Abstract:

The invention relates to 2-aza-bicyclo[2.2.2]octane compounds, their pharmaceutically acceptable salts and pharmaceutically acceptable compositions comprising such a compound. The invention also relates to uses of the compounds for modulating the glycine transporter 1 (GlyT1) and for the treatment of psychosis, cognitive disorders, bipolar disorders, depression disorders, anxiety disorders, posttraumatic stress disorders and pain.
2-AZA-BICYCLO[2.2.2]OCTANE COMPOUNDS AND USES THEREOF

CROSS-REFERENCE TO RELATED PATENT APPLICATION

[1] This patent claims the benefit of priority to U.S. Provisional Patent Application No. 61/148,015 (filed January 28, 2009). The entire text of the above patent application is incorporated by reference into this patent.

FIELD OF INVENTION

[2] This invention relates to 2-aza-bicyclo[2.2.2]octane compounds (and salts thereof). This invention also relates to pharmaceutical compositions comprising such a compound, uses of such a compound (including, for example, treatment methods and medicament preparations), and processes for making such a compound.

BACKGROUND

[3] Since the discovery of the unique behavioral effects of PCP, a number of studies have been performed to evaluate the degree of similarity between the symptoms and neurocognitive deficits induced by NMDA antagonists and those observed endogenously in schizophrenia. Studies were conducted first using PCP itself, until the drug was withdrawn from the market in the late 1960s. In those studies, PCP was found to induce not only symptoms, but also neuropsychological deficits that closely resemble those of schizophrenia. More recent studies with ketamine strongly support and extend the initial observations. Such studies led to the hypothesis that the psychotic and cognitive effects experienced by both disease sufferers and people treated with NMDA antagonists resulted from reduced NMDA receptor mediated neurotransmission. This has been termed the NMDA hypofunction hypothesis for schizophrenia. According to the hypothesis, novel treatments for schizophrenia and other psychotic diseases may result from increased NMDA activation in the central nervous system. In principle, this could be achieved by treatment with direct NMDA agonists; however, such compounds are known to cause neurotoxicity. Glycine is a requisite co-agonist for NMDA receptor, and increases in its concentration may result in increased NMDA activation. The concentration of glycine is regulated by the action of the glycine transporter. Treatment with compounds that modulate the glycine transporter may
increase the synaptic glycine level and thus result in NMDAr potentiation and improvement in
disease symptomology.

compounds corresponding in structure to:

\[
\begin{aligned}
&\text{R}^1 \text{H}N \text{O} \quad \text{(R}_2^2)_n \\
&\text{R}^1 \text{is selected from H and Ci-C}_6\text{-alkyl;}
\end{aligned}
\]

\[
\begin{aligned}
each \text{R}^2 \text{is independently selected from halogen, -CN, C}_2\text{-C}_6\text{-alkenyl,}
&\text{C}_2\text{-C}_6\text{-alkynyl, C}_3\text{-C}_6\text{-cycloalkyl, -SO}_2\text{NR}_3\text{R}_4, -\text{NH}_2, -\text{S-Ci-C}_6\text{-alkyl, C}_1\text{-C}_6\text{-alkoxy, and Ci-C}_6\text{-alkyl, wherein:}
\end{aligned}
\]

\[
\begin{aligned}
&\text{the Ci-C}_6\text{-alkyl and Ci-C}_6\text{-alkoxy are optionally}
&\text{substituted with one or more halogens;}
&\text{each } \text{R}^3 \text{and } \text{R}^4 \text{is independently selected from H and Ci-C}_6\text{-alkyl; and}
&\text{n is selected from 1, 2, and 3.}
\end{aligned}
\]

[5] Many people around the world continue to suffer from various psychoses and
other cognitive disorders despite existing treatments. Accordingly, there is a need for new
compounds and/or compositions, such as those that modulate the glycine transporter and
methods of treatment of such diseases, disorders, or conditions employing such compounds or
compositions.

U.S. Patent Appl. Publ. No. 2009/0030033 discusses the use of such compounds for treating
conditions, including schizophrenia, bi-polar disorder, mania and manic depression, anxiety,
and other cognitive conditions.


SUMMARY OF INVENTION

[6] This invention relates to, inter alia, 2-aza-bicyclo[2.2.2]octane compounds; treatment methods using the 2-aza-bicyclo[2.2.2]octane compounds (e.g., method for treating psychosis and other cognitive disorders and as pharmacological tools); uses of the 2-aza-bicyclo[2.2.2]octane compounds to make medicaments; compositions comprising the 2-aza-bicyclo[2.2.2]octane compounds (e.g., pharmaceutical compositions); methods for manufacturing the 2-aza-bicyclo[2.2.2]octane compounds; and intermediates used in such manufacturing methods.

[7] Briefly, this invention is directed, in part, to the compound of Formula (I) or a salt thereof. Formula (I) corresponds to:

Here:

[8] A¹ may be phenyl optionally substituted with 1, 2, or 3 R⁵ groups. Alternatively, A¹ is a 5- or 6-membered heteroaryl optionally substituted with 1, 2, or 3 R⁷ groups.

[9] A² may be phenyl substituted with 1, 2, or 3 R² groups. Alternatively, A² is a heteroaryl optionally substituted with 1, 2, or 3 R⁶ groups.

[10] R¹ is selected from hydrogen, Ci-C₆-alkyl, C₃-C₆ cycloalkyl, 3-6 membered heterocycloalkyl, Cs-Cg-cycloalkyl-C¹⁺-alkyl, aryl-C₄-alkyl, heterocycloalkyl-Ci-C₄⁺ alkyl, heteroaryl-Ci-C₄⁺-alkyl, and C₃-C₈-alkenyl. The C₃-C₈-cycloalkyl-Ci-C₄⁺-alkyl, aryl-C₄⁺, C₄⁺-alkyl, and heteroaryl-Ci-C₄⁺-alkyl, in turn, are optionally substituted with one or more independently selected halogens.

[11] Each R² is independently selected from halogen, -CN, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 5- or 6-membered heterocyclyl, -SOR, -SO₂R, -NH₂, -SR, C₁-C₆⁺ alkoxy, Ci-C₆⁺-alkyl, and C₁-C₄⁺-alkoxy-C₁-C₄⁺-alkyl. The C₁-C₆⁺-alkyl, Ci-C₆⁺-alkoxy, and C₃⁺-C₆⁺ cycloalkyl, in turn, are optionally substituted with one or more independently selected halogens. In addition, the heterocyclyl is optionally substituted with 1, 2, or 3 R⁶ groups.
[12] Each $R^5$ is independently selected from $C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, $C_1$-$C_6$-alkoxy, -CN, halogen, -$SO_2R$, -$SOR$, -$SR$, and heterocyclyl. The $C_r$-$C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, and $C_i$-$C_6$-alkoxy, in turn, are optionally substituted with one or more independently selected halogens. In addition, the heterocyclyl is optionally substituted with $C_i$-$C_4$-alkyl or halogen.

[13] Each $R^6$ is independently selected from $C_6$-alkyl, $C_3$-$C_6$-alkoxy, halogen, -$SO_2R$, -$SOR$, -$SR$, phenyl, -$CF_3$, -$OCF_3$, -$CN$, and heterocyclyl. The heterocyclyl, in turn, is optionally substituted with $C_i$-$C_4$-alkyl.

[14] Each $R^7$ is independently selected from $C_6$-alkyl, $C_4$-alkoxy, -$CF_3$, -$OCF_3$, -$CN$, -$SO_2R$, -$SOR$, -$SR$, phenyl, heterocyclyl, and $d$-$C_4$-alkoxy. The $C_i$-$C_6$-alkyl, $C_3$-$C_8$-cycloalkyl, and $C_i$-$C_4$-alkoxy, in turn, are optionally substituted.

[15] Each $R$ is independently selected from $C_6$-alkyl, $C_3$-$C_8$-cycloalkyl-$C_i$-$C_6$-alkyl, and $NR_3R^4$.

[16] Each $R^3$ and $R^4$ is independently selected from H and $C_6$-alkyl.

[17] This invention excludes compounds (and pharmaceutically acceptable salts thereof) that satisfy both the following $A^1$ and $A^2$ definitions:

- $A^1$ is phenyl; and
- $A^2$ is phenyl substituted with 1, 2, or 3 groups selected from halogen, -CN, $C_2$-$C_6$ alkenyl, $C_2$-$C_6$ alkynyl, $C_3$-$C_6$ cycloalkyl, -$SO_2NR_3R^4$, -$NH_2$, -$S$-$C_i$-$C_6$-alkyl, $C_i$-$C_6$-alkoxy, and $C_i$-$C_6$-alkyl, wherein:
  - the $C_i$-$C_6$-alkyl and $C_i$-$C_6$-alkoxy are optionally substituted with one or more halogens.

[18] This invention also excludes the following compounds (and pharmaceutically acceptable salts thereof):
This invention also is directed, in part, to a pharmaceutical composition. The composition comprises a compound of Formula (I) or a pharmaceutically acceptable salt thereof. The composition also comprises a pharmaceutically acceptable carrier or diluent.

This invention also is directed, in part, to a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in treating a condition (typically a disorder).

This invention also is directed, in part, to a method of using a compound of Formula (I) or a pharmaceutically acceptable salt thereof to treat a condition.

This invention also is directed, in part, to a method of treating a condition in a patient in need of such treatment. The method comprises administering a compound of Formula (I) or a pharmaceutically acceptable salt thereof to the patient.
This invention also is directed, in part, to a use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament (e.g., a pharmaceutical composition) for treating a condition.

Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this specification.

DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

This description of illustrative embodiments is intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may readily adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This description and its specific examples, while indicating embodiments of this invention, are intended for purposes of illustration only. This invention, therefore, is not limited to the illustrative embodiments described in this specification, and may be variously modified. In addition, it is to be appreciated that various features of the invention that are, for clarity reasons, described in the context of separate embodiments, also may be combined to form a single embodiment. Conversely, various features of the invention that are, for brevity reasons, described in the context of a single embodiment, also may be combined to form sub-combinations thereof.

As noted above, this invention is directed, in part, to the compound of Formula (I) or a salt thereof. Formula (I) corresponds to:

The substituents of Formula (I) are defined as follows:

In some embodiments, $A^1$ is phenyl (i.e., unsubstituted phenyl). In these embodiments, the compound corresponds to Formula (II):
Excluded from such embodiments, however, are compounds wherein \( A^2 \) is phenyl substituted with 1, 2, or 3 groups independently selected from halogen, -CN, \( \text{C}_2^2 \text{-C}_6^6 \) alkynyl, \( \text{C}_3^3 \text{-C}_6^6 \) cycloalkyl, -SO\(_2\)NR\(_3\)R\(_4\), -NH\(_2\), -S-C\(_6^6\)-alkyl, Ci-C\(_6^6\)-alkyl, Ci-C\(_6^6\)-alkoxy, halo-C\(_6^6\)-alkyl, and halo-C\(_6^6\)-alkoxy.

[28] In some embodiments, \( A^1 \) is phenyl substituted with 1, 2, or 3 \( R^5 \) groups. In some such embodiments, \( A^1 \) is phenyl substituted with 1 \( R^5 \) group. In other embodiments, \( A^1 \) is phenyl substituted with 2 \( R^5 \) groups. And in other embodiments, \( A^1 \) is phenyl substituted with 3 \( R^5 \) groups.

[29] In some embodiments, \( A^1 \) is a 5- or 6-membered heteroaryl (i.e., unsubstituted 5- or 6-membered heteroaryl). In some embodiments, the heteroaryl is 5-membered. In some such embodiments, the heteroaryl is imidazolyl. In other such embodiments, the heteroaryl is furanyl. In some embodiments, the heteroaryl that is substituted is 6-membered. In some such embodiments, the heteroaryl is selected from pyridinyl.

[30] In some embodiments, \( A^1 \) is a 5- or 6-membered heteroaryl substituted with 1, 2, or 3 \( R^7 \) groups. In some such embodiments, \( A^1 \) is 5- or 6-membered heteroaryl substituted with 1 \( R^7 \) group. In other embodiments, \( A^1 \) is 5- or 6-membered heteroaryl substituted with 2 \( R^7 \) groups. And in other embodiments, \( A^1 \) is 5- or 6-membered heteroaryl substituted with 3 \( R^7 \) groups. In some embodiments, the heteroaryl that is substituted is 5-membered. In some such embodiments, the heteroaryl that is substituted is imidazolyl. In other such embodiments, the heteroaryl that is substituted is furanyl. In some embodiments, the heteroaryl that is substituted is 6-membered. In some such embodiments, the heteroaryl that is substituted is pyridinyl.

[31] In some embodiments, \( A^2 \) is phenyl substituted with 1, 2, or 3 \( R^2 \) groups. In some such embodiments, \( A^2 \) is a phenyl substituted with 1 \( R^2 \) group. In other embodiments, \( A^2 \) is a phenyl substituted with 2 \( R^2 \) groups. And in other embodiments, \( A^2 \) is a phenyl
substituted with 3 R² groups. Excluded from such embodiments, however, are compounds
(and salts thereof) wherein both the following A¹ and A² definitions are satisfied:

A¹ is phenyl \( i.e., \) the compound corresponds to Formula (II)); and
A² is phenyl substituted with 1, 2, or 3 groups independently selected
from halogen, -CN, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl,
-SO₂NR³R⁴, -NH₂, -S-C₆-alkyl, C₆-C₈-alkyl, C₈-C₁₆-alkoxy, halo-C₆-C₈-
alkyl, and halo-C₆-alkoxy.

[32] In some embodiments, A² is a heteroaryl \( i.e., \) unsubstituted heteroaryl). In
some embodiments, the heteroaryl is 5-membered. In some such embodiments, for example,
A² is selected from oxazolyl, imidazolyl, thiazolyl, and isoxazolyl. In some embodiments, the
heteroaryl is 6-membered. In some such embodiments, A² is pyridinyl. In some
embodiments, the heteroaryl is 9-membered. In some such embodiments, A² is selected from
imidazopyridinyl and benzoimidazolyl.

[33] In some embodiments, A² is heteroaryl substituted with 1, 2, or 3 R⁶ groups.
In some such embodiments, A² is a heteroaryl substituted with 1 R⁶ group. In other
embodiments, A² is a heteroaryl substituted with 2 R⁶ groups. And in other embodiments, A²
is a heteroaryl substituted with 3 R⁶ groups. In some embodiments, the heteroaryl that is
substituted is 5-membered. In some such embodiments, the heteroaryl is selected from
oxazolyl, imidazolyl, thiazolyl, and isoxazolyl. In some embodiments, the heteroaryl that is
substituted is 6-membered. In some such embodiments, the heteroaryl is pyridinyl. In some
embodiments, the heteroaryl that is substituted is 9-membered. In some such embodiments, the
heteroaryl is selected from imidazopyridinyl and benzoimidazolyl.

[34] In some embodiments, A² is a pyridinyl substituted with 1 R⁶ group. In other
embodiments, A² is a pyridinyl substituted with 2 R⁶ groups. And in other embodiments, A²
is a pyridinyl substituted with 3 R⁶ groups.

[35] In the above embodiments, each R is independently selected from Ci-C₆-alkyl,
C₃-C₈-cycloalkyl-Ci-C₆-alkyl, and NR³R⁴.

[36] In some such embodiments, an R is Ci-C₆-alkyl. In some such embodiments,
R is methyl. In other embodiments, R is ethyl. And, in other embodiments, R is propyl.

[37] In some such embodiments, an R is C₃-C₈-cycloalkyl-Ci-C₆-alkyl.

[38] In some such embodiments, an R is NR³R⁴.
In some such embodiments, every R is independently selected Ci-C₆-alkyl.

In some such embodiments, every R is independently selected C₃-C₈-cycloalkyl-Ci-C₆-alkyl.

In some such embodiments, every R is independently selected NR³R⁴.

R¹ is selected from hydrogen, Ci-C₆-alkyl, C₃-C₆ cycloalkyl, 3-6 membered heterocycloalkyl, C₃-C₈-cycloalkyl-Ci-C₄-alkyl, aryl-Ci-C₄-alkyl, heterocycloalkyl-Ci-C₄-alkyl, heteroaryl-Ci-C₄-alkyl, and C₃-C₈-alkenyl. The C₃-C₈-cycloalkyl-Ci-C₄-alkyl, aryl-Ci-C₄-alkyl, and heteroaryl-Ci-C₄-alkyl, in turn, are optionally substituted with one or more independently selected halogens.

In some embodiments, R¹ is hydrogen.

In some embodiments, R¹ is Ci-C₆-alkyl. In some such embodiments, R¹ is methyl. In other such embodiments, R¹ is ethyl. In still other such embodiments, R¹ is propyl.

In some embodiments, R¹ is C₃-Cs alkenyl.

In some embodiments, R¹ is C₃-C₆ cycloalkyl.

In some embodiments, R¹ is C₃-C₆-cycloalkyl-Ci-C₄-alkyl optionally substituted with one or more halogen.

In some embodiments, R¹ is aryl-Ci-C₄-alkyl optionally substituted with one or more halogen.

In some embodiments, R¹ is heteroaryl-Ci-C₄-alkyl optionally substituted with one or more halogen.

Each R² is independently selected from halogen, -CN, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, 5- or 6- membered heterocyclyl (i.e., a 5- or 6-membered heterocycloalkyl, 5- or 6-membered heterocycloalkenyl, or 5- or 6-membered heteroaroyl), -SOR, -SO₂R, -NH₂, -SR, Ci-C₆-alkoxy, C₆-C₆-alkyl, and Ci-C₆-alkoxy-Ci-C₄-alkyl. The C₁-C₆-alkyl, Ci-C₆-alkoxy, and C₃-C₆ cycloalkyl, in turn, are optionally substituted with one or more independently selected halogens. And the heterocyclyl is optionally substituted with 1, 2, or 3 R⁶ groups.
Each $R^2$ is independently selected from halogen, -CN, C$_2$-C$_6$ alkenyl, C$_2$-C$_6$ alkylnyl, C$_3$-C$_6$ cycloalkyl, 5- or 6- membered heterocyclyl, -SOR, -SO$_2$R, -NH$_2$, -SR, C$_1$-C$_6$-alkoxy, and C$_2$-C$_6$-alkyl. The C$_3$-C$_6$-alkyl, C$_6$-alkoxy, and C$_2$-C$_6$ cycloalkyl, in turn, are optionally substituted with one or more independently selected halogens. And the heterocyclyl is optionally substituted with 1, 2, or 3 $R^6$ groups.

In some embodiments, each $R^2$ is selected from halogen, 5- or 6- membered heterocyclyl, -SOR, -NH$_2$, C$_6$-alkoxy, C$_6$-alkyl, and C$_4$-alkoxy-C$_4$-alkyl. The C$_2$-C$_6$-alkyl and C$_2$-C$_6$-alkoxy, in turn, are optionally substituted with one or more independently selected halogens.

In some embodiments, at least one $R^2$ is C$_6$-alkyl optionally substituted with one or more halogens. In some such embodiments, for example, at least one $R^2$ is methyl. In other such embodiments, at least one $R^2$ is -CF$_3$.

In some embodiments, at least one $R^2$ is C$_6$-alkoxy. In some such embodiments, for example, at least one $R^2$ is methoxy.

In some embodiments, at least one $R^2$ is C$_4$-alkoxy-C$_4$-alkyl. In some such embodiments, for example, at least one $R^2$ is methoxymethyl.

In some embodiments, at least one $R^2$ is halogen. In some such embodiments, for example, at least one $R^2$ is chloro. In other such embodiments, at least one $R^2$ is bromo. In still other such embodiments, at least one $R^2$ is fluoro.

In some embodiments, at least one $R^2$ is -SO$_2$R. In some such embodiments, for example, at least one $R^2$ is methylsulfonyl.

In some embodiments, at least one $R^2$ is -NH$_2$.

In some embodiments, at least one $R^2$ is a 5- or 6- membered heterocyclyl. In some such embodiments, for example, at least one $R^2$ is a 5-membered heterocycloalkyl, such as, for example, a pyrrolidinyl. In other such embodiments, at least one $R^2$ is a 5-membered heteroaryl, such as, for example, pyrazolyl.

In some embodiments wherein more than one $R^2$ is present, each $R^2$ is different.

In some embodiments wherein more than one $R^2$ is present, the $R^2$ are the same.

Each $R^3$ and $R^4$ is independently selected from H and C$_6$-alkyl.
In some embodiments, at least one R3 is H.

In some embodiments, every R3 is H.

In some embodiments, at least one R3 is H, and at least one R4 is H.

In some embodiments, every R3 and every R4 is H.

In some embodiments, at least one R5 is heteroaryl. In some such embodiments, for example, at least one R5 is pyrazolyl.

R heterocyclyl heterocycloalkenyl, dimethylaminosulfonyl.

for embodiments, example, allen propylsulfonyl.

Each R5 is independently selected from Ci-C6-alkyl, Cs-Cs-cycloalkyl, C1-C6-alkoxy, -CN, halogen, -SO2R, -SOR, -SR, and heterocyclyl (i.e., a heterocycloalkyl, heterocycloalkenyl, or heteroaryl). The Ci-C6-alkyl, Cs-Cs-cycloalkyl, and Ci-C6-alkoxy, in turn, are optionally substituted with one or more independently selected halogens. And the heterocyclyl is optionally substituted with Ci-C4-alkyl or halogen.

In some embodiments, at least one R5 is halogen. In some such embodiments, for example, at least one R5 is fluoro. In other such embodiments, for example, at least one R5 is bromo. In still other such embodiments, for example, at least one R5 is chloro.

In some embodiments, at least one R5 is Ci-C6-alkyl. In some such embodiments, for example, at least one R5 is methyl.

In some embodiments, at least one R5 is Ci-C6-alkoxy. In some such embodiments, for example, at least one R5 is methoxy.

In some embodiments, at least one R5 is -SO2R. In some such embodiments, for example, at least one R5 is propylsulfonyl. In other such embodiments, at least one R5 is dimethylaminosulfonyl. In other such embodiments, at least one R5 is cyclopropylmethylsulfonyl.

In some embodiments, at least one R5 is heteroaryl. In some such embodiments, for example, at least one R5 is pyrazolyl.
In some embodiments, at least one \( R^5 \) is heteroaryl substituted with \( C_1-C_4 \)-alkyl or halogen. In some such embodiments, for example, at least one \( R^5 \) is methylpyrazolyl.

In some embodiments wherein more than one \( R^5 \) is present, each \( R^5 \) is different.

In some embodiments wherein more than one \( R^5 \) is present, the \( R^5 \) are the same.

Each \( R^6 \) is independently selected from \( C_1-C_6 \)-alkyl, \( C_1-C_6 \)-alkoxy, halogen, \( -SO_2R, -SOR, -SR, \) phenyl, \( -CF_3, -OCF_3, -CN \), and heterocyclyl (i.e., heterocycloalkyl, heterocycloalkenyl, or heteroaryl). The heterocyclyl, in turn, is optionally substituted with \( C_1-C_{10} \)-alkyl.

In some embodiments, each \( R^6 \) is independently selected from \( C_1-C_6 \)-alkyl, \( C_1-C_6 \)-alkoxy, halogen, \( -SR \), phenyl, and \( -CF_3 \).

In some embodiments, at least one \( R^6 \) is halogen. In some such embodiments, for example, at least one \( R^6 \) is fluoro. In other such embodiments, at least one \( R^6 \) is chloro. In still other such embodiments, at least one \( R^6 \) is bromo.

In some embodiments, at least one \( R^6 \) is \( C_1-C_6 \)-alkyl. In some such embodiments, for example, at least one \( R^6 \) is methyl.

In some embodiments, at least one \( R^6 \) is \( CF_3 \).

In some embodiments, at least one \( R^6 \) is \( C_1-C_6 \)-alkoxy. In some such embodiments, for example, at least one \( R^6 \) is methoxy.

In some embodiments, at least one \( R^6 \) is phenyl.

In some embodiments, at least one \( R^6 \) is \( -SR \). In some such embodiments, for example, at least one \( R^6 \) is methylsulfanyl.

In some embodiments wherein more than one \( R^6 \) is present, each \( R^6 \) is different.

In some embodiments wherein more than one \( R^6 \) is present, the \( R^6 \) are the same.

Each \( R^7 \) is independently selected from \( C_1-C_6 \)-alkyl, \( C_1-C_4 \)-alkoxy, \( -CF_3, -OCF_3, -CN, -SO_2R, -SOR, -SR \), phenyl, \( C_1-C_4 \)-alkoxy, and heterocyclyl (i.e., a heterocycloalkyl, heterocycloalkenyl, or heteroaryl). The \( C_1-C_6 \)-alkyl, \( C_3-C_8 \)-cycloalkyl, and \( C_1-C_4 \)-alkoxy, in turn, are optionally substituted. In some such embodiments, The \( C_1-C_6 \)-
alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, and Ci-C<sub>4</sub>-alkoxy, in turn, are optionally substituted with one or more independently selected halogen.

[94] In some embodiments, each R<sup>7</sup> is independently selected from Ci-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -CN, -SO<sub>2</sub>R, -SOR, -SR, and Ci-C<sub>4</sub>-alkoxy. Each Ci-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, and Ci-C<sub>4</sub>-alkoxy, in turn, are optionally substituted with one or more independently selected halogens.

[95] In some embodiments, each R<sup>7</sup> is independently selected from Ci-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>4</sub>-alkoxy, -CN, -SO<sub>2</sub>R, -SOR, -SR, and Ci-C<sub>4</sub>-alkoxy. Each Ci-C<sub>6</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, in turn, are optionally substituted with one or more independently selected halogens.

[96] In some embodiments, at least one R<sup>7</sup> is Ci-C<sub>4</sub>-alkoxy optionally substituted with one or more halogens. In some such embodiments, for example, at least one R<sup>7</sup> is methyl. In other such embodiments, at least one R<sup>7</sup> is -CF<sub>3</sub>.

[97] In some embodiments, at least one R<sup>7</sup> is phenyl.

[98] In some embodiments, at least one R<sup>7</sup> is heterocyclyl.

[99] In some embodiments wherein more than one R<sup>7</sup> is present, each R<sup>7</sup> is different.

[100] In some embodiments wherein more than one R<sup>7</sup> is present, the R<sup>7</sup> are the same.

[101] In some embodiments, A<sup>1</sup> is phenyl; and A<sup>2</sup> is phenyl substituted with 1, 2, or 3 R<sup>2</sup> groups. Excluded from such embodiments, however, are compounds wherein A<sup>2</sup> is phenyl substituted with 1, 2, or 3 groups independently selected from halogen, -CN, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>2</sub>-C<sub>6</sub> alkynyl, C<sub>3</sub>-C<sub>6</sub> cycloalkyl, -SO<sub>2</sub>NR<sup>3</sup>R<sup>4</sup>, -NH<sub>2</sub>, -S-Ci-C<sub>6</sub>-alkyl, Ci-C<sub>6</sub>-alkyl, Ci-C<sub>6</sub>-alkoxy, halo-Ci-C<sub>6</sub>-alkyl, and halo-Ci-C<sub>6</sub>-alkoxy.

[102] In some embodiments, A<sup>1</sup> is phenyl (i.e., the compound corresponds in structure to Formula (II)), and A<sup>2</sup> is heteroaryl.

[103] In some embodiments, A<sup>1</sup> is phenyl; and A<sup>2</sup> is a heteroaryl substituted with 1, 2, or 3 R<sup>6</sup> groups. In some such embodiments, for example, the compound corresponds in structure to:
In some embodiments, \( A_1 \) is phenyl substituted with 1, 2, or 3 \( R_5 \) groups; and \( A_2 \) is phenyl substituted with 1, 2, or 3 \( R_2 \) groups.

In some embodiments, \( A_1 \) is a heteroaryl. \( A_2 \) is a heteroaryl substituted with 1, 2, or 3 \( R_6 \) groups.

In some embodiments, \( A_1 \) is a 5- or 6-membered heteroaryl, and \( A_2 \) is a heteroaryl substituted with 1, 2, or 3 \( R_6 \) groups.

In some embodiments, the compound or salt is a compound or salt described in Table 1 below.

In some embodiments, the compound or salt is a compound corresponding to the non-salt structure shown in Table 1 below or a pharmaceutically acceptable salt thereof.
In some embodiments, the compound or salt is a compound shown in Table 2 below or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound or salt is a compound shown in Table 3 below or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound or salt is a single optical isomer, a racemic mixture, or any other mixture of optical isomers corresponding to a structure below or a pharmaceutically acceptable salt of such an isomer, racemic mixture, or other mixture of optical isomers:

5
In some such embodiments, for example, the compound or salt is a single optical isomer, a racemic mixture, or any other mixture of optical isomers corresponding to the structure below or a pharmaceutically acceptable salt of such an isomer, racemic mixture, or other mixture of optical isomers:

\[
\text{structure}
\]

In such embodiments, the compound or salt could comprise, for example, the following isomer or a pharmaceutically acceptable salt thereof:

\[
\text{structure}
\]

In other such embodiments, the compound or salt could alternatively comprise the following isomer or a pharmaceutically acceptable salt thereof:
In still other such embodiments, the compound or salt could comprise a racemic mixture of the above two isomers (i.e., a mixture of the two isomers wherein the ratio of the two isomers is approximately 50:50) or a pharmaceutically acceptable salt thereof. And in still other such embodiments, the compound or salt could comprise any other mixture of the above two isomers or a pharmaceutically acceptable salt thereof.

[119] In some embodiments, the compound or salt is a single optical isomer, a racemic mixture, or any other mixture of optical isomers corresponding to a structure below or a pharmaceutically acceptable salt of such an isomer, racemic mixture, or other mixture of optical isomers:
The following compounds (and pharmaceutically acceptable salts thereof) are excluded from this invention:

- 

- 

- 

- 

[120] The following compounds (and pharmaceutically acceptable salts thereof) are excluded from this invention:

- 

-
All the compounds of this invention include at least one chiral carbon, *i.e.*, the carbon linking the 2-aza-bicyclo[2.2.2]octane group with A¹ and the amino:

![Chemical structures]

[121] All the compounds of this invention include at least one chiral carbon, *i.e.*, the carbon linking the 2-aza-bicyclo[2.2.2]octane group with A¹ and the amino:
Formula (I) is intended to encompass any single chiral isomer corresponding to Formula (I), as well as any mixture of chiral isomers (e.g., the racemate) corresponding to Formula (I). Thus, Formula (I) encompasses a single chiral isomer corresponding to Formula (IA):

![Formula (IA)](image)

Formula (I) also encompasses a single chiral isomer corresponding to Formula (IB):

![Formula (IB)](image)

Formula (I) also encompasses a racemic mixture of the above chiral isomers (i.e., a mixture of the two isomers wherein the ratio of the two isomers is approximately 50:50). And Formula (I) encompasses any other mixture of the above two chiral isomers wherein the ratio of the two isomers is other than approximately 50:50.

[122] In some embodiments, a single chiral isomer corresponding to Formula (I) (or a salt thereof) is obtained by isolating it from a mixture of isomers (or a salt thereof) using, for example, chiral chromatographic separation. In other embodiments, a single chiral isomer of Formula (I) (or a salt thereof) is obtained through direct synthesis from, for example, a chiral starting material. In some embodiments, the ratio of one chiral isomer to its mirror chiral isomer (in, for example, a pharmaceutical composition) is greater than about 9:1. In some such embodiments, the ratio is at least about 98:2. In still yet other such embodiments, the ratio is at least about 99:1. And in still yet other such embodiments, one chiral isomer is present without any detectible amount of its mirror chiral isomer.

[123] When a structure shows the chirality of a carbon, it depicts the direction of one of the chiral carbon's substituents with a dark wedge or hashed wedge, like those shown in the
above two Formulas (IA) and (IB), respectively. Unless otherwise indicated, the carbon substituent pointing in the opposite direction is hydrogen. This notation is consistent with conventional organic chemistry nomenclature rules. Thus, for example, Formula (IA) can alternatively be depicted as follows in Formula (IA-I):

![Formula (IA-I)](image)

Similarly, Formula (IB) can alternatively be depicted as follows in Formula (IB-I):

![Formula (IB-I)](image)

[124] Contemplated salts of the compounds of this invention include both acid addition salts. A salt may be advantageous due to one or more of its chemical or physical properties, such as stability in differing temperatures and humidities, or a desirable solubility in water, oil, or other solvent. In some instances, a salt may be used to aid in the isolation or purification of the compound. In some embodiments (particularly where the salt is intended for administration to an animal, or is a reagent for use in making a compound or salt intended for administration to an animal), the salt is pharmaceutically acceptable.

[125] In general, an acid addition salt can be prepared using various inorganic or organic acids. Such salts can typically be formed by, for example, mixing the compound with an acid (e.g., a stoichiometric amount of acid) using various methods known in the art. This mixing may occur in water, an organic solvent (e.g., ether, ethyl acetate, ethanol, isopropanol, or acetonitrile), or an aqueous/organic mixture. Examples of inorganic acids that typically may be used to form acid addition salts include hydrochloric, hydrobromic, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Examples of organic acids include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic, and sulfonic classes
of organic acids. Specific examples of organic salts include cholate, sorbate, laurate, acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid (and derivatives thereof, e.g., dibenzoyltartrate), citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate (and derivatives thereof), embonate (pamoate), ethanesulfonate, benzenesulfonate, pantothenate, 2-hydroxyethanesulfonate, sulfanilate, cyclohexylaminosulfonate, algenic acid, β-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate. In some embodiments, the salt is selected from acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edentate, edisylate, estolate, esylate, fumarate, glucopente, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, maleate, maleate, mandelate, mesylate, methylbromide, methylthiolate, myethylsulfate, mutate, napsylate, nitrate, N-methylglucarnine ammonium salt, olate, oxalate, pamoate(eminonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, sulfonate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate. In some embodiments, the salt comprises a citric acid salt or a formic acid salt.

[126] The compounds of Formula (I) and salts thereof are intended to encompass any tautomer that may form. A "tautomer" is any other structural isomer that exists in equilibrium resulting from the migration of a hydrogen atom, e.g., amide-imidic acid tautomerism.

[127] It is contemplated that an amine of a compound of Formula (I) or a salt thereof may form an N-oxide. Such an N-oxide is intended to be encompassed by the compounds of Formula (I) and salts thereof. An N-oxide can generally be formed by treating an amine with an oxidizing agent, such as hydrogen peroxide or a per-acid (e.g., a peroxycarboxylic acid). See, e.g., Advanced Organic Chemistry, by Jerry March, 4th Edition, Wiley Interscience.

N-oxides also can be made by reacting the amine with m-CPBA, for example, in an inert solvent, such as dichloromethane. See L. W. Deady, Syn. Comm., 1, pp. 509-514 (1977).
[128] It is contemplated that a compound of Formula (I) or salt thereof could form isolatable atropisomer in certain solvents at certain temperatures. The compounds of Formula I and salts thereof are intended to encompass any such atropisomers. Atropisomers can generally be isolated using, for example, chiral LC.

[129] The compounds of Formula (I) and salts thereof are intended to encompass any isotopically-labeled (or "radio-labeled") derivatives of a compound of Formula (I) or salt thereof. Such a derivative is a derivative of a compound of Formula (I) or salt thereof wherein one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number typically found in nature. Examples of radionuclides that may be incorporated include $^2$H (also written as "D" for deuterium), $^3$H (also written as "T" for tritium), $^{11}$C, $^{13}$C, $^{14}$C, $^{13}$N, $^{15}$N, $^{15}$O, $^{17}$O, $^{18}$O, $^{18}$F, $^{35}$S, $^{36}$Cl, $^{82}$Br, $^{75}$Br, $^{76}$Br, $^{77}$Br, $^{123}$I, $^{124}$I, $^{125}$I, and $^{131}$I. The radionuclide that is used will depend on the specific application of that radio-labeled derivative. For example, for in vitro receptor labeling and competition assays, $^3$H or $^{14}$C are often useful. For radio-imaging applications, $^{11}$C or $^{18}$F are often useful. In some embodiments, the radionuclide is $^3$H. In some embodiments, the radionuclide is $^{14}$C. In some embodiments, the radionuclide is $^{11}$C. And in some embodiments, the radionuclide is $^{18}$F.

[130] The compounds of Formula (I) and salts thereof are intended to cover all solid-state forms of the compounds of Formula (I) and salts thereof. The compounds of Formula (I) and salts thereof also are intended to encompass all solvated (e.g., hydrated) and unsolvated forms of the compounds of Formula (I) and salts thereof.

[131] The compounds of Formula (I) and salts thereof also are intended to encompass coupling partners in which a compound of Formula (I) or a salt thereof is linked to a coupling partner by, for example, being chemically coupled to the compound or salt or physically associated with it. Examples of coupling partners include a label or reporter molecule, a supporting substrate, a carrier or transport molecule, an effector, a drug, an antibody, or an inhibitor. Coupling partners can be covalently linked to a compound of Formula (I) or salt thereof via an appropriate functional group on the compound, such as an amino group. Other derivatives include formulating a compound of Formula (I) or a salt thereof with liposomes.
This invention provides, in part, methods to treat various disorders in animals, particularly mammals. Mammals include, for example, humans. Mammals also include, for example, companion animals (e.g., dogs, cats, and horses), livestock animals (e.g., cattle and swine); lab animals (e.g., mice and rats); and wild, zoo, and circus animals (e.g., bears, lions, tigers, apes, and monkeys).

As shown below in the Examples, compounds and salts of this invention have been observed to modulate, and, in particular, act as antagonist against, the glycine transporter 1 ("GIyT1"). Accordingly, it is believed that the compounds and salts of this invention can be used to modulate the glycine transporter to treat various conditions mediated by (or otherwise associated with) the glycine transporter. In some embodiments, the compounds and salts of this invention exhibit one or more of the following characteristics: desirable potency, desirable efficacy, desirable stability on the shelf, desirable tolerability for a range of patients, and desirable safety.

In some embodiments, a compound of Formula (I) or a salt thereof is used to modulate (typically antagonize) GIyT1.

In some embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a condition (typically a disorder) associated with GIyT1 activity.

In some embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a psychosis in a patient in need of such treatment.

In some embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a cognitive disorder in a patient in need of such treatment.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a psychotic disorder.

In some embodiments, for example, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat schizophrenia.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a schizoaffective disorder.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a delusional disorder.
In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a brief psychotic disorder.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a shared psychotic disorder.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a psychotic disorder due to a general medical condition.

Mood disorders include, for example, a) depressive disorders, including but not limited to major depressive disorders and dysthymic disorders; b) bipolar depression and/or bipolar mania including but not limited to bipolar i, including but not limited to those with manic, depressive or mixed episodes, and bipolar ii; c) cyclothymiac's disorders; and d) mood disorders due to a general medical condition.

In some embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a bipolar disorder.

In some embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a cognitive disorder selected from mania and manic depression disorders.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat an anxiety disorder. In some such embodiments, the anxiety disorder comprises a disorder selected from a panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of any panic disorder, specific phobia, social phobia, an obsessive-compulsive disorder, a stress related disorder, a post-traumatic stress disorder, an acute stress disorder, a generalized anxiety disorder, and a generalized anxiety disorder due to a general medical condition.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a post-traumatic stress disorder.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat dementia.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a sleep disorder.
In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a disorder that is often first diagnosed in infancy, childhood, or adolescence. Such disorders generally include, for example, mental retardation, downs syndrome, learning disorders, motor skills disorders, communication disorders, pervasive developmental disorders, attention-deficit and disruptive behavior disorders, feeding and eating disorders of infancy or early childhood, tic disorders, and elimination disorders.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a substance-related disorder. Such disorders include, for example, substance dependence; substance abuse; substance intoxication; substance withdrawal; alcohol-related disorders; amphetamines (or amphetamine-like)-related disorders; caffeine-related disorders; cannabis-related disorders; cocaine-related disorders; hallucinogen-related disorders; inhalant-related disorders; nicotine-related disorders; opioid-related disorders; phencyclidine (or phencyclidine-like)-related disorders; and sedative-, hypnotic- or anxiolytic-related disorders.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat an attention-deficit and disruptive behavior disorder.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat an eating disorder.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a personality disorder. Such disorders include, for example, obsessive-compulsive personality disorders.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat an impulse-control disorder.

In some embodiments a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat a tic disorder. Such disorders include, for example, Tourette's disorder, chronic motor or vocal tic disorder; and transient tic disorder.

Many of the above conditions and disorder(s) are defined for example in the American Psychiatric Association: diagnostic and statistical manual of mental disorders, fourth edition, text revision, Washington, DC, American Psychiatric Association, 2000.
It is contemplated that a compound or salt of this invention may be used to treat pain. Such pain may be, for example, chronic pain, neuropathic pain, acute pain, back pain, cancer pain, pain caused by rheumatoid arthritis, migraine, or visceral pain.

It is contemplated that a compound of Formula I or a pharmaceutically acceptable salt thereof may be administered orally, bucally, vaginally, rectally, via inhalation, via insufflation, intranasally, sublingually, topically, or parenterally (e.g., intramuscularly, subcutaneously, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, intracerebroventricularly, or by injection into the joints).

In some embodiments, a compound or salt of this invention is administered orally.

In some embodiments, a compound or salt of this invention is administered intravenously.

In some embodiments, a compound or salt of this invention is administered intramuscularly.

In some embodiments, a compound or salt of this invention is used to make a medicament (i.e., a pharmaceutical composition). In general, the pharmaceutical composition comprises a therapeutically effective amount of the compound or salt. Pharmaceutical compositions comprising a compound or salt of this invention can vary widely. Although it is contemplated that a compound or salt of this invention could be administered by itself (i.e., without any other active or inactive ingredient), the pharmaceutical composition normally will instead comprise one or more additional active ingredients and/or inert ingredients. The inert ingredients present in the pharmaceutical compositions of this invention are sometimes collectively referred to as "carriers and diluents." Methods for making pharmaceutical compositions and the use of carriers and diluents are well known in the art. See, e.g., for example, Remington’s Pharmaceutical Sciences, Mack Publishing Company, Easton, PA, 15th Edition, 1975.

Pharmaceutical compositions comprising a compound of Formula I or pharmaceutically acceptable salt thereof can vary widely. For example, it is contemplated that the compositions may be formulated for a variety of suitable routes and means of administration, including oral, rectal, nasal, topical, buccal, sublingual, vaginal, inhalation, insufflation, or parenteral administration. It is contemplated that such compositions may, for
example, be in the form of solids, aqueous or oily solutions, suspensions, emulsions, creams, ointments, mists, gels, nasal sprays, suppositories, finely divided powders, and aerosols or nebulisers for inhalation. In some embodiments, the composition comprises a solid or liquid dosage form that may be administered orally.

[167] Solid form compositions may include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier may comprise one or more substances. Such substances are generally inert. A carrier also may act as, for example, a diluent, flavoring agent, solubilizer, lubricant, preservative, stabilizer, suspending agent, binder, or disintegrating agent. It also may act as, for example, an encapsulating material. Examples of often suitable carriers include pharmaceutical grade mannitol, lactose, magnesium carbonate, magnesium stearate, talc, lactose, sugar (e.g., glucose and sucrose), pectin, dextrin, starch, tragacanth, cellulose, cellulose derivatives (e.g., methyl cellulose and sodium carboxymethyl cellulose), sodium saccharin, low-melting wax, and cocoa butter.

[168] In powders, the carrier is typically a finely divided solid, which is in a mixture with the finely divided active component. In tablets, the active component is typically mixed with the carrier having the desirable binding properties in suitable proportions and compacted into the desired shape and size.

[169] For preparing suppository compositions, a low-melting wax (e.g., a mixture of fatty acid glycerides and cocoa butter) is typically first melted, followed by dispersing the active ingredient therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify. Examples of non-irritating excipients that may be present in suppository compositions include, for example, cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights, and fatty acid esters of polyethylene glycol.

[170] Liquid compositions can be prepared by, for example, dissolving or dispersing the compound or a salt of this invention in a carrier, such as, for example, water, water/propylene glycol solutions, saline aqueous dextrose, glycerol, or ethanol. In some embodiments, aqueous solutions for oral administration can be prepared by dissolving a compound or salt of this invention in water with a solubilizer (e.g., a polyethylene glycol). Colorants, flavoring agents, stabilizers, and thickening agents, for example, also may be
added. In some embodiments, aqueous suspensions for oral use can be made by dispersing the compound or salt of this invention in a finely divided form in water, together with a viscous material, such as, for example, one or more natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, or other suspending agents. If desired, the liquid composition also may contain other non-toxic auxiliary inert ingredients, such as, for example, wetting or emulsifying agents, pH buffering agents and the like, for example, sodium acetate, sorbitan monolaurate, triethanolamine sodium acetate, sorbitan monolaurate, triethanolamine olate, etc. Such compositions also may contain other ingredients, such as, for example, one or more pharmaceutical adjuvants.

[171] In some embodiments, the pharmaceutical composition comprises from about 0.05% to about 99% (by weight) of a compound or salt of this invention. In some such embodiments, for example, the pharmaceutical composition comprises from about 0.10% to about 50% (by weight) of a compound or salt of this invention.

[172] When a compound or salt of this invention is administered as a sole therapy for treating a condition (typically a disorder or disease), a "therapeutically effective amount" is an amount sufficient to reduce or completely alleviate symptoms or other detrimental effects of the condition; cure the condition; reverse, completely stop, or slow the progress of the condition; reduce the risk of the condition getting worse; or delay or reduce the risk of onset of the condition.

[173] The optimum dosage and frequency of administration will depend on the particular condition being treated and its severity; the species of the patient; the age, size and weight, diet, and general physical condition of the particular patient; brain/body weight ratio; other medication the patient may be taking; the route of administration; the formulation; and various other factors known to physicians (in the context of human patients), veterinarians (in the context of non-human patients), and others skilled in the art.

[174] It is contemplated that in some embodiments, the optimum amount of a compound or salt of this invention is greater than about 10 μg/kg of body weight per day. In some embodiments, the optimum amount of a compound or salt of this invention is at least about 0.1 mg/kg of body weight per day. In some embodiments, the optimum amount is no greater than about 20 mg/kg of body weight per day. In some embodiments, the optimum amount is from about 0.1 mg/kg to about 20 mg/kg of body weight per day.
It is contemplated that the pharmaceutical compositions can be in one or more unit dosage forms. Accordingly, the composition may be divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be, for example, a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these in packaged forms. The unit dosage form alternatively can be a packaged preparation in which the package contains discrete quantities of the composition, such as, for example, packeted tablets, capsules, or powders in vials or ampoules. Unit dosage forms may be prepared by, for example, various methods well known in the art of pharmacy.

It is contemplated that a dosage can be given once daily or in divided doses, such as, for example, from 2 to 4 times per day.

It is contemplated that a compound of Formula (I) or a salt thereof may be administered concurrently, simultaneously, sequentially, or separately with one or more other pharmaceutically active compounds. It is contemplated that, in some such embodiments, the other pharmaceutically active compound(s) may be one or more other compounds of Formula (I) and/or pharmaceutically acceptable salts thereof. It also is contemplated that, in some embodiments, the other pharmaceutically active compound(s) may be selected from one or more of the following: antidepressants; antipsychotics; anxiolytics; anticonvulsants; Alzheimer's therapies; Parkinson's therapies; agents for treating extrapyramidal symptoms; migraine therapies; stroke therapies; neuropathic pain therapies; nociceptive pain therapies; insomnia therapies; mood stabilizers; agents for treating ADHD; agents used to treat substance abuse disorders, dependence, and withdrawal; a cognitive enhancing agent; a memory enhancing agent; an anti-inflammatory agent; and a selective serotonin reuptake inhibitor (or "serotonin-specific reuptake inhibitor" or SSRI"). It is also contemplated that a compound of Formula (I) or salt thereof may be administered as part of a combination therapy with radiotherapy. In addition, it is contemplated that a compound of Formula (I) or salt thereof may be administered as a combination therapy with chemotherapy. In some such embodiments, the chemotherapy includes one or more of the following categories of anti-tumor agents: antiproliferative/antineoplastic drugs, cytostatic agents, anti-invasion agents, inhibitors of growth factor function, antiangiogenic agents, vascular damaging agents, endothelin receptor antagonists, antisense therapies, gene therapy approaches, and immunotherapy approaches. It also is contemplated that a compound of Formula (I) or salt
thereof may be useful as an analgesic agent for use during general anesthesia or monitored anesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anesthetic state (e.g., amnesia, analgesia, muscle relaxation, and sedation). Such a combination may include, for example, one or more inhaled anesthetics, hypnotics, anxiolytics, neuromuscular blockers, and/or opioids.

[178] In some embodiments in which a combination therapy is used, the amount of a compound of Formula (I) or a salt thereof and the amount of the other pharmaceutically active agent(s) are, when combined, therapeutically effective to treat a targeted disorder in the animal patient. In this context, the combined amounts are "therapeutically effective amount" if they are, when combined, sufficient to reduce or completely alleviate symptoms or other detrimental effects of the disorder; cure the disorder; reverse, completely stop, or slow the progress of the disorder; reduce the risk of the disorder getting worse; or delay or reduce the risk of onset of the disorder. Typically, such amounts may be determined by one skilled in the art by, for example, starting with the dosage range described in this patent for a compound of Formula (I) or a salt thereof and an approved or otherwise published dosage range(s) of the other pharmaceutically active compound(s).

[179] When used in a combination therapy, it is contemplated that a compound of Formula (I) or a salt thereof and the other active ingredients may be administered in a single composition, completely separate compositions, or a combination thereof. It also is contemplated that the active ingredients may be administered concurrently, simultaneously, sequentially, or separately. The particular composition(s) and dosing frequency(ies) of the combination therapy will depend on a variety of factors, including, for example, the route of administration, the condition being treated, the species of the patient, any potential interactions between the active ingredients when combined into a single composition, any interactions between the active ingredients when they are administered to the animal patient, and various other factors known to physicians (in the context of human patients), veterinarians (in the context of non-human patients), and others skilled in the art.

[180] This invention also is directed, in part, to a kit comprising a compound of Formula (I) or a salt thereof. In some embodiments, the kit further comprises one or more additional components, such as, for example: (a) an apparatus for administering the compound of Formula (I) or salt thereof; (b) instructions for administering the compound of
Formula (I) or salt thereof; (c) a carrier, diluent, or excipient (e.g., a re-suspending agent); and (d) an additional active ingredient, which may be in the same and/or different dosage forms as the compound of Formula (I) or salt thereof. In some embodiments (particularly when the kit is intended for use in administering the compound of Formula I or salt thereof to an animal patient), the salt is a pharmaceutically acceptable salt.

EXAMPLES

[181] The following examples are merely illustrative of embodiments of the invention, and not limiting to the remainder of this disclosure in any way.

A. [3HJ Glycine Uptake Assay

Reagents

[182] Preparation of recombinant human GlyTIb-CHO cells (hGlyTIb-CHO). The human GlyTIb CDS (GC002087, NM_006934) was cloned downstream of a CMV promoter in a bicistronic expression vector containing a hygromycin B resistance gene. CHO-K1 cells (ATCC) were transfected with the recombinant vector containing GlyTIb using Lipofectamine 2000 (Invitrogen) and cultured in Ham's/F12 media supplemented with 10% fetal bovine serum, 2 mM L-glutamine at 37°C, 5% CO₂, 90% humidity. Twenty-four hours after transfection, cells were diluted and switched to media containing 0.5 mg/ml hygromycin B. Antibiotic resistant cells were obtained after 21 days of culture in the presence of hygromycin B. Clonal stable cell lines were isolated by FACS single cell deposition into 96-well plates. Clonal cell lines were assessed for GlyTIb expression by measuring uptake of [3H]-glycine and the clone showing the highest uptake was selected for the development of the glycine uptake assay.

[183] Cell culture: Cells used were Recombinant hGlyTIb/CHO. These cells were cultured in cell culture medium (Ham's/F12 (Modified) (Mediatech, 10-080-CM), containing 10% FBS, 2 mM L-glutamine (Invitrogen 25030-149) and 0.5 mg/mL hygromycin B (Invitrogen, 10687-010)) in 175 cm² flasks until near confluence before use in the assay.

[184] Cell suspension: Cell medium in a cell culture flask containing near confluent cells was removed and 5 mL of cell stripper was added to submerge all cells on the surface of the culture flask. Cell stripper was removed immediately and the flask incubated in a 37°C
incubator for ~5 min. Cells were shaken loose and suspended in 5 mL of PBS. After splitting cells to initiate a new flask(s), the cells remaining were collected by centrifugation, counted, and resuspended in assay buffer to a density of ~2 million/mL. The cell suspension was kept at room temperature before use. The assays buffer was 10 mM HEPES, pH 7.4, containing 150 mM NaCl, 5 mM KCl, 1.5 mM CaCl$_2$, 1.5 mM MgCl$_2$, 0.45 mg/mL L-alanine (added fresh), and 1.8 mg/mL D-glucose (added fresh).

SPA and isotope mixture: WGA PTV beads were suspended in assay buffer (2 mg/ml) containing 60 nM [3H]Glycine (PerkinElmer (NET-004, [2-3H]Glycine, 53.3 Ci/mmol, 1 mCi/mL)) and 20 µM unlabeled glycine and the suspension was kept at room temperature before assay.

Assay of glycine uptake: To the wells of an OptiPlate, 2 µl DMSO containing a test compound was spotted. This was followed by addition of 98 µl of cell suspension (~1 million/ml final). After incubating cells with compound for ~15 min, 100 µl of the SPA (200 µg/well final) and isotope mixture (30 nM isotope with 10 µM cold glycine, final) was added to initiate the glycine uptake. At 2 h, the plate was read on a TopCount to quantify SPA counts.

B. HPLC Analysis

The ADH, OJH, IA, and IC chiral supercritical fluid chromatography (SFC) columns were obtained from Chiral Technologies, West Chester, PA.

Mass spectroscopy method: MS1

Instrumentation: Waters Acquity SQD
Ionization mode: Electrospray
Column: Acquity UPLC BEH C18 2.1x50mm x 1.7um
Mobile phase A: Water:Acetonitrile/Formic acid (98:2:0.1 v/v)
Mobile Phase B: Water:Acetonitrile/Formic acid (2:98:0.05 v/v)
Gradient: Time (%B): 0(5); 0.9(95); 1.2(95); 1.3(5); 1.4(5).

Mass spectroscopy method: MS2

Instrumentation: Agilent TOF 6210 fronted by an Agilent 1200 LC
Ionization mode: Electrospray
Column: Zorbax SB-C8 2.1x30mm x 1.8um
Mobile phase A: Water:Acetonitrile:Formic acid (98:2:0.1 v/v)
Mobile Phase B: Water:Acetonitrile:Formic acid (2:98:0.05 v/v)
Gradient: Time (%B): 0(5); 1.5(95); 1.9(95); 2(5).

When run in high-resolution mode, a reference lock mass was infused.

[190] Mass spectroscopy method: MS3

Instrumentation: Waters ZMD fronted by an Agilent 1100 LC
Ionization mode: Electrospray
Column: Zorbax SB-C8 2.1x30mm x 1.8um
Mobile phase A: Water:Acetonitrile:Formic acid (98:2:0.1 v/v)
Mobile Phase B: Water:Acetonitrile:Formic acid (2:98:0.05 v/v)
Gradient: Time (%B): 0(5); 3.0(90); 4.0(90); 4.5(5).

C. Illustrative Compounds of This Invention and Their [1H] Glycine Uptake Assay Results

[191] The examples below illustrate a variety of different compounds of this invention. The examples also provide a variety of generic schemes for preparing compounds of this invention, as well as specific examples illustrating those schemes. It is expected that one skilled in the art of organic synthesis, after reading these examples alone or in combination with the general knowledge in the art, can adapt and apply the methods to make any compound encompassed by this invention. The general knowledge in the art includes, for example:

i) Conventional procedures for using protective groups and examples of suitable protective groups, which are described in, for example, Protective Groups in Organic Synthesis, T.W. Green, P.G.M. Wuts, Wiley-Interscience, New York (1999).

ii) References discussing various organic synthesis reactions, include textbooks of organic chemistry, such as, for example, Advanced Organic Chemistry, March 4th ed, McGraw Hill (1992); and Organic Synthesis, Smith, McGraw Hill,


iv) Databases of synthetic transformations, including Chemical Abstracts, which may be searched using either CAS Online or SciFinder; and Handbuch der Organischen Chemie (Beilstein), which may be searched using SpotFire.
Method 1 depicts a generalized scheme suitable for racemic synthesis of compounds of Formula I. Those skilled in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds of Formula I.

Step A. Preparation of methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate from methyl 3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate.

To a solution of methyl 3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate (15 g, 81.88 mmol; prepared according to the procedures of Casabona, D.; Cativiela, C. Tetrahedron, 2006, 62, 10000-10004) and iodomethane (10.24 mL, 163.75 mmol) in DMF (300 mL) at 0 °C was added 60% sodium hydride in mineral oil (3.93 g, 98.25 mmol). After stirring vigorously for 25 min, the mixture was poured into 50% aqueous sodium chloride. Ethyl acetate was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (x4), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 0-100% ethyl acetate in hexanes) to afford an oily crystalline solid. This sample was dried under high vacuum to afford methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate (15.98 g, 99%) as a dry off-white crystalline solid. IH NMR (300 MHz, chloroform-d) δ ppm 1.64 - 1.94 (m, 6 H), 2.06 - 2.22 (m, 2 H), 2.63 (quin, J = 2.8 Hz, 1 H), 2.88 (s, 3 H), 3.82 (s, 3 H). m/z (ES+), (M+H)+ 198.1.

Step B. Preparation of (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methanol from methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate.

To a solution of sulfuric acid (4.22 mL, 79.10 mmol) in tetrahydrofuran (2.5 mL) at 0°C was added 2.0 M lithium aluminum hydride in tetrahydrofuran (79 mL, 158.19 mmol) dropwise. After 15 min, methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate (4.8 g, 24.34 mmol) was added via cannula as a solution in tetrahydruran (2.5 mL). After 3 min, the reaction was warmed to room temperature. After another 15 min, the reaction was recooled to 0°C and quenched with sodium sulfate decahydrate. The mixture was dilute with ethyl
acetate, stirred for 15 min, and filtered. The filtrate was then concentrated and filtered a final
time to afford crude (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methanol (3.07 g, 81%) of 95%
purity as a clear colorless oil that crystallized to form a white solid on standing. 1H NMR
(300 MHz, chloroform-d) δ ppm 1.22 - 1.40 (m, 2 H), 1.50 - 1.75 (m, 5 H), 1.79 - 1.94 (m, 2 H), 1.97 - 2.08 (m, 1 H), 2.29 (s, 3 H), 2.79 (d, J = 1.1 Hz, 2 H), 3.34 (d, J = 4.7 Hz, 2 H). m/z
(ES+), (M+H) + 156.1.

[196] Step C. Preparation of 2-methyl-2-azabicyclo[2.2.2]octane-1-carbaldehyde from
(2-methyl-2-azabicyclo[2.2.2]octan-l-yl)methanol.

CH₃

To a solution of DMSO (5.61 mL, 79.10 mmol) in dichloromethane (99 mL) at -78 °C was
added oxalyl chloride (3.46 mL, 39.55 mmol) slowly. After stirring for 30 min, (2-methyl-2-
azabicyclo[2.2.2]octan-l-yl)methanol (3.07 g, 19.78 mmol) was added as a solution (20 mL)
in dichloromethane via cannula. After 15 min, triethylamine (27.6 mL, 197.76 mmol) was
added and the white mixture was warmed to -40 °C before being quenched with saturated
aqueous sodium bicarbonate. The mixture was extracted with dichloromethane (x3), and the
combined organic layers were dried over sodium sulfate, filtered, and concentrated. The
resulting yellow oil, 2-methyl-2-azabicyclo[2.2.2]octane-1-carbaldehyde (2.89 g, 95%) of
70% purity (contaminated with DMSO), was used without further purification. 1H NMR (300
MHz, chloroform-d) δ ppm 1.48 - 1.79 (m, 7 H), 1.91 - 2.03 (m, 2 H), 2.33 (s, 3 H), 2.75 -
2.87 (m, 2 H), 9.50 (s, 1 H). m/z (ES+), (M+MeOH+H) + 186.2

To a solution of 2-methyl-2-azabicyclo[2.2.2]octane-1-carbaldehyde (1.09 g, 7.11 mmol) and tetraethoxytitanium (2.68 mL, 12.80 mmol) in tetrahydrofuran (17.78 mL) was added 2-methylpropane-2-sulfinamide (1.035 g, 8.54 mmol). After 20 h, the reaction was quenched by the dropwise addition of saturated aqueous sodium bicarbonate (1.5 mL) and subsequent dilution with ethyl acetate. The resulting white mixture was vigorously stirred for 30 min and then filtered. The filtrate was concentrated and the resulting yellow residue was purified by flash column chromatography (SiO₂, 100% ethyl acetate, then 5-30% methanol in ethyl acetate). The product fractions were concentrated and the resulting residue was taken up in ethyl acetate, filtered, and reconcentrated to afford 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide (1.150 g, 63.0%) as a clear colorless oil that solidified on standing. This material was stored at 0°C prior to use. IH NMR (300 MHz, chloroform-d) δ ppm 1.19 (s, 9 H), 1.57 - 1.82 (m, 7 H), 1.92 - 2.16 (m, 2 H), 2.27 (s, 3 H), 2.80 - 2.91 (m, 2 H), 7.95 (s, 1 H). m/z (ES+), (M+H)+ 257.3.

A solution of 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfynamide (0.256 g, 1.0 mmol) in tetrahydrofuran (3.0 mL) was cooled to 0°C, and phenylmagnesium bromide (IM in tetrahydrofuran, 2.5 mL, 2.5 mmol) was added dropwise over 5 min. The mixture was stirred for 2 hours, and then additional phenylmagnesium bromide (IM in tetrahydrofuran, 1.5 mL, 1.5 mmol) was added. After stirring for another 60 min, the reaction mixture was quenched with a 1:1 mixture of saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide (10 mL), extracted with ethyl acetate (x3) and the combined organic layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and concentrated. This afforded 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)propane-2-sulfynamide (310 mg, 93%) as a light yellow solid, which was used without further purification. 

**IH NMR (300 MHz, chloroform-d) δ ppm:**
- 1.07 - 1.21 (m, 1 H), 1.25 (s, 9 H), 1.29 - 1.49 (m, 4 H), 1.56 - 1.65 (m, 2 H), 1.68 - 1.84 (m, 1 H), 1.85 - 1.99 (m, 1 H), 2.44 (s, 3 H), 2.48 - 2.58 (m, 1 H), 3.31 (dt, J = 11.0, 1.2 Hz, 1 H), 4.35 (s, 1 H), 5.13 (s, 1 H), 7.19 - 7.35 (m, 5 H).
- m/z (ES+), (M+H)+ 335.2

A solution of 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-l-yl)(phenyl)methyl)propane-2-sulfamamide (0.390 g, 1.17 mmol) in methanol (4.0 mL) was cooled in an ice/water bath and treated with 4.0 M hydrochloric acid in 1,4-dioxane (1.0 mL, 4.00 mmol). The mixture was stirred for 30 min, and then the cooling bath was removed. After another 30 min the reaction mixture was concentrated under reduced pressure. The residue was partitioned between water and dichloromethane, and the organic layer was discarded. The aqueous layer was made basic with concentrated aqueous ammonium hydroxide and extracted with dichloromethane (x2). The aqueous layer was then saturated with sodium chloride and further extracted with dichloromethane. The combined organic layers following basification were washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered, and concentrated. The resulting oil was vacuum dried at ambient temperature for 30 min to afford (2-methyl-2-azabicyclo[2.2.2]octan-l-yl)(phenyl)methanamine (0.263 g, 98%) as a solid. 1H NMR (300 MHz, chloroform-d) δ ppm 1.00 - 1.13 (m, 1 H), 1.29 - 1.47 (m, 3 H), 1.48 - 1.70 (m, 5 H), 1.72 - 1.86 (m, 1 H), 1.97 - 2.08 (m, 1 H), 2.43 - 2.49 (m, 1 H), 2.45 (s, 3 H), 3.28 (dt, J=10.6, 2.4 Hz, 1 H), 4.04 (s, 1 H), 7.19 - 7.37 (m, 5 H). m/z (ES+), (M+H)+ 231.2.

A mixture of (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine (0.025g, 0.11 mmol), 3,5-dichloroisonicotinic acid (0.026g, 0.14 mmol), and HOBT (0.021g, 0.14 mmol) in DMF (1.0 mL) was treated with TBTU (0.044g, 0.14 mmol) and DIPEA (0.050 mL, 0.29 mmol). The mixture was stirred at room temperature for 18 hours and was then concentrated. The resulting residue was treated with ethyl acetate and washed with saturated aqueous potassium carbonate, water, and then saturated aqueous sodium chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated. This new residue was purified by flash column chromatography (SiO\textsubscript{2}, 0-5% (2 M ammonia in methanol) in dichloromethane) to afford an oil that solidified on standing. This solid was triturated with hexanes and dried under vacuum at 50°C for 4 hours to afford 3,5-dichloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)isonicotinamide (30 mg, 68.4%) as a solid. IH NMR (300 MHz, chloroform-d) δ ppm 1.25 - 1.75 (m, 8 H), 1.89 - 2.05 (m, 1 H), 2.42 (s, 3 H), 2.44 - 2.57 (m, 1 H), 3.16 - 3.30 (m, 1 H), 4.81 (s, 1 H), 7.02 - 7.40 (m, 6 H), 8.52 (s, 2 H). m/z (ES+), (M+H)\textsuperscript{+} 404.1290, 406.1265; MS2, HPLC t\textsubscript{R} = 0.83 min.
Example 2. Preparation of N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2-(methylthio)nicotinamide.

N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2-(methylthio)nicotinamide was prepared according to the procedures of Example 1, Steps A-G, with the following modifications: In Step F, no workup was performed and (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine dihydrochloride was obtained via concentration of the reaction mixture; this material was carried on to Step G without further purification. In Step G, 2-(methylthio)nicotinic acid was substituted for 3,5-dichloroisonicotinic acid. Also in Step G, purification of the final product was conducted via preparative HPLC (C18, 65%-93% acetonitrile in water containing ammonium carbonate, pH 10) and subsequent drying of fractions using a Genevac afforded N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2-(methylthio)nicotinamide as a white solid. 1H NMR (500 MHz, DMSO-d6) δ ppm 1.20 - 1.60 (m, 7 H), 1.77 - 1.87 (m, 1 H), 1.98 - 2.09 (m, 1 H), 2.33 (br. s., 3 H), 2.43 (s, 3 H), 2.46 - 2.53 (m, 1 H), 2.95 - 3.13 (m, 1 H), 4.99 (d, J=7.0 Hz, 1 H), 7.17 - 7.26 (m, 2 H), 7.27 - 7.36 (m, 4 H), 7.72 (d, J=7.0 Hz, 1 H), 8.42 - 8.49 (m, 1 H), 8.53 (dd, J=4.7, 1.7 Hz, 1 H). m/z (ES+), (M+H)+ 382.1948, 380.1794; MS2, HPLC tR = 0.81 min.
Method 2 depicts a generalized scheme suitable for preparation of compounds of Formula I by chiral resolution of an intermediate. Those of skill in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds of Formula I.

Example 3. Preparation of (R)-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2-(methylthio)nicotinamide citric acid salt.

A mixture of (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine (1.27 g, 5.51 mmol; Example 1, Step F), sodium bicarbonate (4.26 g, 50.71 mmol), dioxane (15.0 mL), and water (15.0 mL) was cooled in an ice/water bath. The vigorously stirring solution was treated with a solution of di-t-butyl-dicarbonate (1.25 g, 5.73 mmol) in dioxane (2 mL). After 5 minutes, the cooling bath was removed and the mixture was stirred at ambient temperature for 2 hours. Additional di-t-butyl-dicarbonate (1.25 g, 5.73 mmol) was added and the mixture was stirred at ambient temperature for another 16 h. Additional sodium bicarbonate (2.0 g) and di-t-butylidicarbonate (1.3 g) were added and stirring was continued for 5 h. The reaction mixture was then partitioned between water and ethyl acetate. The layers were separated, the aqueous layer was saturated with sodium chloride and further extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and evaporated. The resulting residue was purified by flash column chromatography (SiO₂, 5% (2 M ammonia in methanol) in dichloromethane) to afford tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate (1.51 g, 83%) as a foam solid. IH NMR (300 MHz, chloroform-d) δ ppm 1.04 - 1.77 (m, 17 H), 1.79 - 1.93 (m, 1 H), 2.34 (s, 3 H), 2.39 - 2.51 (m, 1 H), 3.26 (dt, J = 10.5, 2.2 Hz, 1 H), 4.38 (br. s., 1 H), 5.75 (br. s., 1 H), 7.14 - 7.31 (m, 5 H). m/z (ES+), (M+H)⁺ 331.331.2384.
Step B. Preparation of (S)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate and (R)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate from tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate

Tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate (4.40 g, 13.3 mmol) was resolved using an IA column and supercritical fluid chromatography conditions (liquid CO₂) employing isocratic 8.5% methanol containing 0.5% dimethylethylamine. This afforded (S)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate (1.95 g, 44%) and (R)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate (2.02 g, 46%) as white solids. (S)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate: ¹H NMR (300 MHz, chloroform-d) δ ppm 1.17 - 1.77 (m, 17 H), 1.79 - 1.93 (m, 1 H), 2.34 (s, 3 H), 2.42 - 2.52 (m, 1 H), 3.18 - 3.34 (m, 1 H), 4.39 (br. s., 1 H), 5.70 - 5.86 (m, 1 H), 7.10 - 7.40 (m, 5 H). m/z (ES+), (M+H)+ 331.2371; MS2, HPLC tR= 0.93 min. (R)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate: ¹H NMR (300 MHz, chloroform-d) δ ppm 1.17 - 1.78 (m, 17 H), 1.79 - 1.94 (m, 1 H), 2.34 (s, 3 H), 2.41 - 2.56 (m, 1 H), 3.27 (d, J = 10.5 Hz, 1 H), 4.39 (br. s., 1 H), 5.77 (br. s., 1 H), 7.15 - 7.39 (m, 5 H). m/z (ES+), (M+H)+ 331.2377; MS2, HPLC tR= 0.92 min. Chiral analytical supercritical fluid (CO₂) chromatography was carried out using a 4.6 x 250 mm ChiralPak IA column with a modifier composed of methanol containing 0.3% isopropyl amine. The flow rate was 2.37 mL/min with the following gradient: isocratic hold at 5% modifier for 1 min, then ramping at 5% per minute to 50% modifier, then holding at this mixture for 5 minutes. Using these conditions, the retention times for (S)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)...
yl)(phenyl)methylcarbamate and (R)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate were 5.5 and 5.9 minutes, respectively.

Step C. Preparation of (S)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine and (R)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine from (S)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate and (R)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate.

Separate solutions of (S)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate and (R)-tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate (6.11 mmol) in methanol (45 mL) were treated with 3N aqueous hydrochloric acid (12.0 mL, 36.00 mmol) and concentrated aqueous hydrochloric acid (3.0 mL, 36.00 mmol). The mixtures were stirred at ambient temperature for 2 hours and then concentrated under reduced pressure. The resulting residues were reconcentrated from methanol (x2; water bath temp: 45-50 °C) and then partitioned between water and dichloromethane. The layers were separated, and the organic layer was discarded. The aqueous layer was basified with concentrated aqueous ammonium hydroxide and then extracted with dichloromethane (x2). The aqueous layer was saturated with sodium chloride and further extracted with dichloromethane. The combined organic layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and concentrated.

The resulting oils were dried under vacuum for 30 min to afford (S)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine and (R)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine as light yellow solids (90% yields for both). (S)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine: 1H NMR (300 MHz, chloroform-d) δ ppm 0.97 - 1.13 (m, 1 H), 1.29 - 1.46 (m, 3 H), 1.47 - 1.72 (m, 6 H), 1.72 - 1.86 (m, 1 H), 1.95 - 2.08 (m, 1 H), 2.41 - 2.52 (m, 1 H), 2.45 (s, 3 H), 3.28 (dt, J = 10.6, 2.5 Hz, 1 H), 4.04 (s, 1 H), 7.14 - 7.41 (m, 5 H). m/z (ES+), (M+H)\(^+\) 231.1859; MS2, HPLC tR = 0.29 min. (R)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine: 1H NMR (300 MHz, chloroform-d) δ ppm 0.94 - 1.14 (m, 1 H), 1.28 - 1.47 (m, 3 H), 1.48 - 1.71...
(m, 5 H), 1.72 - 1.87 (m, 1 H), 1.96 - 2.09 (m, 1 H), 2.43 - 2.52 (m, 1 H), 2.46 (s, 3 H), 3.28 (at, J = 10.6, 2.5 Hz, 1 H), 4.04 (s, 1 H). m/z (ES+), (M+H) + 231.1858; MS2, HPLC tR = 0.29 min.

[208] Absolute Stereochemical Configuration: The absolute chiral form of the two amines above was established through the synthesis of L-((lS,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-N-((S)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)methanesulfonamide:

This compound was prepared by reacting presumed (S)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine with excess ((lS,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonyl chloride and triethyl amine in dichloromethane for 16 h. IH NMR (300 MHz, chloroform-d) δ ppm 0.75 (s, 3 H), 1.05 (s, 3 H), 1.08 - 1.22 (m, 1 H), 1.24 - 1.75 (m, 10 H), 1.80 (d, J = 18.3 Hz, 1 H), 1.84 - 2.04 (m, 3 H), 2.26 (dt, J = 18.3, 4.0 Hz, 1 H), 2.32 - 2.43 (m, 1 H), 2.46 (s, 3 H), 2.55 (dt, J = 11.2, 2.7 Hz, 1 H), 2.73 (d, J = 14.8 Hz, 1 H), 2.97 (d, J = 15.0 Hz, 1 H), 3.26 (d, J = 11.2 Hz, 1 H), 4.51 (s, 1 H), 7.27 - 7.41 (m, 5 H). m/z (ES+), (M+H) + 445.4. Cooling a solution of this sulfonamide in hot hexanes containing just enough acetone to solublize (~5%) afforded crystals along the edges of the solution. These crystals via x-ray diffraction allowed for the unambiguous assignment of (S) stereochemistry to the previously arbitrarily assigned (S) enantiomer of (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine. The opposite enantiomer was assigned the (R) stereochemistry.

Either enantiomer can be carried on as described in Step D to afford desired products.
Step D. Preparation of (R)-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2-(methylthio)nicotinamide citric acid salt from (R)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine.

The desired compound was prepared according to the procedure of Example 1, Step G, with the following modifications: The acid 2-(methylthio)nicotinic acid was substituted for 3,5-dichloroisonicotinic acid and (R)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine was substituted for (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine. Also, the oil obtained from flash column chromatography was dissolved in acetonitrile and treated with one equivalent of citric acid monohydrate in water. The mixture was then lyophilized from water and acetonitrile to provide the citric acid salt of (R)-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2-(methylthio)nicotinamide as a white solid, which was further dried under vacuum at 50°C for 4 hours. IH NMR (300 MHz, MeOD) δ ppm 1.46 - 2.00 (m, 7 H), 2.09 - 2.25 (m, 1 H), 2.36 - 2.52 (m, 4 H), 2.59 - 2.80 (m, 4 H), 2.97 - 3.17 (m, 4 H), 3.69 - 3.83 (m, 1 H), 5.51 (s, 1 H), 7.15 (dd, J=7.5, 5.0 Hz, 1 H), 7.31 - 7.51 (m, 5 H), 7.79 (dd, J=7.6, 1.5 Hz, 1 H), 8.50 (dd, J=5.0, 1.8 Hz, 1 H). m/z (ES+), (M-citrate) + 382.1940; MS2, tR = 0.84 min.
**Method 3. Enantioselective Synthesis of Compounds of Formula I**

Method 3 depicts a generalized scheme suitable for enantioselective synthesis of compounds of Formula I. Those of skill in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds of Formula I. R and n can be selected as described elsewhere herein.

**Example 4. Preparation of (R)-3-bromo-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)isonicotinamide.**
[212] **Step A. Preparation of** 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carbaldehyde **from** methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate.

![Chemical Structure](image)

To a cloudy solution of methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate (0.224 g, 1.14 mmol; Example 1, Step A) in tetrahydrofuran (5.68 mL) at -78 °C was added 2.0 M lithium aluminum hydride in tetrahydrofuran (0.568 mL, 1.14 mmol) dropwise, maintaining the reaction temperature below -68 °C. After 5 min, concentrated aqueous hydrochloric acid (0.095 mL, 1.14 mmol) was added dropwise, resulting in an exotherm, and the reaction temperature reached -38 °C before being cooled back down to -78 °C. After 10 min, the reaction was warmed to -20 °C, and then the white mixture was diluted with ethyl acetate and saturated aqueous sodium potassium tartrate (Rochelle's salt). The layers were separated, the aqueous layer was extracted with ethyl acetate (x2), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford crude 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carbaldehyde (0.189 g, 100%) containing a small amount of alcohol (~15%) as a clear colorless oil. IH NMR (300 MHz, chloroform-d) δ ppm 1.65 - 1.96 (m, 8 H), 2.56 - 2.71 (m, 1 H), 3.02 (s, 3 H), 9.85 (s, 1 H). m/z (ES+), (M+MeOH+H)^+ 200.16.

[213] **Step B. Preparation of** (R)-2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide **from** crude 2-methyl-3-oxo-2-azabicyclo [2.2.2] octane-1-carbaldehyde.

![Chemical Structure](image)

To a solution of crude 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carbaldehyde (0.726 g, 4.34 mmol) and tetraethoxytitanium (2.003 mL, 9.55 mmol) in tetrahydrofuran (10.85 mL) was added (R)-2-methylpropane-2-sulfamidine (0.632 g, 5.21 mmol). The resulting slightly cloudy white solution was stirred at ambient temperature for 15 h and then quenched with
saturated aqueous sodium bicarbonate (10 drops). The resulting mixture was diluted with ethyl acetate (10 mL) and stirred vigorously for 30 min before being filtered through a pad of sodium sulfate. The filtrate was concentrated, and the resulting residue was purified by flash column chromatography (SiO₂, 0-100% ethyl acetate in dichloromethane) to afford (R)-2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfamidine (0.553 g, 47%) as a clear oil which solidified to a white solid on standing. IH NMR (500 MHz, chloroform-d) δ ppm 1.23 (s, 9H), 1.76-1.86 (m, 4H), 1.87 - 1.97 (m, 4H), 1.97 - 2.04 (m, 1H), 2.94 (s, 3H), 8.24 (s, 1H). m/z (ES+), (M+H)+ 271.2.


[215] A solution of (R)-2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfamidine (0.100 g, 0.37 mmol) in tetrahydrofuran (2.0 mL) at -78 °C was treated with trimethylaluminum (2 M in toluene, 0.200 mL, 0.40 mmol). Phenyllithium (1.8 M in di-n-butyl ether, 0.230 mL, 0.41 mmol) was added dropwise over 5 minutes. After 45 min, the reaction mixture was quenched with 1:1 concentrated aqueous ammonium hydroxide and saturated aqueous ammonium chloride. The cooling bath was removed, and the mixture was warmed to ambient temperature. The mixture was then extracted with ethyl acetate (x2), and the combined organic layers were washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and concentrated. The resulting solid was vacuum dried at ambient temperature for 20 min to afford (R)-2-methyl-N-((R)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)propane-2-sulfinamide (0.140 g, 109%) containing a small amount of ethyl acetate. IH NMR (300 MHz, chloroform-d) δ ppm 1.02 - 1.20 (m, 1 H), 1.26 (s, 9 H), 1.42 -
2.05 (m, 7 H), 2.55 - 2.63 (m, 1 H), 3.20 (s, 3 H), 3.76 (s, 1 H), 4.80 (s, 1 H), 7.34 (s, 5 H).
m/z (ES+), (M+H) + 349.3.

[216] Stereochemical Determination: Reduction of the amide (See Step D below) and conversion of the resulting sulfamamide to the corresponding Boc carbamate (as described in Example 3) allowed for the determination that this compound was of 98% (R)-2-methyl-N-((R)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)propane-2-sulfamamide using SFC conditions as described in Example 3, Step B. If the (S) enantiomer was desired, (S)-2-methylpropene-2-sulfamamide was used. If the racemate was desired, 2-methylpropene-2-sulf amid could be used.


A solution of (R)-2-methyl-N-((R)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)propane-2-sulfamid (0.369g, 1.06 mmol) in tetrahydrofuran (6.0 mL) was treated with carbonylhydridotris(triphenylphosphate)rhodium(I) (0.030 g, 0.033 mmol) and diphenylsilane (0.500 mL, 2.69 mmol). After 1 hour, nitrogen was bubbled through the reaction mixture. Additional rhodium catalyst (0.010g, 0.011 mmol) and diphenylsilane (0.250 mL, 1.35 mmol) were added, and the mixture was stirred at ambient temperature for 16 h. The reaction was then diluted with ether and extracted with IN aqueous hydrogen chloride (x2). The organic layer was discarded, and the aqueous layers were combined and basified with concentrated aqueous ammonium hydroxide. The aqueous layer was then extracted with ethyl acetate (x3), and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO2, 5% (2 M ammonia in methanol) in dichloromethane) to afford (R)-2-
methyl-N-((R)-(2-methyl-2-azabicyclo[2.2.2]octan-l-yl)(phenyl)methyl)propane-2-
sulfinamide (300mg, 83%) as a light yellow oil that solidified on standing. 1H NMR (300 MHz, chloroform-d) δ ppm 1.02 - 1.48 (m, 13 H), 1.48 - 2.00 (m, 5 H), 2.45 (s, 3 H), 2.48 - 2.63 (m, 1 H), 3.30 (dd, J=10.2, 1.6 Hz, 1 H), 4.35 (s, 1 H), 5.14 (s, 1 H), 7.18 - 7.37 (m, 5 H).

[218] Step E. Preparation of (R)-(2-methyl-2-azabicyclo[2.2.2]octan-l-
yl)(phenyl)methanamine from (R)-2-methyl-N-((R)-(2-methyl-2-azabicyclo[2.2.2]octan-l-yl)(phenyl)methyl)propane-2-sulfinamide.

The compound (R)-(2-methyl-2-azabicyclo[2.2.2]octan-l-yl)(phenyl)methanamine was prepared from (R)-2-methyl-N-((R)-(2-methyl-2-azabicyclo[2.2.2]octan-l-yl)(phenyl)methyl)propane-2-sulfinamide using the procedure of Example 1, Step F. This material could then be used as described in Example 1, Step G, to prepare single enantiomers of desired benzamides. 1H NMR (300 MHz, chloroform-d) δ ppm 0.95 - 1.14 (m, 1 H), 1.29 - 1.46 (m, 3 H), 1.48 - 1.71 (m, 5 H), 1.73 - 1.86 (m, 1 H), 1.97 - 2.08 (m, 1 H), 2.41 - 2.52 (m, 4 H), 3.28 (dt, J = 10.6, 2.5 Hz, 1 H), 4.04 (s, 1 H), 7.16 - 7.39 (m, 5 H). m/z (ES+), (M+H)+ 231.1847.

[219] Step F. Preparation of (R)-3-bromo-N-((2-methyl-2-
azabicyclo[2.2.2]octan-l-yl)(phenyl)methyl)isonicotinamide from (R)-(2-methyl-2-
azabicyclo[2.2.2]octan-l-yl)(phenyl)methanamine.
The desired compound was prepared according to the procedure of Example 1, Step G, with the following modifications: The acid 3-bromoisonicotinic acid was substituted for 3,5-dichloroisocotinic acid and (R)-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine was substituted for (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methanamine. Also, no workup was performed. Hence, the crude reaction mixture was filtered, diluted with methanol and purified directly via preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford the desired product as a white foam solid upon concentration. IH NMR (300 MHz, chloroform-d) δ ppm 1.29 - 1.50 (m, 4 H), 1.55 - 1.79 (m, 4 H), 1.88 - 2.04 (m, 1 H), 2.36 (s, 3 H), 2.50 (d, J=10.7 Hz, 1 H), 3.24 (d, J=10.7 Hz, 1 H), 4.80 (d, J=2.7 Hz, 1 H), 7.26 - 7.36 (m, 5 H), 7.44 (d, J=4.6 Hz, 2 H), 8.58 (d, J=4.8 Hz, 1 H), 8.79 (s, 1 H). m/z (ES+), (M+H)+ = 414.3, 416.3; MS!, HPLC tR = 0.44 min.


Method 4 depicts a generalized scheme suitable for the stereoselective synthesis of sulfonamides of Formula I. Those skilled in the art will readily recognize various reagents.
and intermediates or changes in moieties that could be used to make additional aryl sulfonamides, either stereoselectively or in racemic form.

[221] Example 5. Preparation of (R*)-N-((4-(N,N-dimethylsulfamoyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2,6-dimethylbenzamide.

![Chemical Structure](image.png)

[222] Step A. Preparation of 4-bromo-N,N-dimethylbenzenesulfonamide from 4-bromobenzene-1-sulfonyl chloride.

A solution of 4-bromobenzene-1-sulfonyl chloride (1.278 g, 5 mmol) in tetrahydrofuran (20 mL) was sequentially treated with triethylamine (0.976 mL, 7.00 mmol) and 2.0 M dimethylamine in tetrahydrofuran (2.75 mL, 5.50 mmol). The resulting white mixture was stirred at room temperature for 1 hour and then filtered. The filtrate was concentrated, and the resulting residue was purified by flash column chromatography (SiO₂, 0-100% ethyl acetate in hexanes) to afford 4-bromo-N,N-dimethylbenzenesulfonamide (0.470 g, 35.6%) as a white solid. IH NMR (300 MHz, chloroform-d) δ ppm 2.72 (s, 6 H), 7.56 - 7.75 (m, 4 H). m/z (ES+), (M+H)+ = 264.1, 266.1.
Step B. Preparation of 4-((R*)-((R)-1,1-dimethylethylsulfinamido)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methyl)-N,N-dimethylbenzenesulfonamide from (R)-2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide.

A solution of (R^-methyl-N^-methyl-S-oxo^-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfanamide (0.324 g, 1.2 mmol; prepared according to the procedures of Example 4, Steps A-B) in tetrahydrofuran (2.95 ml) at -78°C was treated with 2 M trimethylaluminum in toluene (0.648 ml, 1.30 mmol). In a separate flask, to a solution of 4-bromo-N,N-dimethylbenzenesulfonamide (0.370 g, 1.4 mmol) in tetrahydrofuran (4.01 ml) at -78°C was added n-butyllithium (0.659 ml, 1.47 mmol) in hexanes dropwise. After 30 min, the aryl lithium solution was added rapidly dropwise in 0.5 mL portions to the solution of sulfanamide and trimethylaluminum over 5 min. After stirring for 90 min, the reaction was quenched with a mixture of 1:1 saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide, and the mixture was warmed to room temperature. The mixture was extracted with ethyl acetate (x2), and the combined organic layers were washed with water and saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 0-100% ethyl acetate in hexanes) to afford 4-((R*)-((R)-1,1-dimethylethylsulfanamido)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methyl)-N,N-dimethylbenzenesulfonamide (0.122 g, 22.3%) as a white solid.

Stereochemistry: This diastereomer was arbitrarily assigned R* stereochemistry based on the stereochemical preference for addition elucidated in Example 4.

1H NMR (500 MHz, chloroform-d) δ ppm: 1.03 - 1.13 (m, 1 H), 1.27 (s, 9 H), 1.53 - 1.67 (m, 4 H), 1.68 - 1.77 (m, 1 H), 1.81 - 1.89 (m, 1 H), 1.93 - 2.03 (m, 1 H), 2.62 (br.
s., 1 H), 2.77 (s, 6 H), 3.19 (s, 3 H), 3.85 (s, 1 H), 4.88 (s, 1 H), 7.52 (d, J=8.2 Hz, 2 H), 7.77 (d, J=8.5 Hz, 2 H). m/z (ES+), (M+H)+ = 456.3.

[224] Step C. Preparation of 4-(((R*)-((R)-l,l-dimethylethylsulfinamido)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-N,N-dimethylbenzenesulfonamide from 4-

To a degassed solution of 4-(((R*)-((R)-l,l-dimethylethylsulfinamido)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methyl)-N,N-dimethylbenzenesulfonamide (122 mg, 0.27 mmol) and diphenylsilane (0.104 ml, 0.56 mmol) in tetrahydrofuran (1.234 ml) was added carbonylhydridotris(triphenylphosphine)rhodium(I) (2.460 mg, 2.68 µmol), resulting in immediate but brief gas evolution. The light yellow reaction was stirred for 1 h and was then quenched with IN aqueous hydrogen chloride. The aqueous layer was washed with ether and was then basified with solid sodium bicarbonate. The aqueous layer was then extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford crude 4-(((R*)-((R)-l,l-dimethylethylsulfinamido)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methyl)-N,N-dimethylbenzenesulfonamide (53.0 mg, 44.8 %) as a white solid. 1H NMR (500 MHz, chloroform-d) δ ppm 1.07 - 1.17 (m, 1 H), 1.25 - 1.29 (m, 10 H), 1.33 (br. s., 1 H), 1.46 (t, J=15.6 Hz, 1 H), 1.55 - 1.65 (m, 3 H), 1.72 - 1.82 (m, 1 H), 1.91 - 2.00 (m, 1 H), 2.44 (s, 3 H), 2.53 - 2.60 (m, 1 H), 2.74 (s, 6 H), 3.31 (d, J=11.6 Hz, 1 H), 4.42 (s, 1 H), 5.27 (s, 1 H), 7.44 (d, J=8.2 Hz, 2 H), 7.70 (d, J=8.5 Hz, 2 H). m/z (APCI+), (M+H)+ = 442.19.
[225] **Step D. Preparation of** (R*)-N-((4-(N,N-dimethylsulfamoyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2,6-dimethylbenzamide **from** 4-((R*)-((R)-1,1-dimethylethylsulfamido)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-N,N-dimethylbenzenesulfonamide.

A solution of 4-((R*)-((R)-1,1-dimethylethylsulfamido)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-N,N-dimethylbenzenesulfonamide (0.053 g, 0.12 mmol) in methanol (3 mL) was treated with 4.0 M hydrochloric acid in dioxane (1 mL, 4.00 mmol). The resulting solution was stirred at room temperature for 5 min and was then concentrated. The resulting residue was taken up in dichloromethane (2 mL) and sequentially treated with DIPEA (0.105 mL, 0.60 mmol) and 2,6-dimethylbenzoyl chloride (0.180 mL, 0.18 mmol). The reaction was stirred at room temperature for 16 h and then concentrated. This new residue was diluted with acetonitrile, filtered, and purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford semi-pure product. This white solid was repurified by flash column chromatography (SiO₂, 0-100% ethyl acetate in hexanes) to afford (R*)-N-((4-(N,N-dimethylsulfamoyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2,6-dimethylbenzamide (0.018 g, 31.9%) as a colorless glass.

**1H NMR** (500 MHz, chloroform-d): δ ppm 1.18 - 1.29 (m, 1 H), 1.36 - 1.49 (m, 3 H), 1.58 - 1.71 (m, 4 H), 1.93 - 2.04 (m, 1 H), 2.34 (s, 6 H), 2.41 (s, 3 H), 2.48 - 2.55 (m, 1 H), 2.74 (s, 6 H), 3.17 - 3.26 (m, 1 H), 4.92 (s, 1 H), 6.97 (br. s., 1 H), 7.03 (d, J=7.3 Hz, 2 H), 7.17 (t, J=7.5 Hz, 1 H), 7.49 (d, J=7.9 Hz, 2 H), 7.73 (d, J=8.2 Hz, 2 H). m/z (ES+), (M+H)+ = 470.4; MS1, HPLC tR = 0.49 min.
Method 5. Stereoselective Synthesis of Chiral Sulfones of Formula I

Method 5 depicts a generalized scheme suitable for the stereoselective synthesis of sulfones of Formula I. Those skilled in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional aryl sulfones, either stereoselectively or in racemic form.
Example 6. Preparation of (R*)-N-((4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2,6-dimethylbenzamide.

Step A. Preparation of (4-bromophenyl)(cyclopropylmethyl)sulfane from 4-bromobenzenethiol.

To a yellow mixture of 4-bromobenzenethiol (3.03 g, 16 mmol), potassium carbonate (3.32 g, 24.00 mmol), and N,N-dimethylformamide (10 ml) was added (bromomethyl)cyclopropane (2.81 g, 20.80 mmol). After a short exotherm, the now colorless solution was stirred for 25 min and then diluted with ethyl acetate. The resulting mixture was filtered through celite and the filtrate was washed with water. The organic phase was dried over magnesium sulfate, filtered and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 0-100% ethyl acetate in hexanes) to afford (4-bromophenyl)(cyclopropylmethyl)sulfane (2.89 g, 74.3%) as a light yellow oil. ¹H NMR (500 MHz, chloroform-d) δ ppm 0.20 - 0.27 (m, 2 H), 0.53 - 0.61 (m, 2 H), 0.98 - 1.09 (m, 1 H), 2.84 (d, J = 7.0 Hz, 2 H), 7.16 - 7.24 (m, 2 H), 7.35 - 7.41 (m, 2 H). m/z (ES+), (M+H)⁺ = 259.0, 261.0.

A solution of (R)-2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfamidine (0.270 g, 1 mmol; Example 4, Steps A-B) in tetrahydrofuran (4 mL) at -78°C was treated with 2.0 M trimethylaluminum in toluene (0.540 ml, 1.08 mmol). In a separate flask, a solution of (4-bromophenyl)(cyclopropylmethyl)sulfane (0.486 g, 2 mmol) in tetrahydrofuran (3.09 ml) was cooled to -78°C. A solution of 2.2 M n-butyllithium in hexanes (0.909 ml, 2.00 mmol) was added dropwise and the resulting solution was stirred at -78°C for 15 min. This solution was then added to that containing (R)-2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfamidine dropwise over 15 min at -78°C. The resulting solution was stirred at -78°C for 30 min and then quenched by addition of a 1:1 mixture of saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide. The resulting mixture was warmed to room temperature, diluted with ethyl acetate, and washed with water (x3). The organic layer was then dried over sodium sulfate, filtered, and concentrated. Purification of the resulting residue by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) afforded (R)-N-((R*)-(4-(cyclopropylmethylthio)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfinamide (0.120 g; 27.6%) as a white solid after lyophilization of product fractions. Stereochemistry: This diastereomer was arbitrarily assigned R* stereochemistry based on the stereochemical preference for addition elucidated in Example 4.

IH NMR (500 MHz, chloroform-^) δ ppm 0.24 - 0.31 (m, 2 H), 0.57 - 0.64 (m, 2 H), 1.04 -
1.11 (m, 1 H), 1.11 - 1.19 (m, 1 H), 1.25 (s, 9 H), 1.46 - 1.63 (m, 3 H), 1.64 - 1.74 (m, 2 H),
1.77 - 1.87 (m, 1 H), 1.89 - 1.97 (m, 1 H), 2.57 - 2.61 (m, 1 H), 2.89 (d, J=7.0 Hz, 2 H), 3.18
(s, 3 H), 3.74 (s, 1 H), 4.75 (s, 1 H), 7.20 - 7.24 (m, 2 H), 7.30 (d, 2 H). m/z (ES+), (M+H)\(^+\) = 435.4.

[230] **Step C. Preparation of** (R*)-tert-butyl (4-(cyclopropylmethylthio)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate **from** (R)-N-((R*)-(4-(cyclopropylmethylthio)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfinamide.

A solution of (R)-N-((R*)-(4-(cyclopropylmethylthio)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfinamide (120 mg, 0.28 mmol) in methanol (3 mL) was treated with 4.0 M hydrochloric acid in dioxane (1 mL, 4.00 mmol). After 5 minutes, the reaction was concentrated and the resulting residue was suspended in ethyl acetate. Saturated aqueous sodium bicarbonate was added followed by di-tert-butyl dicarbonate (0.192 mL, 0.83 mmol). The resulting mixture was stirred vigorously for 16 h, and the layers were then separated. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried over magnesium sulfate, filtered, and concentrated. This new residue was purified by flash column chromatography (SiO\(_2\), 0-100% ethyl acetate in hexanes) to afford (R*)-tert-butyl (4-(cyclopropylmethylthio)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate (0.087 g, 73.2%) as a clear colorless oil. 1H NMR (500 MHz, chloroform-d) \(\delta\) ppm 0.23 - 0.29 (m, 2 H), 0.55 - 0.63 (m, 2 H), 1.01 - 1.11 (m, 1 H), 1.19 - 1.24 (m, 1 H), 1.39 (br. s., 9 H), 1.49 - 1.64 (m, 3 H), 1.66 - 1.75 (m, 3 H), 1.77 - 1.87 (m, 1 H), 2.59 (d, J=2.1 Hz, 1 H), 2.87 (d, J=7.0 Hz, 2 H), 3.07 (s, 3 H), 4.94 (br. s., 1 H), 5.31 (br. s., 1 H), 7.15 (d, J=8.2 Hz, 2 H), 7.30 (d, J=8.5 Hz, 2 H). m/z (ES+), (M+H)\(^+\) = 431.4.
[231] Step D. Preparation of (R*)-tert-butyl (4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate from (R*)-tert-butyl (4-(cyclopropylmethylthio)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate.

A solution of (R*)-tert-butyl (4-(cyclopropylmethylthio)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate (0.087 g, 0.20 mmol) in dichloromethane (1.347 ml) was treated with 3-chlorobenzoperoxoic acid (0.100 g, 0.44 mmol). The resulting mixture was stirred at room temperature for 2 hours and then partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The organic phase was washed with additional sodium bicarbonate (x2), dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO₂, 0-100% ethyl acetate in hexanes) to afford (R*)-tert-butyl (4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate (0.064 g; 68.5%) as a clear colorless oil.

IH NMR (500 MHz, chloroform-d) δ ppm: 0.16 (br. s., 2 H), 0.57 (d, J=5.5 Hz, 2 H), 1.03 (ddd, J=7.4, 3.6, 3.4 Hz, 1 H), 1.10 - 1.19 (m, 1 H), 1.23 - 1.28 (m, 1 H), 1.38 (br. s., 9 H), 1.52 - 1.67 (m, 4 H), 1.68 - 1.80 (m, 2 H), 1.83 (d, J=7.6 Hz, 1 H), 2.61 (br. s., 1 H), 2.94 - 3.14 (m, 4 H), 5.04 (br. s., 1 H), 5.44 (br. s., 1 H), 7.47 (d, J=8.2 Hz, 2 H), 7.91 (d, J=7.9 Hz, 2 H). m/z (ES+), (M+H)⁺ = 463.4.
[232] Step E. Preparation of (R*)-tert-butyl (4-cyclopropylmethylsulfonyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate from (R*)-tert-butyl (4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methyl-carbamate.

To a degassed solution of (R*)-tert-butyl (4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate (64 mg, 0.14 mmol) and diphenylsilane (0.0539 ml, 0.29 mmol) in tetrahydrofuran (0.638 ml) was added carbonylhydridotris(triphenylphosphine)rhodium(I) (1.271 mg, 1.38 µmol), resulting in brief but immediate gas evolution. The light yellow reaction was stirred for 1 hour and was then quenched with IN aqueous hydrogen chloride. The aqueous layer was washed with ether and was then basified with solid sodium bicarbonate. The aqueous layer was extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford crude (R*)-tert-butyl (4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate (35.0 mg, 56.4 %) as a colorless oil. IH NMR (500 MHz, chloroform-d) δ ppm 0.10 - 0.22 (m, 2 H), 0.51 - 0.63 (m, 2 H), 0.98 - 1.10 (m, 1 H), 1.14 - 1.24 (m, 2 H), 1.28 - 1.46 (m, 9 H), 1.62 (br. s., 5 H), 1.65 - 1.73 (m, 1 H), 1.83 - 1.96 (m, 1 H), 2.34 (s, 3 H), 2.46 - 2.55 (m, 1 H), 2.94 - 3.01 (m, 1 H) 3.01 - 3.09 (m, 1 H) 3.27 (d, J=10.4 Hz, 1 H) 4.46 (br. s., 1 H) 5.89 (br. s., 1 H), 7.42 (d, J=8.2 Hz, 2 H), 7.84 (d, J=8.2 Hz, 2 H). m/z (ES+), (M+H)+ = 449.5.
Step F. Preparation of (R*)-N-((4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2,6-dimethylbenzamide from (R*)-tert-butyl (4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate.

Concentrated aqueous hydrochloric acid (0.5 mL) was added to (R*)-tert-butyl (4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylcarbamate (0.035 g, 0.08 mmol). After 1 minute, gas evolution ceased, and the reaction was diluted with methanol (1 mL) and concentrated to a white foam. The material was dried under high vacuum for 10 minutes and then dissolved in DMF (1 mL). To this solution were added DIPEA (0.136 ml, 0.78 mmol), HOBt (0.017 g, 0.11 mmol), and 2,6-dimethylbenzoic acid (0.026 g, 0.17 mmol) followed by TBTU (0.035 g, 0.11 mmol). The light yellow reaction was stirred at room temperature for 16 h and was then quenched with saturated aqueous sodium bicarbonate. The resulting mixture was extracted with ethyl acetate (x3) and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) and the product fractions were lyopholized to afford semipure product. Repurification via flash column chromatography (SiO2, 0-10% methanol in dichloromethane) afforded (R*)-N-((4-(cyclopropylmethylsulfonyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2,6-dimethylbenzamide (0.007 g, 18.7%) as a white solid upon lyopholization. 1H NMR (500 MHz, chloroform-d) δ ppm 0.09 - 0.18 (m, 2 H), 0.51 - 0.61 (m, 2 H), 1.00 - 1.09 (m, 1 H), 1.18 - 1.28 (m, 1 H), 1.36 - 1.52 (m, 3 H), 1.52 - 1.73 (m, 4 H), 1.93 - 2.03 (m, 1 H), 2.33 (s, 6 H), 2.42 (s, 3 H), 2.51 (d, J=10.7 Hz, 1 H), 2.95 - 3.03 (m, 1 H), 3.03 - 3.11 (m, 1 H), 3.21 (d, J=10.7 Hz, 1 H), 4.93 (br. s., 1 H), 7.00
Example 7. Preparation of (R*)-2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(methylsulfonyl)phenyl)methyl)benzamide.

The compound (R*)-2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(methylsulfonyl)phenyl)methyl)benzamide was prepared according to the procedures of Example 6, Steps B-F, substituting 4-bromothioanisole for (4-bromophenyl)(cyclopropylmethyl)sulfane in Step B. 1H NMR (500 MHz, chloroform-d) δ ppm 1.17 - 1.29 (m, 1 H), 1.34 - 1.50 (m, 3 H), 1.56 - 1.71 (m, 4 H), 1.94 - 2.02 (m, 1 H), 2.35 (s, 6 H), 2.41 (s, 3 H), 2.51 (d, J=11.0 Hz, 1 H), 3.09 (s, 3 H), 3.20 (d, J=11.0 Hz, 1 H), 4.92 (d, J=3.1 Hz, 1 H), 6.96 (br. s., 1 H), 7.04 (d, J=7.6 Hz, 2 H), 7.18 (t, J=7.6 Hz, 1 H), 7.52 (d, J=8.5 Hz, 2 H), 7.90 (d, J=8.2 Hz, 2 H). m/z (ES+), (M+H)+ = 441.2081; MS2, HPLC tR = 0.76 min.
Method 6. Racemic Synthesis of Sulfones of Formula I

Method 6 depicts a generalized scheme suitable for the racemic synthesis of sulfones of Formula I. Those skilled in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional aryl sulfones, either stereoselectively or in racemic form.

Step A. Preparation of (4-bromophenyl)(propyl)sulfane from 4-bromobenzenethiol.

To a yellow mixture of 4-bromobenzenethiol (3.0 g, 15.87 mmol), potassium carbonate (3.29 g, 23.80 mmol), and N,N-dimethylformamide (79 ml) was added 1-iodopropane (1.703 ml, 17.45 mmol). The mixture instantly became colorless. After 50 min, the mixture was filtered and the filtrate was concentrated to minimal volume. This residue was purified by flash column chromatography (SiO₂, 0-10% ethyl acetate in hexanes) with elution at the solvent front to afford (4-bromophenyl)(propyl)sulfane (2.54 g, 69.3 %) as a light gold oil. IH NMR (300 MHz, chloroform-d) δ ppm 1.02 (t, 3 H), 1.66 (sxt, J=7.3 Hz, 2 H), 2.87 (t, J=7.3 Hz, 2 H), 7.13 - 7.22 (m, 2 H), 7.29 - 7.46 (m, 2 H).

Step B. Preparation of 1-(hydroxymethyl)-2-methyl-2-azabicyclo[2.2.2]octan-3-one from methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate.
To a solution of methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate (2.6 g, 13.18 mmol; Example 1, Step A) in tetrahydrofuran (66 mL) at 0°C was added 2.0 M lithium aluminum hydride in tetrahydrofuran (12 ml, 24.00 mmol). After 45 min, the reaction was quenched sequentially by dropwise addition of water (712 uL), 15% aqueous sodium hydroxide (712 uL) and additional water (1000 uL). The resulting mixture was stirred for 60 min and then filtered. The filtrate was concentrated and the resulting white solid was purified by flash column chromatography (SiO2, 0-30% methanol in ethyl acetate) to afford 1-(hydroxymethyl)-2-methyl-2-azabicyclo[2.2.2]octan-3-one (1.020 g, 45.7 %) as a white solid. IH NMR (300 MHz, chloroform-d) δ ppm 1.44 - 1.60 (m, 2 H), 1.65 - 1.90 (m, 6 H), 2.51 - 2.69 (m, 1 H), 3.04 (s, 3 H), 3.79 (d, J=5.3 Hz, 2 H). m/z (ES+), (M+H)+ = 170.1.

[239] Step C. Preparation of 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carbaldehyde from 1-(hydroxymethyl)-2-methyl-2-azabicyclo[2.2.2]octan-3-one.

To a solution of DMSO (0.839 ml, 11.82 mmol) in dichloromethane (20 mL) at -78°C was added via syringe oxaly chloride (0.517 ml, 5.91 mmol). After 30 min, a solution of 1-(hydroxymethyl)-2-methyl-2-azabicyclo[2.2.2]octan-3-one (0.5 g, 2.95 mmol) at -78°C in dichloromethane (10 mL) was added via cannula. After 30 min, the reaction was quenched with triethylamine (29.5 mmol), affording a cloudy mixture. After 15 min, this reaction was concentrated to a yellow solid, which was redissolved in ethyl acetate and water. The layers were separated, and the aqueous layer was extracted with ethyl acetate (x2). The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford crude 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carbaldehyde (0.390 g, 79 %) as a red gold liquid. This crude material was used to generate the corresponding racemic 2-methylpropane-2-sulfamamide as described in Example 4, Step B, without further purification. IH NMR (300 MHz, chloroform-d) δ ppm 1.58 - 1.95 (m, 8 H), 2.65 - 2.71 (m, 1 H), 3.02 (s, 3 H), 9.85 (s, 1 H). m/z (ES+), (M+MeOH+H)+ = 200.1. 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carbaldehyde can be prepared more efficiently according to the procedures of Example 4, Step A.

Approximately 26 mg of (4-bromophenyl)(propyl)sulfane was added to a mixture of magnesium (0.100 g, 4.12 mmol) in tetrahydrofuran (0.5 ml) followed by one drop of 1,2-dibromoethane. The mixture was warmed to reflux and (4-bromophenyl)(propyl)sulfane (1.0 g, 4.33 mmol) in tetrahydrofuran (3.0 mL) was added dropwise, maintaining the reaction under reflux conditions. After 1.5h, the orange-yellow reaction was cooled to room temperature. To a slightly cloudy solution of 2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-l-yl)methylene)propane-2-sulfinamide (0.393 g, 1.45 mmol; prepared according to the procedures of Example 4, Step B, substituting 2-methylpropane-2-sulfamidem for (R)-2-methylpropane-2-sulfamidem) in tetrahydrofuran (1 ml) at 0°C was added (4-(propylthio)phenyl)magnesium bromide (1.106 g, 4.33 mmol) slowly, resulting in a yellow solution. After 3 days, the reaction was quenched with a 1:1 mixture of saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford crude 2-methyl-N-((lS)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-l-yl)(4-(propylthio)phenyl)methyl)propane-2-sulfinamide. The crude 2-methyl-N-((lS)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-l-yl)(4-(propylthio)phenyl)methyl)propane-2-sulfinamide was dissolved in methanol (2 mL) and treated with 4.0 M hydrochloric acid in dioxane (3.63 mL, 14.50 mmol). After 5 min, the solution was concentrated; the resulting residue was dissolved in dichloromethane and di-tert-butyl dicarbonate (0.475 g, 2.18 mmol) and triethylamine (4.35 mmol) were added in one portion. After 3 h, the light orange solution was concentrated and purified by flash column
chromatography (SiO$_2$, 0-100% ethyl acetate in hexanes) to afford tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate (0.238 g, 39.2%) as a light brown viscous residue. 1H NMR (300 MHz, chloroform-$d$) $\delta$ ppm 1.04 (t, $J=7.3$ Hz, 3 H), 1.38 (br. s., 9 H), 1.47 - 1.91 (m, 10 H), 2.55 - 2.64 (m, 1 H), 2.91 (t, $J=7.3$ Hz, 2 H), 3.08 (s, 3 H), 4.93 (br. s., 1 H), 5.29 (br. s., 1 H), 7.12 - 7.18 (m, 2 H), 7.24 - 7.29 (m, 2 H). m/z (ES+), (M+H)$^+$ = 419.3.

[241] **Step E. Preparation of** tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate **from** tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate.

To a light orange solution of tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate (0.235 g, 0.56 mmol) in DMF (2.81 ml) was added oxone (0.518 g, 0.84 mmol). After 1.5 h, the mixture was diluted with water and saturated aqueous sodium chloride. The mixture was extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by flash column chromatography (SiO$_2$, 0-100% ethyl acetate) to afford tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate (0.111 g, 43.9%) as a clear colorless viscous oil. 1H NMR (300 MHz, chloroform-$d$) $\delta$ ppm 1.03 (t, $J=7.4$ Hz, 3 H), 1.39 (br. s., 9 H), 1.54 - 1.91 (m, 10 H), 2.59 - 2.65 (m, 1 H), 3.04 - 3.11 (m, 2 H), 3.09 (s, 3 H), 5.04 (br. s., 1 H), 5.38 (br. s., 1 H), 7.47 (d, $J=8.4$ Hz, 2 H), 7.89 (d, $J=8.4$ Hz, 2 H). m/z (ES+), (M+H)$^+$ = 451.3.

To a solution of diphenylsilane (0.573 mg, 3.1 1 µmol) and tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate (0.07 g, 0.16 mmol) in tetrahydrofuran (0.777 ml) was added carbonylhydridotris(triphenylphosphine)rhodium(I) (0.287 ml, 0.31 mmol), resulting in immediate but brief gas evolution. After 45 min, the reaction was quenched with IN aqueous hydrogen chloride, basified with 50% aqueous sodium hydroxide and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO2, 0-100% ethyl acetate in hexanes, then 10% methanol in ethyl acetate) to afford tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate (0.045 g, 66.6 %) as a faint yellow residue. IH NMR (300 MHz, chloroform-d) δ ppm 1.03 (t, 3 H), 1.11 - 1.30 (m, 4 H), 1.36 (br. s., 9 H), 1.52 - 1.97 (m, 7 H), 2.36 (br. s., 3 H), 2.51 (d, J=1.50 Hz, 1 H), 2.99 - 3.12 (m, 2 H), 3.20 - 3.37 (m, 1 H), 4.40 - 4.56 (m, 1 H), 5.98 (br. s., 1 H), 7.42 (d, J=8.3 Hz, 2 H), 7.81 (d, J=8.3 Hz, 2 H). m/z (ES+), (M+H)+ = 437.3.

To a solution of 2-chloro-3-(trifluoromethyl)benzoic acid (0.674 g, 3.00 mmol) in dichloromethane (6.00 ml) was added oxalyl chloride (0.525 ml, 6.00 mmol) and one drop of DMF. After 30 min, the reaction was concentrated to a yellow oil. This oil was then redissolved in dichloromethane (3 mL) to provide a 1 M solution of 2-chloro-3-(trifluoromethyl)benzoyl chloride. To a solution of tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate (0.045 g, 0.10 mmol) was added concentrated aqueous hydrochloric acid (0.5 mL). After gas evolution ceased, the now lightly cloudy solution was concentrated to dryness. The resulting residue was redissolved in dichloromethane (1.031 ml), and triethylamine (0.115 ml, 0.82 mmol) was added followed by 1.0 M 2-chloro-3-(trifluoromethyl)benzoyl chloride in dichloromethane (0.930 ml, 0.93 mmol). This new orange solution was stirred at room temperature for 10 min and was then quenched with methanol and concentrated. This material was purified by preparative HPLC (C18, acetonitrile in water containing 2% formic acid) to afford 2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methyl)-3-(trifluoromethyl)benzamide (0.0301 g, 53.8%) as a white solid upon lyophilization from acetonitrile and water. IH NMR (500 MHz, DMSO-\(\text{d}_6\)) \(\delta\) ppm 0.93 (t, \(J=7.4\) Hz, 3 H), 1.19 - 1.30 (m, 2 H), 1.33 - 1.45 (m, 2 H), 1.49 - 1.65 (m, 5 H), 1.80 (br. s., 1 H), 2.02 - 2.09 (m, 1 H), 2.41 (s, 3 H), 2.55 (d, \(J=10.8\) Hz, 1 H), 3.00 - 3.05 (m, 1 H), 3.26 - 3.30 (m, 2 H), 5.16 (d, \(J=7.6\) Hz, 1 H), 7.54 - 7.64 (m, 4 H), 7.84 (d, \(J=8.4\) Hz, 2 H), 7.92 (t, \(J=4.7\) Hz, 1 H), 9.06 (d, \(J=7.6\) Hz, 1 H). m/z (ES+), (M+H)+ = 543.1695, 545.1664; MS2, HPLC tR = 1.00 min.

Method 7 depicts a generalized scheme suitable for the racemic synthesis of substituted compounds of Formula I. Those skilled in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds, either stereoselectively or in racemic form.


To a slightly cloudy solution of 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfamidine (0.1 g, 0.39 mmol; Example 1, Steps A-D) in tetrahydrofuran (0.390 ml) at 0°C was added 1.0 M (3-methoxyphenyl)magnesium bromide in tetrahydrofuran (0.975 ml, 0.98 mmol) slowly, resulting in an orange solution. After 30 min, another 2.5 equivalents of Grignard reagent were added and the reaction was warmed to room temperature. After 2 h, the reaction was quenched with a 1:1 mixture of saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and
concentrated to afford crude N-((3-methoxyphenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfamamide as a yellow oil. To a solution of crude N-((3-methoxyphenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfamamide from above in methanol (2 mL) was added 4.0 M hydrochloric acid in dioxane (0.975 mL, 3.90 mmol), resulting in a color change from yellow to red. After 15 min, the red solution was concentrated to afford crude (3-methoxyphenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methanamine as the dihydrochloride salt. This salt was dissolved in dichloromethane (3.90 mL), treated with triethylamine (0.272 mL, 1.95 mmol) and 3.0 M 2-chloro-3-(trifluoromethyl)benzoyl chloride in dichloromethane (0.156 mL, 0.47 mmol; prepared according to the procedures of Example 8, Step G). After 10 min, another 300 uL of both triethylamine and acyl chloride were added. After 30 min, the reaction was quenched with methanol and concentrated. The resulting residue was first purified by preparative HPLC under basic conditions (C18, acetonitrile in water containing ammonium carbonate, pH 10) followed by repurification under acidic conditions (C18, acetonitrile in water containing 2% formic acid) to afford 2-chloro-N-((3-methoxyphenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide (0.024 g, 12.7%) as a white solid upon lyophilization from acetonitrile and water. 1H NMR (500 MHz, DMSO-d6) δ ppm 1.22 - 1.32 (m, 2 H), 1.32 - 1.43 (m, 2 H), 1.48 - 1.59 (m, 3 H), 1.79 - 1.88 (m, 1 H), 1.96 - 2.06 (m, 1 H), 2.38 (s, 3 H), 2.51 - 2.54 (m, 1 H), 3.01 - 3.08 (m, 1 H), 3.75 (s, 3 H), 5.02 (d, J=8.1 Hz, 1 H), 6.81 (dd, J=9.0, 1.7 Hz, 1 H), 6.87 - 6.92 (m, 2 H), 7.22 (t, J=8.1 Hz, 1 H), 7.57 (d, J=8 Hz, 1 H), 7.62 (t, J=7.7 Hz, 1 H), 7.91 (dd, J=7.9, 1.5 Hz, 1 H), 8.88 (d, 1 H). m/z (ES+), (M+H)+ = 467.1716, 469.1688; MS2, HPLC tR = 1.03 min.

The compound 2-chloro-N-((3-fluorophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide was prepared according to the procedures of Example 9, substituting 1.0 M (3-fluorophenyl)magnesium bromide in tetrahydrofuran for 1.0 M (3-methoxyphenyl)magnesium bromide in tetrahydrofuran and purifying the final product via preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10). IH NMR (300 MHz, chloroform-d) δ ppm 1.33 - 1.54 (m, 4 H), 1.56 - 1.75 (m, 4 H), 1.88 - 2.04 (m, 1 H), 2.37 (s, 3 H), 2.50 (d, J=10.8 Hz, 1 H), 3.24 (d, J=10.8 Hz, 1 H), 4.80 (d, J=3.4 Hz, 1 H), 6.90 - 7.04 (m, 2 H), 7.07 (d, J=7.8 Hz, 1 H), 7.25 - 7.32 (m, 1 H), 7.35 (br. s., 1 H), 7.42 (t, J=7.8 Hz, 1 H), 7.68 (d, J=7.6 Hz, 1 H), 7.76 (dd, J=7.8, 1.1 Hz, 1 H). m/z (ES+), (M+H)+ = 455.2, 457.2; MS, HPLC tR = 0.62 min.
Example 11. Preparation of 2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(m-tolyl)methyl)-3-(trifluoromethyl)benzamide formic acid salt

The compound 2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(m-tolyl)methyl)-3-(trifluoromethyl)benzamide formic acid salt was prepared according to the procedures of Example 9, substituting 1.0 M m-tolylmagnesium chloride in tetrahydrofuran for 1.0 M (3-methoxyphenyl)magnesium bromide in tetrahydrofuran and concentrating product fractions under vacuum following purification rather than lyophilization. 1H NMR (300 MHz, chloroform-d) δ ppm 1.39 - 2.09 (m, 9 H), 2.38 (s, 3 H), 2.70 (d, J=11.6 Hz, 1 H), 2.87 (s, 3 H), 3.85 (dt, J=11.6, 2.8 Hz, 1 H), 5.30 (d, J=8.8 Hz, 1 H), 7.11 - 7.21 (m, 3 H), 7.23 - 7.29 (m, 1 H), 7.36 (t, J=7.7 Hz, 1 H), 7.47 (dd, J=7.8, 1.3 Hz, 1 H), 7.70 (dd, J=7.8, 1.2 Hz, 1 H), 8.15 (s, 1 H), 10.95 (d, J=8.6 Hz, 1 H). m/z (ES+), (M+H)+ = 451.2, 453.3; MSI, HPLC tR = 0.66 min.
Example 12. Preparation of 2-chloro-N-((3-chlorophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide

The compound 2-chloro-N-((3-chlorophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide was prepared according to the procedures of Example 9, substituting 0.5 M (3-chlorophenyl)magnesium bromide in tetrahydrofuran for 1.0 M (3-methoxyphenyl)magnesium bromide in tetrahydrofuran. Additionally, the final product was purified first by preparative LCMS (C18, acetonitrile in water containing ammonium carbonate, pH 10), then preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10), and finally flash column chromatography (SiO2, 0-100% ethyl acetate in hexanes) in order to remove all impurities. 1H NMR (300 MHz, chloroform-d) δ ppm 1.29 - 1.79 (m, 8 H), 1.90 - 2.03 (m, 1 H), 2.38 (s, 3 H), 2.51 (d, J=10.9 Hz, 1 H), 3.26 (d, J=10.8 Hz, 1 H), 4.79 (d, J=3.4 Hz, 1 H), 7.13 - 7.32 (m, 4 H), 7.43 (t, J=7.7 Hz, 2 H), 7.67 (d, J=7.6 Hz, 1 H), 7.77 (dd, J=7.9, 1.1 Hz, 1 H). m/z (ES+), (M+H)+ = 471.2, 473.3; MSi, HPLC tR = 0.82 min.

Method 8 depicts a generalized scheme suitable for the racemic synthesis of furans of Formula I. Those skilled in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds, either stereoselectively or in racemic form.

Example 13. Preparation of 2-chloro-N-(furan-2-yl-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide

To a solution of furan (0.071 ml, 0.98 mmol) in 2 mL of tetrahydrofuran at 0°C was added 1.82 M n-butyllithium in hexanes (0.514 ml, 0.94 mmol) dropwise slowly, resulting in a clear colorless solution that gradually became yellow. After 60 min, to the now yellow solution was added 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfamamide (0.1 g, 0.39 mmol; Example 1, Steps A-D) in tetrahydrofuran (0.5 mL) via cannula. The resulting yellow solution gradually became red-orange over 25 min. A second batch of 2-furyllithium was prepared, this time at room temperature in an analogous manner but with stirring for only 5 min. This new batch was added to the orange reaction via cannula. After 10 min, the reaction was quenched with saturated aqueous sodium chloride. The resulting mixture was extracted with ethyl acetate (x3) and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The resulting residue was dissolved in methanol (3.90 ml) and treated with 4 M hydrochloric acid in dioxane (5.0 ml, 20.00 mmol). After 5 min, the light yellow solution was concentrated to an orange residue. This residue was redissolved in dichloromethane (3.90 ml) and triethylamine (0.272 ml, 1.95 mmol) and 1.1 M 2-chloro-3-(trifluoromethyl)benzoyle chloride in dichloromethane (0.422 ml, 0.47 mmol; prepared according to the procedures of Example 8, Step G) were added sequentially. After 10 min, the reaction was quenched with methanol and concentrated. The resulting residue was redissolved in 1:1 DMSO/methanol, filtered and purified by preparative HPLC.
(C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford a light yellow residue. This residue was further purified by flash column chromatography (SiO2, 0-100% ethyl acetate in hexanes) to afford 2-chloro-N-(furan-2-yl(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide (0.017 g, 10.21%) as a white solid upon lyophilization. IH NMR (300 MHz, chloroform-d) δ ppm 1.39 - 1.89 (m, 8 H), 1.89 - 2.01 (m, 1 H), 2.34 (s, 3 H), 2.58 (d, J=10.7 Hz, 1 H), 3.10 (d, J=10.6 Hz, 1 H), 5.02 (d, J=5.4 Hz, 1 H), 6.26 (d, J=3.2 Hz, 1 H), 6.35 (dd, J=3.2, 1.8 Hz, 1 H), 6.96 (br. s., 1 H), 7.36 (d, J=0.9 Hz, 1 H), 7.41 (t, J=7.8 Hz, 1 H), 7.66 - 7.73 (m, J=6.7 Hz, 1 H), 7.75 (d, J=7.8 Hz, 1 H). m/z (ES+), (M+H)+ = 427.2, 429.2; MS l, HPLC tR = 0.58 min.


Method 9 depicts a generalized scheme suitable for the racemic synthesis of substituted furans of Formula 1. Those skilled in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds, either stereoselectively or in racemic form.

Step A. Preparation of tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methylcarbamate from 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide.

To a solution of 2-methylfuran (0.211 ml, 2.34 mmol) in ether (3.90 ml) at -10°C was added 1.67 M n-butyllithium in hexanes (1.168 ml, 1.95 mmol). The resulting solution was allowed to warm to room temperature and stirred for 16 h. The now red-brown solution was recooled to 0°C, and 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide (0.1 g, 0.39 mmol; Example 1, Steps A-D) in 1:1:1 toluene:ether:dichloromethane (1.5 mL) was added dropwise rapidly. After 10 min, the reaction was quenched with a mixture of 1:1 saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide (10 mL) and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford crude 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)propane-2-sulfinamide. To crude 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)propane-2-
sulfinamide (0.39 mmol) in methanol (1.950 ml) was added 4.0 M hydrochloric acid in
dioxane (2.0 ml, 8.00 mmol). After 1 min, the opaque purple solution was concentrated to
dryness. To this black residue was added ethyl acetate and saturated aqueous sodium bicarbonate followed by di-tert-butyl dicarbonate (0.226 ml, 0.98 mmol). After 20 min, the
reaction was extracted with ethyl acetate (x3) and the combined organic layers were dried
over sodium sulfate, filtered and concentrated. The resulting residue was purified by
preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to
afford tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methylcarbamate (0.062 g, 47.3 %) of as a light yellow oil. IH NMR (300 MHz,
chloroform-d) δ ppm 1.39 (s, 9 H), 1.44 - 1.92 (m, 9 H), 2.24 (s, 3 H), 2.29 (s, 3 H), 2.55 (d, J=10.4 Hz, 1 H), 3.09 (ddd, J=10.4, 2.2, 2.1 Hz, 1 H), 4.49 (d, J=5.1 Hz, 1 H), 5.32 (d, J=5.3 Hz, 1 H), 5.87 (dd, J=3.0, 0.9 Hz, 1 H), 6.00 (d, J=3.0 Hz, 1 H). (ES+), (M+H)+ = 335.3.


\[ \text{To tert-butyl (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methylcarbamate (0.061 g, 0.18 mmol) was added concentrated aqueous hydrochloric acid (1.5 mL, 2.25 mmol). After 1 min, the brown solution was concentrated to dryness to afford crude (2-methyl-2-azabicyclo [2.2.2]octan-1-yl)(5-methylfuran-2-yl) methanamine dihydrochloride (0.054 g, 96%). A solution of crude (2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl) methanamine dihydrochloride (0.027 g, 0.09 mmol), 2-chloro-3-(trifluoromethyl) benzoic acid (0.022 g, 0.10 mmol), and HOBt (0.020 g, 0.13 mmol) in DMF (0.586 ml) was treated with TBTU (0.040 g, 0.12 mmol) and DIPEA (0.077 ml, 0.44 mmol) sequentially. After 2.1}
hr, the reaction mixture was diluted with methanol, filtered, and purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford semi-pure product. This material was further purified by flash column chromatography (SiO₂, 0-15% (2% ammonia in methanol) in ethyl acetate) to afford 2-chloro-N-((2-methyl-2-
azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)-3-(trifluoromethyl)benzamide (0.029 g, 74.9 %) as a white foam solid. 1H NMR (300 MHz, chloroform-d) δ ppm 1.41 - 1.74 (m, 7 H), 1.74 - 1.88 (m, 1 H), 1.88 - 2.02 (m, 1 H), 2.27 (s, 3 H), 2.34 (s, 3 H), 2.57 (d, J=10.6 Hz, 1 H), 3.09 (d, J=10.6 Hz, 1 H), 4.96 (d, J=5.7 Hz, 1 H), 5.91 (dd, J=3.0, 0.9 Hz, 1 H), 6.12 (d, J=3.1 Hz, 1 H), 6.94 (br. s., 1 H), 7.41 (t, J=7.8 Hz, 1 H), 7.69 (d, J=7.7 Hz, 1 H), 7.75 (dd, 1 H). (ES+), (M+H)+ = 441.3, 443.3; MS1, HPLC tR = 0.61 min.


Method 10 depicts a generalized scheme suitable for the chiral synthesis of substituted furans of Formula I via resolution of a final product. Those skilled in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds, either stereoselectively or in racemic form.
**Example 15. Preparation of** (S*)-2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)benzamide and (R*)-2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)benzamide

The compound 2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)benzamide was resolved using an ADH column and supercritical fluid chromatography conditions (liquid CO₂) employing isocratic 13% methanol containing 0.5% dimethylethylamine. This afforded faster eluting (R*)-2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)benzamide and slower eluting (S*)-2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)benzamide. Both compounds were separately treated with 1.0 equivalent of citric acid monohydrate in 10% methanol in dichloromethane to provide both enantiomers as their citric acid salts upon concentration and subsequent lyophilization from acetonitrile and water.

Relative Stereochemistry: In general, the absolute stereochemistry of individual isomers obtained in this manner was not determined. Arbitrary designations were used (R*, S*). (R*)-2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)benzamide citric acid salt: IH NMR (500 MHz, MeOD) δ ppm 1.70 - 1.92 (m, 5 H), 1.98 (br. s., 1 H), 2.01 - 2.14 (m, 2 H), 2.14 (s, 6 H), 2.30 (s, 3 H), 2.31 - 2.40 (m, 1 H), 2.61 - 2.78 (m, 4 H), 3.02 (s, 3 H), 3.30 - 3.56 (m, 1 H), 5.61 (s, 1 H), 6.05 (d, J=0.6 Hz, 1 H), 6.41 (d, J=3.0 Hz, 1 H), 7.02 (d, J=7.6 Hz, 2 H), 7.17 (t, J=7.6 Hz, 1 H), m/z (ES+), (M-citrate) + 367.3; MSL, HPLC tR= 0.53 min. (S*)-2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)benzamide citric acid salt: IH NMR (500 MHz, MeOD) δ ppm 1.69 - 1.90 (m, 5 H), 1.98 (br. s., 1 H), 1.99 - 2.12 (m, 2 H), 2.14 (s, 6 H), 2.27 - 2.36 (m, 1 H), 2.30 (s, 3 H), 2.61 - 2.76 (m, 4 H), 3.02 (s, 3 H), 3.30 -
3.39 (m, 1 H), 3.42 - 3.53 (m, 1 H), 5.60 (s, 1 H), 6.05 (dd, J=3.1, 0.9 Hz, 1 H), 6.40 (d, J=3.0 Hz, 1 H), 7.02 (d, J=7.6 Hz, 2 H), 7.17 (t, J=7.6 Hz, 1 H). m/z (ES+), (M-citrate) + 367.3; MSI, HPLC tR= 0.53 min.

Method 1 depicts a generalized scheme suitable for the stereoselective synthesis of isoquinuclidine N-Me sulfones of Formula I. Those skilled in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional aryl sulfones, either stereoselectively or in racemic form.


\[
\text{citric acid salt}
\]


To a slightly cloudy solution of (R)-2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-l-yl)methylene)propane-2-sulfamamide (0.598 g, 2.21 mmol; prepared according to the procedures of Example 8, Steps B-C, and Example 4, step B) in tetrahydrofuran (1 ml) at 0°C was added (4-(propylthio)phenyl)magnesium bromide (1.106 g, 4.33 mmol; Example 8, Step
D) slowly, resulting in a yellow solution. After 3 days, the reaction was quenched with 1:1 saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO\textsubscript{2}, 0-100% ethyl acetate in hexanes, then 0-15% methanol in ethyl acetate) to afford faster eluting diastereomer (R)-2-methyl-N-((S*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)propane-2-sulfinamide (0.162 g) as a white foam solid, and 582 mg of a mixture of (R)-2-methyl-N-((S*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)propane-2-sulfinamide and (R)-2-methyl-N-((R*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)propane-2-sulfinamide as a white foam solid. The mixture of diastereomers (582 mg) was dissolved in methanol (5 mL), filtered and purified by reverse phase HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10), affording additional faster eluting (R)-2-methyl-N-((S*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)propane-2-sulfinamide (0.112 g) for a total of 274 mg (29.3%). Also isolated was pure slower eluting (R)-2-methyl-N-((R*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)propane-2-sulfinamide (0.236 g, 25.2%) as a white foam solid. Those skilled in the art will recognize that the mixture of diastereomers obtained in this fashion could be entirely purified by preparative HPLC as described above, rather than first attempting to purify the mixture with flash column chromatography. Relative Stereochemistry: In general, the absolute stereochemistry of individual isomers obtained in this manner was not determined. Arbitrary designations were used ((R,R*), (R,S*)). (R)-2-methyl-N-((S*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)propane-2-sulfinamide: 1H NMR (500 MHz, chloroform-d) \( \delta \) ppm 1.03 (t, \( J=7.4 \) Hz, 3 H), 1.06 - 1.14 (m, 1 H), 1.25 (s, 9 H), 1.43 - 1.59 (m, 2 H), 1.61 - 1.74 (m, 4 H), 1.77 - 1.93 (m, 3 H), 2.60 (br. s., 1 H), 2.90 (t, \( J=7.2 \) Hz, 2 H), 3.12 (s, 3 H), 3.86 (d, \( J=9.9 \) Hz, 1 H), 4.65 (d, \( J=10.1 \) Hz, 1 H), 7.17 (d, \( J=7.9 \) Hz, 2 H), 7.26 - 7.29 (m, 2 H). m/z (ES\textsuperscript{+}), (M+H\textsuperscript{+}) 423.3; MSLHPLC \( t_R=0.77 \) min. (R)-2-methyl-N-((R*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)propane-2-sulfinamide: 1H NMR (300 MHz, chloroform-d) \( \delta \) ppm 1.06 (t, \( J=7.4 \) Hz, 3 H), 1.09 - 1.20 (m, 1 H), 1.25 (s, 9 H), 1.42 - 2.02 (m, 9 H), 2.47 - 2.65 (m, 1 H), 2.93 (t, \( J=7.3 \) Hz, 2 H), 3.18 (s, 3 H), 3.74
(s, 1 H), 4.75 (s, 1 H), 7.16 - 7.32 (m, 4 H). m/z (ES+), (M+H)+ 423.3; MS, HPLC tR = 0.87 min.


To (R)-2-methyl-N-((S*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)-methyl)propane-2-sulfinamide (0.274 g, 0.65 mmol) was added methanol (3 mL) and 4.0 M hydrochloric acid in dioxane (3 mL, 98.74 mmol). After 2 min, the light green solution was concentrated to minimal volume. To this residue was added saturated aqueous sodium bicarbonate (2 mL) and ethyl acetate (2 mL) followed by di-tert-butyl dicarbonate (0.452 mL, 1.94 mmol) with vigorous stirring. After 3 h, the mixture was extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO2, 0-100% ethyl acetate in hexanes) to afford (S*)-tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate (0.254 g, 94%) as a white foam solid. 1H NMR (300 MHz, chloroform-d) δ ppm 1.05 (t, J=7.4 Hz, 3 H), 1.18 - 1.31 (m, 1 H), 1.39 (br. s., 9 H), 1.48 - 1.90 (m, 9 H), 2.54 - 2.64 (m, 1 H), 2.92 (t, J=7.3 Hz, 2 H), 3.09 (s, 3 H), 4.95 (br. s., 1 H), 5.31 (br. s., 1 H), 7.10 - 7.18 (m, J=8.3 Hz, 2 H), 7.25 - 7.32 (m, 2 H). m/z (ES+), (M+H)+ 419.3.
[261] Step C. Preparation of (S*)-2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methyl)-3-(trifluoromethyl)benzamide citric acid salt from (S*)-tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate

The compound (S*)-2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methyl)-3-(trifluoromethyl)benzamide was prepared according to the procedures of Example 8, Steps E-G, substituting (S*)-tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate for tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate in Step E.

Those skilled in the art will recognize that (R*)-2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methyl)-3-(trifluoromethyl)benzamide could also be prepared by substituting (R*)-tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate for tert-butyl (2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate in Step E. The resulting pure product obtained from preparative HPLC was converted to the corresponding citrate salt by treatment with citric acid monohydrate (1.0 equivalents) and lyophilization from acetonitrile and water. Those skilled in the art will recognize that alternative coupling conditions could also have been employed, such as treating a solution of the desired amine and benzoic acid in DMF with a mixture of HOBt, TBTU, and DIPEA. 1H NMR (500 MHz, MeOD) δ ppm 1.01 (t, J=7.4 Hz, 3 H), 1.44 - 1.55 (m, 1 H), 1.58 - 1.89 (m, 7 H), 1.94 (s, 0 H), 2.15 - 2.26 (m, 1 H), 2.39 (br. s., 1 H), 2.58 - 2.75 (m, 4 H), 3.03 (s, 3 H), 3.09 (d, J=11.8 Hz, 1 H), 3.18 - 3.25 (m, 2 H), 3.75 (br. s., 1 H), 5.64 (s, 1 H), 7.59 (t, J=7.6 Hz, 1 H), 7.70 (d,
Method 12 depicts a generalized scheme suitable for the stereoselective synthesis of isoquinuclidine N-H sulfones of Formula I. Those skilled in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional aryl sulfones, either stereoselectively or in racemic form.
Example 17. Preparation of \((R^*)-N-(2\text{-azabicyclo}[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methyl)-2,6-dimethylbenzamide.

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

Step A. Preparation of \((4\text{-bromophenyl})(propyl)sulfane\) from 4-bromobenzenethiol.

To a yellow mixture of 4-bromobenzenethiol (3.0 g, 15.87 mmol), potassium carbonate (3.29 g, 23.80 mmol), and N,N-dimethylformamide (10 ml) was added 1-iodopropane (2.013 ml, 20.63 mmol). The mixture instantly became colorless. After 25 min, the now brownish mixture was filtered and the filtrate was diluted with ethyl acetate (200 mL). This new mixture was filtered, and the filtrate was concentrated to minimal volume. This residue was purified by flash column chromatography (SiO\textsubscript{2}, 0-10\% ethyl acetate in hexanes) with elution at the solvent front to afford \((4\text{-bromophenyl})(propyl)sulfane\) (3.55 g, 97\%) as a light gold oil. IH NMR (300 MHz, \textit{chloroform-d}) \(\delta\) ppm 1.02 (t, 3 H), 1.66 (sxt, \(J=7.3\) Hz, 2 H), 2.80 - 2.92 (m, 2 H), 7.12 - 7.21 (m, 2 H), 7.30 - 7.46 (m, 2 H).

Step B. Preparation of \((R)-N-((2\text{-allyl}-3\text{-oxo}-2\text{-azabicyclo[2.2.2]octan-1-yl})\text{-methylene})-2\text{-methylpropane-2-sulfamidine}\) from methyl 3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{H} \\
\text{CH}_3 \\
\end{array}
\]

The compound \((R)-N-((2\text{-allyl}-3\text{-oxo}-2\text{-azabicyclo[2.2.2]octan-1-yl})\text{-methylene})-2\text{-methylpropane-2-sulfamidine}\) was prepared from methyl 3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate (Casabona, D.; Cativiela, C. \textit{Tetrahedron}, 2006, 62, 10000-10004) according to
the procedures of Example 1, Step A, substituting allyl iodide for methyl iodide, and Example 4, Steps A-B, substituting methyl 2-allyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate for methyl 2-methyl-3-oxo-2-azabicyclo[2.2.2]octane-1-carboxylate in Step A. IH NMR (500 MHz, chloroform-d) δ ppm 1.22 (s, 9 H), 1.74 - 2.06 (m, 8 H), 2.73 (br. s., 1 H), 3.96 - 4.08 (m, 1 H), 4.11 - 4.22 (m, 1 H), 5.09 - 5.27 (m, 2 H), 5.73 - 5.84 (m, 1 H), 8.30 (s, 1 H). m/z (ES+), (M+H)+ 297.2.


A slightly cloudy solution of (4-(propylthio)phenyl)magnesium bromide (1.277 g, 5.0 mmol; Example 8, Step D) in tetrahydrofuran (5.0 mL) was added to (R)-N-((2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)-2-methylpropane-2-sulfinamide (0.498 g, 1.68 mmol)) also in tetrahydrofuran (1 mL) via syringe. The reaction became yellow-orange in color and was stirred at room temperature for 2 h before being quenched with a 1:1 mixture of saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide. This mixture was diluted with ethyl acetate and the layers were separated. The aqueous layer was extracted with ethyl acetate (x2) and the combined organic layers were stored at 0°C. After 10 days, the organic layers were concentrated, diluted with methanol, filtered, and purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford faster eluting (R)-N-((S*)-(2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)-2-methylpropane-2-sulfinamide (0.205 g, 27.2 %) as a white foam solid and slower eluting (R)-N-((R*)-(2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)-2-methylpropane-2-sulfinamide (0.299 g, 39.7 %) as a white foam solid. Relative Stereochemistry: In general, the absolute stereochemistry of individual
isomers obtained in this manner was not determined. Arbitrary designations were used
((R,R*), (R,S*)). (R)-N-((S*)-(2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-
(propylthio)phenyl)methyl)-2-methylpropane-2-sulfamidem: 1H NMR (300 MHz,
chloroform-d) δ ppm 0.93 - 1.01 (m, 1 H), 1.02 (t, J=7.3 Hz, 3 H), 1.27 (s, 9 H), 1.38 - 1.51
(m, 1 H), 1.57 - 1.76 (m, 5 H), 1.80 - 1.93 (m, 3 H), 2.63 (br. s., 1 H), 2.89 (t, J=7.3 Hz, 2 H),
3.85 - 3.98 (m, 2 H), 4.81 - 4.94 (m, 2 H), 5.21 - 5.35 (m, 2 H), 5.84 - 5.99 (m, 1 H), 7.09 (d, 
J=8.3 Hz, 2 H), 7.26 (d, J=8.3 Hz, 2 H). m/z (ES+), (M+H)+ 448.3; MSI, HPLC tR= 0.81
min. (R)-N-((R*)-(2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-
(propylthio)phenyl)methyl)-2-methylpropane-2-sulfamidem: 1H NMR (300 MHz,
chloroform-d) δ ppm 1.05 (t, J=7.4 Hz, 3 H), 1.08 - 1.15 (m, 1 H), 1.23 (s, 9 H), 1.54 - 1.64
(m, 2 H), 1.65 - 1.78 (m, 5 H), 1.79 - 1.99 (m, 2 H), 2.60 - 2.66 (m, 1 H), 2.93 (t, J=7.2 Hz, 2 H),
3.93 (s, 1 H), 4.23 (dd, J=16.7, 6.1 Hz, 1 H), 4.54 - 4.65 (m, 1 H), 4.89 (s, 1 H), 5.22 - 5.44 (m, 2 H), 5.89 - 6.04 (m, 1 H), 7.15 - 7.21 (m, J=8.5 Hz, 2 H), 7.26 (d, J=8.5 Hz, 2 H).
m/z (ES+), (M+H)+ 448.3; MSI, HPLC tR= 0.89 min.

[267] Step D. Preparation of (R*)-tert-butyl (2-allyl-3-oxo-2-
azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate from (R)-N-((R*)-
(2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)-2-
methylpropane-2-sulfamidem.

To (R)-N-((R*)-(2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methyl)-
2-methylpropane-2-sulfamidem (0.296 g, 0.66 mmol) in methanol (1.0 mL) was added 4.0 M
hydrochloric acid in dioxane (1.5 mL, 49.37 mmol). After 5 min, the reaction was
concentrated to a yellow oil and then treated with saturated aqueous sodium bicarbonate (1.5
mL) and ethyl acetate (2 mL) followed by di-tert-butyl dicarbonate (0.383 mL, 1.65 mmol).
The resulting mixture was stirred vigorously for 16 h and then extracted with ethyl acetate
(x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated.
The resulting residue was purified by flash column chromatography (SiO₂, 0-50% ethyl
acetate in hexanes) to afford (R*)-tert-butyl (2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate (0.252 g, 86 %) as a white foam solid. 1H NMR (500 MHz, chloroform-d) δ ppm 1.03 (t, J=7.3 Hz, 3 H), 1.12 - 1.20 (m, 1 H), 1.37 (br. s., 9 H), 1.53 - 1.65 (m, 3 H), 1.69 (dd, J=14.6, 7.3 Hz, 2 H), 1.71 - 1.77 (m, 3 H), 1.81 - 1.90 (m, 1 H), 2.60 - 2.65 (m, 1 H), 2.90 (t, J=7.2 Hz, 2 H), 3.91 (dd, J=16.3, 6.9 Hz, 1 H), 4.54 (br. s., 1 H), 5.05 (br. s., 1 H), 5.19 (d, J=10.1 Hz, 1 H), 5.24 - 5.39 (m, 2 H), 5.86 - 5.98 (m, 1 H), 7.11 (d, J=8.5 Hz, 2 H), 7.26 (d, J=8.6 Hz, 2 H). m/z (ES+), (M+H)+ = 445.4.


To a solution of (R*)-tert-butyl (2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylthio)phenyl)methylcarbamate (0.252 g, 0.57 mmol) in dichloromethane (2.83 ml) was added 3-chloroperoxybenzoic acid (0.279 g, 1.25 mmol). The resulting solution was stirred for 30 min and was then purified by flash column chromatography (SiO2, 0-100% ethyl acetate in hexanes) to afford (R*)-tert-butyl (2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate (0.248 g, 92 %) as a white foam solid. 1H NMR (300 MHz, chloroform-d) δ ppm 1.02 (t, J=7.4 Hz, 3 H), 1.02 - 1.14 (m, 1 H), 1.38 (br. s., 9 H), 1.64 (d, J=3.2 Hz, 4 H), 1.78 (d, J=7.2 Hz, 5 H), 2.61 - 2.70 (m, 1 H), 3.02 - 3.15 (m, 2 H), 3.83 (dd, J=16.2, 7.4 Hz, 1 H), 4.58 (br. s., J=15.8 Hz, 1 H), 5.12 - 5.46 (m, 4 H), 5.83 - 6.05 (m, 1 H), 7.43 (d, J=8.2 Hz, 2 H), 7.87 (d, J=8.2 Hz, 2 H). m/z (ES+), (M+H)+ = 477.4.
Step F. Preparation of (R*)-tert-butyl (2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate from (R*)-tert-butyl (2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate.

To a solution of sulfuric acid (0.041 ml, 0.76 mmol) in tetrahydrofuran (2 mL) at 0°C was added 2.0 M lithium aluminum hydride in tetrahydrofuran (0.761 ml, 1.52 mmol). After 15 min, to the slightly cloudy solution was added (R*)-tert-butyl (2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate (0.145 g, 0.30 mmol) as a solution in tetrahydrofuran (1 mL) via syringe. After 10 min, the reaction was quenched with sodium sulfate decahydrate, diluted with ethyl acetate, and stirred vigorously for 10 min. The mixture was then filtered, and the filtrate was concentrated to afford crude (R*)-tert-butyl (2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate (0.113 g, 80%) as a white foam solid. 1H NMR (300 MHz, chloroform-d) δ ppm 1.02 (t, J=7.5 Hz, 3 H), 1.10 - 1.23 (m, 1 H), 1.22 - 1.45 (m, 12 H), 1.55 - 1.72 (m, 4 H), 1.72 - 1.93 (m, 3 H), 2.58 - 2.68 (m, 1 H), 2.91 (dd, J=13.7, 7.4 Hz, 1 H), 3.02 - 3.14 (m, 3 H), 3.39 - 3.51 (m, 1 H), 4.52 - 4.58 (m, 1 H), 5.12 (d, J=9.7 Hz, 1 H), 5.22 (d, J=17.1 Hz, 1 H), 5.77 - 5.92 (m, 1 H), 5.99 (br. s., 1 H), 7.41 (d, J=8.4 Hz, 2 H), 7.73 - 7.89 (m, 2 H). m/z, (ES+) (M+H)+ 463.3.

Step G. Preparation of (R*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(4-propylsulfonyl)phenyl)methyl)-2,6-dimethylbenzamide from (R*)-tert-butyl (2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methylcarbamate.
To (R*)-tert-butyl (2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(4-(propylsulfonyl)phenyl)methylcarbamate (0.108 g, 0.23 mmol) was added 12 N aqueous hydrochloric acid (1.0 mL, 32.91 mmol), resulting in gas evolution. After 2 min, 0.5 mL of methanol were added, and the resulting solution was concentrated to a clear glass. This glass was reconcentrated from 100% methanol and then from 10% methanol in chloroform to afford crude (R*)-(2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(4-(propylsulfonyl)phenyl)methanamine dihydrochloride as a milky-white glass that was dried under vacuum for four days. To a solution of crude (R*)-(2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(4-(propylsulfonyl)phenyl)methanamine dihydrochloride (0.23 mmol) and DIPEA (0.249 mL, 1.42 mmol) in dichloromethane was added 2,6-dimethylbenzoyl chloride (0.570 mL, 0.57 mmol). After 40 min, the reaction was quenched with methanol and concentrated. The resulting residue was basified with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford a clear residue. This residue was purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford (R*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(4-(propylsulfonyl)phenyl)methyl)-2,6-dimethylbenzamide (0.080 g, 56.8 %) as a white foam solid. 

**[271] Step H. Preparation of (R*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(4-(propylsulfonyl)phenyl)methyl)-2,6-dimethylbenzamide from (R*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(4-(propylsulfonyl)phenyl)methyl)-2,6-dimethylbenzamide.**
To a degassed solution of tetrakis(triphenylphosphine)palladium(0) (1.682 mg, 1.46 µmol) and 1,3-dimethylbarbituric acid (0.068 g, 0.44 mmol) in dichloromethane (3 mL) at 30°C was added a solution of (R*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(4-(propylsulfonyl)phenyl)methyl)-2,6-dimethylbenzamide (0.072 g, 0.15 mmol) in 2 mL of dichloromethane, resulting in a light yellow solution. This solution was maintained at 30°C with stirring for 5 min and was then quenched with saturated aqueous sodium bicarbonate. The mixture was then extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting orange residue was purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford (R*)-N-((2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)methyl)-2,6-dimethylbenzamide (0.061 g, 92%) as a white foam solid. 

\[\text{IH NMR (300 MHz, chloroform-d)} \delta \text{ ppm 1.02 (t, } J=7.4 \text{ Hz, 3 H), 1.16 - 1.29 (m, 1 H), 1.42 - 1.88 (m, 10 H), 2.00 - 2.13 (m, 1 H), 2.24 (s, 6 H), 2.87 (s, 2 H), 3.01 - 3.13 (m, 2 H), 4.87 (d, } J=7.6 \text{ Hz, 1 H), 7.02 (d, } J=7.6 \text{ Hz, 2 H), 7.09 - 7.21 (m, 2 H), 7.48 (d, } J=8.2 \text{ Hz, 2 H), 7.89 (d, } J=8.4 \text{ Hz, 2 H). m/z (ES+), (M+H)^+ = 455.4; MSI, HPLC tR = 0.51 min.}\]

[272] **Method 13. Stereoselective Synthesis of N-Propyl Isoquinuclidines of Formula I**

Method 13 depicts a generalized scheme suitable for the stereoselective synthesis of quinuclidine N-propyl sulfones of Formula I. Those skilled in the art will readily recognize...
various reagents and intermediates or changes in moieties that could be used to make additional N-alkyl aryl sulfones, either stereoselectively or in racemic form.

[273] Example 18. **Preparation of (R*)-2,6-dimethyl-N-(phenyl(2-propyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)benzamide.**

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{N} \\
\text{H}_3\text{C} & \quad \text{HN} \quad \text{O} \\
\text{CH}_3 & \quad \text{CH}_3
\end{align*}
\]


\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{H}_3\text{C} & \quad \text{HN} \quad \text{SO} \\
\text{CH}_2 & \quad \text{CH}_3 \\
\text{H}_3\text{C} & \quad \text{CH}_3
\end{align*}
\]

To (R)-N-((2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)-2-methylpropane-2-sulfamidamide (0.5 g, 1.69 mmol; Example 17, Step B) in tetrahydrofuran (15.09 ml) at -78°C was added trimethylaluminum (0.843 ml, 1.69 mmol). To this solution was then added dropwise 1.8 M phenyllithium in di-n-butylether (0.937 ml, 1.69 mmol), keeping the reaction temperature below -70°C. After 10 min, another 200 µL of phenyllithium solution was added dropwise. After 30 min, the reaction was quenched with a solution of 1:1 saturated aqueous ammonium chloride and concentrated aqueous ammonium hydroxide and the resulting mixture was extracted with ethyl acetate (×3). The combined organic layers were dried over sodium sulfate, filtered and concentrated to afford a cloudy residue. This residue was diluted with ethyl acetate, filtered, and the filtrate was reconcentrated to a yellow oil. This oil was then purified by flash column chromatography (SiO₂, 0-100% ethyl acetate in hexanes) to afford (R)-N-((R*)-(2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2-methylpropane-2-sulfamidamide (0.654 g, 104 %) as a white foam solid. Stereochemistry: This diastereomer was arbitrarily assigned R* stereochemistry based on the stereochemical
preference for addition elucidated in Example 4. IH NMR (300 MHz, chloroform-d) δ ppm
0.98 - 1.12 (m, 1 H), 1.23 (s, 9 H), 1.49 - 2.04 (m, 7 H), 2.55 - 2.70 (m, 1 H), 3.95 (s, 1 H),
4.25 (dd, J=16.9, 5.9 Hz, 1 H), 4.53 - 4.68 (m, 1 H), 4.94 (s, 1 H), 5.25 (d, J=10.3 Hz, 1 H),
5.37 (d, J=17.3 Hz, 1 H), 5.90 - 6.07 (m, 1 H), 7.26 - 7.40 (m, 5 H). m/z (ES+), (M+H)^+ =
375.3.


To a solution of (R)-N-((R*)-(2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2-methylpropane-2-sulfinamide (0.654 g, 1.75 mmol) in methanol (3 mL) was added 4.0 M hydrochloric acid in dioxane (2.0 ml, 8.00 mmol). After 1 min, the reaction was concentrated to a white foam solid. This solid was treated with 10 mL of saturated aqueous sodium bicarbonate and ethyl acetate (10 mL). To this mixture was added di-tert-butyl dicarbonate (0.973 ml, 4.19 mmol), and the resulting mixture was stirred vigorously for 16 h. This mixture was then extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiC^, 0-100% ethyl acetate in hexanes) to afford (R*)-tert-butyl (2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate (0.578 g, 89%) as a white foam solid. This material was further purified using an ADH column and supercritical fluid chromatography conditions (liquid CO₂) employing isocratic 15% methanol containing 0.5% dimethylethylamine to remove undesired minor diastereomer (S*)-tert-butyl (2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate, present in <1%. This afforded (R*)-tert-butyl (2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methylcarbamate (0.571 g, 88%) as a white foam solid. IH NMR (300 MHz, chloroform-d) δ ppm 1.06 - 1.20 (m, 1 H), 1.36 (br. s., 9 H), 1.55 - 1.93 (m, 7 H), 2.62 (quin, J=2.7 Hz, 1 H), 3.93 (dd, J=16.2, 7.2 Hz, 1 H), 4.58 (d, J=15.0 Hz, 1 H), 5.00 - 5.15 (m, 1 H),
5.21 (dd, \( J = 10.3, 1.3 \text{ Hz}, 1 \text{ H} \)), 5.26 - 5.40 (m, 2 H), 5.85 - 6.02 (m, 1 H), 7.18 - 7.24 (m, 2 H), 7.26 - 7.37 (m, 3 H). m/z (ES+), (M+H)+ = 371.3.


To (R*)-tert-butyl (2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(phenyl)methylcarbamate (0.2 g, 0.56 mmol; prepared according to the procedures of Example 17, Step F, substituting (R*)-tert-butyl (2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(phenyl)methylcarbamate for (R*)-tert-butyl (2-allyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(4-(propylsulfonyl)phenyl)-methylcarbamate) was added 12N aqueous hydrochloric acid (1.0 ml, 12.00 mmol). After gas evolution ceased (10 min), the resulting cloudy solution was concentrated to a glass. This glass was reconcentrated from 10% methanol in dichloromethane, treated with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiC\(^\wedge\), 0-60% ethyl acetate in hexanes) to afford (R*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-l-yl)(phenyl)methyl)-2,6-dimethylbenzamide (0.152 g, 82 %) as a sticky light yellow oil. IH NMR (300 MHz, chloroform-\( d \)) \( \delta \) ppm 1.28 - 1.76 (m, 8 H), 1.82 - 1.97 (m, 1 H), 2.32 (s, 6 H), 5.21 (dd, \( J = 10.3, 1.3 \text{ Hz}, 1 \text{ H} \)), 5.26 - 5.40 (m, 2 H), 5.85 - 6.02 (m, 1 H), 7.18 - 7.24 (m, 2 H), 7.26 - 7.37 (m, 3 H). m/z (ES+), (M+H)+ = 371.3.
H), 2.80 (s, 3 H), 2.90 - 2.99 (m, 1 H), 3.06 (dd, \(J=13.6, 8.1\) Hz, 1 H), 3.55 - 3.66 (m, 1 H), 4.96 (d, \(J=4.2\) Hz, 1 H), 5.19 (d, \(J=17.3\) Hz, 1 H), 5.74 (dddd, \(J=IIA, 10.0, 7.9, 3.7\) Hz, 1 H), 6.91 (br. s., 1 H), 6.98 - 7.04 (m, 1 H), 7.11 - 7.18 (m, 1 H), 7.22 - 7.36 (m, 5 H) . m/z (ES+), (M+H)+ = 389.4.

[277] Step D. Preparation of (R*)-2,6-dimethyl-N-(phenyl(2-propyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)benzamide from (R*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2,6-dimethylbenzamide.

To a degassed solution of (R*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(phenyl)methyl)-2,6-dimethylbenzamide (0.0384 g, 0.06 mmol) in methanol (2.0 mL) was added 10 wt% palladium on carbon (15 mg, 0.14 mmol). The mixture was subjected to a hydrogen atmosphere and stirred for 4 h before being filtered and concentrated. The resulting residue was dissolved in methanol, filtered, and then purified via preparative HPLC (C18, acetonitrile in water containing ammonium bicarbonate, pH 10) to afford (R*)-2,6-dimethyl-N-(phenyl(2-propyl^-azabicyclo[2.2.2]octan-1-yl)methyl^-benzamide (0.012 g, 47.8 %) as a white solid upon lyophilization from acetonitrile and water. 1H NMR (300 MHz, chloroform-d) \(\delta\) ppm 0.84 (t, \(J=7.4\) Hz, 3 H), 1.25 - 1.67 (m, 9 H), 1.67 - 1.81 (m, 1 H), 1.83 - 1.98 (m, 1 H), 2.33 (s, 6 H), 2.35 - 2.48 (m, 1 H), 2.60 - 2.68 (m, 1 H), 2.72 - 2.85 (m, 1 H), 2.96 - 3.09 (m, 1 H), 4.98 (d, \(J=4.2\) Hz, 1 H), 6.69 (br. s., 1 H), 6.97 (d, \(J=7.6\) Hz, 2 H), 7.05 - 7.13 (m, 1 H), 7.16 - 7.36 (m, 5 H). m/z (ES+), (M+H)+ = 391.4; MS l, HPLC tR = 0.56 min.
Method 14. Racemic Synthesis of 3-Pyridyl Compounds of Formula I

Method 14 depicts a generalized scheme suitable for racemic synthesis of 3-pyridyl compounds of Formula I. Those of skill in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds of Formula I as either racemates or single enantiomers.

Step A. Preparation of 2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-3-yl)methyl)propane-2-sulfinamide from 2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfamidine.

To 3-bromopyridine (0.445 mL, 4.62 mmol) in ether (4.6 mL) at -78°C was added dropwise, slowly, 1.67M n-butyllithium in hexanes (2.82 mL, 4.72 mmol), keeping the reaction temperature below -68°C and affording a light yellow-brown mixture. This mixture was stirred at -78°C for 30 min and then 2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide (0.5 g, 1.85 mmol; prepared according to the procedures of Example 4, Steps A-B, substituting 2-methylpropane-2-sulfamidine for (R)-2-methylpropane-2-sulfamidine) was added via cannula, also as a solution in ether (2 mL) and tetrahydrofuran (1.5 mL) at -78°C. The now red-brown reaction was maintained at -78°C for 2h. The mixture was then warmed to room temperature and quenched with saturated aqueous sodium chloride. The resulting mixture was extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to a yellow residue. This residue was purified by flash column chromatography (SiO₂, 0-20% methanol in ethyl acetate) to afford 2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-3-yl)methyl)propane-2-sulfamidine (0.256 g, 39.6%) as a light orange solid. ¹H NMR (300 MHz, chloroform-d)  δ ppm 1.05 - 1.18 (m, 1 H), 1.26 (s, 9 H), 1.48 - 2.05 (m, 7 H), 2.54 - 2.70 (m, 1 H), 3.20 (s, 3 H), 3.71 - 3.87 (m, 1 H), 4.83 (s, 1 H), 7.31 (dd, J = 7.8, 4.8 Hz, 1 H), 7.64 (dt, 1 H), 8.55 - 8.66 (m, 2 H). m/z (ES⁺), (M+H)⁺ = 350.3.
**Step B. Preparation of** 1-(amino(pyridin-3-yl)methyl)-2-methyl-2-azabicyclo[2.2.2]octan-3-one from 2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-3-yl)methyl)propane-2-sulfinamide.

To 2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-3-yl)methyl)propane-2-sulfinamide (0.236 g, 0.68 mmol) in methanol (4.93 ml) was added 4.0 M hydrochloric acid in dioxane (0.338 ml, 1.35 mmol). The resulting orange solution was stirred at room temp for 16 h and was then quenched with 1N aqueous sodium hydroxide (1.486 ml, 1.49 mmol). This solution was concentrated under vacuum briefly (water bath temperature: 400°C) to reduced volume and then diluted with saturated aqueous sodium chloride. The resulting mixture was extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to afford crude 1-(amino(pyridin-3-yl)methyl)-2-methyl-2-azabicyclo[2.2.2]octan-3-one (0.189 g, 114%) of an estimated 70% purity as an orange oil. This oil was used immediately in the next step.

**IH NMR** (300 MHz, chloroform-d) δ ppm 0.99 - 1.11 (m, 1 H), 1.39 - 1.97 (m, 8 H), 2.08 - 2.20 (m, 1 H), 2.53 - 2.64 (m, 1 H), 3.24 (s, 3 H), 4.39 (s, 1 H), 7.27 - 7.35 (m, 1 H), 7.72 (dt, J=7.8, 2.0 Hz, 1 H), 8.55 (dd, J=4.8, 1.7 Hz, 1 H), 8.59 (d, J=2.3 Hz, 1 H). m/z (ES+), (M+H)+ = 246.3.

**Step C. Preparation of** 2-chloro-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-3-yl)methyl)-3-(trifluoromethyl)-benzamide from 1-(amino(pyridin-3-yl)methyl)-2-methyl-2-azabicyclo[2.2.2]octan-3-one.
To a solution of crude L-(amino(pyridin-3-yl)methyl)-2-methyl-2-azabicyclo[2.2.2]octan-3-one (0.189 g, 0.54 mmol) in dichloromethane (2.0 mL) were added sequentially DIPEA (0.283 mL, 1.62 mmol) and 1.2 M 2-chloro-3-(trifluoromethyl)benzoyl chloride in dichloromethane (prepared according to the procedures of Example 8, Step G). The resulting red solution was stirred at room temperature for 10 min and then quenched with saturated aqueous sodium bicarbonate. The resulting mixture was extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated to an orange residue. This material was purified by flash column chromatography (SiO₂, 0-30% methanol in ethyl acetate) to afford 2-chloro-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-3-yl)methyl)-3-(trifluoromethyl)benzamide (0.083 g, 33.9%) as a light orange solid.

IH NMR (300 MHz, chloroform-d) δ ppm 1.22 - 1.32 (m, 1 H), 1.56 - 1.93 (m, 7 H), 2.63 (br. s., 1 H), 3.13 (s, 3 H), 5.52 (d, J=7.8 Hz, 1 H), 7.08 (d, J=7.4 Hz, 1 H), 7.33 (dd, J=7.8, 4.8 Hz, 1 H), 7.46 (t, J=7.8 Hz, 1 H), 7.63 - 7.73 (m, 2 H), 7.82 (dd, J=7.8, 1.1 Hz, 1 H), 8.58 (dd, J=4.8, 1.5 Hz, 1 H), 8.65 (d, J=2.3 Hz, 1 H). m/z (ES+), (M+H)+ = 452.3, 454.3.


To a degassed solution of diphenylsilane (0.069 mL, 0.37 mmol) and 2-chloro-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-3-yl)methyl)-3-(trifluoromethyl)benzamide (0.08 g, 0.18 mmol) in tetrahydrofuran (1.701 mL) was added carbonyldihydridotris(triphenylphosphine)rhodium(I) (0.016 g, 0.02 mmol) in one portion. After gas evolution ceased, the light orange-yellow reaction was stirred at room temperature for 30 min. Another 2 equivalents of silane and 0.1 equivalents of catalyst were added and the reaction was stirred for another 60 min. The orange solution was then poured into IN
aqueous hydrogen chloride, and the mixture was washed with ether. The aqueous layer was
then basified with 1 N aqueous sodium hydroxide and extracted with ethyl acetate (x3). The
combined ethyl acetate layers were dried over sodium sulfate, filtered, and concentrated, and
the resulting residue was purified by preparative HPLC (C18, acetonitrile in water containing
ammonium carbonate, pH 10) to afford 2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-
yl)(pyridin-3-yl)methyl)-3-(trifluoromethyl)benzamide (0.029 g, 37.7 %) as a white solid. 1H
NMR (300 MHz, chloroform-d) δ ppm 1.30 - 1.53 (m, 4 H), 1.56 - 1.79 (m, 4 H), 1.90 - 2.06
(m, 1 H), 2.39 (s, 3 H), 2.52 (d, J=11.0 Hz, 1 H), 3.25 (d, J=11.0 Hz, 1 H), 4.84 (d, J=3.4 Hz,
1 H), 7.21 - 7.30 (m, 1 H), 7.39 (br. s., 1 H), 7.43 (t, J=7.8 Hz, 1 H), 7.61 (d, J=8.0 Hz, 1 H),
7.68 (d, J=7.6 Hz, 1 H), 7.76 (d, J=1.1 Hz, 1 H), 8.51 (d, J=3.6 Hz, 1 H), 8.56 (br. s., 1 H).
m/z (ES+), (M+H)+ = 438.3, 440.3; MS, HPLC tR = 0.47 min.


Method 15 depicts a generalized scheme suitable for stereoselective synthesis of 4-pyridyl
compounds of Formula I. Those of skill in the art will readily recognize various reagents and
intermediates or changes in moieties that could be used to make additional compounds of
Formula I as either racemates or single enantiomers.
Example 20. Preparation of (R)-2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)-3-(trifluoromethyl)benzamide

Step A. Preparation of from (R)-2-methyl-N-((R*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide from (R)-2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide.

In a flask was combined at -78°C tetrahydrofuran (1 mL) and 1.43 M n-butyllithium in hexanes (1.086 ml, 1.55 mmol). After 5 min, a solution of 4-bromopyridine (0.187 g, 0.96 mmol) in tetrahydrofuran (0.5 mL) was added dropwise. Slow addition afforded a red-brown opaque solution. When 5 min had passed after pyridine addition, the solution was added via cannula to a solution of (R^-methyl-N^-methyl-S-oxo^-azabicycloP^P.Joctan-l-yl)methylene)propane-2-sulf ^n^namide (0.2 g, 0.74 mmol; prepared according to the procedures of Example 4, Steps A-B) in tetrahydrofuran (6.31 ml) at -78°C using positive pressure. This afforded a light brown-red solution. After 15 min, the reaction was quenched with saturated aqueous sodium chloride and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting yellow oil was purified by flash column chromatography (SiC^, isocratic 100% ethyl acetate then isocratic 20% methanol in ethyl acetate) to afford (R)-2-methyl-N-(R^)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)propane-2-sulf ^n^namide (0.115 g, 44.5 %) as a white foam solid. Stereochemistry: This diastereomer was arbitrarily assigned R^*
stereochemistry based on the stereochemical preference for addition elucidated in Example 4.

I H NMR (500 MHz, chloroform-d) δ ppm 1.11 - 1.18 (m, 1 H), 1.27 (s, 9 H), 1.54 - 1.65 (m, 4 H), 1.68 - 1.78 (m, 1 H), 1.79 - 1.89 (m, 1 H), 1.91 - 2.00 (m, 1 H), 2.60 - 2.64 (m, 1 H), 3.18 (s, 3 H), 3.79 (s, 1 H), 4.77 (s, 1 H), 7.27 (d, J=5.8 Hz, 2 H), 8.62 (d, J=5.8 Hz, 2 H).

m/z (ES+), (M+H)⁺ = 350.3.

[287] Step B. Preparation of (R*)-2-chloro-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)-3-(trifluoromethyl)benzamide from (R)-2-methyl-N-((R*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)propane-2-sulfinamide.

The compound (R*)-2-chloro-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)-3-(trifluoromethyl)benzamide was prepared from (R)-2-methyl-N-((R*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)propane-2-sulfinamide according to the procedures of Example 19, Steps B-C, substituting (R)-2-methyl-N-((R*)-(2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)propane-2-sulfinamide for 2-methyl-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)propane-2-sulfinamide in Step B.

I H NMR (500 MHz, chloroform-d) δ ppm 1.55 - 1.88 (m, 8 H), 2.62 (br. s., 1 H), 3.10 (s, 3 H), 5.46 (d, J=7.6 Hz, 1 H), 7.22 (d, J=7.6 Hz, 1 H), 7.30 (d, J=6.1 Hz, 2 H), 7.47 (t, J=7.8 Hz, 1 H), 7.70 (dd, J=7.6, 1.5 Hz, 1 H), 7.81 (d, J=7.9 Hz, 1 H), 8.63 (d, J=6.1 Hz, 2 H). m/z (ES+), (M+H)⁺ = 452.3.
[288] Step C. Preparation of (R*)-2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)-3-(trifluoromethyl)benzamide from (R*)-2-chloro-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)-3-(trifluoromethyl)benzamide.

To a degassed solution of (R*)-2-chloro-N-((2-methyl-3-oxo-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)-3-(trifluoromethyl)benzamide (0.034 g, 0.08 mmol), diphenylsilane (0.035 ml, 0.19 mmol) and tetrahydrofuran (1.470 ml) was added carbonylhydridotris(triphenylphosphine)rhodium(I) (10.37 mg, 0.01 mmol). The resulting light yellow solution was stirred at room temperature for 16 h and then another 35 uL of diphenylsilane and 11 mg of catalyst were added. After 1 h, the reaction was quenched with IN aqueous hydrochloric acid. After stirring vigorously for 5 min, the reaction was basified with saturated aqueous sodium bicarbonate, extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was first purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford semipure product. This residue was then purified by flash column chromatography (SiC^\, 100% EtOAc, then 0-30% methanol in ethyl acetate) to afford (R*)-2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)-3-(trifluoromethyl)benzamide (0.012 g, 35.5 %) as a clear colorless residue. This material was lyophilized from 300 uL of acetonitrile to afford the desired product as a white lyopholate (10.6 mg). 1H NMR (500 MHz, chloroform-d) δ ppm 1.30 - 1.54 (m, 4 H), 1.58 - 1.70 (m, 3 H), 1.79 - 1.88 (m, 1 H), 1.95 - 2.03 (m, 1 H), 2.42 (s, 3 H), 2.54 (d, J=11.0 Hz, 1 H), 3.30 (d, J=10.7 Hz, 1 H), 4.82 (d, J=3.4 Hz, 1 H), 7.23 (d, J=6.1 Hz, 2 H), 7.44 (t, J=7.8 Hz, 1 H), 7.66 (d, J=6.7 Hz, 1 H), 7.78 (d, J=7.9 Hz, 1 H), 7.89 (br. s., 1 H), 8.57 (d, J=6.1 Hz, 2 H). m/z (ES+), (M+H)^+ = 438.3, 440.3; MS^1, HPLC tR = 0.44 min.
Method 16. Stereoselective Synthesis of 3-Pyrazole Compounds of Formula I

Method 16 depicts a generalized scheme suitable for stereoselective synthesis of 3-pyrazole compounds of Formula I. Those of skill in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds of Formula I as either racemates or single enantiomers. R and n can be selected as described elsewhere herein.
Example 21. Preparation of (S*)-N-(2-azabicyclo[2.2.2]octan-1-yl(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-chloro-3-(trifluoromethyl)benzamide


To a solution of 1,3-dibromobenzene (0.642 ml, 5.31 mmol) in tetrahydrofuran (1.5 mL) at -78°C was added dropwise 1.13 M n-butyllithium in hexanes (3.76 ml, 4.25 mmol), keeping the reaction temperature below -70°C. After 30 min, a solution of (S)-N-((2-allyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)-2-methylpropane-2-sulfinamide (1.0 g, 3.54 mmol; prepared according to the procedures of Example 1, Steps A-D, substituting allyl iodide for iodomethane in Step A and (S)-2-methylpropane-2-sulfinamide for 2-methylpropane-2-sulfinamide in Step D) in tetrahydrofuran (1.5 mL) was added via syringe, again maintaining a reaction temperature below -70°C. After 30 min, the now light brown-orange solution was quenched with saturated aqueous ammonium chloride, basified with saturated aqueous sodium bicarbonate, and extracted with ethyl acetate (x3). The combined organic layers were
dried over sodium sulfate, filtered and concentrated. The resulting residue was dissolved in methanol, filtered, and purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford (S)-N-((S*)-(2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-bromophenyl)methyl)-2-methylpropane-2-sulfinamide (0.153 g, 9.83 %) as a clear residue.

Stereochemistry: This diastereomer was arbitrarily assigned (S, S*) stereochemistry based on the stereochemical preference for addition elucidated in Example 4. 

**Step B. Preparation of (S)-N-((S*)-(2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-methylpropane-2-sulfinamide from (S)-N-((S*)-(2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-bromophenyl)methyl)-2-methylpropane-2-sulfinamide.**

To a degassed solution of DMF (2.321 ml) and ethanol (1.161 ml) containing (S)-N-((S*)-(2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-bromophenyl)methyl)-2-methylpropane-2-sulfinamide (0.153 g, 0.35 mmol) was added potassium carbonate (0.115 g, 0.84 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-1H-pyrazole (0.124 g, 0.59 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.040 g, 0.03 mmol). The light yellow mixture was warmed to 75°C. After 2.5 h, the now orange-red solution was poured into saturated aqueous sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate (x3). The
combined organic layers were dried over sodium sulfate, filtered, and concentrated. The light brown residue was dissolved in methanol (~4 mL), filtered, and purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford (S)-N-((S*)-(2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-methylpropane-2-sulfamidine (0.115 g, 75.0%) as a clear faintly yellow oil. IH NMR (300 MHz, chloroform-d) δ ppm: 1.27 (s, 9 H), 1.28 - 1.38 (m, 2 H), 1.39 - 1.71 (m, 5 H), 1.71 - 1.98 (m, 2 H), 2.63 - 2.77 (m, 1 H), 2.90 (dd, J=13.7, 7.4 Hz, 1 H), 3.10 (d, J=11.6 Hz, 1 H), 3.74 - 3.87 (m, 1 H), 3.93 (s, 3 H), 4.50 (s, 1 H), 5.13 (d, J=10.1 Hz, 1 H), 5.23 (s, 1 H), 5.27 (dd, J=17.3, 9 Hz, 1 H), 5.77 - 5.94 (m, 1 H), 7.12 (d, J=7.6 Hz, 1 H), 7.27 (t, J=7.5 Hz, 1 H), 7.35 (d, 2 H), 7.56 (s, 1 H), 7.71 (s, 1 H). m/z (ES+), (M+H)+ 441.3

[293] Step C. Preparation of (S*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-chloro-3-(trifluoromethyl)benzamide from (S)-N-((S*)-(2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-methylpropane-2-sulfamidine.

To (S)-N-((S*)-(2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-methylpropane-2-sulfamidine (0.115 g, 0.26 mmol) in methanol (2.61 ml) was added 4.0 M hydrochloric acid in dioxane (1.5 ml, 6.00 mmol). After 30 s, the clear solution was concentrated to afford crude (2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methanamine dihydrochloride as a white solid. A solution of crude (2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methanamine dihydrochloride (0.26 mmol), 2-chloro-3-(trifluoromethyl)benzoic acid (0.064 g, 0.29 mmol), and HOBt (0.058 g, 0.38 mmol) in DMF (1.733 ml) was treated with TBTU (0.117 g, 0.36
mmol) and DIPEA (0.226 ml, 1.30 mmol) sequentially. After 16 h, the reaction mixture was diluted with methanol, filtered, and purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford (S*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-chloro-3-(trifluoromethyl)benzamide (0.101 g, 71.5 %) as a light yellow foam solid. IH NMR (300 MHz, chloroform-d) δ ppm 1.32 - 1.78 (m, 8 H), 1.91 - 2.02 (m, 1 H), 2.47 - 2.70 (m, 1 H), 2.94 - 3.13 (m, 2 H), 3.48 - 3.65 (m, 1 H), 3.94 (s, 3 H), 4.93 (d, J=3.7 Hz, 1 H), 5.07 (d, J=10.4 Hz, 1 H), 5.20 (dd, J=17.1, 1.1 Hz, 1 H), 5.64 - 5.88 (m, 1 H), 7.17 (d, J=7.4 Hz, 1 H), 7.27 - 7.45 (m, 5 H), 7.58 (s, 1 H), 7.66 (dd, J=1.1, 1.3 Hz, 1 H), 7.73 (s, 0 H), 7.76 (dd, J=1.1, 1.0 Hz, 1 H). m/z (ES+), (M+H)+ 543.3, 545.3.

[294] Step D. Preparation of (S*)-N-(2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-chloro-3-(trifluoromethyl)benzamide from (S*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-chloro-3-(trifluoromethyl)benzamide.

To a degassed solution of tetrakis(triphenylphosphine)palladium(0) (2.107 mg, 1.82 µmol) and 1,3-dimethylbarbituric acid (0.085 g, 0.55 mmol) in dichloromethane (3 mL) at 30°C was added a solution of (S*)-N-((2-allyl-2-azabicyclo[2.2.2]octan-1-yl)(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-chloro-3-(trifluoromethyl)benzamide (0.099 g, 0.18 mmol) in 2 mL of dichloromethane, resulting in a light yellow solution. This solution was maintained at 30°C with stirring for 20 min. The light yellow solution was then cooled to room temperature and quenched with saturated aqueous sodium chloride. The resulting mixture was extracted with dichloromethane (x2) and ethyl acetate (x1), and the combined organic layers were dried over
sodium sulfate, filtered, and concentrated. The resulting orange residue was purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford (S*)-N-(2-azabicyclo[2.2.2]octan-1-yl(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-chloro-3-(trifluoromethyl)benzamide (0.056 g, 61.2 %) as a white foam solid. 1H NMR (300 MHz, chloroform-\textit{d}) δ ppm 1.37 - 1.90 (m, 8 H), 2.13 - 2.31 (m, 1 H), 2.83 - 3.09 (m, 2 H), 3.92 (s, 3 H), 4.97 (br. s., 1 H), 7.16 (d, J=7.2 Hz, 1 H), 7.29 - 7.45 (m, 3 H), 7.48 (br. s., 1 H), 7.62 - 7.69 (m, 2 H), 7.70 (s, 1 H), 7.75 (dd, J=I. I, 1.0 Hz, 1 H). m/z (ES+), (M+H)+ 503.3, 505.3.

[295] **Method 17. Racemic Synthesis of 3-Pyrazole Compounds of Formula I**

Method 17 depicts a generalized scheme suitable for racemic synthesis of 3-pyrazole compounds of Formula I. Those of skill in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds of Formula I as either racemates or single enantiomers.
Example 22. Preparation of N-((3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-chloro-3-(trifluoromethyl)benzamide

Step A. Preparation of N-((3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfinamide from 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide

To a solution of 1.67 M n-butyllithium in hexanes (1.401 ml, 2.34 mmol) in tetrahydrofuran (8 ml) at -75°C was added 1,3-dibromobenzene (0.353 ml, 2.93 mmol) dropwise over 2.5 min, keeping the reaction temperature below -73°C. After 1.5 h, 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide (0.5 g, 1.95 mmol; prepared according to the procedures of Example 1, Steps A-D) was added rapidly via syringe as a solution in tetrahydrofuran (2 mL) to the light yellow slurry. The resulting light orange solution was warmed to room temperature. In a separate flask, to 1.67 M n-butyllithium in hexanes (1.401 ml, 2.34 mmol) in tetrahydrofuran (8 mL) at -78°C was added 1,3-dibromobenzene (0.353 ml, 2.93 mmol) rapidly. After 2.5 h, the light orange solution containing 2-methyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methylene)propane-2-sulfinamide was added to this new white slurry rapidly via cannula, affording a dark red solution. After 10 min, the reaction was diluted with saturated aqueous sodium chloride and extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by preparative HPLC
(C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford semi-pure N-((3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfamamide (0.521 g, 64.6 %) as a yellow solid.  IH NMR (500 MHz, chloroform-d) δ ppm 1.08 - 1.20 (m, 1 H), 1.26 (s, 9 H), 1.33 - 1.40 (m, 2 H), 1.41 - 1.49 (m, 1 H), 1.56 - 1.65 (m, 3 H), 1.71 - 1.80 (m, 1 H), 1.86 - 1.98 (m, 1 H), 2.42 (s, 3 H), 2.48 - 2.58 (m, 1 H), 3.30 (ddd, J=1 LL, 2.6, 1.6 Hz, 1 H), 4.31 (s, 1 H), 5.14 (s, 1 H), 7.12 - 7.19 (m, 2 H), 7.39 (dt, J=7.2, 1.9 Hz, 1 H), 7.43 (d, 1 H).  m/z (ES+), (M+H)+ 413.2, 415.2.


To N-((3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfamamide (0.3 g, 0.73 mmol) in methanol (3.0 ml) was added 4.0 M hydrochloric acid in dioxane (3.0 ml, 98.74 mmol).  After 5 min, the orange solution was concentrated to afford crude (3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methanamine dihydrochloride as an orange residue.  To a solution of crude (3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methanamine, dihydrochloride (0.088 g, 0.23 mmol) and DIPEA (0.201 ml, 1.15 mmol) in DMF (2.300 ml) was added HOBT (0.049 g, 0.32 mmol), 2-chloro-3-(trifluoromethyl)benzoic acid (0.057 g, 0.25 mmol), and TBTU (0.103 g, 0.32 mmol) sequentially.  After 15 min, the reaction was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (x3).  The combined organic layers were dried over sodium sulfate, filtered, and concentrated.  The resulting residue was purified by prep HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford N-((3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-chloro-3-(trifluoromethyl)benzamide (0.048 g, 40.3 %) as a white foam solid.  IH NMR (500 MHz,
**Example 23. Preparation of N-((3-(1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-chloro-3-(trifluoromethyl)benzamide**

To a degassed solution of N-((3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-chloro-3-(trifluoromethyl)benzamide (0.043 g, 0.08 mmol; Example 22) in 1,2-dimethoxyethane (2.0 ml) and water (0.400 ml) was added sequentially 4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-1H-pyrazole (0.033 g, 0.17 mmol), 2 M aqueous sodium carbonate (0.083 ml, 0.17 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.029 g, 0.03 mmol). To the now lightly cloudy yellow mixture was then added ethanol (0.1 mL) and the mixture was warmed to 100°C. After 16 h, the reaction was diluted with saturated aqueous sodium chloride. This new mixture was extracted with ethyl acetate (x3), and the combined organic layers were dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford N-((3-(1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-chloro-3-(trifluoromethyl)-benzamide (0.015 g, 36.0 %) as a white amorphous solid. 1H NMR (300 MHz, chloroform-d) δ ppm 1.36 - 1.55 (m, 4 H), 1.55 - 1.71 (m, 3 H), 1.75 - 1.88 (m, 1 H), 1.93 - 2.08 (m, 1 H), 2.43 (s, 3 H), 2.53 (d, J=10.7 Hz, 1 H), 3.27 (d, J=10.6 Hz, 1 H), 4.91 (br. s., 1 H), 7.21 (d, J=7.0 Hz, 1 H), 7.28 - 7.45 (m, 4 H), 7.61 - 7.81 (m, 5 H), 10.83 - 11.45 (m, 1 H). m/z (ES+), (M+H)+ 503.3, 505.3; MS1, HPLC tR = 0.54 min.
Method 18. Racemic Synthesis of 3-N-alkylpyrazole Compounds of Formula I

Method 18 depicts a generalized scheme suitable for racemic synthesis of 3-pyrazole compounds of Formula I. Those of skill in the art will readily recognize various reagents and intermediates or changes in moieties that could be used to make additional compounds of Formula I as either racemates or single enantiomers.

Example 24. Preparation of 2-chloro-N-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide
Step A. Preparation of 2-methyl-N-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)propane-2-sulfinamide from N-((3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfinamide

To a degassed solution of DMF (3.55 ml) and ethanol (1.774 ml) containing N-((3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-methylpropane-2-sulfinamide (0.220 g, 0.53 mmol; Example 22, Step A) was added potassium carbonate (0.074 g, 0.53 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)-1H-pyrazole (0.190 g, 0.90 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.615 g, 0.53 mmol). The light yellow mixture was warmed to 75°C. After 2.5 h, the now orange-red solution was poured into saturated aqueous sodium bicarbonate, and the resulting mixture was extracted with ethyl acetate (x3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The light brown residue was dissolved in methanol (~4 mL), filtered, and purified by preparative HPLC (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford 2-methyl-N-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)propane-2-sulfinamide (0.169 g, 77%) as a white foam solid. 

1H NMR (300 MHz, chloroform-d) δ ppm 1.12 - 1.24 (m, 1 H), 1.27 (s, 9 H), 1.31 - 1.49 (m, 3 H), 1.54 - 1.65 (m, 3 H), 1.73 - 1.85 (m, 1 H), 1.87 - 1.99 (m, 1 H), 2.45 (s, 3 H), 2.49 - 2.58 (m, 1 H), 3.28 - 3.35 (m, 1 H), 3.94 (s, 3 H), 4.37 (s, 1 H), 5.15 (s, 1 H), 7.12 (d, J=7.6 Hz, 1 H), 7.25 - 7.31 (m, 1 H), 7.33 - 7.39 (m, 2 H), 7.56 (s, 1 H), 7.71 (s, 1 H). m/z (ES+), (M+H)+ 415.4.
Step B. Preparation of 2-chloro-N-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide from 2-methyl-N-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)propane-2-sulfinamide.

To 2-methyl-N-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)propane-2-sulfinamide (0.808 g, 1.95 mmol) in methanol (3.90 mL) was added 4.0 M hydrochloric acid in dioxane (3.0 mL, 12.00 mmol). After 1 min, the light yellow solution was concentrated to afford crude (3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methanamine dihydrochloride as a white/off-white solid. To a solution of crude (3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methanamine dihydrochloride (0.08 mmol), 2-chloro-3-(trifluoromethyl)benzoic acid (0.019 g, 0.08 mmol), DIPEA (0.066 ml, 0.38 mmol), and HOBT (0.016 g, 0.1 mmol) in N,N-dimethylformamide (1.0 ml) was added TBTU (0.034 g, 0.1 mmol). After 10 min, the reaction was filtered, diluted with methanol (2.5 mL) and purified by preparative LCMS (C18, acetonitrile in water containing ammonium carbonate, pH 10) to afford 2-chloro-N-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide (10.90 mg, 27.9 %) as an off white solid. 1H NMR (300 MHz, chloroform-d) δ ppm 1.32 - 1.54 (m, 4 H), 1.54 - 1.81 (m, 4 H), 1.91 - 2.08 (m, 1 H), 2.40 (s, 3 H), 2.51 (d, J=10.9 Hz, 1 H), 3.26 (d, J=10.7 Hz, 1 H), 3.94 (s, 3 H), 4.84 (d, J=3.5 Hz, 1 H), 7.16 (d, J=7.4 Hz, 1 H), 7.27 - 7.48 (m, 5 H), 7.58 (s, 1 H), 7.68 (d, J=7.6 Hz, 1 H), 7.73 (s, 1 H), 7.76 (d, J=7.9 Hz, 1 H). m/z (ES+), (M+H)+ 517.3, 519.3; MS3, HPLC tR = 2.21 min.

The activity and usefulness of the compounds can be assessed in assays known to those skilled in the art. Some compounds of the invention have potency equal to or better than 1µM (i.e., IC₅₀ ≤ 1µM). Some compounds in accordance with the invention have
potency equal to or better than 0.5 µM \( (i.e., \text{IC}_{50} \leq 0.5 \mu M) \). Some compounds in accordance with the invention have potency equal to or better than 0.1 µM \( (i.e., \text{IC}_{50} \leq 0.1 \mu M) \). Still further compounds in accordance with the invention have potency equal to or better than 0.05 µM \( (i.e., \text{IC}_{50} \leq 0.05 \mu M) \). Potency was measured in the \([\text{3H}]\)Glycine Uptake Assay substantially as described herein.
<p>| Table 1 |
|------------------|------------------|
| <strong>Name</strong> | <strong>Mass spectroscopy mass (HPLC retention time, method)</strong> | <strong>IC&lt;sub&gt;50&lt;/sub&gt;</strong> (μM) |
| 3,5-dichloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)phenyl)methylisonicotinamide | 404.1290, 406.1265 (0.83 min, MS2) | 0.018 |
| N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)phenyl)methyl)-2-(methylthio)isonicotinamide | 382.1948, 380.1794 (0.81 min, MS2) | 0.005 |
| <strong>Structure</strong> |  |  |
| <img src="image1" alt="Structure 1" /> |  | <img src="image2" alt="Structure 2" /> |
| <strong>Ex</strong> |  |  |
| 1 |  | 2 |</p>
<table>
<thead>
<tr>
<th>Name</th>
<th>Mass spectroscopy mass ion(s) (HPLC retention time, method)</th>
<th>IC_{50} (µM)</th>
<th>Structure</th>
<th>Ex</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-N-(2-methyl-2-azabicyclo[2.2.1]octan-1-yl)(phenyl)methyl-2-(methylthio)nicotinamide citric acid salt</td>
<td>382.1940 (0.84 min; MS2)</td>
<td>0.003</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td>3</td>
</tr>
<tr>
<td>(R)-3-bromo-N-(2-methyl-2-azabicyclo[2.2.1]octan-1-yl)(phenyl)methyl isonicotinamide</td>
<td>414.3, 416.3 (0.44 min, MS1)</td>
<td>0.075</td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>4</td>
</tr>
</tbody>
</table>

133

SUBSTITUTE SHEET (RULE 26)
<p>| Name | (R*)-N-(4-(N,N-dimethyl-sulfamoyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2,6-dimethylbenzamide |
| Name | (R*)-N-(4-(cyclopropylmethyl)sulfonyl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2,6-dimethylbenzamide |
| Synthesis Method | 4 | 5 |
| IC₅₀ (µM) | 0.021 | 0.0009 |
| Ex | 5 | 6 |</p>
<table>
<thead>
<tr>
<th>Name</th>
<th>(R)-2,6-dimethyl-N,N'-((2-methyl-2-azabicyclo[2.2.2]octan-1-y)4-(methylsulfonyl)phenyl)methylenediamine</th>
<th>2-chloro-N-(2-methyl-2-azabicyclo[2.2.2]octan-1-y)4-(propylsulfonyl)phenyl)methylenediamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthesis Method</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>IC₅₀ (µM)</td>
<td>0.090</td>
<td>0.002</td>
</tr>
<tr>
<td>Structure</td>
<td><img src="image1" alt="Structure Image 1" /></td>
<td><img src="image2" alt="Structure Image 2" /></td>
</tr>
<tr>
<td>Ex</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Ex</td>
<td>Structure</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>9</td>
<td><img src="image1" alt="Structure" /></td>
<td>0.177</td>
</tr>
<tr>
<td>10</td>
<td><img src="image2" alt="Structure" /></td>
<td>0.023</td>
</tr>
<tr>
<td>Name</td>
<td>Synthesis Method</td>
<td>IC₅₀ (µM)</td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>------------------</td>
<td>----------</td>
</tr>
<tr>
<td>2-chloro-N-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)( trifluoromethyl)benzamide formic acid salt</td>
<td>7</td>
<td>0.029</td>
</tr>
<tr>
<td>2-chloro-N-(3-chlorophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)( trifluoromethyl)benzamide</td>
<td>7</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Ex 11 12

**SUBSTITUTE SHEET (RULE 26)**
<table>
<thead>
<tr>
<th>Name</th>
<th>2-chloro-N-[(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl]-3-(trifluoromethyl)benzamide</th>
<th>2-chloro-N-[(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl]-3-(trifluoromethyl)benzamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>IC_{50} (µM)</td>
<td>0.078</td>
<td>0.078</td>
</tr>
<tr>
<td>Synthesis Method</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Mass spectroscopy mass ion(s) (HPLC retention time, method)</td>
<td>427.2, 429.2; (0.58 min, MS1)</td>
<td>441.3, 443.3; (0.61 min, MS1)</td>
</tr>
<tr>
<td>Name</td>
<td>Synthesis Method</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; (μM)</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>(S&lt;sup&gt;+&lt;/sup&gt;)-2,6-dimethyl-N-(2-(methyl-2-azabicyclo[2.2.2]octan-1-yl)(5- methylfuran-2-yl)benzamide</td>
<td>10</td>
<td>0.001</td>
</tr>
<tr>
<td>(R&lt;sup&gt;+&lt;/sup&gt;)-2,6-dimethyl-N-(2-(methyl-2-azabicyclo[2.2.2]octan-1-yl)(5- methylfuran-2-yl)benzamide citric acid salt</td>
<td>10</td>
<td>0.242</td>
</tr>
<tr>
<td>Ex</td>
<td>Structure</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>---------------------</td>
</tr>
<tr>
<td>16</td>
<td><img src="image1" alt="Structure" /></td>
<td>0.192</td>
</tr>
<tr>
<td>17</td>
<td><img src="image2" alt="Structure" /></td>
<td>0.002</td>
</tr>
<tr>
<td>Name</td>
<td>Mass spectroscopy mass (MS retention time, method)</td>
<td>Synthesis Method</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>---------------------------------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>(R*)-2,6-dimethyl-N-(2-phenyl-2-azabicyclo[2.2.2]octan-1-yl)methylbenzamide</td>
<td>391.4 (0.56 min; MS1)</td>
<td>13</td>
</tr>
<tr>
<td>2-chloro-N-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(trifluoromethyl)benzamide</td>
<td>438.3, 440.3 (0.47 min; MS1)</td>
<td>14</td>
</tr>
</tbody>
</table>

**Structure**

![Image of molecular structures]
<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>Synthesis Method</th>
<th>Name</th>
<th>Mass spectroscopy mass ion(s) (HPLC retention time, method)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>0.018</td>
<td>15</td>
<td>(R*)-2-chloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(pyridin-4-yl)methyl)-3-(trifluoromethyl)benzamide</td>
<td>438.3, 440.3 (0.44 min; MS1)</td>
</tr>
<tr>
<td>21</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>0.048</td>
<td>16</td>
<td>(S*)-N-(2-azabicyclo[2.2.2]octan-1-yl(3-(1-methyl-1H-pyrazol-4-yl)phenyl)methyl)-2-chloro-3-(trifluoromethyl)benzamide</td>
<td>503.3, 505.3 (0.58 min, MS1)</td>
</tr>
<tr>
<td>Ex</td>
<td>Structure</td>
<td>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</td>
<td>Synthesis Method</td>
<td>Name</td>
<td>Mass spectroscopy mass ion(s) (HPLC retention time, method)</td>
</tr>
<tr>
<td>-----</td>
<td>------------</td>
<td>----------------------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------------------------------</td>
</tr>
<tr>
<td>22</td>
<td><img src="image" alt="Structure 22" /></td>
<td>0.009</td>
<td>17</td>
<td>N-((3-bromophenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-chloro-3-(trifluoromethyl)benzamide</td>
<td>515.2, 517.2 (2.41 min; MS3)</td>
</tr>
<tr>
<td>23</td>
<td><img src="image" alt="Structure 23" /></td>
<td>0.008</td>
<td>17</td>
<td>N-((3-(1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-2-chloro-3-(trifluoromethyl)benzamide</td>
<td>503.3, 505.3 (0.54 min; MS1)</td>
</tr>
<tr>
<td>Ex</td>
<td>Structure</td>
<td>IC$_{50}$ (µM)</td>
<td>Synthesis Method</td>
<td>Name</td>
<td>Mass spectroscopy mass ion(s) (HPLC retention time, method)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>----------------</td>
<td>------------------</td>
<td>------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>24</td>
<td><img src="image1" alt="Structure" /></td>
<td>0.008</td>
<td>18</td>
<td>2-chloro-N-((3-(1-methyl-1H-pyrazol-4-yl)phenyl)(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)methyl)-3-(trifluoromethyl)benzamide</td>
<td>517.3, 519.3 (2.21 min; MS3)</td>
</tr>
<tr>
<td>25</td>
<td><img src="image2" alt="Structure" /></td>
<td>0.006</td>
<td>9</td>
<td>2,6-dimethyl-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)methyl)benzamide</td>
<td>367.3 (0.54 min; MS1)</td>
</tr>
<tr>
<td>Mass spectroscopy mass (HPLC retention time, method)</td>
<td>399.3 (0.49 min, MS1)</td>
<td>404, 1288, 406, 1283 (0.82 min, MS2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>---------------------</td>
<td>-----------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>2,6-dimethoxy-N-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(5-methylfuran-2-yl)benzamide</td>
<td>(R)-3,5-dichloro-N-((2-methyl-2-azabicyclo[2.2.2]octan-1-yl)phenyl)methylisonicotinamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthesis Method</td>
<td>9</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IC₅₀ (µM)</td>
<td>0.138</td>
<td>0.045</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

![Chemical Structures](image)

<p>| Ex   | 26 | 27 |</p>
<table>
<thead>
<tr>
<th>Name</th>
<th>Mass spectroscopy mass (HPLC retention time, method)</th>
<th>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</th>
<th>Synthesis Method</th>
<th>Ex</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-2,3-dichloro-N-(2-methyl-2-azabicyclo[2.2.1]heptan-1-yl)isonicotinamide</td>
<td>404.3, 406.3; (0.51 min, MSI)</td>
<td>0.006</td>
<td>4</td>
<td>28</td>
</tr>
<tr>
<td>2,3-dichloro-N-(2-methyl-2-azabicyclo[2.2.1]heptan-1-yl)benzamide</td>
<td>407.2, 409.2; (0.57, MSI)</td>
<td>0.008</td>
<td>9</td>
<td>29</td>
</tr>
</tbody>
</table>

**Structure**

![Structure 1](image1.png)

![Structure 2](image2.png)
<table>
<thead>
<tr>
<th>Name</th>
<th>Structure</th>
<th>Synthesis Method</th>
<th>IC₅₀ (µM)</th>
<th>Ex</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R)-3-fluoro-N-(2-methyl-2-azabicyclo[2.2.1]-7-yllphenyl)methyl)isonicotinamide citric acid salt</td>
<td><img src="" alt="Structure 1" /></td>
<td>4</td>
<td>694.9 (0.53 min, MS1)</td>
<td>30</td>
</tr>
<tr>
<td>(R*)-2,6-dimethyl-N-(2-methyl-2-azabicyclo[2.2.1]7-ylethyl)phenyl)methyl) benzamide</td>
<td><img src="" alt="Structure 2" /></td>
<td>11</td>
<td>0.002</td>
<td>31</td>
</tr>
<tr>
<td>Name</td>
<td>Structure</td>
<td>Synthesis Method</td>
<td>IC$_{50}$ (µM)</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-----------</td>
<td>------------------</td>
<td>----------------</td>
<td></td>
</tr>
<tr>
<td>(S*)-2,6-dimethyl-N-1-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-propylsulfonyl)benzamide</td>
<td><img src="image" alt="Structure S" /></td>
<td>11</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>(R*)-2-amino-6-chloro-N-1-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)(4-propylsulfonyl)phenyl)benzamide</td>
<td><img src="image" alt="Structure R" /></td>
<td>11</td>
<td>0.0002</td>
<td></td>
</tr>
</tbody>
</table>

**Mass spectroscopy ion(s)**
- (HPLC retention time, method)
  - 469.4 (0.53 min, MS1)
  - 490.23 (0.51 min, MS1)
<table>
<thead>
<tr>
<th><strong>Name</strong></th>
<th>(R*)-2,3-dichloro-N-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)-(4-phenylpropyl)benzamide citrate salt</th>
<th>(R*)-3,5-dichloro-N-(2-methyl-2-azabicyclo[2.2.2]octan-1-yl)-(4-propylsulfonyl)phenyl)methylpicolinamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synthesis Method</strong></td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td><strong>IC&lt;sub&gt;50&lt;/sub&gt; (µM)</strong></td>
<td>0.0003</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td><img src="image2.png" alt="Structure 2" /></td>
</tr>
<tr>
<td><strong>Ex</strong></td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>Ex</td>
<td>Structure</td>
<td>IC$_{50}$ (µM)</td>
</tr>
<tr>
<td>----</td>
<td>-----------</td>
<td>----------------</td>
</tr>
<tr>
<td>36</td>
<td><img src="image" alt="Structure" /></td>
<td>0.0003</td>
</tr>
</tbody>
</table>
Additional compounds and isomer mixtures made in accordance with the above-described methods include those shown below in Tables 2-4. The isomer mixtures in Table 2 exhibited an IC50 of less than 0.250 µM. The compounds in Table 3 exhibited an IC50 of from 0.250 to 13 µM. And the compounds in Table 4 exhibited an IC50 of greater than 13 µM (i.e., the compounds in Table 4 have relatively less or no activity for the tested target).
<table>
<thead>
<tr>
<th>Ex</th>
<th>Structure</th>
<th>Additional Compounds Exhibiting an IC(_{50}) of Less Than 0.250 (\mu)M</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td><img src="image" alt="Chemical Structure" /></td>
<td>Mass Spectroscopy mass ion(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IC(_{50}) ((\mu)M)</td>
</tr>
</tbody>
</table>

(The absolute conformation of isomer 1 and isomer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)
Structure

Ex 38 39

IC₅₀ (µM)
0.012 0.024

Mass Spectroscopy mass ion(s) (HPLC retention time, method)
503.3, 505.3 (0.56; MS1)
515.2, 517.1, 519.1 (0.73; MS1)

a = Isoemer 1/Isoemer 2 = 9:1
(The absolute conformation of Isoemer 1 and Isoemer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)

a = Isoemer 1/Isoemer 2 = 9:1
(The absolute conformation of Isoemer 1 and Isoemer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)
Table 3
Compounds Exhibiting an IC₅₀ of from 0.250 to 13 µM

<table>
<thead>
<tr>
<th>Example 40</th>
<th>Example 41</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

(This is the chiral isomer of Example 33. The absolute conformation of this isomer has not been determined. Thus, it is unknown whether it has the R or S conformation.)

<table>
<thead>
<tr>
<th>Example 42</th>
<th>Example 43</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Chemical Structure" /></td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 44</th>
<th>Example 45</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>
Example 46

Example 47

Example 48

Example 49

(This is the chiral isomer of Example 34. The absolute conformation of this isomer has not been determined. Thus, it is unknown whether it has the R or S conformation.)

Example 50

Example 51
<table>
<thead>
<tr>
<th>Example 52</th>
<th>Example 53</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Molecule" /></td>
<td><img src="image2.png" alt="Molecule" /></td>
</tr>
<tr>
<td>Example 54</td>
<td>Example 56</td>
</tr>
<tr>
<td><img src="image3.png" alt="Molecule" /></td>
<td><img src="image4.png" alt="Molecule" /></td>
</tr>
<tr>
<td>Example 57</td>
<td></td>
</tr>
<tr>
<td><img src="image5.png" alt="Molecule" /></td>
<td></td>
</tr>
</tbody>
</table>

(This is the chiral isomer of the compound of Example 17. The absolute conformation of this isomer has not been determined. Thus, it is unknown whether it has the R or S conformation.)
Example 58

Example 59

(This is the chiral isomer of the compound of Example 35. The absolute conformation of this isomer has not been determined. Thus, it is unknown whether it has the R or S conformation.)

Example 60

Example 61

a = Isomer 1/Isomer = 9:1
(The absolute conformation of Isomer 1 and Isomer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)

Example 62

Example 63
Example 64

Example 65

Example 66

Example 67

Example 68

Example 69

\[ a = \text{Isomer 1/Isomer } = 9:1 \]

(The absolute conformation of Isomer 1 and Isomer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)
Example 70

\[ \text{CH}_3 \text{HN} \equiv \text{O} \]
\[ \text{Cl} \]
\[ \text{Cl} \]

\[ \text{Br} \]

\( a = \text{Isomer 1/Isomer 2} = 9:1 \)
(The absolute conformation of Isomer 1 and Isomer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)

Example 71

\[ \text{CH}_3 \text{HN} \equiv \text{O} \]
\[ \text{CH}_3 \]
\[ \text{Cl} \]

\( a = \text{Isomer 1/Isomer 2} = 9:1 \)
(The absolute conformation of Isomer 1 and Isomer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)

Example 72

\[ \text{CH}_3 \text{HN} \equiv \text{O} \]
\[ \text{Cl} \]
\[ \text{Cl} \]

\( a = \text{Isomer 1/Isomer 2} = 9:1 \)
(The absolute conformation of Isomer 1 and Isomer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)

Example 73

\[ \text{CH}_3 \text{HN} \equiv \text{O} \]
\[ \text{Cl} \]
\[ \text{O} \]
\[ \text{H}_3 \text{C} \]

\( a = \text{Isomer 1/Isomer 2} = 9:1 \)
(The absolute conformation of Isomer 1 and Isomer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)

Example 74

\[ \text{CH}_3 \text{HN} \equiv \text{O} \]
\[ \text{Cl} \]

\( a = \text{Isomer 1/Isomer 2} = 9:1 \)
(The absolute conformation of Isomer 1 and Isomer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)

Example 75
Example 76

Example 77

(The absolute conformation of this isomer has not been determined. Thus, it is unknown whether it has the R or S conformation.)

Example 78

Example 79

\[ a = \text{Isomer 1/Isomer 2} = 9:1 \]

(The absolute conformation of Isomer 1 and Isomer 2 has not been determined. Thus, it is unknown which isomer is the R isomer and which is the S isomer.)
<table>
<thead>
<tr>
<th>![Chemical Structure 1]</th>
<th>![Chemical Structure 2]</th>
</tr>
</thead>
<tbody>
<tr>
<td>(The absolute conformation of this isomer has not been determined. Thus, it is unknown whether it has the R or S conformation.)</td>
<td>(The absolute conformation of this isomer has not been determined. Thus, it is unknown whether it has the R or S conformation.)</td>
</tr>
<tr>
<td>![Chemical Structure 3]</td>
<td>![Chemical Structure 4]</td>
</tr>
<tr>
<td>(The absolute conformation of this isomer has not been determined. Thus, it is unknown whether it has the R or S conformation.)</td>
<td>(The absolute conformation of this isomer has not been determined. Thus, it is unknown whether it has the R or S conformation.)</td>
</tr>
</tbody>
</table>

Table 4
Compounds Exhibiting an IC\textsubscript{50} Greater Than 13 \textmu M
Unless otherwise indicated, the following apply in this patent:

The modifier "C_mC_n" means that the modified group contains from m to n carbon atoms. For example, the term "Ci_C6-alkyl" means an alkyl group containing from 1 to 6 carbon atoms. Illustrating further, "C3-C6-alkenyl" means an alkenyl having from 3 to 6 carbon atoms, with at least one double bond.


The term "hydrocarbon means a chemical structure comprising only carbon and hydrogen atoms.

The term "alkyl" means a fully saturated straight or branched hydrocarbon group. In some embodiments, the alkyl comprises from 1 to 12 carbon atoms. In some embodiments, the alkyl comprises from 1 to 6 carbon atoms. And in some embodiments, the alkyl comprises from 1 to 3 carbon atoms. Examples of alkyl groups include, for example, methyl; ethyl; isopropyl; 1-methylpropyl; 2-methylpropyl; n-butyl, t-butyl; isobutyl; 3-methylbutyl; pentyl; hexyl; isohexyl; heptyl; 4,4-dimethylpentyl; diethylpentyl; octyl; 2,2,4-trimethylpentyl; nonyl; decyl; undecyl; and dodecyl. An alkyl may be optionally substituted.

The term "alkenyl" is a straight or branched hydrocarbon comprising from 1 to 3 carbon-carbon double bonds. In some embodiments, the chain comprises up to 20 carbon atoms. In some embodiments, the chain comprises up to 10 carbon atoms. In still other embodiments, the chain comprises from 3 to 8 carbon atoms. In still other embodiments, the chain comprises from 3 to 6 carbon atoms. An alkenyl may be optionally substituted.

"Alkynyl" as used herein refers to a straight or branched hydrocarbon comprising from 1 to 3 carbon-carbon triple bonds. In some embodiments, the hydrocarbon comprises up to 20 carbon atoms. In some embodiments, the hydrocarbon comprises up to 10
carbon atoms. In still other embodiments, the hydrocarbon comprises from 2 to 8 carbon atoms. In still other embodiments, the hydrocarbon comprises from 2 to 6 carbon atoms.

[313] The term "alkoxy" means -O-alkyl. Examples of alkoxy include methoxy, ethoxy, propoxy, and butoxy. An alkoxy may be optionally substituted.

[314] The term "cycloalkyl" means a fully saturated cyclic hydrocarbon group. The cycloalkyl may comprise one or more rings. In some embodiments, the cycloalkyl comprises a single ring. In some embodiments, the cycloalkyl comprises from 3 to 10 carbons. In other embodiments, the cycloalkyl comprises from 3 to 6 carbons. Examples of cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. A cycloalkyl may be optionally substituted.

[315] The term "cycloalkylalkyl" means an alkyl group substituted at its terminal carbon with a cycloalkyl. An example of a cycloalkylalkyl is cyclopropylethyl, which corresponds to:

[316] The term "heterocyclyl" means an unsaturated, partially saturated, or fully saturated ring system wherein 1, 2, or 3 of the ring atoms is/are heteroatoms independently selected from N, O, and S, with the remaining ring atoms being carbon. In some embodiments, the heterocyclyl has from 3 to 10 atoms. In some embodiments, the heterocyclyl has from 4 to 9 ring atoms. In some embodiments, the heterocyclyl has from 3 to 8 ring atoms. In some embodiments, the heterocyclyl has from 3 to 6 ring atoms. In some embodiments, the heterocyclyl has 5 rings atoms, i.e., it is a 5-membered ring. In some embodiments, the heterocyclyl has 6 rings atoms, i.e., it is a 6-membered ring. A heterocyclyl may be monocyclic or polycyclic. A heterocyclyl also may be optionally substituted. Examples of single-ring heterocyclyls include furanyl, thienyl (also known as "thiophenyl" and "thiofuranyl"), oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), and 1,3,4-oxadiazolyl), pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxathiazolyl, oxatriazolyl (including 1,2,3,4-oxatriazolyl and 1,2,3,5-oxatriazole), pyridinyl, diazynyl (including pyridazinyl (also known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl"), and pyrazinyl (also known as "1,4-diazinyl"), triazinyl
(including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and a-triazinyl (also known as "1,2,3-triazinyl"), oxathiazinyl (including 1,2,5-oxathiazinyl and 1,2,6-oxathiazinyl), oxepinyl, thiepinyl, dihydrofuranyl, tetrahydrofuranyl, dihydrothienyl (also known as "dihydrothiophenyl"), tetrahydrothienyl (also known as "tetrahydrothiophenyl"), isopyrrolyl, pyrrolinyl, pyrrolidinyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, dithiolyl, oxathiolyl, oxathiolanyl, oxazolidinyl, isoxazolidinyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, and 1,3,4-dioxazolyl), pyranyl (including 1,2-pyran and 1,4-pyran), dihydropyran, tetrahydropyran, piperidinyl, pipazinyl, oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, and 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl and p-isoxazinyl), oxadiazenyl (including 1,4,2-oxadiazenyl and 1,3,5,2-oxadiazenyl), morpholinyl, azepinyl, and diazepinyl. A heterocycl alternatively may be 2 or 3 rings fused together, such as, for example, indolizinyl, pyranopyrrolyl, purinyl, imidazopyrazinyl, imidazolopyridazyl, pyridopyridinyl (including pyrido [3, 4-b] -pyridinyl, pyrido [3, 4-b] -pyridinyl, pyrido [4, 3-b] -pyridinyl, and naphthyridinyl), pteridinyl, pyridazinotetrazinyl, pyrazinotetrazinyl, pyrimidinotetrazinyl, pyridinyl, pyrazolopyrimidinyl, pyrazolopyrazinyl, pyrazolopyridazyl, or 4H-quinolizinyl. In some embodiments, the multi-ring heterocycls are selected from indolizinyl, pyranopyrrolyl, purinyl, pyridopyridinyl, pyridinyl, and 4H-quinolizinyl. Other examples of fused-ring heterocycls include benzo-fused heterocycls, such as, for example, benzofuran (also known as "coumaronyl"), isobenzofuran, benzoxazolyl, benzoisoxazolyl (also known as "indoxazinyl"), anthranilyl, benzothienyl (also known as "benzothiophenyl", "thionaphthenyl", and "benzothiofuranyl"), isobenzothienyl (also known as "isobenzothiophenyl", "isothionaphthenyl", and "isobenzothiofuranyl"), benzothiazolyl, benzoisothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, isoindazolyl (also known as "benzpyrazolyl"), benzimidazolyl, benzotriazolyl, benzazinyl (including quinolinyl (also known as "1 -benzazinyl") and isoquinolinyl (also known as "2-benzazinyl")), phthalazinyl, quinoxalinyl, benzodiazinyl (including cinnolinyl (also known as "1,2-benzodiazenyl") and quinazolinyl (also known as "1,3-benzodiazenyl").
chromenyl, isochromenyl, thiochromenyl, isothiochromenyl, benzodioxanyl, tetrahydroisoquinolinyl, benzoazinyl (including 1,3,2-benzoazinyl, 1,4,2-benzoazinyl, 2,3,1 -benzoazinyl, and 3,1,4-benzoazinyl), benzoisoxazinyl (including 1,2-benzisoxazinyl and 1,4-benzisoxazinyl), benzoxadiazinyl, and xanthlenyl. In some embodiments, the benzo-fused heterocyclyls are benzofuranyl, isobenzofuranyl, benzoazolyl, benzoisoxazolyl, anthranilyl, benzothiienyl, isobenzothiienyl, benzothiazolyl, benzothiaziazolyl, benzoxadiazolyl, indolyl, isoindazolyl, benzoimidazolyl, benzotriazolyl, benzoazinyl, phthalazinyl, quinolinyl, benzodiazinyl, carbazolyl, acridinyl, isoindolyl, indoleninyl, benzodioxolyl, chromanyl, isochromanyl, thiochromanyl, benzodioxanyl, tetrahydroisoquinolinyl, benzoxazinyl, benzoisoxazinyl, and xanthlenyl. The term "2-fused-ring" heterocyclyl means a saturated, non-aromatic partially-saturated, or heteroaryl containing two fused rings. Such heterocyclyls include, for example, benzofuranyl, isobenzofuranyl, benzoazolyl, benzoisoxazolyl, anthranilyl, benzothiienyl, isobenzothiienyl, benzothiazolyl, benzoisothiazolyl, benzothiadiazolyl, indolizinyl, pyranopyrrolyl, benzoxadiazolyl, indolyl, isoindazolyl, benzoimidazolyl, benzotriazolyl, benzoazinyl, phthalazinyl, quinolinyl, benzodiazinyl, carbazolyl, acridinyl, isoindolyl, indoleninyl, benzodioxolyl, chromanyl, isochromanyl, thiochromanyl, benzodioxanyl, tetrahydroisoquinolinyl, benzoxazinyl, benzoisoxazinyl, and xanthlenyl. The term "heterocycloalkyl" means a fully saturated heterocyclyl. A heterocycloalkyl may be monocyclic or polycyclic. In some embodiments, the heterocycloalkyl has from 3 to 10 ring atoms. In some embodiments, the heterocycloalkyl has from 4 to 9 ring atoms. In some embodiments, the heterocycloalkyl has from 3 to 8 ring
atoms. In some embodiments, the heterocycloalkyl has from 3 to 6 ring atoms. In some embodiments, the heterocycloalkyl is a 5-membered ring. In some embodiments, for example, the heterocycloalkyl is a pyrrolidinyl. In some embodiments, the heterocycloalkyl is a 6-membered ring. A heterocycloalkyl may be optionally substituted.

[318] The term "heterocycloalkenyl" means a non-aromatic, partially-saturated saturated heterocyclyl. A heterocycloalkenyl may be monocyclic or polycyclic. In some embodiments, the heterocycloalkenyl has from 4 to 10 ring atoms. In some embodiments, the heterocycloalkenyl has from 4 to 8 ring atoms. In some embodiments, the heterocycloalkenyl is a 5-membered ring. In some embodiments, the heterocycloalkenyl is a 6-membered ring.

A heterocycloalkenyl may be optionally substituted.

[319] The term "aryl" means an aromatic hydrocarbon ring structure. The aryl may be monocyclic or polycyclic. Aryls include phenyl and naphthyl. In some embodiments, aryl has 6-10 ring atoms. An aryl may be optionally substituted.

[320] The term "arylalkyl" means an alkyl group substituted at its terminal carbon with an aryl. An example of a arylalkyl is phenylethyl, which corresponds to:

\[
\begin{array}{c}
\text{CH}_2 \text{CHPh} \\
\text{Ph}
\end{array}
\]

[321] The term "heteroaryl" means an aromatic heterocyclyl. A heteroaryl may be monocyclic or polycyclic. A heteroaryl also may be optionally substituted. In some embodiments, the heteroaryl is a 5-membered ring. In some embodiments, the heteroaryl is a 6-membered ring. In some embodiments, the heteroaryl is an 8-membered bicyclic ring. In some embodiments, the heteroaryl is a 9-membered bicyclic ring. In some embodiments, the heteroaryl is a 10-membered bicyclic ring. Examples of 5-membered heteroaryls include furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiodiazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxathiazolyl, and oxatriazolyl. Examples of 6-membered heteroaryls include pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, and oxathiazinyl. Examples of 7-membered heteroaryls include oxepinyl and thiepinyl. Examples of 9-membered heteroaryls include fused-ring systems, such as, for example benzofuranyl, isobenzofuranyl, benzoxazolyl, benzoisoxazolyl, anthranilyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzoisothiazolyl, benzothiadiazolyl, indolizinyl, pyranopyrrolyl, benzoxadiazolyl, indolyl, isoindazolyl, benzoimidazolyl, benzotriazolyl,
purinyl, imidazopyrazinyl, imidazopyridinyl, and imidazolopyridazyl. Examples of 10-membered heteroaryls include fused-ring systems such as, for example, quinolinyl, isoquinolinyl, pyridopyridinyl, phthalazinyl, quinoxalinyl, benzodiazinyl, pteridinyl, pyridazinotetrazinyl, pyrazinotetrazinyl, pyrimidinotetrazinyl, benzoimidazothiazolyl, carbazolyl, and acridinyl. In some embodiments, the heteroaryl is selected from furanyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl, pyrazolyl, and imidazolyl. In some such embodiments, the heteroaryl is selected from oxazolyl, isoxazolyl, thiazolyl, imidazolyl, and furanyl. In some embodiments, the heteroaryl is selected from pyridinyl, pyrazinyl, pyridazinyl, and triazinyl. In some such embodiments, the heteroaryl is pyridinyl. In some embodiments, the heteroaryl is selected from benzoazolyl, benzoisoxazolyl, anthranilyl, benzothienyl, isobenzothienyl, and purinyl. And, in some embodiments, the heteroaryl is selected from quinolinyl, isoquinolinyl, and benzodiazinyl. And in some embodiments, the heteroaryl is imidazopyridinyl, such as, for example:

\[ \text{[322]} \] The terms "halogen" and "halo" means chlorine, bromine, fluorine, or iodine. In some embodiments, the halogen atoms in a molecule are selected from the group consisting of chlorine or fluorine. In some embodiments, the halogen atoms in a molecule are chlorine. And in some embodiments, the halogen atoms in a molecule are fluorine. When the term "halo" is used to modify a moiety, that moiety is substituted by one or more independently selected halogens. Thus, for example, "halo-C\(\text{\textsubscript{6}}\)-alkyl" means a C\(\text{\textsubscript{6}}\)-alkyl substituted by
one or more independently selected halogens. Examples of halo-C\textsubscript{6}-alkyl include -CHCl\textsubscript{2}, -CHF\textsubscript{2}, and -CF\textsubscript{3}.

[323] The term "pharmaceutically acceptable" is used to characterize a moiety (e.g., a salt, dosage form, carrier, or diluent) as being appropriate for use in accordance with sound medical judgment. In general, a pharmaceutically acceptable moiety has one or more benefits that outweigh any deleterious effect that the moiety may have. Deleterious effects may include, for example, excessive toxicity, irritation, allergic response, and other problems and complications.

[324] The term "boc" means tert-butoxy carbonyl.

[325] The term "CO\textsubscript{2}" means carbon dioxide.

[326] The term "DIPEA" means N,N-diisopropylethylamine.

[327] The term "DMF" means N,N-dimethylformamide.

[328] The term "DMSO" means dimethyl sulfoxide.

[329] The term "DMSO-56" means deuterated dimethyl sulfoxide.

[330] The term "EtOAc" means ethyl acetate.

[331] The term "IH NMR" means proton nuclear magnetic resonance.

[332] The term "HOBT" means 1-hydroxybenzotriazole hydrate.

[333] The term "HPLC" means high performance liquid chromatography.

[334] The terms "h" and "hr" means hour or hours.

[335] The term "LCMS" means liquid chromatography mass spectral detection.

[336] The term "m-CPBA" means meta-chloroperbenzoic acid.

[337] The term "m/z" means mass to charge ratio.

[338] The term "MeOH" means methanol.

[339] The term "min" means minute or minutes.

[340] The term "MS" means mass spectrum.

[341] The term "NMR" means nuclear magnetic resonance.

[342] The term "SFC" means supercritical fluid chromatography.

[343] The term "TBTU" means O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate.

[344] The term "tR" means retention time.
References made in the singular may also include the plural. For example, "a" and "an" may refer to either one or more than one.

The term "optionally substituted" means that the modified group, structure, or molecule may be either: (1) substituted with a substituent at one or more substitutable positions, or (2) not substituted.

The words "comprise," "comprises," and "comprising" in this patent (including the claims) are to be interpreted inclusively rather than exclusively. This interpretation is intended to be the same as the interpretation that these words are given under United States patent law.

The above detailed description of illustrative embodiments is intended only to acquaint others skilled in the art with the invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This invention, therefore, is not limited to the above embodiments, and may be variously modified.
WHAT IS CLAIMED IS:

1. A compound or a pharmaceutically acceptable salt thereof, wherein:
   the compound corresponds to Formula I:

   \[
   \text{(I)}
   \]

   \( A^1 \) is selected from:
   - phenyl optionally substituted with 1, 2, or 3 \( R^5 \) groups; and
   - a 5- or 6-membered heteroaryl optionally substituted with 1, 2, or 3 \( R^7 \) groups;

   \( A^2 \) is selected from:
   - phenyl substituted with 1, 2, or 3 \( R^2 \) groups; and
   - a heteroaryl optionally substituted with 1, 2, or 3 \( R^6 \) groups;

   \( R^1 \) is selected from hydrogen, \( \text{C}_6 \)-alkyl, \( \text{C}_3 \)-cycloalkyl, 3-6 membered heterocycloalkyl, \( \text{C}_3 \)-C8-cycloalkyl-C4-alkyl, aryl-C4-alkyl, heterocycloalkyl-C4-alkyl, heteroaryl-C4-alkyl, and \( \text{C}_6 \)-alkenyl, wherein:
   - the \( \text{C}_3 \)-C8-cycloalkyl-C4-alkyl, aryl-C4-alkyl, and heteroaryl-C4-alkyl are optionally substituted with one or more independently selected halogens;
   - each \( R^2 \) is independently selected from halogen, -CN, \( \text{C}_2 \)-C6 alkenyl, \( \text{C}_2 \)-C6 alkenyl,

   \( C_3 \)-C6 cycloalkyl, 5- or 6-membered heterocyclyl, -SOR, \( \text{SO}_2 \)-R, \(-\text{NH}_2\), \(-\text{SR}\), \( \text{C}_6 \)-alkoxy, \( \text{Ci}-\text{C}_6 \)-alkyl, and \( \text{Ci}-\text{C}_4 \)-alkoxy-Ci-C4-alkyl, wherein:
   - the \( \text{Ci}-\text{C}_6 \)-alkyl, \( \text{Ci}-\text{C}_6 \)-alkoxy, and \( \text{C}_3 \)-C6 cycloalkyl are optionally substituted with one or more independently selected halogens; and
   - the heterocyclyl is optionally substituted with 1, 2, or 3 \( R^6 \) groups;

   each \( R^5 \) is independently selected from \( \text{Ci}-\text{C}_6 \)-alkyl, \( \text{C}_3 \)-Cs-cycloalkyl, \( \text{Ci}-\text{C}_6 \)-alkoxy, -CN, halogen, -SO2R, -SOR, -SR, and heterocyclyl, wherein:
the Ci-C₆-alkyl, C₃-Cs-cycloalkyl, and Ci-C₆-alkoxy are optionally substituted with one or more independently selected halogens; and
the heterocyclyl is optionally substituted with Ci-C₄-alkyl or halogen;
each R⁶ is independently selected from Ci-C₆-alkyl, Ci-C₆-alkoxy, halogen, -SO₂R,
-SOR, -SR, phenyl, -CF₃, -OCF₃, -CN, and heterocyclyl, wherein:
the heterocyclyl is optionally substituted with Ci-C₄-alkyl;
each R⁷ is independently selected from Ci-C₆-alkyl, Ci-C₄-alkoxy, -CF₃, -OCF₃, -CN,
-SO₂R, -SOR, -SR, phenyl, heterocyclyl, and Ci-C₄-alkoxy, wherein:
the Ci-C₆-alkyl, C₃-Cs-cycloalkyl, and Ci-C₄-alkoxy are optionally substituted;
each R is independently selected from Ci-C₆-alkyl, C₃-C₈-cycloalkyl-Ci-C₆-alkyl, and
NR³R⁴;
each R³ and R⁴ is independently selected from H and Ci-C₆-alkyl;
compounds (and pharmaceutically acceptable salts thereof) satisfying both the
following A¹ and A² definitions are excluded:
A¹ is phenyl; and
A² is phenyl substituted with 1, 2, or 3 groups selected from halogen,
-CN, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, -SO₂NR³R⁴, -NH₂, -S-Ci-
C₆-alkyl, Ci-C₆-alkoxy, and Ci-C₆-alkyl, wherein:
the Ci-C₆-alkyl and Ci-C₆-alkoxy are optionally substituted with one or more halogens; and
compounds (and pharmaceutically acceptable salts thereof) corresponding to any of
the following structures are excluded:
2. A compound or pharmaceutically acceptable salt thereof according to claim 1, wherein each \( R_2 \) is independently selected from halogen, \(-CN, C_2-C_6\) alkenyl, \( C_2-C_6\) alkynyl, \( C_3-C_6\) cycloalkyl, 5- or 6-membered heterocyclyl, \(-SOR, -SO_2R, -NH_2, -SR, Ci-C_6\)-alkoxy, and \( Ci-C_6\)-alkyl, wherein:

- the \( Ci-C_6\)-alkyl, \( Ci-C_6\)-alkoxy, and \( C_3-C_6\) cycloalkyl are optionally substituted with one or more independently selected halogens; and
- the heterocyclyl is optionally substituted with 1, 2, or 3 \( R^6 \) groups.

3. A compound or pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein \( R^1 \) is selected from hydrogen, \( Ci-C_6\)-alkyl, \( C_3-C_6\) cycloalkyl, 3-6 membered
heterocycloalkyl, C₃-C₈-cycloalkyl-Ci-C₄-alkyl, aryl-Ci-C₄-alkyl, heterocycloalkyl-Ci-C₄-alkyl, heteroaryl-Ci-C₄-alkyl, and C₃-Cs-alkenyl.

4. A compound or pharmaceutically acceptable salt thereof in accordance with any one of claims 1 to 3, wherein each R⁷ is independently selected from Ci-C₆-alkyl, C₁-C₄-alkoxy, -CF₃, -OCF₃, -CN, -SO₂R, -SOR, -SR, phenyl, heterocyclyl, and C₁-C₄-alkoxy, wherein:

the Ci-C₆-alkyl, C₃-Cs-cycloalkyl, and Ci-C₄-alkoxy are optionally substituted with one or more independently selected halogen.

5. A compound or pharmaceutically acceptable salt thereof in accordance with any one of claims 1 to 3, wherein A¹ is phenyl.

6. A compound or pharmaceutically acceptable salt thereof in accordance with any one of claims 3 to 5, wherein A² is a heteroaryl substituted with 1, 2, or 3 R⁶ groups.

7. A compound or pharmaceutically acceptable salt thereof in accordance with claim 6, wherein A² is a pyridinyl substituted with 1, 2, or 3 R⁶ groups.

8. A compound or pharmaceutically acceptable salt thereof in accordance with claim 6, wherein A² is a heteroaryl substituted with 1 R⁵ group.

9. A compound or pharmaceutically acceptable salt thereof in accordance with claim 6, wherein A² is a pyridinyl substituted with 1 R⁶ group.

10. A compound or pharmaceutically acceptable salt thereof in accordance with claim 8 or 9, wherein R⁶ is -SR.

11. A compound or pharmaceutically acceptable salt thereof in accordance with claim 10, wherein R is Ci-Ce-alkyl.
12. A compound or pharmaceutically acceptable salt thereof in accordance with claim 11, wherein R is methyl

13. A compound or pharmaceutically acceptable salt thereof in accordance with any one of claims 1 to 12, wherein R¹ is Ci-C₆-alkyl.

14. A compound or pharmaceutically acceptable salt thereof in accordance with claim 13, wherein R¹ is methyl.

15. A compound or pharmaceutically acceptable salt thereof in accordance with claim 1, wherein the compound comprises a single optical isomer, racemic mixture, or other mixture of optical isomers corresponding to a structure selected from:

- [Chemical structure image]
- [Chemical structure image]
- [Chemical structure image]
- [Chemical structure image]
and
16. A compound or pharmaceutically acceptable salt thereof in accordance with claim 1, wherein the compound comprises a single optical isomer, racemic mixture, or other mixture of optical isomers corresponding to the following structure:

17. A compound or pharmaceutically acceptable salt thereof in accordance with claim 16, wherein the compound corresponds to the following structure:
18. A compound or pharmaceutically acceptable salt thereof in accordance with claim 1, wherein the compound comprises a single optical isomer, racemic mixture, or other mixture of optical isomers corresponding to a structure selected from:
19. A pharmaceutically acceptable salt according to any one of claims 1 to 18, wherein the salt comprises a citric acid salt or a formic acid salt.

20. A pharmaceutical composition, wherein the composition comprises:
   a compound or a pharmaceutically acceptable salt according to any one of claims 1 to 19, and
   a pharmaceutically acceptable carrier or diluent.

21. A method of using a compound or a pharmaceutically acceptable salt according to any one of claims 1 to 19 for the treatment of a psychosis.

22. A method of using a compound or a pharmaceutically acceptable salt according to any one of claims 1 to 19 for the treatment of a cognitive disorder.

23. A method for treating a psychosis in a patient in need of such treatment, wherein the method comprises administering a therapeutically effective amount of a compound or salt thereof according to any one of claims 1 to 19 to the patient.

24. A method for treating a cognitive disorder in a patient in need of such treatment, wherein the method comprises administering a therapeutically effective amount of a compound or salt thereof according to any one of claims 1 to 19 to the patient.

25. The use of a compound or salt thereof according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment of a psychosis.
26. The use of a compound or salt thereof according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment of a cognitive disorder.

27. A method or use of any one of claims 22, 24, and 26, wherein the cognitive disorder comprises schizophrenia.

28. A method or use of any one of claims 22, 24, and 26, wherein the cognitive disorder comprises a disorder selected from bipolar disorders.

29. A method or use of any one of claims 22, 24, and 26, wherein the cognitive disorder comprises a disorder selected from mania and/or manic depression disorders.

30. A method or use of any one of claims 22, 24, and 26, wherein the cognitive disorder comprises a disorder selected from anxiety disorders.

31. A method or use of any one of claims 22, 24, and 26, wherein the cognitive disorder comprises a post-traumatic stress disorder.

32. A compound or salt thereof according to any one of claims 1 to 19 for use in the treatment of a psychosis.

33. A compound or salt thereof according to any one of claims 1 to 19 for use in the treatment of a cognitive disorder.

34. A compound or salt thereof according to claim 33, wherein the cognitive disorder comprises schizophrenia, bi-polar disorders, mania and manic depression disorders, and anxiety disorders.

35. A method of using a compound or salt thereof according to any one of claims 1 to 19 for the treatment of pain.
36. A method for treating pain in a patient in need of such treatment, wherein the method comprises administering a therapeutically effective amount of a compound or salt thereof according to any one of claims 1-19 to the patient.

37. A compound or salt thereof according to any one of claims 1 to 19 for use in the treatment of pain.

38. The use of a compound or salt thereof according to any one of claims 1 to 19 in the manufacture of a medicament for the treatment of pain.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC:** see extra sheet

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:** A61K, C07D

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

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**EPO-INTERNAL, WPI DATA, PAJ, CHEM. ABS DATA, CROSSFIRE PATENTCHEMISTRY**

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>P, X</td>
<td>US 20090030033 A1 (ALBERT, JEFFREY SCOTT ET AL), 29 January 2009 (29.01.2009), the whole document</td>
<td>1-38</td>
</tr>
<tr>
<td>A</td>
<td>FR 2861076 A1 (SANOFI–SYNTHELABO), ZZ April 2005 (22.04.2005), page 3, line 16 — line 18; page 19, line 1 — line 14, claims 1,5, examples 2-13, 15-18, pages 13-14</td>
<td>1-38</td>
</tr>
<tr>
<td>A</td>
<td>FR 2906251 A1 (SANOFI AVENTIS), 28 March 2008 (28.03.2008), page 2, line 1 — line 2; page 16, line 1 — page 17, line 4, claim 1, examples 14-30</td>
<td>1-38</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

**Date of the actual completion of the international search** 19 April 2010

**Date of mailing of the international search report** 27-04-2010

**Name and mailing address of the ISA/Swedish Patent Office**

Box 5055, S-102 42 STOCKHOLM

Facsimile No. +46 8 666 02 86

Form PCiyiSA/210 (second sheet) (July 2009)
**INTERNATIONAL SEARCH REPORT**

**Box No. π 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.: 21-24, 27-31 and 35-36
   
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   Claim 21-24, 27-31 and 35-36 relate to a method for treatment of the human or animal body by therapy, see PCT rule ...

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

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

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

2.  
   
   **✗** As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fees.

3.  
   
   **✗** As only some of the required additional search fees were timely paid by the applicant this international search report covers only those claims for which fees were paid, specifically 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 and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2008)
Nevertheless, a search has been made for these claims. The search has been directed to the technical content of the claims.
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>FR 2842804 A1 (SANOFI-SYNTHELABO), 30 January 2004 (30.01.2004), page 2, line 20 - line 24; page 23, line 32 - page 24, line 6, claim 1, examples table 1, page 15</td>
</tr>
<tr>
<td>A</td>
<td>FR 2842805 A1 (SANOFI-SYNTHELABO), 30 January 2004 (30.01.2004), page 2, line 38 - page 3, line 1; page 38, line 27 - line 39, examples</td>
</tr>
<tr>
<td>A</td>
<td>FR 2861071 A1 (SANOFI-SYNTHELABO), 22 April 2005 (22.04.2005), page 20, line 36 - page 21, line ZZ, claims 1, 8, examples 1-9, table 1, page 16</td>
</tr>
<tr>
<td>A</td>
<td>FR 2861073 A1 (SANOFI-SYNTHELABO), 22 April 2005 (22.04.2005), page 17, line 31 - page 18, line 23, claims 1, 4, examples 1-7, table 1, pages 14-15</td>
</tr>
<tr>
<td>A</td>
<td>FR 2861074 A1 (SANOFI-SYNTHELABO), ZZ April 2005 (22.04.2005), page 2, line 24 - line 30; page 20, line 31 - page 21, line 8, claims 1, 4, examples 1-18</td>
</tr>
<tr>
<td>A</td>
<td>WO 03089411 A1 (SANOFI-SYNTHELABO), 30 October 2003 (30.10.2003), page 2, line 21 - line 23; page 33, line 32 - page 34, line 6, claim 1</td>
</tr>
<tr>
<td>A</td>
<td>WO 2008018639 A2 (TAISHO PHARMACEUTICAL CO., LTD.), 14 February 2008 (14.02.2008), claims 1, 34, 35, abstract, table 1, pages 138-149</td>
</tr>
<tr>
<td>A</td>
<td>WO 2006067414 A2 (GLAXO GROUP LIMITED), 29 June 2006 (29.06.2006), claims 1, 6, 8, 10, abstract, examples 1-26</td>
</tr>
</tbody>
</table>
International patent classification (IPC)
COTD 471/08 (2006.01)
A61K 31/439 (2006.01)
A61P 25/04 (2006.01)
A61P 25/18 (2006.01)
A61P 25/22 (2006.01)
A61P 25/24 (2006.01)

Download your patent documents at www.prv.se
The cited patent documents can be downloaded:
• From "Cited documents" found under our online services at www.prv.se (English version)
• From "Anförda dokument" found under "e-tjanster" at www.prv.se (Swedish version)
Use the application number as username. The password is NSLLIZCGZB.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.
### INTERNATIONAL SEARCH REPORT

**International application No.**
PCT/SE2010/050070

<table>
<thead>
<tr>
<th>Country</th>
<th>Application No.</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>20090030033</td>
<td>29/01/2009</td>
</tr>
<tr>
<td>FR</td>
<td>2861076</td>
<td>22/04/2005</td>
</tr>
<tr>
<td>AT</td>
<td>386036 T</td>
<td>15/03/2008</td>
</tr>
<tr>
<td>AU</td>
<td>2004281217 A</td>
<td>28/04/2005</td>
</tr>
<tr>
<td>BR</td>
<td>PI0415489 A</td>
<td>26/12/2006</td>
</tr>
<tr>
<td>CA</td>
<td>2542647 A</td>
<td>28/04/2005</td>
</tr>
<tr>
<td>CN</td>
<td>1882587 A</td>
<td>20/12/2006</td>
</tr>
<tr>
<td>CN</td>
<td>101684118 A</td>
<td>31/03/2010</td>
</tr>
<tr>
<td>DE</td>
<td>602004011806 D,T</td>
<td>05/02/2009</td>
</tr>
<tr>
<td>DK</td>
<td>1680421 T</td>
<td>09/06/2008</td>
</tr>
<tr>
<td>EC</td>
<td>SP066511 A</td>
<td>10/10/2006</td>
</tr>
<tr>
<td>EP</td>
<td>1680421 A,B</td>
<td>13/02/2008</td>
</tr>
<tr>
<td>ES</td>
<td>1680421 T3</td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>2300837 T</td>
<td>16/06/2008</td>
</tr>
<tr>
<td>HR</td>
<td>20080186 T</td>
<td>31/05/2008</td>
</tr>
<tr>
<td>JP</td>
<td>2007508361 T</td>
<td>05/04/2007</td>
</tr>
<tr>
<td>KR</td>
<td>20060109432 A</td>
<td>20/10/2006</td>
</tr>
<tr>
<td>NO</td>
<td>20062030 A</td>
<td>07/07/2006</td>
</tr>
<tr>
<td>NZ</td>
<td>547163 A</td>
<td>29/01/2010</td>
</tr>
<tr>
<td>PT</td>
<td>1680421 E</td>
<td>13/05/2008</td>
</tr>
<tr>
<td>RU</td>
<td>2346945 C</td>
<td>20/02/2009</td>
</tr>
<tr>
<td>RU</td>
<td>2006116889 A</td>
<td>27/11/2007</td>
</tr>
<tr>
<td>SG</td>
<td>147435 A</td>
<td>28/11/2008</td>
</tr>
<tr>
<td>UA</td>
<td>81186 C</td>
<td>10/12/2007</td>
</tr>
<tr>
<td>US</td>
<td>7288656 B</td>
<td>30/10/2007</td>
</tr>
<tr>
<td>US</td>
<td>7619089 B</td>
<td>17/11/2009</td>
</tr>
<tr>
<td>US</td>
<td>20080070941 A</td>
<td>20/03/2008</td>
</tr>
<tr>
<td>US</td>
<td>20100022548 A</td>
<td>28/01/2010</td>
</tr>
<tr>
<td>WO</td>
<td>2005037783 A</td>
<td>07/07/2005</td>
</tr>
<tr>
<td>ZA</td>
<td>200603861 A</td>
<td>27/12/2007</td>
</tr>
<tr>
<td>AR</td>
<td>062896 A</td>
<td>10/12/2008</td>
</tr>
<tr>
<td>AU</td>
<td>2007301880 A</td>
<td>03/04/2008</td>
</tr>
<tr>
<td>CA</td>
<td>2663080 A</td>
<td>03/04/2008</td>
</tr>
<tr>
<td>CN</td>
<td>101573113 A</td>
<td>04/11/2009</td>
</tr>
<tr>
<td>CR</td>
<td>10658 A</td>
<td>24/06/2009</td>
</tr>
<tr>
<td>EA</td>
<td>200970312 A</td>
<td>30/12/2009</td>
</tr>
<tr>
<td>EP</td>
<td>2077837 A</td>
<td>15/07/2009</td>
</tr>
<tr>
<td>JP</td>
<td>2010504311 T</td>
<td>12/02/2010</td>
</tr>
<tr>
<td>KR</td>
<td>20090080947 A</td>
<td>27/07/2009</td>
</tr>
<tr>
<td>MX</td>
<td>2009003083 A</td>
<td>02/04/2009</td>
</tr>
<tr>
<td>NO</td>
<td>20091351 A</td>
<td>22/06/2009</td>
</tr>
<tr>
<td>SV</td>
<td>2009003191 A</td>
<td>27/10/2009</td>
</tr>
<tr>
<td>US</td>
<td>20090258899 A</td>
<td>15/10/2009</td>
</tr>
<tr>
<td>UY</td>
<td>30604 A</td>
<td>02/05/2008</td>
</tr>
<tr>
<td>WO</td>
<td>2008037881 A</td>
<td>22/05/2008</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (April 2005)
<table>
<thead>
<tr>
<th>Country</th>
<th>Application No.</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>AT 383338</td>
<td>15/01/2008</td>
</tr>
<tr>
<td>AU</td>
<td>AU 2003273475</td>
<td>23/02/2004</td>
</tr>
<tr>
<td>DE</td>
<td>DE 60318583</td>
<td>08/01/2009</td>
</tr>
<tr>
<td>EP</td>
<td>EP 1527048</td>
<td>09/01/2008</td>
</tr>
<tr>
<td>ES</td>
<td>ES 2297205</td>
<td>01/05/2008</td>
</tr>
<tr>
<td>JP</td>
<td>JP 2005537293</td>
<td>08/12/2005</td>
</tr>
<tr>
<td>US</td>
<td>US 20050153963A</td>
<td>14/07/2005</td>
</tr>
<tr>
<td>US</td>
<td>US 20070155789A</td>
<td>05/07/2007</td>
</tr>
<tr>
<td>WO</td>
<td>WO 2004013101A</td>
<td>13/05/2004</td>
</tr>
<tr>
<td>FR</td>
<td>FR 2842804</td>
<td>30/01/2004</td>
</tr>
<tr>
<td>AU</td>
<td>AU 2003273474</td>
<td>23/02/2004</td>
</tr>
<tr>
<td>WO</td>
<td>WO 2004013100A</td>
<td>15/04/2004</td>
</tr>
<tr>
<td>FR</td>
<td>FR 2861071</td>
<td>22/04/2005</td>
</tr>
<tr>
<td>AT</td>
<td>AT 359268</td>
<td>15/05/2007</td>
</tr>
<tr>
<td>AU</td>
<td>AU 2004281216A</td>
<td>28/04/2005</td>
</tr>
<tr>
<td>BR</td>
<td>BR PI0415433A</td>
<td>05/12/2006</td>
</tr>
<tr>
<td>CA</td>
<td>CA 2542925A</td>
<td>28/04/2005</td>
</tr>
<tr>
<td>CN</td>
<td>CN 1882541</td>
<td>20/12/2006</td>
</tr>
<tr>
<td>DE</td>
<td>DE 602004005886D,T</td>
<td>17/01/2008</td>
</tr>
<tr>
<td>DK</td>
<td>DK 1682503T</td>
<td>16/07/2007</td>
</tr>
<tr>
<td>SE</td>
<td>SE 1682503T3</td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>ES 2282916T</td>
<td>16/10/2007</td>
</tr>
<tr>
<td>HR</td>
<td>HR 20070203T</td>
<td>30/06/2007</td>
</tr>
<tr>
<td>JP</td>
<td>JP 2007508360T</td>
<td>05/04/2007</td>
</tr>
<tr>
<td>NO</td>
<td>NO 20062031A</td>
<td>06/07/2006</td>
</tr>
<tr>
<td>NZ</td>
<td>NZ 547166A</td>
<td>27/11/2009</td>
</tr>
<tr>
<td>PT</td>
<td>PT 1682503E</td>
<td>31/05/2007</td>
</tr>
<tr>
<td>RU</td>
<td>RU 2351589C</td>
<td>10/04/2009</td>
</tr>
<tr>
<td>RU</td>
<td>RU 2006116886A</td>
<td>27/11/2007</td>
</tr>
<tr>
<td>US</td>
<td>US 20060223861A</td>
<td>05/10/2006</td>
</tr>
<tr>
<td>WO</td>
<td>WO 2005037782A</td>
<td>07/07/2005</td>
</tr>
<tr>
<td>Country</td>
<td>Application Number</td>
<td>Date</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------</td>
<td>------------</td>
</tr>
<tr>
<td>FR</td>
<td>2861073</td>
<td>22/04/2005</td>
</tr>
<tr>
<td>AT</td>
<td>361923</td>
<td>28/04/2005</td>
</tr>
<tr>
<td>AU</td>
<td>2004281215</td>
<td>28/04/2005</td>
</tr>
<tr>
<td>BR</td>
<td>PI0415452</td>
<td>28/04/2005</td>
</tr>
<tr>
<td>CA</td>
<td>2542370</td>
<td>20/12/2006</td>
</tr>
<tr>
<td>CN</td>
<td>1882581</td>
<td>05/11/2008</td>
</tr>
<tr>
<td>DE</td>
<td>602004006431 D,T</td>
<td>10/01/2008</td>
</tr>
<tr>
<td>DK</td>
<td>1680418 T</td>
<td>10/09/2007</td>
</tr>
<tr>
<td>EP</td>
<td>1680418 A,B</td>
<td>09/05/2007</td>
</tr>
<tr>
<td>SE</td>
<td>1680418 T3</td>
<td>16/12/2007</td>
</tr>
<tr>
<td>ES</td>
<td>2287782 T</td>
<td>30/09/2007</td>
</tr>
<tr>
<td>HK</td>
<td>1098456 A</td>
<td>02/08/2006</td>
</tr>
<tr>
<td>HR</td>
<td>20070327 T</td>
<td>29/01/2009</td>
</tr>
<tr>
<td>JP</td>
<td>2007508359 T</td>
<td>17/07/2009</td>
</tr>
<tr>
<td>KR</td>
<td>20060087598 A</td>
<td>12/05/2006</td>
</tr>
<tr>
<td>NO</td>
<td>20062151 A</td>
<td>10/04/2009</td>
</tr>
<tr>
<td>NZ</td>
<td>547165 A</td>
<td>28/01/2009</td>
</tr>
<tr>
<td>PT</td>
<td>1680418 E</td>
<td>20/12/2006</td>
</tr>
<tr>
<td>RU</td>
<td>2351596 C</td>
<td>05/04/2007</td>
</tr>
<tr>
<td>RU</td>
<td>2006116887 A</td>
<td>10/09/2007</td>
</tr>
<tr>
<td>US</td>
<td>7335670 B</td>
<td>05/10/2006</td>
</tr>
<tr>
<td>US</td>
<td>20060223886 A</td>
<td>05/04/2009</td>
</tr>
<tr>
<td>WO</td>
<td>2005037781 A</td>
<td>14/07/2005</td>
</tr>
<tr>
<td>ZA</td>
<td>200603941 A</td>
<td>28/11/2007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Country</th>
<th>Application Number</th>
<th>Date</th>
<th>Filing Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>FR</td>
<td>2861074</td>
<td>22/04/2005</td>
<td>15/06/2007</td>
</tr>
<tr>
<td>AU</td>
<td>2004281214</td>
<td>28/04/2005</td>
<td></td>
</tr>
<tr>
<td>BR</td>
<td>PI0415504</td>
<td>12/12/2006</td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>2542373</td>
<td>12/12/2006</td>
<td></td>
</tr>
<tr>
<td>CN</td>
<td>1882540 A</td>
<td>20/12/2006</td>
<td></td>
</tr>
<tr>
<td>EP</td>
<td>1680402 A</td>
<td>28/04/2005</td>
<td></td>
</tr>
<tr>
<td>JP</td>
<td>2007508358 T</td>
<td>28/08/2006</td>
<td></td>
</tr>
<tr>
<td>KR</td>
<td>20060090479 A</td>
<td>10/05/2006</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>20062105 A</td>
<td>27/11/2007</td>
<td></td>
</tr>
<tr>
<td>NZ</td>
<td>547164 A</td>
<td>10/04/2009</td>
<td></td>
</tr>
<tr>
<td>RU</td>
<td>2351588 C</td>
<td>05/10/2006</td>
<td></td>
</tr>
<tr>
<td>RU</td>
<td>2006116885 A</td>
<td>27/11/2007</td>
<td></td>
</tr>
<tr>
<td>WO</td>
<td>2005037792 A</td>
<td>28/04/2005</td>
<td></td>
</tr>
<tr>
<td>ZA</td>
<td>200603937 A</td>
<td>28/01/2009</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Application Number</td>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>--------------------</td>
<td>------------</td>
<td></td>
</tr>
<tr>
<td>AT</td>
<td>361279</td>
<td>15/05/2007</td>
<td></td>
</tr>
<tr>
<td>AU</td>
<td>2003262420</td>
<td>19/02/2009</td>
<td></td>
</tr>
<tr>
<td>BR</td>
<td>0309397</td>
<td>01/03/2005</td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>2481461</td>
<td>12/01/2010</td>
<td></td>
</tr>
<tr>
<td>CN</td>
<td>1662497</td>
<td>31/08/2005</td>
<td></td>
</tr>
<tr>
<td>CN</td>
<td>100482646</td>
<td>29/04/2009</td>
<td></td>
</tr>
<tr>
<td>DE</td>
<td>60313602</td>
<td>10/01/2008</td>
<td></td>
</tr>
<tr>
<td>DK</td>
<td>1499589</td>
<td>10/09/2007</td>
<td></td>
</tr>
<tr>
<td>EC</td>
<td>SP045369</td>
<td>10/03/2005</td>
<td></td>
</tr>
<tr>
<td>EP</td>
<td>1499589</td>
<td>02/05/2007</td>
<td></td>
</tr>
<tr>
<td>SE</td>
<td>1499589</td>
<td>03/02/2000</td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>22864443</td>
<td>01/12/2007</td>
<td></td>
</tr>
<tr>
<td>FR</td>
<td>2838739</td>
<td>28/05/2004</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>20040977</td>
<td>30/04/2008</td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td>7479</td>
<td>30/09/2004</td>
<td></td>
</tr>
<tr>
<td>JP</td>
<td>2005527593</td>
<td>15/09/2005</td>
<td></td>
</tr>
<tr>
<td>KR</td>
<td>20080075236</td>
<td>14/08/2008</td>
<td></td>
</tr>
<tr>
<td>MA</td>
<td>27192</td>
<td>03/01/2005</td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>PA04010326</td>
<td>05/07/2005</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>20044388</td>
<td>19/01/2005</td>
<td></td>
</tr>
<tr>
<td>NZ</td>
<td>536015</td>
<td>30/11/2006</td>
<td></td>
</tr>
<tr>
<td>PL</td>
<td>373195</td>
<td>22/08/2005</td>
<td></td>
</tr>
<tr>
<td>PT</td>
<td>1499589</td>
<td>10/08/2007</td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>78025</td>
<td>15/02/2007</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>7326722</td>
<td>05/02/2008</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>20050159450</td>
<td>11/01/2005</td>
<td></td>
</tr>
<tr>
<td>ZA</td>
<td>200408154</td>
<td>10/10/2005</td>
<td></td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (April 2005)