable salt thereof.

20. The use of the compound of Claim 1 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of atherosclerosis.
21. A pharmaceutical composition comprising the compound of Claim 1 or a pharmaceutically acceptable salt thereof, a pharmaceutically acceptable carrier, and one or more active ingredients selected from the group consisting of:

(i) HMG-CoA reductase inhibitors;
(ii) bile acid sequestrants;
(iii) niacin and related compounds;
(iv) PPARα agonists;
(v) cholesterol absorption inhibitors;
(vi) acyl CoA:cholesterol acyltransferase (ACAT) inhibitors;
(vii) phenolic anti-oxidants;
(viii) microsomal triglyceride transfer protein (MTP)/ApoB secretion inhibitors;
(ix) anti-oxidant vitamins;
(x) thyromimetics;
(xi) LDL (low density lipoprotein) receptor inducers;
(xii) platelet aggregation inhibitors;
(xiii) vitamin B12 (also known as cyanocobalamin);
(xiv) folic acid or a pharmaceutically acceptable salt or ester thereof;
(xv) FXR and LXR ligands;
(xvi) agents that enhance ABCA1 gene expression; and
(xvii) ileal bile acid transporters.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7  C07D263/20  C07D263/22  C07D263/24  C07D233/32  C07D207/26
C07D285/10  C07D401/04  C07D413/04  C07D413/06  C07D413/10
C07D417/04  C07D417/10  A61K31/4015  A61K31/4166  A61K31/421

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7  C07D  A61K  A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>A</td>
<td>WO 99/15487 A (BAYER AKTIENGESELLSCHAFT) 1 April 1999 (1999–04–01) the whole document</td>
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<tr>
<td>A</td>
<td>EP 0 605 729 A (TAIHO PHARMACEUTICAL CO., LTD.) 13 July 1994 (1994–07–13) the whole document</td>
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</table>

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents:
- 'A' document defining the general state of the art which is not considered to be of particular relevance
- 'E' earlier document but published on or after the international filing date
- 'L' document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- 'O' document relating to an oral disclosure, use, exhibition or other means
- 'P' document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search: 17 October 2005
Date of mailing of the international search report: 21/10/2005
Name and mailing address of the ISA:
European Patent Office, P.B. 6918 Patentlaan 2
NL – 2280 HJ Rijswijk
Tel. (+31–70) 540-2040, Tx. 31 865 epo nl, Fax (+31–70) 340-3016
Authorized officer: Allard, M

Form PCT/ISA/2/10 (second sheet) (January 2004)
INTERNATIONAL SEARCH REPORT

Box II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [x] Claims Nos.: Because they relate to subject matter not required to be searched by this Authority, namely:
   Although claims 18 and 19 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.: Because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.: Because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

2. [ ] As all searchable claims could be searched without effort Justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (January 2004)
<table>
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