Abstract:

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Title:

Abstract:

Disclosed are compounds of Formula (I), or a pharmaceutically acceptable salt thereof, wherein W and Q and G are defined herein. Also disclosed are methods of using such compounds as inhibitors of Bcl-2 family antiapoptotic proteins for the treatment of cancer; and pharmaceutical compositions comprising such compounds.
SUBSTITUTED SULFONAMIDES USEFUL AS ANTIAPOPTOTIC BCL INHIBITORS

FIELD OF THE INVENTION

[0001] The invention relates to substituted sulfonamide compounds that are useful as anti-cancer agents. This invention also relates to a method of using the compounds in the treatment of proliferative and other diseases and to pharmaceutical compositions containing the compounds.

BACKGROUND OF THE INVENTION

[0002] Apoptosis, or programmed cell death, plays an important role ensuring a proper balance between cell proliferation and cell loss in multicellular organisms. Disruption of this pathway is implicated in many human diseases, including cancer (Reed, J.C., *Cell Death and Differentiation*, 13:1379-1386 (2006)). Targeting critical apoptosis regulators is an attractive approach for the development of anticancer therapeutics and therapies for other human diseases caused by biologically impaired apoptosis.

[0003] Proteins belonging to the Bcl-2 (B-cell lymphocyte/leukemia-2) family play a central role in regulating apoptosis (Chan, S.-L. et al, *Clin. and Exper. Pharmacol. and Physiol.*, 31:1 19-128 (2004)). This family contains proteins promoting cell survival (Bcl-2, Bcl-b, Bcl-Xl, Bcl-w, Mcl-1, A1) and proteins promoting cell death (*i.e.*, Bak, Bax, Bim, Bid, etc). Family members share up to four Bcl-2 homology (BH) domains and formation of homo- or heterodimers via these BH domains modulates each other's function(s) as cell death agonists or antagonists. Cellular ratios between proapoptotic and prosurvival family members dictate cellular fate. For example, prosurvival Bcl-2 family protein levels are elevated in many cancers enabling tumor cells more resistant to apoptosis. Consequently, antagonizing prosurvival Bcl-2 family protein function in tumor cells is a promising strategy for the development of anticancer therapeutics. Conceptually this therapeutic strategy is also applicable towards other diseases brought about by the disrupted cellular balance of proapoptotic and prosurvival Bcl-2 family proteins.
There remains a need for compounds that are useful as Bcl-2 family prosurvival protein antagonists.

Applicants have found potent compounds that have activity as small molecule Bcl-2 family prosurvival protein antagonists for cancer treatment and other diseases caused by impaired apoptosis. These compounds are provided to be useful as pharmaceuticals with desired stability, bioavailability, therapeutic index, and toxicity values that are important to their drugability.

SUMMARY OF THE INVENTION

The invention is directed to compounds of Formula (I) that are useful as inhibitors of Bcl-2 family antiapoptotic proteins, and are useful for the treatment of cancer, or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates or prodrugs thereof.

The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method for inhibition of Bcl-2 family antiapoptotic proteins comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides a method for treating cancers comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof.

The present invention also provides the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for use in therapy.
The present invention also provides the use of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, solvates, or prodrugs thereof, for the manufacture of a medicament for the treatment of cancers.

These and other features of the invention will be set forth in the expanded form as the disclosure continues.

**DETAILED DESCRIPTION OF THE INVENTION**

The first aspect of the invention provides substituted sulfonamide compounds of Formula (I):

\[
\begin{align*}
\text{W} & \quad \text{(I)} \\
\text{Q} & \quad \text{or pharmaceutically acceptable salts or prodrugs thereof, wherein:} \\
\text{W} & \quad \text{is:} \\
\text{Q} & \quad \text{(a) naphthalenyl or isoquinolinyl, each substituted with zero to 3 substituents} \\
\text{Q} & \quad \text{independently selected from -OH, -CN, halo, -N0}_2, \text{-C(0)OH, -C(0)0(Ci-4 alkyl),} \\
\text{Q} & \quad \text{-S(0)_2(Ci-4 alkyl), -S(CH_2)_3C(0)OH, -S(CH_2)_3NH}_2, \text{C_4 alkoxy,} \\
\text{Q} & \quad \text{-OCH(CH}_3\text{)CH}_2\text{N(Ci-4 alkyl)_2, -O(CH}_2\text{)_3R}_x, -0(CH}_2\text{)_3N(CH}_3\text{)_2, -0(CH}_2\text{)_4OH,} \\
\text{Q} & \quad \text{-0(CH}_2\text{)_3OCCH^OCphenyl), -N(Ci-4 alkyl)_2, -C(0)N(d-4 alkyl)_2, -C(0)R}_x, \text{and/or -NHC(0)R}_x;}
\end{align*}
\]
wherein said bicyclic heterocyclyl is substituted with zero to 3 substituents independently selected from: halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, -(CH₂)₁₋₄(C(0)OH), -(CH₂)₁₋₄NH₂, -(CH₂)₁₋₄N₃, -(CH₂)₁₋₄N(CH₃)(C₁₋₄ hydroxyalkyl), -(CH₂)₁₋₄N(CH₃)(CH₂)₁₋₄OCH₃, -(CH₂)₁₋₄O(CH₂)₁₋₄N(C₁₋₄ alkyl)₂, -(CH₂)₁₋₄O(CH₂)₁₋₄OH, -(CH₂)₁₋₄O(CH₂)₁₋₄O(CH₂)₁₋₄(C₁₋₄ alkyl),
\[\text{G is:}\]
\[(a) \quad -\text{N} (\text{C}_1 \text{₋}_4 \text{ alkyl})_2; \text{ or}\]
\[(b) \quad \text{a bicyclic heterocyclyl selected from:}\]

\[\text{R₁R₂}^-\]
\[-\text{(CH}_2\text{)}_{1\text{-}3}\text{O(phenyl)}, \quad \text{(CH}_2\text{)}_{1\text{-}3}\text{OCH}_3, \quad \text{(CH}_2\text{)}_{1\text{-}3}\text{N(CH}_3\text{)}_2, \quad \text{(CH}_2\text{)}_{1\text{-}3}\text{OCH}(\text{CH}_2\text{)}_1\text{CH}_3, \quad \text{(CH}_2\text{)}_{1\text{-}3}\text{N(CH}_3\text{)}_2, \quad \text{(CH}_2\text{)}_{1\text{-}3}\text{CH}_3, \quad \text{(CH}_2\text{)}_{1\text{-}3}\text{R}_x\]

Ria is H, halo, Ci-6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]

\[\begin{align*}
\text{Rib is H, Cl, 6 alkyl, -CF, Ci-4 hydroxyalkyl, -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4 alkyl), -(CH}_2\text{)}_{1\text{-}3}\text{O(Ci-4}
\end{align*}\]
(b) \(-(\text{CH}_2)_0-2(\text{phenyl})\) wherein said phenyl is substituted with zero to 2 substituents independently selected from Cl, I, C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkoxy, -\((\text{CH}_2)_0-3\text{C}(0)\text{OH}, -\text{C(0)O(Ci}_4\text{)alkyl}, -\text{(CH}_2)_1-\text{C(0)(Ci}_4\text{)alkyl}, \text{phenyl}, \text{halophenyl}, \text{halophenoxy}, \text{phenyl acetic acid}, \text{and/or } -\text{(CH}_2)_1-\text{c(0)R}_X; \text{or}

![Diagram](image)

or \(R_a\) and \(R_b\) together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring substituted with zero to 1 substituent selected from Ci\textsubscript{4} alkyl and -\((\text{CH}_2)_1-3\text{(phenyl)}.\)

10 [0015] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

\(W\) is:

![Diagram](image)

15 \(Q\) is:

(a) naphthalenyl substituted with zero to 3 substituents independently selected from -OH, -CN, Cl, Br, I, -N0\textsubscript{2}, -N(CH\textsubscript{3})\textsubscript{2}, -C(0)OH, -C(0)OCH\textsubscript{2}CH\textsubscript{3}, -S(0)\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}, Ci-3 alkoxy, -OCH(CH\textsubscript{3})\textsubscript{2}N(CH\textsubscript{3})\textsubscript{2}, -0(CH\textsubscript{2})\textsubscript{3}N(CH\textsubscript{3})\textsubscript{2}, -OCH\textsubscript{2}(phenyl), -OCH\textsubscript{2}(dichlorophenyl), -OCH\textsubscript{2}(benzoic acid), -OCH\textsubscript{2}(methyl benzoate), -OCH\textsubscript{2}(methylsulfonylphenyl), -OCH\textsubscript{2}(furanyl), -OCH\textsubscript{2}(N-methyl- 1H-imidazolyl), -0(CH\textsubscript{2})\textsubscript{3}(N-methylpyrrolidinyl), -0(CH\textsubscript{2})\textsubscript{3}(morpholinyl), -0(CH\textsubscript{2})\textsubscript{3}(pyrrolidinyl), -0(CH\textsubscript{2})\textsubscript{3}(piperidinyl), 0(CH\textsubscript{2})\textsubscript{3}(N-methylpiperazinyl), -0(CH\textsubscript{2})\textsubscript{3}(pyridinyl), -OCH\textsubscript{2}CH\textsubscript{2}OH, -OCH\textsubscript{2}CH\textsubscript{2}0 (C\textsubscript{1-2} alkyl), -OCH\textsubscript{2}CH\textsubscript{2}0(phenyl), -C(0)N(CH\textsubscript{3})\textsubscript{2}.
-C(0)(N-methylpiperazinyl), -C(0)(morpholinyl), and/or
-NHC(0)(dichlorophenyl);

(b) isoquinolinyl substituted with -OCH₂CH₃(morpholinyl), -SCH₂CH₂NH₂, or
-SCH₂C(0)OH;

(c) each substituted with zero to 3 substituents independently selected from Cl, Br, I, -CH₂CH₃, -CH₂(cyclohexyl),
-CH₂(phenyl), -CH₂(difluorophenyl), -(CH₂)₂(dichlorophenyl),
-CH₂(chloropyridinyl), -CH₂(1-methyl-1H-indolyl), -(CH₂)₂(morpholinyl),
-C(0)(cyclohexyl), -C(0)(dichlorophenyl), -C(0)(morpholinyl),

-CH₂CH₂(morpholinyl), -C(0)(N-methylpiperazinyl), -C(0)(morpholinyl), and/or
-NHC(0)(dichlorophenyl);

isoquinolinyl substituted with -OCH₂C₂H₅(morpholinyl), -SCH₂CH₂NH₂, or
-SCH₂C(0)OH;

(d) ethyl, pentyl, or -CH₂CH₂(trimethylsilyl)), provided that W is

15 (a) -N(CH₃)₂; or
(b) a bicyclic heterocyclyl selected from:

wherein said bicyclic heterocyclyl is substituted with zero to 2 substituents independently

selected from: Br, -CH₃, -CF₃, -CH₂OH, -CH₂NH₂, -CH₂N₃,
-CH₂N(CH₃)(CH₂CH₂OH), -CH₂N(CH₃)(CH₂CH₂OCH₃),
-CH₂OCH₂CH₂N(CH₃)₂, -CH₂OCH₂CH₂OH, -CH₂OCH₂CH₂O(phenyl),
-CH₂OCH₂CH₂CH₂OCH₃, -CH₂(pyrrolidinyl), -CH₂(N-methyl piperazinyl),
\(-\text{CH}_2/N-(2\text{-hydroxyethyl)piperazinyl}), -\text{CH}_2(\text{morpholinyl}), -\text{OCH}_3, -\text{C(O)OH}, -\text{(CH}_2)_n-N(\text{CH}_3)_2, -\text{N(\text{CH}_3)}(\text{CH}_2\text{CH}_2\text{OCH}_3), -\text{CH}_2\text{C}(\text{0})\text{NHC(CH}_2\text{OH})_3, \text{ or } -\text{CH}_2\text{C}(\text{0})\text{NC}(\text{CH}_3)(\text{CH}_2\text{hydroxyalkyl})_2, -\text{CH}_2\text{C}(\text{0})\text{NHCH}_2\text{C}(\text{N-methyl piperazinyl});\)

\[
\begin{align*}
&\text{R}_i \text{ is } \text{H}, \text{Cl}, \text{Br}, -\text{CH}_3, \text{butyl}, -\text{CF}_3, -(\text{CH}_2)_2\text{OH}, -\text{CH}_2\text{CH}_2\text{OCH}_3, -\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}, \\
&\text{R} \text{b} \text{ is } \text{phenyl substituted with zero to 1 substituent selected from propyl, } -(\text{CH}_2)_n-\text{OH}, -\text{O(\text{CH}_3)_o-CH}_3, -\text{O(\text{CH}_2)_o-CH}_3, -\text{-OCH}_2\text{CH=CH}_2, -\text{O(\text{phenyl), } -O(\text{chlorophenyl), } -\text{C(O)OCH}_3, and phenyl; } \\
\end{align*}
\]
(b) \(-(CH_2)_0-2(phenyl)\) wherein said phenyl is substituted with zero to 2 substituents independently selected from Cl, I, \textit{C}_1-\textit{C}_4 alkyl, \textit{C}_1-\textit{C}_4 alkoxy, \textit{-(CH_2)_0-C(0)OH}, \textit{-C(0)OCH}_3, \textit{-CH_2C(0)OCH}_2\textit{CH}_3, phenyl, chlorophenyl, fluorophenoxy, chlorophenoxy, phenyl acetic acid, and/or \textit{-\((CH_2)_2C(0)(piperidinyl)\)carboxylic acid}; or

\[
\begin{align*}
\text{CH}_3
\end{align*}
\]

or \(R_a\) and \(R_b\) together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring substituted with zero to 1 substituent selected from propyl and \(-\textit{CH}_2\textit{CH}_2\textit{(phenyl)}.\)

[0016] One embodiment provides compounds of Formula (I), pharmaceutically acceptable salts or prodrugs thereof, wherein \(W\) is:

\[
\begin{align*}
\text{N} & \\
\text{R}_1 & \text{N} & \\
\text{R}_2 & \text{N} \text{ or } \text{R}_3 & \\
\text{N} & \text{R}_4 & \\
\text{R}_5 & \text{N} & \\
\text{R}_6 & \\
\end{align*}
\]

wherein \(G\), \(Q\), \(R_{1a}\), \(R_{1b}\), \(R_2\), and \(R_3\) are defined in the first aspect.

[0017] One embodiment provides compounds of Formula (I), pharmaceutically acceptable salts or prodrugs thereof, wherein \(W\) is:

\[
\begin{align*}
\text{N} & \\
\text{R}_1 & \text{N} & \\
\text{R}_2 & \text{N} \text{ or } \text{R}_3 & \\
\text{N} & \text{R}_4 & \\
\text{R}_5 & \text{N} & \\
\text{R}_6 & \\
\end{align*}
\]

wherein \(G\), \(Q\), \(R_{1a}\), \(R_2\), \(R_{2b}\), \(R_{2c}\), and \(R_3\) are defined in the first aspect.

[0018] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

- 9 -
Compounds of this embodiment are represented by Formula (II):

or pharmaceutically acceptable salts or prodrugs thereof, wherein $R_1$, $R_{1a}$, $R_2$, $R_3$, $G$ and $Q$ are defined in the first aspect.

One embodiment provides compounds of Formula (II) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

$Q$ is

(a) naphthalenyl substituted with zero to 3 substituents independently selected from

- $\text{OH}$, $\text{-CN}$, $\text{Cl}$, $\text{Br}$, $\text{I}$, $\text{N0}_2$, $\text{-N(CH}_3)_2$, $\text{-C(0)OH}$, $\text{-C(0)OCH}_2\text{CH}_3$, $\text{-S(0)CH}_2\text{CH}_3$, $\text{C}_1$-$\text{C}_3$ alkoxy, $\text{-OCH(CH}_3)\text{CH}_2\text{N(CH}_3)_2$, $\text{-0(CH}_2)_3\text{N(CH}_3)_2$, $\text{-OCH}_2\text{(phenyl)}$, $\text{-OCH}_2\text{(benzoic acid)}$, $\text{-OCH}_2\text{(methyl benzoate)}$, $\text{-OCH}_2\text{(methylsulfonylphenyl)}$, $\text{-OCH}_2\text{(furanyl)}$, $\text{-OCH}_2\text{(N-methyl-1H-imidazolyl)}$, $\text{-0(CH}_2)_2\text{(N-methylpyrrolidinyl)}$, $\text{-0(CH}_2)_2\text{(morpholinyl)}$, $\text{-0(CH}_2)_2\text{(pyrrolidinyl)}$, $\text{-0(CH}_2)_2\text{(piperidinyl)}$, $\text{0(CH}_2)_2\text{(N-methyl piperazinyl)}$, $\text{-0(CH}_2)_2\text{(pyridinyl)}$, $\text{-0(CH}_2)_2\text{OH}$, $\text{-0(CH}_2)_2\text{(C}_1$-$\text{C}_3$ alkyl), $\text{-0(CH}_2)_2\text{OH}$, $\text{-0(CH}_2)_2\text{O}(\text{phenyl})$, $\text{-C(0)N(CH}_3)_2$, $\text{-C(0)(N-methylpiperazinyl)}$, $\text{-C(0)(morpholinyl)}$, and/or $\text{-NH(0)(dichlorophenyl)}$;

(b) isoquinolinyl substituted with $\text{-OCH}_2\text{CH}_2\text{(morpholinyl)}$, $\text{-SCH}_2\text{CH}_2\text{NH}_2$, or $\text{-SCH}_2\text{C(0)OH}$; or

(c) each substituted with zero to 3 substituents independently selected from $\text{Cl}$, $\text{Br}$, $\text{I}$, $\text{-CH}_2\text{CH}_3$, $\text{-CH}_2\text{(cyclohexyl)}$, $\text{-CH}_2\text{(phenyl)}$, $\text{-CH}_2\text{(difluorophenyl)}$, $\text{-CH}_2\text{H}_2\text{(dichlorophenyl)}$, $\text{-CH}_2\text{(chloropyridinyl)}$, $\text{-CH}_2\text{(1-methyl-1H-indolyl)}$, $\text{-CH}_2\text{H}_2\text{(morpholinyl)}$, $\text{-CH}_2\text{H}_2\text{(dichlorophenyl)}$, $\text{-CH}_2\text{H}_2\text{OH}$, $\text{-CH}_2\text{H}_2\text{O}(\text{phenyl})$, $\text{-C(0)N(CH}_3)_2$, $\text{-C(0)(N-methylpiperazinyl)}$, $\text{-C(0)(morpholinyl)}$, and/or $\text{-NH(0)(dichlorophenyl)}$;
-C(0)(cyclohexyl), -C(0)(dichlorophenyl), -C(0)(morpholinyl),
-C(0)((morpholinoethoxy)pyridinyl), -C(0)OCH₃, -C(0)CH₂(dichlorophenyl),
-C(0)(CH₂)₃(morpholinyl), -C(0)CH₂S(phenyl), -CH₂CH₂S(phenyl),
-CH=CHCH₃, -CH=CHCH₂CH₃, and/or morpholinyl;

G is a bicyclic heterocyclyl selected from:

![bicyclic heterocyclyl structures]

wherein said bicyclic heterocyclyl is substituted with zero to 2 substituents independently selected from: Br, -CH₃, -CF₃, -CH₂OH, -CH₂NH₂, -CH₂N(CH₃)(CH₂CH₂OH),
-CH₂N(CH₃)(CH₂CH₂OCH₃), -CH₂OCH₂CH₂N(CH₃)₂, -CH₂OH(CH₂)₂OH,
-CH₂(CH₂)₂phenyl, -CH₂O(CH₂)₂OCH₃, -CH₂N(CH₃)₂, -CH₂0(CH₂)₂OH,
-CH₂0(CH₂)₂0(phenyl), -CH₂0(CH₂)₃OCH₃, -CH₂(pyrrolidinyl), -CH₂(N-methyl piperazinyl),
-CH₂(N-(2-hydroxyethyl)piperazinyl), -CH₂(morpholinyl), -OCH₃,
-C(0)OH, -(CH₂)₃N(CH₃)₂, -N(CH₃)(CH₂CH₂OCH₃),

![additional structures]

R₁ is H, -CH₃, -CF₃, -(CH₂)₂OH, -CH₂C(0)OH, -(CH₂)₂OC(0)NH₂,
-CH₂C(0)NH(CH₂OH)₂, -(CH₂)₂OC(0)NHCH(CH₂OH)₂, -(CH₂)₂OC(0)NHCH₂CH₂OH,
-CH₂C(0)NHCH(CH₂OH)₃, or -(CH₂)₂OC(0)NHCH₂CH₂(N-methyl piperazinyl);

R₂ is H, CI, Br, C₁₋₃ hydroxalkyl, -(CH₂)₂C(0)OH, -(CH₂)₃N(CH₃)₂, or benzoic acid;

R₃ is -N(C₃₋₄alkyl)₂ or -C(0)NRₐRₐ;

Rₐ is H, C₁₋₄ alkyl, or C₃₋₄ fluoroalkyl; and

Rₐ is:

(a) CI₋₄ alkyl, C₃₋₄ fluoroalkyl, -(CH₂)₂C(0)OH, -(CH₂)₂C(0)O(butyl),
-CH₂(naphthalenyl), -(CH₂)₂C(0)NHCH(CH₂OH)₂, -(CH₂)₂C(0)NHC(CH₂OH)₃,
or -(CH₂)₂C(0)NHCH₂CH₂(N-methyl piperazinyl);
(b) 
\[-(\text{CH}_2)_3-2(\text{phenyl})\] wherein said phenyl is substituted with zero to 2 substituents independently selected from Cl, I, C$_{1-4}$ alkyl, C$_{1-4}$ alkoxy, -C(0)OH, -(CH$_2$)$_2$-C(0)OH, -C(0)OCH$_3$, -CH$_2$C(0)OCH$_2$CH$_3$, phenyl, chlorophenyl, fluorophenoxy, chlorophenoxy, phenyl acetic acid, and/or

\[-(\text{CH}_2)_2\text{C(0)(piperidinyl carboxylic acid)};\]
or

![Chemical structure](image)

[0020] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

\[W\] is . Compounds of this embodiment are represented by Formula (III):

![Chemical structure](image)

or pharmaceutically acceptable salts or prodrugs thereof, wherein $R_{1a}$, $R_{2a}$, $R_3$, $G$ and $Q$ are defined in the first aspect.

[0021] One embodiment provides compounds of Formula (III) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

$Q$ is ethyl, pentyl, -(CH$_2$)$_2$(trimethylsilyl), or naphthalenyl substituted zero to 2 substituents independently selected from Cl and/or Br;

$G$ is substituted with zero to 1 substituent selected from -CH$_2$OH, -CH$_2$N$_3$, and -CH$_2$NH$_2$;

$Ria$ is -CH$_3$ or butyl;
R2a is phenyl substituted with zero to 1 substituent selected from propyl, -OH,
\(-(\text{CH}_2)_2\text{O}H, \text{-OCH}_3, \text{-O(CH}_2)_3\text{CH}_3, \text{-O(CH}_2)_3\text{OH, -OCH}_2\text{CH(OH)CH}_2\text{OH,}
\text{-OCH}_2\text{CH=CH}_2, \text{-O(phenyl), -O(chlorophenyl), C(0)OCH}_3, \text{and phenyl}; and
\[0022\] One embodiment provides compounds of Formula (I) or pharmaceutically
acceptable salts or prodrugs thereof, wherein:

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{N} & \quad \text{R}_3
\end{align*}
\]
\[\text{W is } \text{R}_3\]. Compounds of this embodiment are represented by Formula (IV):

\[
\begin{align*}
\text{R}_1 & \quad \text{R}_2 \\
\text{N} & \quad \text{R}_3 \\
\text{O} & \quad \text{G}
\end{align*}
\]
\[\text{(IV)}\]

or pharmaceutically acceptable salts or prodrugs thereof, wherein \(\text{R}_1, \text{R}_2, \text{R}_3, \text{G}\) and \(\text{Q}\) are defined in the first aspect.

\[0023\] One embodiment provides compounds of Formula (IV) or pharmaceutically
acceptable salts or prodrugs thereof, wherein:
\(\text{Q}\) is naphthalenyl substituted with zero to 1 substituent selected from \(\text{Cl}\) and \(\text{I}\):

\[
\begin{align*}
\text{G is } & \quad \text{G}\text{ substituted with zero to 1 substituent selected from -CH}_2\text{OH and}
\text{-CH}_2\text{NH}_2;
\end{align*}
\]
\(\text{R}_1\) is \(\text{H, -CH}_3, -(\text{CH}_2)_2\text{OH, -(CH}_2)i_3\text{(phenyl), -(CH}_2)_2\text{,3(morpholinyl),}
-(\text{CH}_2)_n\text{(N-methyl piperazinyl), -(CH}_2)_2\text{OCH}_3, -(\text{CH}_2)_2\text{0(CH}_2)_2\text{OH,}
-(\text{CH}_2)_3\text{N(CH}_3)_2, -(\text{CH}_2)\text{C(0)OH, or -(CH}_2)\text{C(0)NHCH}_3;}
\[0024\] \(\text{R}_2\) is \(\text{H; and}
\]
\(\text{R}_3\) is \(\text{-C(0)N(n-butyl)}_2\).

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[0024] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

\[
\begin{array}{c}
\text{R}^3 \\
\text{R}^2
\end{array}
\]

W is . Compounds of this embodiment are represented by Formula (V):

\[
\begin{array}{c}
\text{R}^2 \\
\text{R}^3 \\
\text{G} \\
\text{Q}
\end{array}
\]

or pharmaceutically acceptable salts or prodrugs thereof, wherein R1b, R2, R3, G and Q are defined in the first aspect.

[0025] One embodiment provides compounds of Formula (V) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

Q is naphthalenyl substituted Cl or I;

\[
\begin{array}{c}
\text{G}
\end{array}
\]

R1b is -CH3;
R2 is H; and
R3 is -C(0)N(n-butyl) 2.

[0026] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

\[
\begin{array}{c}
\text{R}^2 \\
\text{R}^3
\end{array}
\]

W is . Compounds of this embodiment are represented by Formula (VI):
or pharmaceutically acceptable salts or prodrugs thereof, wherein \( R_{1a}, R_{2b}, R_{2c}, R_3, G \) and \( Q \) are defined in the first aspect.

[0027] One embodiment provides compounds of Formula (VI) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

- \( Q \) is:
  - (a) naphthalenyl substituted with zero to 1 substituent selected from CI; or
  - (b) substituted with zero to 1 substituent selected from \(-\text{CH}_2(\text{dichlorophenyl})\);

- \( G \) is

- \( R_{1a} \) is H or Br;
- \( R_{2b} \) is H;
- \( R_{2c} \) is H; and
- \( R_3 \) is \(-\text{N}(\text{n-butyl})_2\) or \(-\text{C}(0)\text{N}(\text{n-butyl})_2\).

[0028] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

\[
\begin{array}{c}
\text{R}_{2a} \\
\text{R}_{2b} \\
\text{R}_3
\end{array}
\]

\( W \) is \( R_3 \). Compounds of this embodiment are represented by Formula (VII):
or pharmaceutically acceptable salts or prodrugs thereof, wherein \( R_1, R_2, R_3, G \) and \( Q \) are defined in the first aspect.

One embodiment provides compounds of Formula (VII) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

- \( Q \) is:
  - (a) naphthalenyl substituted with zero to 1 substituent selected from Cl and I; or
  - (b) substituted with zero to 1 substituent selected from \(-\text{CH}_2\text{CH}_3\) and \(-\text{CH}_2(\text{dichlorophenyl})\);

- \( G \) is:
  - (a) \(-\text{N}(\text{CH}_3)_2\);
  - (b) substituted with zero to 1 substituent selected from \(-\text{CF}_3\), \(-\text{CH}_2\text{OH}, \) and \(-\text{CH}_2\text{NH}_2\); or
  - (c) 

\( R_i \) is H, Cl, Br, \(-\text{CH}_3\), or \(-\text{C}(\text{O})\text{OCH}_2\text{CH}_3\);

\( R_2 \) is H;

\( R_3 \) is \(-\text{NR}_a\text{R}_b\);

\( R_a \) is \( \text{C}_{1-5} \text{ alkyl} \); and

\( R_b \) is \( \text{C}_{1-5} \text{ alkyl, } -\text{CH}_2(\text{cyclopropyl}), \) or \(-\text{CH}_2(\text{dichlorophenyl})\);

or \( R_a \) and \( R_b \) together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring substituted with zero to 1 substituent selected from propyl and \(-\text{CH}_2\text{CH}_2(\text{phenyl})\).
[0030] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein:

W is:

\[
\begin{array}{c}
\text{N} \\
\text{R}_2 \\
\text{R}_1a \\
\text{R}_3 \\
\text{R}_1b \\
\text{R}_2b \\
\text{R}_3 \\
\text{R}_2c \\
\text{R}_3 \\
\end{array}
\]

Q is:

(a) naphthalenyl substituted with zero to 3 substituents independently selected from -OH, -CN, Cl, Br, I, -NO\(_2\), -N(CH\(_3\))\(_2\), -C(0)OH, -C(0)OCH\(_2\)CH\(_3\), -S(0)\(_2\)CH\(_2\)CH\(_3\), C\(_{1-3}\) alkoxy, -OCH(CH\(_3\))CH\(_2\)N(CH\(_3\))\(_2\), -O(CH\(_2\))\(_3\)N(CH\(_3\))\(_2\), -OCH\(_2\)(phenyl), -OCH\(_2\)(dichlorophenyl), -OCH\(_2\)(benzoic acid), -OCH\(_2\)(methyl benzoate), -OCH\(_2\)(methylsulfonylphenyl), -OCH\(_2\)(furanyl), -OCH\(_2\)(N-methyl-1H-imidazolyl), -OCH\(_2\)(N-methylpyrrolidinyl), -OCH\(_2\)(N-methylpiperazinyl), -OCH\(_2\)(pyrrolidinyl), -OCH\(_2\)(piperidinyl), -OCH\(_2\)(phenyl), -OCH\(_2\)(dichlorophenyl), -OCH\(_2\)(N-methylpyrrolidinyl), -OCH\(_2\)(morpholinyl), -OCH\(_2\)(dichlorophenyl), -OCH\(_2\)(morpholinyl), -OCH\(_2\)(N-methylpiperazinyl), -OCH\(_2\)(pyrrolidinyl), -OCH\(_2\)(piperidinyl), -OCH\(_2\)(phenyl), -OCH\(_2\)(N-methylpyrrolidinyl), -OCH\(_2\)(N-methylpiperazinyl), -OCH\(_2\)(morpholinyl), -NHC(0)(dichlorophenyl);  

(b) isoquinolinyl substituted with -OCH\(_2\)CH\(_2\)(morpholinyl), -SCH\(_2\)CH\(_2\)NH\(_2\), or -SCH\(_2\)C(0)OH, or  

\[
\begin{array}{c}
\text{N} \\
\text{R}_2 \\
\text{R}_1a \\
\text{R}_3 \\
\text{R}_1b \\
\text{R}_2b \\
\text{R}_3 \\
\text{R}_2c \\
\text{R}_3 \\
\end{array}
\]

(c) each substituted with zero to 3 substituents independently selected from Cl, Br, I, -CH\(_2\)CH\(_3\), -CH\(_2\)(cyclohexyl), -CH\(_2\)(phenyl), -CH\(_2\)(difluorophenyl), -CH\(_2\)(dichlorophenyl), -CH\(_2\)(chloropyridinyl), -CH\(_2\)(1-methyl-1H-indolyl), -(CH\(_2\))\(_i\), -(CH\(_2\))\(_j\)(morpholinyl), -(CH\(_2\))\(_i\), -(CH\(_2\))\(_j\)(morpholinyl), -C(0)(cyclohexyl), -C(0)(dichlorophenyl), -C(0)(morpholinyl), -C(0)((morpholinoethoxy)pyridinyl), -C(0)OCH\(_3\), -C(0)CH\(_2\)(dichlorophenyl), -C(0)(CH\(_2\))\(_i\) (morpholinyl), -C(0)CH\(_2\)S(phenyl), -CH\(_2\)CH\(_2\)S(phenyl), -CH=CHCH\(_3\), -CH=CHCH\(_2\)CH\(_3\), and/or morpholinyl;

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G is:
(a) \(-\text{N}(\text{CH}_3)_2\); or
(b) a bicyclic heterocyclyl selected from:

![Chemical structures]

wherein said bicyclic heterocyclyl is substituted with zero to 2 substituents independently selected from: Br, -CH_3, -CF_3, -CH_2OH, -CH_2NH_2, -CH_2N_3,
-CH_2N(CH_3)(CH_2CH_2OH), -CH_2N(CH_3)(CH_2CH_2OCH_3),
-CH_2OCH_2CH_2N(CH_3)_2, -CH_2OCH_2CH_2OH, -CH_2OCH_2CH_2O(phenyl),
-CH_2OCH_2CH_2CH_2OCH_3, -CH_2(pyrrolidinyl), -CH_2(N-methyl piperazinyl),
-CH_2(N-(2-hydroxyethyl)piperazinyl), -CH_2(morpholiny), -OCH_3, -C(0)OH,
-(CH_2)_1-\text{N}(\text{CH}_3)_2, -\text{N}(\text{CH}_3)(\text{CH}_2CH_2OCH_3),

\[\text{R}_1\] is H, Cl, Br, -CH_3, butyl, -CF_3, -(CH_2)_3OH, -CH_2CH_2OCH_3, -CH_2CH_2OCH_2CH_2OH,
-CH_2C(0)OH, -(CH_2)_2N(\text{CH}_3)_2, -CH_2C(0)\text{NHCH}_3, -(\text{CH}_2)_3\text{N}(\text{phenyl}),
-(\text{CH}_2)_2\text{morpholinyl}, -(\text{CH}_2)_2-N(\text{methyl piperazinyl}), -(\text{CH}_2)_2\text{OC}(0)\text{NH},
-CH_2\text{C(0)NHS}(0)\text{N}(\text{cyclopropyl}), -(\text{CH}_2)_2\text{OC}(0)\text{NH}(\text{N-methyl piperazinyl}), \text{or}
-(\text{CH}_2)_2\text{OC}(0)\text{NH}(\text{CH}_2)_2\text{OCH}_2\text{NH}(\text{N-methyl piperazinyl});

\[\text{Rib}\] is H, -CH_3, butyl, -CF_3, -(CH_2)_2OH, -CH_2CH_2OCH_3, -CH_2CH_2OCH_2CH_2OH,
-CH_2C(0)OH, -(CH_2)_{2,3}\text{N}(\text{CH}_3)_2, -CH_2C(0)\text{NHCH}_3, -(\text{CH}_2)_{2,3}\text{N}(\text{phenyl}),
-(\text{CH}_2)_{2,3}\text{morpholinyl}, -(\text{CH}_2)_{2,3}\text{N}(\text{methyl piperazinyl}), -(\text{CH}_2)_{2,3}\text{OC}(0)\text{NH},
-CH_2\text{C(0)NHS}(0)\text{N}(\text{cyclopropyl}), -(\text{CH}_2)_{2,3}\text{OC}(0)\text{NH}(\text{N-methyl piperazinyl}), \text{or}
-(\text{CH}_2)_{2,3}\text{OC}(0)\text{NH}(\text{CH}_2)_2\text{OCH}_2\text{NH}(\text{N-methyl piperazinyl});

\[\text{R}_2\] is:
(a) H, Cl, Br, C_1, 3 hydroxyalkyl, -(CH_2)_2C(0)OH, or -(CH_2)_3N(\text{CH}_3)_2; or
(b) phenyl substituted with zero to 1 substituent selected from propyl, -(CH₂)₁₋₂OH,
-0(CH₃)₀₋₂0H, -0(CH₂)₂OH, -OCH₂CH(OH)CH₂OH, -C(0)OH,
-OCH₂CH=CH₂, -O(phenyl), -O(chlorophenyl), -C(0)OCH₃, and phenyl;
one of R₂b and R₂c is H and the other of R₃¼ and R₃½ is R₂;
R₃ is -C(0)NR₃ aR₄ or -NR₃ aR₄; 
R₄ is H, C₁₋₅ alkyl, or C₁₋₄ fluoroalkyl; and
R₅ is
(a) C₁₋₅ alkyl, C₃₋₄ fluoroalkyl, -(CH₂)₂C(0)OH, -(CH₂)₂C(0)OH(butyl),
-CH₂(cyclopropyl), -CH₂(naphthalenyl), -(CH₂)₂C(0)NHCH(Ci₃ hydroxyalkyl)₂,
-(CH₂)₂C(0)NHCH(₂OH)₂, or -(CH₂)₂C(0)NHCH₂C₇H₃(N-methyl piperazinyl);
(b) -(CH₂)₀₋₂(phenyl) wherein said phenyl is substituted with zero to 2 substituents
independently selected from Cl, I, C₁₋₄ alkyl, C₁₋₄ alkoxy, -(CH₂)₀₋₂C(0)OH,
-C(0)OCH₃, -(CH₂)₂C(0)OCH₂CH₃, phenyl, chlorophenyl, fluorophenoxy,
chlorophenoxy, phenyl acetic acid, and/or -(CH₂)₂C(0)(piperidinyl carboxylic acid); or

or R₆ and R₇ together with the nitrogen atom to which they are attached, form a
pyrrolidinyl ring substituted with zero to 1 substituent selected from propyl and
-CH₂CH₂(phenyl).

[0031] One embodiment provides compounds of Formula (I) or pharmaceutically
acceptable salts or prodrugs thereof, wherein Q is naphthalenyl substituted with zero to 3
substituents independently selected from -OH, -CN, halo, -N₀₂, -C(0)OH, -C(0)(0)(Ci₃ alkylnal)
-0(0)₂(Ci₄ alkyl), Ci₄ alkoxy, -OCH(CH₃)₂CH₂N(Ci₄ alkyl)₂, -0(CH₂)₁₋₅R₅,
-0(CH₂)₃N(CH₃)₂, -0(CH₂)₃OH, -O(CH₂)₁₋₅O(Ci₄ alkyl), -0(CH₂)₁₋₅0(phenyl), -N(d- alkylnal)₂,
-0(0)N(Ci₃ alkylnal)₂, -C(0)R₆, and/or -NH(C(0)_R₇; wherein each R₇ is
independently C₁₋₆ cycloalkyl, phenyl, chlorophenyl, difluorophenyl, dichlorophenyl,
benzoic acid, methyl benzoate, methylsufonylphenyl, pyridinyl, chloropyridinyl, furanyl,
pyrrolidinyl, piperidinyl, morpholinyl, (morpholinoethoxy)pyrindinyl,
N-methylpyrrolidinyl, N-methylpiperazinyl, N-methyl- IH-imidazolyl,
1-methyl-1H-indolyl, and/or N-(2-hydroxyethyl)piperazinyl. For example, included in the present embodiment are compounds in which Q is naphthalenyl substituted with zero to 3 substituents independently selected from -OH, -CN, Cl, Br, I, -NO2, -N(CH3)2, -C(0)OH, -C(0)OCH2CH3, -S(0)2CH2CH3, Cl, alk oxy, -OCH(CH3)CH2N(CH3)2,

-0(CH2)2N(CH3)2, -OCH2(phenyl), -OCH2(dichlorophenyl), -OCH2(benzoic acid), -OCH2(methyl benzoate), -OCH2(methylsulfonylphenyl), -OCH2(furanyl), -OCH3(N-methyl-1H-imidazolyl), -0(CH2)2(N-methylpyrrolidinyl), -0(CH2)3(morpholinyl), -0(CH2)3(pyrrolidinyl), -0(CH2)3(piperidinyl), 0(CH2)2(N-methylpipеразинyl), -0(CH2)2(pyridinyl), -OCH2CH2OH, -OCH2CH20(C1-2 alkyl), -OCH2CH20(phenyl), -C(0)N(CH3)2, -C(0)(N-methylpipеразинyl), -C(0)(morpholinyl), and/or -NHC(0)(dichlorophenyl).

[0032] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein Q is isoquinolinyl substituted with

-OCH2CH2(morpholinyl), -SCH2C(0)OH.

[0033] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein Q is:

![Chemical structures]

each substituted with zero to 3 substituents independently selected from halo, C1-4 alkyl, C(0)(d_4 alkyl), -C(0)R, -C(0)(CH2)iR, -C(0)(d_4 alkyl), -(CH2)iR,

-C(0)(CH2)1-3S(phenyl), -(CH2)i3S(phenyl), C2-4 alkenyl, and/or morpholinyl. For example, included in the present embodiment are compounds in which Q is:

![Chemical structures]

each substituted with zero to 3 substituents independently selected from Cl, Br, I, -CH2CH3, -CH2(cyclohexyl), -CH2(phenyl), -CH2(difluorophenyl), -(CH2)i2(dichlorophenyl), -CH2(chloropyridinyl), -CH2(1-methyl-1H-indolyl), -(CH2)i2(morpholinyl), -C(0)(cyclohexyl), -C(0)(dichlorophenyl), -C(0)(morpholinyl), -C(0)((morpholinoethoxy)pyridinyl), -C(0)OCH3, -C(0)CH2(dichlorophenyl), -20-
-C(0)(CH$_2$)$_{1-3}$(morpholinyl), -C(0)CH$_2$S(phenyl), -CH$_2$CH$_2$S(phenyl), -CH=CHCH$_3$, -CH=CHCH$_2$CH$_3$, and/or morpholinyl.

[0034] One embodiment provides compounds of Formula (III) or pharmaceutically acceptable salts or prodrugs thereof, wherein Q is Ci.6 alkyl or -(CH$_2$)$_i$-3(trimethylsilyl), with the proviso that W is . Included in this embodiment are compounds in which Q is ethyl, pentyl, or -CH$_2$CH$_2$-(trimethylsilyl)).

[0035] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein G is -N(Ci.4 alkyl)$_2$. Included in this embodiment are compounds in which G is -N(CH$_3$)$_2$. Also include in this embodiment are compounds in which Q is naphthalenyl substituted with zero to 1 substituent selected from Cl or I; substituted with zero to 1 substituent selected from -CF$_3$, -CH$_2$OH, or -CH$_2$NH$_2$; or

[0036] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein G is a bicyclic heterocyclyl selected from: wherein said bicyclic heterocyclyl is substituted with zero to 3 substituents independently selected from: halo, Ci.4 alkyl, Ci.4 fluoroalkyl, Ci.4 hydroxyalkyl, Ci.4 alkoxy, -(CH$_2$)$_{2,3}$C(0)OH, -(CH$_2$)$_{1,3}$NH$_2$, -(CH$_2$)$_{1,3}$N$_3$, -(CH$_2$)$_{1,3}$N(CH$_3$)(Ci.4 hydroxyalkyl), -(CH$_2$)$_{1,3}$N(CH$_3$)$_2$, -(CH$_2$)$_{1,3}$O(CH$_2$)$_{1,3}$OCH$_3$, -(CH$_2$)$_{1,3}$O(CH$_2$)$_{1,3}$N(Ci.4 alkyl)$_2$, -(CH$_2$)$_{1,3}$O(CH$_2$)$_{1,3}$OH, -(CH$_2$)$_{1,3}$O(CH$_2$)$_{1,3}$N(Ci.4 alkyl), -(CH$_2$)$_{1,3}$O(CH$_2$)$_{1,3}$O(phenyl), -(CH$_2$)$_{1,3}$O(CH$_2$)$_{1,3}$CH$_3$, -(CH$_2$)$_{1,3}$Rx, -(CH$_2$)$_{0,3}$N(CH$_3$)$_2$, -(CH$_2$)$_{1,3}$O(N(Ci.4 alkyl),
[0037] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein G is a bicyclic heterocyclyl selected from:

wherein said bicyclic heterocyclyl is substituted with zero to 2 substituents independently selected from: Br, -CH₃, -CF₃, -CH₂OH, -CH₂NH₂, -CH₂N(CH₃)(CH₂CH₂OH), -CH₂N(CH₃)(CH₂CH₂OCH₃), -CH₂OCH₂CH₂N(CH₃)₂, -CH₂OCH₂CH₂OH, -CH₂OCH₂CH₂0(phenyl), -CH₂OCH₂CH₂CH₂OCH₃, -CH₂(pyrrolidinyl), -CH₂(N-methyl piperazinyl), -CH₂(N-(2-hydroxyethyl)piperazinyl), -CH₂(morpholinyl), -OCH₃, -C(0)OH, -(CH₂)₂-iN(CH₃)₂, -(N(CH₃)(CH₂CH₂OCH₃),

[0038] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein Rₗ is H, Cl, Br, -CH₃, butyl, -CF₃, -(CH₂)₂OH, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OH, -CH₂C(0)(OH), -(CH₂)₃N(CH₃)₂, -CH₂C(0)NHCH₃, -(CH₂)₁₋₃(phenyl), -(CH₂)₂₋₃(morpholinyl), -(CH₂)₂₋₃(N-methyl piperazinyl), -(CH₂)₂₋₃OC(0)NH₂, -CH₂C(0)NH(0)₂(cyclopropyl), -(CH₂)₂₋₃OC(0)NH(0)₂(N-methyl piperazinyl), or -(CH₂)₂₋₃OC(0)NHCH₂(N-methyl piperazinyl). Included in this embodiment are compounds in which Rₗ is H, -CH₃, butyl, -CF₃, -(CH₂)₂₋₃OH, -CH₂C(0)OH, -(CH₂)₂₋₃OC(0)NH₂, -CH₂C(0)NH(0)₂(cyclopropyl), -(CH₂)₂₋₃OC(0)NH(0)₂(N-methyl piperazinyl), or -(CH₂)₂₋₃OC(0)NHCH₂(N-methyl piperazinyl). Also included in this embodiment are compounds in which Ri is H, -CH₃, -(CH₂)₂₋₃OH, -(CH₂)₁₋₃(phenyl), -(CH₂)₂₋₃(morpholinyl), -(CH₂)₂₋₃(N-methyl piperazinyl),
-\((\text{CH}_2)_2\text{OCH}_3\), -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OH}, -(\text{CH}_2)_3\text{N}(\text{CH}_3)_2, -\text{CH}_2\text{C}(0)\text{OH}, or \\
-\text{CH}_2\text{C}(0)\text{NHCH}_3.

[0039] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein \(\text{R}_i\) is \(\text{H}, -\text{CH}_3, -\text{CF}_3, -(\text{CH}_2)_2\text{OH},
\text{CH}_2\text{H}_2\text{OCH}_3, -\text{CH}_2\text{H}_2\text{OCH}_2\text{CH}_2\text{OH}, -\text{CH}_2\text{C}(0)\text{OH}, -(\text{CH}_2)_3\text{N}(\text{CH}_3)_2,
-\text{CH}_2\text{C}(0)\text{NHCH}_3, -(\text{CH}_2)_2\text{O}(\text{phenyl}), -(\text{CH}_2)_2\text{N}(\text{morpholinyl}), -(\text{CH}_2)_2\text{N}(N\text{-methyl piperazinyl}), -(\text{CH}_2)_2\text{OC}(0)\text{NH}_2, -\text{CH}_2\text{C}(0)\text{NHS}(0)_2\text{cyclopropyl),
-(\text{CH}_2)_2\text{OC}(0)\text{N}(N\text{-methyl piperazinyl}), \text{or}-(\text{CH}_2)_2\text{OC}(0)\text{NH}(\text{CH}_2)_2(N\text{-methyl piperazinyl}).

Included in this embodiment are compounds in which \(\text{R}_i\) is \(\text{H}, -\text{CH}_3, \text{butyl}, -\text{CF}_3,
\text{or}-(\text{CH}_2)_2\text{OH}, -\text{CH}_2\text{C}(0)\text{OH}, -(\text{CH}_2)_2\text{OC}(0)\text{NH}_2, -\text{CH}_2\text{C}(0)\text{NHS}(0)_2\text{cyclopropyl),
-(\text{CH}_2)_2\text{OC}(0)\text{N}(N\text{-methyl piperazinyl}), \text{or}-(\text{CH}_2)_2\text{OC}(0)\text{NHCH}_2\text{CH}_2\text{N}(N\text{-methyl piperazinyl}).

Also included in this embodiment are compounds in which \(\text{R}_i\) is \(\text{H}, -\text{CH}_3,
-(\text{CH}_2)_2\text{OH}, -(\text{CH}_2)_2\text{O}(\text{phenyl}), -(\text{CH}_2)_2\text{N}(\text{morpholinyl}), -(\text{CH}_2)_2\text{N}(N\text{-methyl piperazinyl}),
-(\text{CH}_2)_2\text{OCH}_3, -(\text{CH}_2)_2\text{O}(\text{CH}_2)_2\text{OH}, -(\text{CH}_2)_3\text{N}(\text{CH}_3)_2, -\text{CH}_2\text{C}(0)\text{OH}, \text{or}
-\text{CH}_2\text{C}(0)\text{NHCH}_3.

[0040] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein \(\text{R}_2\) is \(\text{H}, \text{Cl}, \text{Br}, \text{C}_{i-3}\text{hydroxyalkyl,}
-(\text{CH}_2)_2\text{C}(0)\text{OH}, \text{or}-(\text{CH}_2)_2\text{N}(\text{CH}_3)_2\). Included in this embodiment are compounds in which \(\text{R}_2\) is \(\text{H}.

[0041] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein \(\text{R}_2\) is phenyl substituted with zero to 1 substituent selected from propyl, -(\text{CH}_2)_2\text{OH}, -(\text{CH}_2)_2\text{O}(\text{CH}_3)_2, -(\text{CH}_2)_2\text{O}\text{OH},
-\text{OCH}_2\text{CH(OH)}\text{CH}_2\text{OH}, -(\text{CH}_2)_2\text{O}(\text{phenyl), -(O(\text{chlorophenyl),}
-\text{C}(0)\text{OCH}_3, \text{or} phenyl. Included in this embodiment are compounds in which \(\text{R}_2\) is \(\text{phenyl substituted with zero to 1 substituent selected from propyl, -OH, -(CH}_2)_2\text{OH,}
-\text{OCH}_3, -(\text{CH}_2)_2\text{O}(\text{CH}_3)_2, -(\text{CH}_2)_2\text{O}\text{OH), -OCH}_2\text{CH(OH)}\text{CH}_2\text{OH, -OCH}_2\text{CH}=\text{CH}_2,
-\text{O(phenyl), -(O(\text{chlorophenyl), C(0)OCH}_3, and phenyl.

[0042] One embodiment provides compounds of Formula (I) or pharmaceutically acceptable salts or prodrugs thereof, wherein \(\text{R}_3\) is \(-\text{CH}_2\text{OH, -C(0)OH, -C(0)OCH}_2\text{CH}_3,
-\text{C(0)NR}_\text{Rb}, \text{or} -\text{NR}_\text{Rb}. Included in this embodiment are compounds in which \(\text{R}_3\) is \(-\text{N(C}_{3,4}\text{alkyl), or -C(0)NR}_\text{Rb, such as, for example, R}_3\) is \(-\text{C(0)N(n-butyl)2 or}
-\text{C(0)NR}_\text{Rb.}
-C(0)N(n-butyl)₂. Also included in this embodiment are compounds in which R₃ is
-CH₂OH, -C(0)OH, or -C(0)OCH₂CH₃.

[0043] One embodiment provides compounds of Formula (I) or pharmaceutically
acceptable salts or prodrugs thereof, wherein Rₐ is H, C₁₋₅ alkyl, or C₁₋₄ fluoroalkyl.
Included in this embodiment are compounds in which Rₐ is H, C₁₋₄ alkyl, or C₁₋₄ fluoroalkyl.

[0044] One embodiment provides compounds of Formula (I) or pharmaceutically
acceptable salts or prodrugs thereof, wherein R₁ is C₁₋₅ alkyl, C₃₋₄ fluoroalkyl,
-(CH₂)₂C(0)OH, -(CH₂)₂C(0)(butyl), -CH₂(cyclopropyl), -CH₂(naphthalenyl),
-(CH₂)₂C(0)NHCH₂ hydroxyalkyl)₂, -(CH₂)₂C(0)NHCH₂(N-methyl piperazinyl). Included in this embodiment are
compounds in which R₁ is C₁₋₅ alkyl, C₃₋₄ fluoroalkyl, -(CH₂)₂C(0)OH,
-(CH₂)₂C(0)(butyl), -CH₂(naphthalenyl), -(CH₂)₂C(0)NHCH₂(N-methyl piperazinyl). Also
included in this embodiment are compounds in which R₆ is C₁₋₅ alkyl, -CH₂(cyclopropyl),
or -CH₂(dichlorophenyl).

[0045] One embodiment provides compounds of Formula (I) or pharmaceutically
acceptable salts or prodrugs thereof, wherein R₆ is -(CH₂)₀₋₂(phenyl) wherein said phenyl
is substituted with zero to 2 substituents independently selected from CI, I, C₁₋₄ alkyl, C₁₋₄ alkoxy,
-C(0)OCH₃, -CH₂C(0)OCH₂CH₃, phenyl, chlorophenol, fluoroophenoxy, chloroophenoxy, phenyl acetic acid, and/or -(CH₂)₂C(0)(piperidinyl
carboxylic acid). Included in this embodiment are compounds in which R₆ is
-(CH₂)₀₋₂(phenyl) wherein said phenyl is substituted with zero to 2 substituents
independently selected from CI, I, C₁₋₄ alkyl, C₁₋₄ alkoxy, -C(0)OH, -(CH₂)₀₋₂C(0)OH,
-C(0)OCH₃, -CH₂C(0)OCH₂CH₃, phenyl, chlorophenol, fluoroophenoxy, chloroophenoxy,
phenyl acetic acid, and/or -(CH₂)₂C(0)(piperidinyl carboxylic acid).

[0046] One embodiment provides compounds of Formula (I) or pharmaceutically
acceptable salts or prodrugs thereof, wherein R₆ is:

[0047] One embodiment provides compounds of Formula (I) or pharmaceutically
acceptable salts or prodrugs thereof, wherein Rₐ and R₆ together with the nitrogen atom to
which they are attached, form a pyrrolidinyl ring substituted with zero to 1 substituent selected from propyl or -CH₂CH₂(phenyl).

[0048] One embodiment provides compounds of Formula (I), pharmaceutically acceptable salts or prodrugs thereof, wherein said compound is selected from N,N-

Dibutyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (1); N,N-dibutyl-4-chloro-1-(4-(5-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (2); N,N-dibutyl-4-chloro-1-(4-(6-(dimethylamino)naphthalen-2-ylsulfonylcarbamoyl)-2-

H-pyrazole-3-carboxamide (3); N,N-dibutyl-4-chloro-1-(4-(5-(dimethylamino)naphthalen-1-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-

1H-pyrazole-3-carboxamide (4); N,N-dibutyl-4-chloro-1-(4-(8-chloronaphthalen-2-

ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-

1H-pyrazole-3-carboxamide (5); N,N-dibutyl-4-chloro-1-(4-(6-chloronaphthalen-2-

ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-

1H-pyrazole-3-carboxamide (6); N,N-dibutyl-4-chloro-1-(4-(8-iodonaphthalen-2-

ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-

1H-pyrazole-3-carboxamide (7); N,N-dibutyl-4-chloro-1-(4-(6-cyanonaphthalen-2-

ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-

1H-pyrazole-3-carboxamide (8); ethyl 7-[(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-

1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl]-1-

naphthoate (9); N,N-dibutyl-4-chloro-1-(4-(7-chloronaphthalen-2-ylsulfonylcarbamoyl)-

2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-

carboxamide (10); N,N-dibutyl-4-chloro-1-(4-(7-iodonaphthalen-2-ylsulfonylcarbamoyl)-

2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-
carboxamide (11); N,N-dibutyl-4-chloro-5-methyl-1-(4-(5-nitronaphthalen-1-

ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-

3-carboxamide (12); N,N-dibutyl-4-chloro-5-methyl-1-(4-(5-nitronaphthalen-2-

ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-

1H-pyrazole-3-carboxamide (13); N,N-dibutyl-4-chloro-1-(4-(6-chloronaphthalen-2-

ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-
1H-pyrazole-3-carboxamide (14); N,N-dibutyl-4-chloro-1-(4-(7-cyanonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (15); ethyl 7-((N-(4-(4-chloro-3-(dibutylcarbamoyl))-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carboxamido)naphthalen-2-ylsulfonylcarbamoyl)-2-naphthoate (16); ethyl 7-((N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carboxamido)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (18); N,N-dibutyl-4-chloro-1-(4-(8-(3,4-dichlorobenzamido)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-1-(4-(7-(benzyloxy)naphthalen-2-ylsulfonylcarbamoyl)-2-((1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (24); N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(3,4-dichlorobenzyloxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (25); methyl 4-((7-(N-(4-(4-chloro-3-(dibutylcarbamoyl))-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carboxamido)naphthalen-1-yl)oxy)methyl)benzoate (26); N,N-dibutyl-4-chloro-1-(4-(7-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (27); N,N-dibutyl-4-chloro-1-(4-(7-(2-phenoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (28); N,N-dibutyl-4-chloro-1-(4-(7-(tetrahydrofuran-2-yl)methoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (29); N,N-dibutyl-4-chloro-1-(4-(7-isopropoxynaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (30); N,N-dibutyl-4-chloro-1-(4-(7-(2-phenoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (31); N,N-dibutyl-4-chloro-1-(4-(7-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (32); N,N-dibutyl-4-chloro-1-(4-(7-(2-phenoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (33); N,N-dibutyl-4-chloro-1-(4-(7-(2-phenoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (34); N,N-dibutyl-4-chloro-1-(4-(7-(2-phenoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (35); N,N-dibutyl-4-chloro-1-(4-(7-(2-phenoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)
ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (29); N,N-dibutyl-4-chloro-1-(4-(7-(2-ethoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (30); 1-(4-(8-bromo-5-(dimethylamino)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (31); N,N-dibutyl-4-chloro-5-methyl-1-(4-(8-(3-morpholinopropoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (32); N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(3-(4-methylpiperazin-1-yl)propoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (33); N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(3-(3-morpholinopropoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (34); N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(3-(4-(methylpiperazin-1-yl)propoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (35); N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(1-(dimethylamino)propan-2-yloxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (36); N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(1-(dimethylamino)propan-2-yloxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (37); N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(2-(1-methylpyrrolidin-2-yl)methoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (38); N,N-dibutyl-4-chloro-1-(4-(7-(1-(dimethylamino)propan-2-yloxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (39); N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(3-(pyridin-4-yl)propoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (40); N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(3-(piperidin-1-yl)propoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (41); N,N-Dibutyl-4-chloro-5-methyl-1-(4-(7-(3-(pyridin-4-yl)propoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (42); 1-(4-(8-
bromo-5-chloronaphthalen-2-ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl) -N,N- dibutyl-4-chloro-5-methyl-l H -pyrazole-3-carboxamide (43); N,N-
dibutyl-4-chloro-l-(4-(5,8-dichloronaphthalen-2-ylsulfonfylcarbamoyl)-2-l (1, 2,3,4-
tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl- 1H-pyrazole-3-carboxamide (44); 7-
(N-(4-(4-Chloro-3-(dibutylcarbamoyl))-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-l-naphthoic acid (45); N,N-
Dibutyl-4-chloro-5-methyl-l-(4-(7-(4-methylpiperazine-1-carbonyl)naphthalen-2-
-ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)- 1H-pyrazole-
3-carboxamide (46); N,N-Dibutyl-4-chloro-5-methyl-l-(4-(7-(morpholine-4-
carbonyl)naphthalen-2-ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)- 
1H-pyrazole-3-carboxamide (47); N,N-Dibutyl-4-chloro-l-(4-(7-(dimethylcarbamoyl)naphthalen-2-
-ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-l H-
pyrazole-3-carboxamide (48); 4-(7-(N-(4-(4-Chloro-3-(dibutylcarbamoyl))-5-methyl-
1H-pyrazol-1-yl)-3-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)naphthalen-1-
yloxy)methyl)benzoic acid (49); N,N-Dibutyl-4-chloro-l-(4-(7-(2-
hydroxyethoxy)naphthalen-2-ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl)-5-methyl- 1H-pyrazole-3-carboxamide (50); N,N-Dibutyl-4-chloro- 
1-(4-(7-hydroxynaphthalen-2-ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl)-5-methyl-l H-pyrazole-3-carboxamide (51); N,N-Dibutyl-4-chloro-l-(4-
(indolin-5-ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-
methyl-1H-pyrazole-3-carboxamide (52); N,N-dibutyl-4-chloro-1-(4-(1-ethylindolin-5-
ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-
1H-pyrazole-3-carboxamide (53); 1-(4-(1H-indol-5-ylsulfonfylcarbamoyl)-2-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-l H-pyrazole-
3-carboxamide (54); N,N-dibutyl-4-chloro-l-(4-(1-(cyclohexanecarbonyl)indolin-5-
ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-
1H-pyrazole-3-carboxamide (55); N,N-dibutyl-4-chloro-1-(4-(1-ethyl-1 H-indol-5-
ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-
1H-pyrazole-3-carboxamide (56); N,N-dibutyl-4-chloro-l-(4-(1-
(cyclohexylmethyl)indolin-5-ylsulfonfylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl)-5-methyl-l H-pyrazole-3-carboxamide (57); N,N-dibutyl-4-chloro-l-(4-
(1-(3,4-dichlorobenzoyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (58);
N,N-dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-(5-methyl-1H-pyrazole-3-carboxamide (59);
1-(4-(1-acetylindolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (60);
1-(4-(1-benzylindolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (61);
N,N-dibutyl-4-chloro-1-(4-(1-(3,4-difluorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (62);
N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(3,4-dichlorobenzyl)-1H-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (63);
N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(3,4-dichlorobenzyl)-1H-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (64);
N,N-dibutyl-4-chloro-1-(4-(1-(1-methyl-1H-indol-6-yl)methyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (65);
N,N-dibutyl-4-chloro-1-(4-(1-(6-chloropyridin-2-yl)methyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (66);
N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(2-(phenylthio)acetyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (67);
N,N-dibutyl-4-chloro-1-(4-(1-(2-(phenylthio)ethyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (68);
N,N-dibutyl-4-chloro-1-(4-(1-(6-chloropyridin-2-yl)methyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (69);
N,N-dibutyl-4-chloro-1-(4-(1-(1-methyl-1H-indol-6-yl)methyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (70);
N,N-dibutyl-4-chloro-1-(4-(1-(1-methyl-1H-indol-6-yl)methyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (71);
4-chloro-5-methyl-1H-pyrazole-3-carboxamide (72); methyl 5-(N-(4-(4-chloro-3-(dibutylcarbamoyl))-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoylsulfamoyl)-1-(3,4-dichlorobenzyl)indoline-2-carboxylate (73); N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(morpholine-4-carbonyl)indolin-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (74); N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(2-morpholinoacetyl)indolin-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (75); 1-(4-(7-bromo-1-ethylindolin-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (76); N,N-dibutyl-4-chloro-5-methyl-1-(4-((2-(2-morpholinoethoxy)pyridin-3-yl)methyl)indolin-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (77); N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(2-(2-morpholinoethoxy)pyridin-3-yl)methyl)indolin-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (78); 1-(4-(3-bromo-1H-indol-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (79); N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(2-morpholinopropanoyl)indolin-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (80); N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(3-chloro-1-ethyl-1H-indol-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (81); N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(3-morpholinopropyl)-1H-indol-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (82); N,N-dibutyl-4-chloro-1-(4-(3-chloro-1-ethyl-1H-indol-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (83); N,N-dibutyl-4-chloro-1-(4-(1-ethyl-3-iodo-1H-indol-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (84); N,N-dibutyl-4-chloro-1-(4-(3,7-dibromo-1-ethyl-1H-indol-5-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (85); N,N-Dibutyl-4-chloro-1-(4-indolin-6-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (86); (E)-1-(4-(5-(But-1-enyl)-1-ethylindolin-6-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (87);
(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl-\(\text{-N,N-dibutyl-4-chloro-5-methyl-lH-pyrazole-3-carboxamide}\) (87); \(\text{N,N-Dibutyl-4-chloro-l-(4-(1-ethyl-5-morpholinooindolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-lH-pyrazole-3-carboxamide}\) (88); \((E)-\text{N,N-Dibutyl-4-chloro-1-(4-(1-ethyl-5-(prop-1-enyl)indolin-6-ylsulfonycarbamoyl)phenyl)-5-methyl-lH-pyrazole-3-carboxamide}\) (89); \(\text{N,N-Dibutyl-4-chloro-l-(4-\(\text{-(3,4-dichlorobenzyl)indolin-6-ylsulfonylcarbamoyl}\)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-lH-pyrazole-3-carboxamide}\) (90); \(\text{N,N-Dibutyl-4-chloro-1-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonycarbamoyl)phenyl)-5-methyl-lH-pyrazole-3-carboxamide}\) (91); \(\text{1-(2-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonycarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-lH-pyrazole-3-carboxamide}\) (92); \((3R)-2-(2-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-lH-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonycarbamoyl)benzoyl)1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid\) (93); \((35)-2-(2-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-lH-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonycarbamoyl)phenyl)-\text{-N,N-dibutyl-4-chloro-5-methyl-lH-pyrazole-3-carboxamide}\) (94); \(\text{N,N-Dibutyl-4-chloro-l-(2-((R)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonycarbamoyl)phenyl)-5-methyl-lH-pyrazole-3-carboxamide}\) (95); \(\text{N,N-Dibutyl-4-chloro-l-(2-(3,4-dihydro-2H-benzo[e][1,3]oxazine-3-carbonyl)-4-(naphthalen-2-ylsulfonycarbamoyl)phenyl)-5-methyl-lH-pyrazole-3-carboxamide}\) (96); \(\text{N,N-Dibutyl-4-chloro-1-(2-(4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonycarbamoyl)phenyl)-1H-pyrazole-3-carboxamide}\) (97); \(\text{N,N-Dibutyl-4-chloro-1-(2-(7-Bromo-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonycarbamoyl)phenyl)-\text{-N,N-dibutyl-4-chloro-5-methyl-lH-pyrazole-3-carboxamide}\) (98); \(\text{l-(2-(7-Bromo-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonycarbamoyl)phenyl)-\text{-N,N-dibutyl-4-chloro-5-methyl-lH-pyrazole-3-carboxamide}\) (99); \(2-(2-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-lH-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonycarbamoyl)benzoyl)1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid\) (100); \(\text{N,N-Dibutyl-4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonycarbamoyl)-2-(7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide}\) (101); \(\text{l-(2-(3-Bromo-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)phenyl)-\text{-N,N-dibutyl-4-chloro-5-methyl-lH-pyrazole-3-carboxamide}\) (102).
(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (102); N,N-Dibutyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-((1,2,3,4-tetrahydroquinazoline-3-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (103); N,N-Dibutyl-4-chloro-1-(2-(1,1-dioxido-3,4-dihydro-2H-benzo[e][1,3]thiazine-3-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (104); N,N-Dibutyl-4-chloro-1-(2-((5)-3-((3-methoxypropoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (105); N,N-Dibutyl-4-chloro-5-methyl-1-(2-((5)-3-((1-methylpiperidin-4-ylamino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (106); N,N-Dibutyl-4-chloro-5-methyl-1-(2-((5)-3-((3-(dimethylamino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (107); N,N-Dibutyl-4-chloro-5-methyl-1-(2-((5)-3-((4-methylpiperazin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (108); N,N-Dibutyl-4-chloro-5-methyl-1-(2-((5)-3-((piperidin-4-ylamino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (109); N,N-Dibutyl-4-chloro-1-(2-((5)-3-((4-hydroxypiperidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-pyrazole-3-carboxamide (110); N,N-Dibutyl-4-chloro-5-methyl-1-(2-((5)-3-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-pyrazole-3-carboxamide (111); N,N-Dibutyl-4-chloro-5-methyl-1-(2-((5)-3-((4-methylpiperazin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-pyrazole-3-carboxamide (112); N,N-Dibutyl-4-chloro-1-(2-((5)-3-((2-methoxyethyl)methylamino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (113); N,N-Dibutyl-4-chloro-1-(2-((5)-3-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (114); N,N-Dibutyl-4-chloro-1-(2-((5)-3-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (115).
methyl-1\textit{H}-pyrazole-3-carboxamide (115); \textit{N,N}-dibutyl-4-chloro-1-(2-((5)-3-((2-(dimethylamino)ethoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1\textit{H}-pyrazole-3-carboxamide (116); 1-(2-((5)-3-((2-(benzyloxy)ethoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1\textit{H}-pyrazole-3-carboxamide (117); \textit{N,N}-dibutyl-4-chloro-5-methyl-1\textit{H}-pyrazole-3-carboxamide (118); \textit{N,N}-dibutyl-4-chloro-5-methyl-1-(2-((5)-3-((2-(benzyloxy)ethoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1\textit{H}-pyrazole-3-carboxamide (119); \textit{N,N}-dibutyl-4-chloro-5-methyl-1-(2-((5)-3-((2-hydroxyethoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1\textit{H}-pyrazole-3-carboxamide (120); (Z)-\textit{N,N}-dibutyl-4-chloro-1-(2-((3-methoxyethyl)methylamino)-2,5-dihydro-1\textit{H}-benzo[l,3]diazepine-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1\textit{H}-pyrazole-3-carboxamide (121); 3-(4-((\textit{N}-Butyl-4-chloro-5-methyl-1-(4-naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1\textit{H}-pyrazole-3-carboxamido)phenyl)propanoic acid (122); \textit{N}-Butyl-4-chloro-\textit{N}-(3,4-dichlorobenzyl)-5-methyl-1-(4-naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1\textit{H}-pyrazole-3-carboxamide (123); 1-(3-(4-(\textit{N}-Butyl-4-chloro-5-methyl-1-(4-naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1\textit{H}-pyrazole-3-carboxamido)phenyl)propanoyl)piperidine-4-carboxylic acid (124); 4-Chloro-\textit{N}-(3,4-dichlorobenzyl)-\textit{N},5-dimethyl-1-(4-naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1\textit{H}-pyrazole-3-carboxamide (125); \textit{N}-butyl-4-chloro-\textit{N}-(3,4-dichlorobenzyl)-5-methyl-1-(4-naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1\textit{H}-pyrazole-3-carboxamide (126); \textit{N}-butyl-4-chloro-\textit{N}-(3,4-dichlorophenethyl)-5-methyl-1-(4-naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1\textit{H}-pyrazole-3-carboxamide (127); \textit{N}-butyl-4-chloro-5-methyl-1-(4-naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1\textit{H}-pyrazole-3-carboxamide (128); 4-chloro-5-methyl-1-(4-naphthalen-2-ylsulfonylcarbamoyl)-2-
(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-bis(4,4,4-trifluorobutyl)-1H-pyrazole-3-carboxamide (129); 4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-bis(3,3,3-trifluoropropyl)-1H-pyrazole-3-carboxamide (130); N-butyl-4-chloro-N-(3-isopropoxybenzyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (131); N-butyl-4-chloro-N-(3-(4-chlorophenoxy)benzyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (132); N-(4-butoxybenzyl)-N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (133); N-butyl-4-chloro-N-(3-(4-chlorophenoxy)phenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (134); N-butyl-4-chloro-N-(3-chlorobenzyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (135); N-butyl-4-chloro-N-(4-chlorobenzyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (136); N-butyl-4-chloro-N-(4-(4-fluorophenoxy)phenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (137); N-butyl-4-chloro-N-(4-(4-chlorophenoxy)phenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (138); N-butyl-4-chloro-N-(3,4-dimethoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (139); N-butyl-4-chloro-N-(3,4-dimethoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (140); N-butyl-4-chloro-N-(4-isopropoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (141); N-butyl-4-chloro-N-(3-chloro-4-methylphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (142); N-(biphenyl-4-yl)-N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (143).
carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (143); N-butyl-4-chloro-N-(4-methoxyphenyl)-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (144); N-butyl-4-chloro-N-(3-methoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (145); N-butyl-N-(3-tert-butylphenyl)-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (146); N-(biphenyl-3-yl)-N-butyl-4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (147); N-butyl-N-(4-tert-butylphenyl)-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (148); N-butyl-4-chloro-N-(2,3-dihydrobenzo[/?](1,4)dioxin-6-yl)-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (149); N-butyl-4-chloro-N-(3-isopropoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (150); N-butyl-4-chloro-5-methyl-N-(naphthalen-2-ylmethyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (151); N-butyl-4-chloro-N-(3' chlorobi phenyl-3-yl)-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (152); N-butyl-4-chloro-N-(4'-chlorobi phenyl-3-yl)-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (153); methyl 4-(N-butyl-4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (154); 4-(N-butyl-4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (155); N-Butyl-4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (156); N-Benzyl-N-butyl-4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1 H-pyrazole-3-carboxamide (157); N-Butyl-4-chloro-5-methyl-N-(3-(2-
(4-methylpiperazin-1-yl)ethylamino)-3-oxopropyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (158); N-Butyl-4-chloro-N-(3-(1,3-dihydroxypropan-2-ylamino)-3-oxopropyl)-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (159); N-Butyl-4-chloro-N-(3-(1,3-dihydroxy-2-(hydroxymethyl)propan-2-ylamino)-3-oxopropyl)-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (160); 4-(N-Butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)benzoic acid (161); 2-(4-(N-Butyl-4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)phenylacetic acid (162); 4-Bromo-N,N-dibutyl-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (163); N,N-Dibutyl-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (164); N,N-Dibutyl-4-(hydroxymethyl)-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (165); 3-(3-(Dibutylcarbamoyl)-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (166); N,N-Dibutyl-4-(3-(dimethylamino)propyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (167); N,N-Dibutyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (168); N,N-Dibutyl-4-chloro-5-(2-hydroxyethyl)-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (170); 2-(4-Chloro-3-(dibutylcarbamoyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (171); N,N-Dibutyl-4-chloro-5-(2-(cyclopropanesulfonamido)-2-oxoethyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (172).
3-carboxamide (172); 2-(4-Chloro-3-(dibutylcarbamoyl)-1-(4-(naphthalen-2-ylsulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazol-5-yl)ethyl carbamate (173); 2-(4-Chloro-3-(dibutylcarbamoyl)-1-(4-(naphthalen-2-ylsulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazol-5-yl)ethyl 4-methylpiperazine-1-carboxylate (174); 2-(4-Chloro-3-(dibutylcarbamoyl)-1-(4-(naphthalen-2-ylsulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazol-5-yl)ethyl 2-(4-methylpiperazin-1-yl)ethyl carbamate (175); tert-Butyl 3-(N-butyl-4-chloro-1-(4-(7-iodonaphthalen-2-ylsulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamido)propanoate (176); N,N-Dibutyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylearbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (177); N-Butyl-4-chloro-N-(3,4-dichlorobenzyl)-1-(4-(8-(ethylsulfonylearbamoyl)naphthalen-2-ylsulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (178); N-Butyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylearbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-(3,4-dichlorobenzyl)-1H-pyrazole-3-carboxamide (179); N-Butyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylearbamoyl)-2-((5)-3-((2-hydroxyethyl)(methyl)amino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-(3,4-dichlorobenzyl)-5-methyl-1H-pyrazole-3-carboxamide (180); N-Butyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylearbamoyl)-2-((5)-3-(dimethylamino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-(3,4-dichlorobenzyl)-5-methyl-1H-pyrazole-3-carboxamide (181); N,N-Dibutyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylearbamoyl)-2-((5)-3-((2-hydroxyethyl)(methyl)amino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-(3,4-dichlorobenzyl)-5-methyl-1H-pyrazole-3-carboxamide (182); N,N-Dibutyl-4-chloro-1-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylearbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (183); N,N-Dibutyl-4-chloro-1-(2-((5)-3-((dimethylamino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylearbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (184); N,N-Dibutyl-4-chloro-5-methyl-1-(4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylearbamoyl)-2-((5)-3-(morpholinomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (185); N-
Butyl-4-chloro-\(N\)-(3,4-dichlorobenzyl)-5-methyl-1-(4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-((5')-3-(morpholinomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl) H-pyrazole-3-carboxamide (186); N-Butyl-4-chloro-\(N\)-(3,4-dichlorobenzyl)-1-(2-((S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide (187); 1-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide (188); \(N,N\)-Dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide (189); \(N,N\)-Dibutyl-4-chloro-1-(4-(ethylindolin-5-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide (190); 4-(4-Chloro-3-(dipropylamino)-5-methyl-1\(H\)-pyrazol-1-yl)-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (191); 4-(4-Chloro-3-(dipropylamino)-5-methyl-1\(H\)-pyrazol-1-yl)-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (192); 4-(4-Chloro-3-(dipropylamino)-5-methyl-1\(H\)-pyrazol-1-yl)-(8-chloronaphthalen-2-ylsulfonyl)benzamide (193); 3-(N-butyl-4-chloro-1-(3,4-dichlorobenzyl)-1\(H\)-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide (194); 4-(4-Chloro-3-(dipropylamino)-5-(trifluoromethyl)-1\(H\)-pyrazol-1-yl)-(8-chloronaphthalen-2-ylsulfonyl)benzamide (195); 4-(4-Chloro-3-(dipropylamino)-5-(trifluoromethyl)-1\(H\)-pyrazol-1-yl)-(8-chloronaphthalen-2-ylsulfonyl)benzamide (196); 3-(N-butyl-4-chloro-1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide (197); \(N,N\)-Dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide (198); 1-(4-(3-bromo-1-(3,4-dichlorobenzyl)-1\(H\)-indol-5-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide (199); 1-(4-(3-bromo-1-(3,4-dichlorobenzyl)-1\(H\)-indol-5-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide (200);
(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl) -N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (199); N-butyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-N-(3-(2-(4-methylpiperazin-1-yl)ethylamino)-3-oxopropyl)-1H-pyrazole-3-carboxamide (200); N-butyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (201); N,N-dibutyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(3-(2-(4-methylpiperazin-1-yl)ethylamino)-3-oxopropyl)lH-pyrazole-3-carboxamide (202); 1-(2-(6-bromo-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (203); (Z)-N-(8-bromo-5-chloronaphthalen-2-ylsulfonylcarbamoyl)-4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-3-(3-(methoxypropoxy)propyl)methyl-1H-benzo[e][1,3]diazepine-2-carboxamide (204); 1-(4-(7-bromo-1-ethylindolin-5-ylsulfonylcarbamoyl)-2-(1-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (205); 4-chloro-1-(4-(1-ethylindolin-5-ylsulfonylcarbamoyl)-2-(5-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dipropyl-1H-pyrazole-3-carboxamide (206); N-(8-bromo-5-chloronaphthalen-2-ylsulfonylcarbamoyl)-4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-3-(5-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (207); 1-(4-(7-bromo-1-ethyl-1H-indol-5-ylsulfonylcarbamoyl)-2-(5-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (208); 1-(4-(7-bromo-1-ethylindolin-5-ylsulfonylcarbamoyl)-2-(5-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dipropyl-1H-pyrazole-3-carboxamide (209); N,N-dibutyl-4-chloro-1-(4-(3,7-dibromo-1-ethyl-1H-indol-5-ylsulfonylcarbamoyl)-2-(5-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (210); 1-(2-(6-bromo-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (211); N,N-dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (212).
ylsulfonylcarbamoyl)-2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl)-5-methyl-1-H-pyrazole-3-carboxamide (212); 2-(4’-(N-butyl-4-chloro-
1-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1-H-pyrazole-3-
carboxamido)methyl)biphenyl-4-yl)acetic acid (213); 2-(4’-((N-(4-chloro-
1-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1-H-pyrazole-3-carboxamido)methyl)biphenyl-4-yl)acetic acid (214); 4-(3-(dibutylcarbamoyl)-1-(4-(1,3,4-dichlorobenzyl)indolin-5-
ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-
1H-pyrazol-4-yl)benzoic acid (215); 4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-
ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-
N,N-dipropyl-1H-pyrazole-3-carboxamide (216); 1-(4-(8-bromo-5-chloronaphthalen-2-
ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-butyl-4-
chloro-N-(4’-chlorobiphenyl-3-yl)-5-methyl-1H-pyrazole-3-carboxamide (217); 1-(4-(8-
bromo-5-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl)-N-butyl-4-chloro-N-(3’-chlorobiphenyl-3-yl)-5-methyl-1H-pyrazole-3-
carboxamide (218); N-butyl-4-chloro-N-(4’-chlorobiphenyl-4-yl)methyl-1-(4-(1-(3,4-
dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (219); N-butyl-4-chloro-N-(4-
chlorophenoxy)phenyl-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-
(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-
carboxamide (220); N-butyl-4-chloro-N-(4’-chlorobiphenyl-3-yl)-1-(4-(5,8-
dichloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (221); N-butyl-4-chloro-N-(3’-
chlorobiphenyl-3-yl)-1-(4-(5,8-dichloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide (222); 1-(4-((1-(2-Aminoethyl)thio)isoquinolin-6-yl)sulfamoyl)carbamoyl)-2-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-
3-carboxamide (330); and 2-(((6-(N-(4-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-
1H-pyrazol-1-yl))-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)
isoquinolin-1-yl)(thio)acetic acid (331).
One embodiment provides compounds of Formula (I), pharmaceutically acceptable salts or prodrugs thereof, wherein said compound is selected from Ethyl 5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (223); Ethyl 5-methyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (224); Ethyl 5-butyl-1-(4-methoxyphenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (225); Ethyl 5-butyl-1-(4-isopropylphenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (226); Ethyl 5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-(3-phenoxyphenyl)-1H-pyrazole-3-carboxylate (227); Ethyl 5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-(4-phenoxyphenyl)-1H-pyrazole-3-carboxylate (228); Ethyl 5-butyl-1-(4-(4-chlorophenoxy)phenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (229); Ethyl 5-butyl-1-(4-(3-chlorophenoxy)phenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (230); Ethyl 1-(4-butoxyphenyl)-5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (231); Ethyl 1-(4-(allyloxy)phenyl)-5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (232); Ethyl 1-(biphenyl-4-yl)-5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (233); Ethyl 5-butyl-1-(3-(methoxycarbonyl)phenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (234); Ethyl 5-butyl-1-(3-(methoxycarbonyl)phenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (235); 4-(5-Butyl-3-(hydroxymethyl)-1-(3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (236); 5-Butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-phenyl-1H-pyrazole-3-carboxylic acid (237); 4-(5-Butyl-3-(hydroxymethyl)-1-(3-
(hydroxymethyl)phenyl)-1 H-pyrazol-4-y1)-N-(naphthalen-2-ylsulfonl)-3-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (238); Ethyl 5-butyl-l-phenyl-4-(2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(2-(trimethylsilyl)ethylsulfonlcarbamoyl)phenyl)-l H-pyrazole-3-carboxylate (239); 4-(5-Butyl-3-(hydroxymethyl)-1-phenyl-1 H-pyrazol-4-y1)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2-(trimethylsilyl)ethylsulfonl)benzamide (240); 4-(5-butyl-1-(hydroxymethyl)-1-(4-phenoxyphenyl)-1H-pyrazol-4-y1)-N-(naphthalen-2-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (241); 4-(5-butyl-1-(4-(4-chlorophenyl)phenyl)-3-(hydroxymethyl)-1 H-pyrazol-4-y1)-N-(naphthalen-2-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (242); 4-(5-butyl-1-(4-(3-chlorophenyl phenyl)-3-(hydroxymethyl)-1 H-pyrazol-4-y1)-N-(naphthalen-2-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (243); 4-(5-butyl-1-(4-butoxyphenyl)-3-(hydroxymethyl)-1 H-pyrazol-4-y1)-N-(naphthalen-2-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (244); 4-(5-butyl-1-(4-2-hydroxyethyl)phenyl)-3-(hydroxymethyl)-1 H-pyrazol-4-y1)-N-(naphthalen-2-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (245); 4-(1-(4-(allyloxy)phenyl)-5-butyl-3-(hydroxymethyl)-1 H-pyrazol-4-y1)-N-(naphthalen-2-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (246); 4-(1-(biphenyl-4-y1)-5-butyl-3-(hydroxymethyl)-1 H-pyrazol-4-y1)-N-(naphthalen-2-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (247); ethyl 5-butyl-4-(4-(8-chloronaphthalen-2-ylsulfonlcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-(4-(3-chlorophenoxy)phenyl)-1H-pyrazole-3-carboxylate (248); ethyl 5-butyl-1-(4-(3-chlorophenoxy)phenyl)-4-(4-(ethylsulfonlcarbamoyl)-2-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxylate (249); ethyl 5-butyl-1-(4-(3-chlorophenoxy)phenyl)-4-(4-(pentylsulfonlcarbamoyl)-2-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxylate (250); ethyl 4-(4-(8-bromo-5-chloronaphthalen-2-ylsulfonlcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-(3-chlorophenoxy)phenyl)-1 H-pyrazole-3-carboxylate (251); 4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(hydroxymethyl)-1 H-pyrazol-4-y1)-N-(8-chloronaphthalen-2-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (252); 4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(hydroxymethyl)-1 H-pyrazol-4-y1)-N-(ethylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)benzamide (253); 4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(pentylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (254); N-(8-bromo-5-chloronaphthalen-2-ylsulfonyl)-4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(hydroxymethyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (255); 4-(5-Butyl-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(pentylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (256); 4-(5-Butyl-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (257); (±)-4-(5-Butyl-1-(4-(2,3-dihydroxypropoxy)phenyl)-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonil)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (258); Ethyl 5-butyl-4-(2-(4-(3-chlorophenoxy)phenyl)-1H-pyrazol-4-yl)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (259); 4-(5-Butyl-3-(hydroxymethyl)-1-phenyl-1H-pyrazol-4-yl)-3-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonil)benzamide (260); Ethyl 4-(2-(4-(3-aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonilcarbamoyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate (261); Ethyl 4-(2-(4-(3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonilcarbamoyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate (262); and 3-(5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(5-butyl-3-(hydroxymethyl)-1-phenyl-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonil)benzamide (263).

One embodiment provides compounds of Formula (I), pharmaceutically acceptable salts or prodrugs thereof, wherein said compound is selected from N,N-Dibutyl-1-methyl-2-(4-(naphthalen-2-ylsulfonilcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazole-4-carboxamide (264); N,N-Dibutyl-1-(2-(methylamino)-2-oxoethyl)-2-(4-(naphthalen-2-ylsulfonilcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazole-4-carboxamide (265); N,N-Dibutyl-1-(3-hydroxypropyl)-2-(4-(naphthalen-2-ylsulfonilcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazole-4-carboxamide (266); N,N-Dibutyl-1-(3-(dimethylamino)propyl)-2-(4-(naphthalen-2-ylsulfonilcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazole-4-carboxamide (267);
N,N-Dibutyl-2-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxamide (268); 2-(4-(Dibutylcarbamoyl)-2-(4-(naphthalen-1-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazol-1-yl)acetic acid (269); N,N-Dibutyl-2-(4-(8-iodonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide (270); N,N-Dibutyl-2-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-phenethyl-1H-imidazole-4-carboxamide (271); 1-Benzyl-N,N-dibutyl-2-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazole-4-carboxamide (273); N,N-Dibutyl-1-(2-hydroxyethyl)-2-(2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-imidazole-4-carboxamide (274); N,N-Dibutyl-2-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(2-methoxyethyl)-1H-imidazole-4-carboxamide (275); N,N-Dibutyl-1-(2-(2-hydroxyethoxy)ethyl)-2-(2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-imidazole-4-carboxamide (276); N,N-Dibutyl-2-(2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(2-morpholinoethyl)-1H-imidazole-4-carboxamide (277); N,N-Dibutyl-2-(2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(3-morpholinopropyl)-1H-imidazole-4-carboxamide (278); N,N-Dibutyl-2-(2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazole-4-carboxamide (279); N,N-Dibutyl-2-(2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(3-(4-methylpiperazin-1-yl)ethyl)-1H-imidazole-4-carboxamide (280); 2-(2-(5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-1-methyl-1H-imidazole-4-carboxamide (281);
2-(2-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-iodonaphthalen-2-ylsulfonylearbamoyl)phenyl)-N,N-dibutyl-1-methyl-1H-imidazole-4-carboxamide (282); and N,N-Dibutyl-2-(4-(8-chloronaphthalen-2-ylsulfonylearbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide (283).

[0051] One embodiment provides compounds of Formula (I), pharmaceutically acceptable salts or prodrugs thereof, wherein said compound is selected from N,N-Dibutyl-5-(4-(8-iodonaphthalen-2-ylsulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide (284); and N,N-Dibutyl-5-(4-(8-chloronaphthalen-2-ylsulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide (285).

[0052] One embodiment provides compounds of Formula (I), pharmaceutically acceptable salts or prodrugs thereof, wherein said compound is selected from N,N-Dibutyl-6-(4-(naphthalen-2-ylsulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)picolinamide (286); 4-(6-(Dibutylamino)pyridin-2-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (287); 4-(3-Bromo-6-(dibutylamino)pyridin-2-yl)-N-(7-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (288); 4-(3-Bromo-6-(dibutylamino)pyridin-2-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (289); and 4-(3-Bromo-6-(dibutylamino)pyridin-2-yl)-N-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (290).

[0053] One embodiment provides compounds of Formula (I), pharmaceutically acceptable salts or prodrugs thereof, wherein said compound is selected from 4-(2-(Dibutylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (291); N-(8-chloronaphthalen-2-ylsulfonyl)-4-(2-(dibutylamino)pyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (292); 4-(2-(dibutylamino)pyrimidin-4-yl)-N-(7-iodonaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (293); 4-(2-(dibutylamino)pyrimidin-4-yl)-N-(1-(ethyl-1H-indol-5-ylsulfonyl))-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (294); 4-(2-(dibutylamino)pyrimidin-4-yl)-N-(1-(3,4-dichlorobenzyl)-1H-indol-5-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (295); and 4-(2-(dibutylamino)pyrimidin-4-yl)-N-(1-(3,4-dichlorobenzyl)-1H-indol-5-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (296).
carbonyl)benzamide (295); 4-(2-(dipentylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (296); N-(naphthalen-2-ylsulfonyl)-4-(2-(3-propylpyrrolidin-1-yl)pyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (297); 4-(2-(butyl(3,4-dichlorobenzyl)amino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (298); 4-(2-(dipropylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (299); 4-(2-((cyclopropylmethyl)(propyl)amino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (300); 4-(2-diethylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (301); N-(naphthalen-2-ylsulfonyl)-4-(2-(3-phenethylpyrrolidin-1-yl)pyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (302); (5)-4-(2-(Dibutylamino)pyrimidin-4-yl)-3-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (303); (5)-3-(3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(2-(dibutylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)benzamide (304); 4-(2-(dibutylamino)pyrimidin-4-yl)-3-(isoindoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide (305); 4-(2-(dibutylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (306); 4-(2-(dibutylamino)pyrimidin-4-yl)-N,N,N3,N3-dimethyl-7-(naphthalen-2-ylsulfonyl)isophthalamide (307); (5)-N-(8-Chloronaphthalen-2-ylsulfonyl)-4-(2-(dibutylamino)pyrimidin-4-yl)-3-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (308); (5)-4-(2-(Dibutylamino)pyrimidin-4-yl)-3-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(7-iodonaphthalen-2-ylsulfonyl)benzamide (309); (5)-4-(2-(Dibutylamino)pyrimidin-4-yl)-N-(l-ethylindolin-5-ylsulfonyl)-3-(3-(hydroxyethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (310); 4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (311); 4-(2-(Dibutylamino)-5-methylpyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (312); 4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (313); 4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (314); N-(8-Chloronaphthalen-2-
ylsulfonyl)-4-(2-(dibutylamino)-5-methylpyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (314); 4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide (315); 4-(5-Bromo-2-(dibutylamino)pyrimidin-4-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide (316); 4-(5-Bromo-2-(dibutylamino)pyrimidin-4-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (317); 4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-N-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (321); 4-(2-(Butyl(3,4-dichlorobenzyl)amino)-5-chloropyrimidin-4-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (322); 4-(5-Chloro-2-(dipropylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (323); 4-(5-Chloro-2-(dipropylamino)pyrimidin-4-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide (324); 4-(5-Bromo-2-(dipropylamino)pyrimidin-4-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide (325); 4-(5-Chloro-2-((cyclopropylmethyl)(propyl)amino)pyrimidin-4-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide (326); 3-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide (327); 4-(5-Chloro-2-(dipropylamino)pyrimidin-4-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (328); and 3-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(5-chloro-2-(dipropylamino)pyrimidin-4-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)benzamide (329).
The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof. This invention encompasses all combinations of the aspects and/or embodiments of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe addition more embodiments. It is also to be understood that each individual element of the embodiments is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

DEFINITIONS

The features and advantages of the invention may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also 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, may also be combined so as to form sub-combinations thereof. Embodiments identified herein as exemplary or preferred are intended to be illustrative and not limiting.

Unless specifically stated otherwise herein, references made in the singular may also include the plural. For example, "a" and "an" may refer to either one, or one or more.

Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference.

Listed below are definitions of various terms used to describe the present invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

Throughout the specification, groups and substituents thereof may be chosen by one skilled in the field to provide stable moieties and compounds.
[0061] In accordance with a convention used in the art,

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is used in structural formulas herein to depict the bond that is the point of attachment of the moiety or substituent to the core or backbone structure.

[0062] The terms "halo" and "halogen", as used herein, refer to F, Cl, Br, and I.

[0063] The term "alkyl" as used herein, refers to both branched and straight-chain saturated aliphatic hydrocarbon groups containing, for example, from 1 to 12 carbon atoms, from 1 to 6 carbon atoms, and from 1 to 4 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (e.g., n-propyl and isopropyl), butyl (e.g., n-butyl, isobutyl, sec-butyl, and tert-butyl), and pentyl (e.g., n-pentyl, isopentyl, 2-methylpentyl, 2-ethylpentyl, 3-methylpentyl, and 4-methylpentyl). When numbers appear in a subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular group may contain. For example, "C_{1-6}alkyl" denotes straight and branched chain alkyl groups with one to six carbon atoms.

[0064] The term "haloalkyl", as used herein, refers to an alkyl group in which one or more hydrogen atoms are replaced by halogen atom(s), the number of which can range from one up to the total number of hydrogen atoms that could otherwise exist in the parent alkyl group. Representative examples of haloalkyl groups include, but are not limited to, chloromethyl (-CH2Cl), trifluoromethyl (-CF3), and 2,2,2-trifluoroethyl (-CH2CF3). When numbers appear in a subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular haloalkyl group may contain. For example, "C_{1-4}haloalkyl" denotes straight and branched chain haloalkyl groups with one to four carbon atoms.

[0065] The term "fluoroalkyl" as used herein is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups substituted with one or more fluorine atoms. For example, "C1-4 fluoroalkyl" is intended to include C1, C2, C3, and C4 alkyl groups substituted with one or more fluorine atoms. Representative examples of fluoroalkyl groups include, but are not limited to, -CF3 and -CH2CF3.

[0066] The term "hydroxyalkyl" includes both branched and straight-chain saturated alkyl groups substituted with one or more hydroxyl groups. For example, "hydroxyalkyl" includes -CH2OH, -CH2CH2OH, and C1-4 hydroxyalkyl.
The term "cyano" refers to the group -CN.

The term "cycloalkyl", as used herein, refers to a group derived from a non-aromatic monocyclic or polycyclic hydrocarbon molecule by removal of one hydrogen atom from a saturated ring carbon atom. Representative examples of cycloalkyl groups include, but are not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. When numbers appear in a subscript after the symbol "C", the subscript defines with more specificity the number of carbon atoms that a particular cycloalkyl group may contain. For example, "cycloalkyl" denotes cycloalkyl groups with three to six carbon atoms.

The term "alkoxy", as used herein, refers to an alkyl group attached to the parent molecular moiety through an oxygen atom, for example, methoxy group (-OCH₃).

"Fluoroalkoxy" and "-O(fluoroalkyl)" represent a fluoroalkyl group as defined above attached through an oxygen linkage (-O-). For example, "Ci₄fluoroalkoxy" is intended to include Ci, C₂, C₃, and C₄ fluoroalkoxy groups.

The term "aryl", as used herein, refers to a group of atoms derived from a molecule containing aromatic ring(s) by removing one hydrogen that is bonded to the aromatic ring(s). Representative examples of aryl groups include, but are not limited to, phenyl, naphthyl, indanyl, indenyl, and 1,2,3,4-tetrahydroanthracene-5-yl.

The term "benzyl", as used herein, refers to a methyl group in which one of the hydrogen atoms is replaced by a phenyl group.

The term "heteroatom" refers to oxygen (O), sulfur (S), and nitrogen (N).

The term "heterocyclo" or "heterocycl" may be used interchangeably and refer to non-aromatic 3- to 7-membered monocyclic groups and 6- to 11-membered bicyclic groups, in which at least one of the rings has at least one heteroatom (O, S or N), said heteroatom containing ring preferably having 1 to 3 heteroatoms independently selected from O, S, and/or N. Each ring of such a group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less, and further provided that the ring contains at least one carbon atom. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. The fused rings completing the bicyclic group may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The heterocyclo group may be attached at
any available nitrogen or carbon atom. The heterocyclo ring may be unsubstituted or may contain one or more substituents as valence allows.

Exemplary monocyclic heterocyclyl groups include oxetanyl, azetidinyl, pyrrolidinyl, imidazolinyl, oxazolidinyl, isoxazolinyl, thiazolidinyl, isothiazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl. Exemplary bicyclic heterocyclo groups include quinuclidinyl.

The term "heteroaryl" refers to substituted and unsubstituted aromatic 5- or 6-membered monocyclic groups and 9- or 10-membered bicyclic groups which have at least one heteroatom (O, S or N) in at least one of the rings, said heteroatom-containing ring preferably having 1, 2, or 3 heteroatoms independently selected from O, S, and/or N. Each ring of the heteroaryl group containing a heteroatom can contain one or two oxygen or sulfur atoms and/or from one to four nitrogen atoms provided that the total number of heteroatoms in each ring is four or less and each ring has at least one carbon atom. The fused rings completing the bicyclic group may contain only carbon atoms and may be saturated, partially saturated, or unsaturated. The nitrogen and sulfur atoms may optionally be oxidized and the nitrogen atoms may optionally be quaternized. Heteroaryl groups which are bicyclic or tricyclic must include at least one fully aromatic ring but the other fused ring or rings may be aromatic or non-aromatic. The heteroaryl group may be attached at any available nitrogen or carbon atom of any ring. The heteroaryl ring system may be unsubstituted or may contain one or more substituents.

Exemplary monocyclic heteroaryl groups include pyrrolyl, pyrazolyl, pyrazolinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, isothiazolyl, furanyl, thiophenyl, oxadiazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, and triazolyl.

Exemplary bicyclic heteroaryl groups include indolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzothienyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuranyl, chromonyl, coumarinyl, benzopyryl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridyl, dihydroisoindolyl, and tetrahydroquinolinyl.
The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; and alkali or organic salts of acidic residues such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th Edition, p. 1418, Mack Publishing Company, Easton, PA (1985), the disclosure of which is hereby incorporated by reference.

Salt(s) of the Formula (I) compounds can be formed by, for example, reacting a Formula (I) compound with, for example, an equivalent amount of acid or base in a medium that allows the newly formed salt to, for example, either be precipitated out, or be isolated via lyophilization. Exemplary acidic salt(s) that the compounds of Formula (I) can form with inorganic and/or organic acids include, but are not limited to, for example, include acetate, ascorbate, benzoate, benzenesulfonate, bisulfate, bitartrate, acid citrate, citrate, ethanesulfonate, formate, fumarate, gentisinate, gluconate, glucaronate, glutamate, hydrochloride, hydrobromide, hydroiodide, isonicotinate, maleate, mesylate, methanesulfonate, nitrate, pantothenate, phosphate, acid phosphate, saccharate, salicylate, succinate, sulfate, tartrate, p-toluensulfonate, trifluoroacetate, lactate, and pamoate [i.e.,
1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts. Such salts can be formed in accordance with methods known to a person of ordinary skill in the art.

Exemplary basic salt(s) that the compounds of Formula (I) can form with inorganic and/or organic bases include, but are not limited to, for example, ammonium salts; alkali metal salts, such as, for example, sodium, lithium and potassium salts: alkaline earth metal salts, such as, for example, calcium and magnesium salts; salts formed with organic bases, such as, for example, benzathines, dicyclohexylamines, 2-amino-2-(hydroxymethyl)propane-1,3-diol (trisamine or tris), hydrabamines (such as, for example, N,N-bis(dehydroabietyl) ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glycamides, and 2-butyl amines; salts formed with amino acids, such as, for example, arginine and lysine; and salts formed by using agents, such as, for example, lower alkyl halides (e.g., methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g., dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g., decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), and aralkyl halides (e.g., benzyl and phenethyl bromides) to quaternize basic nitrogen-containing groups. Such salts can be formed in accordance with methods known to a person of ordinary skill in the art.

In addition, compounds of Formula (I) are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% of a compound of Formula (I) ("substantially pure"), which is then used or formulated as described herein. Such "substantially pure" compounds of Formula (I) are also contemplated herein as part of the present invention.

Any compound that can be converted in vivo to provide the bioactive agent (i.e., the compound of Formula (I)) is a prodrug within the scope and spirit of the invention.

The term "prodrugs" as employed herein includes amides and carbamates formed by reacting one or more amino groups of compounds of Formula (I) with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate amides, ureas, carbamates, and the like.

Various forms of prodrugs are well known in the art and are described in:

b) Bundgaard, H. ed., *Design of Prodrugs*, Elsevier (1985);
c) Bundgaard, H., Chapter 5, "Design and Application of Prodrugs".


[0087] In addition, compounds of the Formula (I) are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% Formula (I) compound ("substantially pure" compound I), which is then used or formulated as described herein. Such "substantially pure" compounds of the Formula (I) are also contemplated herein as part of the present invention.

[0088] "Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent. The present invention is intended to embody stable compounds.

[0089] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention alone or an amount of the combination of compounds claimed or an amount of a compound of the present invention in combination with other active ingredients effective to act as an antagonist of Bel, or effective to treat cancer.

[0090] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) preventing the disease-state from occurring in a mammal, in particular, when such mammal is predisposed to the disease-state but has not yet been diagnosed as having it; (b) inhibiting the disease-state, *i.e.*, arresting it development; and/or (c) relieving the disease-state, *i.e.*, causing regression of the disease state.

[0091] Compounds of the present invention may contain one or more additional asymmetric carbon atoms and therefore exist in two or more stereoisomeric forms. The present invention includes all of the possible individual stereoisomers, the individual tautomeric forms thereof, together with mixtures thereof. Separation of diastereoisomers may be achieved by conventional techniques, *e.g.*, by fractional crystallization,
chromatography or HPLC of a stereoisomeric mixture of a compound of the present invention, or a suitable salt or derivative thereof. An individual enantiomer of the compound may also be prepared from a corresponding optically pure intermediate or by resolution, such as by HPLC of the corresponding racemate using a suitable chiral support or by fractional crystallization of the diastereoisomeric salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate. All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form.

[0092] The compounds of the present invention are intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include $^{13}$C and $^{14}$C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

[0093] Also embraced within this invention is a class of pharmaceutical compositions comprising the compound of Formula (I) or a pharmaceutically acceptable salt thereof in association with one or more non-toxic, pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of Formula (I) may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for example, be administered orally, mucusally, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly intraternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles. For example, the pharmaceutical carrier may contain a mixture of mannitol or lactose and microcrystalline cellulose. The mixture may contain additional components such as a lubricating agent, e.g., magnesium stearate and a disintegrating agent such as crosnepovidone. The carrier mixture may be filled into a gelatin capsule or compressed as a tablet.
The pharmaceutically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, including humans and other mammals.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, capsule, suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient from about 0.5 to 2000 mg, preferably from about 0.5 to 500 mg, more preferably from about 0.5 to 150 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods.

The amounts of compounds that are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex, the medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 100 mg/kg body weight, preferably between about 0.05 and about 50 mg/kg body weight and most preferably between about 0.05 to 20 mg/kg body weight, may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered orally, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinyl alcohol, and/or polyvinylpyrrolidone, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose.

The oily phase of the emulsions comprising compounds of Formula (I) may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an
oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together
with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both
an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-
called emulsifying wax, and the wax together with the oil and fat make up the so-called
emulsifying ointment base which forms the oily dispersed phase of the cream
formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of
the present invention include Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol,
glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or
other materials well known in the art.

[0099] The choice of suitable oils or fats for the formulation is based on achieving the
desired cosmetic properties, since the solubility of the active compound in most oils
likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream
should preferably be a non-greasy, non-staining and washable product with suitable
consistency to avoid leakage from tubes or other containers. Straight or branched chain,
mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol
diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl
stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These
may be used alone or in combination depending on the properties required. Alternatively,
high melting point lipids such as white soft paraffin and/or liquid paraffin or other
mineral oils can be used.

[00100] Formulations for parenteral administration may be in the form of aqueous or
non-aqueous isotonic sterile injection solutions or suspensions. These solutions and
suspensions may be prepared from sterile powders or granules using one or more of the
carriers or diluents mentioned for use in the formulations for oral administration or by
using other suitable dispersing or wetting agents and suspending agents. The compounds
may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil,
cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, tragacanth gum,
and/or various buffers. Other adjuvants and modes of administration are well and widely
known in the pharmaceutical art. The active ingredient may also be administered by
injection as a composition with suitable carriers including saline, dextrose, or water, or
with cyclodextrin (i.e., CAPTISOL®), cosolvent solubilization (i.e., propylene glycol) or
micellar solubilization (i.e., Tween 80).
The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in propylene glycol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, and buffers. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and perfuming agents.

Pharmaceutical compositions of this invention comprise the compound of Formula (I), or a pharmaceutically acceptable salt thereof, and optionally an additional agent selected from any pharmaceutically acceptable carrier, adjuvant, and vehicle. Alternate compositions of this invention comprise a compound of the Formula (I) described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

Pharmaceutically acceptable carriers, adjuvants, and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-alpha-tocopherol polyethylene glycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.
Cyclodextrins such as alpha-, beta-, and gamma-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds of the formulae described herein.

UTILITY

[00105] The compounds of Formula (I) are useful as small molecule Bcl-2 family prosurvival protein antagonists for cancer treatment and other diseases caused by impaired apoptosis.

[00106] As stated above, the compounds of Formula (I) are of interest for their antiproliferative effects. Such compounds of the invention are expected to be useful in a wide range of disease states including cancer, psoriasis, and rheumatoid arthritis.

[00107] Thus, the present invention provides methods for the treatment of a variety of cancers, including, but not limited to, the following:

carcinoma including that of the bladder (including accelerated and metastatic bladder cancer), breast, colon (including colorectal cancer), kidney, liver, lung (including small and non-small cell lung cancer and lung adenocarcinoma), ovary, prostate, testes, genitourinary tract, lymphatic system, rectum, larynx, pancreas (including exocrine pancreatic carcinoma), esophagus, stomach, gall bladder, cervix, thyroid, and skin (including squamous cell carcinoma);


hematopoietic tumors of myeloid lineage including acute and chronic myelogenous leukemias, myelodysplastic syndrome, myeloid leukemia, and promyelocytic leukemia;

tumors of the central and peripheral nervous system including astrocytoma, neuroblastoma, glioma, and schwannomas;

tumors of mesenchymal origin including fibrosarcoma, rhabdomyosarcoma, and osteosarcoma; and
other tumors including melanoma, xenoderma pigmentosum, keratoactanthoma, seminoma, thyroid follicular cancer, and teratocarcinoma.

[00108]  The present invention provides methods for the treatment of a variety of non-cancerous proliferative diseases. The invention is useful to treat GIST, Breast cancer, pancreatic cancer, colon cancer, NSCLC, CML, and ALL, sarcoma, and various pediatric cancers.

[00109]  The present invention provides methods for the treatment of a variety of proliferative diseases, including a method for treating mesothelioma, bladder cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, breast cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, bone cancer, ovarian cancer, cervical cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal, and duodenal), chronic lymphocytic leukemia, esophageal cancer, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, testicular cancer, hepatocellular cancer (hepatic and biliary duct), primary or secondary central nervous system tumor, primary or secondary brain tumor, Hodgkin's disease, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphomas, lymphoblastic leukemia, follicular lymphoma, lymphoid malignancies of T-cell or B-cell origin, melanoma, multiple myeloma, oral cancer, small cell lung cancer, cancer of the kidney and ureter, renal cell carcinoma, carcinoma of the renal pelvis, neoplasms of the central nervous system, primary central nervous system lymphoma, non Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, cancer of the spleen, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma, or a combination thereof.

[00110]  In one embodiment, a method is provided for treating cancer comprising administering compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof to a mammal in need thereof. The method of this embodiment can be used to treat a variety of cancers, including, but not limited to, breast cancer, ovarian cancer, and
prostate cancer. Preferably, the method of this embodiment is used to treat prostate cancer or breast cancer. In one method of this embodiment, compound of Formula (I) is administered in a therapeutically effective amount.

[00111] The amount of a compound of Formula (I) which is administered and the dosage regimen for treating a particular cancer depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg body weight,

preferably between about 0.05 and about 50 mg/kg body weight and most preferably between about 0.05 to 20 mg/kg body weight, may be appropriate may be appropriate. The daily dose can be administered in one to four doses per day.

[00112] In treating cancer, a combination of chemotherapeutic agents and/or other treatments (e.g., radiation therapy) is often advantageous. The second (or third) agent may have the same or different mechanism of action than the primary therapeutic agent. It may be especially useful to employ cytotoxic drug combinations wherein the two or more drugs being administered act in different manners or in different phased of the cell cycle, and/or where the two or more drugs have overlapping toxicities or side effects, and/or where the drugs being combined each has a demonstrated efficacy in treating the particular disease state manifested by the patient.

[00113] Accordingly, a compound of Formula (I) may be administered in combination with other anti-cancer treatments useful in the treatment of cancer or other proliferative diseases. The invention herein further comprises use of a compound of Formula (I) in preparing medicaments for the treatment of cancer, and/or it comprises the packaging of a compound of Formula (I) herein together with instructions that the compound be used in combination with other anti-cancer or cytotoxic agents and treatments for the treatment of cancer. The present invention further comprises combinations of a compound of Formula (I) and one or more additional agents in kit form, e.g., where they are packaged together or placed in separate packages to be sold together as a kit, or where they are packaged to be formulated together.

[00114] The compound of Formula (I) can be formulated or co-administered with other therapeutic agents that are selected for their particular usefulness in addressing side
effects associated with the aforementioned conditions. For example, the compound of Formula (I) may be formulated with agents to prevent nausea, hypersensitivity and gastric irritation, such as antiemetics, and H1 and H2 antihistaminics.

[00115] The phrase "anti-cancer treatment" includes but is not limited to, for example, radiation therapy and surgery.

[00116] The other anti-cancer agents may be selected from any one or more of the following: alkylating agents (including nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimine derivatives, and triazenes); anti-angiogenics (including matrix metalloproteinase inhibitors); antimitabolites (including adenosine deaminase inhibitors, folic acid antagonists, purine analogues, and pyrimidine analogues); antibodies or antibodies (including monoclonal antibodies, CTLA-4 antibodies, anthracyclines); aromatase inhibitors; cell-cycle response modifiers; enzymes; farnesyl-protein transferase inhibitors; hormonal and antihormonal agents and steroids (including synthetic analogs, glucocorticoids, estrogens/anti-estrogens [e.g., SERMs], androgens/anti-androgens, progestins, progesterone receptor agonists, and luteinizing hormone-releasing [LHRH] agonists and antagonists); insulin-like growth factor (IGF)/insulin-like growth factor receptor (IGFR) system modulators (including IGFR1 inhibitors); integrin-signaling inhibitors; kinase inhibitors (including multi-kinase inhibitors and/or inhibitors of Src kinase or Src/abl, cyclin dependent kinase [CDK] inhibitors, panHer, Her-1 and Her-2 antibodies, VEGF inhibitors, including anti-VEGF antibodies, EGFR inhibitors, mitogen-activated protein [MAP] inhibitors, MEK inhibitors, Aurora kinase inhibitors, PDGF inhibitors, and other tyrosine kinase inhibitors or serine/threonine kinase inhibitors; microtubule-disruptor agents, such as eteineascidins or their analogs and derivatives; microtubule-stabilizing agents such as taxanes, and the naturally-occurring epothilones and their synthetic and semi-synthetic analogs; microtubule-binding, destabilizing agents (including vinca alkaloids); topoisomerase inhibitors; prenyl-protein transferase inhibitors; platinum coordination complexes; signal transduction inhibitors; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors, and immune modulators.

[00117] The above other therapeutic agents, when employed in combination with a compound of Formula (I), can be used, for example, in those amounts indicated in the
Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

[00118] In one embodiment, a method is provided for treating cancer comprising administering to a mammal in need thereof a compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof; administering a glucocorticoid; and optionally, one or more additional anticancer agent. Examples of suitable glucocorticoids include, but are not limited to, dexamethasone and prednisolone.

[00119] In one embodiment, a method is provided for treating cancer comprising administering to a mammal in need thereof a compound of Formula (I) or a pharmaceutically acceptable salt or prodrug thereof; administering a mineralocorticoid receptor antagonist; and optionally, one or more additional anticancer agent. Examples of suitable mineralocorticoid receptor antagonists include, but are not limited to, eplerenone.

[00120] In another embodiment, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is used to treat prostate cancer.

[00121] In one embodiment, the patient is an animal.

[00122] In another embodiment, the patient is a mammalian species including, but not limited to, for example, humans and domestic animals, such as, for example, dogs, cats, and horses.

[00123] In one embodiment, the present invention provides a compound of Formula (I) or a pharmaceutically acceptable salt thereof for use in therapy.

[00124] In one embodiment, the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer, including prostate cancer, is provided.

[00125] In one embodiment, the use of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer, including breast cancer, is provided.

METHODS OF PREPARATION

[00126] The compounds of the present invention may be prepared by synthetic routes that include processes analogous to those well-known in the chemical arts, particularly in light of the description provided herein. For illustrative purposes, general Schemes 1-13 below show general methods for preparing the compounds of the present invention, as
well as key intermediates. For a more detailed description of the individual reaction steps, see the Example section below. Those skilled in the art will appreciate that other synthetic routes may be used to synthesize the inventive compounds. Although specific starting materials and reagents are depicted in the Schemes and discussed below, other starting materials and reagents can easily be substituted to provide a variety of compounds of the present invention. In addition, many of the compounds prepared by the methods below can be further modified in light of this disclosure using conventional chemistry well known to those skilled in the art.

[00127] General routes to analogues described in the invention are illustrated in Schemes 1-34. The substituted pyrazole and aryl fluoride coupling fragments 3 and 7 can be prepared as shown in Scheme 1. Halogenation of commercially available pyrazole 1 with, for example, NCS or NBS provides derivative 2. Conversion to the amide Intermediate 3 can occur via treatment with a secondary amine in the presence of w-BuLi or through a two-step procedure employing a coupling reagent, such as EDC, after hydrolysis to the carboxylic acid. Synthesis of coupling partner 7 commences from 2-fluoro-5-iodobenzoic acid (Aldrich, 4), which can be converted to either the ethyl ester (6, Y = Et) under acidic conditions or to the tetrahydroisoquinoline derivative (6, Y = 1,2,3,4-tetrahydroisoquinoline) via the acid chloride. Palladium-catalyzed carbonylation in the presence of an alcohol, such as ethanol or benzyl alcohol, furnishes the activated phenyl Intermediate 7.

Scheme 1

![Scheme 1 Diagram](image-url)
Fully functionalized pyrazole analogues can be prepared using the synthetic routes outlined in Schemes 2-4. Base-mediated coupling of pyrazole 3 and aryl fluoride 7 provides Intermediate 8, which can be hydrolyzed using conditions dependent on the nature of R³. For example, hydrolysis of an ethyl ester can occur using basic conditions, while catalytic hydrogenation with palladium on carbon cleaves a benzyl ester. Treatment with sulfonamide 13 or 14 in the presence of a coupling reagent affords acylsulfonamides 10. For derivatives in which Y = OEt, hydrolysis of the ethyl ester can be followed by coupling with substituted tetrahydroisoquinoline 15 or benzodiazepine 16 to furnish analogue 12.

Similarly, pyrazole Intermediate 2 can be coupled with aryl fluorides 7 (R³ = Bn) under basic conditions to give Intermediate 17 (Scheme 3). Hydrogenolysis with palladium on carbon and conversion to the acylsulfonamide in the presence of a coupling reagent affords analogue 12.
reagent, such as EDC, can be followed by hydrolysis to provide the carboxylic acids 20. Conversion to amide 21 can occur via a two-step procedure in which the corresponding acid chloride is subjected to various amines in the presence of base, such as triethylamine or diisopropylethylamine (Hunig's base). Alternatively, the acid chloride can be generated in situ using 1-chloro-\(N,N\)-2-trimethyl-l-propenylamine (Ghosez's reagent) and then treated with an amine under basic conditions to afford analogue 21.

Scheme 3

[Tetrahydroisoquinoline derivatives such as 24 can be prepared using the synthetic route outlined in Scheme 4, which is based on similar chemistry previously reported. (Goble, S.D. et al, PCT International Application No. 2004/082616). Carboxylic acids (11, Scheme 1) can be converted to benzylic amides 23 in the presence of an appropriate amine 22 and a coupling reagent, such as EDC. The resulting amides]
are then deprotected in cases where Y has a protecting group. For example, if Y-P is S-t-Bu, 23 could be treated with 2-nitrobenzenesulfonyl chloride in acetic acid, and the resulting disulfide can be reduced with NaBH₄ to generate the free thiol. Exposure to paraformaldehyde, in the presence or absence of an acid catalyst such as TsOH, can provide the cyclized Intermediate 24. Subsequent oxidation in cases where Y = S can be achieved using, for example, m-CPBA to give sulfones 25.

Scheme 4

[00131] Preparation of pyrazole analogues containing carbamate or carboxylic acid functionality can be achieved using the synthetic route outlined in Scheme 5. Pyrazole starting material 26 can be accessed following a previously published procedure. (Qi, X. et al, Angew. Chem. Int. Ed., 46:3242-3244 (2007)). Conversion to the elaborated Intermediate 29 can be accomplished using chemistry described in Scheme 1, and removal of the protecting group under acidic conditions, (e.g., HCl) provides the primary alcohol 30. Further functionalization to access carbamates such as 31 can occur upon exposure to trichloroacetyl isocyanate followed by treatment with base (e.g., potassium carbonate in MeOH), or 4-nitrophenyl carbonochloridate followed by treatment with a primary or secondary amine in the presence of a base, such as triethylamine. Alternatively, primary alcohol 30 can undergo oxidation with, for example, Jones Reagent to give the carboxylic acid 32.
Pyrazole derivatives 36 and 38 may be prepared according to the synthetic sequence outlined in Scheme 6. From Intermediate 33, which can be prepared according to the chemistry described in Scheme 1 (see 8: X = Br, R¹ = Bn), palladium-catalyzed cross-coupling with β-butyl acrylate can provide the α,β-unsaturated ester 34. Conversion of the benzyl ester to the acyl sulfonamides 35 can occur as outlined in Scheme 1. Deprotection of the β-butyl ester is possible under acidic conditions (e.g., TFA) and subsequent hydrogenation using catalytic palladium on carbon generates the saturated carboxylic acid analogue 36. Following deprotection, Intermediate 35 can also be converted to the primary alcohol 37 via a two-step procedure involving reduction of the acyl imidazole and subsequent hydrogenation. Mesylation of the alcohol followed by displacement with dimethylamine under basic conditions (e.g., diisopropylethylamine) can provide the tertiary amine 36.
In an alternative approach to compounds related to 37, hydroxymethyl pyrazole 40 can be prepared as demonstrated in Scheme 7. Intermediate 39 can be prepared following the sequence outlined in Scheme 1 (see 9: X = Br, Y = 1,2,3,4-tetrahydroisoquinoline). Lithium-halogen exchange with w-BuLi, for example, and quenching with DMF can provide the formylated pyrazole. Conversion to the acylsulfonamide is possible in the presence of coupling reagent such as EDC as previously described in Scheme 2. Finally, reduction of the aldehyde with, for example, NaBH₄ provides the primary alcohol 40.
Functionalized amide derivatives, such as 43, may be prepared according to the synthetic route illustrated in Scheme 8. Ester 41, available following the sequence described in Scheme 3, can be hydrolyzed under acidic or basic conditions to give carboxylic acid 42. Coupling with a primary or secondary amine in the presence of a coupling reagent (e.g., EDC or HATU) and a base (e.g., triethylamine or Hunig's base) affords the desired amide 43.

Tetrahydrosinoquinoline derivatives 45 and 47 can be prepared using the sequences described in Scheme 9. Alkylation of 44, available following the synthetic
route outlined in Scheme 2, in the presence of tetrabutylammonium iodide can provide alkoxy compound 45. Alternatively, functionalized amino derivatives may be prepared via reductive amination of 46 (prepared according to Scheme 2) with various ketones in the presence of, for example, sodium triacetoxyborohydride.

Incorporation of various substituents at the 5-position of the indoline in compound 48, which is prepared as described in Scheme 2, can be accomplished as shown in Scheme 10. Palladium-catalyzed coupling with a range of vinyl boronic acids in the presence of potassium metaphosphate can provide derivatives such as 49. Alternatively, 5-aminoindoline compounds 50 are available through the copper-catalyzed
coupling of an amine with 48 in the presence of, for example, potassium carbonate and L-proline.

Scheme 10

Aminopyrazole derivatives 54 and 60 are available following the synthetic routes outlined in Schemes 11 and 12, respectively. Reductive amination of 3-amino-5-methylpyrazole (Aldrich) with a variety of aldehydes in the presence of sodium triacetoxyborohydride can provide 52 (Scheme 11). Exposure to NCS gives pyrazole Intermediate 53 which can be elaborated to the fully functionalized compound 54 as described previously (Scheme 2, A and B as defined therein).

Scheme 11

Likewise, compounds such as 60 may be derived from 3-amino-5-trifluoromethylpyrazole (56, Scheme 12). The p-ethoxy-p-enamino ketone 55, prepared as described previously in the literature, (Hojo, M. et al, *Synthesis*, 195-198 (1990)) can
undergo cyclocondensation with benzylhydrazine to give 56 (Martins, M.A.P. et al, Synthesis, 1485-1493 (2006)) as a mixture of regioisomers. Exposure to propionic acid and sodium borohydride can then provide the dipropylaminopyrazole 57. Removal of the benzyl group using, for example, transfer hydrogenation with formic acid and catalytic palladium on carbon gives 58 which, after chlorination, can be converted to the fully elaborated derivative 60 as previously described in Scheme 2 (A and B as defined therein).

Scheme 12

[00139] A variety of functionalized naphthalenesulfonamide intermediates may be accessed using the synthetic sequences illustrated in Schemes 13-16. Commercially available naphthalenes such as 61 can be converted to the corresponding sulfonic acids 62 with chlorosulfonic acid (Scheme 13). Treatment with phosphorus oxychloride followed by exposure to ammonia can generate the sulfonamide products 63.

Scheme 13

[00140] Commercially available aminonaphthalenesulfonic acids 64 can be converted to various functionalized intermediates as shown in Scheme 14. The corresponding
naphthyl halides 65 can be generated under acidic conditions by treatment with sodium nitrite and copper (I) chloride (X = Cl), or by treatment with potassium nitrite, potassium hydroxide and potassium iodide (X = I). Conversion to the sulfonamide 66 can occur via the sulfonyl chloride as described previously in Scheme 13. Palladium-catalyzed reaction of Intermediate 66 with sodium ethanethiolate, zinc cyanide, or carbon monoxide in ethanol can provide sulfonamides 67-69, respectively. Subsequent oxidation of 67 with, for example, m-CPBA provides the analogous sulfonate derivative 70.

Scheme 14

\[
\begin{align*}
\text{HO}_3\text{S} & \quad \text{NH}_2 \\
\text{6'} & \quad \text{NaNO}_2, \text{CuCl}, \text{HCl} \\
\text{or} & \\
\text{KOH}, \text{KKNNO}_3, \text{H}_2\text{SO}_4, \text{KI} & \quad \text{X} = \text{Cl or I} \\
\text{6'} & \quad \text{cyanuric chloride or PODCl} \\
\text{then} & \\
\text{NH}_3, \text{NH}_4\text{OH} & \quad \text{H}_2\text{N}-\text{N}=\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{H}_2\text{N}=\text{S} & \quad \text{SO}_2\text{Et} \\
\text{70} & \quad \text{m-CBPA} \\
\text{H}_2\text{N}=\text{S} & \quad \text{ET} \\
\text{67} & \quad \text{H}_2\text{N}=\text{N}=\text{O} \\
\text{68} & \quad \text{H}_2\text{N}=\text{N}=\text{O} \\
\text{69} & \quad \text{H}_2\text{N}=\text{N}=\text{O} \\
\text{Pd(dppfCl)2, NaSEt} & \\
\text{PdPPPh3, ZnCN} & \\
\text{Pd(PPh3)4, OcO, EtOH} & \\
\end{align*}
\]

[00141] Alkoxynaphthalene sulfonamides such as 73 can be prepared as depicted in Scheme 15. Treatment of hydroxynaphthalene sulfonate 71 with a base in the presence of sodium iodide and tetrabutylammonium iodide can effect the displacement of various leaving groups, such as but not limited to mesylate, bromide or iodide, to generate alkoxynaphthalene sulfonic acid 72. Conversion to the corresponding sulfonamide can occur as described previously (Scheme 13).

Scheme 15

\[
\begin{align*}
\text{NaO}_2\text{S} & \quad \text{OH} \\
\text{71} & \quad \text{R-LG, base, Nal, TBAI} \\
& \quad \text{LG = leaving group} \\
\text{HO}_3\text{S} & \quad \text{OR} \\
\text{72} & \quad \text{POCl}_3 \\
\text{then} & \\
\text{NH}_3, \text{NH}_4\text{OH} & \quad \text{OR} \\
\text{73} & \\
\end{align*}
\]
5-Aminonaphthalene-2-sulfonic acid (Aldrich) can be converted to a variety of functionalized derivatives as shown in Scheme 16. Following Boc-protection of the amine to give 75, halogenation with NBS or NCS followed by acid-mediated deprotection with, for example, trifluoroacetic acid can generate Intermediate 76. Reductive alkylation with formaldehyde in the presence of triethylsilane, followed by conversion to the sulfonamide (as shown in Scheme 2) can provide 77. Alternatively, Intermediate 78 can be accessed following the sequence previously described in Scheme 14.

Various indole and indoline intermediates can be prepared following the synthetic sequences outlined in Schemes 17-19. Acetylincloline sulfonyl chlorides such as 79 (Borror, A.L. et al, J. Org. Chem., 53:2047-2052 (1988)) can be converted to sulfonamide 80 using ammonia in the presence of a base, such as triethylamine, followed by treatment with acid (Scheme 17). Exposure to a base (e.g., potassium carbonate) and a variety of acid chlorides then affords the functionalized sulfonamide 81. Reduction of the resulting amide with, for example, a borane-THF complex solution, followed by oxidation with DDQ can generate the alkylindole 85. Alternatively, 85 can be accessed via oxidation of sulfonamide 80 with DDQ, followed by acylation and reduction of the amide as described above. Incorporation of a halogen at the 3-position of the indole can
occur through alkylation of Intermediate 83 (as described in Scheme 15), followed by
subjection to NCS, NBS or iodine to give compounds such as 87.

Scheme 17

[00144] Functionalized 6-indolinesulfonamides 93 can be prepared as depicted in
Scheme 18. Acylation of commercially available indoline (88), as described previously
in Scheme 17, can be followed by bromination with, for example, bromine in the
presence of acetic acid to give 5-bromoindolines 90. Installation of the sulfonamide
moiety can occur using the two-step procedure previously outlined in Scheme 13 to give
compound 91. Removal of the bromine using hydrogen and catalytic palladium on
carbon can afford Intermediate 92, which then undergoes reduction as previously
described in Scheme 17 to give compounds such as 93.
Scheme 18

[Scheme image]

[00145] Sulfonamide compound 97 can be prepared from 6-chloronicotinic acid (Aldrich, 94) according to the synthetic route outlined in Scheme 19. Coupling with 2-morpholinoethanol (Aldrich, 95) in the presence of a base, such as potassium ?-butoxide, can generate Intermediate 96. Following conversion to the acid chloride with oxalyl chloride and catalytic DMF, coupling with indolinesulfonamide 80 (prepared in Scheme 17) in the presence of a base, such as potassium carbonate, can provide the functionalized sulfonamide product 97.

Scheme 19

[Scheme image]

[00146] Tetrahydroisoquinoline Intermediates 100 and 103 can be accessed using the synthetic routes shown in Scheme 20. From aldehyde 98, (Schiller, P.W. et al, J. Med. Chem., 36:3182-3187 (1993)) reductive amination as described above can give compound 99, which after Boc-deprotection (described previously) can afford amino derivatives such as 100. Alkoxy derivatives 103 can arise from selective acylation of
tetrahydroisoquinoline 101 (Aldrich) with acetic anhydride in ethyl acetate and methanol, followed by alkylation as described in Scheme 15. Deprotection under acidic (e.g., HCl) or basic (e.g., KOH) conditions can then generate products such as 103.

Benzodiazepines 105 can be synthesized using the two-step procedure depicted in Scheme 21. To this end, benzodiazepinone 104 (Boyer, J.H. et al, J. Chem. Soc., Perkin Trans. I, 2137-2140 (1988)) is subjected to phosphorus oxychloride and then treated with various amines to give compounds such as 105.

Boronic ester Intermediates 110 and 113 can be prepared using the synthetic routes outlined in Schemes 22 and 23. Commercially available dimethyl 4-hydroxyisophthalate (106, TCI) can undergo selective hydrolysis to give mono-acid 107 by refluxing in pyridine. Esterification of benzoic acid 107 with 2-butanol can give bis-ester 108, which reacts with triflic anhydride to give triflate 109. Palladium-catalyzed coupling with bis(pinacolato)diboron then provides Intermediate 110.
Alternatively, benzoic acid 107 can be converted to the acid chloride and then reacted with 1,2,3,4-tetrahydroisoquinoline to give phenol 108 (Scheme 23). Following conversion to the triflate as described above, palladium-catalyzed cross-coupling with bis(neopentyl glycolato)diboron can afford the functionalized boronic ester 113.

Aminopyridine analogs 120 and 121 can be prepared using the synthetic route outlined in Scheme 24. Commercially available 2,6-dibromopyridines 114 can be converted to 2-aminopyridine 115 upon exposure to dibutylamine in the presence of a base, such as potassium carbonate. Suzuki coupling with Intermediate 110 (prepared in
Scheme 22) provides the biaryl compound 116. Selective hydrolysis under basic conditions converts the methyl ester to benzoic acid 117. Compound 117 can react with sulfonamide 118 (prepared according to Scheme 14) to give acylsulfonamide 119 after acid-mediated removal of the β-butylerster. Coupling with substituted various tetrahydroisoquinolines forms the desired product 120. When $R^2 = N_3$, reduction of the azide can be accomplished using, for example, triphenylphosphine to give compound 121.

[00151] Aminopyrimidine analogs can be prepared using the synthetic routes outlined in Schemes 25 and 26. Commercially available trisubstituted pyrimidines 122 can be converted to biaryl compounds, such as 123, via Suzuki coupling reactions with boronic ester Intermediate 113 (prepared in Scheme 23). Displacement of the chlorine with various amines, followed by hydrolysis of the ester and coupling with substituted sulfonamides can be accomplished using the chemistry previously outlined in Scheme 24.
Alternatively, aminopyrimidine compounds such as 130 and 131 can be synthesized according to the route outlined in Scheme 26. From dichloropyrimidine 122, Suzuki coupling with boronic ester Intermediate 110 (prepared in Scheme 22) can provide biaryl compound 128. Subsequent conversion to the dialkylamine and elaboration to the final products 130 and 131 can be achieved using chemistry previously described in Scheme 24.
Trisubstituted imidazole analogs, such as compound 138, can be prepared using the synthetic routes outlined in Schemes 27-31. Commercially available methyl 1H-imidazole-4-carboxylate (132, Maybridge) is SEM protected using an appropriate base such as sodium hydride and selectively brominated using radical bromination methods such as NBS to give bromoimidazole 134. Hydrolysis using aqueous base followed by HATU-mediated amide coupling with suitable amides such as dibutylamine provides imidazole 135. Intermediate 136 is then obtained through Suzuki coupling of imidazole 135 with Intermediate 113 (prepared in Scheme 23). Various alkylation reactions are performed on the imidazole nitrogen by removing the SEM group with suitable reagents such as TFA and coupling a desired alkyl halide such as methyl iodide using an appropriate base such as potassium carbonate to give compound 137. Following procedures previously outlined in Scheme 2, various naphthylsulfonamides 13 can be installed to afford compounds with general structure 138.
Additionally, imidazoles with amide appendages on the imidazole nitrogen (Scheme 28) can be prepared by installing the appropriate $\beta$-butyl ester in the same fashion outlined by Scheme 27 to give 139. Hydrolysis using an acidic medium such as TFA and subsequent HATU-mediated amidation with suitable amides such as dibutylamine can give Intermediate 140. Following procedures previously outlined in Scheme 2, various naphthylsulfonamides 13 were installed to afford compounds of general structure 141.
Alternatively, substituted tetrahydroisoquinoline derivatives such as 145 can be synthesized according to the route outlined in Scheme 29. Intermediate 142 is accessed by reacting compound 107 with benzyl bromide and a suitable base such as potassium hydrogen carbonate. Using methods described in Scheme 22, boronic ester 143 is subsequently obtained. Following the procedures for imidazole coupling described in Scheme 27 can afford compounds such as 144. Lastly, using synthetic steps in Scheme 2, substituted tetrahydroisoquinolines and naphthylsulfonamides were installed in the appropriate locations to give compound 145.
Incorporation of alcohol tethers on the imidazole nitrogen (Scheme 30) can be achieved by installing the desired £-butyl-dimethylsilanol in the same fashion outlined in Scheme 27 to give 146. Leveraging procedures from Scheme 2, substituted tetrahydroisoquinolines and naphthylsulfonamides can be installed in their appropriate locations to afford compound 147. Analogs encompassed by compound 148 may be obtained by removing the silyl protecting groups with a suitable acid such as concentrated hydrochloric acid.
Regioisomeric imidazoles can be accessed through the synthetic route shown in Scheme 31. Amide 150 can be obtained from the commercially available carboxylic acid 149 using similar amide formation and bromination procedures from Scheme 27, where the site of bromination changes as a function of the imidazole substitution. Also, following methods used in Scheme 27, Intermediates 150 and 113 were coupled together and appropriately manipulated to give compounds of structure 151.

\[A = \text{HN-SO}_{\text{Ph}}(\text{R})_n\]
[00158] Fully functionalized, regioisomeric pyrazole analogs 160 can be accessed through the synthetic routes outlined in Schemes 32-34. Iodination of the commercially available benzoic acid 152 (Matrix) in the presence of iodine, palladium (II) acetate, (diacetoxyiodo)benzene and tetrabutylammonium iodide provides iodide 153. Coupling of Intermediate 153 with substituted tetrahydroisoquinoline derivatives, followed by palladium-mediated carbonylation of the requisite Intermediate 154 furnishes aldehyde 155. Treatment of Intermediate 155 with substituted nitro alkane derivatives gives Intermediate 156. The alcohol of compound 156 can be acetylated with acetic anhydride and upon elimination affords alkene 157. Treatment of 157 with various ethyl 2-(2-phenylhydrazono)acetate derivatives in the presence of potassium tert-butoxide provides pyrazoles 158. Hydrolysis of the tert-butyl ester moiety of 158, followed by coupling of substituted sulfonamide derivatives in the presence of a coupling reagent, such as EDC furnishes the desired acylsulfonamides 160.
Reduction or base-mediated hydrolysis of the ester moiety of pyrazoles 160 provides the desired alcohols 161 and carboxylic acid derivatives 162, respectively (Scheme 33 and 34).
All reactions were carried out with continuous magnetic stirring under a nitrogen or argon atmosphere. All evaporations and concentrations were carried out on a rotary evaporator under reduced pressure. Commercial reagents were used as received without additional purification. Solvents were commercial anhydrous grades and were used without further drying or purification. Flash chromatography was performed using prepacked REDISEP® Rf silica gel columns on a CombiFlash Companion machine.
Preparative Reverse Phase (RP) HPLC was performed with a linear gradient elution using H₂O/MeOH or H₂O/MeCN mixtures buffered with 0.1% trifluoroacetic acid or 10 mM NH₄OAc and detection at 220 nm on one of the following columns: Shimadzu Sunfire S10 30 x 250 mm (flow rate = 40 mL/min), or C18 PHENOMENEX® Luna S5 ODS 21 x 100 mm (flow rate = 20 mL/min), or YMC S5 ODS 20 x 100 mm (flow rate = 20 mL/min) or Waters XBridge C18 19 x 250 mm (flow rate = 20 mL/min).

All final products were characterized by ¹H NMR, RP HPLC and electrospray ionization (ESI) or atmospheric pressure ionization (API) mass spectrometry (MS). ¹H NMR spectra were obtained a 500 MHz or a 400 MHz Bruker instrument. Field strengths are expressed in units of δ (parts per million, ppm) relative to the solvent peaks, and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; sext, sextet; br s, broad singlet; m, multiplet.

ABBREVIATIONS

<p>| Ac  | acetyl |
| AcOH | acetic acid |
| Ac₂O | acetic anhydride |
| aq. | aqueous |
| Bn  | benzyl |
| Boc | ?-butyl carbamate |
| Boc₂O | di-?-butyl dicarbonate |
| Bu  | butyl |
| Bu₄NI | tetrabutylammonium iodide |
| CDI | 1,1’-carbonyldiimidazole |
| cone. | concentrated |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCE | dichloroethane |
| DCM | dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DIAD | diisopropyl azodicarboxylate |
| DIEA | diisopropylethylamine |
| DMAP | 4-Ν,Ν-dimethylaminopyridine |</p>
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>DMF</td>
<td>dimethyl formamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>EDC</td>
<td>l-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>Et₃N</td>
<td>triethyl amine</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HATU</td>
<td>0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate</td>
</tr>
<tr>
<td>HNBu2</td>
<td>dibutyl amine</td>
</tr>
<tr>
<td>( \等情况)</td>
<td>1-benzylhydrazine</td>
</tr>
<tr>
<td>HOBT</td>
<td>hydroxybenzotriazole</td>
</tr>
<tr>
<td>HPLC</td>
<td>high pressure liquid chromatography</td>
</tr>
<tr>
<td>( i-\text{-PrOH} )</td>
<td>isopropanol</td>
</tr>
<tr>
<td>( i-\text{-Pr₂EtN} )</td>
<td>di(isopropyl)ethylamine</td>
</tr>
<tr>
<td>KOAc</td>
<td>potassium acetate</td>
</tr>
<tr>
<td>m</td>
<td>minute(s)</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>m-chloro-3-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>Me₂NH</td>
<td>dimethyl amine</td>
</tr>
<tr>
<td>MTBE</td>
<td>methyl tert-butyl ether</td>
</tr>
<tr>
<td>Na(OAc)₃BH</td>
<td>sodium triacetoxyborohydride</td>
</tr>
<tr>
<td>NaSeEt</td>
<td>sodium ethanethiolate</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>w-BuLi</td>
<td>w-butyl lithium</td>
</tr>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
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Example 1
Intermediate 1A: Ethyl 4-chloro-5-methyl-1H-pyrazole-3-carboxylate

[00163] To a solution of ethyl 5-methyl-1H-pyrazole-3-carboxylate (Maybridge, 4.41 g, 28.6 mmol) in DMF (14 mL) was added N-chlorosuccinimide (3.86 g, 28.9 mmol). The resulting solution was heated at 60 °C for 3 h and then cooled to room temperature. Water was added until a white precipitate formed, and the solid was collected by filtration washing with water. The solid was dissolved in CH2Cl2, washed with water (2x), dried over MgSO4 and concentrated in vacuo to provide the title compound (5.14 g, 90%) as a white solid. 1H NMR (CDCl3) δ 8.03 (s, 1H), 4.42 (q, J = 7.0 Hz, 2H), 2.32 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); MS(ESI+)* m/z 188.9 (M+H)+.

Intermediate IB: N,N-Dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide

[00164] To a solution of w-butylamine (900 µL, 5.30 mmol) in THF (4.0 mL) was added w-BuLi (5.0 mL, 7.95 mmol, 2.5M solution in hexanes) at -78 °C. After stirring at -78 °C for 30 min, a solution of ethyl 4-chloro-5-methyl-1H-pyrazole-3-carboxylate (500 mg, 2.65 mmol) in 2.0 mL of THF was added dropwise via syringe. The reaction mixture was allowed to warm to room temperature overnight and quenched with sat. aq. NH4Cl solution. The aqueous layer was extracted with CH2Cl2 (3x), and the combined organic extracts were dried over Na2SO4, filtered and concentrated in vacuo to give a crude oil. Purification using flash column chromatography (gradient from 0% to 7%...
MeOH/CH₂Cl₂) provided the title compound (589 mg, 82%) as a colorless oil. ¹H NMR (CD₃OD) δ 3.51 (t, J = 7.4 Hz, 2H), 3.38-3.32 (m, 2H), 1.68-1.62 (m, 2H), 1.56-1.50 (m, 2H), 1.45-1.38 (m, 2H), 1.22-1.15 (m, 2H) 0.98 (t, J = 7.4 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); MS(ESI⁺) m/z 272.1 (M+H)⁺.

Intermediate 1C: (3,4-Dihydroisoquinolin-2(1H)-yl)(2-fluoro-5-iodophenyl)methanone

[00165] To a suspension of 2-fluoro-5-iodobenzoic acid (Aldrich, 5.27 g, 19.8 mmol) in CH₂Cl₂ (35.0 mL) was added oxalyl chloride (14.9 mL, 29.7 mmol, 1M solution in CH₂Cl₂) followed by 2 drops of DMF via syringe. Gas evolution was initiated and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was then quenched with sat. aq. NH₄Cl solution and extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to give crude 2-fluoro-5-iodobenzoyl chloride which was used directly in the next step.

[00166] The crude product obtained above was dissolved in CH₂Cl₂ (49.6 mL) and cooled to 0 °C. To the solution were added 1,2,3,4-tetrahydroisoquinoline (2.7 mL, 21.8 mmol) followed by 2,6-lutidine (4.6 mL, 39.7 mmol). The resulting reaction mixture was stirred at room temperature for 1 h. The reaction mixture was washed in HCl (2 x) and the organic layer was extracted with CH₂Cl₂ (2 x). The combined organic extracts were washed with sat. aq. NaCl solution and dried over Na₂SO₄. Filtration and concentration in vacuo provided the title compound (7.55 g, 95%) as a viscous, yellow oil. ¹H NMR (CDCl₃, 1:5:1 mixture of amide rotamers) δ 7.78-7.66 (m, 2H), 7.26-7.12 (m, 3.5H), 6.98-6.86 (m, 1.5H), 4.92 (s, 1.5H), 4.50 (br s, 0.5H), 3.65-3.52 (m, 1.5H), 3.04-2.95 (m, 1H), 2.92-2.82 (m, 1.5H); MS(ESI⁺) m/z 382.1 (M+H)⁺.

Intermediate ID: Ethyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate
To 2-neck round bottom flask equipped with a reflux condenser was added (3,4-dihydroisoquinolin-2(1H)-yl)(2-fluoro-5-iodophenyl)methanone (8.39 g, 22.0 mmol) and MeCN (65.0 mL). Et₃N (6.2 mL, 44.0 mmol), EtOH (6.4 mL, 110 mmol, 200 proof) and Pd(dppf)₂Cl₂ (1.29 g, 1.76 mmol) were then added, and a 3-way stopcock was attached to the reflux condenser with one outlet connected to a balloon and the other connected to a CO tank. The flask was evacuated and purged with CO from the balloon (3 x), and then heated at 75 °C under CO for 7 h. The reaction mixture was then concentrated in vacuo and the residue was purified by flash chromatography (gradient from 0% to 40% EtOAc/hexanes) to afford the title compound (5.52 g, 77%) as a clear, tan oil. ¹H NMR (CDCl₃, 1.5:1 mixture of amide rotamers) δ 8.20-8.07 (m, 1.5H), 7.26-7.10 (m, 5H), 6.92 (d, J = 7.3 Hz, 0.5H), 4.95 (s, 2H), 4.50 (br s, 1H), 4.42-4.35 (m, 2H), 3.57 (t, J = 5.7 Hz, 1H), 3.00 (t, J = 5.9 Hz, 1H), 2.88 (t, J = 5.6 Hz, 1H), 1.42-1.36 (m, 3H); MS(ESI⁺) m/z 328.2 (M+H)⁺.

Intermediate IE: Ethyl 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

To a solution of ethyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (645 mg, 1.97 mmol) and N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (1.07 g, 3.94 mmol) in NMP (9.9 mL) was added K₂CO₃ (1.09 g, 7.88 mmol). The resulting reaction mixture was stirred at 125 °C for 3 h, cooled to room temperature and quenched with 10% aq. LiCl solution. The solution was extracted with EtOAc (3 x) and the combined organic extracts were washed with 10% LiCl (3 x), dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash...
chromatography (25% EtOAc/CHCl₃) to afford the title compound (930 mg, 81%). 

1H NMR (DMSO-d₆, 2:1 mixture of amide rotamers) δ 8.32 (s, 0.5H), 8.23-8.13 (m, 1H), 8.1-8.00 (m, 1H), 7.76-7.87 (m, 0.5H), 7.28-7.08 (m, 3.5H), 7.03-6.94 (m, 0.5H), 4.87-4.51 (m, 2H), 4.43-4.27 (m, 2.5H), 3.86-3.75 (m, 0.5H), 3.63-3.32 (m, 3H), 3.23-3.07 (m, 1H), 3.05-2.94 (m, 1H), 2.85-2.62 (m, 2H), 2.27 (s, 2H), 2.22 (s, 1H), 1.48-1.09 (m, 9H), 1.04-0.92 (m, 2H), 0.90-0.82 (m, 3H), 0.70-0.63 (m, 3H); MS(ESI⁺) m/z 579.4 (M+H)⁺.

Intermediate IF: 4-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

![Chemical structure of Intermediate IF](image)

[00169] To a solution of ethyl 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (930 mg, 1.61 mmol) in EtOH (5.0 mL) and THF (5.0 mL) was added 2N NaOH (4.0 mL, 8.03 mmol). The resulting reaction mixture was stirred at 40 °C for 1 h, cooled to room temperature and quenched with 6N HCl. The solution was extracted with CHCl₃ (3 x), and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to afford the title compound (885 mg, 99%), which was used without further purification. 

1H NMR (DMSO-d₆, 2:1 mixture of amide rotamers) δ 8.32 (s, 0.5H), 8.14 (dd, J = 8.36, 1.98 Hz, 1H), 8.07-7.98 (m, 1H), 7.83-7.72 (m, 1H), 7.28-7.06 (m, 3H), 7.03-6.93 (m, 0.5H), 4.68-4.65-4.47 (m, 1H), 4.42-4.24 (m, 0.5H), 3.88-3.70 (m, 0.5H), 3.66-3.34 (m, 3.5H), 3.23-3.06 (m, 1H), 3.04-2.94 (m, 1H), 2.87-2.70 (m, 2H), 2.26 (s, 2H), 2.21 (s, 1H), 1.47-1.34 (m, 0.5H), 1.33-1.06 (m, 5.5H), 1.01-0.91 (m, 2H), 0.88-0.82 (m, 3H), 0.70-0.62 (m, 3H); MS(ESI⁺) m/z 551.3 (M+H)⁺.

Example 1:

[00170] To a mixture of 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (30 mg, 0.054 mmol) and naphthalene-2-sulfonamide (18 mg, 0.087 mmol) in DMF (0.5 mL) and THF (1.0 mL)
was added EDC (21 mg, 0.11 mmol) followed by DMAP (20 mg, 0.16 mmol). The resulting reaction mixture was stirred at room temperature for 3 h. The solvents were removed in vacuo and the residue was purified by preparative HPLC to give the title compound (27 mg, 64%). ¹H NMR (CD₃OD, 2:1 mixture of amide rotamers) δ 8.73 (s, 1H), 8.13-8.03 (m, 4H), 8.01 (d, J = 8.2 Hz, 1H), 7.99-7.95 (m, 1H), 7.76-7.64 (m, 3H), 7.25-7.05 (m, 3.5H), 6.90 (d, J = 7.7 Hz, 0.5H), 5.03-4.87 (m, 1H), 4.68-4.38 (m, 2H), 4.09-3.92 (m, 0.5H), 3.78-3.36 (m, 2.5H), 3.26-2.55 (m, 4H), 2.33 (s, 2H), 2.28 (s, 1H), 1.55-0.86 (m, 12H), 0.76 (t, J = 7.4 Hz, 2H), 0.70 - 0.65 (m, 1H); MS(ESI⁺) m/z 740.2 (M+H)⁺.

Intermediate 2
5-Chloronaphthalene-2-sulfonamide

[00171] 5-Chloronaphthalene-2-sulfonyl chloride (Toronto, 531 mg, 2.03 mmol) was treated with N⁷/₄ (10.2 mL, 5.08 mmol, 0.5 M solution in dioxanes) and stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo, redissolved in sat. aq. NaHCO₃ solution and extracted with CHCl₃ (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (200 mg, 37%). ¹H NMR (DMSO-d₆) δ 8.53 (d, J = 1.8 Hz, 1H), 8.36 (d, J = 9.0 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 9.0 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.70-7.62 (m, 1H); MS(EST) m/z 240.3 (M-H)⁻.

Intermediate 3
6-(Dimethylamino)naphthalene-2-sulfonamide

[00172] Following a procedure analogous to the synthesis of Intermediate 2, 6-(dimethylamino)naphthalene-2-sulfonyl chloride (Aldrich, 63 mg, 0.23 mmol) was converted to the title compound (14 mg, 25%). MS(EST) m/z 249.4 (M-H)⁻.
Intermediate 4

5-(Dimethylamino)naphthalene-1-sulfonamide

Following a procedure analogous to the synthesis of Intermediate A in Example 2, 5-(dimethylamino)naphthalene-1-sulfonamide chloride (Aldrich, 500 mg, 1.85 mmol) was converted to the title compound (36 mg, 8%). 1H NMR (DMSO-d6) δ 8.10 (d, J = 8.6 Hz, 1H), 7.96 (d, J = 8.6 Hz, 1H), 7.79 (dd, J = 13.2, 7.3 Hz, 1H), 7.35-7.13 (m, 4H), 6.93 (d, J = 7.3 Hz, 1H), 3.01 (s, 6H); MS(ESF) m/z 249.4 (M-H)-.

Intermediate 5

8-Chloronaphthalene-2-sulfonamide

Intermediate 5A: 8-Chloronaphthalene-2-sulfonic acid

A solution of 8-amino-2-naphthalenesulfonic acid (Aldrich, 1.00 g, 4.48 mmol) in water (3.0 mL) and cone. HCl (7.0 mL) was cooled to 0 °C. A solution of NaN3 (143 µL, 4.48 mmol) in water (3.0 mL) was added dropwise while maintaining the temperature below 5 °C. The reaction mixture was stirred at 0 °C for 1 h. In a separate flask, CuCl (214 µL, 8.96 mmol) was dissolved in cone. HCl (7.0 mL) and the solution was cooled to 0 °C. The copper solution was added to the diazonium solution at 0 °C in portions to control the gas evolution. The reaction mixture was allowed to stir at 0 °C for 1 h and then at room temperature for 12 h. The reaction mixture was then diluted with 10% aq. NH4Cl solution and extracted with EtOAc (3 x). The combined organic extracts were washed again with aq. 10% NH4Cl solution, dried over Na2SO4, filtered and concentrated in vacuo to give the title compound (740 mg, 65%). 1H NMR
(DMSO-d$_6$) $\delta$ 8.43 (s, 1H), 7.95 (dd, $J = 17.1$, 8.5 Hz, 2H), 7.80 (dd, $J = 8.4$, 1.5 Hz, 1H), 7.71 (dd, $J = 7.5$, 1.1 Hz, 1H), 7.57-7.45 (m, 1H); MS(EST) m/z 241.2 (M-H)$^-$. 

Intermediate 5: 

[00175] 8-Chloronaphthalene-2-sulfonic acid (740 mg, 3.05 mmol) and 2,4,6-trichloro-1,3,5-triazine (562 mg, 3.05 mmol) were stirred in acetone (25.0 mL) at room temperature. Et$_3$N (425 µL, 3.05 mmol) was then added, and the reaction mixture was stirred at reflux overnight. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated in vacuo and used in the next step without further purification. 

[00176] The crude product obtained above was treated with NH$_3$ (30.3 mL, 0.5M solution in dioxanes) at room temperature. Cone. NH$_3$OH (10.0 mL) was added, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo to remove the volatiles, and the remaining slurry was treated with water. The solid that precipitated was collected via filtration, washed with water and dried under high vacuum overnight to give the title compound (145 mg, 19%). ¹H NMR (DMSO-d$_6$) $\delta$ 8.66 (br s, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 8.14-7.93 (m, 2H), 7.87 (d, $J = 6.8$ Hz, 1H), 7.69 (br s, 1H), 7.59 (br s, 2H); MS(EST) m/z 240.3 (M-H)$^-$. 

Intermediate 6 

6-Chloronaphthalene-2-sulfonamide

![6-Chloronaphthalene-2-sulfonamide](image)

Intermediate 6A: 6-Chloronaphthalene-2-sulfonic acid

![6-Chloronaphthalene-2-sulfonic acid](image)

[00177] Following a procedure analogous to that for the synthesis of Intermediate 5A, 6-aminonaphthalene-2-sulfonic acid (Aldrich, 2.00 g, 8.96 mmol) was converted to the title compound (760 mg, 33%). ¾ NMR (DMSO-d$_6$) $\delta$ 8.18 (s, 1H), 8.1 1-7.98 (m, 2H).
7.87 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.53 (dd, J = 8.8, 1.5 Hz, 1H);
MS(ESI') m/z 241.2 (M-H)^-.

Intermediate 6:

5  [00178] Following a procedure analogous to that for the synthesis of Intermediate 5, 6-chloronaphthalene-2-sulfonic acid (760 mg, 3.13 mmol) was converted to the title compound (600 mg, 71%). ¾ NMR (DMSO-d₆) δ 8.48 (br s, 1H), 8.37-8.02 (m, 3H), 7.94 (br s, 1H), 7.68 (br s, 1H), 7.60-7.33 (m, 2H).

10 Intermediate 7

8-Iodonaphthalene-2-sulfonamide

[00179] To a solution of KOH (560 mg, 9.99 mmol) in water (16.0 mL) was added 8-amino-2-naphthalenesulfonic acid (Aldrich, 2.23 g, 9.99 mmol) with warming. KNO₃ (850 mg, 9.99 mmol) was then added. The solution was cooled to room temperature and added dropwise to IN H₂SO₄ (14.0 mL, 14.0 mmol) over 35 min at 0 °C, keeping the internal temperature at or below 0 °C. After stirring for a further 10 min, a solution of KI (2.00 g, 12.1 mmol) in water (10.0 mL) was added dropwise over 5 min. The reaction mixture was then stirred at room temperature for 2 h and then on a steam bath for 1 h. The solution was cooled to room temperature treated with EtOH. The reaction mixture was concentrated to near dryness in vacuo and the remaining slurry was filtered, washing the solids with EtOH. The filtrate was concentrated in vacuo to afford the title compound (2.42 g, 65%) which was used in the next step without further purification. MS(EST) m/z 333.2 (M-H)^-.

25 [00180] The crude product obtained above was treated with POCI₃ (30.0 mL, 322 mmol), and the resulting reaction mixture was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The residue was azeotroped with PhMe (3 x) and then treated with NH₃ (0.5M solution in dioxane) while cooling in an ice bath. Cone. NH₄OH (10.0 mL, 601 mmol) was added, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was
concentrated *in vacuo*, water was added and the solution was acidified with cone. HCl. The solution was saturated with NaCl and extracted with EtOAc (7 x). The combined organic extracts were dried over MgSO₄, filtered and concentrated *in vacuo* to afford the title compound (1.80 g, 71%). ¹H NMR (DMSO-d₆) δ 8.55-8.51 (m, 1H), 8.28 (dd, *J* = 7.4, 1.0 Hz, 1H), 8.14 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 7.94 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.58 (s, 2H), 7.48-7.41 (m, 1H); MS(EST) *m/z* 332.3 (M-H)⁻.

Intermediate 8

8-Cyanonaphthalene-2-sulfonamide

![Intermediate 8](image)

[00181] A solution of 8-iodonaphthalene-2-sulfonamide (Intermediate 7, 100 mg, 0.30 mmol), ZnCN (11 µL, 0.180 mmol) and Pd(PPh₃)₄ (14 mg, 0.012 mmol) in DMF (1.5 mL) was purged with argon for 5 min. The reaction mixture was then heated to 125 °C in a microwave reactor for 30 min. Additional ZnCN (33 µL, 0.54 mmol) and Pd(PPh₃)₄ (280 mg, 0.24 mmol) were added, and the reaction mixture was heated at 125 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with 10% aq. LiCl solution and extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by preparative HPLC to give the title compound (22 mg, 30%). ¹H NMR (CD₃OD) δ 8.77 (d, *J* = 0.9 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 8.19 (d, *J* = 7.3 Hz, 1H), 8.14 (d, *J* = 1.8 Hz, 1H), 7.85-7.75 (m, 1H); MS(ESI⁺) *m/z* 250.1 (M + NH₄⁺).

Intermediate 9

Ethyl 7-sulfamoyl-l-naphthoate

![Intermediate 9](image)

[00182] To a solution of 8-iodonaphthalene-2-sulfonamide (Intermediate 7, 200 mg, 0.60 mmol) in dioxane (2.0 mL) in a microwave tube was added EtOH (400 µL, 6.00 mmol), molybdenum hexacarbonyl (81 µL, 0.60 mmol) and Pd(OAc)₂ (17 mg, 0.075
mmol). DBU (270 µL, 1.80 mmol) was then added, and the sealed tube was placed in the microwave and heated at 100 °C for 20 min. The reaction mixture was cooled to room temperature and quenched with 10% aq. LiCl solution. The solution was extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified using preparative HPLC to give the title compound (22 mg, 13%).

\[ \text{HNMR (CD₃OD) } \delta 9.54 (d, J = 0.9 \text{ Hz}, 1\text{H}), 8.31 (dd, J = 7.4, 1.2 \text{ Hz}, 1\text{H}), 8.20 (d, J = 8.4 \text{ Hz}, 1\text{H}), 8.13 (d, J = 8.8 \text{ Hz}, 1\text{H}), 8.00 (dd, J = 8.7, 1.9 \text{ Hz}, 1\text{H}), 7.72 (dd, J = 8.2, 7.4 \text{ Hz}, 1\text{H}), 4.50 (q, J = 7.0 \text{ Hz}, 2\text{H}), 1.48 (t, J = 7.2 \text{ Hz}, 3\text{H}); \]

\[ \text{MS(EST) } m/z 278.4 (M-H)^- \].

Intermediate 10:

7-Chloronaphthalene-2-sulfonamide

\[ \text{(Int-10)} \]

Intermediate 10A: 7-Chloronaphthalene-2-sulfonic acid

\[ \text{(Int-10A)} \]

[00183] A solution of sodium 7-aminonaphthalene-2-sulfonate (Pfaltz and Bauer, 1.00 g, 4.08 mmol) in water (6.0 mL) and conc. HCl (6.0 mL) was cooled to 0 °C. A premixed solution of NaN₃ (295 mg, 4.28 mmol) in water (3.0 mL) was added slowly, maintaining the temperature close to 0 °C. The resulting reaction mixture was stirred at room temperature for 30 min. A solution of CuCl (807 mg, 8.16 mmol) in water (1.0 mL) and conc. HCl (4.0 mL) was then added dropwise over 30 min, maintaining the temperature close to 0 °C. The reaction mixture was stirred at room temperature for 2 h, then concentrated in vacuo and dissolved in a small amount of water. The solids were filtered off and retained. The filtrate was concentrated in vacuo, purified by preparative HPLC and combined with the filtered solids to give the title compound (843 mg, 85%) as a dark grey solid. MS(EST) m/z 241.2 (M-H)^-.
Following a procedure analogous to that for the synthesis of Intermediate 5, 7-chloronaphthalene-2-sulfonic acid (500 mg, 2.06 mmol) was converted to the title compound (84 mg, 17%). MS(ESF) \textit{m/z} 240.3 (M-H). 

Intermediate 11

7-Iodonaphthalene-2-sulfonamide

\[ \text{(Int-11)} \]

Intermediate 11A: 7-Iodonaphthalene-2-sulfonic acid

\[ \text{(Int-11A)} \]

A solution of sodium 7-aminonaphthalene-2-sulfonate (Pfaltz and Bauer, 1.00 g, 4.06 mmol) in water (6.0 mL) and cone. HCl (2.0 mL) was cooled to 0 °C. A premixed solution of NaNO\textsubscript{2} (280 mg, 4.06 mmol) in water (2.0 mL) was added slowly, maintaining the temperature close to 0 °C. The reaction mixture was stirred at 0 °C for 1 h. A solution of Nal (609 mg g, 4.06 mmol) in water (3.0 mL) and cone. HCl (1.0 mL) was then added dropwise over 30 min, maintaining a temperature close to 0 °C. The reaction mixture was stirred at room temperature for 2 h and then heated to 90 °C for 1 h. The reaction mixture was cooled to room temperature, treated with EtOH (10.0 mL) and concentrated \textit{in vacuo}. EtOH (10 mL) was added and the mixture was filtered to give the title compound (1.07 g, 79%) as a tan solid. \textsuperscript{1}H NMR (DMSO-\textit{d}_\textsubscript{6}) \textit{\delta} 8.45 (s, 1H), 8.09 (s, 1H), 8.76 (d, \textit{J} = 8.6 Hz, 1H), 7.80-7.68 (m, 3H); MS(EST) \textit{m/z} 333.2 (M-H). 

Intermediate 11:

7-Iodonaphthalene-2-sulfonic acid (650 mg, 1.95 mmol) was treated with POCI\textsubscript{3} (5.0 mL, 53.6 mmol), and the resulting reaction mixture was heated at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated \textit{in vacuo}. The residue was azeotroped with PhMe (3 x) and then treated with NH\textsubscript{3} (6.0 mL, 277.0 mmol, 0.5M solution in dioxane) while cooling in an ice bath. Cone. NH\textsubscript{4}OH (6.0 mL) was added, and the reaction mixture was allowed to warm to room temperature. The reaction
mixture was concentrated \textit{in vacuo}, water was added and the solution was acidified with HCl (pH = 4). The solution was saturated with NaCl and extracted with EtOAc (7 x). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated \textit{in vacuo} to afford the title compound (300 mg, 46%). $^{1}$H NMR (CDCl$_3$) $\delta$ 8.37 (br s, 2H), 7.99-7.85 (m, 3H), 7.66 (d, $J$ = 8.6 Hz, 1H); MS(EST) $m$/z 332.2 (M-H)$^-$. 

\textbf{Intermediate 12}

5-Nitronaphthalene-1-sulfonamide

\begin{align*}
\text{H}_2\text{N}&\text{SO}_3\text{O} \quad \text{NO}_2 \quad \text{(Int-12)}
\end{align*}

To a solution of nitronaphthalene (2.1 g, 12.1 mmol) in CH$_2$Cl$_2$ (50.0 mL) at 0 °C was added chlorosulfonic acid (5.0 mL, 75 mmol) dropwise. The resulting red solution was allowed to warm to room temperature overnight and then poured over ice. The layers were separated and the aqueous layer was extracted with EtOAc (3 x). The combined organic extracts were washed with sat. aq. NaCl solution, dried over Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo}. The residue was treated with NH$_3$ (0.5M solution in dioxane) and the resulting solution was stirred at room temperature overnight. The reaction mixture was then treated with EtOH and concentrated \textit{in vacuo}. The solid was collected via filtration and purified by preparative HPLC to give the title compound (1.00 g, 32%). $^{1}$H NMR (CD$_3$OD) $\delta$ 8.73-8.56 (m, 2H), 8.43 (dd, $J$ = 8.1, 1.8 Hz, 2H), 8.19 (dd, $J$ = 9.4, 1.8 Hz, 1H), 7.18 (t, $J$ = 7.9 Hz, 1H); MS(EST) $m$/z 251.3 (M-H)$^-$. 

\textbf{Intermediate 13}

5-Nitronaphthalene-2-sulfonamide

\begin{align*}
\text{H}_2\text{N}&\text{SO} \quad \text{NO}_2 \quad \text{(Int-13)}
\end{align*}

The filtrate from above (Intermediate 12) was concentrated \textit{in vacuo} to give the regioisomeric product, 5-nitronaphthalene-2-sulfonamide (1.00g, 32%). $^{1}$H NMR (CD$_3$OD) $\delta$ 9.12 (d, $J$ = 8.8 Hz, 1H), 8.59 (d, $J$ = 8.8 Hz, 1H), 8.43 (d, $J$ = 7.3 Hz, 1H), 8.30 (d, $J$ = 6.8 Hz, 1H), 7.85 (dd, $J$ = 8.7, 7.6 Hz, 2H); MS(EST) $m$/z 251.3 (M-H)$^-$. 

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Intermediate 14
8-(Ethylsulfonyl)naphthalene-2-sulfonamide

Intermediate 14A: 8-(Ethylthio)naphthalene-2-sulfonamide

[00189] A solution of 8-iodonaphthalene-2-sulfonamide (Intermediate 7, 100 mg, 0.30 mmol), [1,1’-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (12 mg, 0.015 mmol) and sodium ethanethiolate (50 mg, 0.60 mmol) in DMF (2 mL) was purged with argon. The reaction mixture was heated to 50 °C for 12 h. Additional sodium ethanethiolate (25 mg, 0.30 mmol) and [1,1’-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (240 mg, 0.30 mmol) were added, and the reaction mixture was heated at 125 °C for 12 h. The reaction mixture was cooled to room temperature, diluted with 10% aq. LiCl solution and extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (24 mg, 30%). ¹H NMR (CD₃OD) δ 9.02-8.98 (m, 1H), 8.08-8.03 (m, 1H), 8.00-7.95 (m, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.73 (dd, J = 7.4, 1.0 Hz, 1H), 7.64-7.57 (m, 1H), 3.09 (q, J = 7.3 Hz, 2H), 1.34 (t, J = 7.4 Hz, 3H); MS(EST) m/z 266.2 (M-H)⁻.

Intermediate 14:

[00190] To a solution of 8-(ethylthio)naphthalene-2-sulfonamide (22 mg, 0.082 mmol) in CH₂Cl₂ (1.0 mL) was added m-CPBA (37 mg, 0.16 mmol). The resulting reaction mixture was stirred overnight at room temperature and then concentrated in vacuo. The residue was dissolved in DMF and purified by preparative HPLC to give the title compound (24 mg, 97%). ³¹P NMR (CD₃OD) δ 9.37 (d, J = 0.9 Hz, 1H), 8.44-8.36
Following a procedure analogous to that for the synthesis of Intermediate 8, 7-iodonaphthalene-2-sulfonamide (Intermediate 11, 75 mg, 0.22 mmol) was converted to the title compound (36 mg, 69%). $^1$H NMR (DMSO-d$_6$) $\delta$ 8.63 (s, 1H), 8.38 (d, $J = 1.7$ Hz, 1H), 8.11 (d, $J = 8.8$ Hz, 1H), 7.92 (ddd, $J = 15.4, 8.6, 1.8$ Hz, 2H), 7.83 (d, $J = 8.6$ Hz, 1H), 7.46 (br s, 2H); MS(EST) $m/z$ 231.3 (M-H)

**Intermediate 15**

7-Cyanonaphthalene-2-sulfonamide

![Structural formula](image)

**Intermediate 16**

Ethyl 7-sulfamoyl-2-naphthoate

![Structural formula](image)

To a solution of 7-iodonaphthalene-2-sulfonamide (Intermediate 11, 70 mg, 0.21 mmol) in DMF (2.0 mL) and EtOH (2.0 mL, 34.2 mmol) was added bis(triphenylphosphine)palladium chloride (74 mg, 0.11 mmol). After purging the solution with nitrogen, the reaction flask was evacuated and refilled with CO. The reaction mixture was heated to 70 °C for 3 h. Pd(OAc)$_2$ (47 mg, 0.21 mmol) was then added, and the reaction flask was evacuated and refilled with CO. After stirring under CO overnight at 70 °C, the reaction mixture was cooled to room temperature, taken up in a biphasic mixture of EtOAc and water, and filtered. The layers were separated and the aqueous layer was extracted with EtOAc (3 x). The combined organic fractions were dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (20 mg, 34%) as a white solid. $^1$H NMR (MeOD) $\delta$ 8.82 (s, 1H), 8.63 (d, $J = 1.3$ Hz, 1H), 8.22 (d, $J = 8.8$ Hz, 1H), 8.17-8.12 (m, 2H), 8.02 (dd, $J = 8.6, 2.0$ Hz, 1H), 7.52 (s, 2H), 4.40 (q, $J = 7.0$ Hz, 2H), 1.38 (t, $J = 7.2$ Hz, 3H); MS(EST) $m/z$ 278.3 (M-H)
Intermediate 17
7-(Ethylsulfonyl)naphthalene-2-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 14, 7-iodonaphthalene-2-sulfonamide (Intermediate 11, 100 mg, 0.30 mmol) was converted to the title compound (22 mg, 96%). 1H NMR (CD$_3$OD) $\delta$ 8.57 (dd, $J = 2.5$, 1.9 Hz, 2H), 8.16-8.08 (m, 2H), 8.05-8.01 (m, 1H), 7.95 (dd, $J = 8.6$, 1.8 Hz, 1H), 3.23 (q, $J = 7.5$ Hz, 2H), 1.16 ($J = 7.4$ Hz, 3H); MS(EST) m/z 298.3 (M-H)$^-$. 

Intermediate 18
7-(Benzyloxy)naphthalene-2-sulfonamide

To a solution of sodium 7-oxidonaphthalene-2-sulfonate (TCI, 100 mg, 0.37 mmol) and (bromomethyl)benzene (89 $\mu$L, 0.75 mmol) in DMF (1.0 mL) was added KOH (21 mg, 0.37 mmol), and resulting reaction mixture was stirred at 60 °C for 12 h. The reaction mixture was cooled to room temperature, taken up in a biphasic mixture of EtOAc and water, and filtered to remove any solids. The layers were separated and the aqueous layer was extracted with EtOAc (3 x). The aqueous layer was concentrated in vacuo to give the crude sulfonic acid which was used in the next step without further purification.

Following a procedure analogous to that for the synthesis of Intermediate 11, the crude product from above was converted to the title compound (89 mg, 76%). 1H NMR (DMSO-$d_6$) $\delta$ 8.30 (d, $J = 1.5$ Hz, 1H), 8.03 (d, $J = 8.6$ Hz, 1H), 7.96 (d, $J = 9.0$ Hz, 1H), 7.72 (dd, $J = 8.6$, 2.0 Hz, 1H), 7.66 (d, $J = 2.4$ Hz, 2H), 7.57-7.51 (m, 1H), 7.47-7.28 (m, 6H), 5.27 (s, 2H); MS(EST) m/z 312.3 (M-H)$^-$. 

Intermediate 19
3,4-Dichloro-N-(7-sulfamoylnaphthalen-1-yl)benzamide

\[ \text{H}_2\text{N}\text{-SO}_2\text{HN-OC-Cl} \]  
(Int-19)

Intermediate 19A: 8-(3,4-Dichlorobenzamido)naphthalene-2-sulfonic acid

\[ \text{HO-SO}_2\text{HN-OC-Cl} \]  
(Int-19A)

[00196] 8-Amino-2-naphthalenesulfonic acid (Aldrich, 1.00 g, 4.48 mmol) and 3,4-
dichlorobenzoyl chloride (938 mg, 4.48 mmol) were dissolved in pyridine (10.0 mL), and
the resulting reaction mixture was stirred at room temperature for 12 h. The reaction
mixture was then concentrated \textit{in vacuo}, and the residue was dissolved in IN HCl. The
solution was extracted with EtOAc (5 x), and the combined organic extracts were dried
over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated \textit{in vacuo} to afford the title compound (1.70 g,
91%). \textsuperscript{1}HNMR (DMSO-d\textsubscript{6}) \( \delta \) 11.30 (s, 1H), 8.93 (d, \( J = 2.0 \) Hz, 1H), 8.83 (s, 1H), 8.65
(dd, \( J = 8.0, 1.9 \) Hz, 1H), 8.58-8.50 (m, 1H), 8.50-8.43 (m, 2H), 8.34 (dd, \( J = 8.6, 1.5 \) Hz,
1H), 8.19-8.14 (m, 2H), 6.14 (br s, 1H); MS(EST) \( m/z \) 394.2 (M-H)

Intermediate 19:

[00197] Following a procedure analogous to that for the synthesis of Intermediate 11,
8-(3,4-dichlorobenzamido)naphthalene-2-sulfonic acid was converted to the title
compound (1.56 g, 92%). \textsuperscript{3}NMR (DMSO-d\textsubscript{6}) \( \delta \) 8.49-8.29 (m, 1H), 8.14-7.97 (m, 2H),
7.96-7.56 (m, 6H), 7.50-7.44 (m, 1H), 7.39 (s, 1H), 6.77 (br s, 1H); MS(EST) \( m/z \) 392.2
(M-H)

Intermediate 20

7-(4-(Methylsulfonyl)benzyloxy)naphthalene-2-sulfonamide

\[ \text{H}_2\text{N-SO}_2\text{O-OC-SO}_2\text{CH}_3 \]  
(Int-20)
Following a procedure analogous to that for the synthesis of Intermediate 18, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 100 mg, 0.37 mmol) and 1-(bromomethyl)-4-(methylsulfonyl)benzene (186 mg, 0.75 mmol) were converted to the title compound (52 mg, 45%). ³¹NMR (DMSO-d₆) δ 8.29 (s, 1H), 8.01-7.95 (m, 3H), 7.90-7.86 (m, 2H), 7.82-7.78 (m, 2H), 7.69-7.64 (m, 1H), 7.44-7.39 (m, 2H), 5.41 (s, 2H), 2.64 (s, 3H); MS(ESI) m/z 390.3 (M-H)

Intermediate 21
8-(3,4-Dichlorobenzyloxy)naphthalene-2-sulfonamide

[00199]

Following a procedure analogous to that for the synthesis of Intermediate 18, sodium 8-hydroxynaphthalene-2-sulfonic acid (100 mg, 0.37 mmol) and 4-(bromomethyl)-1,2-dichlorobenzene (81 µL, 0.56 mmol) were converted to the title compound (17 mg, 10%). ¹H NMR (DMF-d₇) δ 8.85 (s, 1H), 8.13 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.91 (d, J = 1.8 Hz, 1H), 7.77-7.72 (m, 1H), 7.70-7.59 (m, 3H), 7.47 (br s, 2H), 7.27 (dd, J = 7.0, 1.3 Hz, 1H), 5.48 (s, 2H); MS(ESI) m/z 380.2 (M-H)

Intermediate 22
7-(3,4-Dichlorobenzyloxy)naphthalene-2-sulfonamide

[00200] Following a procedure analogous to that for the synthesis of Intermediate 18, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 100 mg, 0.37 mmol) and 4-(bromomethyl)-1,2-dichlorobenzene (108 µL, 0.75 mmol) were converted to the title compound (89 mg, 62%). ¹H NMR (DMSO-d₆) δ 8.30 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.73 (dd, J = 8.6, 1.8 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 2.6 Hz, 1H), 7.52 (dd, J = 8.3, 1.9 Hz, 1H), 7.43-7.38 (m, 3H), 5.28 (s, 2H); MS(ESI) m/z 380.2 (M-H)
Intermediate 23

7-((Tetrahydrofuran-2-yl)methoxy)naphthalene-2-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 18, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 100 mg, 0.37 mmol) and 2-(bromomethyl)tetrahydrofuran (62 mg, 0.37 mmol) were converted to the title compound (21 mg, 18%). MS(ESi) m/z 306.3 (M-H)^-.

Intermediate 24

7-Isopropoxynaphthalene-2-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 18, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 100 mg, 0.37 mmol) and 2-bromopropane (46 mg, 0.37 mmol) were converted to the title compound (98 mg, 98%).

\[ ^1H \text{NMR (DMSO-d}_6) \delta 8.30 (s, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.69 (dd, J = 8.6, 1.8 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.38 (s, 2H), 7.28 (dd, J = 8.9, 2.5 Hz, 1H), 4.81 (quin, J = 6.0 Hz, 1H), 1.34 (d, J = 5.9 Hz, 6H); MS(ESi) m/z 264.4 (M-H)^- \]

Intermediate 25

7-(2-Phenoxyethoxy)naphthalene-2-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 18, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 100 mg, 0.37 mmol) and (2-bromoethoxy)benzene (150 mg, 0.75 mmol) were converted to the title compound (84 mg, 66%). MS(ESi) m/z 342.3 (M-H)^-.
Intermediate 26
Methyl 4-((7-sulfamoylnaphthalen-1-yloxy)methyl)benzoate

![Methyl 4-((7-sulfamoylnaphthalen-1-yloxy)methyl)benzoate](Int-26)

Intermediate 26A: 8-Hydroxynaphthalene-2-sulfonic acid

![8-Hydroxynaphthalene-2-sulfonic acid](Int-26A)

[00204] A solution of 8-amino-2-naphthalenesulfonic acid (Aldrich, 2.40 g, 10.8 mmol) and 3.9M aq. NaHSO₃ solution (20.0 mL, 77.0 mmol) in water (10.0 mL) was refluxed for 15 h. The reaction mixture was then basified with 30% aq. NaOH solution (430 mg, 10.8 mmol) and refluxed for 4 h. The reaction mixture was neutralized with cone. HCl and then concentrated in vacuo. The remaining solid was azeotroped with 1:1 MeOH/PhMe (3 x) to give the title compound (2.41 g, 95%). ^1H NMR (DMSO-d₆) δ 9.43 (br s, 1H), 8.36 (s, 1H), 7.96 d, J = 8.4 Hz, 1H), 7.88-7.78 (m, 2H), 7.52 (t, J = 7.8 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H); MS(EST) m/z 222.3 (M-H)^+.  

Intermediate 26B: 8-(4-(Methoxycarbonyl)benzyloxy)naphthalene-2-sulfonic acid

![8-(4-(Methoxycarbonyl)benzyloxy)naphthalene-2-sulfonic acid](Int-26B)

[00205] 8-Hydroxynaphthalene-2-sulfonic acid (110 mg, 0.49 mmol), KOH (110 mg, 1.96 mmol), methyl 4-(bromomethyl)benzoate (112 mg, 0.49 mmol) and NaI (7.4 mg, 0.49 mmol) were stirred in DMF (1.0 mL) at room temperature for 1 h and then at 60 °C for 72 h. The reaction mixture was cooled to room temperature, diluted with water and purified using preparative HPLC to give the title compound (60 mg, 31%). MS(ESI) m/z 371.3 (M-H)^+.  

Intermediate 26:
Following a procedure analogous to that for the synthesis of Intermediate 11, 8-(4-(methoxycarbonyl)benzyloxy)naphthalene-2-sulfonic acid (60 mg, 0.16 mmol) was converted to the title compound (48 mg, 72%). 1H NMR (CD$_3$OD) δ 8.95 (t, J = 2.5 Hz, 1H), 8.21-8.08 (m, 2H), 8.04-7.92 (m, 2H), 7.74 (dd, J = 8.7, 2.8 Hz, 2H), 7.64-7.52 (m, 2H), 7.23-7.07 (m, 1H), 5.51-5.43 (m, 2H), 4.01-3.94 (m, 3H); MS(ESF) m/z 370.3 (M-H)$^-$.

**Intermediate 27**

8-(2-Morpholinoethoxy)naphthalene-2-sulfonamide

**Intermediate 27A**

8-(2-Morpholinoethoxy)naphthalene-2-sulfonic acid

Following a procedure analogous to that for the synthesis of Intermediate 26B, 8-hydroxynaphthalene-2-sulfonic acid (200 g, 0.89 mmol) and 4-(2-chloroethyl)morpholine, HCl (332 g, 1.78 mmol) were converted to the title compound (100 mg, 32%). MS(ESF) m/z 336.3 (M-H)$^-$.

**Intermediate 27**

8-(2-Morpholinoethoxy)naphthalene-2-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 11, 8-(2-morpholinoethoxy)naphthalene-2-sulfonic acid (100 mg, 0.30 mmol) was converted to the title compound (27 mg, 27%). 1H NMR (CD$_3$OD) δ 8.82 (d, J = 1.8 Hz, 1H), 8.05-8.01 (m, 1H), 7.99-7.94 (m, 1H), 7.63-7.60 (m, 2H), 7.16 (dd, J = 5.3, 3.3 Hz, 1H), 4.70-4.65 (m, 2H), 4.00 (t, J = 4.7 Hz, 4H), 3.79-3.74 (m, 2H), 3.49 (d, J = 4.2 Hz, 2H), 3.33 (ddd, J = 3.2, 1.8, 1.7 Hz, 2H); MS(ESF) m/z 335.3 (M-H)$^-$.

**Intermediate 28**

7-(2-Methoxyethoxy)naphthalene-2-sulfonamide
Following a procedure analogous to that for the synthesis of Intermediate 18, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 100 mg, 0.37 mmol) and 1-bromo-2-methoxy ethane, HBr (164 mg, 0.75 mmol) were converted to the title compound (30 mg, 29%). ³¹NMR (CDCl₃) δ 7.82-7.75 (m, 5H), 7.27-7.22 (m, 3H), 4.17 (br s, 2H), 3.80 (br s, 2H), 3.47 (s, 3H); MS(ESF) m/z 280.3 (M-H)

Intermediate 29
7-Methoxynaphthalene-2-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 18, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 100 mg, 0.37 mmol) and iodomethane (106 mg, 0.75 mmol) were converted to the title compound (47 mg, 53%). ¹H NMR (DMSO-d₆) δ 8.31 (s, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.71 (dd, J = 8.6, 1.8 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.40 (s, 2H), 7.32 (dd, J = 9.0, 2.6 Hz, 1H), 3.90 (s, 3H); MS(ESF) m/z 236.3 (M-H)

Intermediate 30
7-(2-Ethoxyethoxy)naphthalene-2-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 11, the crude material from above was converted to the title compound (146 mg, 66%). ¹H NMR (CDCl₃) δ 8.36 (s, 1H), 8.22 (s, 1H), 7.90 (d, J = 8.6 Hz, 1H), 7.83-7.79 (m, 1H), 7.70-7.66 (m, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 9.0, 2.6 Hz, 1H), 3.90 (s, 3H); MS(ESF) m/z 236.3 (M-H)
7.76 (dd, J = 8.6, 2.0 Hz, 1H), 7.63 (dd, J = 8.6, 1.8 Hz, 1H), 7.38-7.34 (m, 1H), 7.24 (d, J = 2.2 Hz, 1H), 4.29-4.25 (m, 2H), 3.90-3.87 (m, 2H), 3.65 (q, J = 7.04 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H); MS(EST) m/z 294.4 (M-H)⁻.

Intermediate 31
8-Bromo-5-(dimethylamino)naphthalene-2-sulfonamide

Intermediate 31A: 5-(tert-Butoxycarbonylamino)naphthalene-2-sulfonic acid

[00213] A solution of 1-naphthylamine-6-sulfonic acid (Aldrich, 2.50 g, 11.2 mmol), di-tert-butyl dicarbonate (5.7 mL, 24.6 mmol) and Et₃N (1.8 mL, 12.9 mmol) was stirred in MeOH (22.0 mL) at room temperature overnight. The reaction mixture was then concentrated in vacuo, and the residue was dissolved in EtOAc. The solution was washed with water, and the aqueous layer was saturated with solid NaCl. The aqueous layer was extracted with EtOAc (2 x), followed by a 9:1 EtOAc/MeOH solution (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (3.60 g, 94%). ¾ NMR (DMSO-d₆) δ 9.21 (s, 1H), 8.10 (d, J = 1.3 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.69 (dd, J = 8.8 Hz, 1.5 Hz, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 1.49 (s, 9H); MS(EST) m/z 322.3 (M-H)⁻.

Intermediate 31B: 5-Amino-8-bromonaphthalene-2-sulfonic acid
To a solution of 5-(tert-butoxycarbonylamino)naphthalene-2-sulfonic acid (2.10 g, 6.49 mmol) in AcOH (53.8 mL) was added N-bromosuccinimide (1.21 g, 6.82 mmol). The resulting reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was dissolved in MeOH, azeotroped with PhMe (3 ×) and used in the subsequent step without purification.

The crude product from above was dissolved in TFA (10.0 mL, 130 mmol) and CH2Cl2 (10.0 mL). The resulting reaction mixture was stirred at room temperature for 2 h and then concentrated in vacuo to give the title compound (2.17 g, 95%).

**[00214]**

Intermediate 31C: 8-Bromo-5-(dimethylamino)naphthalene-2-sulfonic acid

A solution of 5-amino-8-bromonaphthalene-2-sulfonic acid (500 mg, 1.66 mmol), formaldehyde (1.3 mL, 16.6 mmol), TFA (1.3 mL, 16.6 mmol) and triethylsilane (577 mg, 4.96 mmol) in DCE (10.0 mL) was heated at 45 °C for 12 h. The reaction mixture was then concentrated in vacuo, and the residue was purified by preparative HPLC to give the title compound (139 mg, 25%).

**[00215]**

NMR (DMSO-d$_6$) δ 8.37 (br s, 1H), 8.03 (d, $J = 8.6$ Hz, 1H), 7.81 (t, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 7.5$ Hz, 1H), 5.24 (br s, 2H); MS(EST) m/z 302.2 (M-H$^-$).

**[00216]**

Following a procedure analogous to that for the synthesis of Intermediate 11, 8-bromo-5-(dimethylamino)naphthalene-2-sulfonic acid (50 mg, 0.15 mmol) was converted to the title compound (27 mg, 52%) after purification using preparative HPLC.
$^1$H NMR (DMSO-d$_6$) δ 8.59 (d, $J = 1.5$ Hz, 1H), 8.41-8.29 (m, 1H), 7.96 (dd, $J = 8.9, 1.9$ Hz, 1H), 7.90 (d, $J = 8.1$ Hz, 1H), 7.57 (s, 2H), 7.24-7.13 (m, 1H), 2.84 (s, 6H); MS(ESF) $m/z$ 312.3 (M-H)$^-$. 

Intermediate 32

8-(3-Morpholinopropoxy)naphthalene-2-sulfonamide

![Chemical Structure](Int-32)

Intermediate 32A: 8-(3-Morpholinopropoxy)naphthalene-2-sulfonic acid

![Chemical Structure](Int-32A)

[00218] To a solution of 8-hydroxynaphthalene-2-sulfonic acid (Intermediate 26A, 300 mg, 1.34 mmol) and pulverized KOH (300 mg, 5.35 mmol) in DMF (2.0 mL) was added 4-(3-chloropropyl)morpholine (438 mg, 2.68 mmol) and Nal (401 mg, 2.68 mmol). The resulting reaction mixture was stirred at 60 °C for 12 h. TBAI (494 mg, 1.34 mmol) was then added followed by 4-(3-chloropropyl)morpholine (438 mg, 2.68 mmol). The reaction mixture was stirred at 60 °C for an additional 12 h, then diluted with water and filtered. The filtrate was purified directly using preparative HPLC to give the title compound (150 mg, 29%). $^3$H NMR (DMSO-d$_6$) δ 8.49-8.34 (m, 1H), 7.80-7.70 (m, 1H), 7.70-7.60 (m, 1H), 7.36-7.19 (m, 2H), 6.89-6.77 (1 H, m), 3.95 (br s, 2H), 3.65 (br s, 4H), 3.48-3.32 (m, 2H), 3.26-3.06 (m, 2H), 2.57-2.44 (m, 2H), 2.37-2.13 (m, 2H); MS(ESF) $m/z$ 350.4 (M-H)$^-$. 

Intermediate 32:

[00219] Following a procedure analogous to that for the synthesis of Intermediate 11, 8-(3-morpholinopropoxy)naphthalene-2-sulfonic acid (150 mg, 0.43 mmol) was converted to the title compound (38 mg, 25%) after purification using preparative HPLC. $^1$H NMR (DMSO-d$_6$) δ 8.65-8.55 (m, 1H), 8.13-8.02 (m, 1H), 7.93-7.84 (m, 1H), 7.68-7.55 (m, 2H), 7.49-7.39 (m, 2H), 7.14 (dd, $J = 5.3, 3.5$ Hz, 1H), 4.30 (t, $J = 6.05$ Hz, 2H),
3.96 (br s, 2H), 3.74-3.62 (m, 2H), 3.48 (br s, 2H), 3.36 (d, J = 15.4 Hz, 2H), 3.16 (br s, 2H), 2.35-2.17 (m, 2H); MS(ESI⁺) m/z 351.1 (M+H)⁺.

Intermediate 33

7-(2-Morpholinoethoxy)naphthalene-2-sulfonamide

Intermediate 33A: 7-(2-Morpholinoethoxy)naphthalene-2-sulfonic acid

[00220] Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 4-(2-chloroethyl)morpholine (223 g, 1.49 mmol) were converted to the title compound (113 mg, 45%). ¹H NMR (DMSO-d₆) δ 9.90 (br s, 1H), 8.10 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.58 (dd, J = 8.1, 1.3 Hz, 1H), 7.49 (d, J = 1.8 Hz, 1H), 7.24 (dd, J = 8.7, 2.3 Hz, 1H), 4.48 (br s, 2H), 3.99 (br s, 2H), 3.65 (br s, 4H), 3.26 (br s, 4H); MS(ESI⁺) m/z 336.3 (M+H)⁺.

Intermediate 33:

[00221] Following a procedure analogous to that for the synthesis of Intermediate 11, 7-(2-morpholinoethoxy)naphthalene-2-sulfonic acid (113 mg, 0.34 mmol) was converted to the title compound (78 mg, 69%). ¹H NMR (CDCl₃) δ 8.37 (s, 1H), 7.91 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.22 (dd, J = 8.6, 1.8 Hz, 1H), 7.77 (dd, J = 9.0, 2.4 Hz, 1H), 7.24 (d, J = 2.2 Hz, 1H), 4.83 (br s, 2H), 4.26 (t, J = 5.6 Hz, 2H), 3.78-3.76 (m, 2H), 2.90 (t, J = 5.6 Hz, 2H), 2.64 (br s, 2H), 1.55 (br s, 2H); MS(ESF) m/z 335.4 (M-H)⁻.

Intermediate 34

7-(3-Morpholinopropoxy)naphthalene-2-sulfonamide
Intermediate 34A: 7-(3-Morpholinopropoxy)naphthalene-2-sulfonic acid

[00222] Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 4-(3-bromopropyl)morpholine (310 mg, 1.49 mmol) were converted to the title compound (180 mg, 69%). $^1$H NMR (DMSO-d$_6$) $\delta$ 9.53 (br s, 1H), 8.06 (s, 1H), 7.82 (d, $J = 9.0$ Hz, 1H), 7.77 (d, $J = 8.6$ Hz, 1H), 7.73-7.68 (m, 1H), 7.55 (dd, $J = 8.4$, 1.5 Hz, 1H), 7.40 (d, $J = 2.2$ Hz, 1H), 4.20 (t, $J = 5.8$ Hz, 2H), 4.00 (d, $J = 11.0$ Hz, 2H), 3.65 (t, $J = 11.6$ Hz, 2H), 3.51 (d, $J = 12.3$ Hz, 2H), 3.37-3.32 (m, 2H), 3.17-3.07 (m, 2H), 2.23-2.16 (m, 2H); MS(ESI$^+$) m/z 350.3 (M+H)$^+$.  

Intermediate 34:

[00223] Following a procedure analogous to that for the synthesis of Intermediate 11, 7-(3-morpholinopropoxy)naphthalene-2-sulfonic acid (113 mg, 0.51 mmol) was converted to the title compound (77 mg, 43%) after purification using flash column chromatography (gradient from 0% to 7% MeOH/CH$_2$Cl$_2$). $^1$H NMR (CDCl$_3$) $\delta$ 8.37 (d, $J = 1.5$ Hz, 1H), 7.90 (d, $J = 8.8$ Hz, 1H), 7.81 (d, $J = 9.0$ Hz, 1H), 7.76 (dd, $J = 8.6$, 1.8 Hz, 1H), 7.31 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.24 (d, $J = 2.4$ Hz, 1H), 4.82 (br s, 2H), 4.17 (t, $J = 6.3$ Hz, 2H), 3.76-3.74 (m, 4H), 2.56 (t, $J = 7.3$ Hz, 2H), 2.50 (br s, 4H); MS(ESI$^+$) m/z 349.4 (M-H)$^+$.  

Intermediate 35

7-(3-(4-Methylpiperazin-1-yl)propoxy)naphthalene-2-sulfonamide

(Int-35)
Intermediate 35A: 7-(3-(4-Methylpiperazin-1-yl)propoxy)naphthalene-2-sulfonic acid

Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 1-(3-bromopropyl)-4-methylpiperazine, 2HBr (571 mg, 1.49 mmol) were converted to the title compound (192 mg, 71%).¹¹ NMR (DMSO-d₆) δ 9.39 (br s, 1H), 8.06 (s, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.55 (dd, J = 8.4, 1.5 Hz, 1H), 7.39 (d, J = 2.2 Hz, 1H), 7.15 (dd, J = 8.9, 2.5 Hz, 1H), 4.17 (t, J = 6.1 Hz, 2H), 3.57-3.29 (m, 5H), 3.16-2.94 (m, 5H), 2.79 (s, 3H), 2.09 (br s, 2H); MS(ESI⁺) m/z 363.4 (M+H)⁺.

Intermediate 35:

Following a procedure analogous to that for the synthesis of Intermediate 11, 7-(3-(4-methylpiperazin-1-yl)propoxy)naphthalene-2-sulfonic acid (180 mg, 0.49 mmol) was converted to the title compound (175 mg, 97%) after purification using flash column chromatography (gradient from 0% to 7% MeOH/CH₂Cl₂).¹² H NMR (CDCl₃) δ 8.37 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.81 (d, J = 9.1 Hz, 1H), 7.52 (dd, J = 8.6, 1.7 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.19 (dd, J = 8.4, 1.6 Hz, 1H), 4.77 (br s, 2H), 4.18 (t, J = 6.0 Hz, 2H), 3.68-3.47 (m, 5H), 3.26-3.03 (m, 5H), 2.62 (s, 3H), 2.39 (br s, 2H); MS(ESF) m/z 362.4 (M-H)⁻.

Intermediate 36

7-((1-Methyl-1H-imidazol-2-yl)methoxy)naphthalene-2-sulfonamide

Intermediate 36A: 7-((1-Methyl-1H-imidazol-2-yl)methoxy)naphthalene-2-sulfonic acid
Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 2-(chloromethyl)-1-methyl-1H-imidazole, HCl (125 mg, 0.75 mmol) were converted to the title compound (129 mg, 54%). MS(ESI+) m/z 317.1 (M+H)+.

Intermediate 36:

Following a procedure analogous to that for the synthesis of Intermediate 11, 7-((1-methyl-1H-imidazol-2-yl)methoxy)naphthalene-2-sulfonic acid (129 mg, 0.41 mmol) was converted to the title compound (77 mg, 60%) after purification using flash column chromatography (gradient from 0% to 7% MeOH/CH₂Cl₂). ½ NMR (DMSO-d₆) δ 8.37 (d, J = 1.5 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.97-7.95 (m, 1H), 7.76 (d, J = 2.4 Hz, 1H), 7.73 (dd, J = 8.6, 1.8 Hz, 1H), 7.41 (s, 2H), 7.39 (dd, J = 8.9, 2.5 Hz, 1H), 7.21 (d, J = 1.1 Hz, 1H), 6.90 (d, J = 1.1 Hz, 1H), 5.29 (s, 2H), 3.71 (s, 3H); MS(ESF) m/z 316.2 (M-H)-.

Intermediate 37

7-((1-(Dimethylamino)propan-2-yloxy)naphthalene-2-sulfonic acid

Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 2-chloro-N,N-dimethylpropan-1-amine, HCl (118 mg, 0.75 mmol) were converted to the title compound (204 mg, 88%). ¹H NMR (DMSO-d₆) δ 9.48 (br s, 1H), 8.08 (d, J = 9.5 Hz, 1H), 7.41 (dd, J = 8.9, 2.5 Hz, 1H), 7.21 (d, J = 1.1 Hz, 1H), 6.90 (d, J = 1.1 Hz, 1H), 5.29 (s, 2H), 3.71 (s, 3H); MS(ESF) m/z 316.2 (M-H)-.

Intermediate 37A:

7-((1-(Dimethylamino)propan-2-yloxy)naphthalene-2-sulfonic acid

Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 2-chloro-N,N-dimethylpropan-1-amine, HCl (118 mg, 0.75 mmol) were converted to the title compound (204 mg, 88%). ¹H NMR (DMSO-d₆) δ 9.48 (br s, 1H), 8.08 (d, J = 9.5
Intermediate 37:

Following a procedure analogous to that for the synthesis of Intermediate 11, 7-(1-(dimethylamino)propan-2-yloxy)naphthalene-2-sulfonic acid (204 mg, 0.66 mmol) was converted to the title compound (112 mg, 55%) after purification using preparative HPLC. ¾ NMR (DMSO-d 6 ) δ 8.33 (s, 1H), 8.06-8.03 (m, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.76-7.73 (m, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.43-7.41 (m, 2H), 7.37 (dd, J = 8.8, 2.4 Hz, 1H), 5.12-5.07 (m, 1H), 4.43-4.32 (m, 1H), 3.53-3.41 (m, 1H), 2.90-2.82 (m, 6H), 1.38-1.33 (m, 3H); MS(ESI +) m/z 310.0 (M+H) +.

Intermediate 38

7-(2-(1-Methylpyrrolidin-2-yl)ethoxy)naphthalene-2-sulfonamide

Intermediate 38A: 7-(2-(1-Methylpyrrolidin-2-yl)ethoxy)naphthalene-2-sulfonic acid

Intermediate 38A: Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 2-(2-chloroethyl)-1-methylpyrrolidine, HC1 (137 mg, 0.75 mmol) were converted to the title compound (173 mg, 69%). MS(ESI +) m/z 336.1 (M+H) +.

Intermediate 38:

Following a procedure analogous to that for the synthesis of Intermediate 11, 7-(2-(1-methylpyrrolidin-2-yl)ethoxy)naphthalene-2-sulfonic acid (173 mg, 0.52 mmol) was converted to the title compound (74 mg, 43%) as an off-white solid after purification using preparative HPLC. ¾ NMR (DMSO-d 6 ) δ 8.32 (s, 1H), 8.06-8.03 (m, 1H), 7.99-
7.95 (m, 1H), 7.76-7.72 (m, 1H), 7.62-7.61 (m, 1H), 7.44-7.43 (m, 2H), 7.36-7.32 (m, 1H), 4.96-4.87 (m, 1H), 4.30-4.21 (m, 2H), 3.67-3.60 (m, 1H), 3.55-3.46 (m, 2H), 3.43-3.39 (m, 1H), 3.28-3.08 (m, 2H), 2.91-2.85 (m, 3H), 2.29-2.22 (m, 1H), 2.17-1.87 (m, 4H), 1.87-1.71 (m, 1H); MS(ESI+) m/z 335.2 (M+H)+.

Intermediate 39

7-(3-(Dimethylamino)propoxy)naphthalene-2-sulfonamide

Intermediate 39A: 7-(3-(Dimethylamino)propoxy)naphthalene-2-sulfonic acid

[00232] Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 3-chloro-N,N-dimethylpropan-1-amine, HCl (118 mg, 0.75 mmol) were converted to the title compound (158 mg, 68%). MS(ESI+) m/z 310.1 (M+H)+.

Intermediate 40

7-(3-(Pyrrolidin-1-yl)propoxy)naphthalene-2-sulfonamide

[00233] Following a procedure analogous to that for the synthesis of Intermediate 11, 7-(3-(dimethylamino)propoxy)naphthalene-2-sulfonic acid (158 mg, 0.51 mmol) was converted to the title compound (23 mg, 15%) as an off-white solid after purification using preparative HPLC. 34 NMR (DMSO-d6) δ 8.33 (s, 1H), 8.04 (s, 1H), 7.87-7.84 (m, 1H), 7.71 (dd, J = 8.4, 1.8 Hz, 1H), 7.40 (s, 2H), 7.33 (d, J = 2.0, 1H), 7.27 (dd, J = 8.6, 2.5, 1H), 4.23-4.20 (m, 2H), 3.66-3.59 (m, 2H), 3.12-3.03 (m, 2H), 2.95 (s, 3H), 2.88 (s, 3H), 1.93-1.85 (m, 2H); MS(ESI+) m/z 309.1 (M+H)+.
Intermediate 40A: 7-(3-(Pyrrolidin-1-yl)propoxy)naphthalene-2-sulfonic acid

Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 1-(3-chloropropyl)pyrrolidine (110 mg, 0.75 mmol) were converted to the title compound (138 mg, 55%). MS(ESI+) m/z 336.1 (M+H)^+.

Intermediate 40:

Following a procedure analogous to that for the synthesis of Intermediate 11, 7-(3-(Pyrrolidin-1-yl)propoxy)naphthalene-2-sulfonic acid (138 mg, 0.41 mmol) was converted to the title compound (34 mg, 24%) as a pale yellow oil after purification using preparative HPLC. ^H NMR (DMSO-d^6) δ 8.33 (s, 1H), 7.96 (s, 1H), 7.93 (d, J = 4.2 Hz, 1H), 7.67 (dd, J = 8.5, 1.7 Hz, 1H), 7.42 (s, 2H), 7.36 (d, J = 2.2 Hz, 1H), 7.29 (dd, J = 8.8, 2.4 Hz, 1H), 4.23-4.20 (m, 2H), 3.66-3.59 (m, 2H), 3.41-3.34 (m, 2H), 3.12-3.03 (m, 2H), 2.22-2.19 (m, 2H), 2.10-2.02 (m, 2H), 1.93-1.85 (m, 2H); MS(ESI+) m/z 335.1 (M+H)^+.

Intermediate 41

7-(3-(Piperidin-1-yl)propoxy)naphthalene-2-sulfonamide

Intermediate 41A: 7-(3-(Piperidin-1-yl)propoxy)naphthalene-2-sulfonic acid
Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 1-(3-chloropropyl)piperidine (121 mg, 0.75 mmol) were converted to the title compound (78 mg, 30%). MS(ESI+) m/z 336.1 (M+H)+.

Intermediate 41:
Following a procedure analogous to that for the synthesis of Intermediate 11, 7-(3-(pyrrolidin-1-yl)propoxy)naphthalene-2-sulfonic acid (109 mg, 0.31 mmol) was converted to the title compound (92 mg, 85%) as an off-white solid. 1H NMR (DMSO-d6) δ 8.29 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.94-7.90 (m, 1H), 7.77 (dd, J = 8.4, 1.5 Hz, 1H), 7.48 (s, 2H), 7.39 (d, J = 2.4 Hz, 1H), 7.29 (dd, J = 8.7, 2.5, 1H), 4.23-4.20 (m, 2H), 3.66-3.59 (m, 2H), 3.41-3.34 (m, 2H), 3.12-3.03 (m, 2H), 2.22-2.19 (m, 2H), 2.10-2.02 (m, 2H), 1.93-1.85 (m, 2H); MS(ESI+) m/z 349.2 (M+H)+.

Intermediate 42

7-(3-(Pyridin-4-yl)propoxy)naphthalene-2-sulfonamide

Intermediate 42A: 7-(3-(Pyridin-4-yl)propoxy)naphthalene-2-sulfonic acid

Following a procedure analogous to that for the synthesis of Intermediate 26B, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 200 mg, 0.75 mmol) and 4-(3-chloropropyl)pyridine (116 mg, 0.75 mmol) were converted to the title compound (109 mg, 43%). 1H NMR (DMSO-d6) δ 8.65, (s, 1H), 8.58 (s, 1H), 8.12 (s, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 5.7 Hz, 1H), 7.57 (dd, J = 8.5, 1.9 Hz,
2H), 7.44 (s, 1H), 7.27 (d, J = 8.7 Hz, 1H), 4.20 (t, J = 6.5 Hz, 2H), 3.10 (t, J = 7.7 Hz, 2H), 2.30-2.21 (m, 2H); MS(ESI⁺) m/z 344.1 (M+H)⁺.

Intermediate 42:

Following a procedure analogous to that for the synthesis of Intermediate 41, 7-(3-(pyridin-4-yl)propoxy)naphthalene-2-sulfonic acid (109 mg, 0.32 mmol) was converted to the title compound (109 mg, 100%). 1H NMR (DMSO-d₆) δ 8.71 (d, J = 6.2 Hz, 2H), 8.31 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.77 (d, J = 5.3 Hz, 1H), 7.73 (dd, J = 8.6, 1.8 Hz, 2H), 7.56 (d, J = 2.4 Hz, 1H), 7.43 (s, 2H), 7.30 (dd, J = 8.9, 2.5 Hz, 1H), 4.18 (t, J = 6.2 Hz, 2H), 3.02 (t, J = 7.6 Hz, 2H), 2.25-2.18 (m, 2H); MS(ESI⁺) m/z 343.2 (M+H)⁺.

Intermediate 43
8-Bromo-5-chloronaphthalene-2-sulfonamide

Intermediate 43A: 8-Bromo-5-chloronaphthalene-2-sulfonic acid

Following a procedure analogous to that for the synthesis of Intermediate 43A, 5-amino-8-bromonaphthalene-2-sulfonic acid (Example 3IB, 1.04 g, 3.46 mmol) was converted to the title compound (740 mg, 63%). 1H NMR (DMSO-d₆) δ 8.48 (br s, 1H), 8.36-8.12 (m, 1H), 8.12-7.81 (m, 2H), 7.66 (br s, 1H); MS(ESI⁻) m/z 321.1 (M-H)⁻.

Intermediate 43:
title compound (319 mg, 41%). $^1$H NMR (DMSO-d$_6$) δ 8.70 (d, $J = 1.5$ Hz, 1H), 8.48-
8.44 (m, 1H), 8.15 (dd, $J = 9.0$, 1.8 Hz, 1H), 8.05 (d, $J = 8.1$ Hz, 1H), 7.82 (d, $J = 8.1$ Hz,
1H), 7.68 (s, 2H); MS(ESI$^+$) $m/z$ 321.7 (M+H$^+$).

Intermediate 44

5,8-Dichloronaphthalene-2-sulfonamide

Intermediate 44A: 5-Amino-8-chloronaphthalene-2-sulfonic acid

[00242] Following a procedure analogous to that for the synthesis of Intermediate 31B, 5-(tert-butoxycarbonylamino)naphthalene-2-sulfonic acid (Intermediate 31A, 3.70 g, 11.44 mmol) and N-chlorosuccinimide (1.60 g, 12.01 mmol) were converted to the title compound (2.95 g, 90%). MS(ESI$^+$) $m/z$ 275.1 (M + NH$_4$)$^+$.

Intermediate 44B: 5,8-Dichloronaphthalene-2-sulfonamide

[00243] Following a procedure analogous to that for the synthesis of Intermediate 5A, 5-amino-8-chloronaphthalene-2-sulfonic acid (765 mg, 2.97 mmol) was converted to the title compound (823 mg, 90%). MS(ESF) $m/z$ 275.2 (M-H)$^-$. 

Intermediate 44:
Following a procedure analogous to that for the synthesis of Intermediate 1, 5,8-dichloronaphthalene-2-sulfonic acid (823 mg, 2.97 mmol) was converted to the title compound (220 mg, 27%). ³¹ NMR (DMSO-d₆) δ 8.72 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 8.8 Hz, 1H), 8.16 (dd, J = 8.9, 1.6 Hz, 1H), 7.88-7.82 (m, 1H), 7.73-7.64 (m, 1H), 4.49 (br s, 2H); MS(ESF) m/z 274.3 (M-H)⁻.

Examples 2 to 44

The following Examples were prepared using 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate IF) and the naphthalene sulfonamide intermediates described above according to the procedure for the synthesis of Example 1.

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<th>Ex. No.</th>
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<th>Name</th>
<th>LCMS (M+H)</th>
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<td>N,N-dibutyl-4-chloro-1-(4-(5-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
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<td>N,N-dibutyl-4-chloro-1-(4-(6-(dimethylamino)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
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<td>N,N'-dibutyl-4-chloro-1-(4-(5-(dimethylamino)naphthalen-1-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
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<td>ethyl 7-(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-1-naphthoate</td>
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<td>16</td>
<td>CO2Et</td>
<td>ethyl 7-[(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoylsulfamoyl)-2-naphthoate</td>
<td>812.3</td>
</tr>
<tr>
<td>17</td>
<td>SO2Et</td>
<td>ethyl 7-[(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoylsulfamoyl)-2-naphthoate</td>
<td>832.1</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>--------</td>
<td>---</td>
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<td>------------</td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>1-(4-(7-(benzyloxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl) N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>846.1</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>N,N-dibutyl-4-chloro-4-(8-(3,4-dichlorobenzamido)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>927.1</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(methylsulfonyl)benzyloxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>924.2</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>N,N-dibutyl-4-chloro-1-(4-(8-(3,4-dichlorobenzyloxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>914.3</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>N,N-dibutyl-4-chloro-1-(4-(7-(3,4-dichlorobenzyloxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>916.3</td>
</tr>
<tr>
<td>23</td>
<td></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-((tetrahydrofuran-2-y1)methoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>840.3</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>---------</td>
<td>---</td>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>24</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-1-(4-(7-isopropoxynaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>798.2</td>
</tr>
<tr>
<td>25</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(2-phenoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>876.3</td>
</tr>
<tr>
<td>26</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>methyl 4-((7-(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)naphthalen-1-yloxy)methyl)benzoate</td>
<td>904.4</td>
</tr>
<tr>
<td>27</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>869.4</td>
</tr>
<tr>
<td>28</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-1-(4-(7-(2-methoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>814.4</td>
</tr>
<tr>
<td>29</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-1-(4-(7-methoxynaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>770.2</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>--------</td>
<td>---</td>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>30</td>
<td><img src="image1" alt="" /></td>
<td>N,N-dibutyl-4-chloro-l-(4-(7-(2-ethoxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>828.3</td>
</tr>
<tr>
<td>31</td>
<td><img src="image2" alt="" /></td>
<td>1-(4-(8-bromo-5-(dimethylamino)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>861.3</td>
</tr>
<tr>
<td>32</td>
<td><img src="image3" alt="" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-l-(4-(8-(3-morpholinoproxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-lH-pyrazole-3-carboxamide</td>
<td>883.4</td>
</tr>
<tr>
<td>33</td>
<td><img src="image4" alt="" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-l-(4-(7-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-lH-pyrazole-3-carboxamide</td>
<td>869.3</td>
</tr>
<tr>
<td>34</td>
<td><img src="image5" alt="" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-l-(4-(7-(3-morpholinoproxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-lH-pyrazole-3-carboxamide</td>
<td>883.4</td>
</tr>
<tr>
<td>35</td>
<td><img src="image6" alt="" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-l-(4-(7-(3-(4-methylpiperazin-1-yl)propoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-lH-pyrazole-3-carboxamide</td>
<td>896.5</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>--------</td>
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<td>----------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>36</td>
<td><img src="image1" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-5'-methyl-1-(4-(7-(1-methyl-1H-imidazol-2-yl)methoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxamide</td>
<td>850.4</td>
</tr>
<tr>
<td>37</td>
<td><img src="image2" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-1-(4-(7-(1-(dimethylamino)propan-2-yl)oxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>841.4</td>
</tr>
<tr>
<td>38</td>
<td><img src="image3" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-1-(4-(7-(2-(1-methylpyrrolidin-2-yl)ethoxy)naphthalene-2-sulfonamido)methyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxamide</td>
<td>867.5</td>
</tr>
<tr>
<td>39</td>
<td><img src="image4" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-1-(4-(7-(3-(dimethylamino)propoxy)-naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>841.4</td>
</tr>
<tr>
<td>40</td>
<td><img src="image5" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(3-(pyrrolidin-1-yl)propoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxamide</td>
<td>867.3</td>
</tr>
<tr>
<td>41</td>
<td><img src="image6" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(7-(3-(piperidin-1-yl)propoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-lH-pyrazole-3-carboxamide</td>
<td>881.5</td>
</tr>
<tr>
<td>Ex. No.</td>
<td><strong>R</strong></td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>----------------------------------------------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>42</td>
<td><img src="image" alt="R" /></td>
<td>N,N-Dibutyl-4-chloro-5-methyl-1-(4-(7-(3-(pyridin-4-yl)propoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>875.4</td>
</tr>
<tr>
<td>43</td>
<td><img src="image" alt="R" /></td>
<td>1-(4-(8-bromo-5-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>852.4</td>
</tr>
<tr>
<td>44</td>
<td><img src="image" alt="R" /></td>
<td>N,N-dibutyl-4-chloro-1-(4-(5,8-dichloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>806.6</td>
</tr>
</tbody>
</table>

Example 45

7-(N-(4-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-1-naphthoic acid

[00246] To a solution of ethyl 7-(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-1-naphthoate (Example 9, 9.4 mg, 0.012 mmol) in EtOH (0.5 mL) and THF (0.5 mL) was added 2N LiOH (58 µL, 0.12 mmol). The reaction mixture was stirred at room temperature for 30 min and then at 40 °C for 2 h. The reaction mixture was quenched with 6N HCl, and then extracted with CHCl₃ (4 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to afford the title compound (9.0...
mg, 94%). \( ^{1} \text{H} \text{NMR} \) (CD\(_3\)OD, 2:1 mixture of amide rotamers) \( \delta \) 9.90 (s, 1H), 8.40 (d, \( J = 7.3 \text{ Hz} \), 1H), 8.23 (d, \( J = 8.4 \text{ Hz} \), 1H), 8.17 (d, \( J = 1.1 \text{ Hz} \), 1H), 8.08 (dd, \( J = 8.4, 1.8 \text{ Hz} \), 1H), 7.98 (t, \( J = 2.2 \text{ Hz} \), 1H), 7.79-7.74 (m, 1H), 7.71-7.64 (m, 1H), 7.24-7.04 (m, 4.5H), 6.90-6.88 (m, 0.5H), 4.53 (br s, 2H), 3.58-3.39 (m, 4H), 3.13 (d, \( J = 1.3 \text{ Hz} \), 1H), 3.05-2.94 (m, 1H), 2.82 (br s, 1H), 2.79-2.66 (m, 1H), 2.33 (s, 2H), 2.28 (s, 1H), 1.49-1.20 (m, 6H), 1.13-0.98 (m, 2H), 0.96-0.84 (m, 3H), 0.80-0.64 (m, 3H); MS(ESI\(^{+}\)) \( m/z \) 782.5 (M-H)\( ^{-}\)

**Example 46**

\( N,N \)-Dibutyl-4-chloro-5-methyl-1-(4-(7-(4-methylpiperazine-1-carbonyl)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1\( \text{H} \)-pyrazole-3-carboxamide

![Chemical Structure](image)

Intermediate 46A: 7-(N-(4-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1\( \text{H} \)-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-2-naphthoic acid

![Chemical Structure](image)

[00247] To a solution of ethyl 7-(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1\( \text{H} \)-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-2-

naphthoate (Example 16, 84 mg, 0.10 mmol) in EtOH (0.5 mL) and THF (0.5 mL) was added 2N LiOH (0.5 mL, 1.03 mmol). The reaction mixture was stirred for 2 h at 40 °C, concentrated to remove volatiles, diluted with water and quenched with IN HCl. The solution was concentrated \textit{in vacuo} and purified by preparative HPLC to afford the title compound (57 mg, 68%) as a white solid. \( ^{1} \text{H} \text{NMR} \) (DMSO-d\(_6\), 2:1 mixture of amide rotamers)
Example 46:

To a solution of 7-(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-2-naphthoic acid (12 mg, 0.015 mmol) in DMF (1.0 mL) were added HATU (12 mg, 0.031 mmol), 2,6-lutidine (5 µL, 0.040 mmol) followed by 1-methylpiperazine (4.6 mg, 0.046 mmol). The resulting reaction mixture was heated to 50 °C for 1.5 h, cooled to room temperature and purified directly by preparative HPLC to give the title compound (2 mg, 14%). ¾ NMR (DMSO-d₆, 2:1 mixture of amide rotamers) δ 8.50 (s, 1H), 8.17 (s, 1H), 8.07-8.02 (m, 2H), 7.99-7.98 (m, 2H), 7.95 (m, 1H), 7.60 (dd, J = 8.5, 1.5 Hz, 1H), 7.56-7.52 (m, 1H), 7.20-7.07 (m, 3.5H), 6.97 (d, J = 7.5 Hz, 0.5H), 4.73 (br s, 1H), 4.56-4.33 (m, 3H), 3.73 (br s, 1H), 3.59-3.40 (m, 3H), 3.50 (br s, 3H), 2.99-2.96 (m, 2H), 2.89 (s, 1H), 2.79-2.63 (m, 5H), 2.53 (br s, 1H), 2.19 (s, 2H), 2.14 (s, 1H), 1.38 (br s, 1H), 1.29-1.14 (m, 6H), 1.01-0.92 (m, 2H), 0.88-0.82 (m, 3H), 0.68-0.61 (m, 3H); MS(ESI⁺) m/z 866.3 (M+H)⁺.

Example 47

N,N'-Dibutyl-4-chloro-5-methyl-1-(4-(7-(morpholine-4-carbonyl)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide

Following a procedure analogous to that for the synthesis of Intermediate 12B of Example 12, 7-(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-rotamers) δ 8.41 (s, 1H), 8.36 (s, 1H), 8.07 (t, J = 7.3 Hz, 2H), 7.99 (d, J = 1.3 Hz, 1H), 7.88 (s, 2H), 7.79 (d, J = 8.8 Hz, 1H), 7.55-7.51 (m, 1H), 7.20-7.07 (m, 3.5H), 6.97 (d, J = 7.5 Hz, 0.5H), 4.10 (br s, 6H), 2.97 (br s, 1.5H), 2.74 (br s, 1.5H), 2.19 (s, 2H), 2.14 (s, 1H), 1.38 (br s, 1H), 1.29-1.12 (m, 6H), 1.01-0.91 (m, 2H), 0.88-0.82 (m, 3H), 0.68-0.61 (m, 3H); MS(ESI⁺) m/z 784.2 (M+H)⁺.
(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoylsulfamoyl)-2-naphthoic acid (Intermediate 46A 12 mg, 0.015 mmol) and morpholine (4 mg, 0.046 mmol) were converted to the title compound (3 mg, 20%). \(^1\)H NMR (1:1 CD\(_3\)OD:CDC\(_{1}\)\(_3\), 2:1 mixture of amide rotamers) \(\delta\) 8.67 (s, 1H), 8.21 (d, \(J = 8.3\) Hz, 1H), 8.14 (dd, \(J = 8.7, 1.5\) Hz, 1H), 8.11 (d, \(J = 1.7\) Hz, 1H), 8.06 (s, 1H), 7.98 (t, \(J = 7.6\) Hz, 2H), 7.60 (d, \(J = 8.3\) Hz, 1H), 7.44-7.42 (m, 1H), 7.19-7.09 (m, 3.5H), 6.89 (d, \(J = 7.2\) Hz, 0.5H), 4.83 (br s, 1H), 4.50 (s, 1H), 4.36 (br s, 1H), 3.79 (br s, 4H), 3.68 (br s, 3H), 3.54 (br s, 3H), 3.45 (s, 1H), 3.00 (br s, 1.5H), 2.83 (br s, 1.5H), 2.29 (s, 2H), 2.24 (s, 1H), 1.50-1.44 (m, 1H), 1.40-1.35 (m, 2H), 1.32-1.16 (m, 4H), 1.12-0.99 (m, 2H), 0.92-0.86 (m, 3H), 0.75 (t, \(J = 7.4\) Hz, 2H), 0.68 (t, \(J = 7.4\) Hz, 1H); MS(ESI\(^+\)) \(\text{m/z}\) 853.3 (M+H\(^+\)).

Example 48

\(N,N\)-Dibutyl-4-chloro-1-(4-(7-(dimethylcarbamoyl)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide

Following a procedure analogous to that for the synthesis of Intermediate 12B of Example 12, 7-(N-(4-(4-Chloro-3-aminopyrrolidin-1-yl)-3-(dibutylcarbamoyl)-5-methyl-\(1H\)-pyrazol-1-yl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoylsulfamoyl)-2-naphthoic acid (Intermediate 46A, 12 mg, 0.015 mmol) and dimethylamine (23 \(\mu\)L, 0.046 mmol, 2M solution in THF) were converted to the title compound (2 mg, 19%). \(^1\)H NMR (1:1 MeOD:CDC\(_3\), 2:1 mixture of amide rotamers) \(\delta\) 8.67 (s, 1H), 8.18 (d, \(J = 8.3\) Hz, 1H), 8.13 (d, \(J = 8.6\) Hz, 1H), 8.07 (s, 1H), 8.05 (s, 1H), 7.97 (d, \(J = 10.3\) Hz, 2H), 7.61-7.58 (m, 2H), 7.42 (br s, 1H), 7.20-7.06 (m, 3.5H), 6.87 (d, \(J = 7.2\) Hz, 0.5H), 4.80 (br s, 1H), 4.23 (br s, 1H), 3.86 (br s, 1H), 3.64 (br s, 1H), 3.54 (br s, 1H), 3.15 (s, 3H), 3.05 (s, 3H), 2.99 (br s, 1.5H), 2.82 (br s, 1.5H), 2.27 (s, 2H), 2.23 (s, 1H), 1.50-1.43 (m, 1H), 1.39-1.35 (m, 2H), 1.31-1.17 (m, 5H), 1.10-0.98 (m, 2H), 0.91-0.85 (m, 3H), 0.74 (t, \(J = 7.4\) Hz, 1.5H), 0.68 (t, \(J = 7.4\) Hz, 1.5H); MS(ESI\(^+\)) \(\text{m/z}\) 811.3 (M+H\(^+\)).
Example 49

4-((7-(N-(4-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)naphthalen-1-yloxy)methyl)benzoic acid

(49)

[00251] Following a procedure analogous to that for the synthesis of Intermediate 46A, methyl 4-((7-(N-(4-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)naphthalen-1-yloxy)benzoate (Example 26, 10 mg, 0.011 mmol) was converted to the title compound (5 mg, 49%). $^1$H NMR (CD$_3$OD, 2:1 mixture of amide rotamers) δ 9.17 (d, J = 1.8 Hz, IH), 8.24-8.00 (m, 6H), 7.81-7.56 (m, 5H), 7.35-7.03 (m, 4.5H), 6.89-6.87 (m, 0.5H), 5.48 (s, 2H), 4.56 (br s, 2H), 3.77-3.42 (m, 4H), 3.24-3.14 (m, 1H), 3.06 (br s, IH), 2.89 (br s, 2H), 2.37 (s, 2H), 2.32 (s, IH), 1.63-1.20 (m, 6H), 1.21-1.03 (m, 2H), 1.01-0.88 (m, 3H), 0.86-0.63 (m, 3H); MS(ESI$^+$) m/z 890.4 (M+H$^+$).

Example 50

N,N-Dibutyl-4-chloro-l-(4-(7-(2-hydroxyethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-l H-pyrazole-3-carboxamide

(50)

Intermediate 50A: 7-Hydroxynaphthalene-2-sulfonamide
Following a procedure analogous to that for the synthesis of Intermediate 11, sodium 7-oxidonaphthalene-2-sulfonate (Pfaltz and Bauer, 1.00 g, 3.73 mmol) was converted to the title compound (40 mg, 5%) after purification using preparative HPLC.

Intermediate 50B: 7-(2-(tert-Butyldimethylsilyloxy)ethoxy)naphthalene-2-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 17, 7-hydroxynaphthalene-2-sulfonamide (40 mg, 0.18 mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (43 mg, 0.18 mmol) were converted to the title compound (33 mg, 48%) after purification using flash column chromatography (gradient from 0% to 2% MeOH/CH₂Cl₂). ¹H NMR (CDCl₃) δ 8.31 (s, 1H), 7.84-7.82 (m, 1H), 7.77-7.73 (m, 2H), 7.26 (dd, J = 8.9, 2.5 Hz, 1H), 7.19 (d, J = 2.2 Hz, 1H), 4.13 (t, J = 4.9 Hz, 2H), 4.02 (t, J = 4.9 Hz, 2H), 0.90 (s, 9H), 0.10 (s, 6H); MS(ESF) m/z 380.4 (M-H)⁻

Intermediate 50C: N,N-Dibutyl-l-(4-(7-(2-(tert-butyldimethylsilyloxy)ethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(l, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-4-chloro-5-methyl-l H-pyrazole-3-carboxamide

(Int-50C)
Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate IF, 40 mg, 0.073 mmol) and 7-(2-(tert-butylidimethylsiloxy)ethoxy)naphthalene-2-sulfonamide (Intermediate 50B, 33 mg, 0.087 mmol) were converted to the title compound (31 mg, 47%) after purification using flash column chromatography (gradient from 0% to 3% MeOH/CH$_2$Cl$_2$). H NMR (CDCl$_3$, 2:1 mixture of amide rotamers) δ 8.62 (s, 1H), 8.11-8.09 (m, 1H), 7.97-7.96 (m, 1H), 7.89-7.88 (m, 2H), 7.84 (d, J = 8.9 Hz, 1H), 7.55-7.52 (m, 1H), 7.40-7.38 (m, 2H), 7.23-7.07 (m, 3.5H), 6.85 (d, J = 7.4 Hz, 0.5H), 4.75 (br s, 1H), 4.63 (br s, 1H), 4.42 (s, 1H), 4.27-4.24 (m, 2H), 3.85-3.81 (m, 2H), 3.46 (br s, 2H), 3.18-3.15 (m, 2H), 3.02 (br s, 1.5H), 2.84 (br s, 1.5H), 2.29 (s, 2H), 2.24 (s, 1H), 1.50-1.45 (m, 1H), 1.41-1.36 (m, 1H), 1.32-1.20 (m, 6H), 1.12-0.99 (m, 1H), 0.93-0.86 (m, 12H), 0.74 (t, J = 7.4 Hz, 2H), 0.68 (t, J = 7.2 Hz, 1H), 0.10 (s, 6H); MS(ESI$^+$) m/z 914.3 (M+H$^+$).

Example 50:

To a solution of N,N-dibutyl-1-(4-(7-(2-(tert-butylidimethylsiloxy)ethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-(l, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (31 mg, 0.034 mmol) in THF (1.0 mL) was added TBAF (68 µL, 0.068 mmol). The resulting reaction mixture was stirred at room temperature for 1 h, then diluted with EtOAc and washed with sat. aq. NaHCO$_3$ solution. The organic layer was dried (MgSC$_2$O$_4$), filtered and concentrated in vacuo. The residue was purified using flash column chromatography (gradient from 0% to 10% MeOH/CH$_2$Cl$_2$) to give the title compound (20 mg, 72% yield) as clear, colorless oil. $^1$H NMR (1:1 CD$_3$OD:CDCl$_3$, 2:1 mixture of amide rotamers) δ 8.58 (s, 1H), 8.07-8.05 (m, 1H), 7.92-7.91 (m, 1H), 7.87-7.86 (m, 2H), 7.82 (d, J = 9.0 Hz, 1H), 7.50-7.48 (m, 1H), 7.35-7.32 (m, 2H), 7.21-7.08 (m, 3.5H), 6.83 (d, J = 7.4 Hz, 0.5H), 4.75 (br s, 1H), 4.62 (br s, 1H), 4.45 (s, 1H), 4.27-4.24 (m, 2H), 3.83-3.80 (m, 2H), 3.45 (br s, 2H), 3.16 (br s, 2H), 3.04-3.03 (m, 1.5H), 2.84 (br s, 1.5H), 2.29 (s, 2H), 2.24 (s, 1H), 1.50-1.45 (m, 1H), 1.41-1.36 (m, 1H), 1.32-1.20 (m, 6H), 1.12-0.99 (m, 1H), 0.91-0.86 (m, 3H), 0.74 (t, J = 7.4 Hz, 2H), 0.68 (t, J = 7.2 Hz, 1H); MS(ESI$^+$) m/z 800.2 (M+H$^+$).
Example 51

\[ N,N\text{-Dibutyl-4-chloro-1-(4-} (7\text{-hydroxynaphthalen-2-ylsulfonylcarbamoyl})-2-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H\text{-pyrazole-3-carboxamide} \]

\[ \text{(51)} \]

To a solution of 1-(4-(7-(benzyloxy)naphthalen-2-ylsulfonylcarbamoyl))-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl \( \text{N,N-dibutyl-4-chloro-5-methyl-1} \text{-pyrazole-3-carboxamide} \) (Example 18, 30 mg, 0.035 mmol) in MeOH (5.0 mL) was added 10% Pd/C (75 mg, 0.71 mmol). The flask was evacuated and purged with \( \text{H}_2 \) from a balloon (2 x), and the reaction mixture was then stirred overnight under an atmosphere of ¾. The reaction mixture was diluted with CH2Cl2 and filtered through a pad of CELITE®, washing with ¾. The filtrate was concentrated \( \text{in vacuo} \) and purified by preparative HPLC to give the title compound (12 mg, 43%). \( ^{1}\text{H NMR (1:1 CD}_3\text{OD-CDCI}_3, 1:1 \text{ mixture of amide rotamers)} \delta 8.37 \text{ (s, 1H), 8.17-8.13 \text{ (m, 1H), 8.05 (s, 1H), 7.93 \text{ (s, 1H), 7.80-7.76 \text{ (m, 2H), 7.70 \text{ (d, J = 8.9 Hz, 1H), 7.34 \text{ (dd, J = 8.5, 1.3 Hz, 1H), 7.23 \text{ (s, 1H), 7.17-7.05 \text{ (m, 4.5H), 6.83 \text{ (d, J = 7.9 Hz, 0.5H), 4.66 \text{ (br s, 2H), 4.41 \text{ (s, 1H), 3.88 \text{ (br s, 1H), 3.51 \text{ (br s, 2H), 3.04-3.00 \text{ (m, 1H), 2.81-2.78 \text{ (m, 1H), 2.24 \text{ (s, 1.5H), 2.20 \text{ (s, 1.5H), 1.49-1.42 \text{ (m, 1H), 1.40-1.33 \text{ (m, 2H), 1.30-1.16 \text{ (m, 5H), 1.09-0.96 \text{ (m, 2H), 0.90-0.84 \text{ (m, 3H), 0.72 \text{ (t, J = 7.4 Hz, 1.5H), 0.67 \text{ (t, J = 7.4 Hz, 1.5H); MS(ESI\text{+}) m/z 756.2 (M+H)+.}}

Example 52

\[ N,N\text{-Dibutyl-4-chloro-1-(4-(indolin-5-ylsulfonylcarbamoyl})-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H\text{-pyrazole-3-carboxamide} \]
Intermediate 52A: l-Acetylindoline-5-sulfonamide

![Structure of Intermediate 52A]

**[00257]** To a solution l-acetylindoline-5-sulfonyl chloride (Borror, A.L. et al, *J. Org. Chem.*, 53:2047-2052 (1988)) (2.00 g, 7.70 mmol) in CH$_2$Cl$_2$ (5.0 mL) was added NH$_3$ (38.5 mL, 19.3 mmol, 0.5M solution in dioxane) and EtsN (2.2 mL, 15.4 mmol). The resulting reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then concentrated *in vacuo*, and the residue was triturated with IN aq. HC1 solution (2 x) and water (1 x) to give the title compound (1.80 g, 97%) as a white solid. $^1$H NMR (DMSO-d$_6$) $\delta$ 8.11 (d, $J = 8.1$ Hz, 1H), 7.64-7.62 (m, 2H), 7.20 (br s, 2H), 4.16 (t, $J = 8.6$ Hz, 2H), 3.19 (t, $J = 8.5$ Hz, 2H), 2.19 (s, 3H); MS(ESI$^+$) m/z 241.0 (M+H)$^+$. 

Intermediate 52B: 1-(4-(1-Acetylindolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide

![Structure of Intermediate 52B]

**[00258]** To a solution of 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate IF, 30 mg, 0.054 mmol) in DMF (2.0 mL) was added HATU (29 mg, 0.076 mmol), l-acetyllindoline-5-sulfonamide (20 mg, 0.082 mmol), DMAP (7 mg, 0.054 mmol) and i-Pr$_2$EtN (0.029 mL, 0.163 mmol). The resulting reaction mixture was stirred at room temperature for 3 h and then diluted with EtOAc and IN aq. HC1 solution. The organic layer was washed with...
INaq. NaOH solution (2 x) followed by INaq. HCl solution (1 x). The combined aqueous layer was extracted with EtOAc (3 x). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo to give a crude oil, which was purified using preparative HPLC to give the title compound (10 mg, 24%). ¹H NMR (CD₃OD, 2:1 mixture of amide rotamers) δ 8.19-8.16 (m, 2H), 8.08-8.06 (m, 1H), 7.89-7.86 (m, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.22-7.10 (m, 3.5H), 6.94 (d, J = 7.3 Hz, 0.5H), 4.75-4.50 (m, 2H), 4.22-4.18 (m, 2H), 3.90-3.40 (m, 4H), 3.15-2.65 (m, 4H), 2.33 (s, 2H), 2.28 (s, 1H), 2.25 (s, 3H), 1.52-1.00 (m, 10H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.67 (m, 1H); MS(ESI⁺) m/z 773.2 (M+H)⁺.

Example 52:

[00259] To a solution of l-(4-(l-acetylindolin-5-ylsulfonylcarbamoyl)-2-(l,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-lH-pyrazole-3-carboxamide (70 mg, 0.091 mmol) in MeOH (4.0 mL) was added conc. HCl (151 µL, 1.81 mmol). The resulting reaction mixture was heated at 75°C for 2 h, then cooled to room temperature and concentrated in vacuo. The crude residue was purified using preparative HPLC to give the title compound (1 mg, 2%). ¹H NMR (CD₃OD, 2:1 mixture of amide rotamers) δ 8.11-8.09 (m, 2H), 8.03-7.99 (m, 1H), 7.72-7.65 (m, 2H), 7.24-7.07 (m, 3.5H), 6.94-6.92 (m, 0.5H), 6.55-6.52 (m, 1H), 4.75-4.50 (m, 2H), 4.16-3.65 (m, 2H), 3.35-3.20 (m, 2H), 3.15-2.65 (m, 6H), 2.32 (s, 2H), 2.27 (s, 1H), 1.52-1.00 (m, 10H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.70-0.66 (m, 1H); MS(ESI⁺) m/z 731.2 (M+H)⁺.

Intermediate 53

1-Ethylindoline-5-sulfonamide

[00260] To a suspension of 1-acetylindoline-5-sulfonamide (Intermediate 52A, 120 mg, 0.50 mmol) in THF (2.0 mL) was added BH₄⁻/THF (5.0 mL, 5.0 mmol, LOM solution in THF). The resulting reaction mixture was stirred at room temperature for 1 h, then quenched carefully with MeOH and concentrated in vacuo to give the title compound (115 mg, 100%) as a white solid. ¹H NMR (CD₃OD) δ 7.56 (dd, J = 8.4, 2.0 Hz, 1H),...
7.48 (d, J = 1.6 Hz, 1H), 6.46-6.44 (m, 1H), 3.51 (t, J = 8.6 Hz, 2H), 3.24-3.20 (m, 2H),
2.99 (t, J = 8.5 Hz, 2H), 1.17-1.13 (m, 3H); MS(ESI⁺) m/z 227.2 (M+H)⁺.

Intermediate 54

1H-Indole-5-sulfonamide

Intermediate 54A: Indoline-5-sulfonamide

[00262] To a suspension of 1-acetylindoline-5-sulfonamide (Intermediate 52A, 1.00 g,
4.16 mmol) in MeOH (12.0 mL) was added cone. HCl (1.7 mL, 20.8 mmol). The
resulting reaction mixture was stirred at room temperature for 18 h and then at 80 °C for
2 h. The reaction mixture was cooled to room temperature and concentrated in vacuo.
The brown residue was dissolved in water and the solution was adjusted to a pH of 7-8
with 1 N aq. NaOH solution. The mixture was then extracted with EtOAc (2 x), and the
combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo
to give the title compound (720 mg, 87%) as a light brown solid. ¹H NMR (DMSO-d₆) δ
7.42-7.38 (m, 2H), 6.86 (s, 2H), 6.47 (d, J = 8.1 Hz, 1H), 6.24-6.22 (m, 1H), 3.53-3.50
(m, 2H), 2.98-2.95 (m, 2H); MS(ESI⁺) m/z 199.1 (M+H)⁺.

Intermediate 54:

[00262] To a suspension of indoline-5-sulfonamide (400 mg, 2.02 mmol) in DCE (12.0
mL) was added DDQ (458 mg, 2.02 mmol). The resulting reaction mixture was stirred at
75 °C for 2 h and then filtered through CELITE®, washing with EtOAc. The filtrate was
concentrated in vacuo and purified using preparative HPLC to give the title compound
(220 mg, 56%) as a white solid after lyophilization. ¹H NMR (CD₃OD) δ 10.97 (br s,
1H), 8.17 (d, J = 1.8 Hz, 1H), 7.66 (dd, J = 8.6, 1.8 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H),
7.41-7.39 (m, 1H), 6.61-6.59 (m, 1H); MS(ESI⁺) m/z 197.1 (M+H)⁺.
Intermediate 55

l-(Cyclohexanecarbonyl)indoline-5-sulfonamide

[00263] To a solution of indoline-5-sulfonamide (Intermediate 54A, 100 mg, 0.50 mmol) in MeCN (5.0 mL) was added cyclohexanecarbonyl chloride (0.14 mL, 1.00 mmol) and K2CO3 (174 mg, 1.26 mmol). The resulting reaction mixture was stirred at room temperature overnight and then diluted with EtOAc and sat. aq. NaHCO3 solution. The organic layer was washed with 1N aq. NaOH solution, followed by 10% aq. LiCl solution. The combined organic extracts were dried over MgSO4, filtered and concentrated in vacuo. The residue was triturated with CH2Cl2 to give the title compound (31 mg, 20%) as a white solid. 1H NMR (DMSO-d6) δ 8.16 (d, J = 6.8 Hz, 1H), 7.64-7.60 (m, 2H), 7.19 (m, 2H), 4.22 (t, J = 8.5 Hz, 2H), 3.21-3.16 (m, 2H), 2.62-2.55 (m, 1H), 1.91-1.65 (m, 5H), 1.45-1.16 (m, 5H); MS(ESI+) m/z 309.1 (M+H)+.

Intermediate 56

l-Ethyl-1H-indole-5-sulfonamide

[00264] Following a procedure analogous to that for the synthesis of Intermediate 54, l-ethylindoline-5-sulfonamide (Intermediate 53, 65 mg, 0.29 mmol) was converted to the title compound (29 mg, 45%). 1H NMR (CD3OD) δ 8.16 (d, J = 1.3 Hz, 1H), 7.70 (dd, J = 8.8, 1.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.40 (d, J = 3.3 Hz, 1H), 6.61-6.60 (m, 1H), 4.28 (t, J = 7.3 Hz, 2H), 1.45 (t, J = 7.3 Hz, 3H); MS(ESI+) m/z 225.2 (M+H)+.

Intermediate 57

l-(Cyclohexylmethyl)indoline-5-sulfonamide
Following a procedure analogous to that for the synthesis of Intermediate 53, 1-(cyclohexanecarbonyl)indoline-5-sulfonamide (Intermediate 55, 120 mg, 0.39 mmol) was converted to the title compound (65 mg, 57%) after purification using preparative HPLC.  

\[ \text{NMR (CD}_3\text{OD)} \delta 7.54 (dd, J = 8.4, 2.0 \text{ Hz}, 1\text{H}), 7.45 (d, J = 1.5 \text{ Hz}, 1\text{H}), 6.38 (d, J = 8.4 \text{ Hz}, 2\text{H}), 3.54 (d, J = 8.7 \text{ Hz}, 2\text{H}), 3.04-2.96 (m, 4\text{H}), 1.80-1.68 (m, 6\text{H}), 1.31-1.23 (m, 3\text{H}), 1.05-0.96 (m, 2\text{H}); \text{MS(ESI}^+\text{)} m/z 295.1 (M+H)^+ \].

Intermediate 58

1-(3,4-Dichlorobenzoyl)indoline-5-sulfonamide

\[ \text{O}_2\text{N} \]

\[ \text{H}_2\text{N} \]

\[ \text{O} \]

\[ \text{Cl} \]

\[ \text{(Int-58)} \]

Following a procedure analogous to that for the synthesis of Intermediate 55, indoline-5-sulfonamide (Intermediate 54A, 195 mg, 0.98 mmol) and 3,4-dichlorobenzoyl chloride (412 mg, 1.97 mmol) were converted to the title compound (132 mg, 36%) after purification using preparative HPLC.  

\[ \text{H NMR (DMSO-d}_6\text{)} \delta 7.92 (d, J = 1.1 \text{ Hz}, 1\text{H}), 7.78 (d, J = 8.1 \text{ Hz}, 1\text{H}), 7.71-7.61 (m, 3\text{H}), 7.26 (s, 2\text{H}), 4.07 (t, J = 8.3 \text{ Hz}, 2\text{H}), 3.16 (t, J = 8.2 \text{ Hz}, 2\text{H}); \text{MS(ESI}^+\text{)} m/z 370.8 (M+H)^+ \].

Intermediate 59

1-(3,4-Dichlorobenzyl)indoline-5-sulfonamide

\[ \text{O}_2\text{N} \]

\[ \text{H}_2\text{N} \]

\[ \text{O} \]

\[ \text{Cl} \]

\[ \text{(Int-59)} \]

Following a procedure analogous to that for the synthesis of Intermediate 53, 1-(3,4-dichlorobenzoyl)indoline-5-sulfonamide (Intermediate 58, 70 mg, 0.19 mmol) was converted to the title compound (41 mg, 61%) after purification using preparative HPLC.  

\[ \text{H NMR (DMSO-d}_6\text{)} \delta 7.63-7.58 (m, 2\text{H}), 7.48-7.43 (m, 2\text{H}), 7.31 (dd, J = 8.3, 2.1 \text{ Hz}, 1\text{H}), 6.91 (s, 2\text{H}), 6.60 (d, J = 8.1 \text{ Hz}, 1\text{H}), 4.41 (s, 2\text{H}), 3.46 (t, J = 8.7 \text{ Hz}, 2\text{H}), 3.03-2.98 (m, 2\text{H}); \text{MS(ESI}^+\text{)} m/z 356.9 (M+H)^+ \].

Intermediate 60

1-Acetylindoline-6-sulfonamide
A solution of 1-acetyl-5-bromoindoline-6-sulfonyl chloride (2.30 g, 6.79 mmol) in NH₃ (54.3 mL, 27.2 mmol, 0.5M solution in dioxane) was stirred at room temperature overnight. The reaction mixture was then concentrated in vacuo, and the residue was triturated with CH₂Cl₂ to give the title compound (1.40 g, 65%) as a brown solid. ³¹NMR (DMSO-d₆) δ 8.73 (s, 1H), 7.63 (s, 1H), 7.15 (s, 2H), 4.15 (t, J = 8.5 Hz, 2H), 3.19 (t, J = 8.6 Hz, 2H), 2.17 (s, 3H); MS(ESI⁺) m/z 321.1 (M+H)⁺.

To a suspension of 1-acetyl-5-bromoindoline-6-sulfonamide (650 mg, 2.04 mmol) in EtOH (10.0 mL) was added 10% Pd/C (433 mg, 0.41 mmol) and Et₃N (852 µL, 6.11 mmol). The reaction mixture was evacuated and purged with ¾ from a balloon (2 x) and allowed to stir under ¾ for 22 h. The reaction mixture then was filtered through a pad of CELITE®, washing with EtOAc. The filtrate was concentrated in vacuo to give the title compound (450 mg, 92%) as a white solid. ³¹NMR (DMSO-d₆) δ 8.49 (s, 1H), 7.46-7.44 (m, 1H), 7.38-7.36 (m, 1H), 7.29 (br s, 2H), 4.15 (t, J = 8.6 Hz, 2H), 3.19 (t, J = 8.5 Hz, 2H), 2.18 (s, 3H); MS(ESI⁺) m/z 241.1 (M+H)⁺.
Following a procedure analogous to that for the synthesis of Intermediate 55, indoline-5-sulfonamide (Intermediate 54A, 100 mg, 0.50 mmol) and benzoyl chloride (64 μL, 0.56 mmol) were converted to the title compound (120 mg, 79%). $^1$H NMR (DMSO-d$_6$) δ 7.70 (s, 1H), 7.65-7.60 (m, 3H), 7.57-7.49 (m, 4H), 7.24 (s, 2H), 4.07 (t, J = 8.5 Hz, 2H), 3.15 (t, J = 8.4 Hz, 2H); MS(ESI$^+$) m/z 303.2 (M+H)$^+$.  

Intermediate 61:

Following a procedure analogous to that for the synthesis of Intermediate 45, 1-benzoylindoline-5-sulfonamide (120 mg, 0.40 mmol) was converted to the title compound (100 mg, 87%) after purification using preparative HPLC. $^1$H NMR (CD$_3$OD) δ 7.56 (dd, J = 8.4, 2.0 Hz, 1H), 7.52-7.51 (m, 1H), 7.35-7.25 (m, 5H), 6.52 (d, J = 8.4 Hz, 1H), 4.38 (s, 2H), 3.49 (t, J = 8.7 Hz, 2H), 3.03 (t, J = 8.6 Hz, 2H); MS(ESI$^+$) m/z 289.2 (M+H)$^+$.  

Intermediate 62

l-(3,4-Difluorobenzyl)indoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 55, indoline-5-sulfonamide (Intermediate 54A, 90 mg, 0.45 mmol) and 3,4-difluorobenzoyl chloride (69 μL, 0.54 mmol) were converted to the title compound (120 mg, 78%). $^1$H NMR (DMSO-d$_6$) δ 7.60-7.21 (m, 6H), 7.01 (s, 2H), 3.85 (t, J = 8.6 Hz, 2H), 2.92 (t, J = 8.6 Hz, 2H); MS(ESI$^+$) m/z 338.9 (M+H)$^+$.  

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Intermediate 62B: 1-(3,4-Difluorobenzyl)indoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 53, 1-benzoylindoline-5-sulfonamide (100 mg, 0.30 mmol) was converted to the title compound (58 mg, 60%) after purification using preparative HPLC. ¹H NMR (DMSO-d₆) δ 7.46-7.35 (m, 4H), 7.18-7.15 (m, 1H), 6.92 (s, 2H), 6.60 (d, J = 8.1 Hz, 1H), 4.39 (s, 2H), 3.46 (t, J = 8.6 Hz, 2H); MS(ESI⁺) m/z 325.1 (M+H)⁺.

Intermediate 63

1-Ethylindoline-6-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 53, 1-acetylindoline-6-sulfonamide (Intermediate 60, 200 mg, 0.83 mmol) was converted to the title compound (50 mg, 27%) after purification using preparative HPLC. ¹H NMR (CDCl₃) δ 7.37 (d, J = 7.5 Hz, 1H), 7.21 (d, J = 9.7 Hz, 2H), 3.59 (t, J = 8.1 Hz, 2H), 3.28 (q, J = 8.1 Hz, 2H), 3.10 (t, J = 8.1 Hz, 2H), 1.26-1.22 (m, 3H); MS(ESI⁺) m/z 227.1 (M+H)⁺.

Intermediate 64

1-(2-(3,4-Dichlorophenyl)acetyl)indoline-5-sulfonamide

To a suspension of 2-(3,4-dichlorophenyl)acetic acid (137 mg, 0.67 mmol) in DCE (2.0 mL) was added oxalyl chloride (908 µL, 1.82 mmol, 2.0M solution in CH₂Cl₂) (0.908 mL, 1.816 mmol) followed by one drop of DMF. The resulting reaction mixture was stirred at room temperature for 40 min and then concentrated in vacuo. To a solution of the crude residue in MeCN (4.0 mL) was added indoline-5-sulfonamide (120 mg, 0.61 mmol) and K₂CO₃ (167 mg, 1.21 mmol). The reaction mixture was stirred at room temperature for 1 h. Additional indoline-5-sulfonamide (40 mg, 0.20 mmol) was added,
and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was then diluted with EtOAc and sat. aq. NaHCO₃ solution. The organic layer was washed with 10% aq. LiCl solution and then dried over MgSO₄, filtered and concentrated in vacuo. The residue was triturated with CH₂Cl₂ to give the title compound (180 mg, 77%) as a pale yellow solid. ³¹NMR (DMSO-d₆) δ 8.11 (d, J = 8.4 Hz, 1H), 7.59 (m, 4H), 7.29 (dd, J = 8.1, 2.0 Hz, 1H), 7.22 (s, 2H), 4.26 (t, J = 8.5 Hz, 2H), 3.94 (s, 2H), 3.24 (t, J = 8.5 Hz, 2H); MS(ESI⁺) m/z 385.0 (M+H)⁺.

Intermediate 65

1-(3,4-Dichlorophenethyl)indoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 53, 1-(2-(3,4-dichlorophenyl)acetyl)indoline-5-sulfonamide (Intermediate 64, 140 mg, 0.363 mmol) was converted to the title compound (89 mg, 66%) after purification using preparative HPLC. ¹H NMR (DMSO-d₆) δ 7.64-7.63 (m, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.43 (dd, J = 8.4, 2.0 Hz, 1H), 7.39 (d, J = 1.5 Hz, 1H), 7.33 (dd, J = 8.3 Hz, 2.1 Hz, 1H), 6.90 (s, 2H), 6.56 (d, J = 8.4 Hz, 1H), 3.49 (t, J = 8.7 Hz, 2H), 3.42-3.38 (m, 2H), 2.95 (t, J = 8.5 Hz, 2H), 2.84 (t, J = 7.5 Hz, 2H); MS(ESI⁺) m/z 371.0 (M+H)⁺.

Intermediate 66

1-(2-(Phenylthio)acetyl)indoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 64, indoline-5-sulfonamide (Intermediate 54A, 120 mg, 0.60 mmol) and 2-(phenylthio)acetic acid (117 mg, 0.70 mmol) were converted to the title compound (100 mg, 45%). ¹H NMR (DMSO-d₆) δ 8.09 (d, J = 8.4 Hz, 1H), 7.67-7.62 (m, 2H), 7.43-7.40 (m, 2H), 7.34-7.30 (m, 2H), 7.22-7.19 (m, 3H), 4.29 (t, J = 8.6 Hz, 2H), 4.17 (s, 2H), 3.23 (t, J = 8.5 Hz, 2H); MS(ESI⁺) m/z 348.9 (M+H)⁺.
Intermediate 67
l-(2-(Phenylthio)ethyl)indoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 53, l-(2-(phenylthio)acetyl)indoline-5-sulfonamide (Intermediate 66, 74 mg, 0.21 mmol) was converted to the title compound (40 mg, 52%) after purification using preparative HPLC.

\[ ^1H \text{NMR (DMSO-}d_6) \delta 7.43-7.33 (m, 6H), 7.21 (t, J = 7.2 \text{ Hz, 1H}), 6.90 (s, 2H), 6.36 (d, J = 8.4 \text{ Hz, 1H}), 3.53 (t, J = 8.6 \text{ Hz, 2H}), 3.39 (t, J = 6.8 \text{ Hz, 2H}), 3.19 (t, J = 6.9 \text{ Hz, 2H}), 2.94 (t, J = 8.6 \text{ Hz, 2H}); \text{MS(ESI}^+) m/z 335.1 (M+H)^+ .

Intermediate 68
l-(3,4-Dichlorobenzyl)-1H-indole-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 54, l-(3,4-dichlorobenzyl)indoline-5-sulfonamide (Intermediate 59, 60 mg, 0.17 mmol) was converted to the title compound (52 mg, 87%).

\[ ^1H \text{NMR (DMSO-}d_6) \delta 8.08 (d, J = 1.3 \text{ Hz, 1H}), 7.70 (d, J = 3.1 \text{ Hz, 1H}), 7.66-7.64 (m, 1H), 7.70 (m, 1H), 7.60-7.56 (m, 2H), 7.50 (d, J = 2.0 \text{ Hz, 1H}), 7.12-7.09 (m, 3H), 6.70 (d, J = 2.6 \text{ Hz, 1H}), 5.50 (s, 2H); \text{MS(ESI}^+) m/z 354.8 (M+H)^+ .

Intermediate 69
l-((6-Chloropyridin-2-yl)methyl)indoline-5-sulfonamide

Intermediate 69A: l-(6-Chloropicolinoyl)indoline-5-sulfonamide
Following a procedure analogous to that for the synthesis of Intermediate 64, indoline-5-sulfonamide (Intermediate 54A, 300 mg, 1.51 mmol) and 6-chloropicolinic acid (262 mg, 1.66 mmol) were converted to the title compound (250 mg, 49%).

**Intermediate 69:**

Following a procedure analogous to that for the synthesis of Intermediate 53, 1-(6-chloropicolinoyl)-l- indole-5-sulfonamide (60 mg, 0.18 mmol) was converted to the title compound (29 mg, 50%) after purification using preparative HPLC. ¹H NMR (DMSO-d₆) δ 8.40 (d, J = 2.0 Hz, 1H), 7.80 (dd, J = 8.1, 2.6 Hz, 1H), 7.52-7.43 (m, 3H), 6.93 (br s, 2H), 6.66 (d, J = 8.4 Hz, 1H), 4.44 (s, 2H), 2.99 (t, J = 8.5 Hz, 2H); MS(ESI⁺) m/z 324.1 (M+H)⁺.

Intermediate 70:

1-((1-Methyl-1H-indol-6-yl)methyl)indoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 56, indoline-5-sulfonamide (Intermediate 54A, 130 mg, 0.66 mmol) and 1-methyl-1H-indole-3-carboxylic acid (Aldrich, 126 mg, 0.721 mmol) were converted to the title compound (21 mg, 9%) after purification using preparative HPLC. ¹H NMR (DMSO-d₆) δ 7.79 (m, 2H), 7.70 (m, 1H), 7.65-7.61 (m, 2H), 7.50 (d, J = 3.1 Hz, 1H), 7.27 (dd, J = 8.3, 1.4 Hz,
1H), 7.23 (s, 2H), 6.52 (d, J = 2.4 Hz, 1H), 4.17 (t, J = 8.4 Hz, 2H), 3.84 (s, 3H), 3.16 (t, J = 8.3 Hz, 2H); MS(ESI+) m/z 356.1 (M+H)+.

Intermediate 70:

Following a procedure analogous to that for the synthesis of Intermediate 53, 1-[(1-methyl-1H-indole-6-carbonyl)indoline-5-sulfonamide (40 mg, 0.11 mmol) was converted to the title compound (20 mg, 52%) after purification using preparative HPLC.

$^1$H NMR (DMSO-d$_6$) $\delta$ 7.55-7.43 (m, 4H), 7.32 (d, J = 2.0 Hz, 1H), 7.02 (dd, J = 8.3, 1.4 Hz, 1H), 6.95 (s, 2H), 6.72 (d, J = 8.3 Hz, 1H), 6.42 (d, J = 2.4 Hz, 1H), 4.50 (s, 2H), 3.84 (s, 3H), 3.48 (t, J = 8.4 Hz, 2H), 3.00 (t, J = 8.3 Hz, 2H); MS(ESI+) m/z 341.1 (M+H)+.

Intermediate 71

5-Bromo-1-ethylindoline-6-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 53, 1-acetyl-5-bromoindoline-6-sulfonamide (Intermediate 60A, 110 mg, 0.34 mmol) was converted to the title compound (53 mg, 50%). $^1$H NMR (DMSO-d$_6$) $\delta$ 7.34 (s, 1H), 7.32 (s, 2H), 7.00 (s, 1H), 3.41 (t, J = 8.5 Hz, 2H), 3.14 (q, J = 7.1 Hz, 2H), 2.95 (t, J = 8.5 Hz, 2H), 1.10 (t, J = 7.2 Hz, 3H); MS(ESI+) m/z 307.1 (M+H)+.

Intermediate 72

5-Bromo-1-(3,4-dichlorobenzyl)indoline-6-sulfonamide

Intermediate 72A: (3,4-Dichlorophenyl)(indolin-1-yl)methanone
To a solution of indoline (2.0 mL, 17.8 mmol) in MeCN (45.0 mL) was added 3,4-dichlorobenzoyl chloride (4.11 g, 19.6 mmol) followed by Et₃N (7.5 mL, 53.5 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was triturated with water and dried under high vacuum to give the title compound (5.2 g, 100%) as a light brown solid. ¹H NMR (DMSO-d₆) δ 7.89 (d, J = 1.1 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 7.3 Hz, 1H), 7.19 (m, 1H), 7.06 (t, J = 7.2 Hz, 1H), 4.00 (t, J = 8.3 Hz, 2H), 3.09 (t, J = 8.3 Hz, 2H); MS(ESI⁺) m/z 292.1 (M+H)⁺.

Intermediate 72B: (5-Bromoindolin-1-yl)(3,4-dichlorophenyl)methanone

To a solution of (3,4-dichlorophenyl)(indolin-1-yl)methanone (2.6 g, 8.90 mmol) in AcOH (8.2 mL, 142 mmol) was added bromine (504 μL, 9.79 mmol) dropwise via syringe at 0 °C. Additional AcOH (6.0 mL) was added, and the reaction mixture was stirred at room temperature for 1 h. Cold water was added to the reaction mixture followed by sat. aq. NaHSO₃ solution. The resulting mixture was stirred for 10 min, and the precipitate was collected via filtration to give the title compound (3.30 g, 100%) as a light brown solid. ¹H NMR (DMSO-d₆) δ 7.90 (d, J = 1.5 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.49 (s, 1H), 7.38 (br s, 1H), 4.02 (t, J = 8.3 Hz, 2H), 3.10 (t, J = 8.3 Hz, 2H); MS(ESI⁺) m/z 371.9 (M+H)⁺.

Intermediate 72C: 5-Bromo-1-(3,4-dichlorobenzoyl)indoline-6-sulfonamide

To sulfurochloridic acid (2.9 mL, 43.1 mmol) was added (5-bromoindolin-1-yl)(3,4-dichlorophenyl)methanone (2.00 g, 5.39 mmol) portionwise at 0 °C. The reaction
mixture was stirred at 65 °C for 6 h and then at room temperature overnight. The reaction mixture poured slowly into ice water and then extracted with CH2Cl2. The organic layer was washed with sat. aq. NaCl solution, dried over MgSO4, filtered and concentrated in vacuo to give a brown solid, which was used in the subsequent step without purification.

[00288] Following a procedure analogous to that for the synthesis of Compound A of Example 52, the crude solid from above was converted to the title compound (310 mg, 16% over two steps) after purification using preparative HPLC. 1H NMR (DMSO-d6) δ 8.65 (br s, 1H), 7.91 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.72 (s, 1H), 7.62 (dd, J = 8.3, 1.9 Hz, 1H), 7.53 (s, 2H), 4.07 (t, J = 8.4 Hz, 2H), 3.16 (t, J = 8.3 Hz, 2H);

MS(ESI+) m/z 450.9 (M+H)+.

Intermediate 72:

[00289] Following a procedure analogous to that for the synthesis of Intermediate 53, 5-bromo-l-(3,4-dichlorobenzoyl)indoline-6-sulfonamide (240 mg, 0.53 mmol) was converted to the title compound (160 mg, 69%) after purification using preparative HPLC. 1H NMR (DMSO-d6) δ 7.63 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.93 (s, 1H), 7.34-7.31 (m, 3H), 7.07 (s, 1H), 4.33 (s, 2H), 3.43 (s, 2H), 3.02 (t, J = 8.5 Hz, 2H); MS(ESI+) m/z 436.9 (M+H)+.

Intermediate 73

Methyl l-(3,4-dichlorobenzyl)-5-sulfamoylindoline-2-carboxylate

(3.23 g, 18.3 mmol) and 3,4-dichlorobenzoyl chloride (4.21 g, 20.1 mmol) were
converted to the title compound (5.30 g, 83%) after purification using flash column chromatography (gradient from 0% to 5% EtOAc/CH₂Cl₂). H NMR (CDCl₃, 1:1 mixture of amide rotamers) δ 7.67 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.41-7.37 (m, 1.5H), 7.23-7.20 (m, 1.5H), 7.04-7.01 (m, 2H), 5.31-5.08 (m, 1H), 3.77-3.75 (m, 3H), 3.62-3.55 (m, 1H), 3.24-3.19 (m, 1H); MS(ESI⁺) m/z 350.1 (M+H)⁺.

Intermediate 73B: Methyl 1-(3,4-dichlorobenzoyl)-5-sulfamoylindoline-2-carboxylate

Following a procedure analogous to that for the synthesis of Intermediate 72C, methyl 1-(3,4-dichlorobenzoyl)indoline-2-carboxylate (2.00 g, 5.71 mmol) was converted to the title compound (200 mg, 14% over two steps). ¾ NMR (CDCl₃) δ 8.19 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 8.4, 2.0 Hz, 1H), 7.76 (s, 1H), 7.72-7.67 (m, 2H), 7.59-7.56 (m, 2H), 7.41-7.39 (m, 1H), 5.14-5.11 (m, 1H), 3.75-3.73 (m, 3H), 3.67-3.60 (m, 1H), 3.29-3.24 (m, 1H); MS(ESI⁺) m/z 428.9 (M+H)⁺.

Intermediate 73:

Following a procedure analogous to that for the synthesis of Intermediate 53, methyl 1-(3,4-dichlorobenzoyl)-5-sulfamoylindoline-2-carboxylate (200 mg, 0.47 mmol) was converted to the title compound (44 mg, 22%) after purification using preparative HPLC. ¾ NMR (DMSO-d₆) δ 7.61 (dd, J = 5.1, 3.1 Hz, 2H), 7.46-7.44 (m, 2H), 7.32 (dd, J = 8.4, 2.0 Hz, 1H), 6.98 (s, 2H), 6.43 (d, J = 8.8 Hz, 1H), 4.61-4.58 (m, 2H), 4.37 (d, J = 16.3 Hz, 1H), 3.63-3.62 (m, 3H), 3.54-3.47 (m, 1H), 3.13 (dd, J = 16.6, 6.1 Hz, 1H); MS(ESI⁺) m/z 415.1 (M+H)⁺.

Intermediate 74

1-(Morpholine-4-carbonyl)indoline-5-sulfonamide
Following a procedure analogous to that for the synthesis of Intermediate 55, indoline-5-sulfonamide (Intermediate 54A, 250 mg, 1.26 mmol) and morpholine-4-carbonyl chloride (206 µL, 1.77 mmol) were converted to the title compound (230 mg, 59%) after purification using preparative HPLC. ¹H NMR (DMSO-d₆) δ 7.61-7.58 (m, 2H), 7.15-7.12 (m, 3H), 3.92 (t, J = 6.5 Hz, 2H), 3.78-3.75 (m, 2H), 3.66-3.63 (m, 4H), 3.10-3.07 (m, 4H); MS(ESI⁺) m/z 312.2 (M+H)⁺.

Intermediate 75

l-(2-Morpholinoacetyl)indoline-5-sulfonamide

![Intermediate 75](image)

Intermediate 75A: l-(2-Chloroacetyl)indoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 55, indoline-5-sulfonamide (Intermediate 54A, 500 mg, 2.52 mmol) and 2-chloroacetyl chloride (221 µL, 2.77 mmol) were converted to the title compound (160 mg, 23%). ¹H NMR (DMSO-d₆) δ 8.13 (d, J = 8.1 Hz, 1H), 7.68-7.66 (m, 2H), 7.24 (s, 2H), 4.58 (s, 2H), 4.20 (t, J = 8.6 Hz, 2H), 3.24 (t, J = 8.5 Hz, 2H); MS(ESI⁺) m/z 275.0 (M+H)⁺.

Intermediate 76

7-Bromo-l-ethylindoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 55, l-(2-chloroacetyl)indoline-5-sulfonamide (160 mg, 0.58 mmol) and morpholine (221 µL, 2.77 mmol) were converted to the title compound (86 mg, 45%). ¹H NMR (DMSO-d₆) δ 8.12 (br s, 1H), 7.65-7.62 (m, 2H), 7.21 (s, 2H), 4.23 (t, J = 8.6 Hz, 2H), 3.60-3.58 (m, 4H), 3.32-3.30 (m, 6H), 3.22-3.16 (m, 2H); MS(ESI⁺) m/z 326.1 (M+H)⁺.
Following a procedure analogous to that for the synthesis of Intermediate 72B, l-ethylindoline-5-sulfonamide (Intermediate 53, 230 mg, 1.02 mmol) was converted to the title compound (225 mg, 72%). 3٤ NMR (DMSO-d$_6$) δ 7.56 (d, J = 1.8 Hz, 1H), 7.36 (d, J = 1.5 Hz, 1H), 7.08 (s, 2H), 3.65-3.55 (m, 4H), 2.99 (t, J = 8.9 Hz, 2H), 1.09 (t, J = 7.0 Hz, 3H); MS(ESI$^+$) m/z 307.1 (M+H)$^+$.  

Intermediate 77  
l-(2-Morpholinoethyl)indoline-5-sulfonamide

Intermediate 77A: l-(2-Chloroethyl)indoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 53, l-(2-chloroacetyl)indoline-5-sulfonamide  (Intermediate 75A, 400 mg, 1.46 mmol) was converted to the title compound (300 mg, 79%). 1H NMR (DMSO-d$_6$) δ 7.45 (dd, J = 8.3, 1.9 Hz, 1H), 7.41 (br s, 1H), 6.91 (s, 2H), 6.56 (d, J = 8.4 Hz, 1H), 3.83-3.80 (m, 2H), 3.60-3.51 (m, 4H), 2.99 (t, J = 8.7 Hz, 2H); MS(ESI$^+$) m/z 261.2 (M+H)$^+$.  

Intermediate 75:  

To a solution of l-(2-chloroethyl)indoline-5-sulfonamide (100 mg, 0.38 mmol) in DMF (2.0 mL) were added NaI (86 mg, 0.58 mmol), KOH (108 mg, 1.92 mmol) and morpholine (201 μL, 2.30 mmol). The resulting reaction mixture was stirred at 72 °C overnight. The reaction mixture was then filtered and purified by preparative HPLC to give the title compound (26 mg, 22%) as a white solid after lyophilization. 1H NMR (DMSO-d$_6$) δ 7.45-7.38 (m, 2H), 6.90 (br s, 2H), 6.49 (d, J = 8.6 Hz, 1H), 3.57-
3.52 (m, 6H), 3.28 (t, J = 6.8 Hz, 2H), 2.44-2.42 (m, 4H), 2.96 (t, J = 8.6 Hz, 4H);
MS(ESI+) m/z 312.0 (M+H)+.

Intermediate 78

1-(6-(2-Morpholinoethoxy)nicotinoyl)indoline-5-sulfonamide

Intermediate 78A: 6-(2-Morpholinoethoxy)nicotinic acid

[00299] To a solution of 6-chloronicotinic acid (Aldrich, 1.00 g, 6.35 mmol) and t-BuOK (1.42 g, 12.7 mmol) in DMSO (10.0 mL) was added 2-morpholinoethanol (1.5 mL, 12.7 mmol) at room temperature. The reaction mixture was then heated at 95 °C for 16 h. Additional t-BuOK (1.42 g, 12.7 mmol), 2-morpholinoethanol (1.54 mL, 12.7 mmol) and DMSO (10.0 mL) were added, and the reaction mixture was heated at 95 °C for another 24 h. The reaction mixture was then cooled to room temperature, poured into ice cold 4N aq. HC1 solution and extracted with EtOAc (3 x). The aqueous layer was concentrated in vacuo to near dryness and purified using preparative HPLC to give the title compound (150 mg, 9%) as a white solid after lyophilization. 1H NMR (DMSO-d6) δ 13.1 (br s, 1H), 8.74 (d, J = 1.8 Hz, 1H), 8.21 (dd, J = 8.6, 2.2 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 4.69 (br s, 4H), 3.96 (br s, 2H), 3.75-3.70 (m, 2H), 3.19 (br s, 4H); MS(ESI+) m/z 253.2 (M+H)+.

Intermediate 78:

[00300] Following a procedure analogous to that for the synthesis of Intermediate 64, indoline-5-sulfonamide (Intermediate 54A, 110 mg, 0.56 mmol) and 6-(2-morpholinoethoxy)nicotinic acid (147 mg, 0.58 mmol) were converted to the title compound (51 mg, 21%). 1H NMR (DMSO-d6) δ 8.52 (d, J = 2.0 Hz, 1H), 8.05 (dd, J = 8.6, 2.4 Hz, 1H), 7.95 (br s, 1H), 7.71-7.66 (m, 2H), 7.26 (s, 2H), 7.02-6.98 (m, 1H),
4.74-4.68 (m, 2H), 4.14 (t, J = 8.4 Hz, 2H), 3.97 (br s, 2H), 3.75-3.49 (m, 6H), 3.17 (t, J = 8.5 Hz, 4H); MS(ESI+) m/z 433.2 (M+H)+.

Intermediate 79

3-Bromo-1H-indole-5-sulfonamide

To a solution of 1H-indole-5-sulfonamide (Intermediate 54, 100 mg, 0.51 mmol) in DMF (2.0 mL) was added N-bromosuccinimide (91 mg, 0.51 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 30 min and then diluted with sat. aq. NaHSO₃ solution and EtOAc. The organic layer was washed with sat. aq. NaCl solution, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified using preparative HPLC to give the title compound (90 mg, 61%) as a white solid after lyophilization. 'HNMR (DMSO-d₆) δ 11.88 (br s, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 2.6 Hz, 1H), 7.65-7.63 (m, 1H), 7.59-7.57 (m, 1H), 7.21 (s, 2H); MS(ESI+) m/z 277.1 (M+H)+.

Intermediate 80

3-Bromo-1-ethyl-1H-indole-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 77, 1-ethyl-1H-indole-5-sulfonamide (Intermediate 56, 70 mg, 0.31 mmol) was converted to the title compound (56 mg, 59%). 'H NMR (DMSO-d₆) δ 7.93 (d, J = 1.3 Hz, 1H), 7.84 (s, 1H), 7.76-7.74 (m, 1H), 7.69-7.66 (m, 1H), 7.23 (s, 2H), 4.28 (q, J = 7.3 Hz, 2H), 1.37 (t, J = 7.3 Hz, 3H); MS(ESI+) m/z 305.2 (M+H)+.

Intermediate 81

1-(3-Morpholinopropanoyl)indoline-5-sulfonamide
Intermediate 81A: l-(3-Chloropropanoyl)indoline-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 55, indoline-5-sulfonamide (Intermediate 54A, 300 mg, 1.51 mmol) and 3-chloropropanoyl chloride (189 µL, 1.97 mmol) were converted to the title compound (430 mg, 98%). $^1$H NMR (DMSO-d$_6$) δ 8.16 (d, $J = 8.1$ Hz, 1H), 7.66-7.63 (m, 2H), 7.22 (s, 2H), 4.18 (t, $J = 8.6$ Hz, 2H), 3.89-3.86 (m, 2H), 3.21 (t, $J = 8.5$ Hz, 2H), 3.03 (t, $J = 6.4$ Hz, 2H);

MS(ESI$^+$) m/z 289.2 (M+H)$^+$. 

Intermediate 81B: To a solution of 1-(3-chloropropanoyl)indoline-5-sulfonamide (210 mg, 0.73 mmol) in DMF (2.0 mL) were added morpholine (509 µL, 5.82 mmol), KOH (82 mg, 1.46 mmol) and TBAI (107 mg, 0.29 mmol). The resulting reaction mixture was stirred at 75 °C for 4 h and then diluted with EtOAc and sat. aq. NaHCO$_3$ solution. The organic layer washed with sat. aq. NaCl solution, dried over MgSO$_4$, filtered and concentrated $\textit{in vacuo}$ to give the title compound (185 mg, 75%) as a white solid. $^3$¹NMR (DMSO-d$_6$) δ 8.14 (d, $J = 8.1$ Hz, 1H), 7.64-7.61 (m, 2H), 7.20 (s, 2H), 4.18 (t, $J = 8.5$ Hz, 2H), 3.58-3.53 (m, 4H), 3.22-3.18 (m, 2H), 2.67-2.62 (m, 4H), 2.41-2.40 (m, 4H); MS(ESI$^+$) m/z 340.3 (M+H)$^+$. 

Intermediate 82

l-(3-Morpholinopropyl)-l H-indole-5-sulfonamide, TFA

To a solution of NaH (163 mg, 4.08 mmol, 60% suspension in mineral oil) in DMF (1.5 mL) at 0 °C were added 1H-indole-5-sulfonamide (Intermediate 54, 80 mg,
0.41 mmol), TBAI (60 mg, 0.16 mmol) and 4-(3-chloropropyl)morpholine (667 mg, 4.08 mmol). The resulting reaction mixture was stirred at 0 °C for 2 h, then quenched with MeOH and concentrated in vacuo. The residue was purified by preparative HPLC (H$_2$O/MeOH/0.1%TFA) to give the title compound (178 mg, 100%) as a white solid after lyophilization. $^1$H NMR (DMSO-d$_6$) δ 8.08 (d, $J = 1.3$ Hz, 1H), 7.72-7.67 (m, 1H), 7.65-7.60 (m, 1H), 7.58 (d, $J = 3.1$ Hz, 1H), 7.14 (s, 2H), 6.67 (dd, $J = 3.2$, 0.6 Hz, 1H), 4.34 (t, $J = 7.0$ Hz, 2H), 4.30-4.23 (m, 1H), 4.12-3.09 (m, 9H), 2.24-2.07 (m, 2H); MS(ESI$^+$) m/z 324.3 (M+H$^+$).

Intermediate 83

3-Chloro-1-ethyl-1H-indole-5-sulfonamide

Following a procedure analogous to that for the synthesis of Intermediate 77, 1-ethyl-1H-indole-5-sulfonamide (Intermediate 56, 50 mg, 0.22 mmol) and N-chlorosuccinimide (36 mg, 0.27 mmol) were converted to the title compound (21 mg, 35%). $^1$H NMR (DMSO-d$_6$) δ 7.99 (d, $J = 1.3$ Hz, 1H), 7.81 (s, 1H), 7.77-7.71 (m, 1H), 7.70-7.64 (m, 1H), 7.22 (s, 2H), 4.26 (q, $J = 7.3$ Hz, 2H), 1.36 (t, $J = 7.2$ Hz, 3H); MS(ESI$^+$) m/z 259.2 (M+H$^+$).

Intermediate 84

1-Ethyl-3-iodo-1H-indole-5-sulfonamide

To a solution of 1-ethyl-1H-indole-5-sulfonamide (Intermediate 56, 175 mg, 0.78 mmol) in DMF (5.0 mL) was added a solution of iodine (218 mg, 0.86 mmol) in DMF (5.0 mL). KOH (109 mg, 1.95 mmol) was then added, and the resulting reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted with EtOAc and sat. aq. NaHSC>3 solution. The organic layer was washed with sat. aq.
NaCl solution, dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (95 mg, 35%) as a pale yellow solid after lyophilization. $^1$H NMR (DMSO-d$_6$) $\delta$ 7.86-7.76 (m, 2H), 7.74-7.61 (m, 2H), 7.21 (s, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 1.36 (t, $J = 7.3$ Hz, 3H); MS(ESI$^+$) m/z 351.1 (M+H)$^+$.  

**Intermediate 85**

3,7-Dibromo-1-ethyl-1H-indole-5-sulfonamide

![Intermediate 85](image)

**Intermediate 85A**: 7-Bromo-1-ethyl-1H-indole-5-sulfonamide

![Intermediate 85A](image)

[00308] Following a procedure analogous to that for the synthesis of Intermediate 54, 7-bromo-1-ethylindoline-5-sulfonamide (Intermediate 76, 140 mg, 0.46 mmol) was converted to the title compound (45 mg, 31%). $^1$H NMR (DMSO-d$_6$) $\delta$ 8.04 (d, $J = 1.8$ Hz, 1H), 7.77 (d, $J = 1.5$ Hz, 1H), 7.63 (d, $J = 3.1$ Hz, 1H), 7.26 (s, 2H), 6.72 (d, $J = 3.3$ Hz, 1H), 4.60 (q, $J = 7.1$ Hz, 2H), 1.38 (t, $J = 7.2$ Hz, 3H); MS(ESI$^+$) m/z 305.2 (M+H)$^+$.  

**Intermediate 85**:  

[00309] Following a procedure analogous to that for the synthesis of Intermediate 79, 7-bromo-1-ethyl-1H-indole-5-sulfonamide (45 mg, 0.15 mmol) was converted to the title compound (57 mg, 100%). $^1$H NMR (DMSO-d$_6$) $\delta$ 7.94 (s, 1H), 7.90 (d, $J = 1.8$ Hz, 1H), 7.85 (d, $J = 1.5$ Hz, 1H), 7.38 (s, 2H), 4.61 (q, $J = 7.1$ Hz, 2H), 1.39 (t, $J = 7.2$ Hz, 3H).  

Examples 53 to 85  

[00310] The following Examples were prepared using 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)benzoic acid (Intermediate IF) and the indole/indoline sulfonamide intermediates described above according to the general procedure for the synthesis of Intermediate 56.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R</th>
<th>Name</th>
<th>LCMS (M+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53</td>
<td></td>
<td>(N,N)-dibutyl-4-chloro-1-(4-(1-ethylindolin-5-yl)sulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>759.3</td>
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<tr>
<td>54</td>
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<td>1-(4-(1H-indol-5-yl)sulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-(N,N)-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>729.3</td>
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<tr>
<td>55</td>
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<td>(N,N)-dibutyl-4-chloro-1-(4-(1-cyclohexane carboxyl)indolin-5-yl)sulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
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<tr>
<td>56</td>
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<td>(N,N)-dibutyl-4-chloro-1-(4-(1-ethyl-1H-indol-5-yl)sulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
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<tr>
<td>Ex. No.</td>
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<td>Name</td>
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<tr>
<td>--------</td>
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<tr>
<td>57</td>
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<td>(N,N\text{-dibutyl-4-chloro-1-(4-(1-}\text{cyclohexylmethyl)indolin-5-ylsulfonylcarbamoyl)-2-}\text{(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide}</td>
<td>827.2</td>
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<tr>
<td>58</td>
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<td>(N,N\text{-dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzoyl)indolin-5-ylsulfonylcarbamoyl)-2-}\text{(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide}</td>
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<tr>
<td>59</td>
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<td>(N,N\text{-dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-}\text{(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide}</td>
<td>891.1</td>
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<tr>
<td>60</td>
<td>Ac</td>
<td>1-(4-(1-acetylindolin-6-ylsulfonylcarbamoyl)-2-\text{(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)}\text{-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide}</td>
<td>773.1</td>
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<td>1-(4-(1-benzylindolin-5-ylsulfonylcarbamoyl)-2-\text{(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)}\text{-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide}</td>
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<td>(N,N\text{-dibutyl-4-chloro-1-(4-(1-(3,4-difluorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-}\text{(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide}</td>
<td>857.1</td>
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<td>63</td>
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<td>(N,N\text{-dibutyl-4-chloro-1-(4-(1-ethylindolin-6-ylsulfonylcarbamoyl)-2-}\text{(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide}</td>
<td>759.1</td>
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<td>Ex. No.</td>
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<td>Name</td>
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<tr>
<td>64</td>
<td><img src="image" alt="" /></td>
<td>(N,N)-dibutyl-4-chloro-1-(4-((1-(2-(3,4\text{-}dichlorophenyl)acetyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide)</td>
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<td>65</td>
<td><img src="image" alt="" /></td>
<td>(N,N)-dibutyl-4-chloro-1-(4-(1-(3,4-dichlorophenethyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td></td>
</tr>
<tr>
<td>66</td>
<td><img src="image" alt="" /></td>
<td>(N,N)-dibutyl-4-chloro-5-methyl-1-(4-(1-(2-phenylthio)acetyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>881.3</td>
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<tr>
<td>67</td>
<td><img src="image" alt="" /></td>
<td>(N,N)-dibutyl-4-chloro-5-methyl-1-(4-(1-(2-phenylthio)ethyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
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<td>68</td>
<td><img src="image" alt="" /></td>
<td>(N,N)-dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)-1H-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>889.3</td>
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<tr>
<td>69</td>
<td><img src="image" alt="" /></td>
<td>(N,N)-dibutyl-4-chloro-1-(4-(1-(6-chloropyridin-2-yl)methyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
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<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
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<tr>
<td>70</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>N,N'-dibutyl-4-chloro-5-methyl-1-(4-(1-((1-methyl-1H-indol-6-yl)methyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>874.1</td>
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<tr>
<td>71</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>1-(4-(5-bromo-1-ethylindolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N'-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>839.2</td>
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<tr>
<td>72</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>1-(4-(5-bromo-1-(3,4-dichlorobenzyl)indolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N'-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>969.2</td>
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<td>73</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>methyl 5-(N-(4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-1-(3,4-dichlorobenzyl)indoline-2-carboxylate</td>
<td>949.3</td>
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<tr>
<td>74</td>
<td><img src="image5.png" alt="Structure" /></td>
<td>N,N'-dibutyl-4-chloro-5-methyl-1-(4-(1-(morpholine-4-carbonyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>844.4</td>
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<td>75</td>
<td><img src="image6.png" alt="Structure" /></td>
<td>N,N'-dibutyl-4-chloro-5-methyl-1-(4-(1-(2-morpholinoacetyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>858.5</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
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<td>----------------------------------------------------------------------</td>
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<tr>
<td>76</td>
<td><img src="image1.png" alt="Molecule 1" /></td>
<td>1-(4-(7-bromo-1-ethylindolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>839.4</td>
</tr>
<tr>
<td>77</td>
<td><img src="image2.png" alt="Molecule 2" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(2-morpholinoethyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>844.4</td>
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<td>78</td>
<td><img src="image3.png" alt="Molecule 3" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-((2-(2-morpholinoethoxy)pyridin-3-yl)methyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>965.6</td>
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<tr>
<td>79</td>
<td><img src="image4.png" alt="Molecule 4" /></td>
<td>1-(4-(3-bromo-1H-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>809.2</td>
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<td>80</td>
<td><img src="image5.png" alt="Molecule 5" /></td>
<td>1-(4-(3-bromo-1-ethyl-1H-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>837.2</td>
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<tr>
<td>81</td>
<td><img src="image6.png" alt="Molecule 6" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(1-(3-morpholinopropanoyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>872.4</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>--------</td>
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<td>------------</td>
</tr>
<tr>
<td>82</td>
<td><img src="image" alt="Structure" /></td>
<td>(N,N)-dibutyl-4-chloro-5-methyl-1-(4-(1-(3-morpholinopropyl)-1H-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>856.3</td>
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<td>83</td>
<td><img src="image" alt="Structure" /></td>
<td>(N,N)-dibutyl-4-chloro-1-(4-(3-chloro-1-ethyl-1H-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>791.4</td>
</tr>
<tr>
<td>84</td>
<td><img src="image" alt="Structure" /></td>
<td>(N,N)-dibutyl-4-chloro-1-(4-(1-ethyl-3-iodo-1H-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>883.2</td>
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<tr>
<td>85</td>
<td><img src="image" alt="Structure" /></td>
<td>(N,N)-dibutyl-4-chloro-1-(4-(3,7-dibromo-1-ethyl-1H-indol-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>915.2</td>
</tr>
</tbody>
</table>

**Example 86**

\(N,N\)-Dibutyl-4-chloro-1-(4-(indolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

![Chemical Structure](image) (86)

[00311] Following a procedure analogous to that for the synthesis of Example 52, 1-(4-(1-acetylindolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-\(N,N\)-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (Example 60, 25 mg, 0.032 mmol) was converted to the title compound (18 mg, 63%) after preparative
HPLC. 'HNMR (CD$_3$OD, 2:1 mixture of amide rotamers) δ 8.08-8.06 (m, 1H), 7.97-7.95 (m, 1H), 7.71-7.67 (m, 1H), 7.49 (dd, $J = 7.7$, 1.8 Hz, 1H), 7.40 (s, 1H), 7.32 (d, $J = 7.9$ Hz, 1H), 7.26-7.09 (m, 3.5H), 6.93 (d, $J = 7.5$ Hz, 0.5H), 4.85-4.40 (m, 2H), 4.00-3.50 (m, 2H), 3.64 (t, $J = 8.5$ Hz, 2H), 3.14-3.10 (m, 2H), 3.16-2.55 (m, 4H), 2.34 (s, 2H), 2.29 (s, 1H), 1.52-1.00 (m, 10H), 0.95-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.70-0.67 (m, 1H); MS(ESI$^+$) m/z 731.3 (M+H$^+$).

Example 87

(E)-1-(4-(5-(But-1-ethylindolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-lH-pyrazole-3-carboxamide

[00312] To a sealed tube containing 1-(4-(5-bromo-l-ethylindolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-lH-pyrazole-3-carboxamide (Example 71, 16 mg, 0.019 mmol) in dioxane (1.0 mL) was added (Zs)-but-1-enyloboronic acid (8 mg, 0.076 mmol), Pd$_2$(dba)$_3$ (9 mg, 10 µmol), 1,1'-bis(di-tert-butylphosphino)ferrocene (9 mg, 0.019 mmol) and potassium metaphosphate (5 mg, 0.038 mmol). The reaction mixture was purged with nitrogen for 1 min and then heated at 90 °C for 16 h. The reaction mixture was then diluted with EtOAc and IN aq. HCl solution. The organic layer was separated, dried over MgSO$_4$ and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (11 mg, 64%) as a pale yellow solid after lyophilization. $^1$H NMR (CD$_3$OD, 2:1 mixture of amide rotamers) δ 8.06-8.05 (m,1H), 7.94 (br s, 1H), 7.65-7.63 (m, 1H), 7.30-7.11 (m, 6.5H), 6.93 (d, $J = 7.0$ Hz, 0.5H), 6.05-5.95 (m, 1H), 4.75-4.50 (m, 2H), 3.95-3.55 (m, 1H), 3.49-3.41 (m, 2H), 3.25 (t, $J = 6.8$ Hz, 2H), 3.15-3.10 (m, 2H), 3.00-2.96 (m, 3H), 2.90-2.65 (m, 2H), 2.33 (s, 2H), 2.28 (s, 1H), 2.21-2.18 (m,
2H), 1.58-1.02 (m, 11H), 1.03-0.95 (m, 5H), 0.93-0.87 (m, 3H), 0.77 (t, J = 7.3 Hz, 2H), 0.69 (t, J = 7.4 Hz, 1H); MS(ESI^+ m/z 813.3 (M+H)^+.

Example 88

\[ \text{N,N-Dibutyl-4-chloro-1-(4-(1-ethyl-5-morpholinoindolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide} \]

[00313] A solution of 1-(4-(5-bromo-1-ethylindolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (Example 71, 35 mg, 0.042 mmol), Z-(-)-proline (5 mg, 0.042 mmol), K₂CO₃ (12 mg, 0.084 mmol) and Cul (4 mg, 0.021 mmol) in DMSO (1.5 mL) was purged with air for 1 min. The resulting mixture was heated at 102 °C open to air for 20 h. The reaction mixture was then diluted with IN aq. HCl solution and EtOAc. The organic layer was separated, dried over MgSO₄ and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (6 mg, 16%) as a white solid after lyophilization. ^H NMR (CD₃OD, 2:1 mixture of amide rotamers) δ 8.24 (dd, J = 8.3, 1.9 Hz, 1H), 8.13-8.10 (m, 1H), 7.60-7.50 (m, 1H), 7.48 (s, 1H), 7.25-7.09 (m, 3.5H), 6.95 (s, 1H), 6.93 (d, J = 7.5 Hz, 0.5H), 4.90-4.50 (m, 2H), 4.20-3.99 (m, 4H), 3.71-3.60 (m, 4H), 3.55-3.49 (m, 2H), 3.26-3.20 (m, 4H), 3.09-3.03 (m, 2H), 2.90-2.60 (m, 4H), 2.33 (s, 2H), 2.28 (s, 1H), 1.55-1.00 (m, 13H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.72-0.68 (m, 1H); MS(ESI^+ m/z 844.5 (M+H)^+.

Example 89

(i)-N,N-Dibutyl-4-chloro-1-(4-(1-ethyl-5-(prop-1-enyl)indolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

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Following a procedure analogous to that for the synthesis of Example 87, 1-(4-(5-bromo-1-ethylindolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N'-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (Example 71, 35 mg, 0.042 mmol) and (Zs)-prop-1-enylboronic acid (14 mg, 0.17 mmol) were converted to the title compound (8 mg, 22%) as a white solid. $^1$H NMR (CD$_3$OD, 2:1 mixture of amide rotamers) $\delta$ 8.03-7.99 (m, 1H), 7.88-7.87 (m, 1H), 7.72-7.67 (m, 1H), 7.31-7.12 (m, 6.5H), 6.94-6.93 (m, 0.5H), 6.05-5.90 (m, 1H), 4.75-4.40 (m, 2H), 3.95-3.55 (m, 1H), 3.47 (t, $J = 8.4$ Hz, 2H), 3.27-3.15 (m, 2H), 3.26 (q, $J = 7.0$ Hz, 2H), 3.01 (t, $J = 7.9$ Hz, 2H), 2.80-2.60 (m, 2H), 2.34 (s, 2H), 2.30 (s, 1H), 2.09-2.07 (m, 1H), 1.85-1.83 (m, 2H), 1.55-0.90 (m, 14H), 0.95-0.87 (m, 3H), 0.77 (t, $J = 7.3$ Hz, 2H), 0.70 (t, $J = 7.4$ Hz, 1H); MS(ESI$^+$) m/z 799.4 (M+H)$^+$. 

Example 90

$N,N'$-Dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

To a solution of 1-(4-(5-bromo-1-(3,4-dichlorobenzyl)indolin-6-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N'-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (Example 72, 30 mg, 0.031 mmol) in $i$-PrOH (4.0 mL) were added Pd$_2$(dba)$_3$ (23 mg, 0.025 mmol), tris(2,4-di-tert-
butylphenyl)phosphite (10 mg, 0.015 mmol) and CS2CO3 (13 mg, 0.040 mmol). The resulting reaction mixture was heated at 80 °C for 20 h, then cooled to room temperature and filtered. The filtrate was concentrated in vacuo, and the residue was purified by preparative HPLC to give the title compound (15 mg, 52%) as a pale yellow solid after lyophilization. 1H NMR (CD3OD, 2:1 mixture of amide rotamers) δ 8.05 (dd, J = 8.4, 2.2 Hz, 1H), 7.97-7.96 (m, 1H), 7.71-7.67 (m, 1H), 7.52 (d, J = 2.0 Hz, 1H), 7.46 (d, J = 8.1 Hz, 1H), 7.38 (dd, J = 7.7, 1.5 Hz, 1H), 7.31 (dd, J = 8.4, 2.0 Hz, 1H), 7.25-7.10 (m, 5.5H), 6.93 (d, J = 7.5 Hz, 0.5H), 4.88-4.60 (m, 2H), 4.36 (s, 2H), 4.10-3.50 (m, 2H), 3.48 (t, J = 8.5 Hz, 2H), 3.15-3.05 (m, 2H), 2.90-2.70 (m, 2H), 2.35 (s, 2H), 2.30 (s, 1H), 1.53-0.98 (m, 10H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.70 (t, J = 7.3 Hz, 1H); MS(ESI+) m/z 891.4 (M+H)+.

Example 91

N,N-Dibutyl-4-chloro-1-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

Intermediate 91A: Ethyl 2-fluoro-5-iodobenzoate

[00316] To a solution of 2-fluoro-5-iodobenzoic acid (Oakwood, 0.99 g, 3.72 mmol) in EtOH (7.4 mL) was added H2SO4 (198 µL, 3.72 mmol). The resulting reaction mixture was stirred at 100 °C overnight and then concentrated in vacuo. The crude oil was purified using flash column chromatography (gradient from 0% to 10% EtOAc/hexanes) to give the title compound (916 mg, 84%) as a colorless oil. 1H NMR (CDCl3) δ 8.24
(dd, J = 6.8, 2.4 Hz, 1H), 7.81 (ddd, J = 8.8, 4.5, 2.4 Hz, 1H), 6.93 (dd, J = 10.3, 8.6 Hz, 1H), 4.41 (q, J = 7.0 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H).

Intermediate 91B: 1-Benzyl 3-ethyl 4-fluoroisophthalate

[00317] Following a procedure analogous to that for the synthesis of Intermediate 91D, ethyl 2-fluoro-5-iodobenzoate (916 mg, 3.11 mmol) and benzyl alcohol (389 µL, 3.74 mmol) were converted to the title compound (871 mg, 92%). 1H NMR (CDCl3) $\delta$ 8.65 (dd, J = 6.9, 2.3 Hz, 1H), 8.23 (ddd, J = 8.7, 4.6, 2.3 Hz, 1H), 7.51-7.32 (m, 5H), 7.20 (dd, J = 10.1, 8.6 Hz, 1H), 5.39 (s, 2H), 4.42 (q, J = 7.0 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H).

Intermediate 91C: 1-Benzyl 3-ethyl 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)isophthalate

[00318] Following a procedure analogous to that for the synthesis of Intermediate 1E, 1-benzyl 3-ethyl 4-fluoroisophthalate (1.50 g, 4.96 mmol) and N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (Intermediate 1B, 2.02 g, 7.44 mmol) were converted to the title compound (2.15 g, 78%). 1H NMR (CDCl3) $\delta$ 8.69 (d, J = 2.0 Hz, 1H), 8.33 (dd, J = 8.1, 2.0 Hz, 1H), 7.51-7.36 (m, 6H), 5.43 (s, 2H), 4.19 (d, J = 7.0 Hz, 2H), 3.50 (s, 2H), 3.41 (s, 2H), 2.15 (s, 3H), 1.70-1.60 (m, 2H), 1.58-1.50 (m, 2H), 1.46-1.34 (m, 2H), 1.25-1.16 (m, 5H), 0.96 (t, J = 7.4 Hz, 3H), 0.83 (t, J = 7.3 Hz, 3H); MS(ESI +) m/z 554.2 (M+H)+.

Intermediate 91D: 4-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)3-(ethoxycarbonyl)benzoic acid
To a 30 mL pressure flask containing 10% Pd/C (59 mg, 0.055 mmol) was added a solution of 1-benzyl 3-ethyl 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)isophthalate (153 mg, 0.28 mmol) in MeOH (5.0 mL). The reaction mixture was stirred under H₂ at 5 psi for 1 h, then filtered through a pipette containing a plug of CELITE® and concentrated in vacuo to give the title compound (110 mg, 85%) as a colorless oil. 

\[ \text{HNMR (CDCl}_3 \text{)} \delta 8.72 (\text{d, } J = 2.0 \text{ Hz, } 1\text{H}), 8.35 (\text{dd, } J = 8.1, 2.0 \text{ Hz, } 1\text{H}), 7.49 (\text{d, } J = 8.1 \text{ Hz, } 1\text{H}), 4.21 (\text{q, } J = 7.3 \text{ Hz, } 2\text{H}), 3.56-3.49 (\text{m, } 2\text{H}), 3.46-3.38 (\text{m, } 2\text{H}), 2.20-2.13 (\text{m, } 3\text{H}), 1.71-1.60 (\text{m, } 2\text{H}), 1.59-1.50 (\text{m, } 1\text{H}), 1.47-1.33 (\text{m, } 2\text{H}), 1.30-1.15 (\text{m, } 5\text{H}), 0.96 (\text{t, } J = 7.3 \text{ Hz, } 3\text{H}), 0.83 (\text{t, } J = 7.4 \text{ Hz, } 3\text{H}); \text{MS(ESI}^+ \text{) } m/z 464.2 (\text{M+H})^+. 

Intermediate 91E: Ethyl 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoate

[00320] Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid (230 g, 0.50 mmol) was converted to the title compound (188 mg, 58%) after purification by flash column chromatography (20% EtOAc/hexanes). \[ \text{^1H NMR (DMSO-d}_6 \text{)} \delta 8.65 (\text{s, } 1\text{H}), 8.40 (\text{d, } J = 2.0 \text{ Hz, } 1\text{H}), 8.25- 8.16 (\text{m, } 2\text{H}), 8.12 (\text{d, } J = 8.6 \text{ Hz, } 1\text{H}), 8.05 (\text{d, } J = 7.9 \text{ Hz, } 1\text{H}), 7.97 (\text{dd, } J = 8.8, 1.8 \text{ Hz, } 1\text{H}), 7.77-7.62 (\text{m, } 3\text{H}), 4.10 (\text{q, } J = 7.2 \text{ Hz, } 2\text{H}), 3.38 (\text{t, } J = 7.4 \text{ Hz, } 1\text{H}), 3.29 (\text{t, } J = 7.4 \text{ Hz, } 1\text{H}), 2.12 (\text{s, } 3\text{H}), 1.62-1.40 (\text{m, } 4\text{H}), 1.36-1.26 (\text{m, } 2\text{H}), 1.36-1.22 (\text{m, } 2\text{H}), 1.18-1.04 (\text{m, } 5\text{H}), 0.90 (\text{t, } J = 7.3 \text{ Hz, } 3\text{H}), 0.74 (\text{t, } J = 7.4 \text{ Hz, } 3\text{H}); \text{MS(ESI}^+ \text{) } m/z 653.3 (\text{M+H})^+. 

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Intermediate 9 IF: 2-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-lH-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid

[00321] To ethyl 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-lH-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoate (1.39 g, 2.13 mmol) in THF (12.0 mL) and MeOH (4.0 mL) was added 0.5N aq. NaOH solution (21.3 mL, 10.7 mmol). The resulting reaction mixture was stirred at room temperature for 1.5 h. The mixture was then neutralized with IN aq. HCl solution (pH = 7) and extracted with EtOAc (3x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude oil was triturated with CH₂Cl₂ (3x) to give the title compound (1.04 g, 78%) as a white solid.

1H NMR (DMSO-d₆) δ 13.36 (br s, 1H), 8.71 (s, 1H), 8.43 (d, J = 2.0 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H), 8.17 (dd, J = 8.4, 2.2 Hz, 2H), 8.07 (d, J = 8.1 Hz, 1H), 7.99 (dd, J = 8.7, 1.9 Hz, 1H), 7.78-7.64 (m, 3H), 3.38 (t, J = 7.4 Hz, 2H), 3.29 (t, J = 7.4 Hz, 2H), 2.10 (s, 3H), 1.58-1.38 (m, 4H), 1.36-1.22 (m, 2H), 1.13 (dq, J = 14.8, 7.4 Hz, 2H), 0.90 (t, J = 7.4 Hz, 3H), 0.74 (t, J = 7.4 Hz, 3H); MS(ESI +) m/z 625.2 (M+H) +.

Example 91:

[00322] To 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-7H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (50 mg, 0.080 mmol) in DMF (800 µL) and THF (800 µL) were added (S)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (Aldrich, 20 mg, 0.12 mmol), HATU (55 mg, 0.14 mmol) and i-Pr₂EtN (70 µL, 0.40 mmol). The resulting reaction mixture was stirred at room temperature for 1.5 h, then concentrated in vacuo and purified by preparative HPLC to give the title compound (44 mg, 70%). 1H NMR (1:1 CD₃OD:CDCl₃, mixture of amide rotamers) δ 8.63 (s, 1H), 8.30-8.15 (m, 1.5H), 8.10-7.84 (m, 5H), 7.65-7.52 (m, 1H), 7.52-7.36 (m, 1H), 7.27-7.04 (m, 4H), 6.91 (br s, 0.5H), 5.25 (d, J = 18.0 Hz, 0.5H), 4.42-4.10 (m, 2.5H), 3.70-3.37 (m, 2H), 3.26 (dd, J = 16.4, 5.4 Hz, 1H), 3.14-2.74 (m, 5H), 2.31-2.22 (m, 3H), 1.60-0.59 (m, 14H); MS(ESI +) m/z 770.3 (M+H) +.
Example 92
1-(2-((5')-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide

Intermediate 92A: (5')-3-(Azidomethyl)-1,2,3,4-tetrahydroisoquinoline

[00323] To a solution of (5')-tert-butyl 3-(azidomethyl)-3,4-dihydroisoquinoline-carboxylate (Page, D. et al, J. Med. Chem., 44:2387-2390 (2001)) (509 mg, 1.77 mmol) in C4 C4 (8.0 mL) was added TFA (2.7 mL, 35.3 mmol). The resulting reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was dissolved in CH2Cl2 and washed with sat. aq. NaHCO₃ solution (2 x). The aqueous layer was extracted with CH2Cl2 (2 x), and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to provide the title compound (302 mg, 91%) as a clear, colorless oil. ¾ NMR (CDCl₃) δ 7.17-7.13 (m, 2H), 7.12-7.08 (m, 1H), 7.07-7.02 (m, 1H), 4.14-4.05 (m, 2H), 3.55 (dd, J = 12.2, 4.4 Hz, 1H), 3.45-3.39 (m, 1H), 3.16-3.09 (m, 1H), 2.82-2.75 (m, 1H), 2.70-2.60 (m, 1H), 2.02 (br s, 1H); MS(ESI⁺) m/z 189.1 (M+H)+.

Example 92:

[00324] Following a procedure analogous to that for the synthesis of Example 91, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 9 IF, 50 mg, 0.080 mmol) was reacted
with (5')-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline (18 mg, 0.10 mmol) to give a crude oil which was used in the subsequent step without purification.

The crude oil from above was dissolved in THF (1.1 mL), and PPh₃ (63 mg, 0.24 mmol) was added followed by 0.5N NaOH (200 µL). The resulting reaction mixture was stirred at 50 °C for 1.5 h, then neutralized with IN aq. HCl solution (100 µL). The volatiles were removed in vacuo, and the residue was purified by preparative HPLC to give the title compound (18 mg, 29%).

1H NMR (1:1 CD₃OD:CDCl₃, mixture of amide rotamers) δ 8.60 (br s, 1H), 8.38-8.11 (m, 2H), 8.11-8.04 (m, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.92-7.83 (m, 2H), 7.58-7.36 (m, 3H), 7.31-7.10 (m, 3H), 7.07-6.92 (m, 1H), 5.10-4.97 (m, 0.5H), 4.87 (br s, 0.5 H), 4.50-4.44 (m, 1.5H), 4.26 (d, J = 18.6 Hz, 0.5H), 3.48 (br s, 1H), 3.33-3.04 (m, 3.5H), 2.98-2.83 (m, 2H), 2.80-2.60 (m, 1H), 2.43-2.19 (m, 3.5H), 1.28 (br s, 2.5 H), 1.38-1.30 (m, 4.5H), 1.02-0.72 (m, 6H), 0.62 (br s, 1H); MS(ESI+) m/z 769.4 (M+H)⁺.

Example 93

(3R)-2-(2-((4-Chloro-3-((dibutylcarbamoyl)l)-5-methyl-1 H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Intermediate 93A: (R)-Methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride

To (5)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Aldrich, 500 mg, 2.82 mmol) in MeOH (2.8 mL) was added SOCl₂ (824 µL, 11.3 mmol) at 0 °C. The resulting reaction mixture was allowed to warm to room temperature over 5 h and then stirred at 50 °C overnight. The reaction mixture was then concentrated in vacuo to give the title compound (457 mg, 71%) as a white solid. ¾ NMR (CDCl₃) δ 7.30-7.23 (m,
2H), 7.20-7.13 (m, 2H), 4.78-4.69 (m, 1H), 4.56-4.45 (m, 1H), 4.43-4.35 (m, 1H), 3.87 (s, 3H), 3.49-3.43 (m, 2H); MS(ESI+) m/z 192.1 (M+H)⁺.

Intermediate 93B: (3R)-Methyl 2-(2-(4-chloro-3-(dibutylcarbamoyl)-5 -methyl- 1H-
pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoyl)-1, 2,3,4-
tetrahydroisoquinoline-3-carboxylate

![Chemical Structure](image)

(Intermediate 93B)

To 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1 H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 9IF, 50 mg, 0.080 mmol) in CH₂Cl₂ (890 µL) was added 1-chloro -N,N-2-trimethylprop-1 -en-1-amine (21 µL, 0.16 mmol). After stirring for 30 min at room temperature, (R)-methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (20 mg, 0.088 mmol) in THF (900 µL) was added followed by i-Pr₂EtN (42 µL, 0.24 mmol). The resulting reaction mixture was stirred at room temperature for 1 h, then quenched with sat. aq. NH₄Cl solution and extracted with EtOAc (1 x). The organic layer was washed with IN aq. HCl solution, and the combined aqueous layer was extracted with EtOAc (2 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (24 mg, 37%). ¹H NMR (1:1 CD₃OD:CDCl₃, 1:1 mixture of amide rotamers) δ 8.62 (d, J = 15.9 Hz, 1H), 8.20 (dd, J = 13.9, 9.0 Hz, 1.5H), 8.13-7.85 (m, 5H), 7.63-7.52 (m, 1.5H), 7.47 (d, J = 8.4 Hz, 1H), 7.24-7.06 (m, 3.5H), 6.93 (d, J = 6.8 Hz, 0.5 H), 5.17 (t, J = 5.4 Hz, 0.5H), 5.02 (d, J = 17.6 Hz, 0.5H), 4.75 (d, J = 5.9 Hz, 1H), 4.49 (d, J = 18.0 Hz, 1.5H), 3.64 (br s, 1.5H), 3.55-3.41 (m, 2.5H), 3.27-3.09 (m, 4H), 3.05-2.99 (m, 0.5H), 2.31 (s, 1.5H), 2.24 (s, 1.5H), 1.50-0.95 (m, 8H), 0.95-0.82 (m, 3H), 0.74 (t, J = 7.5 Hz, 1.5H), 0.71-0.63 (m, 1.5H); MS(ESI⁺) m/z 798.3 (M+H)⁺.
[00328] To (3R)-methyl 2-(2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-yl)-5-(naphthalen-2-ylsulfonylcarmamoyl)benzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (38 mg, 0.048 mmol) in MeOH (500 µL) was added IN aq. NaOH solution (480 µL, 0.48 mmol). The resulting reaction mixture was stirred at 40 °C for 1 h, then acidified (pH = 2) with IN aq. HCl solution and extracted EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude oil was purified by preparative HPLC to give the title compound (16 mg, 41%). ¹H NMR (1:1 CD₃OD:CDCl₃, 1:5:1 mixture of amide rotamers) δ 8.65-8.54 (m, 1H), 8.23-8.12 (m, 1.5H), 8.08-7.82 (m, 5H), 7.61-7.50 (m, 1H), 7.42-7.34 (m, 1H), 7.21-7.04 (m, 4H), 6.89 (d, J = 6.8 Hz, 0.5H), 5.19 (t, J = 5.2 Hz, 0.5H), 4.98 (d, J = 17.6 Hz, 0.5H), 4.69-4.62 (m, 1H), 3.54-3.40 (m, 1H), 3.25-2.80 (s, 5.5H), 2.58 (dt, J = 14.2, 7.1 Hz, 0.5H), 2.27-2.22 (s, 1H), 1.55-0.77 (m, 11H), 0.76-0.60 (m, 3H); MS(ESI⁺) m/z 784.4 (M+H)+.

Example 94

(35)-2-(2-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-yl)-5-(naphthalen-2-ylsulfonylcarmamoyl)benzoyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

Intermediate 94A: (5)-Methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride

[00329] Following a procedure analogous to that for the synthesis of Intermediate 93A, (5)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Aldrich, 500 mg, 2.82 mmol) was converted to the title compound (526 mg, 82%). ¹H NMR (CDCl₃) δ 7.30-7.23 (m, 2H), 7.20-7.13 (m, 2H), 4.78-4.69 (m, 1H), 4.56-4.45 (m, 1H), 4.43-4.35 (m, 1H), 3.87 (s, 3H), 3.49-3.43 (m, 2H); MS(ESI⁺) m/z 192.1 (M+H)+.
Example 94:

Following a procedure analogous to that for the synthesis of Intermediate 85, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 9IF, 30 mg, 0.048 mmol) was reacted with (5)-methyl 1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (12 mg, 0.053 mmol) to give a crude oil which was used in the subsequent step without purification.

The crude oil from above was converted to the title compound (19 mg, 51%) following a procedure analogous to that for the synthesis of Example 93. 1H NMR (1:1 CD3OD:CDCl3, 1.5:1 mixture of amide rotamers) δ 8.65-8.54 (m, 1H), 8.23-8.12 (m, 1.5H), 7.61-7.50 (m, 1H), 7.42-7.34 (m, 1H), 7.21-7.04 (m, 4H), 6.89 (d, J = 6.8 Hz, 0.5H), 5.19 (t, J = 5.2 Hz, 0.5H), 4.98 (d, J = 17.6 Hz, 0.5H), 4.69-4.62 (m, 1H), 3.54-3.40 (m, 1H), 3.25-2.80 (m, 5.5H), 2.58 (dt, J = 14.2, 7.1 Hz, 0.5H), 2.27 (s, 2H), 2.22 (s, 1H), 1.55-0.77 (m, 11H), 0.76-0.60 (m, 3H); MS(ESI+) m/z 784.4 (M+H)+.

Example 95

N,N-Dibutyl-4-chloro-1-(2,5-dihydro-2-((R)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

![Chemical Structure](image)

To a solution of (3R)-methyl 2-(2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoyl)-l,2,3,4-tetrahydroisoquinoline-3-carboxylate (Intermediate 85, 40 mg, 0.050 mmol) in THF (835 μL) and MeOH (170 μL) was added NaBH₄ (4 mg, 0.10 mmol). The resulting reaction mixture was stirred at room temperature for 1 h. Additional NaBH₄ (20 mg, 0.50 mmol) was added and stirring was continued at room temperature for 30 min. The reaction...
mixture was then quenched with water, poured into sat. aq. NH₄Cl solution and extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered, concentrated in vacuo and purified by preparative HPLC to give the title compound (13 mg, 34%). 'H NMR (1:1 CD₃OD:CDCl₃, mixture of amide rotamers) δ 8.68-8.77 (m, 1H), 8.23 (s, 0.5H), 8.13-7.99 (m, 4.5H), 7.95 (d, J = 7.0 Hz, 1.5H), 7.72-7.61 (m, 1H), 7.58-7.45 (m, 1H), 7.23-7.03 (m, 4H), 6.67 (br s, 0.5H), 5.24 (d, J = 18.0 Hz, 0.5H), 4.87 (br s, 0.5H), 4.49 (br s, 0.5H), 4.28 (d, J = 17.4 Hz, 1H), 4.12 (br s, 1H), 3.63-3.52 (m, 1H), 3.51-3.34 (m, 1.5H), 3.27-2.92 (m, 4H), 2.83-2.53 (m, 1H), 2.28-2.25 (m, 3H), 1.62-0.83 (m, 11H), 0.77-0.69 (m, 2H), 0.64 (br s, 1H); MS(ESI+) m/z 770.3 (M+H)+.

Example 96

\[ \text{N,N-Dibutyl-4-chloro-1-(2-(3,4-dihydro-2H-benzo[e][1,3]oxazine-3-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide} \]

\[ \text{(96)} \]

Intermediate 96A: 4-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-N3-(2-hydroxybenzyl)-N1-(naphthalen-2-ylsulfonyl)isophthalamide

\[ \text{(Int-96A)} \]

Following a procedure analogous to that for the synthesis of Intermediate 93B, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 91F, 21 mg, 0.034 mmol) and 2-(aminomethyl)phenol, HCl (27 mg, 0.17 mmol) were converted to the title compound (12 mg, 44%) following purification by preparative HPLC. \(^1\)H NMR (CDCl₃) δ 8.78 (d, J = 1.5 Hz, 1H), 8.46 (d, J = 2.0 Hz, 1H), 8.11-8.07 (m, 2H), 8.04 (d, J = 7.9 Hz, 1H), 7.98
Example 96: A solution of 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-N-3-(2-hydroxybenzyl)-N1-(naphthalen-2-ylsulfonyl)isophthalamide (10 mg, 0.014 mmol), paraformaldehyde (40 mg), 4Å molecular sieves (100 mg) and 4-methylbenzenesulfonic acid monohydrate (10 mg, 0.058 mmol) in PhMe (1.2 mL) was heated in a sealed tube at 100 °C for 30 min. Additional paraformaldehyde (14 mg) was added, and the reaction mixture was heated at 105 °C for 5 h. The solution was then filtered, and the filtrate was concentrated in vacuo and purified by preparative HPLC to give the title compound (2 mg, 18%) as a white solid. 1H NMR (CD3OD, 2:1 mixture of amide rotamers) δ 8.67 (s, 1H), 8.23-7.92 (m, 7H), 7.73-7.57 (m, 3H), 7.22-7.10 (m, 1.5H), 7.04-6.71 (m, 1.5H), 5.15 (br s, 2H), 3.60-2.99 (m, 6H), 2.32 (s, 2H), 2.29 (s, 1H), 1.72-1.04 (m, 7H), 1.02-0.72 (m, 7H); MS(ESI+) m/z 742.6 (M+H)+.

Example 97

N,N-Dibutyl-4-chloro-5-methyl-1-(2-(1-methyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-H-pyrazole-3-carboxamide

Following a procedure analogous to that for the synthesis of Intermediate 93B, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 9IF, 32 mg, 0.051 mmol) and 1-methyl-1,2,3,4-tetrahydroisoquinoline (Parkway Scientific, 8 mg, 0.056 mmol) were converted to the title compound (12 mg, 31%) following purification by preparative HPLC. 1H NMR
N,N-Dibutyl-4-chloro-1-(2-(4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

Example 98

Following a procedure analogous to that for the synthesis of Intermediate 93B, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 9IF, 32 mg, 0.051 mmol) and 4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline (Milestone Pharmtech, 9 mg, 0.056 mmol) were converted to the title compound (14 mg, 34%) following purification by preparative HPLC. ¹H NMR (DMSO-d₆, 1:1 mixture of amide rotamers) δ 8.64 (s, 1H), 8.20 (d, J = 7.7 Hz, 1H), 8.14-7.90 (m, 5H), 7.78-7.59 (m, 3H), 7.36 (t, J = 7.7 Hz, 1H), 7.26-7.13 (m, 2H), 7.11-7.02 (m, 0.5H), 6.99-6.89 (m, 0.5H), 4.85-4.20 (m, 2H), 3.58 (br s, 0.5H), 3.51-2.98 (m, 5H), 2.57-2.52 (m, 0.5H), 2.24 (s, 1.5H), 2.18 (s, 1.5H), 1.43-0.94 (m, 14H), 0.82 (t, J = 7.3 Hz, 1H), 0.74 (t, J = 7.3 Hz, 2H), 0.69 (t, J = 7.4 Hz, 1.5H), 0.64 (t, J = 7.4 Hz, 1.5H); MS(ESI⁺) m/z 768.3 (M+H)⁺.

Example 99

1-(2-(7-Bromo-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide
Following a procedure analogous to that for the synthesis of Intermediate 93B, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1'H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 9IF, 35 mg, 0.056 mmol) and 7-bromo-1,2,3,4-tetrahydroisoquinoline, HCl (Arch, 15 mg, 0.062 mmol) were converted to the title compound (18 mg, 39%) following purification by preparative HPLC. \(^1\)H NMR (1:1 CD\(_3\)OD:CDCl\(_3\), 1.5:1 mixture of amide rotamers) \(\delta\) 8.64 (br s, 1H), 8.14 (d, \(J = 8.6\) Hz, 1H), 8.09-7.82 (m, 5.5H), 7.66-7.52 (m, 1.5H), 7.49-7.35 (m, 1H), 7.32-7.18 (m, 1.5H), 7.06-6.94 (m, 1.5H), 4.73 (br s, 0.5H), 4.43 (s, 1H), 3.99 (br s, 0.5H), 3.69-3.34 (m, 3H), 3.24-2.65 (m, 5H), 2.27 (s, 2H), 2.23 (s, 1H), 1.58-0.95 (m, 8H), 0.91 (t, \(J = 7.3\) Hz, 1.5H), 0.88 (t, \(J = 7.3\) Hz, 1.5H), 0.76 (t, \(J = 7.4\) Hz, 2H), 0.68 (t, \(J = 7.4\) Hz, 1H); MS(ESI\(^+\)) \(m/z\) 820.2 (M+H\(^+\)).

**Example 100**

2-(2-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1'H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid

Following a procedure analogous to that for the synthesis of Intermediate 93B, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1'H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 9IF, 35 mg, 0.056 mmol) was reacted with methyl 1,2,3,4-tetrahydroisoquinoline-7-carboxylate, HCl (14 mg, 0.062 mmol) to give a crude oil which was used in the subsequent step without purification.

The crude oil from above was converted to the title compound (7 mg, 16%) following a procedure analogous to that for the synthesis of Example 93. \(^1\)H NMR
(DMSO-d$_6$, 1.5:1 mixture of amide rotamers) $\delta$ 8.70-8.62 (m, 1H), 8.26-8.18 (m, 1H), 8.15-8.09 (m, 1H), 8.09-8.02 (m, 3H), 7.95 (s, 1.5H), 7.80-7.77 (m, 0.5H), 7.76-7.65 (m, 4H), 7.57-7.54 (m, 0.5H), 7.29-7.21 (m, 1H), 4.88-4.75 (m, 0.5H), 4.67-4.54 (m, 1H), 4.45-4.31 (m, 0.5H), 3.99-3.88 (m, 0.5H), 3.57-3.44 (m, 2H), 3.26-2.94 (m, 2H), 2.89 (s, 3H), 2.59-2.53 (m, 0.5H), 2.22 (s, 2H), 2.18 (s, 1H), 1.40-1.30 (m, 0.5H), 1.28-0.78 (m, 10H), 0.67 (t, $J = 7.4$ Hz, 2H), 0.58 (t, $J = 7.2$ Hz, 1H); MS(ESI$^+$) m/z 784.3 (M+H$^+$).

**Example 101**

*N,N*-Dibutyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(7-trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1*H*-pyrazole-3-carboxamide

![Chemical Structure](image)

**[00340]** Following a procedure analogous to that for the synthesis of Intermediate 93B, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1*H*-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 91F, 21 mg, 0.034 mmol) and 7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (7 mg, 0.037 mmol) were converted to the title compound (20 mg, 71%) following purification by preparative HPLC. $^1$H NMR (1:1 CD$_3$OD:CDCl$_3$, 1.5:1 mixture of amide rotamers) $\delta$ 8.69-8.58 (m, 1H), 8.19-8.13 (m, 1H), 8.08-8.02 (m, 2H), 8.01-7.97 (m, 1H), 7.95-7.91 (m, 1H), 7.90-7.86 (m, 1H), 7.60-7.54 (m, 2H), 7.45-7.34 (m, 2.5H), 7.28-7.23 (m, 1H), 7.17-7.14 (m, 0.5H), 4.89-4.64 (m, 1.5H), 4.52 (s, 1H), 4.16-4.02 (m, 0.5H), 3.70-3.34 (m, 2.5H), 3.24-2.75 (m, 4.5H), 2.28 (s, 2H), 2.23 (s, 1H), 1.51-0.93 (m, 8H), 0.87 (dt, $J = 17.8$, 7.4 Hz, 3H), 0.75 (t, $J = 7.4$ Hz, 2H), 0.64 (t, $J = 7.4$ Hz, 1H); MS(ESI$^+$) m/z 808.3 (M+H$^+$).

**Example 102**

1-(2-(3-Bromo-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-*N,N*-dibutyl-4-chloro-5-methyl-1*H*-pyrazole-3-carboxamide
Following a procedure analogous to that for the synthesis of Intermediate 93B, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 9 IF, 25 mg, 0.040 mmol) and 3-bromo-5,6,7,8-tetrahydro-1,6-naphthyridine (D-L Chiral, 9 mg, 0.044 mmol) were converted to the title compound (16 mg, 45%) following purification by preparative HPLC. \(^1\)H NMR (1:1 CD\(_3\)OD:CDCl\(_3\), 1.5:1 mixture of amide rotamers) \(\delta\) ppm 8.69-8.65 (m, 1H), 8.47-8.41 (m, 1H), 8.21-8.16 (m, 1H), 8.09-8.05 (m, 2H), 8.04-8.00 (m, 1H), 7.99-7.95 (m, 1.5H), 7.94-7.90 (m, 1H), 7.78-7.74 (m, 0.5H), 7.66-7.57 (m, 1.5H), 7.53-7.43 (m, 1.5H), 7.49-7.43 (m, 1H), 4.57-4.51 (m, 1H), 3.71-3.61 (m, 1.5H), 3.58-3.39 (m, 1H), 3.31-2.85 (m, 5.5H), 2.31 (s, 1.5H), 2.28 (s, 1.5H), 1.57-1.02 (m, 8H), 0.93 (dt, \(J = 14.4, 7.4\) Hz, 3H), 0.79 (t, \(J = 7.4\) Hz, 1.5H), 0.74 (t, \(J = 7.4\) Hz, 1.5H); MS(ESI +) \(m/z\) 821.0 (M+H\(^+\)).

Example 103

\(N,N\)-Dibutyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroquinazoline-3-carbonyl)phenyl)-1H-pyrazole-3-carboxamide

Intermediate 103A: \(N^3\)-(2-Aminobenzyl)-4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-N\(^1\)-(naphthalen-2-ylsulfonyl)isophthalamide
To a solution of 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 91F, 50 mg, 0.080 mmol) in CH₂Cl₂ (1.1 mL) and DMF (0.2 mL) was added 2-(aminomethyl)aniline (20 mg, 0.16 mmol) followed by EDC (34 mg, 0.18 mmol) and 1-hydroxy-7-azabenzotriazole (290 µL, 0.18 mmol, 0.6 M solution in DMF). The resulting reaction mixture was stirred at room temperature overnight, then quenched with sat. aq. NH₄Cl solution and extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (gradient from 0% to 10% MeOH/CH₂Cl₂) provided the title compound (35 mg, 60%) as a pale yellow, oily solid. MS(ESI⁺) m/z 729.2 (M+H)⁺.

Example 103:

To a solution of 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 91F, 50 mg, 0.080 mmol) in CH₂Cl₂ (1.1 mL) and DMF (0.2 mL) was added 2-(aminomethyl)aniline (20 mg, 0.16 mmol) followed by EDC (34 mg, 0.18 mmol) and 1-hydroxy-7-azabenzotriazole (290 µL, 0.18 mmol, 0.6 M solution in DMF). The resulting reaction mixture was stirred at room temperature overnight, then quenched with sat. aq. NH₄Cl solution and extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by flash column chromatography (gradient from 0% to 10% MeOH/CH₂Cl₂) provided the title compound (35 mg, 60%) as a pale yellow, oily solid. MS(ESI⁺) m/z 729.2 (M+H)⁺.

Example 104
**Intermediate 104A**: (2-(tert-Butylthio)phenyl)methanamine

![Chemical Structure](image)

(104)

[00344] To a solution of 2-(tert-butylthio)benzonitrile (Guiu, E. et al, *J. Organomet. Chem.*, 689:1911-1918 (2004)) (1.00 g, 5.23 mmol) in THF (10.5 mL) was added BH$_3$·THF (10.5 mL, 10.5 mmol, 1.0M solution in THF) via syringe. The resulting clear, colorless solution was stirred at room temperature for 1.5 h and then at 50 °C for 2 h. The reaction mixture was cooled to room temperature, and MeOH (2.5 mL) was added carefully via syringe (gas evolution) followed by IN aq. HCl solution (12.0 mL). The mixture was poured into EtOAc and the layers were separated. The aqueous layer was basified with IN aq. NaOH solution (pH = 12) and then extracted with CH$_2$Cl$_2$ (5 x). The combined CH$_2$Cl$_2$ extracts were dried over MgSO$_4$, filtered and concentrated *in vacuo* to give the title compound (288 mg, 28%) as a colorless oil. $^1$H NMR (CDCl$_3$) δ 7.57-7.53 (m, 1H), 7.44-7.40 (m, 1H), 7.37-7.32 (m, 1H), 7.25-7.19 (m, 1H), 4.07 (s, 2H), 1.30 (s, 9H); MS(ESI$^+$) m/z 196.2 (M+H)$^+$. **Intermediate 104B**: $N,N$-Dibutyl-4-chloro-1-(2-(3,4-dihydro-2H-benzo[e][1,3]thiazine-3-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide
To a solution of 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 91F, 50 mg, 0.080 mmol) in DMSO (1.3 mL) was added (2-(tert-butylthio)phenyl)methanamine (23 mg, 0.12 mmol) followed by EDC (31 mg, 0.16 mmol) and DMAP (5 mg, 0.040 mmol). The resulting reaction mixture was stirred at room temperature for 1.5 h, then quenched with sat. aq. NH₄Cl solution, washed with IN aq. HCl solution and extracted with EtOAc (3x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated **in vacuo** to provide a crude oil which was used in the subsequent step without purification.

The crude oil from above (36 mg, 0.040 mmol) was dissolved in AcOH (1.0 mL) and 2-nitrophethyl hypochlorothioite (8 mg, 0.044 mmol) was added. The resulting reaction mixture was stirred at room temperature overnight and then concentrated **in vacuo** to give a crude oil which was used in the subsequent step without purification.

The crude oil from above was dissolved in EtOH (1.0 mL) and NaBH₄ (3 mg, 0.089 mmol) was added. The resulting reaction mixture was stirred for 5 min, and then HCl (4N solution in dioxane) was added until the color changed to pale yellow. The reaction mixture was concentrated **in vacuo** and redissolved in PhMe (2.0 mL). To the solution were added 4Å molecular sieves followed by TsOH (2 mg, 11 μmol). The reaction mixture was stirred at 81 °C for 4 h, then filtered through a pipette containing a plug of cotton. The filtrate was concentrated **in vacuo**, redissolved in CH₂Cl₂ and passed through a syringe filter to remove the remaining paraformaldehyde. Purification using preparative HPLC provided the title compound (10 mg, 31%) as a white solid after lyophilization. 'H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ ppm 8.56 (s, 1H), 8.30-8.19 (m, 1.5H), 8.10 (d, J = 1.8 Hz, 0.5H), 8.04-7.97 (m, 2H), 7.96-7.87 (m, 2H), 7.66-7.49 (m, 3H), 7.27-7.08 (m, 3H), 7.06-6.99 (m, 0.5H), 6.96-6.88 (m, 0.5H), 4.78-4.55 (m, 3H), 3.60-3.36 (m, 3H), 3.21-3.17 (m, 2H), 2.31 (s, 1.5H), 2.24 (s, 1.5H), 1.63-1.47 (m, 2.5H), 1.45-1.25 (m, 3H), 1.20-1.03 (m, 2.5H), 0.99-0.87 (m, 3H), 0.84-0.68 (m, 3H); MS(ESI⁺) m/z 758.1 (M+H)⁺.
Example 104:

[00348] To a solution of N,N-dibutyl-4-chloro-l-(2-(3,4-dihydro-2 \(H\)-benzo[e][1,3]thiazine-3-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-\(1H\)-pyrazole-3-carboxamide (32 mg, 0.042 mmol) in CH\(_2\)Cl\(_2\) (1.0 mL) was added m-CPBA (47 mg, 0.21 mmol). The resulting reaction mixture was stirred at room temperature for 2 h 15 min. Additional m-CPBA (47 mg, 0.21 mmol) was added, and stirring was continued at room temperature for 1 h. The reaction mixture was then diluted with EtOAc and washed with 20% aq. NaHSO\(_3\) solution, followed by sat. aq. NaHCO\(_3\) solution and sat. aq. NaCl solution. The organic layer was dried over Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. Purification using preparative HPLC provided the title compound (11.2 mg, 33%) as a white solid after lyophilization. \(^1\)H NMR (CD\(_3\)OD, 2:1 mixture of amide rotamers) \(\delta\) 8.61-8.49 (m, 1H), 8.36-8.22 (m, 1.5H), 8.08-7.82 (m, 5.5H), 7.68-7.43 (m, 5.5H), 7.25-7.16 (m, 0.5H), 5.63-5.59 (m, 0.5H), 5.40-5.05 (m, 1.5H), 5.02-4.90 (m, 1H), 4.79-4.56 (m, 1H), 3.71-3.55 (m, 0.5H), 3.55-3.38 (m, 2H), 3.27-3.19 (m, 1.5H), 2.30 (s, 1H), 2.24 (s, 2H), 1.66-1.52 (m, 2H), 1.50-1.25 (m, 3.5H), 1.22-1.08 (m, 2.5H), 0.99-0.86 (m, 3H), 0.85-0.72 (m, 3H); MS(ESI\(^+\)) m/z 790.2 (M+H\(^+\)).

Example 105

N,N-Dibutyl-4-chloro-1-(2-((5)-3-((3-methoxypropoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-\(1H\)-pyrazole-3-carboxamide

(105)

[00349] A solution of (5)-N,N-dibutyl-4-chloro-1-(2-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-\(1H\)-pyrazole-3-carboxamide (Example 91, 21 mg, 0.028 mmol) in DMF (900 \(\mu\)L) was cooled to 0 °C, and NaH (2 mg, 0.061 mmol, 60% suspension in mineral oil) was
added followed by 1-bromo-3-methoxypropane (9 mg, 0.061 mmol). The resulting reaction mixture was stirred warming to room temperature over 1 h and then heated at 130 °C for 3 h. Additional NaH (2 mg, 0.061 mmol, 60% suspension in mineral oil) and 1-bromo-3-methoxypropane (9 mg, 0.061 mmol) were added, and stirring was continued overnight at 130 °C. Additional NaH (2 mg, 0.061 mmol, 60% suspension in mineral oil) and 1-bromo-3-methoxypropane (9 mg, 0.061 mmol) were added, and stirring was continued at 135 °C for 24 h. TBAI (10 mg, 0.027 mmol) was then added, and stirring was continued at 140 °C for 72 h. After quenching with sat. aq. NH₄Cl solution, the reaction mixture was diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. Purification using preparative HPLC provided the title compound (4 mg, 18%) as an off-white solid after lyophilization. ¹H NMR (CD₃OD, mixture of amide rotamers) δ 8.82-8.69 (m, 1H), 8.29-8.20 (m, 1H), 8.16-7.92 (m, 5.5H), 7.78-7.57 (m, 3H), 7.31-7.05 (m, 3H), 6.94-6.85 (m, 0.5H), 5.24-5.36 (m, 1H), 5.09-4.91 (m, 1H), 4.53-4.47 (m, 0.5H), 4.30-4.16 (m, 1.5H), 3.64-2.73 (m, 12H), 2.62-2.49 (m, 1H), 2.38-2.24 (m, 4H), 1.83-0.86 (m, 13H), 0.80-0.70 (m, 2.5H), 0.67-0.60 (m, 0.5H); MS(ESI⁺) m/z 842.3 (M+H)⁺.

**Example 106**

N,N-Dibutyl-4-chloro-5-methyl-1-(2-((5)-3-((1-methylpiperidin-4-ylamino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-pyrazole-3-carboxamide

![Chemical Structure](image)

To a solution of 1-(2-((5)-3-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-pyrazole-3-carboxamide (Example 92, 25 mg, 0.032 mmol) in CH₂Cl₂ (500 µL) and i-PrOH (500 µL) was added 1-methylpiperidin-4-one (4 µL, 0.032 mmol) followed by Na(OAc)sBH (10 mg, 0.049 mmol). The resulting reaction mixture was stirred at room
temperature overnight, then quenched with 2 mL of MeOH followed by 2 mL of IN aq. NaOH solution. The mixture was poured in sat. aq. NH₄Cl solution, and the aqueous layer was extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified using preparative HPLC to give the title compound (10 mg, 31%) as a white solid after lyophilization. ¹H NMR (CD₃OD, mixture of amide rotamers) δ 8.59-8.52 (m, 1H), 8.51-8.45 (m, 0.5H), 8.40-8.34 (m, 0.5H), 8.26-8.12 (m, 1H), 8.06-7.86 (m, 4H), 7.69-7.45 (m, 3H), 7.29-7.20 (m, 3.5H), 7.04-6.91 (m, 0.5H), 5.33-5.21 (m, 0.5H), 5.08-4.94 (m, 0.5H), 4.63-4.53 (m, 0.5H), 4.34-4.23 (m, 1H), 4.17-4.03 (m, 0.5H), 3.54-3.34 (m, 3.5H), 3.22-2.51 (m, 1H, 2.43-2.32 (m, 1H), 2.29 (s, 3H), 2.18-1.99 (m, 1H), 1.84-1.67 (m, 1.5H), 1.65-0.85 (m, 12H), 0.81-0.70 (m, 2.5H), 0.69-0.58 (m, 1H); MS(ESI⁺) m/z 866.4 (M+H)⁺.

Example 107

\[ \text{N,N-Dibutyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-((5)-3-((piperidin-4-ylamino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide} \]

Following a procedure analogous to that for the synthesis of Example 106, (5)-1-(2-(3-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (30 mg, 0.039 mmol) was reacted with tert-butyl4-oxopiperidine-1-carboxylate (9 mg, 0.047 mmol) to give a crude oil which was used in the subsequent step without purification.

The crude oil from above was dissolved in CH₂Cl₂ (1.0 mL) and TFA (240 µL, 3.12 mmol) was added. The resulting reaction mixture was stirred at room temperature for 1.5 h and then concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (10 mg, 26%) as a white solid after lyophilization. ¹H NMR (CD₃OD, mixture of amide rotamers) δ 8.79-8.69 (m, 1H), 8.59-
8.48 (m, 0.5H), 8.21-7.96 (m, 5H), 7.85-7.55 (m, 4.5H), 7.43-7.09 (m, 2.5H), 7.04-6.90 (m, 0.5H), 5.26-5.10 (m, 0.5H), 4.73-4.34 (m, 2H), 4.25-4.13 (m, 2H), 3.52-2.79 (m, 10H), 2.44-2.14 (m, 4.5H), 2.11-1.74 (m, 1.5H), 1.72-0.69 (m, 15H), 0.63-0.46 (m, 1.5H); MS(ESI⁺) m/z 852.5 (M+H)⁺.

Intermediate 108
(5)-N,N-Dimethyl-1-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanamine hydrochloride

[00353] To a solution of (5)-tert-butyl 3-(((dimethylamino)methyl)-3,4-dihydroisoquinoline-2(1 H)-carboxylate (Edwards, P.J., European Patent Application No. 1598341 (2005)) (66 mg, 0.23 mmol) in CH₂Cl₂ (2.3 mL) was added TFA (1.4 mL, 18.1 mmol). After stirring for 3 h at room temperature, the reaction mixture was concentrated in vacuo. Next, HCl (IN solution in Et₂O) was added and the mixture was concentrated in vacuo (3 x) to give a crude oil which was used without purification in the preparation of Example 108. MS(ESI⁺) m/z 790.2 (M+H)⁺.

Intermediate 109
(5)-4-((1,2,3,4-Tetrahydroisoquinolin-3-yl)methyl)morpholine

Intermediate 109A: (5)-tert-Butyl 3-(morpholinomethyl)-3,4-dihydroisoquinoline-2(1 H)-carboxylate

[00354] Following a procedure analogous to that for the synthesis of Example 106, (5)-tert-butyl 3-formyl-3,4-dihydroisoquinoline-2(1 H)-carboxylate (Aubry, S. et al,
Tetrahedron Lett., 47:1319-1323 (2006)) (71 mg, 0.27 mmol) and morpholine (28 μL, 0.33 mmol) were converted to the title compound (80 mg, 89%). H NMR (CDCl$_3$, mixture of rotamers) δ 7.24-7.20 (m, 4H), 4.85-4.66 (m, 1H), 4.54-4.42 (m, 1H), 4.30-4.17 (m, 1H), 3.67 (br s, 4H), 3.13-2.96 (m, 1H), 2.93-2.69 (m, 1H), 2.62-2.29 (m, 5H), 2.18-2.01 (m, 1H), 1.51 (s, 9H); MS(ESI$^+$) m/z 333.2 (M+H)$^+$.  

Intermediate 109:

[00355] To a solution of (5)-tert-butyl 3-(morpholinomethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (80 mg, 0.24 mmol) in CH$_2$C$_2$ (2.0 mL) was added TFA (1.5 mL, 19.3 mmol). The resulting reaction mixture was stirred at room temperature for 2 h, then concentrated in vacuo and used without purification in the preparation of Example 109. MS(ESI$^+$) m/z 233.2 (M+H)$^+$.  

Intermediate 110:

(5)-1-((1,2,3,4-Tetrahydroisoquinolin-3-yl)methyl)piperidin-4-ol

[00356] Following a procedure analogous to that for the synthesis of Example 107, (5)-tert-butyl 3-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (57 mg, 0.22 mmol) and piperidin-4-ol (26 mg, 0.26 mmol) provided a crude oil which was used without purification in the preparation of Example 110. MS(ESI$^+$) m/z 247.2 (M+H)$^+$.  

Intermediate 111:

(5)-3-(Pyrrolidin-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline

[00357] Following a procedure analogous to that for the synthesis of Example 107, (5)-tert-butyl 3-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (57 mg, 0.22 mmol) and pyrrolidine (16 mg, 0.22 mmol) provided a crude oil which was used without purification in preparation of Example 111. MS(ESI$^+$) m/z 217.1 (M+H)$^+$.  

- 195 -
Intermediate 112
(5)-3-((4-Methylpiperazin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline

[00358] Following a procedure analogous to that for the synthesis of Example 107, (5)-tert-butyl 3-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (57 mg, 0.22 mmol) and 1-methylpiperazine (26 mg, 0.26 mmol) provided a crude oil which was used without purification in the preparation of Example 112. MS(ESI+) m/z 246.1 (M+H)+.

Intermediate 113
(5)-2-Methoxy-N-methyl-N-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)ethanamine

[00359] Following a procedure analogous to that for the synthesis of Example 107, (5)-tert-butyl 3-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (58 mg, 0.22 mmol) and 2-(methylamino)ethanol (21 µL, 0.27 mmol) provided a crude oil which was used without purification in the preparation of Example 113. MS(ESI+) m/z 235.2 (M+H)+.

Intermediate 114
(5)-2-(Methyl((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)amino)ethanol

[00360] Following a procedure analogous to that for the synthesis of Example 107, (5)-tert-butyl 3-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (58 mg, 0.22 mmol) and 2-(methylamino)ethanol (21.4 µL, 0.27 mmol) provided a crude oil which was used without purification in the preparation of Example 114. MS(ESI+) m/z 221.1 (M+H)+.
Intermediate 115

(5')-2-(4-((1,2,3,4-Tetrahydroisoquinolin-3-yl)methyl)piperazin-1-yl)ethanol

(Int-115)

[00361] Following a procedure analogous to that for the synthesis of Example 107, (5)-\textit{tert}-butyl 3-formyl-3,4-dihydroisoquinoline-2(1\textit{H})-carboxylate (58 mg, 0.22 mmol) and 2-(piperazin-1-yl)ethanol (33 µL, 0.267 mmol) provided a crude oil which was used without purification in the preparation of Example 115. MS(ESI\textsuperscript{+}) m/z 276.2 (M+H\textsuperscript{+}).

Intermediate 116

(5)-N,N-Dimethyl-2-((1,2,3,4-tetrahydroisoquinolin-3-yl)methoxy)ethanamine

(Int-116)

Intermediate 116A: (5)-1-(3-(Hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone

[00362] To (S)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (Aldrich, 350 mg, 2.14 mmol) in EtOAc (4.3 mL) and MeOH (1.1 mL) was added Ac\textsubscript{2}O (243 µL, 2.57 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. K2CO\textsubscript{3} was then added to neutralize the AcOH, and the reaction mixture was filtered through a pad of CELITE\textsuperscript{®}, washing with EtOAc. The filtrate was concentrated \textit{in vacuo} to give the title compound (316 mg, 72%) as a white solid. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 1:5:1 mixture of amide rotamers) \textsuperscript{δ} 7.26-7.10 (m, 4H), 5.17 (d, J = 18.0 Hz, 0.5H), 4.90 (dt, J = 5.1, 9.4 Hz, 0.5H), 4.66-4.44 (m, 1H), 4.39-4.23 (m, 1H), 3.66-3.55 (m, 1H), 3.55-3.45 (m, 1H), 3.14
Intermediate 116B: (5)-l-(3-(2-(Dimethylamino)ethoxy)methyl)-3,4-dihydroisoquinolin-2(1\text{H})-yl)ethanone

\[
\begin{align*}
\text{(Int-116B)}
\end{align*}
\]

[00363] To 2-chloro-N,N-dimethylethanamine (63 mg, 0.59 mmol) in DMF (1.0 mL) was added NaH (156 mg, 3.90 mmol, 60% suspension in mineral oil) at 0 °C. After stirring for 20 min at 0 °C, (5')-l-(3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1\text{H})-yl)ethanone (40 mg, 0.20 mmol) was added, and the resulting suspension was stirred at room temperature for 10 min. TBAI (7 mg, 0.019 mmol) was then added, and the reaction mixture was heated at 70 °C for 1.5 h. The mixture was then poured into sat. aq. NH\textsubscript{4}Cl solution and EtOAc. The layers were separated, and the organic layer was washed with sat. aq. NH\textsubscript{4}Cl solution. The aqueous layer was extracted with EtOAc (3 x), and the combined organics were washed with sat. aq. NaCl solution and dried over Na\textsubscript{2}SO\textsubscript{4}. Filtration and concentration in vacuo provided a crude oil which was triturated with hexanes (3 x) to give the title compound (29 mg, 54%) as a pale yellow oil. MS(ESI\textsuperscript{+}) \textit{m/z} 206.1 (M+H\textsuperscript{+}).

Intermediate 116: [00364] To a solution of (5)-l-(3-(2-(dimethylamino)ethoxy)methyl)-3,4-dihydroisoquinolin-2(1\text{H})-yl)ethanone (29 mg, 0.11 mmol) in EtOH (1.0 mL) and water (125 \textmu L, 5.30 mmol) was added cone. HCl (160 \textmu L, 5.30 mmol). The resulting reaction mixture was stirred at 70 °C overnight. Additional MeOH (1.0 mL) and cone. HCl (260 \textmu L, 7.85 mmol) were added, and the solution was heated at 100 °C for 4 h. Cone. HCl (160 \textmu L, 5.30 mmol) was again added, and after stirring at 100 °C for 3 h, an additional 1 mL of cone. HCl was added. The reaction mixture was stirred at 100 °C for 36 h, then cooled to room temperature and concentrated in vacuo to give a crude brown oil which was used without purification in the preparation of Example 116.
Intermediate 117

(5')-3-((2-(Benzyloxy)ethoxy)methyl)-1,2,3,4-tetrahydroisoquinoline

![Diagram]

Intermediate 117A: (5)-1-(3-((2-(Benzyloxy)ethoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone

![Diagram]

Following a procedure analogous to that for the synthesis of Intermediate 116B, (5')-l-(3-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (Intermediate 116A, 40.0 mg, 0.20 mmol) and ((2-bromoethoxy)methyl)benzene (92 µL, 0.58 mmol) were converted to the title compound (43 mg, 65%) after purification by flash column chromatography (gradient from 0% to 50% EtOAc/hexanes). $^1$H NMR (CDCl$_3$, 2:1 mixture of amide rotamers) δ 7.41-7.25 (m, 5H), 7.24-7.06 (m, 4H), 5.10 (d, $J = 18.0$ Hz, 1H), 4.66-4.44 (m, 3H), 4.39 (q, $J = 5.9$ Hz, 0.5H), 4.26 (d, $J = 17.8$ Hz, 0.5H), 3.68-3.47 (m, 5H), 3.44-3.27 (m, 1.5H), 3.10 (dd, $J = 5.8$, 16.0 Hz, 0.5H), 3.01-2.80 (m, 1H), 2.24 (s, 2H), 2.19 (s, 1H); MS(ESI$^+$) m/z 340.2 (M+H)$^+$.  

Intermediate 117:

To a solution of (5)-l-(3-((2-(benzyloxy)ethoxy)methyl)-3,4-dihydroisoquinolin-2(1H)-yl)ethanone (29 mg, 0.086 mmol) in EtOH (1.3 mL) and water (0.4 mL) was added KOH (77 mg, 1.38 mmol). The resulting reaction mixture was stirred at 78 °C for 4 h. Additional KOH (400 mg, 7.17 mmol) was added, and the reaction mixture was stirred at 95 °C overnight. The reaction mixture was then transferred to a pressure vial, rinsing with EtOH (1 mL), and additional KOH (400 mg, 7.17 mmol) was added. The vial was sealed with a Teflon cap and heated at 100 °C for 8 h. The reaction mixture was then quenched with water and extracted (6 x). The
combined organic extracts were dried over \( \text{Na}_2\text{SO}_4 \), filtered and concentrated \textit{in vacuo} to give a crude oil which was used without purification in the preparation of Example 117.

Intermediate 118

\[
3-((4\text{-methylpiperazin-1-yl})\text{methyl})-1,2,3,4\text{-tetrahydroisoquinoline}
\]

Intermediate 118A: tert-Butyl 3-((4-methylpiperazin-1-yl)methyl)-3,4-dihydroisoquinoline-2(1\text{\textit{H}})-carboxylate

[00367] Following a procedure analogous to that for the synthesis of Example 106, tert-butyl 3-formyl-3,4-dihydroisoquinoline-2(1\text{\textit{H}})-carboxylate (Molander, G.A. et al, \textit{Tetrahedron}, 61:2631-2643 (2005)) (95 mg, 0.36 mmol) and 1-methylpiperazine (44 mg, 0.44 mmol) were converted to the title compound (110 mg, 88%), which was used in the subsequent step without purification. MS(ESI\textsuperscript{+}) \textit{m/z} 346.3 (M+H\textsuperscript{+}).

Intermediate 118:

[00368] Following a procedure analogous to that for the synthesis of Intermediate 109B, tert-butyl 3-((4-methylpiperazin-1-yl)methyl)-3,4-dihydroisoquinoline-2(1\text{\textit{H}})-carboxylate (110 mg, 0.32 mmol) provided a crude oil which was used without purification in the preparation of Example 118.

Examples 108 to 118

[00369] The following Examples were prepared using 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1\text{\textit{H}}-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 9IF) and the tetrahydroisoquinoline intermediates described above according to the general procedure for the synthesis of Example 91.
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R</th>
<th>Name</th>
<th>LCMS (M+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>108</td>
<td><img src="image" alt="R1" /></td>
<td>N,N-dibutyl-4-chloro-1-(2-((S)-3-((dimethylamino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>797.3</td>
</tr>
<tr>
<td>109</td>
<td><img src="image" alt="R2" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(2-((S)-3-(morpholinomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>839.3</td>
</tr>
<tr>
<td>110</td>
<td><img src="image" alt="R3" /></td>
<td>N,N-dibutyl-4-chloro-1-(2-((S)-3-((4-hydroxypiperidin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>853.3</td>
</tr>
<tr>
<td>111</td>
<td><img src="image" alt="R4" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-((S)-3-(pyrrolidin-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>823.2</td>
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<tr>
<td>112</td>
<td><img src="image" alt="R5" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-1-(2-((S)-3-((4-methylpiperazin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>852.3</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>--------</td>
<td>--------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>113</td>
<td><img src="image1" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-l-(2-((S)-3-(((2-methoxyethyl)(methyl)amino)-methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>841.2</td>
</tr>
<tr>
<td>114</td>
<td><img src="image2" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-l-(2-((S)-3-(((2-hydroxyethyl)(methyl)amino)-methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>827.2</td>
</tr>
<tr>
<td>115</td>
<td><img src="image3" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-l-(2-((S)-3-((4-(2-hydroxyethyl)piperazin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
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<tr>
<td>116</td>
<td><img src="image4" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-l-(2-((S)-3-(((2-(dimethylamino)ethoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>841.3</td>
</tr>
<tr>
<td>117</td>
<td><img src="image5" alt="Structure" /></td>
<td>l-(2-((S)-3-((2-(benzyloxy)ethoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
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</tr>
<tr>
<td>118</td>
<td><img src="image6" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-5-methyl-l-(2-(3-((4-methylpiperazin-1-yl)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>852.3</td>
</tr>
</tbody>
</table>
Example 119

*N,N*-Dibutyl-4-chloro-1-(2-((S)-3-((2-hydroxyethoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1*H*-pyrazole-3-carboxamide

[00370] A solution of (5)-1-(2-((3-(dimethylamino)-2,5-dihydro-1*H*-benzo[e][1,3]diazepine-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-*N,N*-dibutyl-4-chloro-5-methyl-*H*-pyrazole-3-carboxamide (Example 117, 35 mg, 0.039 mmol) in *CHCl₃* (1.0 mL) was cooled to -78 °C, and boron trichloride (270 μL, 0.27 mmol) was added dropwise via syringe. The resulting solution was stirred at -78 °C for 1 h and then at room temperature overnight. Additional boron trichloride (270 μL, 0.27 mmol) was added, and the reaction mixture was stirred at room temperature for 5 h. After quenching with sat. aq. NH₄Cl, the solution was extracted with EtOAc (3x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by preparative HPLC to give the title compound (10 mg, 31%). ³¹NMR (1:1 CD₃OD:CDCl₃, mixture of amide rotamers) δ 8.65 (s, 1H), 8.40 (s, 0.5H), 8.19-8.11 (m, 1H), 8.09-7.83 (m, 4H), 7.63-7.52 (m, 2.5H), 7.47-7.30 (m, 1H), 7.26-6.98 (m, 3.5H), 6.88 (br s, 0.5H), 5.25 (d, *J* = 18.3 Hz, 0.5H), 4.36-4.07 (m, 3H), 3.75-3.17 (m, 6.5H), 3.12-2.61 (m, 4H), 2.51 (d, *J* = 16.4 Hz, 0.5H), 2.35-2.17 (m, 3.5H), 1.68-0.79 (m, 11.5H), 0.75-0.56 (m, 2.5H); MS(ESI⁺) *m/z* 814.2 (M+H)⁺.

Example 120

*N,N*-Dibutyl-4-chloro-1-(2-(3-(dimethylamino)-2,5-dihydro-*H*-benzo[e][1,3]diazepine-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-*H*-pyrazole-3-carboxamide
To a solution of 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 91F, 36 mg, 0.058 mmol) in DCE (1.0 mL) was added 1-chloro-N,N-2-trimethylprop-1-en-1-amine (15 µL, 0.12 mmol). The resulting reaction mixture was stirred at room temperature for 1.5 h. A solution of N,N-dimethyl-2,5-dihydro-1H-benzo[e][1,3]diazepin-3-amine (Rodriguez, H.R. et al, J. Org. Chem., 33:670-676 (1968)) (11 mg, 0.058 mmol) in THF (1.0 mL) was then added, followed by DMAP (7 mg, 0.058 mmol) and i-Pr2EtN (50 µL, 0.29 mmol). The resulting reaction mixture was stirred at room temperature for 12 h, then concentrated in vacuo and purified by preparative HPLC to give the title compound (11 mg, 24%).

**Example 121**

(Z)-N,N-Dibutyl-4-chloro-1-(2-((2-methoxyethyl)(methyl)amino)-2,5-dihydro-1H-benzo[e][1,3]diazepine-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

![Chemical Structure](image)
Intermediate 121A: (E)-N-(2-Methoxyethyl)-N-methyl-2,5-dihydro-1H-benzo[e][1,3]diazepin-3-amine

![Intermediate 121A](image)

A mixture of 4,5-dihydro-1H-benzo[e][1,3]diazepin-3(2H)-one (Boyer, J.H. et al., *J. Chem. Soc., Perkin Trans. I*, 2137-2140 (1988)) (70 mg, 0.43 mmol) and POCl₃ (805 µL, 8.63 mmol) was heated at 106 °C for 2 h. The reaction mixture was then concentrated in vacuo, dissolved in CHCl₃ and azeotroped with PhMe. The residue was dissolved in THF (1.0 mL) and treated with 2-methoxy-N-methyl Ethanamine (70 µL, 0.65 mmol). The resulting reaction mixture was stirred at room temperature overnight and then concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (29 mg, 28%). ¾ NMR (CDCl₃) δ 7.38-7.31 (m, 2H), 7.31-7.21 (m, 2H), 5.95 (br s, 1H), 4.61 (d, J = 4.6 Hz, 2H), 4.39 (d, J = 4.6 Hz, 2H), 3.56-3.51 (m, 2H), 3.42 (s, 3H), 3.40-3.36 (m, 2H), 3.10 (s, 3H); MS(ESI⁺) m/z 234.1 (M+H)⁺.

Example 121:

Following a procedure analogous to that for the synthesis of Example 91, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 91F, 30 mg, 0.048 mmol) and (E)-N-(2-methoxyethyl)-N-methyl-2,5-dihydro-1H-benzo[e][1,3]diazepin-3-amine (17 mg, 0.072 mmol) were converted to the title compound (18 mg, 44%). ¾ NMR (DMSO, 1:1 mixture of amide rotamers) δ 8.55 (br s, 1H), 8.25-8.15 (m, 2H), 8.12-8.03 (m, 2H), 8.00-7.86 (m, 2H), 7.77-7.61 (m, 3H), 7.39-7.27 (m, 1H), 7.23-7.11 (m, 2H), 6.99 (br s, 1H), 5.48 (br s, 0.5H), 5.31 (br s, 0.5H), 5.05-4.81 (m, 2H), 4.72 (br s, 1H), 4.46 (br s, 1H), 4.14 (br s, 2H), 3.82 (br s, 1H), 3.70 (br s, 1H), 3.63-3.54 (m, 2H), 3.48 (br s, 1H), 3.24 (t, 7.5 Hz, 4H), 2.99 (br s, 1H), 2.16 (br s, 3H), 1.58-1.46 (m, 3H), 1.35-1.06 (m, 6H), 0.95-0.80 (m, 6H); MS(ESI⁺) m/z 840.4 (M+H)⁺.

Example 122
3-(4-(N-Butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)phenyl)propanoic acid

Intermediate 122A: Methyl 3-(4-(butylamino)phenyl)propanoate

Following a procedure analogous to that for the synthesis Example 106, methyl 3-(4-aminophenyl)propanoate (Jakobsen, CM. et al, J. Med. Chem., 44:4696-4703 (2001)) (896 mg, 5.00 mmol) and butyraldehyde (397 mg, 5.50 mmol) were converted to the title compound (420 mg, 44%). ¹H NMR (CDCl₃) δ 7.01 (d, J = 8.4 Hz, 2H), 6.60-6.47 (m, 2H), 3.68 (s, 3H), 3.10 (t, J = 7.2 Hz, 2H), 2.89-2.77 (m, 2H), 2.62-2.46 (m, 2H), 1.66-1.53 (m, 2H), 1.43 (qd, J = 15.0, 7.3 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H); MS(ESI⁺) m/z 236.0 (M+H⁺).

Intermediate 122B: Benzyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate ID, (3,4-dihydroisoquinolin-2(1H)-yl)(2-fluoro-5-iodophenyl)methanone (1.25 g, 3.28 mmol) and benzyl alcohol (410 µl, 3.94 mmol) were converted to the title compound (1.03 g, 81%). ¹H NMR (CDCl₃, 2:1 mixture of amide rotamers) δ 8.23-8.11 (m, 3H), 7.52-7.34...
Intermediate 122C: Ethyl 1-(4-(benzyloxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-4-chloro-5-methyl-1H-pyrazole-3-carboxylate

\[
\text{Chemical Structure Image (Int-122C)}
\]

Following a procedure analogous to that for the synthesis of Intermediate IE, ethyl 4-chloro-5-methyl-1H-pyrazole-3-carboxylate (Intermediate 1A, 509 mg, 2.70 mmol) and benzyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (1.00 g, 2.57 mmol) were converted to the title compound (690 mg, 48%).

\[
\begin{align*}
&\text{NMR (CDCl}_3, 1.5:1 \text{ mixture of amide rotamers) } \\
&\delta 8.35-8.28 (m, 1H), 8.18 (t, J = 1.9 Hz, 1H), 7.76 (d, J = 8.4 Hz, 0.5H), 7.70 (d, J = 8.4 Hz, 0.5H), 7.50-7.45 (m, 2H), 7.43-7.31 (m, 3H), 7.23-7.07 (m, 3.5H), 6.90 (d, J = 7.9 Hz, 0.5H), 5.42 (s, 2H), 4.76-4.54 (m, 1H), 4.47 (s, 1H), 4.16 (q, J = 7.0 Hz, 2.5H), 3.64 (br s, 1.5H), 3.13-3.02 (m, 0.5H), 2.81 (t, J = 6.1 Hz, 1H), 2.34 (s, 2H), 2.26 (s, 1H), 1.21 (t, J = 7.0 Hz, 1H), 1.12 (t, J = 7.2 Hz, 2H); MS(ESI \text{+}) m/z 558.4 (M+H). \\
\end{align*}
\]

Intermediate 122D: 4-(4-Chloro-3-(ethoxycarbonyl)-5-methyl-1H-pyrazol-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

\[
\text{Chemical Structure Image (Int-122D)}
\]

Following a procedure analogous to that for the synthesis of Intermediate 9ID, ethyl 1-(4-(benzyloxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-4-chloro-5-methyl-1H-pyrazole-3-carboxylate (690 mg, 1.24 mmol) was converted to the
title compound (500 mg, 86%). 'H NMR (DMSO-d$_6$, 1.5:1 mixture of amide rotamers) δ 8.17 (dd, $J = 2.0$, 8.4 Hz, 1H), 8.06 (s, 1H), 7.86 (d, $J = 8.1$ Hz, 0.5H), 7.80 (d, $J = 8.1$ Hz, 0.5H), 7.23-7.06 (m, 3.5H), 6.98 (d, $J = 6.8$ Hz, 0.5H), 6.89-4.34 (m, 2H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.95 (br s, 0.5H), 3.53 (t, $J = 5.5$ Hz, 1.5H), 3.01-2.61 (m, 2H), 2.26 (s, 2H), 2.21 (s, 1H), 1.11 (t, $J = 7.2$ Hz, 1H), 1.07 (t, $J = 7.0$ Hz, 2H); MS(ESI$^+$) $m/z$ 468.1 (M+H)$^+$.  

Intermediate 122E: Ethyl 4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate

![Intermediate 122E](image)

[00378] Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(ethoxycarbonyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (800 mg, 1.71 mmol) and naphthalene-2-sulfonamide (372 g, 1.80 mmol) were converted to the title compound (1.10 g, 93%) after purification using flash column chromatography (3% MeOH/CHCl$_3$ with 0.1% AcOH). 'H NMR (DMSO-d$_6$, 2:1 mixture of amide rotamers) δ 8.57 (br s, 1H), 8.42 (d, $J = 1.3$ Hz, 0.5H), 8.30 (s, 0.5H), 8.24-7.85 (m, 5H), 7.75-7.58 (m, 2.5H), 7.42 (s, 1.5H), 7.22-7.05 (m, 2.5H), 6.96 (d, $J = 7.3$ Hz, 0.5H), 4.69-3.66 (m, 4H), 3.60-3.11 (m, 2H), 3.04-2.62 (m, 2H), 2.23-2.18 (m, 2H), 2.15 (s, 1H), 1.16-0.98 (m, 3H); MS(ESI$^+$) $m/z$ 657.2 (M+H)$^+$.  

Intermediate 122F: 4-Chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylic acid

![Intermediate 122F](image)
Following a procedure analogous to that for the synthesis of Example 45, ethyl 4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate (125 mg, 0.19 mmol) was converted to the title compound (120 mg, 97%). $^1$H NMR (DMSO-d$_6$, 2:1 mixture of amide rotamers) δ 8.70 (s, 1H), 8.24 (d, $J = 7.9$ Hz, 1H), 8.16 (d, $J = 8.6$ Hz, 1H), 8.11-8.04 (m, 3H), 8.02-7.95 (m, 1H), 7.84-7.64 (m, 3H), 7.22-7.04 (m, 3.5H), 6.95 (d, $J = 7.0$ Hz, 0.5H), 4.82-4.18 (m, 2H), 3.96-3.56 (m, 2H), 3.05-2.64 (m, 2H), 2.21 (s, 2H), 2.16 (s, 1H); MS(ESI$^+$) m/z 629.2 (M+H)$^+$.  

Intermediate 122G: Methyl 3-(4-(N-buty1-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)phenyl)propanoate

![Chemical Structure](Int-122G)

To a solution of 4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylic acid (116 mg, 0.18 mmol) in CH$_2$C$_2$ (1.0 mL) was added oxalyl chloride (48 µL, 0.55 mmol) followed by 1 drop of DMF. The resulting reaction mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was dissolved in CD$_3$OD (1.0 mL), and methyl 3-(4-(butylamino)phenyl)propanoate (Intermediate 122A, 17 mg, 0.074 mmol) and i-P$^\text{EtN}$ (32 µL, 0.18 mmol) were added. The reaction mixture was stirred at room temperature for 2 h and then concentrated in vacuo. The crude oil was purified by preparative HPLC to give the title compound (30 mg, 57%). $^1$H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 8.73 (s, 1H), 8.10 (d, $J = 9.0$ Hz, 1H), 8.07-8.06 (m, 1H), 8.04-8.00 (m, 2H), 7.94-7.91 (m, 1H), 7.74-7.66 (m, 2H), 7.48 (br s, 1H), 7.39 (br s, 1H), 7.21-7.19 (m, 3.5H), 7.03 (br s, 1H), 6.98-6.96 (m, 0.5H), 6.90 (br s, 1H), 6.70 (d, $J = 8.6$ Hz, 1H), 6.43 (br s, 1H), 4.73 (br s, 1H), 4.44 (br s, 1H), 4.26 (br s, 1H), 4.10 (br s, 1H), 3.90 (br s, 1H), 3.60-3.56 (m, 3H), 3.48 (br s, 2H), 2.94 (br s, 1H), 2.79-
2.71 (m, 2H), 2.54-2.46 (m, 2H), 2.12 (s, 3H), 1.43-1.24 (m, 4H), 0.89-0.83 (m, 3H); MS(ESI + ) m/z 847.0 (M+H) +.

Example 122: 

Following a procedure analogous to that for the synthesis Example 1F, ethyl 3-(4-(N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)phenyl)propanoate (20 mg, 0.024 mmol) was converted to the title compound (12 mg, 64%). 1H NMR (CD3OD, 1:1 mixture of amide rotamers) δ 8.72 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 8.07-8.03 (m, 2H), 8.00 (d, J = 7.9 Hz, 1H), 7.94-7.90 (m, 1H), 7.73-7.65 (m, 2H), 7.47 (br s, 0.5H), 7.36 (br s, 0.5H), 7.20-7.19 (m, 4H), 7.05 (br s, 1H), 6.96-6.91 (m, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.55 (br s, 1H), 4.73 (br s, 0.5H), 4.45 (br s, 0.5H), 4.24 (br s, 0.5H), 4.09 (br s, 0.5H), 3.89 (br s, 0.5H), 3.64 (br s, 0.5H), 3.49 (br s, 2H), 3.08 (br s, 0.5H), 2.95 (br s, 0.5H), 2.82-2.71 (m, 2H), 2.51-2.43 (m, 2H), 2.11 (s, 3H), 1.41-1.23 (m, 4H), 0.89-0.83 (m, 3H); MS(ESI + ) m/z 832.8 (M+H) +.
Example 124

1-(3-(4-(N-Butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)phenyl)propanoyl)piperidine-4-carboxylic acid

\[
\text{HO}_2\text{C} \begin{array}{c}
\text{N} \backslash \text{O} \\
\text{N}^\text{Bu} \end{array} \text{Me}
\]

To a solution of 3-(4-(N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)phenyl)propanoic acid (Example 122, 5 mg, 0.006 mmol) in DMF were added ethyl piperidine-4-carboxylate (2 mg, 0.012 mmol), HATU (5 mg, 0.012 mmol) and i-Pr$_2$EtN (3 µL, 0.018 mmol). The reaction mixture was stirred at room temperature for 1 h, then quenched with cold water and extracted with Ø4 Ø4 (3 x). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated in vacuo to give a crude oil which was used in the subsequent step without purification.

Following a procedure analogous to that for the synthesis Intermediate IF, the crude oil from above was converted to the title compound (7 mg, 72%). $^1$H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 8.72 (s, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 8.07-8.06 (m, 1H), 8.04-8.00 (m, 2H), 7.95-7.92 (m, 1H), 7.73-7.65 (m, 2H), 7.48 (br s, 1H), 7.39 (br s, 1H), 7.21-7.19 (m, 4H), 7.06 (br s, 1H), 6.98 (br s, 0.5H), 6.93 (br s, 0.5H), 6.86 (d, $J = 8.1$ Hz, 1H), 6.54 (br s, 1H), 4.46 (br s, 1H), 4.29 (br s, 2H), 4.09 (br s, 1H), 3.89 (br s, 1H), 3.78 (br s, 1H), 3.64 (br s, 1H), 3.48 (br s, 2H), 3.24-3.19 (m, 1H), 3.05 (br s, 2H), 2.94 (br s, 1H), 2.85-2.70 (m, 4H), 2.61-2.51 (m, 2H), 2.12 (s, 3H), 1.90-1.82 (m, 2H), 1.51-1.21 (m, 6H), 0.89-0.83 (m, 3H); MS(ESI $^+$) $m/z$ 944.2 (M+H)$^+$.
Example 125

4-Chloro-N-(3,4-dichlorobenzyl)-N,5-dimethyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide

[00385] To a solution of 4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylic acid (Intermediate 122F, 25 mg, 0.040 mmol) in CH₂Cl₂ (0.5 mL) was added 1-chloro-N,N-2-trimethylprop-1-en-1-amine (11 µL, 0.079 mmol) via syringe. The resulting reaction mixture was stirred at room temperature for 30 min. 1-(3,4-Dichlorophenyl)-N-methylmethanamine (Maybridge, 8 mg, 0.044 mmol) and THF (0.5 mL) were added followed by i-P⁴F₁₀N (14 µL, 0.079 mmol). The reaction mixture was stirred at room temperature for 10 min, then concentrated in vacuo and purified by preparative HPLC to give the title compound (6 mg, 19%). ¹H NMR (1:1 CD₂OD:CDCl₃, 2:1 mixture of amide rotamers) δ 8.58 (s, 1H), 8.12 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.98-7.94 (m, 1.5H), 7.91-7.83 (m, 2H), 7.59-7.48 (m, 2H), 7.43-7.23 (m, 3H), 7.21-6.95 (m, 4.5H), 6.90-6.75 (m, 1H), 4.50 (d, J = 11.7 Hz, 2.5H), 4.30-4.10 (m, 1H), 3.82 (br s, 1H), 3.63-3.43 (m, 1.5H), 2.84-2.67 (m, 3.5H), 2.60 (s, 1H), 2.57 (s, 0.5H), 2.28-2.22 (m, 2.5H), 2.20 (s, 0.5H); MS(ESI⁺) m/z 802.0 (M+H)⁺.

Intermediate 126

N-(3,4-Dichlorobenzyl)butan-1-amine

(Int-126)
[00386] Following a procedure analogous to that for the synthesis of Example 106, 3,4-dichlorobenzaldehyde (10.0 g, 57.1 mmol) and butan-1-amine (4.18 g, 57.1 mmol) were converted to the title compound (7.09 g, 53%). 1H NMR (CDCl$_3$) $\delta$ 7.45 (d, $J$ = 2.0 Hz, 1H), 7.40 (d, $J$ = 8.1 Hz, 1H), 7.19 (dd, $J$ = 2.0, 8.1 Hz, 1H), 3.79 (s, 2H), 2.68-2.59 (m, 2H), 1.59-1.45 (m, 2H), 1.36 (qd, $J$ = 7.3, 15.0 Hz, 2H), 0.92 (t, $J$ = 7.4 Hz, 3H); MS(ESI$^+$) m/z 232.1 (M+H)$^+$. 

Intermediate 127  
$N$-(3,4-Dichlorophenethyl)butan-1-amine

\[ \text{Cl} \quad \text{H} \quad \text{CH}_3 \]

[Int-127]

[00387] Following a procedure analogous to that for the synthesis of Example 106, 2-(3,4-dichlorophenyl)ethanamine (1.27 g, 6.68 mmol) and butyraldehyde (600 µL, 6.68 mmol) were converted to the title compound (390 mg, 24%). 1H NMR (CDCl$_3$) $\delta$ 7.37 (d, $J$ = 8.1 Hz, 1H), 7.32 (d, $J$ = 2.0 Hz, 1H), 7.06 (dd, $J$ = 2.1, 8.3 Hz, 1H), 2.97-2.90 (m, 2H), 2.88-2.81 (m, 2H), 2.75-2.66 (m, 2H), 1.53 (quin, $J$ = 7.5 Hz, 2H), 1.34 (qd, $J$ = 7.4, 15.0 Hz, 2H), 0.92 (t, $J$ = 7.3 Hz, 3H); MS(ESI$^+$) m/z 246.1 (M+H)$^+$. 

Intermediate 128  
$N$-Butyl-4,4,4-trifluorobutan-1-amine

\[ \text{F}_3\text{C} \quad \text{H} \quad \text{CH}_3 \]

[Int-128]

[00388] Following a procedure analogous to that for the synthesis of Example 106, butan-1-amine (293 mg, 4.00 mmol) and 4,4,4-trifluorobutanal (504 mg, 4.00 mmol) were converted to a crude oil which was used without purification. MS(ESI$^+$) m/z 184.1 (M+H)$^+$. 

Intermediate 129  
Bis(4,4,4-trifluorobutyl)amine

\[ \text{F}_3\text{C} \quad \text{H} \quad \text{CF}_3 \]

[Int-129]
Following a procedure analogous to that for the synthesis of Example 106, 4,4,4-trifluorobutan-1-amine, HCl (598 mg, 4.00 mmol), Et<sub>3</sub>N (550 µL, 4.00 mmol) and 4,4,4-trifluorobutanal (504 mg, 4.00 mmol) provided a colorless oil which was used directly in the preparation of Example 129. MS(ESI<sup>+</sup>) m/z 192.1 (M+H)<sup>+</sup>.

Intermediate 130
Bis(3,3,3-trifluoropropyl)amine

[00390] The title compound was prepared as previously described: PCT International Application No. WO 2008/156614.

Intermediate 131
N-(3-Isopropoxybenzyl)butan-1-amine

Following a procedure analogous to that for the synthesis of Example 106, (3-isopropoxyphenyl)methanamine (Matrix, 200 mg, 1.21 mmol) and butyraldehyde (110 µL, 1.21 mmol) were converted to the title compound (43 mg, 16%). ¹H NMR (CDCl<sub>3</sub>) δ 7.29-7.17 (m, 1H), 6.99-6.74 (m, 3H), 4.57 (td, J = 6.1, 12.1 Hz, 1H), 3.80 (s, 2H), 2.65 (t, J = 7.3 Hz, 2H), 1.63-1.50 (m, 2H), 1.40-1.24 (m, 8H), 0.90 (t, J = 7.3 Hz, 3H); MS(ESI<sup>+</sup>) m/z 222.2 (M+H)<sup>+</sup>.

Intermediate 132
N-(3-(4-Chlorophenoxy)benzyl)butan-1-amine

Following a procedure analogous to that for the synthesis of Example 106, (3-(4-chlorophenoxy)phenyl)methanamine (ASDI, 533 mg, 2.28 mmol) and butyraldehyde (210 µL, 2.28 mmol) were converted to the title compound (211 mg, 32%). ¹H NMR (CDCl<sub>3</sub>) δ 7.41-7.19 (m, 4H), 7.14-7.06 (m, 1H), 6.99-6.87 (m, 3H), 3.98-3.86 (m, 2H),...
2.80-2.66 (m, 2H), 1.66 (quin, \( J = 7.5 \) Hz, 2H), 1.42-1.24 (m, 2H), 1.00-0.81 (m, 3H); MS(ESI \(^+\)) \( m/z \) 290.1 (M+H)\(^+\).

Intermediate 133

N-(4-Butoxybenzyl)butan-1-amine

\[
\text{H}_3\text{C}\xrightarrow{}\text{O} \quad \text{N} \quad \text{H} \quad \xrightarrow{}\text{CH}_3
\]

[Int-133]

Following a procedure analogous to that for the synthesis of Example 106, (4-butoxyphenyl)methanamine, HCl (500 mg, 2.79 mmol), \( i\)-Pr\(_2\)EtN (490 \( \mu \)L, 2.79 mmol) and butyraldehyde (250 \( \mu \)L, 2.79 mmol) were converted to the title compound (466 mg, 71%). \( ^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.47 (d, \( J = 8.4 \) Hz, 2H), 6.89 (d, \( J = 8.6 \) Hz, 2H), 3.95 (s, 2H), 3.89 (t, \( J = 6.6 \) Hz, 2H), 2.79-2.70 (m, 2H), 1.85-1.65 (m, 4H), 1.50-1.40 (m, 2H), 1.37-1.27 (m, 2H), 0.96 (t, \( J = 7.4 \) Hz, 3H), 0.89 (t, \( J = 7.3 \) Hz, 3H); MS(ESI \(^+\)) \( m/z \) 236.2 (M+H)\(^+\).

Intermediate 134

N-Butyl-3,4-dichloroaniline

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

[Int-134]

Following a procedure analogous to that for the synthesis of Example 106, 3,4-dichloroaniline (1.62 g, 10.0 mmol) and butyraldehyde (721 mg, 10.0 mmol) were converted to the title compound (1.24 g, 57%). \( ^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.17 (d, \( J = 8.8 \) Hz, 1H), 6.65 (d, \( J = 2.9 \) Hz, 1H), 6.41 (dd, \( J = 2.8, 8.7 \) Hz, 1H), 3.05 (t, \( J = 7.0 \) Hz, 2H), 1.65-1.53 (m, 2H), 1.43 (qd, \( J = 7.3, 15.0 \) Hz, 2H), 0.98 (t, \( J = 7.4 \) Hz, 3H); MS(ESI \(^+\)) \( m/z \) 218.1 (M+H)\(^+\).

Intermediate 135

N-(3-Chlorobenzyl)butan-1-amine

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

[Int-135]
Following a procedure analogous to that for the synthesis of Example 106, (3-chlorophenyl)methanamine (750 mg, 5.30 mmol) and butyraldehyde (480 µL, 5.30 mmol) were converted to the title compound (331 mg, 32%). $^1$H NMR (CDCl$_3$) δ 7.64-7.55 (m, 2H), 7.44-7.33 (m, 2H), 4.02 (s, 2H), 2.84-2.72 (m, 2H), 1.84 (td, $J = 7.8, 15.8$ Hz, 2H), 1.38 (sxt, $J = 7.5$ Hz, 2H), 0.91 (t, $J = 7.4$ Hz, 3H); MS(ESI $^+$) m/z 198.1 (M+H)$^+$.  

Intermediate 136

$N$-(4-Chlorobenzyl)butan-1-amine

[00396] Following a procedure analogous to that for the synthesis of Example 106, (4-chlorophenyl)methanamine (750 mg, 5.30 mmol) and butyraldehyde (480 µL, 5.30 mmol) were converted to the title compound (421 mg, 40%). $^1$H NMR (CDCl$_3$) δ 7.55 (d, $J = 8.4$ Hz, 2H), 7.41-7.34 (m, 2H), 3.98 (s, 2H), 2.78-2.70 (m, 2H), 1.79 (td, $J = 7.7, 15.6$ Hz, 2H), 1.36 (qd, $J = 7.4, 15.1$ Hz, 2H), 0.95-0.88 (m, 4H); MS(ESI $^+$) m/z 198.1 (M+H)$^+$.  

Intermediate 137

$N$-Butyl-4-(4-fluorophenoxy)aniline

[00397] To a solution of 4-(4-fluorophenoxy)aniline (Apollo, 500 mg, 2.46 mmol) and butyraldehyde (240 µL, 2.71 mmol) in DCE (5.0 mL) were added 4 Å molecular sieves. The resulting reaction mixture was stirred at room temperature for 1 h. Next, Na(OAc)$_3$BH (782 mg, 3.69 mmol) was added, and the reaction mixture was stirred at room temperature overnight. Concentration in vacuo afforded a crude residue which was purified by flash column chromatography (10% EtOAc/hexanes) to give the title compound (400 mg, 62%). $^1$H NMR (CDCl$_3$) δ 7.28-7.21 (m, 2H), 7.20-7.13 (m, 4H), 6.91-6.85 (m, 2H), 3.82 (br s, 1H), 3.39 (t, $J = 7.0$ Hz, 2H), 1.96-1.85 (m, 2H), 1.79-1.67 (m, 2H), 1.26 (t, $J = 7.4$ Hz, 3H); MS(ESI $^+$) m/z 260.1 (M+H)$^+$.  

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Intermediate 138

*N*-Butyl-4-(4-chlorophenoxy)aniline

\[ \text{(Int-138)} \]

Following a procedure analogous to that for the synthesis of Intermediate 137, 4-(4-chlorophenoxy)aniline (Aldrich, 500 mg, 2.28 mmol) and butyraldehyde (230 µL, 2.50 mmol) were converted to the title compound (450 mg, 71%). $^1$H NMR (CDCl$_3$) $\delta$ 7.34-7.16 (m, 2H), 6.99-6.84 (m, 4H), 6.72-6.62 (m, 2H), 4.19 (br s, 1H), 3.17 (t, $J = 12$ Hz, 2H), 1.75-1.61 (m, 2H), 1.60-1.42 (m, 2H), 1.03 (t, $J = 7.4$ Hz, 3H); MS(ESI $^+$) $m/z$ 275.8 (M+H)$^+$.  

Intermediate 139

*N*-((l-Methyl-lH-indol-2-yl)methyl)butan-1-amine

\[ \text{(Int-139)} \]

Following a procedure analogous to that for the synthesis of Intermediate 137, (1-methyl-lH-indol-2-yl)methanamine (500 mg, 3.12 mmol) and butyraldehyde (310 µL, 3.43 mmol) were converted to the title compound (70 mg, 6%). $^1$H NMR (CDCl$_3$) $\delta$ 7.62-7.54 (m, 1H), 7.36-7.27 (m, 1H), 7.27-7.16 (m, 1H), 7.17-7.03 (m, 1H), 6.50 (s, 1H), 4.05 (s, 2H), 3.77 (s, 3H), 2.82-2.70 (m, 2H), 1.60 (ddd, $J = 15.1$, 7.5, 7.4 Hz, 2H), 1.45-1.16 (m, 2H), 0.96-0.87 (m, 3H).

Intermediate 140

*N*-Butyl-3.4-dimethoxyaniline

\[ \text{(Int-140)} \]

Following a procedure analogous to that for the synthesis of Intermediate 137, 3,4-dimethoxyaniline (500 mg, 3.26 mmol) and butyraldehyde (290 µL, 3.26 mmol) were converted to the title compound (600 mg, 83%). $^1$H NMR (CDCl$_3$) $\delta$ 6.81-6.70 (m, 1H),...
6.27-6.21 (m, 1H), 6.16 (dd, J = 8.5, 2.5 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.08 (t, J = 7.0 Hz, 2H), 1.56-1.40 (m, 4H), 0.99-0.93 (m, 3H); MS(ESI+) m/z 210.2 (M+H)+.

Intermediate 141

N-Butyl-4-isopropoxyaniline

[00401] Following a procedure analogous to that for the synthesis of Intermediate 137, 4-isopropoxyaniline (500 mg, 3.31 mmol) and butyraldehyde (300 µL, 3.31 mmol) were converted to the title compound (600 mg, 83%). $^1$H NMR (CDCl$_3$) δ 6.88-6.74 (m, 2H), 6.67-6.51 (m, 2H), 4.41-4.30 (m, 1H), 3.08 (t, J = 7.0 Hz, 2H), 1.66-1.37 (m, 2H), 1.30 (s, 3H), 0.99-0.87 (m, 3H); MS(ESI+) m/z 208.2 (M+H)+.

Intermediate 142

N-Butyl-3-chloro-4-methylaniline

[00402] Following a procedure analogous to that for the synthesis of Intermediate 137, 3-chloro-p-toluidine (Aldrich, 430 µL, 3.53 mmol) and butyraldehyde (320 µL, 3.13 mmol) were converted to the title compound (600 mg, 79%). $^1$H NMR (CDCl$_3$) δ 7.06-6.93 (m, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.43 (dd, J = 8.1, 2.4 Hz, 1H), 3.56 (br s, 1H), 3.08 (t, J = 7.2 Hz, 2H), 2.26 (s, 3H), 1.66-1.50 (m, 2H), 1.49-1.33 (m, 2H), 1.00-0.89 (m, 3H).

Intermediate 143

N-Butylbiphenyl-4-amine

[00403] Following a procedure analogous to that for the synthesis of Intermediate 137, 4-aminodiphenyl (500 mg, 2.95 mmol) and butyraldehyde (280 µL, 3.10 mmol) were converted to the title compound (610 mg, 84%). $^1$H NMR (CDCl$_3$) δ 7.62-7.53 (m, 2H), 6.77-6.70 (m, 2H), 6.16 (dd, J = 8.5, 2.5 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.08 (t, J = 7.0 Hz, 2H), 1.56-1.40 (m, 4H), 0.99-0.93 (m, 3H); MS(ESI+) m/z 210.2 (M+H)+.
7.52-7.35 (m, 4H), 7.35-7.16 (m, 1H), 6.75-6.60 (m, 2H), 3.71 (br s, 1H), 3.17 (t, \( J = 7.0 \) Hz, 2H), 1.68-1.57 (m, 2H), 1.52-1.39 (m, 2H), 1.00 (t, \( J = 7.4 \) Hz, 3H).

Intermediate 144

\[
\text{\( \text{N-Butyl-4-methoxyaniline} \) (Int-144)}
\]

[00404] Following a procedure analogous to that for the synthesis of Intermediate 137, 4-methoxyaniline (500 mg, 4.06 mmol) and butyraldehyde (360 \( \mu \)L, 4.06 mmol) were converted to the title compound (700 mg, 88%). \( \text{\textsuperscript{1}H NMR} \) (CDC\(_3\)) \( \delta \) 6.89-6.73 (m, 2H), 6.69-6.50 (m, 2H), 3.76 (s, 3H), 3.10 (t, \( J = 7.2 \) Hz, 2H), 1.70-1.28 (m, 4H), 1.02-0.90 (m, 3H); MS(ESI\(^+\)) \( m/z \) 180.1 (M+H).  

Intermediate 145

\[
\text{\( \text{N-Butyl-3-methoxyaniline} \) (Int-145)}
\]

[00405] Following a procedure analogous to that for the synthesis of Intermediate 137, 3-methoxyaniline (460 \( \mu \)L, 4.06 mmol) and butyraldehyde (360 \( \mu \)L, 4.06 mmol) were converted to the title compound (700 mg, 88%). \( \text{\textsuperscript{1}H NMR} \) (CDC\(_3\)) \( \delta \) 7.36-7.20 (m, 1H), 6.56-6.32 (m, 3H), 4.02-3.95 (m, 3H), 3.87 (br s, 1H), 3.30 (t, \( J = 7.0 \) Hz, 2H), 1.86-1.71 (m, 2H), 1.71-1.58 (m, 2H), 1.19-1.10 (m, 3H); MS(ESI\(^+\)) \( m/z \) 179.9 (M+H).  

Intermediate 146

\[
\text{\( \text{3-tert-Butyl 1-\text{N-butyraniline}} \) (Int-146)}
\]

[00406] Following a procedure analogous to that for the synthesis of Intermediate 137, 3-tert-butylaniline (500 mg, 3.35 mmol) and butyraldehyde (300 \( \mu \)L, 3.35 mmol) were converted to the title compound (600 mg, 80%). \( \text{\textsuperscript{1}H NMR} \) (CDC\(_3\)) \( \delta \) 7.15 (t, \( J = 7.8 \) Hz, 1H), 6.79-6.74 (m, 1H), 6.66 (t, \( J = 2.1 \) Hz, 1H), 6.47 (ddd, \( J = 8.0, 2.3, 0.7 \) Hz, 1H), 3.61
Following a procedure analogous to that for the synthesis of Intermediate 137, biphenyl-3-amine (500 mg, 2.95 mmol) and butyraldehyde (265 µL, 2.95 mmol) were converted to the title compound (600 mg, 83%). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.65-7.57 (m, 2H), 7.55-7.41 (m, 2H), 7.40-7.32 (m, 1H), 7.31-7.23 (m, 1H), 6.99-6.90 (m, 1H), 6.85 (t, \(J = 2.0\) Hz, 1H), 6.64 (ddd, \(J = 8.0, 2.4, 0.9\) Hz, 1H), 3.78 (br s, 1H), 3.21 (t, \(J = 7.2\) Hz, 2H), 1.75-1.59 (m, 2H), 1.54-1.44 (m, 2H), 1.01 (t, \(J = 7.4\) Hz, 3H); MS(ESI\(^+\)) \(m/\text{z}\) 226.1 (M+H\(^+\)).

Following a procedure analogous to that for the synthesis of Intermediate 137, 4-tert-butylaniline (400 mg, 2.68 mmol) and butyraldehyde (240 µL, 2.68 mmol) were converted to the title compound (500 mg, 84%). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.27-7.19 (m, 2H), 6.60 (d, \(J = 8.8\) Hz, 2H), 3.61 (br s, 1H), 3.13 (t, \(J = 7.0\) Hz, 2H), 1.68-1.53 (m, 2H), 1.50-1.40 (m, 2H), 1.32 (s, 9H), 0.99 (t, \(J = 7.3\) Hz, 3H); MS(ESI\(^+\)) \(m/\text{z}\) 206.1 (M+H\(^+\)).
Following a procedure analogous to that for the synthesis of Intermediate 137, 1,4-benzodioxan-6-amine (410 µL, 3.31 mmol) and butyraldehyde (300 µL, 3.31 mmol) were converted to the title compound (620 mg, 83%). \( ^1H \text{NMR} (\text{CDCl}_3) \delta 6.77-6.58 (\text{m}, 1\text{H}), 6.28-5.96 (\text{m}, 2\text{H}), 4.30-4.12 (\text{m}, 4\text{H}), 3.04 (\text{t}, J = 12 \text{ Hz}, 2\text{H}), 1.65-1.49 (\text{m}, 2\text{H}), 1.49-1.37 (\text{m}, 2\text{H}), 0.95 (\text{t}, J = 7.4 \text{ Hz}, 3\text{H}); \text{MS(ESI}^+) m/z 208.3 (\text{M}+\text{H})^+.

Intermediate 150

\( \text{N-Butyl-3-isopropoxyaniline} \)

[00410]

Following a procedure analogous to that for the synthesis of Intermediate 137, 3-isopropoxyaniline (485 µL, 3.31 mmol) and butyraldehyde (310 µL, 3.47 mmol) were converted to the title compound (610 mg, 84%). \( ^1H \text{NMR} (\text{CDCl}_3) \delta 7.15-6.96 (\text{m}, 1\text{H}), 6.37-6.01 (\text{m}, 2\text{H}), 4.60-4.39 (\text{m}, 1\text{H}), 3.75 (\text{br s}, 1\text{H}), 3.10 (\text{t}, J = 7.0 \text{ Hz}, 2\text{H}), 1.68-1.52 (\text{m}, 2\text{H}), 1.50-1.38 (\text{m}, 2\text{H}), 1.34 (\text{s}, 3\text{H}), 1.33 (\text{s}, 3\text{H}), 0.97 (\text{t}, J = 7.4 \text{ Hz}, 3\text{H}).

Intermediate 151

\( \text{N-(Naphthalen-2-ylmethyl)butan-1-amine} \)

[00411]

Following a procedure analogous to that for the synthesis of Intermediate 137, 2-naphthalenemethanamine (500 mg, 3.18 mmol) and butyraldehyde (315 µL, 3.50 mmol) were converted to the title compound (100 mg, 15%). \( ^1H \text{NMR} (\text{CDCl}_3) \delta 7.87-7.78 (\text{m}, 4\text{H}), 7.78-7.69 (\text{br s}, 1\text{H}), 7.56 (\text{dd}, J = 8.4, 1.5 \text{ Hz}, 1\text{H}), 7.52-7.43 (\text{m}, 2\text{H}), 4.06 (\text{s}, 2\text{H}), 2.78-2.69 (\text{m}, 2\text{H}), 1.65 (\text{dt}, J = 15.4, 7.6 \text{ Hz}, 2\text{H}), 1.38-1.23 (\text{m}, 2\text{H}), 0.88 (\text{t}, J = 7.4 \text{ Hz}, 3\text{H}); \text{MS(ESI}^+) m/z 214.1 (\text{M}+\text{H})^+.

Intermediate 152

\( \text{N-Butyl-3'-chlorobiphenyl-3'-amine} \)

[00409]
Following a procedure analogous to that for the synthesis of Intermediate 137, 3’-chlorobiphenyl-3-amine (Oakwood, 15 mg, 0.074 mmol) and butyraldehyde (7 µL, 0.074 mmol) were converted to a crude oil which was used without purification in the preparation of Example 143. ¹H NMR (CDCl₃) δ 8.17 (d, J = 0.9 Hz, 1H), 7.86-7.42 (m, 3H), 7.41-7.07 (m, 3H), 6.78-6.57 (m, 1H), 3.00-2.87 (m, 2H), 1.63-1.46 (m, 2H), 1.47-1.34 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); MS(ESI⁺) m/z 260.2 (M+H)⁺.

Intermediate 153

N-Butyl-4’-chlorobiphenyl-3-amine

Following a procedure analogous to that for the synthesis of Intermediate 137, 4’-chlorobiphenyl-3-amine (ChemBridge, 285 mg, 1.40 mmol) and butyraldehyde (125 µL, 1.40 mmol) were converted to the title compound (300 mg, 74%). ¹H NMR (CDCl₃) δ 7.73-7.62 (m, 2H), 7.57-7.44 (m, 3H), 7.43-7.34 (m, 2H), 7.29-7.19 (m, 1H), 3.04-2.96 (m, 2H), 1.67-1.59 (m, 2H), 1.47 (dd, J = 15.1, 7.4 Hz, 2H), 0.99 (t, J = 7.3 Hz, 3H); MS(ESI⁺) m/z 260.2 (M+H)⁺.

Intermediate 154

Methyl 4-(butylamino)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 137, 4-aminobenzoic acid methyl ester (Aldrich, 500 mg, 3.31 mmol) and butyraldehyde (300 µL, 3.31 mmol) were converted to the title compound (600 mg, 82%). ¹H NMR (CDCl₃) δ 7.91-7.80 (m, 2H), 6.59-6.46 (m, 2H), 3.86 (s, 3H), 3.18 (t, J = 7.0 Hz, 2H), 1.67-1.58 (m, 2H), 1.48-1.37 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); MS(ESI⁺) m/z 208.1 (M+H)⁺.

Intermediate 155

Ethyl 2-(4-(butylamino)phenyl)acetate
Following a procedure analogous to that for the synthesis of Intermediate 137, ethyl 2-(4-aminophenyl)acetate (500 mg, 2.79 mmol) and butyraldehyde (250 µl, 2.79 mmol) were converted to the title compound (600 mg, 87%). ¹H NMR (CDCl₃) δ 7.12-7.04 (m, 2H), 6.60-6.52 (m, 2H), 4.14 (q, J = 7.0 Hz, 2H), 3.49 (s, 2H), 3.11 (t, J = 7.0 Hz, 2H), 1.66-1.50 (m, 2H), 1.50-1.36 (m, 2H), 1.25 (t, J = 7.0 Hz, 3H), 0.96 (t, J = 7.3 Hz, 3H); MS(ESI⁺) m/z 236.3 (M+H)⁺.

Examples 126 to 155

The following Examples were prepared using 4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylic acid (Intermediate 122F) and the amine intermediates described above according to the procedure for the synthesis of Example 125.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R</th>
<th>Name</th>
<th>LCMS (M+H)</th>
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<tbody>
<tr>
<td>126</td>
<td></td>
<td>N-butyl-4-chloro-N-(3,4-dichlorobenzyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>844.0</td>
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<td>127</td>
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<td>N-butyl-4-chloro-N-(3,4-dichlorophenethyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>858.1</td>
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<td>Name</td>
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<tr>
<td>128</td>
<td>( \text{Bu} )</td>
<td>( \text{N-butyl-4-chloro-5-methyl-1-} ) (4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-(4,4,4-trifluorobuty1)-1H-pyrazole-3-carboxamide</td>
<td>794.1</td>
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<tr>
<td>129</td>
<td>( \text{CF}_3 )</td>
<td>4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-bis(4,4,4-trifluorobuty1)-1H-pyrazole-3-carboxamide</td>
<td>834.1</td>
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<tr>
<td>130</td>
<td>( \text{CF}_3 )</td>
<td>4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-bis(3,3,3-trifluoropropyl)-1H-pyrazole-3-carboxamide</td>
<td>820.1</td>
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<td>131</td>
<td>( \text{CF}_3 )</td>
<td>( \text{N-butyl-4-chloro-N-(3-isopropoxybenzyl)-5-methyl-1-} ) (4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>832.2</td>
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<tr>
<td>132</td>
<td>( \text{CF}_3 )</td>
<td>( \text{N-butyl-4-chloro-N-(3-(4-chlorophenox)benzyl)-5-methyl-1-} ) (4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>900.2</td>
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<td>133</td>
<td>( \text{OBu} )</td>
<td>( \text{N-(4-butoxybenzyl)-N-butyl-4-chloro-5-methyl-1-} ) (4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>846.2</td>
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<td>Ex. No.</td>
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<tr>
<td>134</td>
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<td>( N)-butyl-4-chloro-( N)-(3,4-dichlorophenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
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<td>135</td>
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<td>( N)-butyl-4-chloro-( N)-(3-chlorobenzyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
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<td>136</td>
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<td>( N)-butyl-4-chloro-( N)-(4-chlorobenzyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>808.1</td>
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<td>137</td>
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<td>( N)-butyl-4-chloro-( N)-(4-(4-fluorophenoxy)phenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>868.5</td>
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<td>138</td>
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<td>( N)-butyl-4-chloro-( N)-(4-(4-chlorophenoxy)phenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>886.3</td>
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<td>139</td>
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<td>( N)-butyl-4-chloro-5-methyl-( N)-(1-methyl-1H-indol-2-yl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>827.1</td>
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<tr>
<td>140</td>
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<td>( N)-butyl-4-chloro-( N)-(3,4-dimethoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>818.6</td>
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<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
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</tr>
<tr>
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<td>---</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>141</td>
<td></td>
<td>(N)-butyl-4-chloro-(N)-(4-isopropoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1(H)-pyrazole-3-carboxamide</td>
<td>816.5</td>
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<td>142</td>
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<td>(N)-butyl-4-chloro-(N)-(3-chloro-4-methylphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1(H)-pyrazole-3-carboxamide</td>
<td>808.1</td>
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<tr>
<td>143</td>
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<td>(N)-(biphenyl-4-yl)-(N)-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1(H)-pyrazole-3-carboxamide</td>
<td>834.4</td>
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<td>144</td>
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<td>(N)-butyl-4-chloro-(N)-(4-methoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1(H)-pyrazole-3-carboxamide</td>
<td>790.1</td>
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<tr>
<td>145</td>
<td></td>
<td>(N)-butyl-4-chloro-(N)-(3-methoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1(H)-pyrazole-3-carboxamide</td>
<td>790.3</td>
</tr>
<tr>
<td>146</td>
<td></td>
<td>(N)-butyl-(N)-(3-tert-butyphenyl)-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1(H)-pyrazole-3-carboxamide</td>
<td>816.3</td>
</tr>
<tr>
<td>147</td>
<td></td>
<td>(N)-(biphenyl-3-yl)-(N)-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1(H)-pyrazole-3-carboxamide</td>
<td>836.3</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>--------</td>
<td>---</td>
<td>----------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>148</td>
<td></td>
<td>N-butyl-N-(4-tert-buty1phenyl)-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>816.4</td>
</tr>
<tr>
<td>149</td>
<td></td>
<td>N-butyl-4-chloro-N-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>818.3</td>
</tr>
<tr>
<td>150</td>
<td></td>
<td>N-butyl-4-chloro-N-(3-isopropoxyphenyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>818.2</td>
</tr>
<tr>
<td>151</td>
<td></td>
<td>N-butyl-4-chloro-5-methyl-N-(naphthalen-2-ylmethyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>824.1</td>
</tr>
<tr>
<td>152</td>
<td></td>
<td>N-butyl-4-chloro-N-(3′-chlorobiphenyl-3-yl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>870.1</td>
</tr>
<tr>
<td>153</td>
<td></td>
<td>N-butyl-4-chloro-N-(4′-chlorobiphenyl-3-yl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide</td>
<td>870.4</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>---------</td>
<td>---</td>
<td>------</td>
<td>-------------</td>
</tr>
<tr>
<td>154</td>
<td>methyl</td>
<td>4-(N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)benzoate</td>
<td>818.1</td>
</tr>
<tr>
<td>155</td>
<td></td>
<td>4-(N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)benzyl propionate</td>
<td>818.1</td>
</tr>
</tbody>
</table>

Example 156

\[ \text{N-Butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-phenyl-1H-pyrazole-3-carboxamide} \]

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[00417] Following a procedure analogous to that for the synthesis of Intermediate 122G, 4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylic acid (Intermediate 122F, 50 mg, 0.079 mmol) and N-butyl-3,4-dichloroaniline (Aldrich, 10 mg, 0.046 mmol) were converted to the title compound. \[^1\text{H} \text{NMR} \ (1:1 \text{CD}_3\text{OD}:\text{CDCl}_3, \text{mixture of amide rotamers}) \delta 8.73 \ (s, 1\text{H}), 8.12-8.00 \ (m, 4\text{H}), 7.97-7.94 \ (m, 1\text{H}), 7.74-7.66 \ (m, 2\text{H}), 7.57 \ (br \ s, 1\text{H}), 7.46 \ (br \ s, 1\text{H}), 7.36 \ (br \ s, 1\text{H}), 7.26-7.19 \ (m, 4.5\text{H}), 7.12-7.10 \ (m, 0.5\text{H}), 7.00 \ (br \ s, 1\text{H}), 6.73 \ (br \ s, 1\text{H}), 6.66 \ (br \ s, 0.5\text{H}), 6.50 \ (br \ s, 0.5\text{H}), 4.66 \ (br \ s, 0.5\text{H}), 4.51 \ (br \ s, 0.5\text{H}), 4.39 \ (br \ s, 0.5\text{H}), 4.25 \ (br \ s, 0.5\text{H}), 4.25 \ (br \ s, 0.5\text{H}), 3.85 \ (br \ s, 2\text{H}), 3.58 \ (br \ s, 2\text{H}), 3.13 \ (br \ s, 1\text{H}), 2.81 \ (br \ s, 1\text{H}), 2.20-2.16 \ (m, 3\text{H}), 1.38-1.21 \ (m, 4\text{H}), 0.93-0.83 \ (m, 3\text{H}); \text{MS(ESI} + \)) m/z 760.2 (M+H) +.  

Example 157

- 228 -
N-Benzyl-N-butyl-4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxamide

[00418] Following a procedure analogous to that for the synthesis of Example 125, 4-chloro-5-methyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxylic acid (Intermediate 122F, 25 mg, 0.040 mmol) and N-benzylbutan-1-amine (Aldrich, 11 µL, 0.064 mmol) were converted to the title compound (21 mg, 68%). ¾ NMR (1:1 CD3OD:CDCl3) δ 8.62 (br s, 1H), 8.15 (d, J = 7.9 Hz, 1H), 8.07-7.82 (m, 5H), 7.64-7.50 (m, 1H), 7.46-7.36 (m, 1.5H), 7.28-6.93 (m, 9H), 6.86 (d, J = 7.3 Hz, 0.5H), 4.62 (d, J = 5.9 Hz, 1H), 4.47-4.11 (m, 2.5H), 3.77-3.36 (m, 2.5H), 3.21-2.94 (m, 1.5H), 2.81-2.65 (m, 2.5H), 2.35-2.14 (m, 3H), 1.74-1.13 (m, 3H), 1.08-0.77 (m, 3H), 0.72-0.58 (m, 1H); MS(ESI+) m/z 774.1 (M+H)^+.

Example 158
N-Butyl-4-chloro-5-methyl-N-(3-(2-(4-methylpiperazin-1-yl)ethylamino)-3-oxopropyl)-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxamide

Intermediate 158A: tert-Butyl 3-(butylamino)propanoate
To a solution of tert-butyl 3-aminopropanoate, HCl (Bachem, 1.59 g, 8.77 mmol) and butyraldehyde (790 µL, 8.77 mmol) in THF (20.0 mL) was added AcOH (1.0 mL, 17.5 mmol). The resulting reaction mixture was stirred at room temperature for 1.5 h. Na(OAc)₃BH (2.60 g, 12.3 mmol) was added portionwise and stirring was continued at room temperature overnight. The reaction mixture was then quenched with IN aq. NaOH (pH = 8-9), and the aqueous layer was extracted with CHCl₃ (3 x). The combined organic extracts were dried over Na₂S₀₄, filtered and concentrated in vacuo to afford a crude oil. Purification by flash column chromatography (gradient from 0% to 100% EtOAc/hexanes) provided the title compound (944 mg, 53%) as a colorless oil.

Intermediate 158B: 3-[(N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)propanoic acid

[00420] Following a procedure analogous to that for the synthesis of Example 125, 4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylic acid (Intermediate 122F, 199 mg, 0.32 mmol) and tert-butyl 3-(butylamino)propanoate (318 mg, 1.58 mmol) provided a yellow oil which was used without purification in the subsequent step.

[00421] The crude oil from above was dissolved in CH₂Cl₂ (5.0 mL) and TFA (4.0 mL, 51.9 mmol) was added. The resulting reaction mixture was stirred at room temperature for 2 h and then concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (107 mg, 43%) as a white solid after
lyophilization. ¹H NMR (CD₃OD, mixture of amide rotamers) δ 8.73 (br s, 1H), 8.15-7.94 (m, 6.5H), 7.75-7.63 (m, 3H), 7.25-7.05 (m, 4H), 6.93-6.87 (m, 0.5H), 5.03-4.86 (m, 1H), 4.71-4.42 (m, 1H), 4.20-4.00 (m, 0.5H), 3.67-3.40 (m, 4H), 3.28-3.05 (m, 1H), 2.90-2.77 (m, 1H), 2.58-2.38 (m, 1H), 2.32 (s, 2H), 2.28-2.24 (m, 1H), 2.18-2.06 (m, 0.5H), 1.28 (s, 4H), 1.15-0.85 (m, 3H), 0.76 (t, J = 7.5 Hz, 1H), 0.68 (t, J = 7.5 Hz, 1H);

MS(ESI⁺) m/z 756.3 (M+H)⁺.

Example 158:

Following a procedure analogous to that for the synthesis of Example 124, 3-(N-buty-l-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)propanoic acid (20 mg, 0.026 mmol) and 2-(4-methyl-piperazin-1-yl)-ethylamine (Aldrich, 12 mg, 0.084 mmol) were converted to the title compound (10 mg, 37%). ¹H NMR (CD₃OD, mixture of amide rotamers) δ 8.73 (br s, 1H), 8.15-7.95 (m, 6.5H), 7.77-7.64 (m, 3.5H), 7.25-7.04 (m, 3.5H), 6.93-6.80 (m, 0.5H), 4.77-4.04 (m, 2H), 3.62-3.52 (m, 2H), 3.48-3.44 (m, 1H), 3.42-3.33 (m, 3H), 3.24 (m, 6H), 2.94-2.61 (m, 9.5H), 2.58-2.39 (m, 1.5H), 2.38-2.31 (m, 2.5H), 2.30-2.20 (m, 1.5H), 1.62-1.13 (m, 4H), 1.13-0.85 (m, 3H), 0.75 (t, J = 7.3 Hz, 1H), 0.68 (t, J = 7.5 Hz, 1H); MS(ESI⁺) m/z 881.5 (M+H)⁺.

Example 159

N-Butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide

Following a procedure analogous to that for the synthesis of Example 124, 3-(N-buty-l-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)propanoic acid (Intermediate 158B, 20 mg, 0.026 mmol) and 2-amino-1,3-propanediol (Aldrich, 8 mg,
0.088 mmol) were converted to the title compound (5 mg, 21%). \(^1\)H NMR (CD\(_3\)OD, 1:1 mixture of amide rotamers) δ 8.72 (br s, 1H), 8.15-7.94 (m, 6.5H), 7.76-7.62 (m, 3.5H), 7.25-7.03 (m, 3.5H), 6.94-6.81 (m, 0.5H), 4.75-4.00 (m, 2H), 3.97-3.70 (m, 2H), 3.65-3.43 (m, 7H), 2.94-2.64 (m, 3H), 2.58-2.12 (m, 5H), 1.58-1.14 (m, 4H), 1.13-0.85 (m, 3H), 0.76 (t, \(J = 7.3\) Hz, 1H), 0.68 (t, \(J = 7.5\) Hz, 1H); MS(ESI \(^+\)) \(m/z\) 829.4 (M+H\(^+\)).

Example 160

\(\text{N-Butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)benzoic acid}\)

Following a procedure analogous to that for the synthesis of Example 124, \(3-(\text{N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)propanoic acid}\) (Intermediate 158B, 20 mg, 0.026 mmol) and 2-amino-2-(hydroxymethyl)propane-1,3-diol (J.T. Baker, 10 mg, 0.083 mmol) were converted to the title compound (4 mg, 18%). \(^1\)H NMR (CD\(_3\)OD, 1:1 mixture of amide rotamers) δ 8.73 (br s, 1H), 8.17-7.94 (m, 7H), 7.75-7.65 (m, 3H), 7.23-7.09 (m, 3.5H), 6.96-6.83 (m, 0.5H), 4.61-4.40 (m, 1H), 4.38-3.91 (m, 3H), 3.73-3.66 (m, 3H), 3.66-3.49 (m, 4H), 3.02-2.97 (m, 1H), 2.89-2.79 (m, 2H), 2.75-2.60 (m, 2H), 2.56 (t, \(J = 6.9\) Hz, 0.5H), 2.38-2.31 (m, 2H), 2.28-2.23 (m, 1.5H), 1.57-1.18 (m, 4H), 1.14-0.84 (m, 3H), 0.76 (t, \(J = 7.3\) Hz, 1H), 0.68 (t, \(J = 7.3\) Hz, 1H); MS(ESI \(^+\)) \(m/z\) 859.4 (M+H).

Example 161

\(4-(\text{N-Butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)benzoic acid}\)
Following a procedure analogous to that for the synthesis of Intermediate 9 IF, methyl 4-(N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)benzoate (Example 154, 2 mg, 2.0 µmol) was converted to the title compound (2 mg, 94%). 1H NMR (CD3OD, 2:1 mixture of amide rotamers) δ 8.71 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.06 (s, 2H), 8.04-7.97 (m, 2.5H), 7.93 (d, J = 2.0 Hz, 0.5H), 7.87 (d, J = 8.6 Hz, 1H), 7.75-7.64 (m, 3H), 7.54 (d, J = 8.1 Hz, 0.5H), 7.41 (d, J = 8.8 Hz, 0.5H), 7.22-7.18 (m, 3.5H), 7.01-6.99 (m, 1.5H), 6.73 (d, J = 7.0 Hz, 1H), 4.97 (br s, 1H), 4.69 (br s, 1H), 4.52-4.31 (m, 2H), 4.17 (br s, 1H), 3.93 (br s, 1H), 3.64-3.43 (m, 1H), 2.94-2.78 (m, 1H), 2.21-2.17 (m, 1H), 2.16 (s, 2H), 2.14 (s, 1H), 2.06-2.00 (m, 1H), 1.64-1.56 (m, 1H), 1.44-1.20 (m, 3H), 0.93-0.81 (m, 3H); MS(ESI+) m/z 804.3 (M+H)+.

Example 162
2-(4-(N-Butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)phenyl)acetic acid

Following a procedure analogous to that for the synthesis of Intermediate IF, ethyl 2-(4-(N-butyl-4-chloro-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamido)phenyl)acetate (Example 155, 1 mg, 9.9 µmol) was converted to the title compound (2 mg, 94%). 1H NMR (CD3OD, 2:1 mixture of amide rotamers) δ 8.71 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 8.06 (s, 2H), 8.04-7.97 (m, 2.5H), 7.93 (d, J = 2.0 Hz, 0.5H), 7.87 (d, J = 8.6 Hz, 1H), 7.75-7.64 (m, 3H), 7.54 (d, J = 8.1 Hz, 0.5H), 7.41 (d, J = 8.8 Hz, 0.5H), 7.22-7.18 (m, 3.5H), 7.01-6.99 (m, 1.5H), 6.73 (d, J = 7.0 Hz, 1H), 4.97 (br s, 1H), 4.69 (br s, 1H), 4.52-4.31 (m, 2H), 4.17 (br s, 1H), 3.93 (br s, 1H), 3.64-3.43 (m, 1H), 2.94-2.78 (m, 1H), 2.21-2.17 (m, 1H), 2.16 (s, 2H), 2.14 (s, 1H), 2.06-2.00 (m, 1H), 1.64-1.56 (m, 1H), 1.44-1.20 (m, 3H), 0.93-0.81 (m, 3H); MS(ESI+) m/z 804.3 (M+H)+.
compound (0.5 mg, 53%). $^1$H NMR (CD$_3$OD, 2:1 mixture of amide rotamers) $\delta$ 8.71 (s, 1H), 8.10 (d, $J = 9.2$ Hz, 1H), 8.06 (s, 2H), 8.03-7.97 (m, 2.5H), 7.94-7.91 (m, 0.5H), 7.73-7.65 (m, 2H), 7.41 (br s, 0.5H), 7.30 (br s, 0.5H), 7.23-7.10 (m, 5H), 7.03-6.96 (m, 1H), 6.90 (d, $J = 8.4$ Hz, 1H), 6.61 (br s, 1H), 4.73 (br s, 1H), 4.48-4.19 (m, 2H), 4.07 (br s, 1H), 3.91 (br s, 1H), 3.54-3.39 (m, 2H), 2.95-2.75 (m, 2H), 2.10 (s, 2H), 2.01 (s, 1H), 1.65-1.55 (m, 1H), 1.40-1.18 (m, 5H), 0.92-0.80 (m, 3H); MS(ESI$^+$) $m/z$ 818.3 (M+H)$^+$.  

**Example 163**

4-Bromo-\(\_N,\_N\_\)-dibutyl-5-methyl-\(\_1\)-\(\_H\)-pyrazole-3-carboxamide

![Chemical Structure](image)

Intermediate 163A: 4-Bromo-\(\_N,\_N\_\)-dibutyl-5-methyl- \(\_1\)-\(\_H\)-pyrazole-3-carboxamide

Following a procedure analogous to that for the synthesis of Intermediate IB, ethyl 4-bromo-5-methyl-\(\_1\)-\(\_H\)-pyrazole-3-carboxylate (Tabrizi, M.A. et al, *Bioorg. Med. Chem.*, 16:2419-2430 (2008)) (5.68 g, 24.4 mmol) was converted to the title compound (5.79 g, 75%). $^1$H NMR (CDCl$_3$) $\delta$ 3.51 (t, $J = 7.4$ Hz, 2H), 3.38-3.26 (m, 2H), 2.34 (s, 3H), 1.73-1.34 (m, 6H), 1.22-1.13 (m, 2H), 1.03-0.75 (m, 6H); MS(ESI$^+$) $m/z$ 316.2 (M+H)$^+$.  

Intermediate 163B: Ethyl 4-(4-bromo-3-(dibutylcarbamoyl)-5 -methyl- \(\_1\)-\(\_H\)-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate
Following a procedure analogous to that for the synthesis of Intermediate IE, 4-bromo-N,N-dibutyl-5-methyl-1H-pyrazole-3-carboxamide (646 mg, 2.04 mmol) and ethyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (Intermediate ID, 1.07 g, 3.27 mmol) were converted to the title compound (660 mg, 48%). \[^1\text{H}\] NMR (CDCl\textsubscript{3}, 2:1 mixture of amide rotamers) \(\delta\) 8.24-8.19 (m, 1H), 8.14-8.10 (m, 1H), 7.45-7.39 (m, 1H), 7.25-7.09 (m, 3.5H), 6.88 (d, \(J = 7.3\) Hz, 0.5H), 4.78 (d, \(J = 8.8\) Hz, 1H), 4.49-4.36 (m, 3H), 3.71-2.69 (m, 8H), 2.32 (s, 2H), 2.28 (s, 1H), 1.54-1.27 (m, 8.5H), 1.11 (d, \(J = 7.7\) Hz, 2H), 0.92 (q, \(J = 7.2\) Hz, 3.5H), 0.79 (t, \(J = 8.0\) Hz, 3H); MS(ESI\textsuperscript{+}) \(m/z\) 625.3 (M+H\textsuperscript{+}).

Example 163:

To a solution of ethyl 4-(4-bromo-3-(dibutylcarbamoyl)-5 -methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (89 mg, 0.14 mmol) in THF (1.4 mL) was added IN aq. NaOH solution (2.1 mL, 2.14 mmol). The resulting reaction mixture was stirred at room temperature for 2 h, then neutralized with IN aq. HCl solution (pH = 6) and extracted with EtOAc (3 x). The combined organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated \textit{in vacuo} to provide a clear, colorless oil which was used in the subsequent step without purification.

Following a procedure analogous to that for the synthesis of Example 1, the crude oil from above was converted to the title compound (70 mg, 61%). \[^1\text{H}\] NMR (DMSO-d\textsubscript{6}, 2:1 mixture of amide rotamers) \(\delta\) 8.73 (s, 1H), 8.27 (d, \(J = 7.9\) Hz, 1H), 8.18 (d, \(J = 8.8\) Hz, 1H), 8.12- 8.03 (m, 3H), 8.02-7.96 (m, 1H), 7.82-7.67 (m, 3H), 7.25-7.05 (m, 3.5H), 6.98 (d, \(J = 7.7\) Hz, 0.5H), 4.80-3.32 (m, 7H), 3.18-2.57 (m, 3H), 2.23 (s, 2H), 2.19 (s, 1H), 1.42-0.79 (m, 11H), 0.72-0.64 (m, 2H), 0.63-0.58 (m, 1H); MS(ESI\textsuperscript{+}) \(m/z\) 803.4 (M+H\textsuperscript{+}).

Example 164
Following a procedure analogous to that for the synthesis of Intermediate IE, 4-bromo-\(N,N\)-dibutyl-5-methyl-1 \(H\)-pyrazole-3-carboxamide (Intermediate 163A, 268 mg, 0.85 mmol) and benzyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (Intermediate 122B, 300 mg, 0.77 mmol) were converted to the title compound (215 mg, 41%). ¾ NMR (DMSO-\(d_6\), 2:1 mixture of amide rotamers) \(\delta\) 8.21 (dd, \(J = 8.3, 1.9\) Hz, 1H), 8.11 (d, \(J = 2.0\) Hz, 0.5H), 8.08-8.03 (m, 0.5H), 7.85 - 7.78 (m, 1H), 7.55-7.33 (m, 5.5H), 7.25-7.06 (m, 3H), 7.05-6.96 (m, 0.5H), 5.47-5.32 (m, 2H), 4.82-4.42 (m, 2H), 3.92-3.71 (m, 0.5H), 3.58-3.34 (m, 3H), 3.23-2.91 (m, 2.5H), 2.82-2.74 (m, 2H), 2.27 (s, 2H), 2.22 (s, 1H), 1.59-1.13 (m, 4H), 1.07-0.80 (m, 7H), 0.72-0.59 (m, 3H); MS(ESI\(^+\)) \(m/z\) 687.5 (M+H\(^+\)).
To benzyl 4-(4-bromo-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (55 mg, 0.080 mmol) in THF (1.0 mL) was added 1N aq. NaOH solution (802 µL, 0.80 mmol). The resulting biphasic mixture was stirred vigorously at room temperature for 2.5 h, then acidified with 1N aq. HCl solution (pH = 3) and extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound (46 mg, 96%) as a clear, colorless oil. MS(ESI⁺) m/z 597.3 (M+H)⁺.

Example 164:

To a solution of 4-(4-bromo-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (26 mg, 0.043 mmol) in THF (1.0 mL) at -78 °C was added t-BuLi (25 µL, 0.043 mmol, 1.7M in pentane) dropwise via gas-tight syringe. The resulting solution was stirred at -78 °C for 5 min. Additional t-BuLi (50 µL, 0.086 mmol, 1.7M in pentane) was added dropwise and the clear, yellow solution was stirred for 15 min. Additional t-BuLi (25 µL, 0.043 mmol, 1.7M in pentane) was then added until the dark green color persisted. The reaction mixture was stirred at -78 °C for 30 min and then at room temperature for 1 h. After quenching slowly with water, the reaction mixture was extracted with EtOAc (3 x). The combined organics were dried over Na₂SO₄, filtered and concentrated in vacuo to give a crude oil that was used in the subsequent step without purification.

Following a procedure analogous to that for the synthesis of Example 1, the crude oil from above was converted to the title compound (9 mg, 26%). ¹H NMR (CD₃OD, 1:5:1 mixture of amide rotamers) δ 8.74 (s, 0.5H), 8.17-7.94 (m, 7.5H), 7.76-7.62 (m, 3H), 7.29-7.04 (m, 3.5H), 6.90 (d, J = 7.7 Hz, 0.5H), 6.42 (dd, J = 4.8, 0.9 Hz, 0.5H), 4.80-4.59 (m, 1.5H), 4.57-4.33 (m, 1H), 4.08 (d, J = 12.1 Hz, 0.5H), 3.70-2.66 (m, 7.5H), 2.35 (d, J = 0.7 Hz, 1.5H), 2.29 (d, J = 0.7 Hz, 1.5H), 1.64-0.85 (m, 10H), 0.80-0.73 (m, 2.5H), 0.71-0.65 (m, 1.5H); MS(ESI⁺) m/z 706.4 (M+H)⁺.
Example 165

\[ \text{N,N-Dibutyl-4-(hydroxymethyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-H-pyrazole-3-carboxamide} \]

![Chemical Structure](image)

(165)

[00435] To 4-(4-bromo-3-(dibutylcarbamoyl)-5-methyl-1-H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate 164B, 52 mg, 0.087 mmol) in THF (1.0 mL) was added NaH (6 mg, 0.26 mmol, 60% suspension in mineral oil) at 0 °C. The suspension was stirred for 15 min at 0 °C and then cooled to -78 °C. w-BuLi (100 μL, 0.25 mmol, 2.5M solution in hexane) was added dropwise via syringe until the dark green color persisted. The reaction mixture was stirred at -78 °C for 15 min and then DMF (68 μL, 0.87 mmol) was added via syringe. The resulting mixture was stirred at -78 °C for 30 min, then quenched with water, warmed to room temperature and transferred to a sep funnel containing sat. aq. NH₄Cl solution and IN aq. HCl solution (1:1). The aqueous layer was extracted with EtOAc (3 x) and the combined organics were dried over Na₂SO₄. Concentration in vacuo provided a crude oil which was used in the next step without purification.

[00436] The crude oil from above was subjected to a procedure analogous to that for the synthesis of Example 1. The resulting crude product was dissolved in THF (880 μL) and MeOH (175 μL). NaBH₄ (7 mg, 0.18 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then quenched with sat. aq. NH₄Cl solution, washed with IN aq. HCl solution and extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (6 mg, 10%) as a white solid after lyophilization. \(^1\)H NMR (CD₃OD, 1.5:1 mixture of amide rotamers) δ 8.57 (s, 1H), 8.22 (td, J = 8.3, 1.9 Hz, 1H), 8.14 (t, J = 1.9 Hz, 1H), 8.05-7.98 (m, 2H), 7.97-7.89 (m, 2H), 7.63-7.54 (m, 2H), 7.48 (dd, J = 8.3, 4.1 Hz, 1H), 7.24-7.06 (m, 3.5H), 6.93 (d, J = 7.3 Hz, 0.5H), 4.84-4.41 (m, 2.5H), 4.09 (br s, 0.5H), 3.70-2.69
Example 166

3-(3-(Dibutylcarbamoyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazol-4-yl)propanoic acid

Intermediate 166A: (±)-Benzyl 4-(4-(3-tert-butoxy-3-oxoprop-1-enyl)-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-y1)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

[00437] To a solution of benzyl 4-(4-bromo-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (Intermediate 164A, 80 mg, 0.12 mmol) in DMF (580 µL) and Et₃N (580 µL) was added (PPh₃)₂PdCl₂ (8 mg, 0.012 mmol) followed by tert-butyl acrylate (58 µL, 0.40 mmol). The reaction mixture was purged with N₂ for 5 min and then heated at 140 °C overnight. The reaction mixture was poured into a separatory funnel containing 1 N aq. HCl solution and EtOAc. The organic layer was washed 1 N aq. HCl solution (2 x) and the aqueous layer was extracted with EtOAc (3 x). The combined organic extracts were washed with sat. aq. NaHCO₃ solution, dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography (gradient from 0% to 35% EtOAc/hexanes) to provide the title compound (42 mg, 50%) as a colorless oil. MS(ESI⁺) m/z 733.5 (M+H)⁺.
Intermediate 166B: (£)-4-(4-(3-tert-Butoxy-3-oxoprop-1-enyl)-3-(dibutylcarbamoyl)-5-
-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

[00438] Following a procedure analogous to that for the synthesis of Intermediate 9 ID, (is)-benzyl 4-(4-(3-tert-butoxy-3-oxoprop-1-enyl)-3-(dibutylcarbamoyl)-5-methyl-1H-
-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (71 mg, 0.096 mmol) was converted to the title compound (59 mg, 94%). MS(ESI^+) m/z 643.4 (M+H)^+.

Intermediate 166C: (E)-tert-Butyl 3-(3-(dibutylcarbamoyl)-5-methyl-1-(4-(naphthalen-2-
ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazol-
-4-yl)acrylate

[00439] Following a procedure analogous to that for the synthesis of Example 1, (E)-
-benzyl 4-(4-(3-tert-butoxy-3-oxoprop-1-enyl)-3-(dibutylcarbamoyl)-5-methyl-1H-
-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (84 mg, 0.13 mmol) was converted to the title compound (49 mg, 45%). MS(ESI^+) m/z 832.5 (M+H)^+.

Example 166:

[00440] To a solution of (E)-tert-butyl 3-(3-(dibutylcarbamoyl)-5-methyl-1-(4-(naphthalen-2-
ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazol-4-yl)acrylate (49 mg, 0.059 mmol) in CH2Cl2 (1.2 mL) was added TFA (340 µL, 4.39 mmol). The resulting reaction mixture was stirred at room temperature for 3.5 h and then concentrated in vacuo to provide a crude oil which was used in the subsequent step without purification.
Following a procedure analogous to that for the synthesis of Intermediate Example 9 ID, the crude oil from above was converted to the title compound (7 mg, 18%) after purification by preparative HPLC. \(^1\)H NMR (CDCl\(_3\), 1.5:1 mixture of amide rotamers) \(\delta\) 8.77 (d, \(J = 5.5\) Hz, 1H), 8.11-8.02 (m, 2H), 8.02-7.87 (m, 4.5H), 7.71-7.60 (m, 1.5H), 7.44-7.35 (m, 1H), 7.24-7.06 (m, 3.5H), 6.79 (d, \(J = 7.2\) Hz, 0.5H), 4.91-4.59 (m, 1.5H), 4.31-4.07 (m, 1H), 3.90-3.65 (m, 1H), 3.56-2.58 (m, 10.5H), 2.20 (s, 1.5H), 2.15 (s, 1.5H), 1.59-1.01 (m, 7H), 0.98-0.81 (m, 4H), 0.80-0.69 (m, 3H); MS(ESI\(^+\)) m/z 778.4 (M+H\(^+\)).

Example 167

\(\text{N,N-Dibutyl-4-(3-(dimethylamino)propyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide}\)

![Chemical structure of Example 167](image)

Intermediate 167A: \(\text{N,N-Dibutyl-4-(3-hydroxypropyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide}\)

![Chemical structure of Intermediate 167A](image)

To a solution of \((E)-\text{tert-butyacrylate}\) 3-(3-dibutylcarbamoyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazol-4-yl)acrylate (Intermediate 166C, 49 mg, 0.059 mmol) in CH\(_2\)Cl\(_2\) (1.2 mL) was added TFA (340 µL, 4.39 mmol). The resulting reaction mixture was
stirred at room temperature for 3.5 h and then concentrated in vacuo to provide a crude oil which was used in the subsequent step without purification.

The crude oil from above was dissolved in THF (2.3 mL) and CDI (15 mg, 0.094 mmol) was added. The resulting reaction mixture was stirred at room temperature for 2 h. Water (570 μL) was added followed by NaBH₄ (12 mg, 0.31 mmol), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched carefully with IN aq. HCl solution (570 μL, 0.57 mmol) (exothermic) and extracted with EtOAc (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to give a crude oil which was subjected to a procedure analogous to that for the synthesis of Intermediate 91D to give the title compound (35 mg, 72%). MS(ESI⁺) m/z 764.5 (M+H)⁺.

Example 167:

To N,N-dibutyl-4-(3-hydroxypropyl)-5-methyl-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (35 mg, 0.045 mmol) in CH₂Cl₂ (1.0 mL) was added Et₃N (25 μL, 0.18 mmol) followed by MsCl (5 μL, 0.068 mmol). The resulting reaction mixture was stirred at room temperature for 1 h, then quenched with sat. aq. NH₄Cl and extracted with CH₂Cl₂ (3 x). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo to give a pale yellow oil which was used in the subsequent step without purification.

The crude oil from above was dissolved in MeCN (1.0 mL) and Me₂NH (91 μL, 0.18 mmol, 2M solution in THF) was added. The resulting reaction mixture was stirred overnight at room temperature. i-Pr₂EtN (16 μL, 0.091 mmol) was then added, and the reaction mixture was stirred at 80 °C for 4 h and then at 80 °C for 3.5 h.

Additional Me₂NH (91 μL, 0.18 mmol, 2M solution in THF) was added, and the reaction mixture was stirred at 80 °C for 2 h. The reaction mixture was then concentrated in vacuo and purified by preparative HPLC to give the title compound (4 mg, 10%) as a yellow solid after lyophilization. ¹H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 8.74 (br s, 1H), 8.17-7.97 (m, 6.5H), 7.79-7.61 (m, 2.5H), 7.31-7.07 (m, 3.5H), 6.94 (d, J = 6.8 Hz, 0.5H), 4.74-4.44 (m, 1.5H), 4.29-3.39 (m, 6H), 3.22-2.36 (m, 10.5H), 2.29 (s,
1.5H), 2.26 (s, 1.5H), 2.03 (br s, 2H), 1.59-1.16 (m, 6H), 1.13-0.80 (m, 7H), 0.77-0.70 (m, 1.5H), 0.63-0.57 (m, 1.5H); MS(ESI+) m/z 791.6 (M+H)+.

Example 168

5 N,N-Dibutyl-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxamide

![Chemical Structure](168)

Intermediate 168A: N,N-Dibutyl-l H-pyrazole-3-carboxamide

[00446] To 1H-pyrazole-3-carboxylic acid (Matrix, 350 mg, 3.12 mmol) in DMF (8.7 mL) were added EDC (658 mg, 3.43 mmol), HOBT (622 mg, 4.06 mmol), j-Pr2EtN (1.6 mL, 9.37 mmol) and w-butylamine (550 µL, 3.28 mmol). The resulting solution was stirred at room temperature overnight. The reaction mixture was then quenched with sat. aq. NH4Cl solution, washed with IN aq. HC1 solution and extracted with EtOAc (3 x). The combined organic extracts were dried over Na2SO4, filtered and concentrated in vacuo. The crude oil was purified using flash column chromatography (gradient from 0% to 5% (MeOH/CH2Cl2) to give the title compound (530 mg, 76%) as a colorless crystalline solid. 1H NMR (CD3OD, 1:5:1 mixture of amide rotamers) δ 7.74 (br s, 1H), 6.67 (br s, 1H), 6.38 (br s, 1H), 3.70-3.39 (m, 4H), 1.64 (quin, J = 7.6 Hz, 4H), 1.36 (dt, J = 14.4, 7.0 Hz, 4H), 1.04-0.88 (m, 6H); MS(ESI+) m/z 224.3 (M+H)+.

Example 168:

[00447] Following a procedure analogous to that for the synthesis of Intermediate IE, N,N-dibutyl-l H-pyrazole-3-carboxamide (150 mg, 0.67 mmol) and ethyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (Intermediate ID, 242 mg, 0.74 mmol) provided a crude oil which was used in the subsequent step without purification.
Following a procedure analogous to that for the synthesis of Intermediate 163C, the crude oil from above was converted to the title compound (212 mg, 48%). $^1$H NMR (CDCl$_3$, mixture of amide rotamers) δ 8.76 (s, 1H), 8.13-7.82 (m, 7H), 7.72-7.57 (m, 3H), 7.24-6.98 (m, 3.5H), 6.82-6.66 (m, 1.5H), 4.97-4.66 (m, 1H), 4.17 (d, $J$ = 16.1 Hz, 0.5H), 4.05-3.65 (m, 2H), 3.61-3.19 (m, 4H), 3.14-3.08 (m, 0.5H), 2.94-2.78 (m, 1H), 2.72-2.59 (m, 0.5H), 2.54-2.37 (m, 0.5H), 1.67-1.08 (m, 7.5H), 0.93 (td, $J$ = 18.0, 7.3 Hz, 3.5H), 0.80 (t, $J$ = 7.3 Hz, 3H); MS(ESI $^+$) m/z 692 (M+H)$^+$.  

Example 169

$N,N$-Dibutyl-4-chloro-l-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l $H$-pyrazole-3-carboxamide

Intermediate 169A: $N,N$-Dibutyl-4-chloro-lH-pyrazole-3-carboxamide

Intermediate 169B: Ethyl 4-(4-chloro-3-(dibutylcarbamoyl)-lH-pyrazol-l-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate
Following a procedure analogous to that for the synthesis of Intermediate IE, N,N-dibutyl-4-chloro-1H-pyrazole-3-carboxamide (100 mg, 0.39 mmol) and ethyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (Intermediate ID, 140 mg, 0.43 mmol) were converted to the title compound (156 mg, 71%). $^1$H NMR (CDCl$_3$, mixture of amide rotamers) $\delta$ 8.23-8.16 (m, 1H), 8.12-8.06 (m, 1H), 7.98-7.85 (m, 1H), 7.71-7.58 (m, 1H), 7.26-7.04 (m, 3.5H), 6.78 (d, $J = 7.5$ Hz, 0.5H), 4.99-4.70 (m, 1H), 4.45-4.24 (m, 2.5H), 4.17-4.01 (m, 1H), 3.79-3.73 (m, 0.5H), 3.57-3.15 (m, 5H), 3.11-2.87 (m, 1H), 2.74 (t, $J = 5.8$ Hz, 1H), 1.67-1.06 (m, 10.5H), 0.86-0.73 (m, 3H); MS(ESI$^+$) m/z 565.3 (M+H$^+$).

Intermediate 169C: 4-(4-Chloro-3-(dibutylcarbamoyl)-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate IF, ethyl 4-(4-chloro-3-(dibutylcarbamoyl)-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (155 mg, 0.27 mmol) was converted to the title compound (138 mg, 94%). MS(ESI$^+$) m/z 537.3 (M+H$^+$).

Example 169:

Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dibutylcarbamoyl)-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (39 mg, 0.072 mmol) was converted to the title compound (29 mg, 54%). $^1$H NMR (DMSO-d$_6$, 2:1 mixture of amide rotamers) $\delta$ 8.79-8.58 (m, 2H), 8.29-
7.92 (m, 6H), 7.88-7.63 (m, 3H), 7.28-7.03 (m, 3.5H), 6.97 (d, J = 7.8 Hz, 0.5H), 4.79-4.61 (m, 1.5H), 4.51 (d, J = 15.8 Hz, 0.5H), 4.26 (d, J = 16.1 Hz, 0.5H), 3.89-3.84 (m, 0.5H), 3.67-3.61 (m, 0.5H), 3.21-2.60 (m, 6.5H), 1.51-1.36 (m, 0.5H), 1.30-0.89 (m, 7.5), 0.86 (t, J = 7.4 Hz, 1H), 0.79 (t, J = 7.2 Hz, 2H), 0.68 (t, J = 7.4 Hz, 2H), 0.60 (t, J = 7.4 Hz, 1H); MS(ESI\(^+\)) \textit{m/z} 726.3 (M+H\(^+\)).

Example 170

\[ \text{N,N-Dibutyl-4-chloro-5-(2-hydroxyethyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide} \]

\[
\text{(170)}
\]

Intermediate 170A: Ethyl 5-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)-1H-pyrazole-3-carboxylate

\[
\text{(Int-170A)}
\]

[00453] CuCN (1.74 g, 19.4 mmol) and LiCl (4.95 g, 117.0 mmol) were dried under high vacuum with stirring at 160 °C overnight and then cooled to room temperature. To a solution of 2-(3-butynyloxy)tetrahydro-2H-pyran (3.1 mL, 19.5 mmol) in THF at -78 °C (40.0 mL) was added \(\text{w-BuLi} \) (12.2 mL, 19.4 mmol, 1.6M solution in hexane). The resulting solution was stirred at -78 °C for 1h and then transferred to a -78 °C suspension of CuCN\(\text{6LiCl} \) (6.70 g, 19.5 mmol, from above) in THF (60.0 mL). The resulting reaction mixture was warmed to -17 °C (dry ice/brine) and stirred for 1.5 h. A solution of ethyl diazoacetate (2.0 mL, 19.4 mmol) in THF (40.0 mL) was then added, and the reaction mixture was stirred at -17 °C for 30 min. The ice bath was removed and stirring was continued at room temperature for 4 h. The reaction mixture was quenched with sat. aq. \(\text{NH}_4\text{Cl} \) solution and extracted with Et\(\text{O} \) (3 x). The combined organic extracts were washed with sat. aq. NaCl solution and then dried over MgSO\(_4\), filtered and concentrated.
in vacuo. The crude oil was purified using flash column chromatography to give the title compound (2.76 g, 53%). ¾ NMR (DMSO-d$_6$) $\delta$ 6.55 (br s, 1H), 4.64-4.53 (m, 1H), 4.24 (q, $J = 7.0$ Hz, 2H), 4.34-3.44 (m, 1H), 3.83 (m, 2H), 3.72-3.53 (m, 1H), 1.76-1.52 (m, 2H), 1.51-1.35 (m, 4H), 1.27 (t, $J = 7.0$ Hz, 3H); MS(ESI $^+$) $m/z$ 269.2 (M+H)$^+$.  

Intermediate 170B: N,N-Dibutyl-5-(2-(tetrahydro-2 H-pyran-2-yloxy)ethyl)-1 H-pyrazole-3-carboxamide

[00454] Following a procedure analogous to that for the synthesis of Intermediate IB, ethyl 5-(2-(tetrahydro-2 H-pyran-2-yloxy)ethyl)-1 H-pyrazole-3-carboxylate (2.15 g, 8.01 mmol) was converted to the title compound (2.35 g, 83%). MS(ESI $^+$) $m/z$ 352.4 (M+H)$^+$.  

Intermediate 170C: N,N-Dibutyl-4-chloro-5-(2-(tetrahydro-2 H-pyran-2-yloxy)ethyl)-1 H-pyrazole-3-carboxamide

[00455] Following a procedure analogous to that for the synthesis of Intermediate 1A, N,N-dibutyl-5-(2-(tetrahydro-2 H-pyran-2-yloxy)ethyl)-1 H-pyrazole-3-carboxamide (355 mg, 1.01 mmol) was converted to the title compound (327 mg, 79%). $^1$H NMR (CD$_3$OD) $\delta$ 4.60 (t, $J = 3.4$ Hz, 1H), 3.94 (td, $J = 9.7$, 6.5 Hz, 1H), 3.79-3.61 (m, 2H), 3.59-3.41 (m, 3H), 3.39-3.25 (m, 2H), 3.04-2.91 (m, 2H), 1.87-1.34 (m, 12H), 1.27-1.09 (m, 2H), 0.99 (t, $J = 7.3$ Hz, 3H), 0.81 (t, $J = 7.4$ Hz, 3H); MS(ESI $^+$) $m/z$ 386.3 (M+H)$^+$.  

Intermediate 170D: Ethyl 4-(4-chloro-3-(dibutylcarbamoyl)-5-(2-(tetrahydro-2 H-pyran-2-yloxy)ethyl)-1 H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate
Following a procedure analogous to that for the synthesis of Intermediate IE, N,N'-dibutyl-4-chloro-5-(2-(tetrahydro-2'H-pyran-2-yloxy)ethyl)-1'H-pyrazole-3-carboxamide (407 mg, 1.06 mmol) and ethyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (380 mg, 1.16 mmol) were converted to the title compound (219 mg, 30%). ¾ NMR (CD$_3$OD, mixture of amide rotamers) δ 8.26 (td, $J = 8.4, 1.8$ Hz, 1H), 8.19-8.10 (m, 1H), 7.98 (d, $J = 8.1$ Hz, 1H), 7.29-7.07 (m, 3.5H), 6.94 (d, $J = 7.5$ Hz, 0.5H), 4.71-4.48 (m, 2H), 4.47-4.39 (m, 2H), 4.16-3.86 (m, 1H), 3.80-3.37 (m, 5H), 3.26-2.58 (m, 5H), 1.87-0.74 (m, 22H), 0.72-0.66 (m, 1H); MS(ESI$^+$) m/z 609.3 (M+H-THP)$^+$. 

Intermediate 170E: N,N'-Dibutyl-4-chloro-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-(2-(tetrahydro-2'H-pyran-2-yloxy)ethyl)-1'H-pyrazole-3-carboxamide

Following a procedure analogous to that for the synthesis of Intermediate 163C, ethyl 4-(4-chloro-3-(dibutylcarbamoyl)-5-(2-(tetrahydro-2'H-pyran-2-yloxy)ethyl)-1'H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (141 mg, 0.20 mmol) was converted to the title compound (104 mg, 60%); MS(ESI$^+$) m/z 770.3 (M+H-THP)$^+$. 

Example 170:

To a solution of N,N'-dibutyl-4-chloro-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-(2-
(tetrahydro-2\textsubscript{H}-pyran-2-yloxy)ethyl)-1 \textsubscript{H}-pyrazole-3-carboxamide (510 mg, 0.60 mmol) in MeOH (6.0 mL) was added cone. HCl (75 µL, 0.90 mmol). The resulting reaction mixture was stirred at room temperature for 45 min and then concentrated \textit{in vacuo}. The residue was purified by flash column chromatography (gradient from 0% to 5% MeOH/CH\textsubscript{2}Cl\textsubscript{2}) to give the title compound (422 mg, 84%) as an off-white solid. \textsuperscript{1}H NMR (CD\textsubscript{3}OD, 2:1 mixture of amide rotamers) δ 8.74 (s, 1H), 8.14-8.04 (m, 4H), 8.03-7.96 (m, 2H), 7.87-7.80 (m, 1H), 7.75-7.65 (m, 2H), 7.25-7.06 (m, 3.5H), 6.92 (d, \textit{J} = 7.5 Hz, 0.5H), 5.00-4.92 (m, 1H), 4.65-4.44 (m, 1H), 4.12-3.95 (m, 0.5H), 3.85-2.69 (m, 1H), 2.54 (br s, 0.5H), 1.52-0.85 (m, 11H), 0.77 (t, \textit{J} = 7.4 Hz, 2H), 0.67 (t, \textit{J} = 7.4 Hz, 1H); MS(ESI\textsuperscript{+}) \textit{m/z} 770.4 (M+H).
7.25-7.06 (m, 3.5H), 6.94 (d, J = 7.0 Hz, 0.5H), 4.77-4.41 (m, 1.5H), 4.09 (br s, 0.5H), 3.79-3.38 (m, 5H), 3.24-2.67 (m, 5H), 1.60-0.84 (m, 1H), 0.78 (t, J = 7.3 Hz, 2H), 0.71-0.65 (m, 1H); MS(ESI+) m/z 784.3 (M+H)+.

Example 172

*N,N*-Dibutyl-4-chloro-5-(2-(cyclopropanesulfonamido)-2-oxoethyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1*H*-pyrazole-3-carboxamide

![Chemical Structure](image)

(172)

To a solution of 2-(4-chloro-3-(dibutylcarbamoyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1*H*-pyrazol-5-yl)acetic acid (Example 171, 24 mg, 0.031 mmol) in THF (625 µL) was added CDI (16 mg, 0.10 mmol). The resulting solution was heated at reflux for 30 min and then cooled to room temperature. Cyclopropanesulfonamide (14 mg, 0.12 mmol) was then added followed by DBU (24 µL, 0.16 mmol), and the resulting reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with EtOAc, washed with IN aq. HCl solution (2 x) and extracted with EtOAc (3 x). The combined organic extracts were washed with sat. aq. NaCl solution, dried over Na2SO4 and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (5 mg, 16%) as a white solid after lyophilization. 1H NMR (CD3OD, 2:1 mixture of amide rotamers) δ 8.74 (s, 1H), 8.16-7.96 (m, 6H), 7.81-7.64 (m, 3H), 7.28-7.05 (m, 3.5H), 6.91 (d, J = 7.5 Hz, 0.5H), 4.71-4.33 (m, 1.5H), 4.12-2.55 (m, 11.5H), 1.53-0.84 (m, 15H), 0.76 (t, J = 7.4 Hz, 2H), 0.67 (t, J = 7.4 Hz, 1H); MS(ESI+) m/z 887.5 (M+H)+.

Example 173

2-(4-Chloro-3-(dibutylcarbamoyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1*H*-pyrazol-5-yl)ethyl carbamate

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To a 0°C solution of N,N-dibutyl-4-chloro-5-(2-hydroxyethyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (Example 170, 20 mg, 0.026 mmol) in CH2Cl2 (0.5 mL) was added trichloroacetyl isocyanate (4 µL, 0.031 mmol). After stirring at 0°C for 30 min, K2C03 (2 mg, 0.014 mmol) and MeOH (0.5 mL) were added. The ice bath was removed, and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then diluted with water and EtOAc. The aqueous layer was extracted with EtOAc (2 x), and the combined organic extracts were washed with sat. aq. NaCl solution, dried over Na2SO4, filtered and concentrated in vacuo to afford a colorless oil. The oil was dissolved in MeOH (3.0 mL) and water (3.0 mL) and K2CO3 (120 mg, 0.84 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes and then partitioned between EtOAc and H2O. The layers were separated, and the aqueous layer was extracted with EtOAc (2 x). The combined organic extracts were washed with sat. aq. NaCl solution, dried over Na2SO4, filtered and concentrated in vacuo to afford the title compound (10 mg, 44%) as a white solid. 1H NMR (CD3OD, 1.5:1 mixture of amide rotamers) δ 8.73 (br s, 1H), 8.13-8.04 (m, 4.5H), 7.02-7.95 (m, 2H), 7.23-7.08 (m, 4H), 7.02-6.88 (m, 0.5H), 4.94-4.89 (m, 1H), 4.67-4.41 (m, 1H), 4.25 (t, J = 6.5 Hz, 2H), 4.18-4.05 (m, 1.5H), 4.01-3.71 (m, 1.5H), 3.65-3.46 (m, 4H), 3.37-3.34 (m, 2H), 3.02 (t, J = 6.5 Hz, 2H), 2.92-2.77 (m, 1.5H), 1.68-1.53 (m, 2H), 1.31-1.25 (m, 3H), 1.20-1.17 (m, 1H), 0.99 (t, J = 7.4 Hz, 2H), 0.94-0.86 (m, 3H), 0.78-0.73 (m, 2H), 0.68 (t, J = 6.4 Hz, 1H); MS(ESI+) m/z 813.5 (M+H)+.

Example 174

2-(4-Chloro-3-(dibutylcarbamoyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1H-pyrazol-5-yl)ethyl 4-methylpiperazine-1-carboxylate
To a solution of N,N-dibutyl-4-chloro-5-(2-hydroxyethyl)-1-(4-(naphthalen-2-
ysulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-
3-carboxamide (Example 170, 110 mg, 0.14 mmol) in CHCl₃ (3.0 mL) was added Et₃N
(22 µL, 0.16 mmol) followed by 4-nitrophenyl carbonochloridate (Aldrich, 32 mg,
0.16 mmol). After stirring at room temperature overnight, additional Et₃N (22 µL, 0.16
mmol) was added. The reaction mixture was heated at reflux for 3 h and then at room
temperature for 2 h. DMAP (20 mg, 0.16 mmol) was then added, and the reaction
mixture was stirred at room temperature for 1 h. The reaction mixture was then diluted
with CHCl₃ and sat. aq. NaCl solution. The aqueous layer was extracted with CHCl₃, and
the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo
to give a crude oil which was used in the subsequent step without purification.

To a sealed tube containing the crude oil from above (44 mg, 0.047 mmol) in
CH₂Cl₂ (1.5 mL) and THF (1.5 mL) was added 1-methylpiperazine (6 µL, 0.052 mmol)
followed by Et₃N (10 µL, 0.072 mmol). The sides of the tube were rinsed with 1:1
CH₂Cl₂/THF (1.0 mL) and the tube was sealed. The reaction mixture was stirred at room
temperature for 3.5 h, then concentrated in vacuo and purified by preparative HPLC to
give the title compound (9 mg, 21%). ¹H NMR (1:1 CD₃OD:CDCl₃, 1.5:1 mixture of
amide rotamers) δ 8.59 (br s, 1H), 8.22-8.17 (m, 1H), 8.09-8.06 (m, 1H), 8.06-8.02 (m,
1H), 7.97 (d, J = 7.8 Hz, 1H), 7.95-7.90 (m, 1.5H), 7.87 (d, J = 7.5 Hz, 1H), 7.59-7.57
(m, 1H), 7.55-7.52 (m, 0.5H), 7.48 (dd, J = 6.7, 8.3 Hz, 1H), 7.20-7.04 (m, 4.5H), 6.87
(d, J = 7.5 Hz, 0.5H), 4.69-4.64 (m, 2H), 4.49 (s, 1H), 4.15-4.08 (m, 1H), 3.74-3.71 (m,
0.5H), 3.54-3.41 (m, 4H), 3.20-3.16 (m, 2H), 3.03-2.97 (m, 4.5H), 2.86-2.85 (m, 0.5H),
2.82-2.78 (m, 4.5H), 2.63 (s, 2H), 1.46-1.36 (m, 2.5H), 1.32-1.23 (m, 4H), 1.11-1.03 (m,
2H), 0.97-0.81 (m, 5H), 0.73 (t, J = 7.4 Hz, 2H), 0.62 (t, J = 7.4 Hz, 1.5H); MS(ESI⁺) m/z
896.4 (M+H).
2-(4-Chloro-3-(dibutylcarbamoyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazol-5-yl)ethyl 2-(4-methylpiperazin-1-yl)ethylcarbamate

Following a procedure analogous to that for the synthesis of Example 174, N,N-dibutyl-4-chloro-5-(2-hydroxyethyl)-1-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide (Example 170, 110 mg, 0.14 mmol) and 2-(4-methylpiperazin-1-yl)ethanamine (7 mg, 0.052 mmol) were converted to the title compound (8 mg, 16%). ^1H NMR (1:1 CD$_3$OD:CDC$_1_3$, mixture of amide rotamers) δ 8.55 (s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.13-8.10 (m, 1H), 8.04-8.00 (m, 1H), 7.97-7.94 (m, 1.5H), 7.91 (d, J = 8.6 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.60-7.57 (m, 0.5H), 7.55-7.52 (m, 1H), 7.42-7.37 (m, 1H), 7.22-7.05 (m, 4.5H), 6.87 (d, J = 7.5 Hz, 0.5H), 4.77-4.70 (m, 2H), 4.52-4.42 (m, 2H), 4.01-3.80 (m, 1H), 3.74-3.62 (m, 1H), 3.41-3.36 (m, 8H), 3.24-3.02 (m, 8H), 3.00-2.96 (m, 1.5H), 2.89-2.84 (m, 4.5H), 2.82-2.76 (m, 2H), 2.64-2.63 (m, 2H), 2.30 (br s, 2H), 1.46-1.02 (m, 9.5H), 0.95 (t, J = 7.4 Hz, 1H), 0.90-0.81 (m, 3.5H), 0.72 (t, J = 7.2 Hz, 2H), 0.62 (t, J = 7.4 Hz, 1H); MS(ESI +) m/z 939.5 (M+H).

Example 176
tert-Butyl 3-(N-butyl-4-chloro-1-(4-(7-iodonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamido)propanoate

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Intermediate 176A: Ethyl 4-chloro-1-(4-(7-iodonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxylate

\[
\begin{align*}
\text{Cl} & \hspace{1cm} \text{Me} \\
\text{OAc} & \hspace{1cm} \text{N} \\
\text{O} & \hspace{1cm} \text{Cl} \\
\text{OEt} & \hspace{1cm} \text{H} \\
\text{N} & \hspace{1cm} \text{SO}_2 \\
\text{I} & \hspace{1cm} \text{I}
\end{align*}
\]

(Int-176A)

[00465] Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(ethoxycarbonyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate 122D, 60 mg, 0.13 mmol) and 7-iodonaphthalene-2-sulfonamide (Intermediate 11, 43 mg, 0.13 mmol) were converted to the title compound (27 mg, 25%) after purification by preparative HPLC. \(^1\)H NMR (CD\(_3\)OD, 2:1 mixture of amide rotamers) \(\delta\) 8.62 (s, 1H), 8.53 (s, 1H), 8.15-7.99 (m, 4H), 7.98-7.91 (m, 1H), 7.79-7.63 (m, 2H), 7.23-7.05 (m, 3.5H), 6.97 (s, 0.5H), 6.89 (d, \(J = 7.3\) Hz, 1H), 4.75-4.53 (m, 1H), 4.47 (s, 1H), 4.43 (q, \(J = 7.0\) Hz, 1H), 4.17-4.05 (m, 1H), 3.83-3.45 (m, 2H), 3.19-2.73 (m, 2H), 2.32 (s, 2H), 2.24 (s, 1H), 1.18 (t, \(J = 7.0\) Hz, 1H), 1.10 (t, \(J = 7.2\) Hz, 2H); MS(ESI\(^+\)) \(m/z\) 783.0 (M+H\(^+\)).

Intermediate 176B: 4-Chloro-1-(4-(7-iodonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxylic acid

\[
\begin{align*}
\text{Cl} & \hspace{1cm} \text{Me} \\
\text{OAc} & \hspace{1cm} \text{N} \\
\text{O} & \hspace{1cm} \text{Cl} \\
\text{OH} & \hspace{1cm} \text{I} \\
\text{N} & \hspace{1cm} \text{SO}_2 \\
\text{I} & \hspace{1cm} \text{I}
\end{align*}
\]

(Int-176B)

[00466] Following a procedure analogous to that for the synthesis of Example 45, ethyl 4-chloro-1-(4-(7-iodonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxylate (26 mg, 0.033 mmol) was converted to the title compound (25 mg, 95%). MS(ESI\(^+\)) \(m/z\) 755.0 (M+H\(^+\)).
Example 176:

Following a procedure analogous to that for the synthesis of Example 122, 4-chloro-1-(4-(7-iodonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-7 H-pyrazole-3-carboxylic acid (25 mg, 0.033 mmol) and tert-butyl 3-(butylamino)propanoate (27 mg, 0.13 mmol) were converted to the title compound (18 mg, 57%). ¹H NMR (CDCl₃, mixture of amide rotamers) δ 8.64 (s, 1H), 8.43 (s, 1H), 8.15-8.05 (m, 1H), 8.01-7.86 (m, 4H), 7.64 (d, J = 8.6 Hz, 1H), 7.42-7.03 (m, 4.5H), 6.80 (d, J = 7.9 Hz, 0.5H), 4.72 (d, J = 11.0 Hz, 1H), 4.40-4.22 (m, 1H), 3.88-2.38 (m, 7.5), 2.33-2.13 (m, 3.5H), 1.63-1.22 (m, 13H), 1.07 (d, J = 7.0 Hz, 1.5H), 0.98-0.84 (m, 1.5H), 0.81-0.63 (m, 2H); MS(ESI⁺) m/z 938.2 (M+H)⁺.

Example 177

N,N-Dibutyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid (Intermediate 9ID, 35 mg, 0.075 mmol) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5, 27 mg, 0.11 mmol) provided a crude oil which was used in the subsequent step without purification.

The crude oil from above was subjected to a procedure analogous to that for the synthesis of Intermediate 164B. The resulting crude product was then subjected to a procedure analogous to that for the synthesis of Example 91 to give the title compound (14 mg, 44%). ¾ NMR (1:1 CD₂SO:CDCl₃, mixture of amide rotamers) δ 9.00 (s, 1H), 8.28-8.10 (m, 2.5H), 8.02-7.93 (m, 1.5H), 7.83 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.54-7.46 (m, 1H), 7.43-7.31 (m, 1H), 7.22-7.03 (m, 3.5 H), 6.87 (br s, 0.5H), 5.22
(d, J = 18.0 Hz, 0.5H), 4.36-4.06 (m, 2H), 3.64-2.71 (m, 8H), 2.35-2.17 (m, 3.5H), 1.63-0.54 (m, 14H); MS(ESI+) m/z 804.2 (M+H)+.

Example 178

N-Butyl-4-chloro-N-(3,4-dichlorobenzyl)-l-(4-(8-(ethylsulfonyl)naphthalen-2-ylsulfonylcarbamoyl)-2-(l,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

[00470] Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(ethoxycarbonyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate 122D, 17 mg, 0.037 mmol) and 8-(ethylsulfonyl)naphthalene-2-sulfonamide (Intermediate 14, 11 mg, 0.037 mmol) provided a crude oil which was used in the subsequent step without purification.

[00471] The crude oil from above was subjected to a procedure analogous to that for the synthesis of Intermediate 164B. The resulting crude oil was then subjected to procedure analogous to that used in the synthesis of Example 125 to give the title compound (1 mg, 3%). 'HNMR (1:1 CD$_3$OD:CDCl$_3$, mixture of amide rotamers) δ 9.59 (s, 1H), 8.41-8.36 (m, 1H), 8.34-8.29 (m, 1H), 8.27-8.20 (m, 2H), 8.12-8.05 (m, 1H), 7.99-7.93 (m, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.59-7.49 (m, 1H), 7.41 - 7.32 (m, 0.5H), 7.32-7.03 (m, 5.5H), 6.91-6.84 (m, 1H), 4.62-4.20 (m, 5H), 3.63 (d, J = 6.4 Hz, 1H), 3.51-3.41 (m, 3H), 3.02 (t, J = 7.9 Hz, 1H), 2.79 (br s, 2H), 2.31 (s, 1H), 2.27 (d, J = 3.6 Hz, 1.5H), 2.19 (s, 0.5H), 1.49-0.79 (m, 8.5H), 0.71 (t, J = 7.4 Hz, 1H), 0.65 (t, J = 7.2 Hz, 0.5H); MS(ESI+) m/z 936.1 (M+H)+.

Example 179
N-Butyl-4-chloro-N-(3,4-dichlorobenzyl)-l-(4-(7-iodonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

Intermediate 179A: 4-Chloro-5-methyl-1H-pyrazole-3-carboxylic acid

[00472] To a solution of ethyl 4-chloro-5-methyl-1H-pyrazole-3-carboxylate (Intermediate 1A, 2.01 g, 10.7 mmol) in MeOH (8.2 mL) and THF (8.2 mL) was added 2N aq. NaOH solution (27 mL, 53.3 mmol). The reaction mixture was stirred at room temperature overnight, then cooled to 0°C and neutralized with IN aq. HCl solution (pH = 3-4). The resulting solid was collected by filtration and washed with water to give the title compound (1.50 g, 87%) as a white solid. 1H NMR (DMSO-d$_6$) $\delta$ 2.19 (br s, 3H); MS(ESI$^+$) m/z 160.9 (M+H)$^+$. 

Intermediate 179B: N-Butyl-4-chloro-N-(3,4-dichlorobenzyl)-5-methyl-1H-pyrazole-3-carboxamide

[00473] Following a procedure analogous to that for the synthesis of Intermediate 168A, 4-chloro-5-methyl-1H-pyrazole-3-carboxylic acid (1.50 g, 9.32 mmol) and N-(3,4-dichlorobenzyl)butan-1-amine (Intermediate 126, 2.16 g, 9.32 mmol) provided the title compound (1.67 g, 48%) as a colorless oil. 1H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 7.50-7.32 (m, 2H), 7.24-7.06 (m, 1H), 4.79-4.55 (m, 2H), 3.47-3.26 (m, 2H),...
2.34-2.19 (m, 3H), 1.71-1.46 (m, 2H), 1.35 (br s, 1H), 1.18 (br s, 1H), 0.93 (d, $J = 6.4$ Hz, 1.5H), 0.81 (d, $J = 6.8$ Hz, 1.5H); MS(ESI $^+$) $m/z$ 376.0 (M+H)$^+$. 

Intermediate 179C: Benzyl 4-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1$H$-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate IE, $N$-butyl-4-chloro-$N$-(3,4-dichlorobenzyl)-5-methyl-1$H$-pyrazole-3-carboxamide (1.73 g, 4.62 mmol) and benzyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (Intermediate 122B, 1.80 g, 4.62 mmol) were converted to the title compound (2.20 g, 64%). ¾ NMR (CDCl$_3$, mixture of amide rotamers) $\delta$ 8.24 (d, $J = 8.4$ Hz, 1H), 8.16-8.09 (m, 1H), 7.53-7.03 (m, 12H), 6.98-6.76 (m, 1H), 5.41 (br s, 2H), 4.86-4.20 (m, 4H), 3.64-3.03 (m, 4H), 2.78 (br s, 2H), 2.37-2.17 (m, 3H), 1.61-1.38 (m, 1H), 1.36-1.21 (m, 2H), 1.18-1.01 (m, 1H), 0.97-0.83 (m, 2H), 0.80-0.67 (m, 1H); MS(ESI $^+$) $m/z$ 745.2 (M+H)$^+$. 

Intermediate 179D: 4-(3-(Butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-7$H$-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 164B, benzyl 4-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1$H$-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (2.20 g, 2.96 mmol) was
converted to the title compound (1.90 g, 98%). $^1$H NMR (DMSO-d$_6$, mixture of amide rotamers) δ 8.15 (d, $J = 8.4$ Hz, 1H), 8.05 (d, $J = 2.2$ Hz, 0.5H), 8.01-7.96 (m, 0.5H), 7.88-7.69 (m, 1H), 7.60-7.48 (m, 1.5H), 7.46-7.38 (m, 0.5H), 7.35-7.26 (m, 1H), 7.24-6.94 (m, 3H), 6.85 (d, $J = 7.5$ Hz, 0.5H), 6.45-6.31 (m, 0.5H), 5.13 (br s, 0.5H), 4.85-4.15 (m, 4H), 3.74-3.36 (m, 2H), 3.23-2.92 (m, 1.5H), 2.82-2.60 (m, 2H), 2.31-2.11 (m, 3H), 1.45-1.08 (m, 3H), 1.05-0.90 (m, 1H), 0.82 (quin, $J = 7.2$ Hz, 2H), 0.71-0.54 (m, 1H); MS(ESI $^+$) m/z 655.1 (M+H) $^+$.  

Example 179:

Following a procedure analogous to that for the synthesis of Example 1, 4-(3-butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (30 mg, 0.046 mmol) and 7-iodonaphthalene-2-sulfonamide (Intermediate 11, 18 mg, 0.055 mmol) were converted to the title compound (17 mg, 37%). $^1$H NMR (1:1 MeOD:CDCl$_3$, 2:1 mixture of amide rotamers) δ 8.59 (s, 1H), 8.44 (s, 1H), 8.07-8.03 (m, 2H), 7.97 (d, $J = 8.3$ Hz, 1H), 7.92-7.88 (m, 2H), 7.68 (d, $J = 8.6$ Hz, 1H), 7.53-7.47 (m, 1H), 7.30-7.03 (m, 5.5H), 6.88 (d, $J = 7.8$ Hz, 0.5H), 6.84 (dd, $J = 6.0$, 2.1 Hz, 1H), 4.79 (br s, 1H), 4.57-4.55 (m, 1H), 4.42 (d, $J = 9.2$ Hz, 0.5H), 4.32-4.22 (m, 1.5H), 3.91 (br s, 1H), 3.58 (m, 1H), 3.47-3.44 (m, 1H), 3.00 (br s, 1.5H), 2.80-2.77 (m, 1.5H), 2.30-2.19 (m, 3H), 1.43-1.32 (m, 2H), 1.29-1.15 (m, 2H), 1.10-0.96 (m, 1H), 0.85 (dt, $J = 10.2$, 7.3 Hz, 1.5H), 0.71 (t, $J = 7.4$ Hz, 1H), 0.65 (t, $J = 7.4$ Hz, 0.5H); MS(ESI $^+$) m/z 970.1 (M+H) $^+$.  

Example 180

N-Butyl-4-chloro-N-(3,4-dichlorobenzyl)-5-methyl-1-(4-(7-(4-methyl piperazine-1-carbonyl)naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide
Intermediate 180A: Ethyl 7-(N-(4-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-2-naphthoate

Following a procedure analogous to that for the synthesis of Example 1, 4-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate 179D, 100 mg, 0.18 mmol) and ethyl 7-sulfamoyl-2-naphthoate (Intermediate 16, 61 mg, 0.22 mmol) were converted to the title compound (84 mg, 57%). MS(ESI) m/z 812.2 (M+H)+.

Intermediate 180B: 7-(N-(4-(Butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-2-naphthoic acid
Following a procedure analogous to that for the synthesis of Intermediate 46A, ethyl 7-(N-(4-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-2-naphthoate (91 mg, 0.10 mmol) was converted to the title compound (73 mg, 83%). NMR (DMSO-d$_6$, mixture of amide rotamers) δ 8.49 (s, 0.5H), 8.45 (s, 0.5H), 8.38 (s, 0.5H), 8.09 (dd, J = 11.9, 8.4 Hz, 1.5H), 8.01-7.79 (m, 3H), 7.60-7.41 (m, 2H), 7.29-6.92 (m, 3.5H), 6.81 (d, J = 8.4 Hz, 0.5H), 4.80-4.16 (m, 3H), 3.68-2.91 (m, 10.5H), 2.81-2.60 (m, 2H), 2.39-2.30 (m, 0.5H), 2.21-2.06 (m, 3H), 1.42-1.06 (m, 3H), 1.01-0.88 (m, 1.5H), 0.86-0.76 (m, 1H), 0.71-0.50 (m, 1.5H); MS(ESI + ) m/z 803.4 (M+H)$^+$. Example 180:

Following a procedure analogous to that for the synthesis of Intermediate 46A, 7-(N-(4-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoyl)sulfamoyl)-2-naphthoic acid (35 mg, 0.039 mmol) was converted to the title compound (8 mg, 21%). HNMR (1:1 CD$_3$OD:CDC$_3$, 2:1 mixture of amide rotamers) δ 8.66 (s, 1H), 8.20-8.18 (m, 1H), 8.14-8.11 (m, 1H), 8.08-8.06 (m, 2H), 7.98 (d, J = 8.9 Hz, 2H), 7.61 (d, J = 8.6 Hz, 1H), 7.43-7.36 (m, 1.5H), 7.32-7.02 (m, 5H), 6.88-6.83 (m, 1.5H), 4.79 (br s, 1H), 4.65 (br s, 1H), 4.45 (s, 1H), 3.93-3.65 (m, 4H), 3.59 (br s, 1H), 3.48 (br s, 1H), 3.04-3.01 (m, 1.5H), 2.92 (br s, 3H), 2.78-2.76 (m, 1.5H), 2.64 (s, 3H), 2.28 (s, 1H), 2.24 (s, 1.5H), 2.17 (s, 0.5H), 1.44-1.34 (m, 1.5H), 1.29-1.18 (m, 3H), 1.07-0.95 (m, 1.5H), 0.85 (q, J = 7.5 Hz, 1.5H), 0.71 (t, J = 7.4 Hz, 1H), 0.65 (t, J = 7.4 Hz, 0.5H); MS(ESI + ) m/z 970.4 (M+H)$^+$. Example 181
N-Butyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-((5')-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-(3,4-dichlorobenzyl)-5-methyl-1H-pyrazole-3-carboxamide

Intermediate 181A: 1-Benzyl 3-ethyl 4-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)isophthalate

Following a procedure analogous to that for the synthesis of Intermediate IE, 1-benzyl 3-ethyl 4-fluoroisophthalate (Intermediate 91B, 270 mg, 0.89 mmol) and N-butyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-((5')-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-(3,4-dichlorobenzyl)-5-methyl-1H-pyrazole-3-carboxamide (Intermediate 179B, 502 mg, 1.34 mmol) were converted to the title compound (458 g, 78%). ¾ NMR (CDCl₃, mixture of amide rotamers) δ 8.68 (dd, J = 19.3, 1.9 Hz, 1H), 8.33 (dt, J = 7.9, 2.0 Hz, 1H), 7.54-7.34 (m, 8H), 7.24-7.07 (m, 1H), 5.43 (d, J = 3.1 Hz, 2H), 4.79-4.63 (m, 2H), 4.19 (q, J = 7.3 Hz, 1H), 3.94 (q, J = 7.2 Hz, 1H), 3.48-3.33 (m, 2H), 2.16 (d, J = 6.6 Hz, 3H), 1.68-1.46 (m, 2H), 1.41-1.31 (m, 1H), 1.25-1.14 (m, 2.5H), 1.09 (t, J = 7.2 Hz, 1.5H), 0.96-0.88 (m, 1.5H), 0.79 (t, J = 7.4 Hz, 1.5H); MS(ESI⁺) m/z 656.0 (M+H)⁺.

Intermediate 181B: 4-(3-(Butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 91D, 1-benzyl 3-ethyl 4-(3-((butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)isophthalate (100 mg, 0.15 mmol) was converted to the title compound (86 mg, 100%). MS(ESI+) m/z 566.0 (M+H)^+.

Example 181:

Following a procedure analogous to that for the synthesis of Example 1, 4-(3-((butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-3-ethoxybenzoic acid (31 mg, 0.055 mmol) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5, 16 mg, 0.066 mmol) were reacted to provide a crude oil which was used in the subsequent step without purification.

The crude oil from above was subjected to a procedure analogous to that for the synthesis of Intermediate 91F. The resulting crude oil was subjected to a procedure analogous to that for the synthesis of Example 91 to give the title compound (20 mg, 33%). ³¹ NMR (1:1 CD₃OD:CDCl₃, mixture of amide rotamers) δ 9.01 (br s, 1H), 8.30-8.10 (m, 3H), 8.02-7.91 (m, 2H), 7.83 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 7.5 Hz, 1H), 7.55-6.84 (m, 7.5H), 6.80-6.61 (m, 0.5H), 5.26-4.98 (m, 1H), 4.88-4.61 (m, 3H), 4.50-4.03 (m, 2H), 3.63-3.28 (m, 3H), 3.16-2.64 (m, 2H), 2.33-2.05 (m, 3H), 1.64-0.95 (m, 4H), 0.92-0.80 (m, 2H), 0.69-0.50 (m, 1H); MS(ESI+) m/z 908.1 (M+H)^+.

Example 182

\( \text{N-Butyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-((5)-3-((2-hydroxyethyl)(methyl)amino)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl}- \) N-(3,4-dichlorobenzyl)-5-methyl-1H-pyrazole-3-carboxamide
Following a procedure analogous to that for the synthesis of Example 91, 2-(3-(butyl-(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-5-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Example 181, 35 mg, 0.048 mmol) and (5)-2-(methyl((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)amino)ethanol (Intermediate 114, 11 mg, 0.048 mmol) were converted to the title compound (11 mg, 25%). ¾ NMR (1:1 CD3OD:CDCl3, mixture of amide rotamers) δ 8.63 (s, 1H), 8.30-8.19 (m, 1.5H), 8.1 1-7.82 (m, 4.5H), 7.65-7.54 (m, 2.5H), 7.51-6.87 (m, 6.5H), 5.17 (br s, 0.5H), 4.77 (br s, 2H), 4.46-4.05 (m, 0.5H), 3.88-3.45 (m, 2H), 3.40-2.78 (m, 7.5H), 2.71-2.62 (m, 6H), 2.35-2.12 (m, 2.5H), 1.54-1.02 (m, 4H), 0.98-0.48 (m, 3H); MS(ESI+) m/z 931.2 (M+H)+.

Example 183

\[ \text{N,N-Dibutyl-4-chloro-1-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide} \]

Intermediate 183A: Ethyl 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)benzoate
Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid (Intermediate 9ID, 90 mg, 0.19 mmol) and 8-(2-morpholinoethoxy)naphthalene-2-sulfonamide (Intermediate 26, 65 mg, 0.19 mmol) were converted to the title compound (105 mg, 70%). MS(ESI+) m/z 782.2 (M+H)+.

Intermediate 183B: 2-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 9IF, ethyl 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)benzoate (105 mg, 0.13 mmol) was converted to the title compound (98 mg, 97%). MS(ESI+) m/z 754.2 (M+H)+.

Example 183:

Following a procedure analogous to that for the synthesis of Example 91, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (15 mg, 0.020 mmol) and (5)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (Aldrich, 10 mg, 0.060 mmol) were converted to the title compound (12 mg, 67%). 1H NMR (CD3OD, 2:1 mixture of amide rotamers) δ 9.26-9.12 (m, 1H), 8.23 (d, J = 1.5 Hz, 0.5H), 8.15-7.94 (m, 3.5H), 7.75-7.59 (m, 3H), 7.31-7.03 (m, 4.5H), 6.91 (s, 0.5H), 5.26 (d, J = 17.8 Hz, 0.5H), 4.75-4.61 (m, 2H), 4.51 (br s, 0.5H), 4.37-2.51 (m, 19.5H), 2.44-2.34 (m, 0.5H), 2.33-2.24 (m, 3H), 1.63-0.83 (m, 11H), 0.74 (t, J = 7.3 Hz, 2H), 0.64 (t, J = 7.3 Hz, 1H); MS(ESI+) m/z 899.3 (M+H)+.
Example 184

\( \text{N,N-Dibutyl-4-chloro-1-(2-((S)-3-(Azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide} \)

\( \text{(184)} \)

Intermediate 184A: \( \text{l-(2-((S)-3-(Azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5\text{-methyl-1H-pyrazole-3-carboxamide}} \)

\( \text{(Int-184A)} \)

[00488] Following a procedure analogous to that for the synthesis of Example 91, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 183B, 50 mg, 0.066 mmol) and (S)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline (Intermediate 92A, 37 mg, 0.20 mmol) were converted to the title compound (45 mg, 73%). \(^1\)H NMR (CD\textsubscript{3}OD, 2:1 mixture of amide rotamers) \(\delta\) 9.23-9.11 (m, 1H), 8.21 (d, \(J = 1.9\) Hz, 0.5H), 8.13-7.93 (m, 3.5H), 7.76-7.58 (m, 3H), 7.32-7.06 (m, 4.5H), 6.93 (d, \(J = 7.2\) Hz, 0.5H), 5.28 (d, \(J = 18.3\) Hz, 0.5H), 4.98 (br s, 0.5H), 4.73-4.62 (m, 2H), 4.59-3.21 (m, 15.5H), 3.18-2.69 (m, 3.5H), 2.58 (d, \(J = 16.1\) Hz, 0.5H), 2.48-2.40 (m, 0.5H), 2.34-2.21 (m, 3H), 1.55-0.82 (m, 11H), 0.78-0.70 (m, 2H), 0.69-0.55 (m, 1H); MS(ESI\(^+\)) \(m/z\) 924.3 (M+H\(^+\)).
Intermediate 184B: 1-(2-((S)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide

To a solution of (5)-l-(2-(3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide (45 mg, 0.049 mmol) and PPI13 (38 mg, 0.15 mmol) in THF (4.0 mL) and water (0.4 mL) was added IN aq. NaOH solution (0.2 mL, 0.20 mmol). The resulting reaction mixture was heated at 50 °C for 3 h and then acidified (pH = 1) with IN aq. HCl solution. The solvent was removed in vacuo, and the residue was purified by preparative HPLC to give the title compound (33 mg, 72%) as a white solid.

H NMR (CD$_3$OD, mixture of amide rotamers) δ 9.16 (s, 1H), 8.29-7.88 (m, 4H), 7.83-7.58 (m, 3H), 7.40-7.08 (m, 4H), 6.99 (br s, 1H), 5.04 (br s, 0.5H), 4.76-4.41 (m, 4H), 4.27-2.66 (m, 18.5H), 2.42-2.20 (m, 4H), 1.64-0.72 (m, 13H), 0.60 (br s, 1H); MS(ESI $^+$) m/z 898.1 (M+H)$^+$.  

Example 184:

To a solution of (5)-l-(2-(3-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide, TFA (20 mg, 0.022 mmol) in MeCN (2.0 mL) was added Et$_3$N (20 µL, 0.14 mmol). After stirring at room temperature for 10 min, 37% formalin (100 µL, 0.022 mmol) and AcOH (100 µL, 0.022 mmol) were added. The resulting reaction mixture was stirred at room temperature for 1 h. Na(CN)BH$_3$ (50 mg, 0.80 mmol) was then added, and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residue was purified by preparative HPLC to give the title compound (11 mg, 51%) as a white solid.

H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 9.17 (br s, 1H), 8.23 (br s, 0.5H), 8.16-7.88 (m, 3.5H), 7.83-7.59 (m, 3H), 7.40-7.11 (m, 4H), 6.98 (d, J = 7.7 Hz, 1H), 5.26
(br s, 1H), 4.70 (br s, 2H), 4.63-4.37 (m, 2H), 4.22-2.59 (m, 24H), 2.41-2.17 (m, 3H), 1.60-0.85 (m, 11H), 0.77 (t, J = 6.8 Hz, 1.5H), 0.66-0.49 (m, 1.5H); MS(ESI+) m/z 926.5 (M+H)+.

Example 185

\[ N,N\text{-Dibutyl-4-chloro-5-methyl-1-(4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-((5)-3-(morpholinomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide} \]

\[
\begin{align*}
\text{Cl} & \quad \text{Me} \\
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{S} \\
\text{O} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\end{align*}
\]

(185)

[00491] Following a procedure analogous to that for the synthesis of Example 91, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 183B, 15 mg, 0.020 mmol) and (5)-4-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)morpholine (Intermediate 109, 18 mg, 0.080 mmol) were converted to the title compound (14 mg, 62%). ^1H NMR

(\text{CD}_3\text{OD}, \text{mixture of amide rotamers}) \delta 9.19-9.04 (m, 1H), 8.26-7.93 (m, 4H), 7.79-7.53 (m, 3H), 7.36-7.09 (m, 4H), 6.99 (d, J = 7.7 Hz, 1H), 5.37-5.16 (m, 1H), 4.75-4.41 (m, 3.5H), 4.22-2.52 (m, 27.5H), 2.37-2.16 (m, 3H), 1.75-0.48 (m, 14H); MS(ESI+) m/z 968.3 (M+H)+.

Example 186

\[ N\text{-Butyl-4-chloro-N-(3,4-dichlorobenzyl)-5-methyl-1-(4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)-2-((5)-3-(morpholinomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxamide} \]
Intermediate 186A: Ethyl 2-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)benzoate

Following a procedure analogous to that for the synthesis of Example 1, 4-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate 179D, 30 mg, 0.046 mmol) and 8-(2-morpholinoethoxy)naphthalene-2-sulfonamide (Intermediate 27, 10 mg, 0.030 mmol) were converted to the title compound (22 mg, 84%). MS(ESI+) m/z 886.1 (M+H)+.

Intermediate 186B: 2-(3-(Butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)benzoic acid

(Int-186B)
Following a procedure analogous to that for the synthesis of Intermediate 91F, ethyl 2-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylearbamoyl)benzoate (75 mg, 0.085 mmol) was converted to the title compound (56 mg, 77%). MS(ESI+), m/z 858.5 (M+H)+.

Example 186:

Following a procedure analogous to that for the synthesis of Example 91, 2-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylearbamoyl)benzoic acid (12 mg, 0.014 mmol) and (5)-4-((1,2,3,4-tetrahydroisoquinolin-3-yl)methyl)morpholine (Intermediate 109, 13 mg, 0.056 mmol) were converted to the title compound (14 mg, 89%). 1H NMR (CD3OD, mixture of amide rotamers) δ 9.24-9.07 (m, 1H), 8.27-7.89 (m, 4H), 7.86-7.57 (m, 3H), 7.54-6.81 (m, 8H), 5.24 (br s, 1H), 5.05-2.54 (m, 28H), 2.41-2.05 (m, 4H), 1.63-0.68 (m, 6H), 0.65-0.49 (m, 1H); MS(ESI+), m/z 1070.2 (M+H)+.

Example 187

N-Butyl-4-chloro-N-(3,4-dichlorobenzyl)-1-(2-((S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylearbamoyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

Following a procedure analogous to that for the synthesis of Example 91, 2-(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1H-pyrazol-1-yl)-5-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylearbamoyl)benzoic acid (Intermediate 186A, 12 mg, 0.014 mmol) and (5)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (Aldrich, 9 mg, 0.056 mmol) were converted to the title compound (10 mg, 70%). 1H NMR (CD3OD, mixture of amide rotamers) δ 9.23-9.09 (m, 1H), 8.24 (dd, J = 1.7, 8.0 Hz, 0.5H), 8.10-7.94 (m, 3.5H), 7.76-7.59 (m, 3H), 7.53-7.29 (m, 1.5H), 7.27-6.80 (m, 6H),
6.68 (d, J = 7.5 Hz, 0.5H), 5.27-5.04 (m, 1H), 4.75-4.59 (m, 3H), 4.54-2.44 (m, 18H),
2.39-2.26 (m, 3H), 2.25-2.06 (m, 1H), 1.65-0.81 (m, 5.5H), 0.75-0.65 (m, 1H), 0.61-0.51
(m, 0.5H); MS(ESI+) m/z 1005.3 (M+H)+.

Example 188
1-(2-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-
morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)phenyl )-N-butyl-4-chloro -N-(3,4-
dichlorobenzyl)-5-methyl-1 H-pyrazole-3-carboxamide

Intermediate 188A: 1-(2-((5)-3-(Azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)phenyl )-N-butyl-
4-chloro -N-(3,4-dichlorobenzyl)-5-methyl-1 H-pyrazole-3-carboxamide

Following a procedure analogous to that for the synthesis of Example 91, 2-
(3-(butyl(3,4-dichlorobenzyl)carbamoyl)-4-chloro-5-methyl-1 H-pyrazol-1-yl)-5-(8-(2-
morpholinoethoxy)naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 186B,
17 mg, 0.020 mmol) and (5)-3-(azidomethyl)-1,2,3,4-tetrahydropyridine
(Intermediate 92A, 15 mg, 0.079 mmol) were converted to the title compound (16 mg,
79%). MS(ESI+) m/z 1028.1 (M+H)+.
Example 188:

Following a procedure analogous to that for the synthesis of Example 182, (5)-l-(2-(3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-(2-morpholinoethoxy)naphthalen-2-ylsulfonylearbamoyl)phenyl )-N-butyl-4-chloro -N-(3,4-dichlorobenzyl)-5-methyl-l H-pyrazole-3-carboxamide (16 mg, 0.016 mmol) was converted to the title compound (7 mg, 43%). ^1H NMR (CD$_3$OD, mixture of amide rotamers) δ 9.14 (s, 1H), 8.36-7.88 (m, 4H), 7.83-6.76 (m, 11H), 5.16-2.62 (m, 23H), 2.46-2.15 (m, 3H), 1.61-0.82 (m, 5.5H), 0.80-0.65 (m, 1H), 0.56 (br s, 0.5H); MS(ESI$^+$) m/z 1002.0 (M+H$^+$).

Example 189

N,N-Dibutyl-4-chloro-1-(4-(l-(3,4-dichlorobenzyl)indolin-5-ylsulfonylearbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide

Intermediate 189A: Ethyl 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-l-yl)-5-(l-(3,4-dichlorobenzyl)indolin-5-ylsulfonylearbamoyl)benzoate

Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid (Intermediate 9ID, 727 mg, 1.57 mmol) and l-(3,4-dichlorobenzyl)indoline-5-sulfonamide (Intermediate 59, 400 mg, 1.12 mmol) were converted to the title compound
Intermediate 189B: 2-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 9IF, ethyl 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)benzoate (355 mg, 0.44 mmol) was converted to the title compound (290 mg, 85%). $^1$HNMR (DMSO-d$_6$) $\delta$ 8.14 (d, $J = 2.0$ Hz, 1H), 8.17 (dd, $J = 8.3$, 2.1 Hz, 1H), 7.69-7.57 (m, 5H), 7.32-7.30 (m, 1H), 6.65 (d, $J = 8.6$ Hz, 1H), 4.45 (s, 2H), 3.53 (t, $J = 8.7$ Hz, 2H), 3.40-3.28 (m, 4H), 3.05 (t, $J = 8.4$ Hz, 2H), 2.11 (s, 3H), 1.56-1.41 (m, 4H), 1.33-1.27 (m, 2H), 1.15-1.08 (m, 2H), 0.91 (t, $J = 7.3$ Hz, 3H), 0.74 (t, $J = 7.4$ Hz, 3H); MS(ESI$^+$) m/z 776.2 (M+H)$^+$.

Example 189:

Following a procedure analogous to that for the synthesis of Example 91, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)benzoic acid (60 mg, 0.077 mmol) and (5')-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (Aldrich, 38 mg, 0.23 mmol) were converted to the title compound (56 mg, 72%). $^1$HNMR (DMSO-d$_6$) $\delta$ 8.23 (d, $J = 1.8$ Hz, 0.5H), 8.08-8.04 (m, 1H), 7.72-7.58 (m, 5.5H) 7.32 (dd, $J = 8.3$, 1.9 Hz, 1H), 7.19-7.06 (m, 4.5H), 6.66 (d, $J = 8.6$ Hz, 0.5H), 5.08 (d, $J = 18.1$ Hz, 1H), 4.45 (s, 2H), 4.40-4.19 (m, 1H), 3.95-3.90 (m, 1H), 3.54 (t, $J = 8.7$ Hz, 2H), 3.41-3.16 (m,
3H), 3.07-2.88 (m, 4H), 2.76-2.54 (m, 1H), 2.35-2.22 (m, 2H), 2.21 (s, 2H), 2.18 (s, 1H), 1.25-0.90 (m, 5H), 0.93-0.79 (m, 6H), 0.66-0.58 (m, 3H); MS(ESI\(^+\)) \textit{m/z} 921.3 (M+H\(^+\)).

Example 190

\(N,N\)-Dibutyl-4-chloro-1-(4-(1-ethylindolin-5-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1\(H\)-pyrazole-3-carboxamide

![Chemical structure of Example 190](image)

Intermediate 190A: Ethyl 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1\(H\)-pyrazol-1-yl)-5-(1-ethylindolin-5-ylsulfonylcarbamoyl)benzoate

![Chemical structure of Intermediate 190A](image)

[00501] Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1\(H\)-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid (Intermediate 9ID, 400 mg, 0.69 mmol) and 1-ethylindoline-5-sulfonamide (Intermediate 53, 172 mg, 0.76 mmol) were converted to the title compound (180 mg, 27%) after purification by preparative HPLC. MS(ESI\(^+\)) \textit{m/z} 672.3 (M+H\(^+\)).

Intermediate 190B: 2-(4-Chloro-3-(dibutylcarbamoyl)-5-methyl-1\(H\)-pyrazol-1-yl)-5-(1-ethylindolin-5-ylsulfonylcarbamoyl)benzoic acid

![Chemical structure of Intermediate 190B](image)
Following a procedure analogous to that for the synthesis of Intermediate 9IF, ethyl 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(1-ethylindolin-5-ylsulfonylcarbamoyl)benzoate (180 mg, 0.27 mmol) was converted to the title compound (58 mg, 32%) after purification by preparative HPLC. $^1$H NMR (DMSO-d$_6$) δ 8.41 (d, $J$ = 2.0 Hz, 1H), 8.17 (dd, $J$ = 8.3, 2.1 Hz, 1H), 7.69-7.64 (m, 2H), 7.52 (d, $J$ = 1.8 Hz, 1H), 6.83 (d, $J$ = 8.6 Hz, 1H), 3.54 (t, $J$ = 8.6 Hz, 2H), 3.28-3.24 (m, 6H), 3.00 (t, $J$ = 8.6 Hz, 2H), 2.10 (s, 3H), 1.57-1.41 (m, 4H), 1.33-1.26 (m, 2H), 1.14-1.08 (m, 5H), 0.91 (t, $J$ = 7.4 Hz, 3H), 0.75 (t, $J$ = 7.3 Hz, 3H); MS(ESI$^+$) m/z 644.3 (M+H)$^+$. 

Example 190:

Following a procedure analogous to that for the synthesis of Example 91, 2-(4-chloro-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-5-(1-ethylindolin-5-ylsulfonylcarbamoyl)benzoic acid (58 mg, 0.090 mmol) and (5)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (Aldrich, 24 mg, 0.14 mmol) were converted to the title compound (70 mg, 94%). ¾ NMR (CD$_3$OD, 2:1 mixture of amide rotamers) δ 8.24 (d, $J$ = 1.8 Hz, 0.5H), 8.07-8.01 (m, 1.5H), 7.77 (dd, $J$ = 8.6, 2.0 Hz, 1H), 7.71 (d, $J$ = 1.5 Hz, 1H), 7.66-7.62 (m, 2H), 7.25-7.10 (m, 3.5H), 6.95-6.93 (m, 0.5H), 6.48-6.46 (m, 1H), 5.30-5.25 (m, 1H), 4.54-4.10 (m, 2H), 3.62-3.56 (m, 4H), 3.45-3.41 (m, 3H), 3.14-3.01 (m, 6H), 2.61-2.40 (m, 2H), 2.32 (s, 2H), 2.29 (s, 1H), 1.46-1.22 (m, 4H), 1.20-1.16 (m, 4H), 1.07-0.90 (m, 5H), 0.77-0.66 (m, 3H); MS(ESI$^+$) m/z 789.4 (M+H)$^+$. 

Example 191

4-(4-Chloro-3-(dibutlamino)-5-methyl-1H-pyrazol-1-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamid e

![Chemical Structure](image)

Intermediate 191A: $N,N$-Dibutyl-5-methyl-1H-pyrazol-3-amine
[00504] Following a procedure analogous to that for the synthesis Example 106, 5-methyl-1H-pyrazol-3-amine (Aldrich, 486 mg, 5.00 mmol) and butyraldehyde (541 mg, 7.50 mmol) were converted to the title compound (555 mg, 53%). $^1$H NMR (CDCl$_3$) $\delta$ 5.34 (s, 1H), 3.17 (t, $J = 7.3$ Hz, 4H), 2.21 (s, 3H), 1.55 (td, $J = 15.1$, 7.5 Hz, 4H), 1.34 (qd, $J = 15.0$, 7.3 Hz, 4H), 0.94 (t, $J = 7.4$ Hz, 6H); MS(ESI$^+$) m/z 210.1 (M+H)$^+$. 

Intermediate 1B: N,N-Dibutyl-4-chloro-5-methyl-1H-pyrazol-3-amine

[00505] Following a procedure analogous to that for the synthesis of Intermediate 1A, N,N-dibutyl-5-methyl-1H-pyrazol-3-amine (419 mg, 2.00 mmol) was converted to the title compound (297 mg, 61%). $^1$H NMR (CDCl$_3$) $\delta$ 3.26-3.17 (m, 4H), 2.19 (s, 3H), 1.57-1.44 (m, 4H), 1.32 (qd, $J = 15.0$, 7.3 Hz, 4H), 0.91 (t, $J = 7.4$ Hz, 6H); MS(ESI$^+$) m/z 243.9 (M+H)$^+$. 

Intermediate 1C: Ethyl 4-(4-chloro-3-(dibutylamino)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

[00506] Following a procedure analogous to that for the synthesis of Intermediate IE, N,N-dibutyl-4-chloro-5-methyl-1H-pyrazol-3-amine (160 mg, 0.66 mmol) and ethyl 4-fluoro-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (Intermediate ID, 258 mg, 0.79 mmol) were converted to the title compound (98 mg, 27%). $^1$H NMR (CDCl$_3$, 2:1 mixture of amide rotamers) $\delta$ 8.19 (d, $J = 8.1$ Hz, 1H), 8.12 (d, $J = 1.7$ Hz, 1H), 7.40 (d, $J = 8.33$ Hz, 1H), 7.08-7.30 (m, 3.5H), 6.92 (d, $J = 7.5$ Hz, 0.5H), 4.95 (d, $J = 17.1$ Hz, 0.5H), 4.68 (d, $J = 17.10$ Hz, 0.5H), 4.31-4.53 (m, 2.5H), 4.12 (d, $J = 4.1$ Hz, 0.5H), 3.51-
3.76 (m, 1.5H), 3.03-3.36 (m, 4.5H), 2.75-3.03 (m, 2H), 2.58 (s, 2H), 2.47 (s, 1H), 1.33-1.51 (m, 7H), 1.13-1.30 (m, 4H), 0.77-0.96 (m, 6H); MS(ESI+) m/z 551.4 (M+H)+.

Example 191:

Following a procedure analogous to that for the synthesis of Example 163, ethyl 4-(4-chloro-3-(dibutylamino)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (10 mg, 0.018 mmol) was converted to the title compound. 'HNMR (CD3OD, 1:1 mixture of amide rotamers) δ 8.72 (s, 1H), 8.10-8.05 (m, 3H), 8.02-7.98 (m, 2H), 7.91-7.89 (m, 1H), 7.73-7.64 (m, 2H), 7.56-7.51 (m, 1H), 7.22-7.07 (m, 3.5H), 6.88 (d, J = 7.5 Hz, 0.5H), 4.82-4.66 (m, 1H), 4.46-4.32 (m, 1H), 3.90-3.84 (m, 0.5H), 3.78-3.72 (m, 0.5H), 3.51-3.45 (m, 1H), 3.10-2.98 (m, 4H), 2.88 (t, J = 5.9 Hz, 1H), 2.76-2.71 (m, 1H), 2.27 (s, 1.5H), 2.20 (s, 1.5H), 1.39-1.25 (m, 4H), 1.22-1.11 (m, 4H), 0.84 (t, J = 6.8 Hz, 3H), 0.81 (t, J = 7.3 Hz, 3H); MS(ESI+) m/z 712.5 (M+H)+.

Example 192

4-(4-Chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide

Intermediate 192A: 5-Methyl-\(N,N\)-dipropyl-1H-pyrazol-3-amine

Following a procedure analogous to that for the synthesis Example 106, 5-methyl-1H-pyrazol-3-amine (Aldrich, 486 mg, 5.00 mmol) and propionaldehyde (436 mg, 7.50 mmol) were converted to the title compound (400 mg, 44%). \(^1\)HNMR (CDCl3) δ 5.34 (s, 1H), 3.20-3.11 (m, 4H), 2.22 (s, 3H), 1.60 (sxt, J = 7.4 Hz, 4H), 0.91 (t, J = 7.4 Hz, 6H); MS(ESI+) m/z 182.2 (M+H)+.
Intermediate 192B: 4-Chloro-5-methyl -N,N-dipropyl-1H-pyrazol-3-amine

Following a procedure analogous to that for the synthesis of Intermediate 1A, 5-methyl -N,N-dipropyl-1H-pyrazol-3-amine (400 mg, 2.21 mmol) was converted to the title compound (290 mg, 61%). ¾NMR (CDCl₃) δ 3.20-3.16 (m, 4H), 2.18 (s, 3H), 1.55 (sxt, J = 7.5 Hz, 4H), 0.88 (t, J = 7.4 Hz, 6H); MS(ESI⁺) m/z 216.1 (M+H)⁺.

Intermediate 192C: 1-Benzyl 3-ethyl 4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)isophthalate

Following a procedure analogous to that for the synthesis of Intermediate IE, 4-chloro-5-methyl -N,N-dipropyl-1H-pyrazol-3-amine (290 mg, 1.34 mmol) and 1-benzyl 3-ethyl 4-fluoroisophthalate (Intermediate 91B, 447 mg, 1.48 mmol) were converted to the title compound (315 mg, 47%). ¾ NMR (CDCl₃) δ 8.55 (d, J = 2.0 Hz, 1H), 8.27 (dd, J = 8.3, 2.1 Hz, 1H), 7.54-7.32 (m, 6H), 5.43 (s, 2H), 4.20 (q, J = 7.0 Hz, 2H), 3.32-3.17 (m, 4H), 2.17 (s, 3H), 1.69-1.54 (m, 6H), 1.21 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.4 Hz, 6H); MS(ESI⁺) m/z 498.2 (M+H)⁺.

Intermediate 192D: 4-(4-Chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 91D, 1-benzyl 3-ethyl 4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)isophthalate (315 mg, 0.63 mmol) was converted to the title compound and used in the subsequent
step without purification. $^1$H NMR (CDCl$_3$) $\delta$ 10.06 (br s, 1H), 8.57 (d, J = 1.8 Hz, 1H), 8.23 (dd, J = 8.1, 2.0 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 4.24 (q, J = 7.3 Hz, 2H), 3.50-3.33 (m, 4H), 2.15 (s, 3H), 1.74-1.53 (m, 4H), 1.28 (s, 3H), 0.94 (t, J = 7.4 Hz, 6H); MS(ESI$^+$) m/z 408.2 (M+H)$^+$.  

Intermediate 192E: Ethyl 2-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoate

Example 192:

Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid (70 mg, 0.17 mmol) and naphthalene-2-sulfonamide (53 mg, 0.26 mmol) were converted to the title compound (50 mg, 49%). $^1$H NMR (CDCl$_3$) $\delta$ 8.76 (s, 1H), 8.49 (d, J = 2.0 Hz, 1H), 8.21-7.96 (m, 4H), 7.92 (d, J = 8.1 Hz, 1H), 7.76-7.58 (m, 2H), 7.45 (d, J = 8.1 Hz, 1H), 4.20 (q, J = 7.0 Hz, 2H), 3.65-3.46 (m, 4H), 2.10 (s, 3H), 1.74-1.56 (m, 4H), 1.25 (t, J = 7.0 Hz, 3H), 0.93 (t, J = 7.3 Hz, 6H); MS(ESI$^+$) m/z 597.2 (M+H)$^+$.  

Example 193:

Following a procedure analogous to that for the synthesis of Intermediate 91F, ethyl 2-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoate (50 mg, 0.084 mmol) provided a crude oil which was used in the subsequent step without purification.  

The crude oil from above was subject to a procedure analogous to that for the synthesis of Example 91 to give the title compound. $^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 8.84-8.66 (m, 1H), 8.18 (br s, 0.5H), 8.12-7.78 (m, 5.5H), 7.72-7.52 (m, 2H), 7.38-6.95 (m, 4.5H), 6.82 (d, J = 7.3 Hz, 0.5H), 5.37-4.96 (m, 1H), 4.59-4.21 (m, 1.5H), 4.08 (br s, 0.5H), 3.84-2.55 (m, 7.5H), 2.39 (d, J = 16.5 Hz, 0.5H), 2.24-2.02 (m, 3H), 1.65-1.19 (m, 4H), 0.94-0.55 (m, 6H); MS(ESI$^+$) m/z 714.2 (M+H)$^+$.  

Example 193
4-(4-Chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-((S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

Intermediate 193A: Ethyl 2-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-5-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)benzoate

Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid (70 mg, 0.17 mmol) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5, 50 mg, 0.21 mmol) were converted to the title compound (78 mg, 72%). MS(ESI+) m/z 631.1 (M+H)+.

Intermediate 193B: 2-(4-Chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-5-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 9IF, ethyl 2-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-5-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)benzoate (76 mg, 0.12 mmol) was converted to the title compound and used in the subsequent step without purification. 1H NMR (CDCl3) δ 9.14 (d, J = 1.8 Hz, 1H), 8.67 (s, 1H), 8.19 (td, J = 8.5, 2.2 Hz, 2H), 8.01 (d, J = 8.8 Hz, 1H), 7.84 (d, J =
8.4 Hz, 1H), 7.69 (dd, J = 7.4, 1.0 Hz, 1H), 7.62-7.54 (m, 1H), 7.36 (d, J = 8.4 Hz, 1H), 3.59-3.41 (m, 6H), 2.14 (s, 3H), 1.73-1.50 (m, 4H), 0.91 (t, J = 7.3 Hz, 6H); MS(ESI<sup>+</sup>) m/z 603.1 (M+H)<sup>+</sup>.

Example 193:

Following a procedure analogous to that for the synthesis of Example 91, 2-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-5-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)benzoic acid (25 mg, 0.041 mmol) was converted to the title compound. "HNMR (CDCl<sub>3</sub>, 1:1 mixture of amide rotamers) δ 9.01 (s, 1H), 8.15-8.05 (m, 3H), 7.84 (d, J = 8.1 Hz, 1H), 7.66-7.63 (m, 1H), 7.54-7.50 (m, 1H), 7.35-7.28 (m, 1H), 7.19-7.06 (m, 3H), 6.99 (d, J = 6.4 Hz, 0.5H), 6.86 (d, J = 7.3 Hz, 0.5H), 5.17-5.12 (m, 1H), 4.87 (br s, 1H), 4.44-4.33 (m, 1H), 4.28-4.24 (m, 1H), 4.17 (br s, 1H), 3.92 (br s, 1H), 3.61-3.44 (m, 1H), 3.25-3.09 (m, 1H), 3.01 (br s, 1H), 2.94 (br s, 1H), 2.83-2.74 (m, 1.5H), 2.52-2.48 (m, 0.5H), 2.18-2.12 (m, 3H), 1.55-1.43 (m, 1H), 1.31-1.15 (m, 3H), 0.87-0.76 (m, 3H), 0.68-0.63 (m, 3H); MS(ESI<sup>+</sup>) m/z 748.5 (M+H)<sup>+</sup>.

Example 194

3-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-N-(8-chloronaphthalen-2-yl)sulfonyl)benzamide

Intermediate 194A: 3-((5)-3-(Azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-N-(8-chloronaphthalen-2-yl)sulfonyl)benzamide

- 281 -
Following a procedure analogous to that for the synthesis of Example 91, 2-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-5-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 193B, 50 mg, 0.083 mmol) and (5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline (Intermediate 92A, 17 mg, 0.091 mmol) were converted to the title compound. "H NMR (CDCl$_3$, 2:1 mixture of amide rotamers)  $\delta$ 9.15 (s, 1H), 8.27-8.13 (m, 1.5H), 8.07-7.80 (m, 2H), 7.72 (d, $J$ = 7.5 Hz, 1.5H), 7.61-7.51 (m, 1H), 7.36 (d, $J$ = 8.4 Hz, 1H), 7.28-7.11 (m, 3.5H), 7.28-7.11 (m, 3H), 7.08-6.98 (m, 1H), 6.94-6.82 (m, 0.5H), 5.34 (d, $J$ = 18.5 Hz, 1H), 4.38-3.93 (m, 3H), 3.48-3.36 (m, 2H), 3.32-2.72 (m, 5H), 2.24 (s, 1H), 2.16 (s, 2H), 1.60-1.12 (m, 4H), 0.94-0.62 (m, 6H); MS(ESI$^+$) m/z 773.2 (M+H$^+$).

Example 194: Following a procedure analogous to that for the synthesis of Intermediate 184B, (5)-3-(3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)benzamide (40 mg, 0.052 mmol) was converted to the title compound. "H NMR (CDCl$_3$, 1:1 mixture of amide rotamers)  $\delta$ 9.15 (s, 1H), 8.23-8.17 (m, 3H), 8.04 (d, $J$ = 8.8 Hz, 1H), 7.98 (dd, $J$ = 8.4, 2.0 Hz, 1H), 7.86 (d, $J$ = 8.1 Hz, 1H), 7.72 (d, $J$ = 7.5 Hz, 1H), 7.59 (t, $J$ = 7.9 Hz, 1H), 7.36 (d, $J$ = 8.4 Hz, 1H), 7.23-7.12 (m, 3.5H), 7.04 (d, $J$ = 7.4 Hz, 0.5H), 6.87 (br s, 1H), 5.36-5.31 (m, 1H), 4.95 (br s, 1H), 4.32 (m, 0.5H), 4.32-4.18 (m, 1.5H), 4.04-3.99 (m, 0.5H), 3.72-3.69 (m, 0.5H), 3.45-3.40 (m, 1H), 3.29-3.22 (m, 2H), 3.08 (br s, 2H), 2.94 (br s, 1H), 2.50-2.46 (m, 1H), 2.19 (s, 1.5H), 2.17 (s, 1.5H), 1.57-1.43 (m, 2H), 1.35-1.22 (m, 2H), 0.90-0.81 (m, 3H), 0.74-0.67 (m, 3H); MS(ESI$^+$) m/z 747.2 (M+H$^+$).

Example 195
4-(4-Chloro-3-(dipropylamino)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

Intermediate 195A: l-Benzyl-5-(trifluoromethyl)-1H-pyrazol-3-amine

[00520] To a solution of (£)-4-amino-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (Martins, M.A.P. et al, Synthesis, 9:1485-1493 (2006)) (1.84 g, 10.1 mmol) in EtOH (50.0 mL) was added Et₃N (3.0 mL, 21.2 mmol) followed by benzylhydrazine, 2HCl (1.97 g, 10.1 mmol). The resulting reaction mixture was stirred at 70 °C overnight and then concentrated in vacuo. The residue was redissolved in EtOAc and washed with sat. aq. NH₄Cl solution (2 x). The aqueous layer was extracted with EtOAc (3 x), and the combined organic extracts were dried over Na₂SO₄, filtered and concentrated in vacuo. The crude oil was purified using flash column chromatography (gradient from 0% to 40% EtOAc/hexanes) to give the title compound (1.25 g, 51%) as a 4:1 mixture of regioisomers by ¹H NMR. ¹H NMR (CDCl₃, major regioisomer) δ 7.41-7.29 (m, 3H), 7.22-7.14 (m, 2H), 5.83 (s, 1H), 5.26 (s, 2H), 3.47 (br s, 2H); MS(ESI⁺) m/z 242.1 (M+H)⁺.

Intermediate 195B: l-Benzyl-N,N-dipropyl-5-(trifluoromethyl)-1H-pyrazol-3-amine

[00521] To a 0 °C solution of propionic acid (12.4 mL, 166.0 mmol) in PhMe (15.0 mL) was added NaBH₄ (1.96 g, 51.8 mmol) portionwise to control the bubbling. The mixture was stirred at 0 °C until the evolution of ¾ ceased. Next, l-benzyl-5-(trifluoromethyl)-1H-pyrazol-3-amine (625 mg, 2.59 mmol) in PhMe (10.0 mL) was then
added dropwise via syringe. The resulting reaction mixture was heated at 10 °C overnight. Additional propionic acid (5.0 mL, 66.9 mmol) and NaBH₄ (1.00 g, 25.9 mmol) were added, and the reaction mixture was stirred overnight at 110 °C. The reaction mixture was then poured into EtOAc and 0.5N aq. NaOH solution (1:1). The layers were separated, and the organic layer was washed with 0.5N aq. NaOH solution. The aqueous layer was extracted with EtOAc (3 x), and the combined organic extracts were washed with sat. aq. NaCl solution and dried over Na₂SO₄. Filtration and concentration in vacuo provided a crude residue which was purified by flash column chromatography (gradient from 0% to 20% EtOAc/hexanes) to give the title compound (597 mg, 64%) as a 4:1 mixture of regioisomers by ¹H NMR. ¹H NMR (CDCl₃, major regioisomer) δ 7.41-7.25 (m, 3H), 7.19 (d, J = 7.0 Hz, 2H), 6.22 (s, 1H), 5.34 (s, 2H), 2.82-2.72 (m, 4H), 1.48-1.33 (m, 4H), 0.78 (t, J = 7.4 Hz, 6H); MS(ESI⁺) m/z 326.2 (M+H)⁺.

Intermediate 195C: N,N-Dipropyl-5-(trifluoromethyl)-1H-pyrazol-3-amine

To a 1 dram pressure vial containing 1-benzyl-N,N-dipropyl-5-(trifluoromethyl)-1H-pyrazol-3-amine (597 mg, 1.83 mmol) in EtOH (9.2 mL) was added 10% Pd/C (585 mg, 5.50 mmol) followed by dropwise addition of formic acid (3.9 mL, 101.0 mmol). The vial was capped, and the resulting black reaction mixture was heated at 78 °C for 1 h. The reaction mixture was filtered through a pad of CELITE® and concentrated in vacuo to give the title compound (401 mg, 93%) as a white solid. ¹H NMR (CDCl₃) δ 5.58 (s, 1H), 3.18-3.11 (m, 4H), 1.69-1.50 (m, 4H), 0.94 (t, J = 7.4 Hz, 6H); MS(ESI⁺) m/z 236.2 (M+H)⁺.

Intermediate 195D: 4-Chloro-N,N-dipropyl-5-(trifluoromethyl)-1H-pyrazol-3-amine

To N,N-dipropyl-5-(trifluoromethyl)-1H-pyrazol-3-amine (250 mg, 1.06 mmol) in DMF (5.3 mL) was added NCS (142 mg, 1.06 mmol). The resulting reaction
mixture was stirred at 100 °C for 1 h and then poured into sat. aq. NH₄Cl solution and
EtOAc (1:1). The organic layer was washed sat. aq. NH₄Cl solution (3 x), and the
combined aqueous layer was extracted with EtOAc (3 x). The combined organic extracts
were dried over Na₂SO₄, filtered and concentrated in vacuo to give the title compound
(287 mg, 100%). ¾ NMR (CDCl₃) δ 3.23-3.14 (m, 4H), 1.59-1.44 (m, 4H), 0.88 (t, J =
7.4 Hz, 6H); MS(ESI⁺) m/z 270.1 (M+H)⁺.

Intermediate 195E: 1-Benzyl 3-ethyl 4-(4-chloro-3-(dipropylamino)-5-(trifluoromethyl)-
1H-pyrazol-1-yl)isophthalate

Following a procedure analogous to that for the synthesis of Intermediate IE, 4-chloro
-N,N-dipropyl-5-(trifluoromethyl)-1H-pyrazol-3-amine (287 mg, 1.06 mmol) and
1-benzyl 3-ethyl 4-fluoroisophthalate (Intermediate 91B, 268 mg, 0.89 mmol) were
converted to the title compound (231 mg, 47%). MS(ESI⁺) m/z 552.3 (M+H)⁺.

Intermediate 195F: 4-(4-Chloro-3-(dipropylamino)-5-(trifluoromethyl)-1H-pyrazol-1-
yl)-3-(ethoxycarbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 91D,
1-benzyl 3-ethyl 4-(4-chloro-3-(dipropylamino)-5-(trifluoromethyl)-1H-pyrazol-1-
yl)isophthalate (131 mg, 0.24 mmol) was converted to the title compound (97 mg, 89%).
¹H NMR (CDCl₃) δ 8.62 (br s, 1H), 8.23 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H),
4.17-4.01 (m, 2H), 2.97-2.81 (m, 4H), 1.50-1.30 (m, 4H), 1.10 (t, J = 7.0 Hz, 3H), 0.74 (t,
J = 7.3 Hz, 6H); MS(ESI⁺) m/z 462.2 (M+H)⁺.

Intermediate 195G: Ethyl 2-(4-chloro-3-(dipropylamino)-5-(trifluoromethyl)-1H-
pyrazol-1-yl)-5-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)benzoate

- 285 -
Following a procedure analogous to that for the synthesis of Example 1, 4-(4-chloro-3-(dipropylamino)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-3-(ethoxycarbonyl)benzoic acid (64 mg, 0.14 mmol) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5, 34 mg, 0.14 mmol) were converted to the title compound (56 mg, 58%). MS(ESI\(^+\)) \textit{m/z} 685.3 (M+H\(^+\)).

Example 195:

Following a procedure analogous to that for the synthesis of Intermediate 9IF, ethyl 2-(4-chloro-3-(dipropylamino)-5-(trifluoromethyl)-1H-pyrazol-1-yl)-5-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)benzoate (56 mg, 0.081 mmol) was converted to the crude benzoic acid which was used in the subsequent step without purification. MS(ESI\(^+\)) \textit{m/z} 657.2 (M+H\(^+\)).

Example 196:

Following a procedure analogous to that for the synthesis of Example 91, the crude benzoic acid from above (25 mg, 0.038 mmol) and (5)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (Aldrich, 7 mg, 0.046 mmol) were converted to the title compound (13 mg, 40%). \textit{\(^1\)}H NMR (CD\(_3\)OD, mixture of amide rotamers) \(\delta\) 9.00 (s, 1H), 8.26-7.96 (m, 4H), 7.92 (d, \(J = 8.4\) Hz, 1H), 7.77-7.52 (m, 3H), 7.28-7.05 (m, 3.5H), 6.93 (d, \(J = 7.5\) Hz, 0.5H), 5.10 (d, \(J = 17.6\) Hz, 0.5H), 4.70-4.42 (m, 1H), 4.35-3.91 (m, 1H), 3.69-3.34 (m, 2H), 3.21-2.76 (m, 6H), 2.63 (d, \(J = 16.3\) Hz, 0.5H), 1.57-1.33 (m, 4H), 0.88-0.72 (m, 6H); MS(ESI\(^+\)) \textit{m/z} 802.4 (M+H\(^+\)).
Following a procedure analogous to that for the synthesis of Example 91, the crude benzoic acid from above (see Example 195, 29 mg, 0.044 mmol) and 1,2,3,4-tetrahydroisoquinoline (7 mg, 0.053 mmol) were converted to the title compound (11 mg, 31%). 1H NMR (CD$_3$OD, mixture of amide rotamers) $\delta$ 8.98 (s, 1H), 8.20-8.06 (m, 3H), 8.05-8.00 (m, 1H), 7.90 (d, $J$ = 8.1 Hz, 1H), 7.71-7.60 (m, 2H), 7.58-7.51 (m, 1H), 7.21-7.04 (m, 3.5H), 6.92 (d, $J$ = 7.3 Hz, 0.5H), 4.83-4.41 (m, 2H), 4.03-3.51 (m, 2H), 3.21-2.74 (m, 6H), 1.60-1.26 (m, 4H), 0.80 (dt, $J$ = 7.4, 4.6 Hz, 6H); MS(ESI$^+$) $m/z$ 772.4 (M+H)$^+$. 

Examples 197 to 222

The following Examples were prepared using the procedures described above.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Structure</th>
<th>Name</th>
<th>LCMS (M+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>197</td>
<td><img src="image" alt="Structure" /></td>
<td>3-(N-buty1-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonyl)carbamoxy)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamido) propanoic acid</td>
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<td>Structure</td>
<td>Name</td>
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<tr>
<td>198</td>
<td><img src="image1" alt="Structure" /></td>
<td>N,N-dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)-1H-indol-5-ylsulfonylearbamoyl)-2-((S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>919.3</td>
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<tr>
<td>199</td>
<td><img src="image2" alt="Structure" /></td>
<td>1-(4-(3-bromo-1-(3,4-dichlorobenzyl)-1H-indol-5-ylsulfonylearbamoyl)-2-((S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
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<td>200</td>
<td><img src="image3" alt="Structure" /></td>
<td>N-butyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylearbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-N-(3-(2-(4-methylpiperazin-1-yl)ethylamino)-3-oxopropyl)-1H-pyrazole-3-carboxamide</td>
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<td><img src="image4" alt="Structure" /></td>
<td>1 -(2-((S)-3-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(3-bromo-1-(3,4-dichlorobenzyl)-1H-indol-5-ylsulfonylearbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>996.2</td>
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<td>Ex. No.</td>
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<td>202</td>
<td><img src="image" alt="Structure 202" /></td>
<td>N,N-dibutyl-4-chloro-1-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-((S)-3-((3-methoxypropoxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>876.4</td>
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<td>203</td>
<td><img src="image" alt="Structure 203" /></td>
<td>1-(2-((S)&gt;3-(aminomethyl)-l,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
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<td><img src="image" alt="Structure 204" /></td>
<td>(Z)-N-(8-bromo-5-chloronaphthalen-2-ylsulfonyl)-4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-3-(3-(dimethylamino)-2,5-dihydro-1H-benzo[1,3]diazepine-2-carbonyl)benzamide</td>
<td>852.1</td>
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<td><img src="image" alt="Structure 205" /></td>
<td>1-(4-(7-bromo-1-ethylindolin-5-ylsulfonylcarbamoyl)-2-((5')-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
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<tr>
<td>206</td>
<td><img src="image" alt="Structure" /></td>
<td>4-chloro-1-(4-(1-ethylindolin-5-ylsulfonylcarbamoyl)-2-((5')-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-N,N-dipropyl-1H-pyrazole-3-carboxamide</td>
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<td><img src="image" alt="Structure" /></td>
<td>N-(8-bromo-5-chloronaphthalen-2-ylsulfonyl)-4-(4-chloro-3-(dipropylamino)-5-methyl-1H-pyrazol-1-yl)-3-((S&gt;3)-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>826.1</td>
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<td><img src="image" alt="Structure" /></td>
<td>1-(4-(7-bromo-1-ethyl-1H-indol-5-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N,N-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
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<td>1-(4-(7-bromo-1-ethylindolin-5-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-4-chloro-5-methyl-N,N-dipropyl-1H-pyrazole-3-carboxamide</td>
<td>841.2</td>
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<td>Ex. No.</td>
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<td><img src="image" alt="Structure" /></td>
<td><em>N,N</em>-dibutyl-4-chloro-1-(4-(3,7-dibromo-1-ethyl-1H-indol-5-ylsulfonylcarbamoyl)-2-((S)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>945.3</td>
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<td><img src="image" alt="Structure" /></td>
<td>1-(2-(6-bromo-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)phenyl)-<em>N,N</em>-dibutyl-4-chloro-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>969.2</td>
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<td><em>N,N</em>-dibutyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>951.3</td>
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<td>2-((4-((N-butyl-4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamido)methyl)biphenyl-4-yl)acetic acid</td>
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<tr>
<td>214</td>
<td><img src="image1" alt="Structure" /></td>
<td>2-(4'-(4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(l, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamido)methyl)biphenyl-4-yl)acetic acid</td>
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<td><img src="image2" alt="Structure" /></td>
<td>4-(3-(dibutylicarbamoyl)-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(l, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazol-4-yl)benzoic acid</td>
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<td>216</td>
<td><img src="image3" alt="Structure" /></td>
<td>4-chloro-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonylcarbamoyl)-2-(l, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-N,N-dipropyl-1H-pyrazole-3-carboxamide</td>
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<tr>
<td>217</td>
<td><img src="image4" alt="Structure" /></td>
<td>1-(4-(8-bromo-5-chloronaphthalen-2-ylsulfonyl)carbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-butyl-4-chloro-N-(4'-chlorobiphenyl-3-yl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>982.1</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Structure</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>218</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>1-(4-(8-bromo-5-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-N-butyl-4-chloro-N-(3′-chlorobiphenyl-3-yl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>982.1</td>
</tr>
<tr>
<td>219</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>N-butyl-4-chloro-N-((4′-chlorobiphenyl-4-yl)methyl)-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-yl)sulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>1035.2</td>
</tr>
<tr>
<td>220</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>N-butyl-4-chloro-N-(4-(4-chlorophenoxy)phenyl)-1-(4-(1-(3,4-dichlorobenzyl)indolin-5-yl)sulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>1037.1</td>
</tr>
<tr>
<td>221</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>N-butyl-4-chloro-N-(4′-chlorobiphenyl-3-yl)-1-(4-(5,8-dichloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxamide</td>
<td>938.1</td>
</tr>
</tbody>
</table>
Example 223

Ethyl 5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquiline-2-carbonyl)phenyl)-1-phenyl-1H-pyrazole-3-carboxylate

Intermediate 223A: tert-Butyl 4-iodo-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

[00531] A 100 mL flask was charged with 3-(tert-butoxycarbonyl)benzoic acid (Matrix, 1.75 g, 7.87 mmol), palladium(II) acetate (0.177 g, 0.787 mmol), iodobenzene diacetate (2.54 g, 7.87 mmol), iodine (2.00 g, 7.87 mmol), and tetrabutylammonium iodide (2.91 g, 7.87 mmol). DCE (30 mL) was added and the dark reaction mixture was stirred at 80 °C for 6 h. The reaction mixture was concentrated in vacuo, diluted with 2M
aq. sodium carbonate solution, and then extracted with ether (2 x). The aqueous layer was made acidic with concentrated HCl and then extracted with EtOAc (2 x). The pooled EtOAc extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to give crude 5-(tert-butoxycarbonyl)-2-iodobenzoic acid (1.7 g, 62%) which was used directly without further purification. A 200 mL round bottom flask was charged with crude 5-(tert-butoxycarbonyl)-2-iodobenzoic acid (1.7 g, 4.88 mmol) and HATU (2.23 g, 5.86 mmol). THF (30 mL), DMF (30.0 mL), and 2,6-lutidine (1.1 mL, 9.77 mmol) were added and the reaction mixture was stirred at room temperature for 1 h. Next, 1,2,3,4-tetrahydroisoquinoline (0.93 mL, 7.3 mmol) was then added. After stirring at room temperature 1 h, the reaction mixture was suspended in EtOAc, and then washed with sat. aq. sodium bicarbonate solution, 10% aq. LiCl solution, and then sat. aq. bicarbonate solution again. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (Isco 120 g column eluting with 0-40% EtOAc / hexanes) to give the title compound (1.46 g, 65%) as a white foam. HNMR (CDCl₃) δ 7.96-7.90 (m, 1H), 7.81-7.80 (m, 1H), 6.70-6.67 (m, 1H), 7.27-7.13 (m, 4H), 5.09-4.83 (m, 1H), 4.45-4.33 (m, 1H), 4.06-4.01 (m, 1H), 3.50-3.44 (m, 1H), 3.05-2.83 (m, 2H), 1.58 (s, 9H); MS(ESI) m/z 464.1 (M+H)⁺.

Intermediate 223B: tert-Butyl 4-formyl-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

[00532] Carbon monoxide was bubbled through a solution of tert-butyl 4-iodo-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (1.36 g, 2.94 mmol) and 1,1'-bis-(diphenylphosphino)-ferrocene) palladium dichloride (0.241 g, 0.294 mmol) in DMF (20 mL) at 70 °C for 10 min. DIPEA (1.28 mL, 7.34 mmol) and trioctylsilane (2.64 mL, 5.87 mmol) were added. The reaction mixture was stirred at 70 °C under CO (balloon) overnight. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with sat. aq. sodium bicarbonate solution, 10% aq. LiCl solution, and
then sat. aq. sodium bicarbonate solution again. The organic layer was dried over anhydrous sodium sulfate and concentrated \textit{in vacuo}. The residue was purified by flash chromatography (Isco 40 g column eluting from 0-40% EtOAc / hexanes) to give the title compound (537 mg, 50%) as a yellow foam. $^1$H NMR (CDCl$_3$, 1.5:1 mixture of amide rotamers) $\delta$ 10.19 (s, 0.5H), 10.14 (s, 0.5H), 8.17-8.13 (m, 1H), 8.03-7.98 (m, 2H), 7.26-7.10 (m, 4H), 5.00 (s, 1H), 4.33 (m, 1H), 4.09 (t, $J = 6$ Hz, 1H), 3.45 (t, $J = 6$ Hz, 1H), 3.04 (t, $J = 6$ Hz, 1H), 2.80 (t, $J = 6$ Hz, 1H), 1.61 (s, 9H); MS(ESI $^+$) $m/z$ 366.2 (M+H)$^+$. 

Intermediate 223C: \textit{t}-Butyl 4-(1-hydroxy-2-nitrohexyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

![Diagram](Int-223C)

[00533] To a solution of \textit{t}-butyl 4-formyl-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (480 mg, 1.31 mmol) in THF (3 mL) at 0 °C was added 1-nitropentane (0.323 mL, 2.63 mmol) followed by potassium tert-butoxide (0.131 mL, 0.131 mmol). The cooling bath was removed and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with EtOAc and washed with sat. aq. sodium bicarbonate solution. The aqueous layer was back-extracted with EtOAc and the pooled organic extracts were dried over anhydrous sodium sulfate and concentrated \textit{in vacuo} to give crude \textit{t}-butyl 4-(1-hydroxy-2-nitrohexyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate as a brown oil (2:1 mixture of diastereomers by LC-MS) which was used directly without further purification. MS(ESI $^+$) $m/z$ 483.3 (M+H)$^+$. 

Intermediate 223D: \textit{t}-Butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate
To a solution of tert-butyl 4-(1-hydroxy-2-nitrohexyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (632 mg, 1.31 mmol) in THF (3 mL) was added acetic anhydride (0.136 mL, 1.44 mmol) and a crystal of DMAP (~5 mg). After stirring at room temperature for 30 min, the reaction mixture was concentrated in vacuo. The residue was suspended in DCM (3.0 mL) and DMAP (192 mg, 1.57 mmol) was added. After stirring at room temperature overnight, the reaction mixture was diluted with DCM and washed with brine. The aqueous layer was back-extracted with DCM and the pooled organic layers were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (Isco 40 g column eluting with 0-25% EtOAc / hexanes) to give the title compound (485 mg, 80%) as a colorless oil. $^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) δ 8.12-8.09 (m, 1H), 8.01-8.00 (m, 1H), 7.97 (s, 0.5H), 7.81 (s, 0.5H), 7.46 (d, $J$ = 8 Hz, 0.5H), 7.39 (d, $J$ = 8 Hz, 0.5H), 7.24-6.79 (m, 4H), 4.94 (s, 1H), 4.31 (s, 1H), 3.47 (t, $J$ = 6 Hz, 1H), 3.00-2.47 (m, 5H), 1.65-1.31 (m, 4H), 1.63 (s, 9H), 0.95-0.86 (m, 3H); MS(ESI$^+$) m/z 465.3 (M+H)$^+$. Intermediate 223E: Ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate.

To a solution of (±)-ethyl 2-(2-phenylhydrazono)acetate (31 mg, 0.16 mmol) in THF (1 mL) at -78 °C was added potassium tert-butoxide (0.161 mL, 0.161 mmol).
After stirring at -78 °C for 15 min, a solution of tert-butyl 4-(2-nitrohex-l-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (75 mg, 0.161 mmol) in THF (1.0 mL) was added. After stirring at -78 °C for 15 min, TFA (0.024 mL, 0.323 mmol) was added and the reaction mixture became colorless. The reaction mixture was stirred at -78 °C for 2 h and was then allowed to warm to room temperature and stirred at room temperature for 30 min. The reaction mixture was quenched with sat. aq. sodium bicarbonate solution and then extracted with EtOAc. The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (Isco 40 g column eluting with 0-40% EtOAc / hexanes) to give the title compound (33 mg, 34%) as a colorless oil. 

\[^1H\text{NMR (CDCl}_3, 1:1 \text{ mixture of amide rotamers)} \delta 8.09 (dd, J = 8, 2 Hz, 1H), 8.05-8.03 (m, 1H), 7.49-7.37 (m, 6H), 7.26-6.81 (m, 4H), 5.02-4.98 (m, 1H), 4.47-4.38 (m, 1H), 4.32-4.27 (m, 2H), 4.16-3.98 (m, 1H), 3.58-3.40 (m, 1H), 2.82-2.51 (m, 4H), 1.61 (s, 9H), 1.28 (t, J = 8 Hz, 1.5H), 1.20 (t, J = 8 Hz, 1.5H), 1.47-0.91 (m, 4H), 0.60-0.56 (m, 3H); MS(ESI\(^+\)) m/z 608.3 (M+H\(^+\)).

Intermediate 223F: 4-(5-Butyl-3-(ethoxycarbonyl)-1-phenyl-1\(H\)-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

[00536] To a solution of ethyl 4-(4-((tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-phenyl-1\(H\)-pyrazole-3-carboxylate (33 mg, 0.054 mmol) in DCM (2.0 mL) was added TFA (1.0 mL). After stirring at room temperature for 1 h, the reaction mixture was concentrated in vacuo. The residue was used directly in the next step without further purification. MS(ESI\(^+\)) m/z 552.3 (M+H\(^+\)).

Example 223:

[00537] Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-3-(ethoxycarbonyl)-1-phenyl-1\(H\)-pyrazole-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)benzoic acid (15 mg, 0.027 mmol) and naphthalene-2-sulfonamide (11 mg, 0.054 mmol) were converted to the title compound (4.9 mg, 24%). ^1H NMR (1:1 CD$_3$OD:CDC1$_3$, 1:1 mixture of amide rotamers) δ 8.76 (s, 1H), 8.19-8.03 (m, 3H), 8.00-7.97 (m, 2H), 7.90-7.89 (m, 1H), 7.73-7.64 (m, 2H), 7.52-7.33 (m, 6H), 7.22-7.06 (m, 3.5H), 6.79-6.78 (m, 0.5H), 4.90-4.85 (m, 0.5H), 4.58-4.50 (m, 0.5H), 4.28-4.21 (m, 2H), 4.06-4.02 (m, 0.5H), 3.92-3.88 (m, 0.5H), 3.50-3.42 (m, 2H), 2.78-2.48 (m, 4H), 1.34-0.94 (m, 7H), 0.56 (t, J = 6 Hz, 3H); MS(ESI$^+$) m/z 741.4 (M+H).

Example 224

Ethyl 5-methyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-phenyl-1H-pyrazole-3-carboxylate

Intermediate 224A: tert-Butyl 4-(1-hydroxy-2-nitropropyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 223C, tert-butyl 4-formyl-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (59 mg, 0.16 mmol) and nitroethane (0.023 mL, 0.32 mmol) were converted to the title compound as a crude brown oil (1:1 mixture of diastereomers by LC-MS) which was used directly without further purification. MS(ESI$^+$) m/z 441.3 (M+H)$^+$. 

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Intermediate 224B: *tert*-Butyl 4-(2-nitroprop-l-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

![chemical structure of Intermediate 224B](image)

Following a procedure analogous to that for the synthesis of Intermediate 223D, *tert*-butyl 4-(1-hydroxy-2-nitropropyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl) benzoate (70 mg, 0.16 mmol) was converted to the title compound (48 mg, 71%) as a colorless oil. $^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 8.10 (dd, $J$ = 8, 4 Hz, 1H), 8.05 (s, 0.5H), 8.03-8.01 (m, 1H), 7.87 (s, 0.5H), 7.48 (d, $J$ = 8 Hz, 0.5H), 7.39 (d, $J$ = 8 Hz, 0.5H), 7.24-6.78 (m, 4H), 4.94 (s, 1H), 4.30 (s, 1H), 3.47 (t, $J$ = 6 Hz, 1H), 3.00 (t, $J$ = 4 Hz, 2H), 2.82 (t, $J$ = 6 Hz, 1H), 2.14 (s, 1.5H), 2.05 (s, 1.5H), 1.60 (s, 9H); MS(ESI$^+$) m/z 423.3 (M+H$^+$).

Intermediate 224C: Ethyl 4-((4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5 -methyl- 1-phenyl-1H-pyrazole-3-carboxylate

![chemical structure of Intermediate 224C](image)

Following a procedure analogous to that for the synthesis of Intermediate 224E, (Zs)-ethyl 2-(2-phenylhydrazono)acetate (22 mg, 0.11 mmol) and *tert*-butyl 4-(2-nitroprop-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (48 mg, 0.11 mmol) were converted to the title compound (42 mg, 65%) as a colorless oil. $^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 8.10 (dd, $J$ = 8, 2 Hz, 1H), 8.06-8.04 (m, 1H), 7.49-7.40 (m, 6H), 7.21-6.81 (m, 4H), 5.02-4.96 (m, 1H), 4.49-4.28 (m, 3H), 4.17-4.03
Intermediate 224D: 4-(3-(Ethoxycarbonyl)-5-methyl-1-phenyl-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-methyl-1H-pyrazole-3-carboxylate (42 mg, 0.074 mmol) was converted to the title compound which was used directly in the next step without purification. MS(ESI⁺) m/z 510.2 (M+H)⁺.

Example 224:

Following a procedure analogous to that for the synthesis of Example 1, 4-(3-(ethoxycarbonyl)-5-methyl-1-phenyl-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (19 mg, 0.037 mmol) and naphthalene-2-sulfonamide (15 mg, 0.074 mmol) were converted to the title compound (13 mg, 50%). ¾ NMR (1:1 CD₃OD:CDC1₃, 1:1 mixture of amide rotamers) δ 8.72-8.71 (m, 1H), 8.09-7.94 (m, 6H), 7.67-7.60 (m, 2H), 7.53-7.39 (m, 6H), 7.19-7.05 (m, 3.5H), 6.80-6.78 (m, 0.5H), 4.90-4.85 (m, 0.5H), 4.58-4.50 (m, 0.5H), 4.29-4.22 (m, 2H), 4.04-4.00 (m, 0.5H), 3.91-3.87 (m, 0.5H), 3.50-3.32 (m, 2H), 2.81-2.48 (m, 2H), 2.12 (s, 3H), 1.23-1.13 (m, 3H); MS(ESI⁺) m/z 699.3 (M+H).
Following a procedure analogous to that for the synthesis of Intermediate 223E, (Zs)-ethyl 2-(2-(4-methoxyphenyl)hydrazono)acetate (24 mg, 0.108 mmol) and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (50 mg, 0.108 mmol) were converted to the title compound (31 mg, 45%) as a colorless oil.

$^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 8.08 (dd, $J = 8$, 2 Hz, 1H), 8.03-8.02 (m, 1H), 7.42-6.81 (m, 9H), 5.02-4.98 (m, 1H), 4.46-4.38 (m, 1H), 4.32-4.26 (m, 2H), 4.15-3.98 (m, 1H), 3.86 (s, 1.5H), 3.85 (s, 1.5H), 3.54-3.33 (m, 1H), 2.81-2.45 (m, 4H), 1.61 (s, 9H), 1.28 (t, $J = 8$ Hz, 1.5H), 1.22 (t, $J = 8$ Hz, 1.5H), 1.30-0.95 (m, 4H), 0.61-0.57 (m, 3H); MS(ESI$^+$) $m/z$ 638.3 (M+H)$^+$.

Intermediate 225B: 4-(5-Butyl-3-(ethoxycarbonyl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (31 mg, 0.049 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI+) m/z 582.3 (M+H)+.

Example 225:
Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-3-(ethoxycarbonyl)-1-(4-methoxyphenyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (14 mg, 0.024 mmol) and naphthalene-2-sulfonamide (10 mg, 0.048 mmol) were converted to the title compound (6.0 mg, 32%).

H NMR (DMSO-d6) δ 8.63 (s, 1H), 8.20 (d, J = 8 Hz, 1H), 8.11-7.93 (m, 5H), 7.76-7.65 (m, 2H), 7.41-6.76 (m, 9H), 4.80-3.80 (m, 6H), 3.83 (s, 3H), 2.70-2.35 (m, 4H), 1.12-0.85 (m, 7H), 0.50 (t, J = 6 Hz, 3H); MS(ESI+) m/z 771.3 (M+H).

Example 226
Ethyl 5-butyl-1-(4-isopropylphenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate
Intermediate 226A: Ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-isopropylphenyl)-1H-pyrazole-3-carboxylate

Following a procedure analogous to that for the synthesis of Intermediate 223E, (Zs)-ethyl 2-(2-(4-zsopropylphenyl)hydrazono)acetate (25.2 mg, 0.108 mmol) and tert-butyl 4-(2-nitrohex-l-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (50 mg, 0.108 mmol) were converted to the title compound (36 mg, 52%) as a pale yellow oil.

\[ \text{\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 1:1 mixture of amide rotamers) } \delta 8.08 \text{ (dd, } J = 8, 2 \text{ Hz, } 1\text{H}), 8.04-8.03 \text{ (m, } 1\text{H}), 7.43-6.81 \text{ (m, } 9\text{H}), 5.02-4.98 \text{ (m, } 1\text{H}), 4.46-4.38 \text{ (m, } 1\text{H}), 4.30-4.27 \text{ (m, } 2\text{H}), 4.15-3.98 \text{ (m, } 1\text{H}), 3.54-3.33 \text{ (m, } 1\text{H}), 2.98-2.50 \text{ (m, } 5\text{H}), 1.61 \text{ (s, } 9\text{H}), 1.29-1.24 \text{ (m, } 7.5\text{H}), 1.22 \text{ (t, } J = 8 \text{ Hz, } 1.5\text{H}), 1.18-0.95 \text{ (m, } 4\text{H}), 0.60-0.56 \text{ (m, } 3\text{H}); \text{ MS(ESI\textsuperscript{+}) } m/z 650.4 \text{ (M+H\textsuperscript{+}).} \]

Intermediate 226B: 4-(5-Butyl-3-(ethoxycarbonyl)-1-(4-wopropylphenyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-isopropylphenyl)-1\(H\)-pyrazole-3-carboxylate (36 mg, 0.055 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI\(^+\)) \(m/z\) 594.3 (M+H\(^+\)).

Example 226:

Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-3-(ethoxycarbonyl)-1-(4-isopropylphenyl)-1\(H\)-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (16 mg, 0.027 mmol) and naphthalene-2-sulfonamide (11 mg, 0.055 mmol) were converted to the title compound (8 mg, 37%). \(^1\)H NMR (CD\(_3\)OD:CDCl\(_3\), 1:1 mixture of amide rotamers) \(\delta\) 8.70 (s, 1H), 8.10-8.04 (m, 3H), 8.01-7.98 (m, 2H), 7.95-7.93 (m, 1H), 7.67-7.59 (m, 2H), 7.44-7.04 (m, 8H), 6.80-6.78 (m, 0.5H), 4.90-4.85 (m, 0.5H), 4.58-4.50 (m, 0.5H), 4.28-4.21 (m, 2H), 4.06-4.02 (m, 0.5H), 3.92-3.88 (m, 0.5H), 3.50-3.42 (m, 2H), 2.80-2.48 (m, 5H), 1.43-0.96 (m, 13H), 0.58 (t, \(J = 6\) Hz, 3H); MS(ESI\(^+\)) \(m/z\) 783.4 (M+H).

Example 227

Ethyl 5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-(3-phenoxyphenyl)-1\(H\)-pyrazole-3-carboxylate

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Intermediate 227A: Ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(3-phenoxyphenyl)-1H-pyrazole-3-carboxylate

Following a procedure analogous to that for the synthesis of Intermediate 223E, (Zs)-ethyl 2-(2-(3-phenoxyphenyl)hydrazono)acetate (37 mg, 0.13 mmol) and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (60 mg, 0.13 mmol) were converted to the title compound (30 mg, 33%) as a pale yellow oil.

\[ \text{H NMR (CDCl}_3, 1:1 \text{ mixture of amide rotamers)} \delta 8.08 (dd, J = 8, 2 \text{ Hz}, 1H), 8.04-8.02 (m, 1H), 7.44-6.78 (m, 14H), 5.02-4.98 (m, 1H), 4.41-4.35 (m, 1H), 4.31-4.26 (m, 2H), 4.16-3.98 (m, 1H), 3.58-3.28 (m, 1H), 2.81-2.50 (m, 4H), 1.61 (s, 9H), 1.28 (t, J = 8 \text{ Hz}, 1.5 H), 1.22 (t, J = 8 \text{ Hz}, 1.5H), 1.13-0.88 (m, 4H), 0.63-0.59 (m, 3H); MS(ESI+) m/z 700.3 (M+H\(^+\)).

Intermediate 227B: 4-(5-Butyl-3-(ethoxycarbonyl)-1-(3-phenoxyphenyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(3-phenoxyphenyl)-1H-pyrazole-3-carboxylate (30 mg, 0.043 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI$^+$) m/z 644.3 (M+H)$^+$. 

Example 227:

Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-3-(ethoxycarbonyl)-1-(3-phenoxyphenyl)-1H-pyrazol-4-yl)-3-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (28 mg, 0.043 mmol) and naphthalene-2-sulfonamide (18 mg, 0.086 mmol) were converted to the title compound (17 mg, 46%). $^1$H NMR (1:1 CD$_3$OD:CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 8.75 (s, 1H), 8.22-7.86 (m, 6H), 7.73-7.62 (m, 2H), 7.49-7.35 (m, 4H), 7.18-6.95 (m, 9.5H), 6.79-6.76 (m, 0.5H), 4.84-4.79 (m, 0.5H), 4.47-4.43 (m, 0.5H), 4.25-4.21 (m, 2H), 4.05-4.01 (m, 0.5H), 3.91-3.87 (m, 0.5H), 3.52-3.46 (m, 2H), 2.77-2.71 (m, 2H), 2.52-2.47 (m, 2H), 1.44-0.97 (m, 7H), 0.60 (t, $J = 6$ Hz, 3H); MS(ESI$^+$) m/z 833.3 (M+H).

Example 228

Ethyl 5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-(4-phenoxyphenyl)-1H-pyrazole-3-carboxylate
Intermediate 228A: Ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-phenoxyphenyl)-1H-pyrazole-3-carboxylate

Following a procedure analogous to that for the synthesis of Intermediate 223E, ( £ )-ethyl 2-(2-(4-phenoxyphenyl)hydrazono)acetate (55 mg, 0.19 mmol) and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (90 mg, 0.19 mmol) were converted to the title compound (68 mg, 50%) as a pale yellow oil.

\(^1\)H NMR (CDCl\(_3\), 1:1 mixture of amide rotamers) \(\delta\) 8.09 (dd, \(J = 8, 2\) Hz, 1H), 8.05-8.03 (m, 1H), 7.44-6.82 (m, 14H), 5.02-4.98 (m, 1H), 4.48-4.39 (m, 1H), 4.34-4.27 (m, 2H), 4.14-3.98 (m, 1H), 3.58-3.35 (m, 1H), 2.83-2.50 (m, 4H), 1.61 (s, 9H), 1.27 (t, \(J = 8\) Hz, 1.5 H), 1.23 (t, \(J = 8\) Hz, 1.5H), 1.16-0.89 (m, 4H), 0.65-0.60 (m, 3H); MS(ESI\(^+\)) m/z 700.3 (M+H\(^+\)).

Intermediate 228B: 4-(5-Butyl-3-(ethoxycarbonyl)-1-(4-phenoxyphenyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-phenoxyphenyl)-1H-pyrazole-3-carboxylate (68 mg, 0.097 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI⁺) m/z 644.2 (M+Fc⁺).

Example 228C:
Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-3-(ethoxycarbonyl)-1-(4-phenoxyphenyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (62 mg, 0.097 mmol) and naphthalene-2-sulfonamide (40 mg, 0.19 mmol) were converted to the title compound (73 mg, 90%). ¾ NMR (1:1 CD₃OD:CDCl₃, 1:1 mixture of amide rotamers) δ 8.74 (s, 1H), 8.15-7.93 (m, 6H), 7.71-7.63 (m, 2H), 7.47-7.32 (m, 4H), 7.21-7.05 (m, 9.5H), 6.80-6.79 (m, 0.5H), 4.86-4.81 (m, 0.5H), 4.45-4.41 (m, 0.5H), 4.28-4.21 (m, 2H), 4.04-4.00 (m, 0.5H), 3.90-3.86 (m, 0.5H), 3.52-3.38 (m, 2H), 2.81-2.47 (m, 4H), 1.41-0.89 (m, 7H), 0.60 (t, J = 6 Hz, 3H); MS(ESI⁺) m/z 833.2 (M+H).

Example 229
Ethyl 5-butyl-1-(4-(4-chlorophenoxy)phenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate
Intermediate 229A: Ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-(4-chlorophenoxy)phenyl)-1H-pyrazole-3-carboxylate

Following a procedure analogous to that for the synthesis of Intermediate 223E, (R)-ethyl 2-(2-(4-(4-chlorophenoxy)phenyl)hydrazono)acetate (41 mg, 0.13 mmol) and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (60 mg, 0.13 mmol) were converted to the title compound (44 mg, 46%) as a pale yellow oil. 1H NMR (CDCl₃, 1:1 mixture of amide rotamers) δ 8.09 (dd, J = 8, 2 Hz, 1H), 8.04-8.03 (m, 1H), 7.43-6.81 (m, 13H), 5.02-4.98 (m, 1H), 4.48-4.38 (m, 1H), 4.33-4.27 (m, 2H), 4.18-3.98 (m, 1H), 3.58-3.32 (m, 1H), 2.85-2.48 (m, 4H), 1.61 (s, 9H), 1.28 (t, J = 8 Hz, 1.5H), 1.20 (t, J = 8 Hz, 1.5H), 1.15-0.91 (m, 4H), 0.63-0.59 (m, 3H); MS(ESI⁺) m/z 734.2 (M+H)⁺.

Intermediate 229B: 4-(5-Butyl-1-(4-(4-chlorophenoxy)phenyl)-3-(ethoxycarbonyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

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Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-(4-chlorophenoxy)phenyl)-1H-pyrazole-3-carboxylate (44 mg, 0.060 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI⁺) m/z 678.2 (M+H)⁺.

Example 229:

Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-1-(4-(4-chlorophenoxy)phenyl)-3-(ethoxycarbonyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (41 mg, 0.06 mmol) and naphthalene-2-sulfonamide (25 mg, 0.12 mmol) were converted to the title compound (12 mg, 22%). ¹H NMR (CD₂OD, 1:1 mixture of amide rotamers) δ 8.73 (s, 1H), 8.11-8.00 (m, 4H), 7.98-7.95 (m, 2H), 7.70-7.64 (m, 2H), 7.46-7.35 (m, 4H), 7.21-7.00 (m, 8.5H), 6.80-6.78 (m, 0.5H), 4.90-4.85 (m, 0.5H), 4.58-4.50 (m, 0.5H), 4.29-4.20 (m, 2H), 4.05-4.00 (m, 0.5H), 3.92-3.88 (m, 0.5H), 3.52-3.42 (m, 2H), 2.81-2.47 (m, 4H), 1.28-0.99 (m, 7H), 0.60 (t, J = 6 Hz, 3H); MS(ESI⁺) m/z 867.2 (M+H).

Example 230

Ethyl 5-butyl-1-(4-(3-chlorophenoxy)phenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate
Intermediate 230A: Ethyl 4-(4-((tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-(3-chlorophenoxy)phenyl)-1H-pyrazole-3-carboxylate

Following a procedure analogous to that for the synthesis of Intermediate 223E, (Zs)-ethyl 2-(2-(4-(3-chlorophenoxy)phenyl)hydrazono)acetate (60 mg, 0.19 mmol) and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (88 mg, 0.19 mmol) were converted to the title compound (62 mg, 45%) as a pale yellow oil. $^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 8.10 (dd, $J$ = 8, 2 Hz, 1H), 8.05-8.04 (m, 1H), 7.44-6.83 (m, 13H), 5.02-4.98 (m, 1H), 4.48-4.38 (m, 1H), 4.33-4.28 (m, 2H), 4.18-3.98 (m, 1H), 3.58-3.32 (m, 1H), 2.85-2.50 (m, 4H), 1.61 (s, 9H), 1.29 (t, $J$ = 8 Hz, 1.5H), 1.19 (t, $J$ = 8 Hz, 1.5H), 1.15-0.81 (m, 4H), 0.65-0.61 (m, 3H); MS(ESI$^+$) m/z 734.3 (M+H$^+$).

Intermediate 230B: 4-((5-Butyl-1-((4-(3-chlorophenoxy)phenyl)-3-((ethoxycarbonyl)-l H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-((4-((tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl)-5-butyl-l-(4-(3-chlorophenoxy)phenyl)-H-pyrazole-3-carboxylate (62 mg, 0.084 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI⁺) m/z 678.2 (M+H)⁺.

Example 230:

Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-l-(4-(3-chlorophenoxy)phenyl)-3-(ethoxycarbonyl)-l-H-pyrazol-4-yl)-3-[(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (57 mg, 0.084 mmol) and naphthalene-2-sulfonamide (35 mg, 0.17 mmol) were converted to the title compound (45 mg, 59%).

NMR (CDCl₃, 1:1 mixture of amide rotamers) δ 8.74 (s, 1H), 8.08 (d, J = 8 Hz, 1H), 7.97-7.88 (m, 5H), 7.65-7.52 (m, 2H), 7.43-6.88 (m, 12.5H), 6.73-6.72 (m, 0.5H), 4.82-4.78 (m, 0.5H), 4.52-4.48 (m, 0.5H), 4.34-3.92 (m, 3H), 3.38-3.29 (m, 2H), 2.80-2.51 (m, 4H), 1.31-0.87 (m, 7H), 0.54 (t, J = 6 Hz, 3H); MS(ESI⁺) m/z 867.2 (M+H).

Example 231

Ethyl 1-(4-butoxyphenyl)-5-butyl-4-(4-naphthalen-2-ylsulfonylcarbamoyl)-1-H-pyrazole-3-carboxylate

Intermediate 231A: Ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-(4-butoxyphenyl)-5-butyl-1H-pyrazole-3-carboxylate
Following a procedure analogous to that for the synthesis of Intermediate 223E, (Zs)-ethyl 2-(2-(4-butoxyphenyl)hydrazono)acetate (51 mg, 0.19 mmol) and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (90 mg, 0.19 mmol) were converted to the title compound (90 mg, 68%) as a pale yellow oil.

$^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 8.11 (dd, $J = 8$, 2 Hz, 1H), 8.07-8.05 (m, 1H), 7.46-6.88 (m, 9H), 5.02-4.98 (m, 1H), 4.48-4.38 (m, 1H), 4.33-4.28 (m, 2H), 4.18-3.98 (m, 3H), 3.58-3.32 (m, 1H), 2.85-2.50 (m, 4H), 1.85-1.79 (m, 2H), 1.61 (s, 9H), 1.59-1.51 (m, 2H), 1.31 (t, $J = 8$ Hz, 1.5H), 1.23 (t, $J = 8$ Hz, 1.5H), 1.13-0.95 (m, 7H), 0.65-0.60 (m, 3H); MS(ESI $^+$) m/z 680.3 (M+H)$^+$.  

Intermediate 23 IB: 4-(l-(4-Butoxyphenyl)-5-butyl-3-(ethoxycarbonyl)-l $H$-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l-(4-butoxyphenyl)-5 -butyl-1H-pyrazole-3-carboxylate (68 mg, 0.10 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI $^+$) m/z 624.3 (M+H)$^+$.  

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Example 231:

Following a procedure analogous to that for the synthesis of Example 1, 4-(1-(4-butoxyphenyl)-5-butyl-3-(ethoxycarbonyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (82 mg, 0.13 mmol) and naphthalene-2-sulfonamide (55 mg, 0.26 mmol) were converted to the title compound (76 mg, 69%). 1H NMR (CD3OD, 1:1 mixture of amide rotamers) δ 8.68 (s, 1H), 8.23-7.97 (m, 6H), 7.69-7.62 (m, 2H), 7.47 (d, J = 8 Hz, 0.5H), 7.41 (d, J = 8 Hz, 0.5H), 7.32-7.30 (m, 1H), 7.29 (d, J = 8 Hz, 1H), 7.21-7.04 (m, 5.5H), 6.79-6.78 (m, 0.5H), 4.61-3.80 (m, 6H), 3.50-3.35 (m, 2H), 2.77-2.45 (m, 4H), 1.84-1.78 (m, 2H), 1.61-1.53 (m, 2H), 1.16-1.01 (m, 10H), 0.59 (t, J = 6 Hz, 3H); MS(ESI+) m/z 813.3 (M+H).

Example 232

Ethyl 5-butyl-1-(4-(2-hydroxyethyl)phenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate

Intermediate 232A: Ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(4-(2-hydroxyethyl)phenyl)-1H-pyrazole-3-carboxylate

Following a procedure analogous to that for the synthesis of Intermediate 223E, (±)-ethyl 2-(2-(4-(2-hydroxyethyl)phenyl)hydrazono)acetate (61 mg, 0.26 mmol)
and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)benzoate (120 mg, 0.26 mmol) were converted to the title compound (29 mg,
17%) as a pale yellow oil. $^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 8.10 (dd, $J$
= 8, 2 Hz, 1H), 8.05-8.03 (m, 1H), 7.44-6.82 (m, 9H), 5.02-4.98 (m, 1H), 4.48-4.38 (m,
1H), 4.32-4.26 (m, 2H), 4.15-3.98 (m, 1H), 3.89-3.88 (m, 2H), 3.58-3.38 (m, 1H), 2.96-
2.92 (m, 2H), 2.88-2.50 (m, 4H), 1.61 (s, 9H), 1.29 (t, $J$ = 8 Hz, 1.5 H), 1.21 (t, $J$ = 8 Hz,
1.5H), 1.13-0.95 (m, 4H), 0.62-0.57 (m, 3H); MS(ESI$^+$) m/z 652.3 (M+H)$^+$.  

Intermediate 232B: 4-(5-Butyl-3-(ethoxycarbonyl)-1-(4-(2-hydroxyethyl)phenyl)-1
H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate
223F, ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-
carbonyl)phenyl)-5-butyl-1-(4-(2-hydroxyethyl)phenyl)-1H-pyrazole-3-carboxylate (29
mg, 0.044 mmol) was converted to the title compound which was used directly in the
next step without further purification. MS(ESI$^+$) m/z 596.3 (M+H)$^+$.  

Example 232:

Following a procedure analogous to that for the synthesis of Example 1, 4-(5-
butyl-3-(ethoxycarbonyl)-1-(4-(2-hydroxy ethyl)phenyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)benzoic acid (26 mg, 0.044 mmol) and naphthalene-2 -
sulfonamide (27 mg, 0.13 mmol) were converted to the title compound (24 mg, 66%). $^1$H
NMR (CD$_3$OD, 1:1 mixture of amide rotamers) $\delta$ 8.73 (s, 1H), 8.1 1-8.06 (m, 3H), 8.01-
7.98 (m, 2H), 7.92-7.89 (m, 1H), 7.72-7.64 (m, 2H), 7.50-6.78 (m, 9H), 4.74-3.94 (m,
4H), 3.83-3.75 (m, 2H), 3.45-3.29 (m, 2H), 2.92-2.89 (m, 2H), 2.84-2.50 (m, 4H), 1.15-
0.89 (m, 7H), 0.56 (t, $J$ = 6 Hz, 3H); MS(ESI$^+$) m/z 785.2 (M+H).
Example 233

Ethyl 1-(4-(allyloxy)phenyl)-5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate

Intermediate 233A: Ethyl 1-(4-(allyloxy)phenyl)-4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1H-pyrazole-3-carboxylate

[00567] Following a procedure analogous to that for the synthesis of Intermediate 223E, (Zs)-ethyl 2-(2-(4-(allyloxy)phenyl)hydrazono)acetate (64 mg, 0.26 mmol) and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (120 mg, 0.26 mmol) were converted to the title compound (114 mg, 67%) as a pale yellow oil. ¹HNMR (CDCl₃, 1:1 mixture of amide rotamers) δ 8.10 (dd, J = 8, 2 Hz, 1H), 8.04-8.03 (m, 1H), 7.43-6.81 (m, 9H), 6.11-6.04 (m, 1H), 5.45-5.40 (m, 1H), 5.34-5.30 (m, 1H), 5.02-4.98 (m, 1H), 4.59-4.57 (m, 2H), 4.48-4.38 (m, 1H), 4.32-4.26 (m, 2H), 4.15-3.98 (m, 1H), 3.58-3.32 (m, 1H), 2.86-2.45 (m, 4H), 1.61 (s, 9H), 1.27 (t, J = 8 Hz, 1.5H), 1.20 (t, J = 8 Hz, 1.5H), 1.11-0.92 (m, 4H), 0.62-0.57 (m, 3H); MS(ESI⁺) m/z 664.4 (M+H)⁺.

Intermediate 233B: 4-(1-(4-(Allyloxy)phenyl)-5-butyl-3-(ethoxycarbonyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 1-(4-(allyloxy)phenyl)-4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1H-pyrazole-3-carboxylate (114 mg, 0.172 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI+) m/z 608.3 (M+H)+.

Example 223:

Following a procedure analogous to that for the synthesis of Example 1, 4-(1-(4-(allyloxy)phenyl)-5-butyl-3-(ethoxycarbonyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (105 mg, 0.172 mmol) and naphthalene-2-sulfonamide (107 mg, 0.516 mmol) were converted to the title compound (116 mg, 82%). 1H NMR (CD3OD, 1:1 mixture of amide rotamers) δ 8.68 (s, 1H), 8.13-7.93 (m, 6H), 7.66-7.59 (m, 2H), 7.45-6.76 (m, 9H), 6.15-6.05 (m, 1H), 5.47-5.43 (m, 1H), 5.32-5.29 (m, 1H), 4.64-4.63 (m, 2H), 4.56-4.15 (m, 4H), 3.91-3.26 (m, 2H), 2.79-2.45 (m, 4H), 1.15-0.92 (m, 7H), 0.60-0.56 (m, 3H); MS(ESI+) m/z 797.3 (M+H).

Example 234

Ethyl 1-(biphenyl-4-yl)-5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate

(234)
Intermediate 234A: Ethyl 1-(biphenyl-4-yl)-4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1H-pyrazole-3-carboxylate

Following a procedure analogous to that for the synthesis of Intermediate 223E, (S)-ethyl 2-(2-(biphenyl-4-yl)hydrazono)acetate (35 mg, 0.13 mmol) and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (60 mg, 0.13 mmol) were converted to the title compound (55 mg, 62%) as a pale yellow solid.

$^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) $\delta$ 8.13 (dd, $J$ = 8, 2 Hz, 1H), 8.09-8.07 (m, 1H), 7.74-7.43 (m, 10H), 7.23-6.86 (m, 4H), 5.02-4.98 (m, 1H), 4.55-4.47 (m, 1H), 4.37-4.31 (m, 2H), 4.20-4.02 (m, 1H), 3.58-3.35 (m, 1H), 2.90-2.51 (m, 4H), 1.61 (s, 9H), 1.32 (t, $J$ = 8 Hz, 1.5H), 1.26 (t, $J$ = 8 Hz, 1.5H), 1.21-0.97 (m, 4H), 0.66-0.62 (m, 3H); MS(ESI $^+$) m/z 684.4 (M+H)$^+$. 

Intermediate 234B: 4-(1-(Biphenyl-4-yl)-5-butyl-3-(ethoxycarbonyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 1-(biphenyl-4-yl)-4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1H-pyrazole-3-carboxylate (55 mg,
0.080 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI⁺) m/z 628.4 (M+H)⁺.

Example 234:

Following a procedure analogous to that for the synthesis of Example 1, 4-(1-(biphenyl-4-yl)-5-butyl-3-methyl-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (46 mg, 0.08 mmol) and naphthalene-2-sulfonamide (33 mg, 0.16 mmol) were converted to the title compound (40 mg, 81%). ¾ NMR (CDCl₃, 1:1 mixture of amide rotamers) δ 8.81 (s, 1H), 8.15-7.90 (m, 6H), 7.69-7.34 (m, 12H), 7.17-6.78 (m, 4H), 4.56-3.95 (m, 4H), 3.50-3.29 (m, 2H), 2.82-2.64 (m, 4H), 1.31-0.87 (m, 7H), 0.62-0.57 (m, 3H); MS(ESI⁺) m/z 817.4 (M+H).

Example 235

Ethyl 5-butyl-1-(3-(methoxycarbonyl)phenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-pyrazole-3-carboxylate

Intermediate 235A: Ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(3-(methoxycarbonyl)phenyl)-1H-pyrazole-3-carboxylate
Following a procedure analogous to that for the synthesis of Intermediate 223E, (E)-methyl 3-(2-(2-ethoxy-2-oxoethylidene)hydrazinyl)benzoate (65 mg, 0.26 mmol) and tert-butyl 4-(2-nitrohex-1-enyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (120 mg, 0.26 mmol) were converted to the title compound (50 mg, 29%). MS(ESI+) m/z 666.3 (M+H)+.

Intermediate 235B: 4-(5-Butyl-3-(ethoxycarbonyl)-1-(3-(methoxycarbonyl)phenyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-(4-(tert-butoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-(3-(methoxycarbonyl)phenyl)-1H-pyrazole-3-carboxylate (70 mg, 0.11 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI+) m/z 610.2 (M+H)+.

Example 235:

Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-3-(ethoxycarbonyl)-1-(3-(methoxycarbonyl)phenyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)benzoic acid (64 mg, 0.11 mmol) and naphthalene-2-sulfonamide (44 mg, 0.21 mmol) were converted to the title compound (68 mg, 77%). \(^1\)H NMR (CDCl\(_3\), 1:1 mixture of amide rotamers) \(\delta\) 8.51 (s, 1H), 8.09-7.79 (m, 8H), 7.69-7.57 (m, 4H), 7.37-7.28 (m, 1H), 7.13-7.00 (m, 3.5H), 6.70-6.69 (m, 0.5H), 4.66-3.95 (m, 4H), 3.85 (s, 1.5H), 3.82 (s, 1.5H), 3.30-3.19 (m, 2H), 2.73-2.42 (m, 4H), 1.12-0.84 (m, 7H), 0.44-0.42 (m, 3H); MS(ESI\(^+\)) \(m/z\) 199.2 (M+H).

Example 236

4-(5-Butyl-3-(hydroxymethyl)-1-phenyl-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

\[\text{HO} \quad \text{N} \quad \text{SO} \quad \text{NH} \quad \text{O} \quad \text{H} \quad \text{C} \]

(236)

[00576] A 25 mL round bottom flask was charged with ethyl 5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-phenyl-1H-pyrazole-3-carboxylate (Example 223, 23 mg, 0.031 mmol). THF (1.0 mL) and then 2M lithium borohydride solution in THF (0.078 mL, 0.16 mmol) were added. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with sat. aq. sodium bicarbonate solution and extracted with EtOAc. The combined organic extracts were dried over anhydrous sodium sulfate and concentrated \textit{in vacuo} to give the crude product. The residue was purified by preparative HPLC to give the title compound (7.3 mg, 34%). \(^1\)H NMR (CDCl\(_3\), 1:1 mixture of amide rotamers) \(\delta\) 8.65 (s, 1H), 8.12-7.91 (m, 6H), 7.63-7.57 (m, 2H), 7.50-6.99 (m, 9.5H), 6.91-6.89 (m, 0.5H), 4.65-4.32 (m, 4H), 3.44-3.15 (m, 2H), 2.88-2.49 (m, 4H), 1.39-0.86 (m, 4H), 0.55-0.49 (m, 3H); MS(ESI\(^+\)) \(m/z\) 699.2 (M+H\(^+\)).

Example 237

5-Butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-phenyl-1H-pyrazole-3-carboxylic acid

- 322 -
A 25 mL round bottom flask was charged with ethyl 5-butyl-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-phenyl-1H-pyrazole-3-carboxylate (Example 223, 52 mg, 0.070 mmol). THF (2.0 mL) and then 1N aq. NaOH solution (0.140 mL, 0.140 mmol) were added. The reaction mixture was stirred at room temperature overnight. After concentration *in vacuo* to remove the THF, the reaction mixture was made acidic (pH 3-4) with cone. HCl. The product was extracted with EtOAc and the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the crude product (50 mg, 100%) as a yellow oil. A portion (approx. 10 mg) was purified by preparative HPLC to give the title compound (4 mg).

**Example 238**

4-(5-Butyl-3-(hydroxymethyl)-1-(3-(hydroxymethyl)phenyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

**H NMR** (CDCl₃, 1:1 mixture of amide rotamers) δ 8.63 (s, 1H), 8.1 1-8.05 (m, 3H), 8.01-7.98 (m, 1H), 7.94 (d, J = 4 Hz, 1H), 7.90 (d, J = 4 Hz, 1H), 7.61-7.55 (m, 2H), 7.52-7.35 (m, 6H), 7.19-7.04 (m, 3.5H), 6.86-6.82 (m, 0.5H), 4.90-4.80 (m, 0.5H), 4.51-4.36 (m, 1.5H), 3.65-3.43 (m, 2H), 2.88-2.49 (m, 4H), 1.12-0.89 (m, 4H), 0.61-0.56 (m, 3H);

**MS(ESI⁺) m/z** 713.3 (M+H)⁺.
[00578] Following a procedure analogous to that for the synthesis of Example 236, ethyl 5-butyl-l-(3-(methoxycarbonyl)phenyl)-4-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-pyrazole-3-carboxylate (25 mg, 0.031 mmol, Example 235) was converted to the title compound (9 mg, 39%). ¹H NMR (CD₃OD) δ 8.69 (s, 1H), 8.11-7.98 (m, 7H), 7.70-7.63 (m, 3H), 7.47-7.33 (m, 3H), 7.22-7.00 (m, 3.5H), 6.95-6.85 (m, 0.5H), 4.80-4.20 (m, 6H), 3.44-3.16 (m, 2H), 2.88-2.45 (m, 4H), 1.10-0.82 (m, 4H), 0.59-0.48 (m, 3H); MS(ESI⁺) m/z 729.2 (M+H)⁺.

Example 239

Ethyl 5-butyl-l-phenyl-4-(2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(2-(trimethylsilyl)ethanesulfonamide)phenyl)-l H-pyrazole-3-carboxylate

[00579] Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-3-(ethoxycarbonyl)-l-phenyl-l H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate 223F, 55 mg, 0.10 mmol) and 2-(trimethylsilyl)ethanesulfonamide (Aldrich, 36 mg, 0.20 mmol) were converted to the title compound (65 mg, 86%). ¹H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 8.08 (dd, J = 8, 2 Hz, 1H), 8.01 (s, 1H), 7.58-7.38 (m, 6H), 7.22-7.10 (m, 3.5H), 6.82-6.78 (m, 0.5H), 4.65-3.86 (m, 6H), 3.54-3.49 (m, 2H), 2.83-2.53 (m, 4H), 1.21-0.99 (m, 9H), 0.59 (t, J = 6 Hz, 3H), 0.10 (s, 9H); MS(ESI⁺) m/z 715.3 (M+H)⁺.

Example 240

4-(5-Butyl-3-(hydroxymethyl)-1-phenyl-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(2-(trimethylsilyl)ethanesulfonamide)benzamide
Following a procedure analogous to that for the synthesis of Example 236, ethyl 5-butyl-l-phenyl-4-(2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(2-(trimethylsilyl) ethylsulfonylcarbamoyl)phenyl)-1H-pyrazole-3-carboxylate (Example 239, 45 mg, 0.063 mmol) was converted to the title compound (24 mg, 55%). $^1$H NMR (1:1 CD$_3$OD:CDC$_1$$_3$) δ 8.02-8.00 (m, 1H), 7.96-7.95 (m, 1H), 7.56-7.23 (m, 5H), 7.13-6.77 (m, 5H), 4.45-4.10 (m, 6H), 3.41-3.37 (m, 2H), 2.90-2.42 (m, 4H), 1.02-0.80 (m, 6H), 0.548-0.44 (m, 3H), 0.01 (s, 9H); MS(ESI$^+$) m/z 673.3 (M+H)$^+$. 

**Examples 241 to 247**

The following Examples were prepared from the corresponding ethyl esters (described above) according to the procedure for the synthesis of Example 236.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R</th>
<th>Name</th>
<th>LCMS (M+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>241</td>
<td><img src="image" alt="R" /></td>
<td>4-(5-butyl-3-(hydroxymethyl)-1-(4-phenoxyphenyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>791.2</td>
</tr>
<tr>
<td>242</td>
<td><img src="image" alt="R" /></td>
<td>4-(5-butyl-1-(4-(4-chlorophenoxy)phenyl)-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>825.2</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>R</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>--------</td>
<td>---</td>
<td>----------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>243</td>
<td><img src="image" alt="Structure" /></td>
<td>4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(hydroxymethyl)-IH-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>825.1</td>
</tr>
<tr>
<td>244</td>
<td><img src="image" alt="Structure" /></td>
<td>4-(5-butyl-1-(4-(4-butoxyphenyl)-3-(hydroxymethyl)-IH-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>771.2</td>
</tr>
<tr>
<td>245</td>
<td><img src="image" alt="Structure" /></td>
<td>4-(5-butyl-1-(4-(2-hydroxyethyl)phenyl)-3-(hydroxymethyl)-IH-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>743.3</td>
</tr>
<tr>
<td>246</td>
<td><img src="image" alt="Structure" /></td>
<td>4-(1-(4-(allyloxy)phenyl)-5-butyl-3-(hydroxymethyl)-IH-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>755.2</td>
</tr>
<tr>
<td>247</td>
<td><img src="image" alt="Structure" /></td>
<td>4-(1-(biphenyl-4-yl)-5-butyl-3-(hydroxymethyl)-IH-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>775.5</td>
</tr>
</tbody>
</table>

Examples 248 to 251

[00582] The following Examples were prepared using 4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(ethoxycarbonyl)-IH-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate 230B) and the corresponding sulfonamide intermediates (described above or commercially available) according to the procedure for the synthesis of Example 1.
The following Examples were prepared from the corresponding ethyl esters (described above) according to the procedure for the synthesis of Example 236.
<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>R</th>
<th>Name</th>
<th>LCMS (M+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>252</td>
<td>![R252]</td>
<td>4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>859.4</td>
</tr>
<tr>
<td>253</td>
<td>![R253]</td>
<td>4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(ethylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>727.5</td>
</tr>
<tr>
<td>254</td>
<td>![R254]</td>
<td>4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(pentylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>769.5</td>
</tr>
<tr>
<td>255</td>
<td>![R255]</td>
<td>N-(8-bromo-5-chloronaphthalen-2-ylsulfonyl)-4-(5-butyl-1-(4-(3-chlorophenoxy)phenyl)-3-(hydroxymethyl)-1H-pyrazol-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>939.4</td>
</tr>
</tbody>
</table>

**Example 256**

4-(5-Butyl-3-(hydroxymethyl)-1-(4-hydroxyphenyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

![Chemical Structure](image)

**[00584]** Isolation of a by-product from Example 246 gave the title compound (16 mg, 16%). \(^1\)H NMR (1:1 CD3OD:CDCl3, 1:1 mixture of amide rotamers) \(\delta 8.65-8.64 \text{ (m, 1H)}, 8.29-7.90 \text{ (m, 6H)}, 7.61-7.56 \text{ (m, 2H)}, 7.32-6.80 \text{ (m, 9H)}, 4.78-4.19 \text{ (m, 6H)}, 2.89-2.41 \text{ (m, 4H)}, 1.05-0.83 \text{ (m, 4H)}, 0.65-0.51 \text{ (m, 3H)}; MS(ESI\textsuperscript{+}) \textit{m/z} 715.2 (M+H).
Example 257

4-(5-Butyl-3-(hydroxymethyl)-1-(4-(3-hydroxypropoxy)phenyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

(257)

[00585] Isolation of a by-product from Example 246 to give the title compound (8.5 mg, 8%). 'HNMR (1:1 CD3OD:CDCl3, 1:1 mixture of amide rotamers) δ 8.74 (s, 1H), 8.11-7.94 (m, 6H), 7.71-7.63 (m, 2H), 7.34-6.82 (m, 9H), 4.55-4.21 (m, 6H), 4.13 (t, J = 8 Hz, 2H), 3.80-3.76 (m, 2H), 2.89-2.41 (m, 4H), 2.04 (t, J = 8 Hz, 2H), 1.02-0.86 (m, 4H), 0.55-0.54 (m, 3H); MS(ESI+) m/z 773.2 (M+H).

Example 258

(±)-4-(5-Butyl-1-(4-(2,3-dihydroxypropoxy)phenyl)-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

(258)

[00586] To a solution of 4-(1-(4-(allyloxy)phenyl)-5-butyl-3-(hydroxymethyl)-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide (Example 246, 30 mg, 0.040 mmol) in tert-BuOH (1 mL), THF (0.3 mL), and water (0.1 mL) at 0 °C was added NMO (5.6 mg, 0.048 mmol) followed by osmium tetroxide (0.062 mL, 7.9 µmol, 4 wt%). After stirring at room temperature overnight, the reaction mixture was diluted with EtOAc, washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (Isco 40 g column eluting with 0-15% methanol/DCM). The resulting solid was lyophilized from acetonitrile/water to give the title compound (22 mg, 70%) as a white solid. 'HNMR (CD3OD, 1:1 mixture of amide rotamers) δ 8.62 (s, 1H), 8.14-7.93
(m, 6H), 7.64-7.57 (m, 2H), 7.40-6.87 (m, 9H), 4.87-4.00 (m, 9H), 3.70-3.67 (m, 2H),
3.12-2.35 (m, 4H), 1.07-0.88 (m, 4H), 0.56-0.52 (m, 3H); MS(ESI+) m/z 789.5 (M+H).

Example 259

**Ethyl 5-butyl-4-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-
(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-phenyl-1H-pyrazole-3-carboxylate**

![Chemical Structure of Example 259](image)

Intermediate 259A: (5)-tert-Butyl 3-(3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)-4-iodobenzoate

![Chemical Structure of Intermediate 259A](image)

[00587] Following a procedure analogous to that for the synthesis of Intermediate 223A, 5-(tert-butoxycarbonyl)-2-iodobenzoic acid (1.67 g, 4.81 mmol) and (S)-3-((tert-
butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline (1.6 g, 5.8 mmol) were
converted to the title compound (1.57 g, 54%). MS(ESI+) m/z 608.1 (M+H)+.

Intermediate 259B: (5)-tert-Butyl 3-(3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)-4-formylbenzoate

- 330 -
Following a procedure analogous to that for the synthesis of Intermediate 223B, (S)-tert-butyl 3-(3-(tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-iodobenzoate (1.57 g, 2.58 mmol) was converted to the title compound (0.58 g, 44%). $^1$H NMR (CDCl$_3$, 1.5:1 mixture of amide rotamers) $\delta$ 10.16 (s, 0.6H), 10.09 (s, 0.4H), 8.19-8.15 (m, 1H), 8.05-7.97 (m, 2H), 7.53-7.11 (m, 4H), 5.48-5.09 (m, 1H), 4.45-3.82 (m, 2H), 3.55-3.42 (m, 3H), 3.20-2.95 (m, 1H), 1.61 (s, 9H), 0.94 (s, 9H), 0.01 (s, 6H); MS(ESI$^+$) $m/z$ 510.3 (M+H)$^+$. 

Intermediate 259C: tert-Butyl 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(1-hydroxy-2-nitrohexyl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 223C, (S)-tert-butyl 3-(3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-formylbenzoate (0.53 g, 1.0 mmol) was converted to the title compound as a crude 1:1 mixture of diastereomers which was used directly without purification. MS(ESI$^+$) $m/z$ 627.3 (M+H)$^+$. 

Intermediate 259D: (5)-tert-Butyl 3-(3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(2-nitrohex-1-enyl)benzoate
[00590] Following a procedure analogous to that for the synthesis of Intermediate 223D, tert-butyl 3-((5')-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(I-hydroxy-2-nitrohexyl)benzoate (652 mg, 1.04 mmol) was converted to the title compound (0.42 g, 66%). $^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) δ 8.13-8.10 (m, 1H), 8.05 (s, 0.5H), 7.96 (d, J = 8 Hz, 1H), 7.82 (s, 0.5H), 7.45 (t, J = 8 Hz, 1H), 7.25-7.10 (m, 3.5H), 6.79 (d, J = 4 Hz, 0.5H), 5.33-5.10 (m, 1H), 4.43-4.19 (m, 1H), 3.81-3.73 (m, 1H), 3.50-3.40 (m, 1H), 3.09-2.98 (m, 1.5H), 2.83-2.60 (m, 3.5H), 1.65-1.32 (m, 4H), 1.61 (s, 9H), 0.96-0.86 (m, 3H), 0.81 (s, 4.5H), 0.77 (s, 4.5H), 0.05 (s, 6H); MS(ESI$^+$) m/z 609.3 (M+H$^+$).

Intermediate 259E: Ethyl 4-(4-(tert-butoxycarbonyl)-2-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate

[00591] Following a procedure analogous to that for the synthesis of Intermediate 223E, (Zs)-ethyl 2-(2-phenylhydrazono)acetate (133 mg, 0.690 mmol) and of (S)-tert-butyl 3-(3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(2-nitrohex-1-yl)benzoate (420 mg, 0.690 mmol) were converted to the title compound (335 mg, 65%). $^1$H NMR (CDCl$_3$, 1:1 mixture of amide rotamers) δ 8.15-8.06 (m, 2H), 7.51-7.39 (m, 5H), 7.22-6.80 (m, 5H), 5.02-4.98 (m, 1H), 4.39-4.04 (m,
3H), 3.82-3.28 (m, 2H), 3.04-3.00 (m, 1H), 2.90-2.78 (m, 1H), 2.61-2.24 (m, 2H), 1.61 (s, 9H), 1.32-0.90 (m, 7H), 0.77 (s, 9H), 0.59 (t, J = 8 Hz, 1.5H), 0.55 (t, J = 8 Hz, 1.5H), 0.00 (s, 9H); MS(ESI+) m/z 752.4 (M+H)+.

Intermediate 259F: 4-(5-Butyl-3-(ethoxycarbonyl)-1-phenyl-1H-pyrazol-4-yl)-3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

![Intermediate 259F](image)

[00592] To a solution of ethyl 4-(4-(tert-butoxycarbonyl)-2-((S)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate (335 mg, 0.445 mmol) in THF (5.0 mL) was added 2,6-lutidine (0.10 mL, 0.89 mmol) followed by TMS-OTf (0.121 mL, 0.668 mmol). After stirring at room temperature for 1 h, the reaction mixture was heated at 50 °C for 1 h. Additional equivalents of both 2,6-lutidine and TMS-OTf were added hourly until consumption of the starting material (6 additions). After cooling to room temperature, the reaction mixture was quenched with sat. aq. sodium bicarbonate solution. The mixture was extracted with EtOAc concentrated in vacuo. The residue was purified by flash chromatography (Isco 40 g column eluting with 0-80% EtOAc / hexanes) to give the title compound (115 mg, 37%). MS(ESI+) m/z 696.3 (M+H)+.

Example 259:

[00593] Following a procedure analogous to that for the synthesis of Example 1, 4-(5-butyl-3-(ethoxycarbonyl)-1-phenyl-1H-pyrazol-4-yl)-3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (55 mg, 0.079 mmol) and naphthalene-2-sulfonamide (82 mg, 0.40 mmol) were converted to give ethyl 5-butyl-4-2-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-l-
phenyl-1H-pyrazole-3-carboxylate (40 mg, 57%). To a solution of ethyl 5-butyl-4-(2-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-phenyl-1H-pyrazole-3-carboxylate (30 mg, 0.034 mmol) in THF (2 mL) at room temperature was added TBAF (0.051 mL, 0.051 mmol). After stirring at room temperature for 1 h, the reaction mixture was diluted with EtOAc, washed with sat. aq. sodium bicarbonate solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by flash chromatography (Iscoc 40 g column eluting with 0-5% methanol / DCM). The residue was lyophilized from acetonitrile / water to give the title compound (23 mg, 88%) as a white solid.

Example 260

4-(5-Butyl-3-(hydroxymethyl)-1-phenyl-1H-pyrazol-4-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide

[00594] Following a procedure analogous to that for the synthesis of Example 236, ethyl 5-butyl-4-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-phenyl-1H-pyrazole-3-carboxylate (Example 259, 38 mg, 0.049 mmol) was converted to the title compound (24 mg, 62%).

$^1$H NMR (CD$_3$OD) $\delta$ 8.67 (s, 1H), 8.17-7.96 (m, 6H), 7.70-6.82 (m, 12H), 5.18-4.73 (m, 1H), 4.54-3.85 (m, 4H), 3.58-3.25 (m, 2H), 2.88-2.39 (m, 4H), 1.16-0.89 (m, 4H), 0.61-0.48 (m, 3H); MS(ESI$^+$) m/z 729.2 (M+H)$^+$. 

Example 261
Ethyl 4-(2-((5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate

Intermediate 261A: Ethyl 4-(2-((5')-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(tert-butoxycarbonyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate

[00595] To a solution of ethyl 4-(4-(tert-butoxycarbonyl)-2-((S)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate (Intermediate 259E, 207 mg, 0.275 mmol) in THF (2.0 mL) at room temperature was added TBAF (0.413 mL, 0.413 mmol). After stirring at room temperature for 1 h, the reaction mixture was diluted with EtOAc, washed with sat. aq. sodium bicarbonate solution, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (Isco 40 g column eluting with 0-70% EtOAc / hexanes) to give ethyl 4-(4-(tert-butoxycarbonyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate (113 mg, 0.177 mmol, 64%) as a colorless oil.

[00596] To a solution of ethyl 4-(4-(tert-butoxycarbonyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate (113 mg, 0.177 mmol) in THF (2 mL) was added triphenylphosphine (55.8
mg, 0.213 mmol) followed by DIAD (0.041 mL, 0.213 mmol) and diphenyl phosphorazidate (58 mg, 0.21 mmol). After stirring at room temperature overnight, a second addition of all three reagents was added (1.2 eq each) and stirring was continued for 3 h. The reaction mixture was diluted with EtOAc, washed with sat. aq. sodium bicarbonate, dried over anhydrous sodium sulfate and concentrated in vacuo. The crude material was purified by flash chromatography (Isco 40 g column eluting with 0-50% EtOAc / hexanes) to give the title compound (86 mg, 73%). ³¹NMR (CDCl₃, 1:1 mixture of amide rotamers) δ 8.25 (s, 0.5H), 8.15-8.10 (m, 1H), 7.97 (s, 0.5H), 7.51-7.34 (m, 5H), 7.25-6.90 (m, 5H), 5.04-4.97 (m, 1.5H), 4.41-3.97 (m, 3.5H), 3.50-3.01 (m, 3.5H), 2.88-2.46 (m, 3.5H), 1.66-1.62 (m, 3H), 1.61 (s, 4.5H), 1.60 (s, 4.5H), 1.18-0.94 (m, 4H), 0.64-0.56 (m, 3H); MS(ESI⁺) m/z 663.5 (M+H)⁺.

Intermediate 26IB: 3-((5)-3-(Azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(5-butyl-3-(ethoxycarbonyl)-1H-pyrazol-4-yl)benzoic acid

![Intermediate 26IB](image)

[00597] Following a procedure analogous to that for the synthesis of Intermediate 223F, ethyl 4-(2-((5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(tert-butoxycarbonyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate (86 mg, 0.13 mmol) was converted to the title compound which was used directly in the next step without further purification. MS(ESI⁺) m/z 607.3 (M+EtF)⁺.

Example 261:

[00598] Following a procedure analogous to that for the synthesis of Example 1, 3-((5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(5-butyl-3-(ethoxycarbonyl)-1-phenyl-1H-pyrazol-4-yl)benzoic acid (79 mg, 0.13 mmol) and naphthalene-2-sulfonamide (54 mg, 0.26 mmol) were converted to the title compound (64 mg, 60%). ¹H NMR (CD₂OD, 1:1 mixture of amide rotamers) δ 8.69-8.64 (m, 1H), 8.17-
7.91 (m, 6H), 7.64-7.41 (m, 8H), 7.20-6.98 (m, 3.5H), 6.79-6.78 (m, 0.5H), 5.09-4.63 (m, 1H), 4.39-4.05 (m, 3H), 3.63-3.08 (m, 3H), 2.82-2.49 (m, 4H), 1.21-0.92 (m, 4H), 1.02 (t, J = 8 Hz, 3H), 0.56-0.51 (m, 3H); MS(ESI+) m/z 796.5 (M+H).

Example 262

Ethyl 4-(2-(((5)-3-(aminomethyl)-1,2,3,4-tetrahydrossoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate

[00599] To the solution of ethyl 4-(2-((5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate (60 mg, 0.075 mmol, Example 261) in THF (2.0 mL) was added triphenylphosphine (59 mg, 0.226 mmol) followed by 0.2 ml of IN NaOH. The reaction mixture was stirred at 50 °C for 2 h. The reaction mixture was quenched with sat. aq. sodium bicarbonate solution and then extracted with EtOAc. The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (Isco 40 g column eluting with 0-15% methanol / DCM). The residue was lyophilized from acetonitrile / water to give the title compound (29 mg, 50%). 'HNMR (CD$_3$OD, 1:1 mixture of amide rotamers)  δ 8.60 (s, 1H), 8.32 (s, 1H), 8.19-7.91 (m, 5H), 7.58-7.34 (m, 8H), 7.21-7.00 (m, 3.5H), 6.79-6.78 (m, 0.5H), 5.21-5.20 (m, 0.5H), 4.74-4.70 (m, 0.5H), 4.43-4.10 (m, 3H), 3.75-3.74 (m, 0.5H), 3.62-3.60 (m, 0.5H), 3.01-3.00 (m, 2H), 2.75-2.48 (m, 4H), 1.13-0.92 (m, 4H), 0.99 (t, J = 8 Hz, 3H), 0.57-0.54 (m, 3H); MS(ESI+) m/z 770.5 (M+H$^+$).

Example 263

3-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydrossoquinoline-2-carbonyl)-4-(5-butyl-3-(hydroxymethyl)-1-phenyl-1H-pyrazol-4-yl)-N-(naphthalen-2-ylsulfonyl)benzamide
Following a procedure analogous to that for the synthesis of Example 236, ethyl 4-(2-((5)-3-(aminomethyl)-1,2,3,4-tetrahydroidoisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-5-butyl-1-phenyl-1H-pyrazole-3-carboxylate (Example 262, 25 mg, 0.032 mmol) was converted to the title compound (18 mg, 73%).

$^1$H NMR (CD$_3$OD) $\delta$ 8.72-8.67 (m, 1H), 8.23-7.93 (m, 6H), 7.73-7.65 (m, 2H), 7.61-6.85 (m, 10H), 5.19-5.15 (m, 1H), 4.62-4.10 (m, 4H), 2.82-2.49 (m, 6H), 1.31-0.87 (m, 4H), 0.61-0.52 (m, 3H); MS(ESI$^+$) m/z 728.5 (M+H)$^+$.  

Example 264

$N,N$-Dibutyl-1-methyl-2-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroidoisoquinoline-2-carbonyl)phenyl)-1H-imidazole-4-carboxamide

Intermediate 264A: Methyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxylate (Int-264A)

To a stirred suspension of sodium hydride (572 mg, 23.8 mmol, 94%) in dry DMF (50 mL) at 0 °C was added methyl 1H-imidazole-4-carboxylate (3.0 g, 23.8 mmol) in DMF (90 mL) and was allowed to warm up to room temperature over 30 min. The reaction mixture was cooled to 0 °C and was treated dropwise with ($\ldots$)
(chloromethoxy)ethyl)trimethylsilane (Aldrich, 4.77 g, 28.6 mmol). The cold bath was
removed and the mixture was stirred for 16 h. The reaction mixture was quenched by the
addition of ice-flakes and then by water, and extracted with EtOAc (3 x). The combined
organic layers were washed with brine, dried over Na₂S0₄ and concentrated in vacuo to
give crude product. The crude material was purified by flash chromatography (gradient
from 2 to 5% MeOH/CH₂Cl₂) to provide the title compound (4.46 g, 73%). ¹H NMR
(CDC1₃) δ 7.72 (s, 1H), 7.61 (s, 1H), 5.29 (s, 2H), 3.90 (s, 3H), 3.49 (t, J = 8.0 Hz, 2H),
0.90 (t, J = 8.0 Hz, 2H), 0.01 (s, 9H); MS(ESI⁺) m/z 257.2 (M+H)⁺.

Intermediate 264B: Methyl 2-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxylate

\[
\begin{align*}
\text{MeO} & \quad \text{N} \\
& \quad \text{SEM} \\
& \quad \text{Br} \\
\end{align*}
\]

(Int-264B)

[00602] To a stirred solution of methyl 1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxylate (5.0 g, 19.5 mmol) in carbon tetrachloride (50 mL) was added N-bromosuccinimide (3.47 g, 19.5 mmol) and AIBN (160 mg, 5 mol%) at room
temperature. The reaction mixture was heated at 60 °C for 3 h, cooled to room
temperature, and filtered through a small pad of CELITE®. The filtrate was concentrated in vacuo to give light yellow colored residue which was dissolved in EtOAc and washed with 10% NaHCO₃ solution. The organic layer was dried over Na₂S0₄ and concentrated
to give crude compound. The crude material was purified by flash chromatography
(gradient from 20 to 30% EtOAc/hexanes), to provide the title compound (2.85 g, 43%).
¹H NMR (CDCl₃) δ 7.76 (s, 1H), 5.30 (s, 2H), 3.90 (s, 3H), 3.55 (t, J = 8.0 Hz, 2H), 0.92
(t, J = 8.0 Hz, 2H), 0.01 (s, 9H); MS(ESI⁺) m/z 335.0 (M+H)⁺.

Intermediate 264C: 2-Bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxylic acid

\[
\begin{align*}
\text{HO} & \quad \text{N} \\
& \quad \text{SEM} \\
& \quad \text{Br} \\
\end{align*}
\]

(Int-264C)

[00603] To a stirred solution of methyl 2-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxylate (2.85 g, 8.50 mmol) in mixed solvents (THF/MeOH/water;
2.2:1; 50 mL) was added LiOH ·H₂O (1.07 g, 25.5 mmol) at 0 °C. The cold bath was removed and stirring was continued for 2 h. The reaction mixture was concentrated in vacuo, diluted with water and washed with MTBE. The aqueous layer was neutralized with 1.5N HCl and extracted with EtOAc (2x). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to provide the title compound (2.4 g, 88%) as a white solid.

Intermediate 264D: 2-Bromo-N,N-dibutyl-l-((2-(trimethylsilyl)ethoxy)methyl)-l H-imidazole-4-carboxamide

![Chemical Structure](Int-264D)

To a stirred solution of 2-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1 H-imidazole-4-carboxylic acid (2.4 g, 7.47 mmol) in dry DMF (40 mL) was added HATU (4.26 g, 11.2 mmol), dibutylamine (1.15 g, 8.9 mmol) and diisopropyl ethylamine (2.84 g, 22.4 mmol) successively at 0 °C. The reaction mixture was allowed to warm to room temperature over 30 minutes and stirring was continued for 16 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc and washed with water. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give crude compound. The crude material was purified by flash chromatography (gradient from 20 to 30% EtOAc/hexanes) to provide the title compound (2.81 g, 87%). ¹H NMR (CDCl₃) δ 7.68 (s, 1H), 5.28 (s, 2H), 3.89 (t, J = 8.0 Hz, 2H), 3.56 (t, J = 8.0 Hz, 2H), 1.57-1.65 (m, 4H), 1.25-1.45 (m, 4H), 0.91-0.95 (m, 8H), 0.01 (s, 9H); MS(ESI⁺) m/z 434.2 (M+H)⁺.

Intermediate 264E: 2-Hydroxy-5-(methoxycarbonyl)benzoic acid

![Chemical Structure](Int-264E)

A solution of dimethyl-4-hydroxyisophthalate (10.0 g, 47.6 mmol) in pyridine (70 mL) was heated to reflux for 15 h. The reaction mixture was concentrated in vacuo...
and acidified with IN HCl at 0 °C. The resulting solid was collected by filtration, washed with water and dried in vacuo to provide the title compound (9.3 g, 100%) as a white solid. ¹H NMR (DMSO-d₆) δ 8.40 (d, J = 2.0 Hz, 1H), 8.06 (dd, J = 8.4, 2.0 Hz, 1H), 7.07 (d, J = 8.4 Hz, 1H), 3.84 (s, 3H); MS(EST) m/z 195.2 (M-H)

Intermediate 264F: Methyl 4-hydroxy-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

![Chemical structure](image)

(9.1 g, 76.5 mmol) in mixed solvents (CH₂Cl₂/THF; 50 mL/50 mL) at room temperature was added thionylchloride (3.03 g, 25.5 mmol). After stirring for 30 min at room temperature, the mixture was treated with a solution of 2-hydroxy-5-(methoxycarbonyl)benzoic acid (5.0 g, 25.48 mmol) in THF (20 mL THF). The formation of a white precipitate was observed and the mixture was stirred for additional 1 h. The precipitate was allowed to settle and the supernatant was added to a mixture of 1,2,3,4-tetrahydroisoquinoline (5.1 g, 38.3 mmol) and triethylamine (5.5 mL, 38.2 mmol) in THF (10 mL) and stirred at room temperature for 1 h. The reaction mixture was concentrate in vacuo, and the resulting crude compound was dissolved in EtOAc, washed with water, followed by IN HCl and then brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give crude product. The crude material was purified by flash chromatography (gradient from 0% to 30% EtOAc/hexanes) to provide the title compound (5.0 g, 63%). ³¹ NMR (DMSO-d₆, 3:1 mixture of amide rotamers) δ 10.84 (s, 1H), 7.88 (dd, J = 8.8, 2.4 Hz, 1H), 7.75 (br s, 1H), 7.30-7.15 (m, 3.5H), 7.01 (d, J = 8.4 Hz, 1.5H), 4.78 (br s, 1.5H), 4.41 (br s, 0.5H), 3.85-3.84 (m, 0.5H), 3.80 (s, 3H), 3.44 (br s, 1.5H), 2.86-2.80 (m, 2H); MS(ESI⁺) m/z 312.2 (M+H)⁺.

Intermediate 264G: Methyl 3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(trifluoromethylsulfonyloxy)benzoate
To a solution of methyl 4-hydroxy-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl) benzoate (3.0 g, 9.63 mmol) and 2,6-dimethylpyridine (3.37 mL, 28.9 mmol), in DCM (40 mL) was added trifluoromethanesulfonic anhydride (2.0 mL, 11.6 mmol) at -78 °C. The cold bath was removed and the reaction mixture was stirred at room temperature for an additional 2 h. The reaction mixture was diluted with DCM, washed with 5% aq. citric acid solution and then with brine. The organic layer was dried over Na₂SO₄ and concentrated in vacuo to give the crude product. Purification using flash chromatography (gradient from 0 to 25%, EtOAc/hexanes) provided the title compound (3.07 g, 72%).

\[ \delta_{\text{NMR (DMSO-d}_6, 1:1 \text{ mixture of amide rotamers)}} 8.22 (dd, J = 8.8, 2.4 Hz, 1H), 8.13 (dd, J = 18.0, 2.0 Hz, 1H) 7.76-7.72 (m, 1H), 7.31-7.10 (m, 3.5H), 7.02 (d, J = 7.6 Hz, 0.5H), 4.79 (br s, 1H), 4.45 (br s, 1H), 3.90 (s, 3H), 3.48 (t, J = 6.0 Hz, 1H), 3.36-3.34 (m, 1H) 2.90-2.80 (m, 2H); MS(ESI⁺) m/z 444.0 (M+H)⁺.

Intermediate 264H: Methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

To a stirred solution of methyl 3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(trifluoromethylsulfonyloxy)benzoate (2.0 g, 4.51 mmol) in PhMe in a pressure tube was added bis(neopentyl glycolato)diboron (1.53 g, 6.76 mmol), Pd(PPh₃)₄ (520 mg, 0.45 mmol) and potassium acetate (1.33 g, 13.5 mmol). The reaction mixture was degassed (bubbled) with argon for 20 min, sealed and heated at 85 °C for 4 h. The reaction mixture was allowed to warm up to room temperature, diluted with EtOAc, washed with water,
dried over \( \text{Na}_2\text{SO}_4 \) and concentrated *in vacuo* to give the title compound (2.3 g), which was used without further purification.

Intermediate 264J: Methyl 4-((4-(dibutylcarbamoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

\[
\text{SEM} \quad \text{O} \quad \text{NBu}_2 \quad \text{O} \quad \text{CO}_2\text{Me}
\]

(Int-264J)

[00609] To a solution of methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (2.0 g, 5.05 mmol) in dioxane (40 mL) was added \( \text{Pd(dppf)}_2\text{Cl}_2 \) (77 mg, 0.10 mmol), 2-bromo-\( N,N \)-dibutyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxamide (910 mg, 2.10 mmol) and \( \text{K}_3\text{PO}_4 \) (1.34 g, 6.31 mmol). The reaction mixture was degassed for 30 min, heated at 100 °C for 16 h and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc and washed with water, dried over \( \text{Na}_2\text{SO}_4 \), and concentrated to give the crude product. The crude material was purified by flash chromatography (gradient from 0% to 80%, EtOAc/hexanes) to provide the title compound (800 mg, 57%). \(^1\)H NMR (CD\(_3\)OD, 1:1 mixture of amide rotamers) \( \delta \) 8.23 (dd, \( J = 6.4, 1.6 \) Hz, 1H), 8.13-8.12 (m, 1H), 7.98 (dd, \( J = 14.4, 8.0 \) Hz, 1H), 7.78 (s, 0.5H), 7.67 (s, 0.5H), 7.24-7.12 (m, 3.5H), 6.93 (d, \( J = 7.2 \) Hz, 0.5H), 5.39 (s, 1H), 5.30 (s, 1H), 4.85-4.75 (m, 2H), 4.58-4.35 (m, 1H), 3.99 (s, 3H), 3.71-3.62 (m, 3H), 3.56 (t, \( J = 6.0 \) Hz, 2H), 3.45-3.36 (m, 2H), 2.90-2.80 (m, 2H), 1.65-1.31 (m, 8H), 1.00-0.91 (m, 5H), 0.80-0.73 (m, 3H), 0.04 (s, 4.5H), 0.02 (s, 4.5H); MS(EST) m/z 646.2 (M-H).
To a solution methyl 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (180 mg, 0.28 mmol) in DCM (4 mL) was added trifluoroacetic acid (4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 4 h. The reaction mixture was concentrated in vacuo. The resulting residue was dissolved in DCM and washed with sat. NaHCO3 solution. The organic layer was dried over Na2SO4 and concentrated to give crude product. The crude material was purified by flash chromatography (gradient from 0 to 5% methanol/CHCl3) to provide the title compound (130 mg, 91%). 1H NMR (CD3OD) δ 8.25-8.06 (m, 2H), 8.00-7.50 (m, 2H), 7.28-6.83 (m, 4H), 4.36 (br s, 1H), 4.01 (br s, 4H), 3.60-3.24 (m, 6H), 2.88-2.69 (m, 2H), 1.60-1.52 (m, 4H), 1.36-1.30 (m, 4H), 1.05-0.90 (m, 6H); MS(EST) m/z 515.2 (M-H). 

Intermediate 264K: Methyl 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

To a stirred solution of methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (80 mg, 0.15 mmol) in dry DMF (3 mL) was added K2CO3 (42 mg, 0.30 mmol) and methyl iodide (22 mg, 0.15 mmol, a solution in 100 µL of DMF) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 4 h. The reaction mixture was diluted with MTBE and washed with water. The organic layer was dried over Na2SO4 and concentrated in vacuo to give crude product. The crude material was purified by flash chromatography.
chromatography (gradient from 0% to 2% MeOH/CH(3)CN) to provide the title compound (65 mg, 79%). 1H NMR (CD3OD) δ 8.25-8.00 (m, 2H), 7.92-7.00 (m, 6H), 4.80-4.60 (m, 2H), 4.02 (s, 3H), 3.70-3.40 (m, 6H), 3.01 (s, 3H), 2.90-2.80 (m, 2H), 1.60-1.50 (m, 4H), 1.50-1.30 (m, 4H), 1.05-0.90 (m, 6H); MS(ESI+) m/z 531.4 (M+H)+.

Intermediate 264L: 4-(4-(Dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

To a solution of methyl 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (65 mg, 0.12 mmol) in mixed solvents (THF/MeOH/H2O; 2:2:1; 5 mL) was added LiOH·H2O (15 mg, 0.36 mmol) at 0 °C. The reaction mixture was allowed to room temperature over 30 min. and stirring was continued for 1 h. The reaction mixture was concentrated to give crude product, which was diluted with water and extracted with MTBE. The aqueous layer was neutralized with 0.5N HCl and extracted with DCM (3×). The combined organic layer was dried over Na2SO4 and concentrated in vacuo to give the title compound (55 mg, 87%). 1H NMR (CD3OD, 1:1 mixture of amide rotamers) δ 8.28 (dd, J = 8.0, 1.6 Hz, 1H), 8.14 (s, 1H), 7.77 (dd, J = 13.6, 8.4 Hz, 1H), 7.63 (s, 0.5H), 7.51 (s, 0.5H), 7.23-7.13 (m, 3.5H), 6.95 (d, J = 9.2 Hz, 0.5H), 4.79 (s, 1H), 4.48 (s, 1H), 3.77 (s, 1.5H), 3.68 (s, 1.5H), 3.58-3.01 (m, 6H), 2.88-2.80 (m, 2H), 1.60-1.40 (m, 2H), 1.39-1.20 (m, 4H), 1.19-1.00 (m, 2H), 0.99-0.90 (m, 3H), 0.85-0.75 (m, 3H); MS(ESI+) m/z 517.4 (M+H)+.

Example 264:

To a solution of 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (40 mg, 0.077) in dry DMF (2 mL) were added HATU (147 mg, 0.387 mmol), naphthalene-2-sulfonamide (48 mg, 0.23 mmol) and diisopropylethyl amine (134 µL, 0.77 mmol) at 0 °C. The reaction mixture...
was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was concentrated in vacuo to dryness, dissolved in water and extracted with EtOAc (3 x). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo to afford crude product. The crude material was purified by preparative TLC to provide the title compound (12 mg, 16%) ¹H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 8.61 (br s, 1H), 8.20-8.14 (m, 1H), 8.08-7.94 (m, 5.5H), 7.63-7.54 (m, 3.5H), 7.20-7.02 (m, 3.5H), 6.86 (d, J = 9.2 Hz, 0.5H), 4.75 (br s, 1H), 4.60 (br s, 1H), 4.40 (br s, 1H), 3.74-3.72 (m, 2H), 3.55-3.50 (m, 4H), 3.07 (s, 1.5H), 2.93 (s, 1.5H), 2.80-2.65 (m, 2H), 1.60-1.50 (m, 4H), 1.50-1.30 (m, 2H), 1.20-1.05 (m, 2H), 1.00-0.90 (m, 3H), 0.85-0.75 (m, 3H);

MS(ESI⁺) m/z 706.2 (M+H)⁺.

Example 265

N,N-Dibutyl-l-(2-(methylamino)-2-oxoethyl)-2-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-l H-imidazole-4-carboxamide

Intermediate 265A: Methyl 4-(l-(2-tert-butoxy-2-oxoethyl)-4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

[00614] Following a procedure analogous to that for the synthesis of Intermediate 264K, methyl 4-(4-(dibutylcarbamoyl)-1 H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (310 mg, 0.6 mmol) and t-butylbromoacetate
(117 mg, 0.6 mmol) were converted to the title compound (300 mg, 90%). MS(ESI\(^+\)) \(m/z\) 631.4 (M+H\(^+\)).

Intermediate 265B: 2-(4-(Dibutylcarbamoyl)-2-(4-(methoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazol-1-yl)acetic acid

![Chemical Structure of Intermediate 265B](Int-265B)

[00615] To a solution of methyl 4-(1-(2-tert-butoxy-2-oxoethyl)-4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (300 mg, 0.44 mmol) in DCM (3.0 mL) was added trifluoroacetic acid (3.0 mL) at 0 °C. The reaction mixture was allowed to room temperature and stirring was continued for 1 h. The reaction mixture was concentrated in vacuo and the resulting residue was dissolved in DCM and washed with sat. NaHCO\(_3\) solution. The organic layer was dried over Na\(_2\)SO\(_4\) and concentrated to give the title compound (200 mg, 80%). MS(ESI\(^+\)) \(m/z\) 575.4 (M+H\(^+\)).

Intermediate 265C: Methyl 4-(4-(dibutylcarbamoyl)-1-(2-(methylamino)-2-oxoethyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

![Chemical Structure of Intermediate 265C](Int-265C)

[00616] To a solution of 2-(4-(dibutylcarbamoyl)-2-(4-(methoxycarbonyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazol-1-yl)acetic acid (180 mg, 0.31 mmol) in dry DMF (5 mL) was added HATU (595 mg, 1.56 mmol), methylamine
(Aldrich, 78 µL, 1.56 mmol, 2.0 M in THF) and diisopropylethyl amine (544 µL, 3.13 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature over 30 min and stirring was continued for 16 h. The reaction mixture was diluted with water, and extracted with EtOAc (3 x). The combined organic layers were dried over Na2SO4 and concentrated in vacuo to give crude product. The crude material was purified by flash chromatography (gradient from 20 to 50% EtOAc/hexanes) to provide (85 mg, 46%). ¾ NMR (CDCl3, 1:1 mixture of amide rotamers) δ 8.22-8.19 (m, 1H), 8.10 (dd, J = 6.0, 1.6 Hz, 1H), 7.58 (s, 0.5H), 7.56-7.52 (m, 1H), 7.50 (s, 0.5H), 7.36-7.10 (m, 3.5H), 6.94 (d, J = 7.6 Hz, 0.5 H), 4.76 (br s, 1H), 4.65 (br s, 3H), 3.98 (s, 3H), 3.97-3.95 (m, 1.5H), 3.73 (t, J = 5.6 Hz, 1.5 H), 3.60-3.30 (m, 3H), 3.00-2.85 (m, 2H), 2.65 (s, 1.5H), 2.64 (s, 1.5H), 1.47-1.24 (m, 6H), 0.96-0.84 (m, 5H), 0.80 (t, J = 7.4 Hz, 1.5H), 0.60 (t, J = 7.4 Hz, 1.5H); MS(ESI+) m/z 588.4 (M+H)+.

Intermediate 265D: 4-(4-(Dibutylcarbamoyl)-1-(2-(methylamino)-2-oxoethyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

![Diagram of Intermediate 265D](Int-265D)

[00617] Following a procedure analogous to that for the synthesis of Intermediate 264L, methyl 4-(4-(dibutylcarbamoyl)-1-(2-(methylamino)-2-oxoethyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (80 mg, 0.13 mmol) was converted to the title compound (60 mg, 77%). MS(ESI+) m/z 574.4 (M+H)+.

Example 265:

[00618] To a solution of 4-(4-(dibutylcarbamoyl)-1-(2-(methylamino)-2-oxoethyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (60 mg, 0.1 mmol) in dry DMF (8 mL) was added EDC (60 mg, 0.3 mmol), naphthalene-2-sulfonylamide (43 mg, 0.2 mmol) and 4-dimethylamino pyridine (19 mg, 0.15 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirring was...
continued for 16 h. The reaction mixture was concentrated in vacuo, dissolved in water and extracted with EtOAc (3 x). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo to afford crude product. The crude material was purified by preparative HPLC to provide the title compound (8 mg, 10%). ¹H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 8.58 (s, 1H), 8.17 (t, J = 6.4 Hz, 1H), 8.11 (s, 1H), 8.04-8.02 (m, 2H), 7.96-7.92 (m, 2H), 7.62-7.54 (m, 4H), 7.23-7.11 (m, 3.5H), 6.95 (d, J = 7.2 Hz, 0.5H), 4.74 (s, 1H), 4.69 (s, 1H), 4.64-4.61 (m, 1H), 4.55 (br s, 1H), 4.18-3.70 (m, 2H), 3.61 (t, J = 6.0 Hz, 2H), 3.55-3.45 (m, 1.5H), 3.30-3.15 (m, 0.5H), 2.88-2.78 (m, 2H), 2.70 (s, 3H), 1.54-1.40 (m, 2H), 1.40-1.20 (m, 4H), 1.20-1.10 (m, 2H), 0.99-0.90 (m, 3H), 0.78 (t, J = 8.4 Hz, 1.5H), 0.69 (t, J = 8.4 Hz, 1.5H); MS(EST) m/z 761.4 (M-H)⁻.

Example 266

\[ N,N\text{-Dibutyl-1-(3-hydroxypropyl)-2-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazole-4-carboxamide} \]

Intermediate 266A: Methyl 4-(4-(dibutylcarbamoyl)-1-(3-hydroxypropyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

To a stirred solution of methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (200 mg, 0.38 mmol) in DMF (8 mL) was added K₂CO₃ (107 mg, 0.77 mmol) and 3-bromopropanol (54 mg, 0.38 mmol).
The reaction mixture was heated at 40 °C for 4 h, cooled to room temperature, diluted with MTBE, and quenched with water. The organic layer was separated and the aqueous layer was extracted with MTBE (3 x). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo to provide crude product. The crude material was purified by flash chromatography (gradient from 10 to 50% EtOAc/hexanes) to provide the title compound (67 mg, 32%). ¹H NMR (CDCl₃, 1:1 mixture of amide rotamers) δ 8.19-8.15 (m, 1H), 8.04 (dd, J = 11.2, 1.6 Hz, 1H), 7.62 (s, 0.5H), 7.55 (s, 0.5H), 7.50-7.46 (m, 1H), 7.25-7.14 (m, 3.5H), 6.94 (d, J = 7.2 Hz, 0.5H), 4.84-4.59 (m, 2H), 4.29-4.13 (m, 2H), 3.96 (s, 3H), 3.82-3.70 (m, 2H), 3.50-3.35 (m, 4H), 3.31-2.88 (m, 4H), 1.89-1.87 (m, 2H), 1.55-1.49 (m, 2H), 1.40-1.05 (m, 6H), 0.93-0.88 (m, 3H), 0.74 (t, J = 7.2 Hz, 1.5H), 0.65 (t, J = 7.2 Hz, 1.5H); MS(ESI⁺) m/z 575.6 (M+H)⁺.

Intermediate 266B: 4-(4-(Dibutylcarbamoyl)-1-(3-hydroxypropyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

[00620] Following a procedure analogous to that for synthesis of Intermediate 264L, methyl 4-(4-(dibutylcarbamoyl)-1-(3-hydroxypropyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (70 mg, 0.12 mmol) was converted to the title compound (60 mg, 88%). MS(EST) m/z 559.4 (M-H)⁻.

Example 266:
[00621] Following a procedure analogous to that for the synthesis of Example 265, 4-(4-(dibutylcarbamoyl)-1-(3-hydroxypropyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (60 mg, 0.11 mmol) was converted to the title compound (24 mg, 30%). ¹H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 8.60 (s, 1H), 8.21-8.17 (m, 1H), 8.10-8.09 (m, 1H), 8.05-8.03 (m, 2H), 7.98-7.93 (m, 2H), 7.63-7.58 (m, 4H), 7.23-7.11 (m, 3.5H), 6.95 (d, J = 6.8 Hz, 0.5H), 4.75 (s, 1H), 4.60 (br
Example 267

\[ \text{N,N'-Dibutyl-1-(3-(dimethylamino)propyl)-2-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazole-4-carboxamide} \]

Intermediate 267A: Methyl 4-(4-(dibutylcarbamoyl)-1-(3-(dimethylamino)propyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

\[ \text{(Int-267A)} \]

[00622] Following a procedure analogous to that for the synthesis of Intermediate 266A, methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (200 mg, 0.38 mmol) and 3-bromo-\( \text{N,N'-dimethylprop-1-amine} \) (77 mg, 0.46 mmol) were converted to the title compound (180 mg, 78%). MS(ESI\(^+\)) \( m/z \) 602.6 (M+H\(^+\)).

Intermediate 267B: 4-(4-(Dibutylcarbamoyl)-1-(3-(dimethylamino)propyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 264L, methyl 4-(4-(dibutylcarbamoyl)-1-(3-(dimethylamino)propyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (180 mg, 0.3 mmol) was converted to the title product (160 mg, 86%). MS(ESI+) m/z 588.4 (M+H)+.

Example 267:

Following a procedure analogous to that for the synthesis of Example 265, 4-(4-(dibutylcarbamoyl)-1-(3-(dimethylamino)propyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (160 mg, 0.27 mmol) was converted to the title compound (30 mg, 14%). 1H NMR (CD3OD, 1:1 mixture of amide rotamers) δ 8.58 (s, 1H), 8.22-8.19 (m, 1H), 8.12-8.10 (m, 1H), 8.05-8.01 (m, 2H), 7.96-7.92 (m, 2H), 7.64-7.56 (m, 4H), 7.25-7.12 (m, 3.5H), 6.98 (d, J = 7.2 Hz, 0.5H), 4.73 (s, 1H), 4.65 (s, 1H), 4.15 (br s, 3H), 3.68-3.64 (m, 2H), 3.49-3.39 (m, 3H), 2.90-2.80 (m, 4H), 2.66 (br s, 6H), 2.00-1.90 (m, 2H), 1.60-1.40 (m, 2H), 1.39-1.25 (m, 3H), 1.22-1.05 (m, 2H), 1.00-0.85 (m, 4H), 0.75 (t, J = 7.2 Hz, 1.5H), 0.63 (t, J = 7.2 Hz, 1.5H); MS(ESI+) m/z 779.1 (M+H)+.

Example 268

N,N-Dibutyl-2-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxamide

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Intermediate 268A: 4-(4-(Dibutylcarbamoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

![Intermediate 268A](image)

Following a procedure analogous to that for the synthesis of Intermediate 264L, methyl 4-(4-(dibutylcarbamoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (350 mg, 0.54 mmol) was converted to the title compound (320 mg, 93%), which was used without further purification. MS(ESI) m/z 631.4 (M-H)^-.

Intermediate 268B: N,N-Dibutyl-2-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxamide

![Intermediate 268B](image)

Following a procedure analogous to that for the synthesis of Example 265, 4-(4-(dibutylcarbamoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (40 mg, 0.063 mmol) was converted to the title compound (20 mg, 38%). ^1H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 8.59 (d, J = 2.8 Hz, 1H), 8.20 (t, J = 7.6 Hz, 1H), 8.11 (br s, 1H), 8.06-8.00 (m, 2H), 7.97-7.91 (m, 2H), 7.82 (d, J = 7.6 Hz, 0.5H), 7.76 (d, J = 7.6 Hz, 0.5H), 7.72 (s, 0.5H), 7.63-7.58 (m, 2.5H), 7.25-7.05 (m, 3.5H), 6.87 (d, J = 6.8 Hz, 0.5H), 5.34 (s, 1H), 5.14 (br s, 1H), 4.78 (s, 1H), 4.63 (s, 1H), 4.40 (br s, 2H), 3.68-3.54 (m, 6H), 2.88-2.80 (m, 2H),
1.65-1.40 (m, 2H), 1.39-1.26 (m, 4H), 1.25-1.05 (m, 4H), 0.99-0.78 (m, 6H), 0.02 (s, 9H); MS(ESI⁺) m/z 821.2 (M-H)

Example 268:

Following a procedure analogous to that for the synthesis of Intermediate 264J, N,N-dibutyl-2-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazole-4-carboxamide (100 mg, 0.12 mmol) was converted to the title compound (16 mg, 19%). ¹H NMR (DMSO-d₆, 1:1 mixture of amide rotamers) δ 12.8 (br s, 1H), 8.52 (br s, 0.5H), 8.13 (br s, 0.5H), 8.00-7.90 (m, 4H), 7.84-7.80 (m, 2H), 7.70-7.58 (m, 3H), 7.25-6.97 (m, 4.5H), 6.87 (d, J = 6.0 Hz, 0.5H), 4.86 (d, J = 17.2 Hz, 0.5H), 4.71 (d, J = 17.2 Hz, 0.5H), 4.31-4.15 (m, 1H), 3.90 (br s, 0.5H), 3.72 (br s, 0.5H), 3.50-3.43 (m, 1H), 3.10-2.87 (m, 4H), 2.62-2.51 (m, 2H), 1.52-1.40 (m, 2H), 1.42-1.00 (m, 6H), 0.86-0.81 (m, 3H), 0.70-0.64 (m, 3H); MS(ESF) m/z 691.2 (M-H)

Example 269

2-(4-(Dibutylcarbamoyl)-2-(4-(naphthalen-1-ylsulfonilcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazol-1-yl)acetic acid

Intermediate 269A: Benzyl 4-(4-(dibutylcarbamoyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate
To a stirred solution of 4-(4-(dibutylcarbamoyl))-L-((2-(trimethylsilyl)ethoxy)methyl)-L-H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (320 mg, 0.96 mmol) in dry DCM (5.0 mL) was added EDC (932 mg, 4.81 mmol), benzyl alcohol (208 mg, 1.92 mmol) and DMAP (235 mg, 1.92 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 16 h. The reaction mixture was diluted with water and extracted with DCM (2 x). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo to give crude product. The crude material was purified by flash chromatography (gradient 10 to 30% EtOAc/hexanes) to provide the title compound (400 mg, 92%). MS(ESI⁺) m/z 723.6 (M+H)⁺.

Intermediate 269B: Benzyl 4-(4-(dibutylcarbamoyl))-L-H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 264J, benzyl 4-(4-(dibutylcarbamoyl))-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (400 mg, 0.55 mmol) was converted to the title compound (300 mg, 91%). ¹H NMR (CDCl₃) δ 8.23-8.19 (m, 1H), 8.03 (d, J = 10.0 Hz, 1H), 7.45-7.34 (m, 7H), 7.23-7.05 (m, 3.5H), 6.76 (d, J = 6.4Hz, 0.5H), 5.39-5.36 (m, 2H), 5.14 (d, J = 16.0 Hz, 1H), 4.81 (d, J = 16.8 Hz, 1H), 4.40-4.14 (m, 2H), 3.83-3.31 (m, 4H), 3.01-2.79 (m, 2H), 1.55-1.1.50 (m, 4H), 1.39-1.33 (m, 4H), 0.99-0.92 (m, 6H); MS(EST) m/z 591.4 (M-H)⁻
Intermediate 269C: Benzyl 4-(4-(dibutylcarbamoyl)-l-(2-ethoxy-2-oxoethyl)-l H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

\[\text{Int-269C}\]

Following a procedure analogous to that for the synthesis of Intermediate 264K, benzyl 4-(4-(dibutylcarbamoyl)-l H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (300 mg, 0.5 mmol) and ethylbromo acetate (84 mg, 0.5 mmol) were converted to the title compound (255 mg, 73%). MS(ESI\(^+\)) \(m/z\) 679.6 (M+H)+.

Intermediate 269D: 4-(4-(Dibutylcarbamoyl)-l-(2-ethoxy-2-oxoethyl)-lH-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

\[\text{Int-269D}\]

To a solution of benzyl 4-(4-(dibutylcarbamoyl)-l-(2-ethoxy-2-oxoethyl)-l H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (250 mg, 0.36 mmol) in MeOH (5.0 mL) was added Pd/C (10%). The resulting reaction mixture was stirred under \(\frac{3}{4}\) atmosphere for 2 h. The reaction mixture was filtered through a small pad of CELITE®, washed thoroughly with MeOH and concentrated in vacuo to provide the title compound (190 mg, 88%). \(^1\)H NMR (DMSO-\(d_6\), 1:1 mixture of amide rotamers)

\[\delta \text{ ppm}\]

13.4 (br s, 1H), 8.07 (d, \(J = 8.0\) Hz, 1H), 7.94 (d, \(J = 9.6\) Hz, 1H), 7.71 (s, 0.5H), 7.65 (s, 0.5H), 7.50 (t, \(J = 8.6\) Hz, 1H), 7.19-7.08 (m, 3.5H), 6.95 (d, \(J = 7.6\) Hz, 0.5H), 4.93 (br s, 2H), 4.63 (br s, 1H), 4.40-4.30 (br s, 1H), 4.15 (q, \(J = 14.0\), 6.8 Hz, 2H), 3.68 (br s,
Intermediate 269E: Ethyl 2-(4-(dibutylcarbamoyl)-2-(4-(naphthalen-1-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazol-1-yl)acetate

\[ \text{HNMR (CD}_3\text{OD, 1:1 mixture of amide rotamers) } \delta 8.61 (s, 1H), 8.14 (t, J = 7.2 Hz, 1H), 8.07-8.03 (m, 3H), 7.98-7.93 (m, 2H), 7.65-7.58 (m, 3.5H), 7.39 (br s, 0.5H), 7.19-7.06 (m, 3.5H), 6.90 (d, J = 6.8 Hz, 0.5H), 4.72 (s, 1H), 4.66 (s, 1H), 4.49 (br s, 1H), 4.39 (br s, 1H), 3.66 (br s, 2H), 3.49 (t, J = 5.6 Hz, 2H), 3.34 (br s, ...)
Example 270

\[ N,N\text{-Dibutyl-2-(4-(8-iodonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide} \]

Following a procedure analogous to that for the synthesis of Example 265, 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate 264L, 45 mg, 0.09 mmol) and 8-iodonaphthalene-2-sulfonamide (Intermediate 6, 72 mg, 0.21 mmol) were converted to the title compound (11 mg, 15%).

\[ \text{HNMR (CD}_3\text{OD, 1:1 mixture of amide rotamers)} \] 8.93 (s, 1H), 8.26 (d, \(J = 7.2\) Hz, 1H), 8.15 (dd, \(J = 8.8, 1.6\) Hz, 2H), 8.05-8.02 (m, 3H), 7.69 (dd, \(J = 15.6, 8.0\) Hz, 1H), 7.58 (s, 0.5H), 7.46 (br s, 0.5H), 7.40 (t, \(J = 7.2\) Hz, 1H), 7.23-7.11 (m, 3.5H), 6.91 (d, \(J = 7.2\) Hz, 0.5H), 4.76 (s, 1H), 4.45 (s, 1H), 3.73 (s, 3H), 3.63-3.52 (m, 6H), 2.82-2.78 (m, 2H), 1.56-1.46 (m, 2H), 1.45-1.27 (m, 4H), 1.20-1.00 (m, 2H), 1.00-0.92 (m, 3H), 0.85-0.75 (m, 3H); MS(ESI\(^+\)) \text{m/z} 832.2 (M+H\(^+\)).

Example 271

\[ N,N\text{-Dibutyl-2-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-phenethyl-1H-imidazole-4-carboxamide} \]
To a solution of 2-hydroxy-5-(methoxycarbonyl)benzoic acid (4.0 g, 20.4 mmol) in DMF (40 mL) was added KHCO$_3$ (2.04 g, 20.4 mmol) and benzyl bromide (3.49 g, 20.4 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirring was continued for 20 h. The reaction mixture was diluted with water, extracted with EtOAc (2 x) and the combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give a crude oil. The crude material was purified by flash chromatography (gradient from 0% to 30% EtOAc/hexanes) to provide the title compound (5.3 g, 92%) as an off-white solid. $^1$H NMR (CDCl$_3$) δ 11.21 (s, 1H), 8.58 (d, $J = 2.0$ Hz, 1H), 8.11 (dd, $J = 8.8, 2.4$ Hz, 1H), 7.47-7.37 (m, 5H), 7.01 (d, $J = 8.8$ Hz, 1H), 5.42 (s, 2H), 3.89 (s, 3H); MS(EST) m/z 285.2 (M-H)$^-$. 

Intermediate 271B: 3-Benzyl 1-methyl 4-(trifluoromethylsulfonyloxy)isophthalate
Following a procedure analogous to that for the synthesis of Intermediate 271G, 3-benzyl 1-methyl 4-hydroxyisophthalate (3.0 g, 10 mmol) was converted to the title compound (3.3 g, 77%). $^1$H NMR (CDCl$_3$) δ 8.71 (d, $J = 2.4$ Hz, 1H), 8.27 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.58-7.47 (d, $J = 6.4$ Hz, 1H), 7.48-7.46 (m, 2H), 7.41-7.35 (m, 3H), 5.43 (s, 2H), 3.95 (s, 3H); MS(ESI$^+$) m/z 436.0 (M+H$_2$O$^+$).

Intermediate 271C: 3-Benzyl 1-methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)isophthalate

![Diagram](Int-271C)

In a resealable pressure tube, a solution of 3-benzyl 1-methyl 4-(trifluoromethylsulfonyloxy)isophthalate (3.3 g, 7.9 mmol) in PhMe under argon was treated with bis(neopentylglycolato) diboron (2.50 g, 11.1 mmol), Pd(Ph$_3$)$_4$ (912 mg, 0.789 mmol) and KOAc (2.32 g, 23.68 mmol). The reaction vessel was purged with argon for 10 min, sealed with a Teflon lid and heated at 85°C for 16 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. The organic layer was washed with water, dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give a crude oil. The crude material was purified by flash chromatography (gradient from 0% to 10% EtOAc/hexane) to provide the title compound (2.2 g, 73%) as an off-white solid. $^1$H NMR (CDCl$_3$) δ 8.61 (d, $J = 1.6$ Hz, 1H), 8.16 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.58 (d, $J = 7.6$ Hz, 1H), 7.47-7.36 (m, 5H), 5.37 (s, 2H), 3.92 (s, 3H), 3.62 (s, 4H), 1.05 (s, 6H); MS(ESI$^+$) m/z 592.0 (3-benzyl 1-dimethyl 4,4’-((1,3,2,4-dioxadiboretane-2,4-diyl) diisophthalate).

Intermediate 271D: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-l-((2-(trimethylsilyl)ethoxy)methyl)-lH-imidazol-2-yl)isophthalate

ethoxy)methyl)- lH-imidazol-2-yl)isophthalate
Following a procedure analogous to that for the synthesis of Intermediate 2641, 3-benzyl 1-methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)isophthalate (1.76 g, 4.62 mmol) and 2-bromo-N,N-dibutyl-l-((2-(trimethylsilyl)ethoxy)methyl)-l-\textit{H}-imidazole-4-carboxamide (1.0 g, 2.31 mmol) were converted to the title compound (900 mg, 62%). $^1$H NMR (CDCl$_3$) $\delta$ 8.66 (d, $J = 1.6$ Hz, 1H), 8.23 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.62 (s, 1H), 7.58 (d, $J = 7.6$ Hz, 1H), 7.36-7.32 (m, 3H), 7.25-7.23 (m, 2H), 5.14 (s, 2H), 4.87 (s, 2H), 3.97 (s, 3H), 3.89 (br s, 2H), 3.45 (br s, 2H), 3.34 (t, $J = 8.0$ Hz, 2H), 1.60-1.54 (m, 2H), 1.39-1.21 (m, 6H), 0.95-0.78 (m, 6H), 0.76 (t, $J = 8.0$ Hz, 2H), -0.06 (s, 9H); MS(ESI$^+$) m/z 622.2 (M+H)$^+$. 

Intermediate 271E: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-l-\textit{H}-imidazol-2-yl)isophthalate

Following a procedure analogous to that for the synthesis of Intermediate 264J, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-l-((2-(trimethylsilyl)ethoxy)methyl)-1\textit{H}-imidazol-2-yl)isophthalate (900 mg, 1.44 mmol) was converted to the title compound (586 mg, 82%, light yellow oil). $^1$H NMR (CD$_3$OD) $\delta$ 8.55 (s, 1H), 8.30 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.63 (s, 1H), 7.35-7.29 (m, 5H), 5.27 (s, 2H), 3.98 (s, 3H), 3.78 (br s, 2H), 3.50 (br s, 2H), 1.67-1.62 (m, 4H), 1.40-1.30 (m, 4H), 0.97-0.93 (m, 6H); MS(ESI$^+$) m/z 492.2 (M+H)$^+$. 

Intermediate 271F: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-l-phenethyl-\textit{H}-imidazol-2-yl)isophthalate
To a stirred solution of 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)isophthalate (200 mg, 0.4 mmol) in dry DMF (5 mL) was added K$_2$CO$_3$ (168 mg, 1.22 mmol) and 2-phenethyl bromide (90 mg, 0.48 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 48 h. The reaction mixture was then cooled to 0 °C, diluted with MTBE and quenched with water. The layers were separated and the aqueous layer was extracted with MTBE (3 x). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give a crude oil. The crude material was purified by flash chromatography (gradient from 10% to 50% EtOAc/hexanes) to provide the title compound (175 mg, 72%). $^1$H NMR (CDCl$_3$) 8.65 (d, $J = 2.0$ Hz, 1H), 8.06 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.53 (s, 1H), 7.36-7.34 (m, 3H), 7.25-7.17 (m, 5H), 6.90 (d, $J = 8.0$ Hz, 1H), 6.81-6.79 (m, 2H), 5.14 (s, 2H), 3.99 (s, 3H), 3.97-3.95 (m, 2H), 3.67 (t, $J = 7.2$ Hz, 2H), 3.50 (br s, 2H), 2.76 (t, $J = 7.2$ Hz, 2H), 1.70-1.60 (m, 4H), 1.40-1.20 (m, 4H), 0.98-0.84 (m, 6H); MS(ESI$^+$) $m/z$ 596.2 (M+H$^+$).

Intermediate 271G: 2-(4-(Dibutylcarbamoyl)-1-phenethyl-1H-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

To a solution of 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-phenethyl-1H-imidazol-2-yl)isophthalate (170 mg, 0.28 mmol) in MeOH (5.0 mL) was added Pd/C (10%). The reaction mixture was stirred under ¾ atmosphere for 2 h. The reaction mixture was then filtered through a small pad of CELITE®, washing thoroughly with
MeOH. The filtrate was concentrated *in vacuo* to provide the title compound (133 mg, 92%), which was used without further purification. MS(ESI+) m/z 506.2 (M+H)+.

Intermediate 271H: Methyl 4-(4-(dibutylcarbamoyl)-l-phenethyl-lH-imidazol-2-yl)-3-(5)-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

[00642] To a solution of 2-(4-(dibutylcarbamoyl)-l-phenethyl-lH-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid (130 mg, 0.25 mmol) in DMF (5 mL) was added HATU (293 mg, 0.77 mmol), (5)-l,2,3,4-tetrahydroisoquinoline-3-yl-methanol (84 mg, 0.51 mmol) and diisopropylethylamine (269 µL, 1.54 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was diluted with water and extracted with MTBE (3 x). The combined organic layer was dried over Na2SO4 and concentrated to give crude product. The crude material was purified by flash chromatography (gradient from 0% to 50% EtOAc/hexanes) to provide the title compound (113 mg, 61%) as a light yellow oil. 1H NMR (DMSO-d6, 1:1 mixture amide rotamers) δ 8.14-8.01 (m, 2H), 7.64 (s, 1H), 7.34 (d, J = 7.2 Hz, 1H), 7.26-7.21 (m, 3H), 7.17-7.03 (m, 5.5H), 6.98 (d, J = 6.8 Hz, 0.5H), 5.03 (d, J = 18.4 Hz, 0.5H), 4.91 (br s, 1H), 4.39 (br s, 0.5H), 4.24 (d, J = 18.4 Hz, 0.5H), 4.16-4.07 (m, 2.5H), 3.91 (s, 3H), 3.88-3.85 (m, 0.5H), 3.76-3.73 (m, 0.5H), 3.65-3.55 (m, 1H), 3.39-3.34 (m, 2H), 3.24-3.00 (m, 2H), 2.96-2.85 (m, 3H), 2.70-2.65 (m, 2H), 1.50 -1.1 l(m, 8H), 0.88-0.76 (m, 6H); MS(ESI+) m/z 651.4 (M+H)+.

Intermediate 2711: 4-(4-(Dibutylcarbamoyl)-l-phenethyl-lH-imidazol-2-yl)-3-(5)-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid
To a solution of methyl 4-(4-(dibutylcarbamoyl)-1-phenethyl-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (110 mg, 0.169 mmol) in mixed solvents (2:2:1 THF/MeOH/H₂O, 5.0 mL) was treated with LiOHH₂O (21 mg, 0.507 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature over 30 min and stirring was continued for 1 h. The reaction mixture was concentrated to give crude product, which was diluted with water and extracted with MTBE. The aqueous layer was neutralized with 0.5N HCl and extracted with DCM (3x). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give the title product (100 mg, 91%), which was used without purification. MS(ESI⁺) m/z 637.2 (M+H)⁺.

Example 271:

To a solution of 4-(4-(dibutylcarbamoyl)-1-phenethyl-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (100 mg, 0.16 mmol) in dry DMF (8 mL) was added EDC (90 mg, 0.48 mmol), 8-chloroanaphthalene-2-sulfonamide (Intermediate 5, 76 mg, 0.32 mmol) and DMAP (28 mg, 0.24 mmol) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was concentrated in vacuo, dissolved in water and extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to afford crude product. The crude material was purified by preparative HPLC to provide the title compound (27 mg, 20%). ¹H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 9.02 (s, 1H), 8.17-8.00 (m, 4H), 7.95 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.61-7.57 (m, 1H), 7.50 (s, 1H), 7.23-6.89 (m, 10H), 5.11 (d, J = 18.0 Hz, 0.5H), 4.70-4.38 (m, 1H), 4.30 (d, J = 18.0 Hz, 0.5H), 4.20-3.95 (m, 3H), 3.63-3.51 (m, 1H), 3.48-3.39 (m, 2H), 3.28-3.21 (m, 1H), 3.18-3.11 (m, 1H), 3.02-2.97 (m,
2.5H), 2.88-2.78 (m, 2.5H), 1.60-1.10 (m, 8H), 1.00-0.80 (m, 6H); MS(ESr) m/z 861.2 (M+H)+.

Example 272

\[ \text{\(N,N\text{-Dibutyl-2-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-(3-phenylpropyl)-1H-imidazole-4-carboxamide}\)}

Intermediate 272A: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)isophthalate

Following a procedure analogous to that for the synthesis of Intermediate 271F, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)isophthalate (200 mg, 0.4 mmol) and (3-bromopropyl)benzene (97 mg, 0.48 mmol) were converted the title compound (187 mg, 74%). 3\textsuperscript{1} NMR (CDCl\textsubscript{3}) 8.65 (d, J = 1.6 Hz, 1H), 8.20 (dd, J = 8.0, 1.6 Hz, 1H), 7.53 (s, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.33-7.30 (m, 4H), 7.24-7.14 (m, 4H), 6.94 (d, J = 8.0 Hz, 2H), 5.13 (s, 2H), 4.00 (s, 3H), 3.99 (br s, 2H), 3.52 (t, J = 7.6 Hz, 2H), 3.46 (br s, 2H), 2.39 (t, J = 7.6 Hz, 2H), 1.82-1.78 (m, 2H), 1.55-1.50 (m, 4H), 1.26-1.22 (m, 4H), 0.96-0.83 (m, 6H); MS(ESI\textsuperscript{+}) m/z 610.2 (M+H)+.
Intermediate 272B: 2-(4-(Dibutylcarbamoyl)-1-(3-phenylpropyl)-1\textsubscript{H}-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 271G, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(3-phenylpropyl)-1\textsubscript{H}-imidazol-2-yl)isophthalate (180 mg, 0.29 mmol) was converted to the title product (143 mg, 93%). MS(ESI\textsuperscript{+}) m/z 520.2 (M+H\textsuperscript{+}).

Intermediate 272C: Methyl 4-(4-(dibutylcarbamoyl)-1-(3-phenylpropyl)-1\textsubscript{H}-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydrossoquinoline-2-carbonyl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(4-(dibutylcarbamoyl)-1-(3-phenylpropyl)-1\textsubscript{H}-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid (140 mg, 0.27 mmol) was converted to the title compound (160 mg, 89%). MS(ESI\textsuperscript{+}) m/z 665.4 (M+H\textsuperscript{+}).

Intermediate 272D: 4-(4-(Dibutylcarbamoyl)-1-(3-phenylpropyl)-1\textsubscript{H}-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 4-(4-(dibutylcarbamoyl)-1-(3-phenylpropyl)-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (180 mg, 0.27 mmol) was converted to the title compound (130 mg, 73%). MS(ESI^+) m/z 651.4 (M+H)^+.

Example 272:

Following a procedure analogous to that for the synthesis of Example 271, 4-(4-(dibutylcarbamoyl)-1-(3-phenylpropyl)-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (125 mg, 0.19 mmol) was converted to the title compound (32 mg, 20%). ^1H NMR (CD_3OD, 1:1 mixture of amide rotamers) δ 9.09 (s, 1H), 8.22-7.96 (m, 5H), 7.79 (d, J = 7.2 Hz, 1H), 7.66-7.59 (m, 2H), 7.51-7.48 (m, 1H), 7.22-7.02 (m, 8.5H), 6.89 (d, J = 7.6 Hz, 0.5H), 5.17 (d, J = 18.0 Hz, 0.5H), 4.50 (br s, 1H), 4.33 (d, J = 18.0 Hz, 0.5H), 3.99-3.94 (m, 3H), 3.70-3.40 (m, 4H), 3.25-2.85 (m, 3H), 2.57-2.52 (m, 3H), 2.06-2.01 (m, 2H), 1.51-1.10 (m, 8H), 1.02-0.91 (m, 3H), 0.85-0.62 (m, 3H); MS(ESI^+) m/z 875.2 (M+H)^+.

Example 273

1-Benzyl-\(N,N\)-dibutyl-2-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1H-imidazole-4-carboxamide
Intermediate 273A: 3-Benzyl 1-methyl 4-(1-benzyl-4-(dibutylcarbamoyl)-lH-imidazol-2-yl)isophthalate

Following a procedure analogous to that for the synthesis of Intermediate 271F, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-lH-imidazol-2-yl)isophthalate (200 mg, 0.40 mmol) and benzylbromide (83 mg, 0.48 mmol) were converted to the title compound (180 mg, 76%). ¾ NMR (CDCl₃) 8.68 (d, J = 1.6 Hz, 1H), 8.15 (dd, J = 8.0, 2.0 Hz, 1H), 7.43 (s, 1H), 7.39-7.34 (m, 4H), 7.28-7.26 (m, 2H), 7.21-7.17 (m, 3H), 6.90-6.88 (m, 2H), 5.15 (s, 2H), 4.64 (s, 2H), 3.96 (s, 3H), 3.90 (br s, 2H), 3.43 (br s, 2H), 1.70-1.59 (m, 4H), 1.37-1.23 (m, 4H), 0.93-0.82 (m, 6H); MS(ESI⁺) m/z 582.2 (M+H)⁺.

Intermediate 273B: 2-(1-Benzyl-4-(dibutylcarbamoyl)-lH-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

To a solution of 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-phenethyl-lH-imidazol-2-yl)isophthalate (100 mg, 0.17 mmol) in EtOAc (5 mL) was added Pd/C
The reaction mixture was stirred under ¾ atmosphere for 6 h, filtered through a small pad of CELITE® and washed thoroughly with MeOH. The solvents were removed in vacuo to provide the title compound (75 mg, 89%), which was used without further purification. MS(ESI+) m/z 506.2 (M+H)+.

Intermediate 273C: Methyl 4-(1-benzyl-4-(dibutylcarbamoyl)-l H-imidazol-2-yl)-3-(5)-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(4-(dibutylcarbamoyl)-l-(3-phenylpropyl)-l H-imidazol-2-yl)-5-(methoxycarbonyl)benzolic acid (75 mg, 0.15 mmol) was converted to the title compound (120 mg). MS(ESI+) m/z 637.4 (M+H)+.

Intermediate 273D: 4-(1-Benzyl-4-(dibutylcarbamoyl)-l H-imidazol-2-yl)-3-(5)-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 4-(1-benzyl-4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (120 mg, 0.27 mmol) was converted to the title compound (130 mg). MS(ESI+) m/z 623.2 (M+H)+.
Following a procedure analogous to that for the synthesis of Example 271, 4-(1-benzyl-4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (125 mg, 0.19 mmol) was converted to the title compound (4 mg, 2%). \( ^1H \) NMR (CD\(_3\)OD $\delta$ 9.06 s, 1H), 8.19-7.97 (m, 5H), 7.78 (d, $J$ = 7.2 Hz, 1H), 7.64 (t, $J$ = 7.2 Hz, 1H), 7.50-7.44 (m, 2H), 7.32-7.30 (m, 3H), 7.23-6.90 (m, 6H), 5.22-5.19 (m, 2H), 4.47 (br s, 1H), 4.33 (d, $J$ = 17.6 Hz, 1H), 4.00-3.95 (m, 1H), 3.70-3.60 (m, 1H), 3.45-3.40 (m, 2H), 3.35-3.25 (m, 3H), 2.95-2.80 (m, 2H), 1.70-1.49 (m, 2H), 1.48-1.10 (m, 6H), 1.00-0.60 (m, 6H); MS(ESF) $m/z$ 845.1 (M-H).

Example 274

\(N,N\)-Dibutyl-l-(2-hydroxyethyl)-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1 H-imidazole-4-carboxamide

Intermediate 274A: 3-Benzyl 1-methyl 4-(l-(2-(tert-butyldimethylsilyloxy)ethyl)-4-(dibutylcarbamoyl)-1 H-imidazol-2-yl)isophthalate

To a stirred solution of 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1 H-imidazol-2-yl)isophthalate (190 mg, 0.40 mmol) in dry DMF (5 mL) was added K\(_2\)CO\(_3\) (160 mg, 1.16 mmol) and (2-bromoethoxy)(tert-butyl)dimethylsilane (92 mg, 0.38 mmol) at 0 °C. The mixture was allowed to warm to room temperature and heated at 50 °C for 24 h. The reaction mixture was cooled to 0 °C, diluted with MTBE and quenched with
The organic layer was separated and the aqueous layer was extracted with MTBE (3 x). The combined organic layer was dried over Na$_2$SO$_4$ and concentrated in vacuo to provide crude product. The crude material was purified by flash chromatography (gradient 10 to 30% ethylacetate/hexane) to provide the title compound (144 mg, 54%).

$^1$H NMR (CD$_3$OD) 8.66 (d, J = 1.6 Hz, 1H), 8.30 (dd, J = 8.0, 2.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.38-7.29 (m, 5H), 5.20 (s, 2H), 3.99 (s, 3H), 3.83-3.82 (m, 2H), 3.77 (t, J = 5.0 Hz, 2H), 3.70 (t, J = 5.0 Hz, 2H), 3.49 (br s, 2H), 1.70-1.55 (m, 4H), 1.45-1.26 (m, 4H), 1.05-0.85 (m, 6H), 0.83 (s, 9H), 0.03 (s, 6H); MS(ESI$^+$) m/z 650.2 (M+H)$^+$.  

Intermediate 274B: 2-(l-(2-(tert-Butyldimethylsilyloxy)ethyl)-4-(dibutylcarbamoyl)-l$^H$-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

[00656] Following a procedure analogous to that for the synthesis of Intermediate 273B, 3-benzyl 1-methyl 4-(l-(2-(tert-butyldimethylsilyloxy)ethyl)-4-(dibutylcarbamoyl)-l$^H$-imidazol-2-yl)isophthalate (140 mg, 0.21 mmol) was converted to the title compound (105 mg, 87%). MS(ESI$^+$) m/z 560.2 (M+H)$^+$.  

Intermediate 274C: Methyl 4-(l-(2-(tert-butyldimethylsilyloxy)ethyl)-4-(dibutylcarbamoyl)-l$^H$-imidazol-2-yl)-3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

[00657] Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(l-(2-(tert-butyldimethylsilyloxy)ethyl)-4-(dibutylcarbamoyl)-l$^H$-imidazol-2-
(S)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline (62 mg, 0.22 mmol) were converted to the title compound (133 mg, 87%). MS(ESI⁺) m/z 820.2 (M+H)⁺.

Intermediate 274D: 4-(1-(2-(tert-butyldimethylsilyloxy)ethyl)-4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 4-(1-(2-(tert-butyldimethylsilyloxy)ethyl)-4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (130 mg, 0.16 mmol) was converted to the title compound (110 mg, 86%). MS(ESI⁺) m/z 806.2 (M+H)⁺.

Intermediate 274E: N,N-Dibutyl-1-(2-(tert-butyldimethylsilyloxy)ethyl)-2-(2-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-imidazole-4-carboxamide

Following a procedure analogous to that for the synthesis of Example 271, 4-(1-(2-(tert-butyldimethylsilyloxy)ethyl)-4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (105 mg, 0.19 mmol) and (S)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline (62 mg, 0.22 mmol) were converted to the title compound (133 mg, 87%). MS(ESI⁺) m/z 820.2 (M+H)⁺.
carbonyl)benzoic acid (100 mg, 0.12 mmol) was converted to the title compound (50 mg, 41%). MS(ESI+) m/z 995.2 (M+H)+.

Example 274:

To a solution of N,N-dibutyl-1-(2-(tert-butylidimethylsilyloxy)ethyl)-2-(2-((5)-3-((tert-butylidimethylsilyloxy)methyl)1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1H-imidazole-4-carboxamide (50 mg, 0.05 mmol) in THF was added 3 drops of cone. HCl at 0 °C. The mixture was allowed to warm to room temperature over 1 h. The reaction mixture was then cooled to 0 °C, quenched with MeOH/NH₃ and concentrated in vacuo to provide a precipitate. The solid was dissolved in water and extracted with EtOAc (4 x). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give the crude product. The crude material was purified by flash chromatography (gradient from 0% to 15% MeOH saturated with NH₃/CHC1₃) to provide the title compound (25 mg, 66%). ¹H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 8.63 (s, 1H), 8.16-8.14 (m, 1.5H), 8.06-7.94 (m, 4.5H), 7.69-7.59 (m, 4H), 7.20-7.13 (m, 3.5H), 6.95 (d, J = 6.8 Hz, 0.5H), 5.15 (d, J = 18.0 Hz, 0.5H), 4.60-4.50 (br s, 1H), 4.30 (d, J = 18.0 Hz, 0.5H), 4.09-3.71 (m, 7.5H), 3.47-3.38 (m, 2.5H), 3.25-3.17 (m, 1H), 2.93-2.64 (m, 2H), 1.51-1.45 (m, 2H), 1.40-1.10 (m, 6H), 0.97-0.68 (m, 6H); MS(ESI+) m/z 767.0 (M+H)+.

Example 275

N,N-Dibutyl-2-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(2-methoxy ethyl)-1H-imidazole-4-carboxamide
Intermediate 275A: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(2-methoxyethyl)-1 \( H \)-imidazol-2-yl)isophthalate

Following a procedure analogous to that for the synthesis of Intermediate 274A, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1 \( H \)-imidazol-2-yl)isophthalate (200 mg, 0.40 mmol) and bromoethylmethylether (68 mg, 0.38 mmol) were converted to the title compound (165 mg, 74%). \( ^1H \) NMR (CDCl\(_3\)) \( \delta \) 8.67 (d, \( J = 1.6 \) Hz, 1H), 8.23 (dd, \( J = 8.0, 2.0 \) Hz, 1H), 7.61 (s, 1H), 7.53 (d, \( J = 8.0 \) Hz, 1H), 7.35-7.32 (m, 3H), 7.25-7.23 (m, 2H), 5.14 (s, 2H), 3.97 (s, 3H), 3.92-3.85 (m, 2H), 3.67 (t, \( J = 5.4 \) Hz, 2H), 3.45-3.41 (m, 2H), 3.17 (s, 3H), 1.70-1.55 (m, 4H), 1.40-1.20 (m, 4H), 0.98-0.82 (m, 6H); MS(ESI\(^+\)) \( m/z \) 550.2 (M+H\(^+\)).

Intermediate 275B: 2-(4-(Dibutylcarbamoyl)-1-(2-methoxyethyl)-1 \( H \)-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 271G, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(2-methoxyethyl)-1 \( H \)-imidazol-2-yl)isophthalate (165 mg, 0.30 mmol) was converted to the title compound (125 mg, 91%). MS(ESI\(^+\)) \( m/z \) 460.2 (M+H\(^+\)).

Intermediate 275C: Methyl 4-(4-(dibutylcarbamoyl)-1-(2-methoxyethyl)-1 \( H \)-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate
Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid (120 mg, 0.26 mmol) was converted to the title compound (110 mg, 62%). MS(ESI⁺) m/z 605.2 (M+H)⁺.

Intermediate 275D: 4-(4-(Dibutylcarbamoyl)-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (110 mg, 0.18 mmol) was converted to the title product (90 mg, 84%). MS(ESI⁺) m/z 591.4 (M+H)⁺.

Example 275:
Following a procedure analogous to that for the synthesis of Example 271, 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (90 mg, 0.152 mmol) was converted to the title product (6 mg, 5%). ³¹NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 8.59 (s, 1H), 8.21-8.17 (m, 2H), 8.06-8.02 (m, 2H), 7.97-7.92 (m, 2H), 7.63-7.57 (m, 4H), 7.20-7.13 (m, 3.5H), 6.94 (d, J = 6.8 Hz, 0.5H), 5.15 (d, J = 18.4 Hz, 0.5H),
4.58 (s, 0.5H), 4.50 (br s, 1H), 4.31 (d, J = 18.4 Hz, 1H), 4.18-4.09 (m, 3H), 3.65-3.43 (m, 6H), 3.30 (s, 3H), 3.16-2.51 (m, 3H); 1.53-1.14 (m, 8H); 0.97-0.73 (m, 6H); MS(ESI⁺) m/z 781.2 (M+H)⁺.

Example 276

*N,N*-Dibutyl-1-(2-(2-hydroxyethoxy)ethyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1*H*-imidazole-4-carboxamide

Intermediate 276A: 3-Benzyl 1-methyl 4-(1-(2-(2-(tert-butyldiphenylsilyloxy)ethoxy)ethyl)-4-(dibutylcarbamoyl)-1*H*-imidazol-2-yl)isophthalate

[00666] Following a procedure analogous to that for the synthesis of Intermediate 274A, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1*H*-imidazol-2-yl)isophthalate (200 mg, 0.40 mmol) and (2-(2-bromoethoxy)ethoxy)(tert-butyl)diphenylsilane (165 mg, 0.40 mmol) were converted to the title compound (280 mg, 84%). ¹H NMR (CDCl₃) δ 8.66 (d, J = 2.0 Hz, 1H), 8.16 (dd, J = 8.0, 2.0 Hz, 1H), 7.62-7.57 (m, 4H), 7.57 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.42-7.32 (m, 9H), 7.24-7.22 (m, 2H), 5.12 (s, 2H), 3.96 (s, 3H), 3.94-3.85 (m, 2H), 3.69-3.63 (m, 4H), 3.46-3.43 (m, 4H), 3.67 (t, J = 5.2 Hz, 2H), 1.65-
1.55 (m, 4H), 1.40-1.15 (m, 4H), 1.01 (s, 9H), 1.00-0.85 (m, 6H); MS(ESr) m/z 819.4 (M+H)+.

Intermediate 276B: 2-(1-(2-(2-(2-(tert-Butyldiphenylsilyloxy)ethoxy)ethyl)-4-(dibutylcarbamoyl)-1 \textit{H}-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 271G, 3-benzyl 1-methyl 4-(l-(2-(2-(tert-butyldiphenylsilyloxy)ethoxy)ethyl)-4-(dibutylcarbamoyl)-1 \textit{H}-imidazol-2-yl)isophthalate (280 mg, 0.34 mmol) was converted to the title compound. (126 mg, 51%). MS(ESI+) m/z 728 (M+H)+.

Intermediate 276C: Methyl 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(l-(2-(2-(tert-butyldiphenylsilyloxy)ethoxy)ethyl)-4-(dibutylcarbamoyl)-1 \textit{H}-imidazol-2-yl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(l-(2-(2-(tert-butyldiphenylsilyloxy)ethoxy)ethyl)-4-(dibutylcarbamoyl)-1 \textit{H}-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid (126 mg, 0.17 mmol) was converted to the title compound (140 mg, 81%). MS(ESI+) m/z 988.4 (M+H)+.
Intermediate 276D: 3-((5)-3-((tert-Bu\textdollar{}yldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(l-(2-(2-(tert-butyldiphenylsilyloxy)ethoxy)ethyl)-4-(dibutylcarbamoyl)-I H-imidazol-2-yl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(l-(2-(2-(tert-butyldiphenylsilyloxy)ethoxy)ethyl)-4-(dibutylcarbamoyl)-I H-imidazol-2-yl)benzoate (140 mg, 0.14 mmol) was converted to the title compound (120 mg, 87%). MS(ESI+) m/z 974.4 (M+H)+.

Intermediate 276E: N,N-Dibutyl-2-(2-(5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-l-(2-(2-(tert-butyldiphenylsilyloxy)ethoxy)ethyl)-IH-imidazole-4-carboxamide

Following a procedure analogous to that for the synthesis of Example 271, 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(1-(2-(2-(tert-butyldiphenylsilyloxy)ethoxy)ethyl)-4-(dibutylcarbamoyl)-IH-imidazol-2-yl)benzoic acid (120 mg, 0.12 mmol) was converted to the title compound (60 mg, 42%). MS(ESI+) m/z 1163.2 (M+H)+.
Example 276:

To a solution of N,N-dibutyl-2-(2-((S)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(2-(2-((tert-butyldimethylsilyloxy)ethoxy)ethyl)-1H-imidazole-4-carboxamide (60 mg, 0.05 mmol) in THF (3.0 mL) was added tetrabutylammonium fluoride (153 µL, 0.15 mmol, 1.0M in THF) at 0 °C. The reaction mixture was allowed to warm to room temperature over 30 min and then stirred for 30 min. The reaction mixture was then quenched with sat. NH₄Cl solution and extracted with DCM (5 x). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give the crude compound, which was dissolved in MeOH and treated with DOWEX® (H⁺) resin. The mixture was filtered, concentrated in vacuo and purified using preparative TLC (15% MeOH (saturated with NH₃)/CHCl₃ to provide the title compound (13 mg, 31%).

1H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 8.58 (s, 1H), 8.21-8.17 (m, 2H), 8.05-8.01 (m, 2H), 7.96-7.91 (m, 2H), 7.74-7.56 (m, 4H), 7.20-7.13 (m, 3.5H), 6.95 (d, J = 8.0 Hz, 0.5H), 5.15 (d, J = 18.0 Hz, 0.5H), 4.68-4.45 (m, 8H), 4.30 (d, J = 18.0 Hz, 0.5H), 4.15-4.10 (m, 2H), 3.72-3.71 (m, 2.5H), 3.63-3.61 (m, 2.5H), 3.50-3.47 (m, 1H) 2.98-2.85 (m, 2H), 1.51-1.42 (m, 2H), 1.35-1.10 (m, 6H), 0.96-0.65 (m, 6H); MS(ESI+) m/z 811.0 (M+H)+.

Example 277

N,N-Dibutyl-2-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(2-morpholinoethyl)-1H-imidazole-4-carboxamide

Intermediate 277A: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(2-morpholinoethyl)-1H-imidazol-2-yl)isophthalate
Following a procedure analogous to that for the synthesis of Intermediate 274A, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)isophthalate (280 mg, 0.57 mmol) and 4-(2-chloroethyl) morpholine hydrochloride (106 mg, 0.57 mmol) were converted to the title compound (240 mg, 70%). $^1$H NMR (CDCl$_3$) $\delta$ 8.68 (d, $J$ = 1.6 Hz, 1H), 8.23 (dd, $J$ = 8.0, 1.6 Hz, 1H), 7.62 (s, 1H), 7.53 (d, $J$ = 8.0 Hz, 1H), 7.36-7.32 (m, 3H), 7.25-7.23 (m, 2H), 5.14 (s, 2H), 3.97 (s, 3H), 3.92 (br s, 2H), 3.60-3.54 (m, 6H), 3.45 (br s, 2H), 2.37 (t, $J$ = 6.4 Hz, 2H), 2.20-2.18 (m, 4H), 1.63-1.56 (m, 4H), 1.38-1.22 (m, 4H), 0.95-0.82 (m, 6H); MS(ESI$^+$) m/z 605.4 (M+H)$^+$. 

Intermediate 277B: 2-(4-(Dibutylcarbamoyl)-1-(2-morpholinoethyl)-1H-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 271G, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(2-morpholinoethyl)-1H-imidazol-2-yl)isophthalate (230 mg, 0.38 mmol) was converted to the title compound (186 mg, 95%). $^1$H NMR (CD$_3$OD) $\delta$ 8.60 (d, $J$ = 1.6 Hz, 1H), 8.23 (dd, $J$ = 8.0, 2.0 Hz, 1H), 7.77 (s, 1H), 7.63 (d, $J$ = 8.0 Hz, 1H), 4.10 (t, $J$ = 6.0 Hz, 2H), 3.99 (s, 3H), 3.86 (br s, 2H), 3.64-3.62 (m, 4H), 3.50-3.48 (m, 2H), 2.80-2.86 (m, 2H), 2.51-2.49 (m, 4H), 1.66-1.62 (m, 4H), 1.40-1.27 (m, 4H), 0.99-0.89 (m, 6H); MS(ESI$^+$) m/z 515.2 (M+H)$^+$. 

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Intermediate 277C: Methyl 4-(4-(dibutylcarbamoyl)-l-(2-morpholinoethyl)-l H-imidazol-2-yl)-3-((5')-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 4-(4-(dibutylcarbamoyl)-l-(2-morpholinoethyl)-l H-imidazol-2-yl)-3-((5')-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (225 mg, 0.34 mmol) was converted to the title compound (225 mg, 94%). ³¹NMR (CDCl₃, 1:1 mixture of amide rotamers) δ 8.21-8.16 (m, 1H), 8.04 (d, J = 6.4 Hz, 1H), 7.64-7.53 (m, 2H), 7.21-7.10 (m, 3.5H), 6.86 (d, J = 7.2 Hz, 0.5H), 5.81 (br s, 0.5H), 5.34 (d, J = 16.0 Hz, 0.5H), 4.90-4.86 (m, 0.5H), 4.42-4.24 (m, 2H), 4.04-3.95 (m, 5.5H), 3.68-3.62 (m, 6H), 3.38-3.30 (m, 2H), 3.24-3.19 (m, 1H), 2.74-2.67 (m, 3H), 2.44-2.43 (m, 5H), 1.60-1.56 (m, 4H), 1.31-1.26 (m, 4H), 0.91-0.87 (m, 6H); MS(ESI⁺) m/z 661.4 (M+H)⁺.

Intermediate 277D: 4-(4-(Dibutylcarbamoyl)-l-(2-morpholinoethyl)-l H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 4-(4-(dibutylcarbamoyl)-l-(2-morpholinoethyl)-l H-imidazol-2-yl)-3-((5')-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (225 mg, 0.34 mmol) was converted to the title compound (225 mg, 94%). ³¹NMR (CDCl₃, 1:1 mixture of amide rotamers) δ 8.21-8.16 (m, 1H), 8.04 (d, J = 6.4 Hz, 1H), 7.64-7.53 (m, 2H), 7.21-7.10 (m, 3.5H), 6.86 (d, J = 7.2 Hz, 0.5H), 5.81 (br s, 0.5H), 5.34 (d, J = 16.0 Hz, 0.5H), 4.90-4.86 (m, 0.5H), 4.42-4.24 (m, 2H), 4.04-3.95 (m, 5.5H), 3.68-3.62 (m, 6H), 3.38-3.30 (m, 2H), 3.24-3.19 (m, 1H), 2.74-2.67 (m, 3H), 2.44-2.43 (m, 5H), 1.60-1.56 (m, 4H), 1.31-1.26 (m, 4H), 0.91-0.87 (m, 6H); MS(ESI⁺) m/z 661.4 (M+H)⁺.
mmol) was converted to the title compound (210 mg, 95%). MS(ESI\(^+)\) \(m/z\) 646.4 (M+H\(^+)\).

Example 277:

Following a procedure analogous to that for the synthesis of Example 271, 4-(4-(dibutylcarbamoyl)-1-(2-morpholinoethyl)-1H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (200 mg, 0.31 mmol) was converted to the title compound (34 mg, 13%). \(^1\)H NMR (CD\(_3\)OD, 1:1 mixture of amide rotamers) \(\delta\) 8.59 (s, 1H), 8.22-8.10 (m, 2H), 8.06-8.01 (m, 2H), 7.96-7.92 (m, 2H), 7.73-7.56 (m, 4H), 7.20-7.10 (m, 3.5H), 6.94 (d, \(J = 7.6 \text{ Hz}\), 0.5H), 5.14 (d, \(J = 19.2 \text{ Hz}\), 0.5H), 4.75-4.50 (m, 2H), 4.31 (d, \(J = 18.4 \text{ Hz}\), 0.5H), 4.08-4.02 (m, 3H), 3.63-3.61 (m, 5.5H), 3.55-3.40 (m, 2.5H), 2.95-2.60 (m, 5H), 2.49-2.38 (m, 4H), 1.52-1.11 (m, 8H), 0.96-0.71 (m, 6H); MS(ESI\(^+)\) \(m/z\) 836.4 (M+H\(^+)\).

Example 278

\(N,N\)-Dibutyl-2-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(3-morpholinopropyl)-1H-imidazole-4-carboxamide

Intermediate 278A: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(3-morpholinopropyl)-1H-imidazol-2-yl)isophthalate
Following a procedure analogous to that for the synthesis of Intermediate 274A, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-H-imidazol-2-yl)isophthalate (130 mg, 0.26 mmol) and 4-(3-chloropropyl)morpholine (53 mg, 0.27 mmol) were converted to the title compound (65 mg, 40%). $^1$H NMR (CD$_3$OD) δ 8.67 (d, $J = 2.0$ Hz, 1H), 8.33 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.62 (s, 1H), 7.38-7.32 (m, 5H), 5.21 (s, 2H), 4.01 (s, 3H), 3.84-3.80 (m, 4H), 3.59-3.50 (m, 6H), 2.20-2.11 (m, 6H), 1.70-1.60 (m, 6H), 1.45-1.25 (m, 4H), 1.05-0.82 (m, 6H); MS(ESI$^+$) m/z 619 (M+H)$^+$.  

Intermediate 278B: 2-(4-(Dibutylcarbamoyl)-1-(3-morpholinopropyl)-1-H-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 271G, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(3-morpholinopropyl)-1-H-imidazol-2-yl)isophthalate (80 mg, 0.13 mmol) was converted to the title compound (70 mg, 97%). MS(ESI$^+$) m/z 529 (M+H)$^+$.  

Intermediate 278C: Methyl 4-(4-(dibutylcarbamoyl)-1-(3-morpholinopropyl)-1-H-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate
Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(4-(dibutylcarbamoyl)-l-(3-morpholinopropyl)-lH-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid (70 mg, 0.132 mmol), was converted to the title compound (80 mg, 91%). MS(ESI⁺) m/z 674.4 (M+H)⁺.

Intermediate 278D: 4-(4-(Dibutylcarbamoyl)- 1-(3-morpholinopropyl)- lH-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 4-(4-(dibutylcarbamoyl)- 1-(3-morpholinopropyl)- lH-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (90 mg, 0.13 mmol) was converted to title compound (85 mg, 96%). MS(ESI⁺) m/z 660.4 (M+H)⁺.

Example 278:

Following a procedure analogous to that for the synthesis of Example 271, 4-(4-(dibutylcarbamoyl)-l-(3-morpholinopropyl)-lH-imidazol-2-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (85 mg, 0.13 mmol) was converted to the title compound (5 mg, 5%). ¾ NMR (CD₃OD) δ 8.59 (s, 1H), 8.21 (br s, 1H), 8.03-7.93 (m, 4H), 7.61-7.59 (m, 4H), 7.19-7.13 (m, 4.5H), 6.94 (d, J = 6.8 Hz, 0.5H), 5.15 (m, 1H), 4.58-4.40 (m, 2H), 4.35-4.15 (m, 4H), 3.64 (m, 5H), 2.75 (br s, 2H), 2.46-2.35 (m, 7H), 2.10-1.96 (m, 4H), 1.65-1.55 (m, 3H), 1.20-1.10 (m, 2H), 1.00-0.85 (m, 9H); MS(ESF) m/z 848.2 (M-H)⁻.
Example 279

$N,N$-Dibutyl-2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylethylcarbamoyl)phenyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazole-4-carboxamide

Intermediate 279A: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)isophthalate

Following a procedure analogous to that for the synthesis of Intermediate 279F, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1H-imidazol-2-yl)isophthalate (200 mg, 0.40 mmol) and 1-(3-bromopropyl)-4-methylpiperazine (112 mg, 0.81 mmol) were converted to the title compound (180 mg, 70%). $^1$H NMR (CD$_3$OD) $\delta$ 8.67 (d, $J = 2.0$ Hz, 1H), 8.33 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 1H), 7.62 (s, 1H), 7.38-7.30 (m, 5H), 5.21 (s, 2H), 4.00 (s, 3H), 3.82-3.78 (m, 4H), 3.50 (br s, 2H), 2.35-2.12 (m, 13H), 1.71-1.64 (m, 6H), 1.41-1.27 (m, 4H), 1.00-0.87 (m, 6H); MS(ESI$^+$) $m/z$ 632.4 (M+H)$^+$. 

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Intermediate 279B: 2-(4-(Dibutylcarbamoyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

[00683] Following a procedure analogous to that for the synthesis of Intermediate 271G, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazol-2-yl) isophthalate (180 mg, 0.28 mmol) was converted to the title compound (110 mg, 71%). MS(ESF) m/z 540.2 (M-H)^-.

Intermediate 279C: Methyl 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazol-2-yl)benzoate

[00684] Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(4-(dibutylcarbamoyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid (110 mg, 0.2 mmol) and (S)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline (73 mg, 0.26 mmol) were converted to the title compound (150 mg, 93%). MS(ESI^+) m/z 802.4 (M+H)^+.

Intermediate 279D: 3-((5)-3-((tert-Butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazol-2-yl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazol-2-yl)benzoate (150 mg, 0.18 mmol) was converted to the title compound (110 mg, 68%). MS(ESI+) m/z 788.4 (M+H)+.

Intermediate 279E: N,N-dibutyl-2-(2-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazole-4-carboxamide

Following a procedure analogous to that for the synthesis of Example 274, 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-(3-(4-methylpiperazin-1-yl)propyl)-1H-imidazol-2-yl)benzoic acid (110 mg, 0.14 mmol) was converted to the title compound (33 mg, 24%). MS(ESI+) m/z 975.2 (M-H).
tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(3-
(4-methylpiperazin-1-yl)propyl)-1 H-imidazole-4-carboxamide (28 mg, 0.028 mmol) was
converted to the title compound (25 mg, 86%). $^1$H NMR (CD$_3$OD, 1:1 mixture of amide
rotamers) δ 8.61 (s, 1H), 8.25-8.20 (m, 2H), 8.09-8.03 (m, 2H), 7.99-7.94 (m, 2 H), 7.67-
7.57 (m, 4H), 7.22-6.94 (m, 4H), 5.16 (d, $J = 17.6$ Hz, 0.5H), 4.58 (br s, 1.5H), 4.30 (d, $J$
= 17.6 Hz, 1H), 4.10 (br s, 3H), 3.58-3.39 (m, 5H), 3.25-3.15 (m, 1H), 2.91-2.55 (m,
15H), 1.92-1.84 (m, 2H), 1.52-1.11 (m, 8H), 0.98-0.79 (m, 6H); MS(ESI$^+$) m/z 863.4
(M+H)$^+$.  

Example 280

$N,N$-Dibutyl-2-(2-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-
(naphthalen-2-ylsulfonylcarbamoyl)phenyl)- 1-(2-(4-methylpiperazin- 1-yl)ethyl)- 1H-
imidazole-4-carboxamide

![Chemical Structure]

Intermediate 280A: 3-Benzyl 1-methyl 4-((l-(2-chloroethyl)-4-(dibutylcarbamoyl)-l  H-
imidazol-2-yl)isophthalate

![Chemical Structure]

[00688] To a solution of 3-benzyl 1-methyl 4-((4-(dibutylcarbamoyl)-l  H-imidazol-2-
yl)isophthalate (275 mg, 0.56 mmol) in dry MeCN (8.0 mL) was added cesium carbonate
(182 mg, 0.56 mmol) and 1-bromo-2-chloroethane (80 mg, 0.56 mmol). The reaction
mixture was heated at 50 °C for 10 h, diluted with water and extracted with EtOAc (3 x). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo to give the crude product. The crude material was purified by flash chromatography (gradient from 0% to 2% MeOH/CH₂Cl₂) to provide the title compound (170 mg, 54%). ¹H NMR (DMSO-d₆) δ 8.46 (d, J = 1.6 Hz, 1H), 8.26 (dd, J = 8.0, 1.6 Hz, 1H), 7.85 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.36-7.33 (m, 3H), 7.27-7.25 (m, 2H), 5.16 (s, 2H), 4.08-4.03 (m, 4H), 3.93 (s, 1.5H), 3.77-3.73 (m, 3.5H), 3.50-3.40 (m, 2H), 1.50-1.45 (m, 4H), 1.35-1.10 (m, 4H), 0.92-0.75 (m, 6H); MS(ESI⁺) m/z 555.0 (M+H)⁺.

Intermediate 280B: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-imidazol-2-yl)isophthalate

[00689] To a solution of 3-benzyl 1-methyl 4-(1-(2-chloroethyl)-4-(dibutylcarbamoyl)-1H-imidazol-2-yl)isophthalate (120 mg, 0.21 mmol) in dry DMF (2 mL) was added diisopropylethyl amine (26.5 mg, 0.21 mmol) and 1-methylpiperazine (21 mg, 0.21 mmol) at room temperature. The reaction mixture was heated at 90 °C for 16 h, diluted with water and extracted with MTBE (3 x). The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo to give the crude product. The crude material was purified by flash chromatography (gradient from 0 to 5% MeOH/CH₂Cl₂) to provide the title compound (60 mg, 45%). MS(ESI⁺) m/z 619.2 (M+H)⁺.

Intermediate 280C: 2-(4-(Dibutylcarbamoyl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 271G, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-(2-(4-(methylpiperazin-1-yl)ethyl)-1H-imidazol-2-yl)isophthalate (70 mg, 0.11 mmol) was converted to the title compound (55 mg, 93%). MS(ESI+) m/z 528.2 (M+H)+.

Intermediate 280D: Methyl 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-(2-(4-(methylpiperazin-1-yl)ethyl)-1H-imidazol-2-yl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(4-(dibutylcarbamoyl)-1-(2-(4-(methylpiperazin-1-yl)ethyl)-1H-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid (55 mg, 0.10 mmol) was converted to the title compound (45 mg, 56%). MS(ESI+) m/z 788.4 (M+H)+.

Intermediate 280E: 3-((5)-3-((tert-Butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-(2-(4-(methylpiperazin-1-yl)ethyl)-1H-imidazol-2-yl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-imidazol-2-yl)benzoate (45 mg, 0.057 mmol) was converted to title compound (35 mg, 79%). MS(ESI) m/z 772.0 (M-H)^-.

Intermediate 280F: N,N'-Dibutyl-2-(2-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-imidazole-4-carboxamide

Following a procedure analogous to that for the synthesis of Example 271, 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-(2-(4-methylpiperazin-1-yl)ethyl)-1H-imidazol-2-yl)benzoic acid (35 mg, 0.045 mmol) was converted to the title compound (12 mg, 28%); MS(ESI) m/z 961.2 (M-H)^-.

Example 280:
Following a procedure analogous to that for the synthesis of Example 274, N,N-dibutyl-2-(2-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-l-(2-(4-methylpiperazin-1-yl)ethyl)-l H-imidazole-4-carboxamide (12 mg, 0.012 mmol) was converted to the title compound (7 mg, 86%). ¹H NMR (CD₂OD, 1:1 mixture of amide rotamers) δ 8.59 (s, 1H), 8.22-8.18 (m, 2H), 8.06-8.01 (m, 2H), 7.97-7.92 (m, 2H), 7.71-7.57 (m, 4H), 7.21-7.13 (m, 3.5H), 6.94 (d, J = 6.8 Hz, 0.5H), 5.15 (d, J = 18.0 Hz, 0.5H), 4.57 (br s, 1.5H), 4.30 (d, J = 18.0 Hz, 1H), 4.10-4.08 (m, 3H), 3.70-3.40 (m, 3H), 3.02-2.68 (m, 9H), 2.54-2.34 (m, 8H), 1.64-1.32 (m, 4H), 1.30-1.11 (m, 4H), 0.97-0.67 (m, 6H); MS(ESI⁺) m/z 848.0 (M+H)⁺.

Example 281

2-(2-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-1-methyl-lH-imidazole-4-carboxamide

Intermediate 281A: 3-Benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)isophthalate

Following a procedure analogous to that for the synthesis of Intermediate 271F, 3-benzyl 1-methyl 4-(4-(dibutylcarbamoyl)-1 H-imidazol-2-yl)isophthalate (370 mg, 0.75 mmol) and methyl iodide (106 mg, 0.75 mmol) were converted to the title compound (260 mg, 68%). ¾ NMR (CDCl₃) δ 8.70 (d, J = 1.2 Hz, 1H), 8.24 (dd, J =
8.0, 1.6 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.43 (s, 1H), 7.37-7.33 (m, 3H), 7.28-7.27 (m, 2H), 5.17 (s, 2H), 3.98 (s, 3H), 3.92 (br s, 2H), 3.45 (br s, 2H), 3.24 (s, 3H), 1.68-1.52 (m, 4H), 1.37-1.24 (m, 4H), 0.94-0.90 (m, 6H); MS(ESI\textsuperscript{+}) m/z 507.0 (M+H\textsuperscript{+}).

Intermediate 281B: 2-(4-(Dibutylcarbamoyl)-1-methyl-lH-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid

![Intermediate 281B](image)

[00696] Following a procedure analogous to that for the synthesis of Intermediate 271G, 3-benzyl-1-methyl-4-(4-(dibutylcarbamoyl)-1-methyl-lH-imidazol-2-yl)isophthalate (260 mg, 0.51 mmol) was converted to the title compound (210 mg, 98%). MS(ESI\textsuperscript{+}) m/z 416.0 (M+H\textsuperscript{+}).

Intermediate 281C: Methyl 3-((5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-methyl-lH-imidazol-2-yl)benzoate

![Intermediate 281C](image)

[00697] Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(4-(dibutylcarbamoyl)-1-methyl-lH-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid (230 mg, 0.55 mmol) and (5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline (135 mg, 0.72 mmol) were converted to the title compound (280 mg, 91%). MS(ESI\textsuperscript{+}) m/z 586.2 (M+H\textsuperscript{+}).

Intermediate 281D: 3-((5)-3-(Azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-methyl-lH-imidazol-2-yl)benzoic acid
Following a procedure analogous to that for the synthesis of Intermediate 2711, methyl 3-((5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)benzoate (280 mg, 0.48 mmol) was converted to the title compound (240 mg, 88%). MS(ESI ^+ ) m/z 572.2 (M+H)^+.

Intermediate 281E: 2-(2-((S)-3-(Azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl )N,N-dibutyl-1-methyl-1H-imidazole-4-carboxamide

Following a procedure analogous to that for the synthesis of Example 271, 3-((5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)benzoic acid (120 mg, 0.21 mmol) was converted to the title compound (98 mg, 62%). MS(ESI ^+ ) m/z 762.0 (M+H)^+.

Example 281:

To a solution of 2-(2-((S)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(naphthalen-2-ylsulfonylcarbamoyl)phenyl )N,N-dibutyl-1-methyl-1H-imidazole-4-carboxamide (60 mg, 0.08 mmol) in THF (5 mL) and water (0.5 mL) at 0 °C was added 1M aq. NaOH solution (50 µL) and PPI_3 (29 mg, 0.11 mmol). The reaction mixture was stirred at 0 °C for 2 h, then warmed to room temperature and stirred for 3 h. The reaction mixture was concentrated in vacuo and the residue was diluted with water and extracted with EtOAc (3 x). The combined organic layers were dried over Na_2SO_4
and concentrated \textit{in vacuo} to give the crude compound. The crude material was purified by preparative HPLC to provide the title compound (17 mg, 30%). $^1$H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) $\delta$ 8.76 (s, 1H), 8.18-8.03 (m, 6H), 7.92 (d, $J = 8.0$ Hz, 0.5H), 7.84 (d, $J = 8.0$ Hz, 0.5H), 7.76-7.65 (m, 2.5H), 7.55 (br s, 0.5H), 7.30-7.15 (m, 3.5H), 6.96 (d, $J = 8.0$ Hz, 0.5H), 5.38 (d, $J = 18.4$ Hz, 0.5H), 5.09 (br s, 0.5H), 4.85-4.42 (m, 2H), 3.82 (s, 3.5H), 3.70-3.40 (m, 4.5H), 3.01-2.90 (m, 1H), 2.86-2.83 (m, 2H), 1.67-1.54 (m, 3.5H), 1.40-1.31 (m, 4.5H), 1.00-0.75 (m, 6H); MS(EST) $m/z$ 732.8 (M-H)$^-$. 

Example 282

$$\begin{align*}
2\text{-}(2\text{-}((5)\text{-}3\text{-}(\text{Aminomethyl})\text{-}1,2,3,4\text{-}\text{tetrahydroisoquinoline-2-carbonyl})\text{-}4\text{-}(8\text{-}\text{iodonaphthalen-2-ylsulfonylcarbamoyl})\text{phenyl})\text{-}N,N\text{-}\text{dibutyl-1-methyl-1H-imidazole-4-carboxamide}
\end{align*}$$

Intermediate 282A: 2\text{-}(2\text{-}((5)\text{-}3\text{-}(\text{Azidomethyl})\text{-}1,2,3,4\text{-}\text{tetrahydroisoquinoline-2-carbonyl})\text{-}4\text{-}(8\text{-}\text{iodonaphthalen-2-ylsulfonylcarbamoyl})\text{phenyl})\text{-}N,N\text{-}\text{dibutyl-1-methyl-1H-imidazole-4-carboxamide}

Following a procedure analogous to that for the synthesis of Example 271, 3\text{-}(5)\text{-}(azidomethyl)\text{-}1,2,3,4\text{-}\text{tetrahydroisoquinoline-2-carbonyl})\text{-}4\text{-}(dibutylcarbamoyl)-1\text{-}\text{methyl-1H-imidazol-2-yl} \text{benzoic acid (Intermediate 281D, 120 mg, 0.21 mmol) and 8-iodonaphthalene-2-sulfonamide (Intermediate 8, 139 mg, 0.42 mmol) were converted to the title compound (76 mg, 41%>). MS(EST) $m/z$ 885.8 (M-H)$^-$. 

[00701]
Example 282:

Following a procedure analogous to that for the synthesis of Example 281, 2-(2-((5')-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-iodonaphthalen-2-ylsulfonylcarbamoyl)phenyl)-N,N-dibutyl-1-methyl-1H-imidazole-4-carboxamide (75 mg, 0.08 mmol) was converted to the title compound (35 mg, 48%). $^1$H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 8.85 (s, 1H), 8.28-8.13 (m, 4H), 7.99-7.94 (m, 2H), 7.75-7.52 (m, 2H), 7.34 (t, $J = 8.0$ Hz, 1H), 7.27-7.17 (m, 3.5H), 7.00 (d, $J = 7.2$ Hz, 0.5H), 5.37 (d, $J = 18.4$ Hz, 0.5H), 5.09 (br s, 0.5H), 4.64-4.50 (m, 1.5H), 4.37 (d, $J = 18.4$ Hz, 0.5H), 3.81-3.69 (m, 4.5H), 3.65-3.40 (m, 2.5H), 3.15-2.90 (m, 1H), 2.87-2.77 (m, 3H), 1.66-1.54 (m, 3H), 1.36-1.31 (m, 5H), 0.98-0.70 (m, 6H); MS(ESI$^+$) $m/z$ 862.0 (M+H)$^+$. 

Example 283

$N,N$-Dibutyl-2-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide

![Chemical Structure](image)

Intermediate 283A: Methyl 3-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)benzoate

![Chemical Structure](image)
Following a procedure analogous to that for the synthesis of Intermediate 271H, 2-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)-5-(methoxycarbonyl)benzoic acid (Intermediate 281B, 170 mg, 0.42 mmol) and \((S)-3-((\text{tert-butyldimethylsilyloxy})\text{methyl})\)-1,2,3,4-tetrahydroisoquinoline (237 mg, 0.85 mmol) were converted to the title compound (248 mg, 87%). MS(ESI\(^{+}\)) \(m/z\) 675 (M+H\(^{+}\)).

Intermediate 283B: 3-((5)-3-((\text{tert-butyldimethylsilyloxy})\text{methyl})-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)benzoic acid

Following a procedure analogous to that for synthesis of Intermediate 271II, methyl 3-((5)-3-((\text{tert-butyldimethylsilyloxy})\text{methyl})-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)benzoate (240 mg, 0.35 mmol) was converted to the title compound (230 mg, 98%). MS(ESI\(^{+}\)) \(m/z\) 662.2 (M+H\(^{+}\)).

Intermediate 283C: \(\text{N,N-Dibutyl-2-(2-((5)-3-((\text{tert-butyldimethylsilyloxy})\text{methyl})-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide}\)
Following a procedure analogous to that for the synthesis of Example 271, 3-((5')-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-2-yl)benzoic acid (230 mg, 0.35 mmol) was converted to the title compound (130 mg, 42%). MS(ESI+ ) m/z 886.0 (M+H)+.

Example 283:

Following a procedure analogous to that for the synthesis of Example 274, N,N-dibutyl-2-(2-((5)-3-((tert-butyldimethylsilyloxy)methyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide (130 mg, 0.15 mmol) was converted to the title compound (80 mg, 71%). 1H NMR (CD3OD, 1:1 mixture of amide rotamers) δ 8.96 (s, 1H), 8.21-8.02 (m, 4H), 7.94-7.91 (m, 1H), 7.73-7.70 (m, 1H), 7.59-7.54 (m, 3H), 7.10-6.86 (m, 4H), 5.20 (d, J = 17.2 Hz, 0.5H), 4.40-3.85 (m, 2.5H), 3.72 (s, 2H), 3.51-3.40 (m, 5H), 3.31-3.00 (m, 1.5H), 2.82-2.59 (m, 2.5H), 1.65-1.15 (m, 8H), 0.94-0.82 (m, 6H); MS(ESI+) m/z 771.0 (M+H)+.

Example 284

\[
\begin{align*}
N,N\text{-Dibutyl-5-(4-(8-iodonaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide}
\end{align*}
\]

Intermediate 284A: N,N-Dibutyl-1-methyl-1H-imidazole-4-carboxamide

\[
\begin{align*}
\text{(Int-284A)}
\end{align*}
\]

Following a procedure analogous to that for the synthesis of Intermediate 284D, 1-methyl-1H-imidazole-4-carboxylic acid (1.0 g, 7.93 mmol) was converted to the title compound (1.3 g, 72%). 1H NMR (DMSO-d6) δ 7.61 (s, 1H), 7.55 (s, 1H), 3.88 (br s, 1H).
2H), 3.67 (s, 3H), 3.32 (br s, 2H), 1.52 (br s, 4H), 1.25 (s, 4H), 0.88 (br s, 6H); MS(ESr) m/z 238.4 (M+H)+.

Intermediate 284B: 5-Bromo-N,N-dibutyl-l-methyl-1H-imidazole-4-carboxamide

Following a procedure analogous to that for the synthesis of Compound B Example 264, N,N-dibutyl-1-methyl-1H-imidazole-4-carboxamide (1.3 g, 5.5 mmol) was converted to the title compound (700 mg, 41%). 1H NMR (CD3OD) δ 7.85 (s, 1H), 3.71 (s, 3H), 3.51-3.46 (m, 4H), 1.70-1.62 (m, 2H), 1.58-1.51 (m, 2H), 1.46-1.40 (m, 2H), 1.23-1.17 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H) 0.80 (t, J = 7.6 Hz, 3H); MS(ESI+) m/z 317.2 (M+H)+.

Intermediate 284C: Methyl 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-5-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

Following a procedure analogous to that for the synthesis of Intermediate 284B, 5-bromo-N,N-dibutyl-l-methyl-1H-imidazole-4-carboxamide (600 mg, 1.9 mmol) and methyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (Intermediate 264H, 1.55 g, 3.8 mmol) were converted to the title compound (400 mg, 40%). MS(ESI+) m/z 531.6 (M+H)+.

Intermediate 284D: 4-(4-(Dibutylcarbamoyl)-1-methyl-1H-imidazol-5-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

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Following a procedure analogous to that for the synthesis of Intermediate 264L, methyl 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-5-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (400 mg, 0.75 mmol) was converted to the title compound (300 mg, 77%). MS(ESI+) m/z 517.6 (M+FF)+.

Example 284:

Following a procedure analogous to that for the synthesis of Example 265, 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-5-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (160 mg, 0.31 mmol) and 8-iodonaphthalene-2-sulfonamide (Intermediate 6, 258 mg, 0.78 mmol) were converted to the title compound (53 mg, 21%). 

$^1$H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 8.87 (s, 1H), 8.21 (dd, $J$ = 7.2, 3.2 Hz, 1H), 8.17-8.14 (m, 1H), 8.12-8.07 (m, 2H), 7.69 (s, 0.5H), 7.62 (s, 0.5H), 7.44 (dd, $J$ = 8.0, 4.4 Hz, 1H), 7.36 (ddd, $J$ = 10.8, 8.0, 3.2 Hz, 1H), 7.21-7.06 (m, 3.5H), 6.95 (d, $J$ = 8.0 Hz, 0.5H), 4.77 (d, $J$ = 17.2 Hz, 0.5H), 4.56-4.50 (m, 1.5H), 3.90 (br s, 1H), 3.70-3.60 (br s, 1H), 3.51 (s, 3H), 3.49-3.35 (m, 3H), 3.30-3.10 (m, 1H), 2.90-2.67 (m, 3H), 1.51-1.09 (m, 8H), 0.90-0.79 (m, 6H); MS(ESI+) m/z 832.4 (M+H)+.

Example 285

$N,N$-Dibutyl-5-(4-(8-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-1-methyl-1H-imidazole-4-carboxamide

Following a procedure analogous to that for the synthesis of Example 265, 4-(4-(dibutylcarbamoyl)-1-methyl-1H-imidazol-5-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (160 mg, 0.31 mmol) and 8-iodonaphthalene-2-sulfonamide (Intermediate 6, 258 mg, 0.78 mmol) were converted to the title compound (53 mg, 21%). 

$^1$H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 8.87 (s, 1H), 8.21 (dd, $J$ = 7.2, 3.2 Hz, 1H), 8.17-8.14 (m, 1H), 8.12-8.07 (m, 2H), 7.69 (s, 0.5H), 7.62 (s, 0.5H), 7.44 (dd, $J$ = 8.0, 4.4 Hz, 1H), 7.36 (ddd, $J$ = 10.8, 8.0, 3.2 Hz, 1H), 7.21-7.06 (m, 3.5H), 6.95 (d, $J$ = 8.0 Hz, 0.5H), 4.77 (d, $J$ = 17.2 Hz, 0.5H), 4.56-4.50 (m, 1.5H), 3.90 (br s, 1H), 3.70-3.60 (br s, 1H), 3.51 (s, 3H), 3.49-3.35 (m, 3H), 3.30-3.10 (m, 1H), 2.90-2.67 (m, 3H), 1.51-1.09 (m, 8H), 0.90-0.79 (m, 6H); MS(ESI+) m/z 832.4 (M+H)+.
carbonyl)benzoic acid (150 mg, 0.29 mmol) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5, 140 mg, 0.58 mmol) were converted to the title compound (26 mg, 12%).

$^1$H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 8.99 (s, 1H), 8.18-8.09 (m, 3H), 8.05 (dd, $J = 8.4, 2.0$ Hz, 1H), 7.94-7.91 (m, 1H), 7.72 (dd, $J = 7.2, 1.2$ Hz, 1H), 7.69 (s, 0.5H), 7.62-7.55 (m, 1.5H), 7.42 (dd, $J = 8.0, 4.8$ Hz, 1H), 7.21-7.13 (m, 3.5H), 6.93 (d, $J = 8.0$ Hz, 0.5H), 4.78 (br s, 0.5H), 4.62-4.49 (m, 1.5H), 3.90 (br s, 0.5H), 3.60 (br s, 0.5H), 3.50 (s, 3H), 3.49-3.39 (m, 2H), 2.85-2.65 (m, 2.5H), 1.50-1.09 (m, 8H), 0.89-0.79 (m, 6H); MS(ESI$^+$) $m/z$ 742.2 (M+H$^+$).

Example 286

$N,N$-Dibutyl-6-(4-(naphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)picolinamide

![Chemical structure](image)

Intermediate 286A: 6-Bromo-$N,N$-dibutylpicolinamide

To a solution of 6-bromopicolinic acid (Aldrich, 404 mg, 2.00 mmol) in DMF (3.0 mL) were added dibutylamine (Aldrich, 258 mg, 2.00 mmol), HATU (760 mg, 2.00 mmol) and DIEA (1.1 mL, 6.00 mmol). The reaction mixture was stirred at room temperature for 3 h and then quenched by adding sat. aq. NH$_4$Cl solution. The mixture was extracted with EtOAc (3 x). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography, gradient from 0 to 20% EtOAc/DCM to give a light brown oil (450 mg, 72%). $^1$HNMR (CDCl$_3$) δ 7.67-7.57 (m, 2H), 7.51 (dd, $J = 7.5, 1.3$ Hz, 1H), 3.53-3.42...
(m, 2H), 3.36-3.27 (m, 2H), 1.72-1.56 (m, 4H), 1.46-1.33 (m, 2H), 1.27-1.15 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H); MS(ESI+) m/z 313.2 (M+H)+.

Intermediate 286B: Methyl 4-(6-(dibutylcarbamoyl)pyridin-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

![Chemical Structure](attachment:structure.png)

(Int-286B)

[00714] A heterogeneous solution containing methyl 3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(trifluoromethylsulfonyloxy)benzoate (Intermediate 271G, 1.03 g, 2.50 mmol), bis(pinacolato)diboron (762 mg, 3.00 mmol), potassium acetate (368 mg, 3.75 mmol), tetrakis(triphenylphosphine)palladium(0) (289 mg, 0.25 mmol) and 1,4-dioxane (15.0 mL) was purged with argon for 5 min and stirred in a sealed tube at 90 °C for 16 h. The resulting solution was stored in the freezer as a 0.17 M solution.

[00715] To a solution of 6-bromo-N,N-dibutylpicolinamide (211 mg, 0.675 mmol) in 1,4-dioxane (4.0 mL) were added aq. 2N potassium phosphate (0.68 mL, 3.35 mmol), Pd(dppf)2C12 (66 mg, 0.09 mmol) and the above boronic ester solution (4.0 mL, 0.68 mmol, 0.17M in 1,4-dioxane). The flask was evacuated and purged with argon (3 x) and then heated at 90 °C for 9 h. The reaction mixture was then diluted with EtOAc and filtered through CELITE®. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (gradient from 0 to 40% EtOAc/DCM) to afford the title compound (167 mg, 47%) as a light yellow semi-solid. 1H NMR (CD3OD, 2:1 mixture of amide rotamers) δ 8.24 (dd, J = 8.3, 1.7 Hz, 1H), 8.08-7.89 (m, 3.5H), 7.83 (dd, J = 8.0, 0.8 Hz, 0.5H), 7.48-7.41 (m, 1H), 7.27-7.10 (m, 3.5H), 6.87 (d, J = 7.5 Hz, 0.5H), 4.50-4.36 (m, 0.5H), 3.97 (s, 2H), 3.96 (s, 1H), 3.93-3.83 (m, 1.5H), 3.62-3.42 (m, 2H), 3.33 (dt, J = 3.2, 1.7 Hz, 1H), 3.27-3.03 (m, 3H), 2.92 (t, J = 5.9 Hz, 1H), 2.79 (d, J = 5.5 Hz, 1H), 1.58-1.23 (m, 5H), 1.13 - 1.04 (m, 3H), 0.93 (t, J = 7.4 Hz, 1H), 0.85 (t, J = 7.3 Hz, 2H), 0.72 (t, J = 7.4 Hz, 2H), 0.64 (t, J = 7.4 Hz, 1H); MS(ESI+) m/z 528.4 (M+H)+.
Intermediate 286C: 4-(6-(Dibutylcarbamoyl)pyridin-2-yl)-3-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

To a solution of methyl 4-(6-(dibutylcarbamoyl)pyridin-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (158 mg, 0.30 mmol) in THF (2.0 mL) and MeOH (2.0 mL) was added 2N NaOH (1.5 mL, 3.00 mmol). The resulting reaction mixture was stirred at room temperature for 2 h. At 0 °C, the reaction mixture was neutralized to pH 4-5 with IN HCl. The solution was extracted with EtOAc (3 x) and the combined organic extracts were dried over MgSO4, filtered and concentrated in vacuo to afford the title compound (146 mg, 95%). MS(ESI + ) m/z 514.4 (M+H)+.

Example 286:

To a solution of 4-(6-(dibutylcarbamoyl)pyridin-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (41 mg, 0.080 mmol) in DMF (1.0 mL) were added EDC (31 mg, 0.16 mmol) and DMAP (29 mg, 0.24 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. The solvent was removed in vacuo and the residue was purified by preparative HPLC to give the title compound (11 mg, 20%). 'HNMR (CD3OD, 2:1 mixture of amide rotamers) δ 8.72 (s, 1H), 8.12-7.83 (m, 7H), 7.77 (dd, J = 7.9, 0.7 Hz, 1H), 7.73-7.63 (m, 3.5H), 7.43-7.36 (m, 1.5H), 7.23-7.09 (m, 3H), 7.08-7.04 (m, 0.5H), 6.81 (d, J = 7.8 Hz, 0.5H), 4.48-4.40 (br s, 1H), 4.33-4.27 (m, 1H), 3.52-3.37 (m, 2.5 H), 3.23-3.10 (m, 1.5H), 3.05 (br s, 1H), 2.90-2.85 (m, 1H), 2.80-2.67 (m, 2H), 1.54-1.39 (m, 4H), 1.35-1.29 (m, 2H), 1.28-1.22 (m, 1H), 1.06-1.01 (m, 1H), 0.90 (t, J = 7.4 Hz, 1H), 0.82 (t, J = 7.4 Hz, 2H), 0.68 (t, J = 7.5 Hz, 2H), 0.60 (t, J = 7.5 Hz, 1H); MS(ESI + ) m/z 703.2 (M+H)+.

Example 287
4-(6-(Dibutylamino)pyridin-2-yl) \( N \)-(naphthalen-2-ylsulfonyl)-3-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

Intermediate 287A: 6-Bromo-\( N,N \)-dibutylpyridin-2-amine

To a solution of 2,6-dibromopyridine (Aldrich, 1.42 g, 6.00 mmol) in DMF (2.0 mL) were added dibutylamine (Aldrich, 388 g, 3.00 mmol) and potassium carbonate (829 mg, 6.00 mmol). The reaction mixture was heated at 90 °C for 20 h. After cooling to room temperature, the reaction mixture was quenched by adding cold water. The mixture was extracted with DCM (3 x), and the combined organic extracts were dried over \( \text{Na}_2\text{SO}_4 \), filtered and concentrated in vacuo to give a crude oil. Purification using flash column chromatography (eluting with DCM) provided the title compound (368 mg, 43%) as a light brown oil. \(^1\text{H NMR} \) (CDCl\(_3\)) \( \delta \) \( 6.22 \) (dd, \( J = 8.4, 7.4 \) Hz, 1H), \( 6.62 \) (d, \( J = 7.0 \) Hz, 1H), \( 6.33 \) (d, \( J = 8.3 \) Hz, 1H), \( 3.49-3.37 \) (m, 4H), \( 1.65-1.52 \) (m, 4H), \( 1.44-1.30 \) (m, 4H), \( 0.98 \) (t, \( J = 7.3 \) Hz, 6H); \( \text{MS(ESI}^+) m/z \) 272.1 (M+H)+.

Intermediate 287B: Methyl 4-(6-(dibutylamino)pyridin-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate
To a solution of 6-bromo-N,N-dibutylpyridin-2-amine (143 mg, 0.50 mmol) in 1,4-dioxane (5.0 mL) were added aq. 2N potassium phosphate (0.750 mL, 1.50 mmol), Pd(dppf)2Cl2 (75 mg, 0.050 mmol) and the boronic ester stock solution prepared in the synthesis of Intermediate 286B (3.0 mL, 0.50 mmol, 0.17 M in 1,4-dioxane). The flask was evacuated and purged with argon (3x) and then heated at 90 °C for 8 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through CELITE®. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (gradient from 0 to 40% EtOAc/DCM) to afford the title compound (127 mg, 51%) as a light yellow solid. 

\[ \text{H NMR (CD}_3\text{OD, 2:1 mixture of amide rotamers) } \delta 8.28 \text{ (dd, } J = 8.3, 1.7 \text{ Hz, 1H), 8.08–7.89 (m, 3.5H), 7.83 \text{ (dd, } J = 8.0, 0.8 \text{ Hz, 0.5H), 7.48–7.41 (m, 1H), 7.27–7.10 (m, 3.5H), 6.86 \text{ (d, } J = 7.5 \text{ Hz, 0.5H), 4.50–4.36 (m, 0.5H), 3.97 \text{ (s, 2H), 3.96 \text{ (s, 1H), 3.93–3.83 (m, 1.5H), 3.62–3.42 (m, 2H), 3.33 (dt, } J = 3.2, 1.7 \text{ Hz, 1H), 3.27–3.03 (m, 3H), 2.92 \text{ (t, } J = 5.9 \text{ Hz, 1H), 2.79 \text{ (d, } J = 5.5 \text{ Hz, 1H), 1.58–1.23 (m, 5H), 1.13–1.04 (m, 3H), 0.93 \text{ (t, } J = 7.4 \text{ Hz, 1H), 0.85 \text{ (t, } J = 7.3 \text{ Hz, 2H), 0.72 (t, } J = 7.4 \text{ Hz, 2H), 0.64 (t, } J = 7.4 \text{ Hz, 1H); MS(ESI\text{+}) m/z 500.5 (M+H)\text{+).} \]

Intermediate 287C: 4-(6-(Dibutylamino)pyridin-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid

To a solution of methyl 4-(6-(dibutylamino)pyridin-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (75 mg, 0.15 mmol) in THF (1.0 mL) and MeOH (1.0 mL) was added 2N NaOH (0.75 mL, 1.50 mmol). The resulting reaction mixture was stirred at room temperature for 1 h. At 0 °C, the reaction mixture was neutralized to pH 4-5 with 1N HCl. The solution was extracted with EtOAc (3x) and the combined organic extracts were dried over MgSO\text{4}, filtered and concentrated in vacuo to give the title compound (69 mg, 95%). MS(ESI\text{+}) m/z 486.4 (M+H)\text{+}.

Example 287:
To a solution of 4-(6-(dibutylamino)pyridin-2-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (20 mg, 0.041 mmol) in DMF (0.5 mL) and DCM (0.5 mL) were added naphthalene-2-sulfonamide (Aldrich, 17 mg, 0.082 mmol), EDC (Aldrich, 16 mg, 0.082 mmol) and DMAP (Aldrich, 15 mg, 0.12 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. The solvents were removed in vacuo and the residue was purified by preparative HPLC to give the title compound (17 mg, 60%) as a white solid.

**Example 288**

4-(3-Bromo-6-(dibutylamino)pyridin-2-yl)-N-(7-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

![Chemical Structure](288)

The title compound was prepared following a procedure analogous to that for the synthesis of Example 287, where 2,3,6-tribromopyridine was used to replace 2,6-dibromopyridine (Intermediate 287A) and 7-chloronaphthalene-2-sulfonamide (Intermediate 9) was used to replace naphthalene-2-sulfonamide (Example 287).

**Example 289**

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4-(3-Bromo-6-(dibutylamino)pyridin-2-yl)-N-(8-chloronaphthalen-2-ylsulfonfyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

[00723] The title compound was prepared following a procedure analogous to that for the synthesis of Example 287, where 2,3,6-tribromopyridine (Matrix Scientific) was used to replace 2,6-dibromopyridine (Intermediate 287A) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5) was used to replace naphthalene-2-sulfonamide (Example 287). MS(ESI+) m/z 789.2 (M+H)+.

Example 290
4-(3-Bromo-6-(dibutylamino)pyridin-2-yl)-N-(1-(3,4-dichlorobenzyl)indolin-5-ylsulfonfyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

[00724] The title compound was prepared following a procedure analogous to that for the synthesis of Example 287, where 2,3,6-tribromopyridine was used to replace 2,6-dibromopyridine (Intermediate 287A) and 1-(3,4-dichlorobenzyl)indoline-5-sulfonamide (Intermediate 51) was used to replace naphthalene-2-sulfonamide (Example 287). MS(ESI+) m/z 904.2 (M+H)+.

Example 291
4-(2-(Dibutylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonfyl)-3-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide
Intermediate 291A: Methyl 4-(2-chloropyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate

To a solution of 2,4-dichloropyrimidine (67 mg, 0.45 mmol) in 1,4-dioxane (0.02 mL) were added aq. 2N potassium phosphate (0.34 mL, 0.68 mmol), Pd(dpff)2Cl2 (33 mg, 0.045 mmol) and the boronic ester stock solution prepared in the synthesis of Intermediate 286B (1.4 mL, 0.50 mmol, 0.17 M in 1,4-dioxane). The flask was evacuated and purged with argon (3 x) and then heated at 90 °C for 9 h. After cooling to room temperature, the reaction mixture was then diluted with EtOAc and filtered through CELITE®. The filtrate was concentrated in vacuo and the residue was purified by flash column chromatography (gradient from 0 to 40% EtOAc/DCM) to afford the title compound (700 mg, 76%) as a light yellow solid. 1H NMR (CD3OD, 1:1 mixture of amide rotamers) δ 8.78 (d, J = 5.3 Hz, 0.5H), 8.62 (d, J = 5.3 Hz, 0.5H), 8.27 (d, J = 1.8 Hz, 0.5H), 8.25 (d, J = 1.8 Hz, 0.5H), 8.11 (d, J = 5.1 Hz, 0.5H), 8.09 (t, J = 1.5 Hz, 1H), 8.02 (d, J = 8.1 Hz, 0.5H), 7.92 (d, J = 5.3 Hz, 0.5H), 7.79 (d, J = 5.1 Hz, 0.5H), 7.27-7.15 (m, 3H), 7.12 -7.07 (m, 0.5H), 6.83 (d, J = 7.5 Hz, 0.5H), 4.44 (br s, 1H), 4.26 (s, 0.5H), 3.98 (s, 3H), 3.74 (br s, 0.5H), 3.61 (t, J = 5.7 Hz, 1H), 3.33 (dt, J = 3.3, 1.7 Hz, 1H), 3.13 (br s, 0.5H), 2.97 (br s, 0.5H), 2.92 (d, J = 5.3 Hz, 1H); MS(ESI+) m/z 408.2 (M+H)+.

Intermediate 291B: 4-(2-(Dibutylamino)pyrimidin-4-yl)-3-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid
To a solution of methyl 4-(2-chloropyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoate (82 mg, 0.20 mmol) in DMF (1.0 mL) were added dibutylamine (Aldrich, 52 mg, 0.40 mmol) and potassium carbonate (83 mg, 0.60 mmol). The reaction mixture was heated at 60 °C for 5 h and 80 °C for 3 h. After cooling to room temperature, the reaction mixture was quenched with cold water. The mixture was extracted with EtOAc (3 x). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo to give the title compound (69 mg, 95%).

MS(ESI⁺) m/z 501.2 (M+H)⁺.

The above residue was dissolved in THF (1.0 ml) and MeOH (1.0 ml). To the solution was added 2M NaOH (1.0 mL, 2.0 mmol). The resulting reaction mixture was stirred at room temperature for 1 h. At 0 °C, the reaction mixture was neutralized to pH 3-4 with IN HCl. The solution was extracted with EtOAc (3 x) and the combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (64 mg, 66% for two steps).

³¹H NMR (CD₃OD, 1:1 mixture of amide rotamers) δ 8.21 (d, J = 5.7 Hz, 1H), 8.16-8.08 (m, 1H), 8.00 (dd, J = 7.8, 1.4 Hz, 1H), 7.96-7.87 (m, 1.5H), 7.79 (d, J = 8.1 Hz, 1H), 7.12-6.89 (m, 3H), 6.87 (d, J = 5.9 Hz, 0.5H), 6.66 (d, J = 7.5 Hz, 0.5H), 4.72 (m, 0.5H), 4.16 (m, 0.5H), 3.48-3.27 (m, 5H), 3.18 (dt, J = 3.2, 1.6 Hz, 2H), 2.79-2.71 (m, 2H), 1.45-1.23 (m, 4H), 1.17-1.04 (m, 4H), 0.88 - 0.81 (m, 3H), 0.80-0.72 (m, 3H); MS(ESI⁺) m/z 487.3 (M+H)⁺.

Example 291:

To a solution of 4-(2-(dibutylamino)pyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (25 mg, 0.051 mmol) in DMF (0.5 mL) and DCM (0.5 mL) were added naphthalene-2-sulfonamide (16 mg, 0.077 mmol), EDC (16 mg, 0.082 mmol) and DMAP (15 mg, 0.12 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. The solvents were removed in vacuo and the
residue was purified by preparative HPLC to give the title compound (20 mg, 59%). $^1$H NMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 8.64 (s, 1H), 8.27 (d, $J = 5.0$ Hz, 0.5H), 8.16-7.92 (m, 5.5H), 7.91-7.82 (m, 1H), 7.76 (d, $J = 8.3$ Hz, 0.5H), 7.69-7.55 (m, 3.5H), 7.22-6.93 (m, 2.5H), 6.84 (d, $J = 5.0$ Hz, 0.5H), 6.71 (d, $J = 7.5$ Hz, 0.5H), 6.65 (d, $J = 5.0$ Hz, 0.5H), 4.72-4.61 (m, 0.5H), 4.37-4.24 (m, 0.5H), 3.69-3.45 (m, 3H), 3.42-3.33 (m, 2H), 3.22 (d, $J = 10.5$ Hz, 2.5H), 2.81 (t, $J = 6.1$ Hz, 0.5H), 2.57 (br. s., 0.5H), 2.14 (br. s., 0.5H), 1.50-1.32 (m, 4H), 1.31-1.17 (m, 4H), 0.94-0.81 (m, 6H); MS(ESI$^+$) m/z 676.7 (M+H)$^+$. 

Examples 292 to 295

[00729] The following Examples were prepared using 4-(2-(dibutylamino)pyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzoic acid (Intermediate 291B) and the sulfonamide intermediates described previously, according to the procedure for the synthesis of Example 291.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>Ar</th>
<th>Name</th>
<th>LCMS (M+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>292</td>
<td><img src="image" alt="Image" /></td>
<td>$N$-(8-chloronaphthalen-2-ylsulfonyl)-4-(2-(dibutylamino)pyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>710.2</td>
</tr>
<tr>
<td>293</td>
<td><img src="image" alt="Image" /></td>
<td>4-(2-(dibutylamino)pyrimidin-4-yl)-$N$-(7-iodonaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>802.1</td>
</tr>
<tr>
<td>294</td>
<td><img src="image" alt="Image" /></td>
<td>4-(2-(dibutylamino)pyrimidin-4-yl)-$N$-(1-ethyl-1H-indol-5-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>695.3</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>Ar Name</td>
<td>LCMS (M+H)</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>---------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>295</td>
<td>4-(2-(dibutylamino)pyrimidin-4-yl)-N-(1-(3,4-dichlorobenzyl)-1H-indol-5-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>825.5</td>
<td></td>
</tr>
</tbody>
</table>

**Examples 296 to 302**

[00730] The following Examples were prepared following a procedure analogous to that for the synthesis of Example 291. Dibutylamine in the synthesis of Intermediate 291B was replaced with corresponding alkyl amines.

\[ -N\left(CH_2CH_2CH_2CH_2CH_3\right)_2 \]

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>-NR'R''</th>
<th>Name</th>
<th>LCMS (M+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>296</td>
<td>-N(CH_2CH_2CH_2CH_2CH_3)_2</td>
<td>4-(2-(dipentylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>704.4</td>
</tr>
<tr>
<td>297</td>
<td>N-(naphthalen-2-ylsulfonl)-4-(2-(3-propylpyrrolidin-1-yl)pyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>660.5</td>
<td></td>
</tr>
<tr>
<td>298</td>
<td>4-(2-(butyl(3,4-dichlorobenzyl)amino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>778.1</td>
<td></td>
</tr>
<tr>
<td>Ex. No.</td>
<td>-NR’R”</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>299</td>
<td>-N(CH₂CH₂CH₃)₂</td>
<td>4-(2-(dipropylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>648.3</td>
</tr>
<tr>
<td>300</td>
<td>-N(CH₂CH₃)₂</td>
<td>4-(2-((cyclopropylmethyl)(propyl)amino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>660.2</td>
</tr>
<tr>
<td>301</td>
<td>-N(CH₂CH₃)₂</td>
<td>4-(2-((diethylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>620.2</td>
</tr>
<tr>
<td>302</td>
<td>-N(CH₂CH₃)₂</td>
<td>N-(naphthalen-2-ylsulfonyl)-4-(2-(3-phenethylpyrrolidin-1-yl)pyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>722.4</td>
</tr>
</tbody>
</table>

Example 303

(5’)-4-(2-(Dibutylamino)pyrimidin-4-yl)-3-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide

Intermediate 303A: 3-tert-Butyl 1-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-yl)isosophalate
A solution of 3-tert-butyl 1-methyl 4-(trifluoromethylsulfonyloxy)isophthalate (Miura, M. et al, Synth. Commun., 36:3809-3820 (2006)) (3.00 g, 7.81 mmol) in 1,4-dioxane (30.0 mL) was degassed with argon for 5 minutes while stirring. Potassium acetate (2.68 g, 27.3 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(l,3,2-dioxaborolane) (2.38 g, 9.37 mmol) and Pd(dppf)Cl₂·CH₂Cl₂ (637 mg, 0.78 mmol) were then added sequentially while bubbling argon through the mixture. After 5 min at room temperature, the argon stream was removed and the reaction mixture was stirred at 70 °C for 16 h in a sealed tube. The reaction mixture was then cooled to room temperature, diluted with DCM, and washed with water and brine solution. The organic layer was dried over MgSO₄, filtered, concentrated in vacuo. The residue was purified by flash column chromatography (eluting with DCM) to afford the title compound (2.30 g, 81%) as a white solid. 

1H NMR (CDCl₃) δ 8.43 (d, J = 1.1 Hz, 1H), 8.13 (dd, J = 8.1, 1.1 Hz, 1H), 7.55 (d, J = 8.1 Hz, 1H), 3.94 (s, 3H), 1.61 (s, 9H), 1.43 (s, 12H); MS(ESI⁺) m/z 307.2 (M+H-C(CH₃)₃)⁺.

Intermediate 303B: 3-tert-Butyl 1-methyl 4-(2-chloropyrimidin-4-yl)isophthalate

[00732] To a solution of 2,4-dichloropyrimidine (1.61 g, 8.78 mmol) in 1,4-dioxane (20.0 mL) were added aq. 2N potassium phosphate (12.8 mL, 25.6 mmol), Pd(dppf)Cl₂·CH₂Cl₂ (268 mg, 0.37 mmol) 3-tert-butyl 1-methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isophthalate (2.65 g, 7.32 mmol). The flask was evacuated and purged with argon (3 x) and then heated at 80 °C for 10 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through CELITE®. The filtrate was
concentrated *in vacuo* and the residue was purified by flash chromatography (gradient from 0 to 40% EtOAc/DCM) to afford the title compound (1.87 g, 67%) as a white solid.

$^1$H NMR (CDCl$_3$) $\delta$ 8.70 (d, $J = 5.1$ Hz, 1H), 8.51 (d, $J = 1.5$ Hz, 1H), 8.29-8.19 (m, 1H), 7.56-7.50 (m, 1H), 7.42 (d, $J = 5.1$ Hz, 1H), 3.98 (s, 3H), 1.43 (s, 9H); MS(ESI$^+$) $m/z$ 349.0 (M+H)$^+$.  

Intermediate 303C: 3-([*tert*-Butoxycarbonyl])-4-([2-([dibutylamino]pyrimidin-4-yl)]benzoic acid

![Intermediate 303C](image)

[00733] Following a procedure analogous to that for the synthesis of Intermediate 291B, 3-*tert*-butyl 1-methyl 4-([2-[chloropyrimidin-4-yl]isophthalate (244 mg, 0.70 mmol) was converted to the title compound (210 mg, 70% for two steps). MS(ESI$^+$) $m/z$ 428.2 (M+H)$^+$.  

Intermediate 303D: [*tert*-Butyl] 2-([2-([dibutylamino]pyrimidin-4-yl)]-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoate

![Intermediate 303D](image)

[00734] Following a procedure analogous to that for the synthesis of Example 291, 3-([*tert*-Butoxycarbonyl])-4-([2-([dibutylamino]pyrimidin-4-yl)]benzoic acid (244 mg, 0.70 mmol) was converted to the title compound (111 mg, 61%). MS(ESI$^+$) $m/z$ 617.2 (M+H)$^+$.  

Intermediate 303E: 2-([2-([Dibutylamino]pyrimidin-4-yl)]-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid
To a solution of tert-butyl 2-(2-(dibutylamino)pyrimidin-4-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoate (110 mg, 0.18 mmol) in DCM (2.0 mL) was added TFA (2.0 mL). The reaction mixture was stirred at room temperature for 3 h and concentrated in vacuo to give the title compound (95 mg, 95%), which was used in subsequent reaction without purification. MS(ESI+) m/z 561.2 (M+H+).

Example 303:
To a solution of crude 2-(2-(dibutylamino)pyrimidin-4-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (17 mg, 0.03 mmol) in DMF (0.8 mL) were added (5)-(1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (Aldrich, 6 mg, 0.036 mmol), HATU (23 mg, 0.06 mmol) and DIEA (19 mg, 0.15 mmol). The reaction mixture was stirred at room temperature for 1 h. The solution was purified by preparative HPLC to give the title compound (8 mg, 37%). ¾ NMR (CD3OD:CDCl3, 1:1 mixture of amide rotamers) δ

9.62 (s, 1H), 8.41 (d, J = 7.5 Hz, 1H), 8.35 (d, J = 8.3 Hz, 1H), 8.26 (br s, 2H), 8.12 (d, J = 8.3 Hz, 1H), 8.01-7.95 (m, 1H), 7.87 (t, J = 7.8 Hz, 1H), 7.63-7.51 (m, 1H), 7.38-7.27 (m, 2H), 7.21-7.05 (m, 4.5H), 6.95-6.86 (m, 0.5H), 4.60 (br s, 0.5H), 4.33 (br s, 1.5H), 3.66 (br s, 1H), 3.55-3.44 (m, 4H), 3.04 (d, J = 7.8 Hz, 1H), 2.82 (br s, 2H), 2.34 (s, 1H), 2.22 (s, 1H), 1.32-1.18 (m, 4H), 1.13-0.97 (m, 2H), 0.88 (dt, J = 10.8, 7.2 Hz, 5H), 0.74 (t, J = 7.4 Hz, 2H), 0.68 (t, J = 7.4 Hz, 1H); MS(ESI+) m/z 706.3 (M+H+).

Example 304
(5)-3-(3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(2-(dibutylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)benzamide
Following a procedure analogous to that for the synthesis of Example 303, 2-(2-(dibutylamino)pyrimidin-4-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 303E, 25 mg, 0.05 mmol) was reacted with ((5)-(3-azidomethyl)-1,2,3,4-tetrahydroisoquinoline (Intermediate 92A, 11 mg, 0.06 mmol) and provided a crude oil which was dissolved in THF (1.1 mL). PPh₃ (10 mg, 0.014 mmol) was added followed by aq. 0.5N NaOH (100 µL). The resulting reaction mixture was stirred at 50 °C for 1.5 h and then neutralized with IN HCl solution (100 µL). The volatiles were removed in vacuo, and the residue was purified by preparative HPLC to give the title compound (5 mg, 52%). MS(ESI⁺) m/z 705.2 (M+H)⁺.

Examples 305 to 307

The following Examples were prepared using 2-(2-(dibutylamino)pyrimidin-4-yl)-5-(naphthalen-2-ylsulfonylcarbamoyl)benzoic acid (Intermediate 303E) and the corresponding commercially available amines according to the procedure for the synthesis of Example 303.

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>-NR'R''</th>
<th>Name</th>
<th>LCMS (M+H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>305</td>
<td></td>
<td>4-(2-(dibutylamino)pyrimidin-4-yl)-3-(isoindoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide</td>
<td>662.2</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>-NR'R&quot;</td>
<td>Name</td>
<td>LCMS (M+H)</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>----------------------------------------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>306</td>
<td>(\text{CF}_3)</td>
<td>4-(2-(dibutylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(7-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide</td>
<td>744.2</td>
</tr>
<tr>
<td>307</td>
<td>(-\text{N(CH}_3)_2)</td>
<td>4-(2-(dibutylamino)pyrimidin-4-yl)-N(3),N(3)-dimethyl-N(7)-(naphthalen-2-ylsulfonyl)isophthalamide</td>
<td>588.2</td>
</tr>
</tbody>
</table>

**Example 308**

\((5')-N-(8\text{-Chloronaphthalen}-2\text{-ylsulfonyl})-4\text{-}(2\text{-dibutylamino)pyrimidin}-4\text{-yl})\text{-}3\text{-}(3\text{-}(hydroxymethyl)-1,2,3,4\text{-tetrahydroisoquinoline}-2\text{-carbonyl)benzamide}

\[\text{(308)}\]

[00739] The title compound was prepared by following a procedure analogous to that for the synthesis of Example 303, where 8-chloronaphthalene-2-sulfonamide (Intermediate 5) was used to replace naphthalene-2-sulfonamide (Intermediate 303D). MS(ESI\(^+\)) \(m/\epsilon\) 740.2 (M+H\(^+\)).

**Example 309**

\((S)-4\text{-}(2\text{-Dibutylamino)pyrimidin}-4\text{-yl})\text{-}3\text{-}(3\text{-}(hydroxymethyl)-1,2,3,4\text{-tetrahydroisoquinoline}-2\text{-carbonyl)\text{-}N-(7\text{-iodonaphthalen}-2\text{-ylsulfonyl)benzamide}}

\[\text{(309)}\]
The title compound was prepared following a procedure analogous to that for the synthesis of Example 303, where 7-iodonaphthalene-2-sulfonamide (Intermediate 10) was used to replace naphthalene-2-sulfonamide (Intermediate 303D). MS(ESI<sup>+</sup>) m/z 832.1 (M+H)<sup>+</sup>.

Example 310

(5)-4-(2-(Dibutylamino)pyrimidin-4-yl)-N-(1-ethylindolin-5-ylsulfonyl)-3-(3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

[00741] The title compound was prepared following a procedure analogous to that for the synthesis of Example 303, where 1-ethylindoline-5-sulfonamide (Intermediate 45) was used to replace naphthalene-2-sulfonamide (Intermediate 303D). MS(ESI<sup>+</sup>) m/z 725.3 (M+H)<sup>+</sup>.

Example 311

4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

[00742] The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where 2,4,5-trichloropyrimidine (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 291A). MS(ESI<sup>+</sup>) m/z 710.2 (M+H)<sup>+</sup>. 
Example 312

4-(2-(Dibutylamino)-5-methylpyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

[00743] The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where 2,4-dichloro-5-methylpyrimidine was used to replace 2,4-dichloropyrimidine (Intermediate 291 A). MS(ESI+) m/z 690.3 (M+H)+.

Example 313

4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

[00744] The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where 2,4,5-trichloropyrimidine was used to replace 2,4-dichloropyrimidine (Intermediate 291 A) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5) was used to replace naphthalene-2-sulfonamide (Example 291). MS(ESI+) m/z 744.1 (M+H)+.

Example 314

N-(8-Chloronaphthalen-2-ylsulfonyl)-4-(2-(dibutylamino)-5-methylpyrimidin-4-yl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide
[00745] The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where 2,4-dichloro-5-methylpyrimidine (TCI) was used to replace 2,4-dichloropyrimidine (Intermediate 291A) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5) was used to replace naphthalene-2-sulfonamide (Example 291). MS(ESI\(^+\)) m/z 724.3 (M+H\(^+\)).

Example 315

4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-3-((5)-3-(hydroxymethyl)-1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide

[00746] The title compound was prepared following a procedure analogous to that for the synthesis of Example 303, where 2,4,5-trichloropyrimidine (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 303B). MS(ESI\(^+\)) m/z 740.4 (M+H\(^+\)).

Example 316

4-(5-Bromo-2-(dibutylamino)pyrimidin-4-yl)-3-((5)-3-(hydroxymethyl)-1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide
The title compound was prepared following a procedure analogous to that for the synthesis of Example 303, where 5-bromo-2,4-dichloropyrimidine (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 303B). MS(ESI\(^{+}\)) \textit{m/z} 786.2 (M+H\(^{+}\)).

Example 317

4-(5-Bromo-2-(dibutylamino)pyrimidin-4-yl)-N-(8-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where 5-bromo-2,4-dichloropyrimidine (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 291A) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5) was used to replace naphthalene-2-sulfonamide (Example 291). MS(ESI\(^{+}\)) \textit{m/z} 790.3 (M+H\(^{+}\)).

Example 318

4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-N-(7-chloronaphthalen-2-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide
The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where 2,4,5-trichloropyrimidine was used to replace 2,4-dichloropyrimidine (Intermediate 291A) and 7-chloronaphthalene-2-sulfonamide (Intermediate 9) was used to replace naphthalene-2-sulfonamide (Example 291).

**Example 319**

Ethyl 4-(4-(7-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-2-(dibutylamino)pyrimidine-5-carboxylate

The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where ethyl 2,4-dichloropyrimidine-5-carboxylate (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 291A) and 7-chloronaphthalene-2-sulfonamide (Intermediate 9) was used to replace naphthalene-2-sulfonamide (Example 291). **HNMR** (CDCl₃, 1:1 mixture of amide rotamers) δ 8.89 (s, 1H), 8.69 (s, 0.5H), 8.49(s, 0.5H), 8.13-8.06 (m, 1.5H), 8.03 (d, J = 1.3 Hz, 0.5H), 7.99-7.82 (m, 5H), 7.62 (dd, J = 8.7, 2.1 Hz, 1H), 7.45-7.45 (m, 1H), 7.23-6.93 (m, 3.5H), 6.69 (d, J = 7.3 Hz, 0.5H), 4.70 (s, 0.5H), 4.39-4.31 (m, 1.5H), 4.20-4.13 (m, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.62-3.47 (m, 4H), 3.41 (br s, 1H), 2.65 (br s, 1.5H), 2.52 (br s, 0.5H), 1.60-1.41 (m, 4H), 1.30-1.13 (m, 4H), 0.99 (t, J = 7.3 Hz, 3H), 0.94 - 0.79 (m, 6H); MS(ESI⁺) m/z 782.3 (M+H)⁺.
Example 320
4-(4-(7-Chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-2-(dibutylamino)pyrimidine-5-carboxylic acid

(320)

[00751] To a solution of ethyl 4-(4-(7-chloronaphthalen-2-ylsulfonylcarbamoyl)-2-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)phenyl)-2-(dibutylamino)pyrimidine-5-carboxylate (Example 319, 23 mg, 0.03 mmol) in THF (1.0 mL) and MeOH (1.0 mL) was added 2N NaOH (0.15 mL, 0.30 mmol). The resulting reaction mixture was stirred at 55 °C for 3 h. At 0 °C, the reaction mixture was neutralized to pH 3-4 with aq. IN HCl. The solution was extracted with EtOAc (3 x) and the combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by preparative HPLC to give the title compound (14 mg, 63%). MS(ESI⁺) m/z 754.3 (M+H)⁺.

Example 321
4-(5-Chloro-2-(dibutylamino)pyrimidin-4-yl)-N-(l-(3,4-dichlorobenzyl)indolin-5-ylsulfonyl)-3-(1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

(321)

[00752] The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where 2,4,5-trichloropyrimidine (Aldrich) was used to
replace 2,4-dichloropyrimidine (Intermediate 291A) and l-(3,4-dichlorobenzyl)indoline-5-sulfonamide (Intermediate 51) was used to replace naphthalene-2-sulfonamide (Example 291). ¾ NMR (DMSO-d₆, 1:1 mixture of amide rotamers) δ 8.45 (s, 1H), 8.08 (s, 1H), 8.05-7.97 (m, 2H), 7.73 (d, J = 8.6 Hz, 0.5H), 7.69-7.50 (m, 4.5H), 7.32 (d, J = 8.4 Hz, 1H), 7.24-7.03 (m, 4H), 6.96 (d, J = 7.0 Hz, 0.5H), 6.67 (d, J = 7.0 Hz, 0.5H), 4.60 (br. s., 0.5H), 4.47 (s, 2H), 4.37 - 4.28 (m, 0.5H), 3.55 (t, J = 8.5 Hz, 2H), 3.45-3.30 (m, 4H), 3.19 (br s, 3H), 3.07 (t, J = 8.5 Hz, 2H), 2.76-2.60 (m, 1.5H), 2.39-2.29 (m, 0.5H), 1.47-1.35 (m, 4H), 1.28-1.15 (m, 4H), 0.87-0.71 (m, 6H); MS(ESI⁺) m/z 861.3 (M+H)⁺.

Example 322

4-(2-(Butyl(3,4-dichlorobenzyl)amino)-5-chloropyrimidin-4-yl)-N-(8-chloronaphthalene-2-sulfonyl)-3-(l,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

![Chemical structure of 322](image)

The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where 2,4,5-trichloropyrimidine (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 291A), N-(3,4-dichlorophenethyl)butan-1-amine (Intermediate 89) was used to replace dibutylamine (Intermediate 291B), and 8-chloronaphthalene-2-sulfonamide (Intermediate 5) was used to replace naphthalene-2-sulfonamide (Example 291). ¹H NMR (CDCl₃, 1:1 mixture of amide rotamers) δ 9.14 (s, 1H), 8.34 (s, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.95 (s, 0.5H), 7.90-7.82 (m, 3.5H), 7.73 (d, J = 6.8 Hz, 1H), 7.65-7.52 (m, 3H), 7.26-7.02 (m, 5H), 6.95 (d, J = 6.8 Hz, 0.5H), 6.82 (d, J = 6.8 Hz, 0.5H), 4.72 (br s, 2H), 4.26 (d, J = 5.7 Hz, 2H), 3.56-3.19 (m, 4H), 2.74 (br s, 1.5H), 2.58 (br s, 0.5H), 1.53-1.41 (m, 2H), 1.34-1.17 (m, 2H), 1.01-0.81 (m, 3H); MS(ESI⁺) m/z 848.3 (M+H)⁺.
4-(5-Chloro-2-(dipropylamino)pyrimidin-4-yl)-N-(napthalen-2-ylsulfonyl)-3-(1, 2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

(323)

[00754]  The title compound was prepared following a procedure analogous to that for the synthesis of Example 291, where 2,4,5-trichloropyrimidine (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 291A) and dipropylamine was used to replace dibutylamine (Intermediate 291B). 'HNMR (CD$_3$OD, 1:1 mixture of amide rotamers) δ 8.70 (s, 1H), 8.13-7.89 (m, 5.5H), 7.82 (s, 0.5H), 7.74-7.58 (m, 3H), 7.53 (s, 1H), 7.23-7.05 (m, 3H), 7.02 (d, J = 6.8 Hz, 0.5H), 6.84 (d, J = 6.8 Hz, 0.5H), 4.67 (br s, 0.5H), 4.28 (br s, 1H), 4.07 (br s, 0.5H), 3.45-3.37 (m, 2H), 3.01 (br s, 2H), 2.89 (br s, 2H), 2.71 (br s, 2H), 1.58-1.43 (m, 4H), 0.87-0.79 (m, 6H); MS(ESI$^+$) m/z 682.2 (M+H$^+$).

Example 324
4-(5-Chloro-2-(dipropylamino)pyrimidin-4-yl)-3-(5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl-N-(napthalen-2-ylsulfonyl)benzamide

(324)

[00755]  The title compound was prepared following a procedure analogous to that for the synthesis of Example 303, where 2,4,5-trichloropyrimidine (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 303B) and dipropylamine was used to replace dibutylamine (Intermediate 303C). 'HNMR (CDCl$_3$, 1:1 mixture of amide rotamers) δ 8.72 (s, 1H), 8.27 (s, 0.5H), 8.11-7.79 (m, 6.5H), 7.77-7.54 (m, 4H), 7.18-7.05 (m, 3H), 6.95 (d, J = 7.0 Hz, 0.5H), 6.84 (d, J = 7.0 Hz, 0.5H), 5.15 (d, J = 18.3 Hz, 0.5H), 4.50 (d, J = 18.3 Hz, 0.5H), 4.32-4.19 (m, 1.5H), 4.04-3.90 (m, 0.5H), 3.70 (br s,
Example 325

4-(5-Bromo-2-(dipropylamino)pyrimidin-4-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide

[00756] The title compound was prepared following a procedure analogous to that for the synthesis of Example 303, where 5-bromo-2,4-dichloropyrimidine (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 303B) and dipropylamine was used to replace dibutylamine (Intermediate 303C).  

HNMR (CD$_3$OD, 1:1 mixture of amide rotamers) $\delta$ 8.69 (s, 1H), 8.33 (s, 0.5H), 8.12-7.88 (m, 5.5H), 7.74-7.55 (m, 4H), 7.19-7.05 (m, 3H), 6.97 (d, J = 6.6 Hz, 1H), 6.90 (d, J = 6.6 Hz, 1H), 5.05 (br s, 0.5H), 5.00 (br s, 0.5H), 4.35 (m, 1.5H), 3.83 (br s, 0.5H), 3.52-3.41 (m, 3H), 3.31-3.14 (m, 3H), 2.73 (m, 1.5H), 2.57-2.42 (m, 0.5H), 1.55-1.33 (m, 4H), 1.01-0.62 (m, 6H); MS(ESI$^+$) m/z 758.1 (M+H)$^+$. 

Example 326

4-(5-Chloro-2-((cyclopropylmethyl)(propyl)amino)pyrimidin-4-yl)-3-((5)-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-N-(naphthalen-2-ylsulfonyl)benzamide

(326)
The title compound was prepared following a procedure analogous to that for the synthesis of Example 303, where 5-bromo-2,4-dichloropyrimidine (Aldrich) was used to replace 2,4-dichloropyrimidine (Intermediate 303B) and N-(cyclopropylmethyl)propan-1-amine (Aldrich) was used to replace dibutylamine (Intermediate 303C). 

\[ \text{H NMR (CD}_2\text{OD, 1:1 mixture of amide rotamers)} \delta 8.73 (s, 1H), 8.24 (s, 0.5H), 8.11-8.01 (m, 3.5H), 7.96 (d, J = 7.9 Hz, 2H), 7.73-7.63 (m, 3H), 7.18-7.06 (m, 3H), 7.01-6.93 (m, 1H), 6.87 (s, 0.5H), 6.85 (s, 0.5H), 5.04 (br s, 0.5H), 4.99 (br s, 0.5H), 4.37-4.28 (m, 1.5H), 3.82 (br s, 0.5H), 3.61-3.49 (m, 2H), 3.30-3.24 (m, 2H), 3.19 (q, J = 7.4 Hz, 2H), 2.82-2.74 (m, 1H), 2.51-2.43 (m, 1H), 1.59-1.47 (m, 2H), 1.40 (m, 2H), 1.34 (t, J = 7.4 Hz, 3H), 0.88-0.71 (m, 2H), 0.42 (br s, 1H); MS(ESI \^+) m/z 724.1 (M+H)\^+.

Example 327

3-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(5-chloro-2-(dipropylamino)pyrimidin-4-yl)-N-(naphthalen-2-ylsulfonyl)benzamide

![Chemical structure](327)

Following a procedure analogous to that for the synthesis of Example 303, 2-(2-(dipropylamino)pyrimidin-4-yl)-5-(naphthalen-2-ylsulfonyl)carbamoylbenzoic acid (30 mg, 0.053 mmol) was reacted with ((5)-3-(azidomethyl)-1,2,3,4-tetrahydroisoquinoline (Intermediate 92A, 15 mg, 0.079 mmol) to give a crude oil, which was used in the subsequent step without purification.

The crude oil from above was dissolved in THF (1.0 mL), and PPh\(_3\) (21 mg, 0.081 mmol) was added followed by 0.5N NaOH (100 µL). The resulting reaction mixture was stirred at 50 °C for 3 h and then neutralized with IN HCl solution (100 µL). The volatiles were removed in vacuo, and the residue was purified by preparative HPLC to give the title compound (14 mg, 37% for two steps). 

\[ \text{H NMR (CD}_2\text{OD, 1:1 mixture of amide rotamers)} \delta 8.78 (s, 1H), 8.19-8.09 (m, 4 H), 8.05 (dd, J = 8.1, 1.8 Hz, 1H), 7.83-7.67 (m, 5H), 7.25-7.12 (m, 2 H), 7.06 (d, J = 6.5 Hz, 1H), 6.95 (d, J = 6.5 Hz, 1H), 5.22

- 427 -
(br s, 1H), 4.35 (s, 2H), 3.54-3.14 (m, 4H), 3.04 (d, J = 6.4 Hz, 2H), 2.84-2.65 (m, 2H), 1.55-1.33 (m, 4H), 1.01-0.62 (m, 6H); MS(ESI+) m/z 711.3 (M+H)+.

Example 328

4-(5-Chloro-2-(dipropylamino)pyrimidin-4-yl) -N-(8-chloronaphthalen-2-ylsulfonyl)-3-((5')-3-(hydroxymethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)benzamide

Example 329

3-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(5-chloro-2-(dipropylamino)pyrimidin-4-yl) -N-(8-chloronaphthalen-2-ylsulfonyl)benzamide

[00760] The title compound was prepared following a procedure analogous to that for the synthesis of Example 303, where 2,4,5-trichloropyrimidine was used to replace 2,4-dichloropyrimidine (Intermediate 303B), dipropylamine was used to replace dibutylamine (Intermediate 303C) and 8-chloronaphthalene-2-sulfonamide (Intermediate 5) was used to replace naphthalene-2-sulfonamide (Intermediate 303C). HNMR (CD3OD, 1:1 mixture of amide rotamers) δ 9.05 (s, 1H), 8.96 (br s, 1H), 8.24 (br s, 1H), 8.14-8.04 (m, 2H), 7.85-7.49 (m, 5H), 7.16-6.89 (m, 3H), 6.82 (br s, 1H), 5.22-5.05 (m, 1H), 4.53 (br. s, 1H), 4.24 (br. s, 1H), 3.45-3.05 (m, 5H), 2.80-2.34 (m, 3H), 1.65-1.50 (m, 4H), 0.99-0.52 (m, 6H); MS(ESI+) m/z 746.1 (M+H)+.

Example 329

3-((5)-3-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline-2-carbonyl)-4-(5-chloro-2-(dipropylamino)pyrimidin-4-yl) -N-(8-chloronaphthalen-2-ylsulfonyl)benzamide

[00761] Following a procedure analogous to that for the synthesis of Example 303, 2-(5-chloro-2-(dipropylamino)pyrimidin-4-yl)-5-(8-chloronaphthalen-2-ylsulfonyl)carbamoyl)benzoic acid (32 mg, 0.053 mmol) was reacted with ((5)-3-
(azidomethyl)-l,2,3,4-tetrahydroisoquinoline  (Intermediate 92A, 20 mg, 0.106 mmol) to
give a crude oil which was used in the subsequent step without purification.

The crude oil from above was dissolved in THF (1.0 mL). PPh₃ (39 mg, 0.15
mmol) was added followed by 0.5N NaOH (100 µL). The resulting reaction mixture was
stirred at 50 °C for 3 h and then neutralized with IN HCl solution (100 µL). The volatiles
were removed in vacuo, and the residue was purified by preparative HPLC to give the
title compound (19 mg, 49% for two steps). ¹H NMR (CDCl₃, 1:1 mixture of amide
rotamers) δ 9.16 (s, 1H), 8.42-8.14 (m, 4 H), 8.02 (d, J = 8.1 Hz, 1H), 7.82 (d, J = 8.6 Hz,
1H), 7.76-7.47 (m, 5H), 7.15-7.04 (m, 2 H), 6.94 (d, J = 6.0 Hz, 0.5H), 6.85 (d, J = 6.0
Hz, 0.5H), 5.43 (br s, 1H), 4.48 (d, J = 17.6 Hz, 1H), 4.28 (d, J = 17.6 Hz, 1H), 3.45-2.98
(m, 5H), 2.88-2.48 (m, 5H), 1.65-1.23 (m, 4H), 1.01-0.51 (m, 6H); MS(ESI⁺) m/z 745.1
(M+H)⁺.

Example 330

1-(4-(((1-((2-Aminoethyl)thio)isoquinolin-6-yl)sulfonyl)carbamoyl)-2-(l,2,3,4-
tetrahydroisoquinoline-2-carbonyl)phenyl
-N,N-dibutyl-4-chloro-5-methyl-l H-pyrazole-
3-carboxamide

[00763] The title compound was prepared following procedures outlined above.

MS(ESI⁺) m/z 816.2 (M+H)⁺.

Example 331

2-((6-((N-(4-Carboxy-3-(dibutylcarbamoyl)-5-methyl-1H-pyrazol-1-yl)-3-(1,2,3,4-
tetrahydroisoquinoline-2-carbonyl)benzoylsulfamoyl)isoquinolin-1-yl)thio)acetic acid
The title compound was prepared following procedures outlined above.

\[ \text{MS(ESI}^+) m/z 831.2 \ (\text{M+H})^+ \].

**1H NMR**

(2:1 mixture of amide rotamers)

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>( \text{DMSO-d}_6 ) δ</th>
<th>1H NMR Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>8.60-8.47 (m, 1H), 8.26-7.93 (m, 5H), 7.79 (d, ( J = 6.8 ) Hz, 1H), 7.67-7.48 (m, 2H), 7.33-7.10 (m, 3.5H), 7.06-6.96 (m, 0.5H), 4.57 (br s, 1H), 4.39-4.06 (m, 1H), 3.62-3.38 (m, 4H), 3.24-3.07 (m, 1H), 3.04-2.91 (m, 1H), 2.85-2.65 (m, 2H), 2.24 (s, 2H), 2.13 (s, 1H), 1.34-1.09 (m, 6H), 1.02-0.91 (m, 2H), 0.89-0.80 (m, 4H), 0.74-0.54 (m, 2H)</td>
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</tr>
<tr>
<td>3</td>
<td>8.23-8.15 (m, 1H), 8.12-8.02 (m, 1H), 8.02-7.92 (m, 1H), 7.88-7.79 (m, 1H), 7.79-7.69 (m, 1H), 7.64-7.45 (m, 2H), 7.30-7.03 (m, 5H), 7.00-6.89 (m, 1H), 4.62-4.27 (m, 2H), 3.62-3.37 (m, 4H), 3.20-3.08 (m, 1H), 3.03 (s, 6H), 3.00-2.92 (m, 1H), 2.80-2.64 (m, 2H), 2.19 (s, 2H), 2.14 (s, 1H), 1.41-1.06 (m, 6H), 1.02-0.91 (m, 2H), 0.89-0.77 (m, 3H), 0.73-0.60 (m, 3H)</td>
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<tr>
<td>4</td>
<td>8.50 (br s, 1H), 8.45-8.12 (m, 2H), 8.10-7.98 (m, 2H), 7.81-7.66 (m, 2H), 7.59 (br s, 1H), 7.30-7.13 (m, 4.5H), 6.98-6.96 (m, 0.5H), 4.74-4.46 (m, 2H), 3.62-3.42 (m, 4H), 3.23-3.07 (m, 1H), 3.03-2.98 (m, 1H), 2.82 (s, 6H), 2.76 (br s, 2H), 2.21 (s, 2H), 2.17 (s, 1H), 1.40-1.10 (m, 6H), 1.02-0.89 (m, 2H), 0.88-0.75 (m, 3H), 0.73-0.55 (m, 3H)</td>
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<tr>
<td>5</td>
<td>8.88 (s, 1H), 8.33-8.23 (m, 1H), 8.18-8.01 (m, 5H), 7.91 (d, ( J = 7.5 ) Hz, 1H), 7.81-7.67 (m, 2H), 7.29-7.13 (m, 3.5H), 6.99-6.97 (m, 0.5H) 4.73 (br s, 1H), 4.56 (br s, 1H), 3.76-3.53 (m, 4H), 3.22-3.07 (m, 1H), 3.03-2.90 (m, 1H), 2.82-2.71 (m, 2H), 2.22 (s, 2H), 2.18 (s, 1H), 1.41-1.06 (m, 6H), 1.03-0.89 (m, 2H), 0.88-0.75 (m, 3H), 0.73-0.54 (m, 3H)</td>
<td></td>
</tr>
<tr>
<td>Ex. No.</td>
<td>¹H NMR (2:1 mixture of amide rotamers)</td>
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<tr>
<td>6</td>
<td>(DMSO-δ₆) δ 8.72 (s, 1H), 8.33-8.24 (m, 1H), 8.24-8.18 (m, 1H), 8.18-7.97 (m, 4H), 7.79-7.65 (m, 3H), 7.24-7.03 (m, 3.5H), 6.99-6.97 (m, 0.5H), 4.80-4.66 (m, 1H), 4.57 (br s, 1H), 3.62-3.41 (m, 4H), 3.15-3.04 (m, 1H), 3.00-2.88 (m, 1H), 2.82-2.73 (m, 2H), 2.22 (s, 2H), 2.18 (s, 1H), 1.38-1.07 (m, 6H), 1.04-0.89 (m, 2H), 0.87-0.76 (m, 3H), 0.73-0.55 (m, 3H)</td>
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<td>7</td>
<td>(DMSO-δ₆) δ 8.78-8.64 (m, 1H), 8.34-8.24 (m, 1H), 8.21-7.97 (m, 5H), 7.80-7.61 (m, 2H), 7.51-7.35 (m, 1H), 7.31-7.12 (m, 3.5H), 7.09-6.98 (m, 0.5H), 4.84-4.66 (m, 1H), 4.62-4.44 (m, 1H), 3.60-3.28 (m, 4H), 3.21-3.08 (m, 1H), 3.07-2.88 (m, 1H), 2.86-2.69 (m, 2H), 2.22 (s, 2H), 2.18 (s, 1H), 1.45-1.08 (m, 6H), 1.05-0.91 (m, 2H), 0.89-0.78 (m, 3H), 0.74-0.57 (m, 3H)</td>
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<tr>
<td>8</td>
<td>(CD₃OD) δ 9.00-8.96 (m, 1H), 8.38-8.33 (m, 1H), 8.27 (d, J = 1.1 Hz, 2H), 8.22-8.18 (m, 1H), 8.13-8.08 (m, 1H), 8.02-7.99 (m, 1H), 7.86-7.80 (m, 1H), 7.71-7.65 (m, 1H), 7.25-7.06 (m, 3.5H), 6.91-6.90 (m, 0.5H), 4.66-4.42 (m, 2H), 3.59-3.37 (m, 4H), 3.14-2.96 (m, 2H), 2.91-2.67 (m, 2H), 2.34 (s, 2H), 2.29 (s, 1H), 1.50-1.21 (m, 6H), 1.13-0.97 (m, 2H), 0.96-0.86 (m, 3H), 0.80-0.65 (m, 3H)</td>
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<tr>
<td>9</td>
<td>(CD₃OD) δ 9.80 (s, 1H), 8.35 (dd, J = 7.3, 1.3 Hz, 1H), 8.26-8.21 (m, 1H), 8.17 (d, J = 1.1 Hz, 2H), 8.09 (dd, J = 8.4, 2.0 Hz, 1H), 7.99 (t, J = 2.3 Hz, 1H), 7.80-7.74 (m, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.25-7.05 (m, 3.5H), 6.91-6.89 (m, 0.5H), 4.64-4.54 (m, 2H), 4.50 (dq, J = 7.1, 1.8 Hz, 2H), 3.57-3.35 (m, 4H), 3.18-2.96 (m, 2H), 2.92-2.62 (m, 2H), 2.33 (s, 2H), 2.28 (s, 1H), 1.51-1.45 (m, 3H), 1.40-1.04 (m, 8H), 0.96-0.86 (m, 3H), 0.80-0.65 (m, 3H)</td>
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<tr>
<td>10</td>
<td>(DMSO-δ₆) δ 8.38 (s, 1H), 8.18 (s, 1H), 7.99 (dd, J = 8.3, 1.7 Hz, 1H), 7.97-7.86 (m, 4H), 7.54-7.47 (m, 2H), 7.15-7.00 (m, 3.5H), 6.91 (d, J = 7.0 Hz, 0.5H), 4.67 (br s, 1H), 4.50-4.26 (m, 3H), 3.04 (br s, 1.5H), 2.90 (br s, 1.5H), 2.68 (br s, 3H), 2.13 (s, 2H), 2.08 (s, 1H), 1.36-1.28 (m, 1H), 1.21-1.06 (m, 6H), 0.94-0.85 (m, 1H), 0.78 (q, J = 7.4 Hz, 3H), 0.62-0.54 (m, 3H)</td>
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<tr>
<td>Ex. No.</td>
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<tr>
<td>11</td>
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<tr>
<td>(DMSO-d$_6$) $\delta$ 8.51 (s, 1H), 8.34 (s, 1H), 7.98 (dd, $J = 8.4$, 1.8 Hz, 1H), 7.93 (d, $J = 1.5$ Hz, 1H), 7.88 (s, 2H), 7.79 (dd, $J = 8.6$, 1.3 Hz, 1H), 7.71-7.69 (m, 1H), 7.53-7.49 (m, 1H), 7.13-7.01 (m, 3.5H), 6.91 (d, $J = 7.5$ Hz, 0.5H), 4.67 (br s, 1H), 4.50-4.27 (m, 3H), 3.05 (br s, 1.5H), 2.92-2.88 (m, 1.5H), 2.68 (br s, 3H), 2.13 (s, 2H), 2.08 (s, 1H), 1.36-1.28 (m, 1H), 1.21-1.08 (m, 6H), 0.91-0.86 (m, 1H), 0.78 (q, $J = 7.4$ Hz, 3H), 0.62-0.54 (m, 3H)</td>
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<tr>
<td>12</td>
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<tr>
<td>(1:1 CD$_3$OD:CDCl$_3$) $\delta$ 9.39-9.19 (m, 1H), 8.57 (d, $J = 8.4$ Hz, 2H), 8.18-8.10 (m, 2H), 8.07 (s, 1H), 7.89-7.74 (m, 1H), 7.68-7.59 (m, 1H), 7.43-7.33 (m, 1H), 7.21-6.99 (m, 3.5H), 6.85-6.83 (m, 0.5H), 4.78-4.61 (m, 2H), 3.49 (br s, 2H), 3.31-3.12 (m, 2H), 2.98 (s, 1H), 2.91-2.63 (m, 3H), 2.26 (s, 2H), 2.22 (s, 1H), 1.48-1.17 (m, 6H), 1.12-0.96 (m, 2H), 0.94-0.81 (m, 3H), 0.77-0.59 (m, 3H)</td>
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<td>13</td>
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<td>(DMSO-d$_6$) $\delta$ 8.88 (s, 1H), 8.68 (d, $J = 8.4$ Hz, 1H), 8.64-8.44 (m, 2H), 8.31-8.19 (m, 1H), 8.10-8.00 (m, 2H), 7.95 (s, 1H), 7.87 (t, $J = 7.9$ Hz, 1H), 7.79-7.66 (m, 1H), 7.24-7.04 (m, 2.5H), 6.97-6.94 (m, 0.5H), 4.71 (br s, 1H), 4.58 (br s, 1H), 3.45 (br s, 4H), 2.94 (br s, 2H), 2.82-2.69 (m, 2H), 2.25 (s, 2H), 2.12 (s, 1H), 1.42-1.08 (m, 6H), 1.02-0.91 (m, 2H), 0.88-0.76 (m, 3H), 0.73-0.56 (m, 3H)</td>
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<td>14</td>
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<td>(CD$_3$OD) $\delta$ 9.61 (s, 1H), 8.42-8.33 (m, 2H), 8.31-8.20 (m, 2H), 8.08 (dd, $J = 8.4$, 2.0 Hz, 1H), 8.02-7.96 (m, 1H), 7.87 (t, $J = 7.9$ Hz, 1H), 7.69-7.61 (m, 1H), 7.25-7.03 (m, 3.5H), 6.89-6.88 (m, 0.5H), 4.67-4.39 (m, 2H), 3.72-3.61 (m, 1H), 3.60-3.52 (m, 1H), 3.47 (dq, $J = 7.4$, 3.9 Hz, 2H), 3.31 (td, $J = 3.3$, 1.7 Hz, 1H), 3.27-3.09 (m, 1H), 3.05-2.96 (m, 1H), 2.89-2.59 (m, 2H), 2.32 (s, 2H), 2.27 (s, 1H), 1.42-1.42 (m, 1H), 1.52-1.15 (m, 9H), 1.13-0.97 (m, 2H), 0.90 (td, $J = 16.3$, 7.4 Hz, 3H), 0.80-0.64 (m, 3H)</td>
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<td>(DMSO-d$_6$) $\delta$ 8.83 (s, 1H), 8.66 (s, 1H), 8.18 (d, $J = 8.6$ Hz, 1H), 8.14 (s, 2H), 8.07-8.04 (m, 1H), 8.02 (d, $J = 1.7$ Hz, 0.5H), 7.98 (d, $J = 1.3$ Hz, 0.5H), 7.90 (dd, $J = 8.5$, 1.0 Hz, 1H), 7.62 (t, $J = 8.8$ Hz, 1H), 7.21-7.10 (m, 3.5H), 6.98 (d, $J = 7.5$ Hz, 0.5H), 4.73 (br s, 1H), 4.58-4.33 (m, 3H), 3.12 (br s, 1.5H), 2.98-2.95 (m, 1.5H), 2.75 (br s, 3H), 2.21 (s, 2H), 2.16 (s, 1H), 1.42-1.35 (m, 1H), 1.30-1.12 (m, 6H), 1.00-0.92 (m, 1H), 0.87-0.82 (m, 3H), 0.69-0.61 (m, 3H)</td>
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<tr>
<td>Ex. No.</td>
<td>$^1$H NMR (2:1 mixture of amide rotamers)</td>
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<td>16</td>
<td>(DMSO-d$_6$) $\delta$ 8.77 (s, 1H), 8.64 (s, 1H), 8.08-8.05 (m, 4H), 8.01 (d, $J = 1.8$ Hz, 1H), 7.97 (d, $J = 1.8$ Hz, 1H), 7.60-7.56 (m, 1H), 7.20-7.07 (m, 3.5H), 6.98 (d, $J = 7.7$ Hz, 0.5 H), 4.75 (br s, 1H), 4.57 (br s, 1H), 4.39 (q, $J = 7.0$ Hz, 2H), 3.74 (br s, 1H), 3.51 (br s, 1H), 3.13 (br s, 1.5H), 2.99-2.95 (m, 1.5H), 2.75 (br s, 3H), 2.20 (s, 2H), 2.15 (s, 1H), 1.38 (t, $J = 7.2$ Hz, 4H), 1.29-1.12 (m, 6H), 1.00-0.93 (m, 1H), 0.88-0.82 (m, 3H), 0.69-0.61 (m, 3H)</td>
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<td>17</td>
<td>(DMSO-d$_6$) $\delta$ 8.65 (s, 1H), 8.61 (s, 1H), 8.17 (d, $J = 8.4$ Hz, 1H), 8.07 (s, 2H), 8.01 (d, $J = 8.2$ Hz, 1H), 7.95 (s, 1H), 7.91-7.88 (m, 1H), 7.53-7.48 (m, 1H), 7.15-7.03 (m, 3.5H), 6.93 (d, $J = 9.0$ Hz, 0.5H), 4.75 (br s, 1H), 4.58-4.33 (m, 3H), 3.34 (q, $J = 7.6$ Hz, 2H), 3.13 (br s, 1.5H), 2.99-2.95 (m, 1.5H), 2.75 (br s, 3H), 2.14 (s, 2H), 2.09 (s, 1H), 1.40-1.32 (m, 1H), 1.18-1.05 (m, 9H), 0.94-0.86 (m, 1H), 0.82-0.77 (m, 3H), 0.63-0.57 (m, 3H)</td>
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<td>18</td>
<td>(DMSO-d$_6$) $\delta$ 8.57 (s, 1H), 8.08-8.05 (m, 3H), 7.99 (d, $J = 9.0$ Hz, 1H), 7.82 (dd, $J = 8.7$, 1.9 Hz, 1H), 7.78 (s, 1H), 7.76-7.73 (m, 1H), 7.53 (d, $J = 7.0$ Hz, 2H), 7.47 (d, $J = 2.6$ Hz, 1H), 7.44-7.40 (m, 2H), 7.37-7.34 (m, 1H), 7.21-7.08 (m, 3.5H), 6.96 (d, $J = 9.1$ Hz, 0.5H), 5.28 (s, 2H), 4.71 (br s, 1H), 4.57-4.32 (m, 3H), 3.13 (br s, 1.5H), 2.97-2.93 (m, 1.5H), 2.75 (br s, 3H), 2.23 (s, 2H), 2.18 (s, 1H), 1.44-1.33 (m, 1H), 1.27-1.16 (m, 6H), 1.02-0.93 (m, 1H), 0.87-0.81 (m, 3H), 0.68 (t, $J = 7.3$ Hz, 2H), 0.62 (t, $J = 7.4$ Hz, 1H)</td>
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<td>19</td>
<td>(1:1 CD$_3$OD:CDCl$_3$) $\delta$ 8.84 (s, 1H), 8.22 (d, $J = 1.9$ Hz, 1H), 8.11-8.03 (m, 3H), 8.01-7.91 (m, 2H), 7.88 (d, $J = 8.3$ Hz, 1H), 7.81 (d, $J = 7.5$ Hz, 1H), 7.70 (t, $J = 7.9$ Hz, 1H), 7.67-7.60 (m, 1H), 7.56 (s, 1H), 7.53-7.43 (m, 1H), 7.25-7.00 (m, 2.5H), 6.84-6.83 (m, 0.5H), 4.41 (br s, 2H), 3.51-3.35 (m, 2H), 3.27-3.08 (m, 2H), 2.98 (s, 1H), 2.87-2.79 (m, 1H), 2.78-2.57 (m, 2H), 2.30 (s, 2H), 2.16 (s, 1H), 1.51-1.16 (m, 6H), 1.10-0.98 (m, 2H), 0.95-0.81 (m, 3H), 0.77-0.62 (m, 3H)</td>
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<tr>
<td>Ex. No.</td>
<td>¹H NMR (2:1 mixture of amide rotamers)</td>
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<td>20</td>
<td>(DMSO-d₆) δ 8.26 (s, 1H), 8.00-7.97 (m, 1H), 7.93 (s, 1H), 7.90 (d, J = 8.4 Hz, 3H), 7.86-7.78 (m, 2H), 7.73-7.67 (m, 2H), 7.62-7.47 (m, 3H), 7.29-7.26 (m, 1H), 7.14-7.03 (m, 3.5H), 6.97 (d, J = 9.0 Hz, 0.5H), 5.33 (s, 2H), 4.67 (br s, 1H), 4.54-4.34 (m, 3H), 3.14 (s, 3H), 2.91 (br s, 2H), 2.69 (br s, 2H), 2.61-2.59 (m, 1H), 2.13 (s, 2H), 2.08 (s, 1H), 1.36-1.28 (m, 1H), 1.27-1.16 (m, 6H), 0.92-0.86 (m, 2H), 0.81-0.76 (m, 3H), 0.62-0.54 (m, 3H)</td>
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<td>21</td>
<td>(1:1 CD₃OD:CDCl₃) δ 9.11 (s, 1H), 8.11-8.03 (m, 2H), 7.98-7.91 (m, 2H), 7.64 (d, J = 1.9 Hz, 1H), 7.58-7.47 (m, 5H), 7.45-7.40 (m, 1H), 7.22-7.05 (m, 4H), 7.02 (d, J = 7.5 Hz, 1H), 5.27 (s, 2H), 4.41 (br s, 2H), 3.25-3.07 (m, 4H), 3.04-2.96 (m, 2H), 2.87-2.72 (m, 2H), 2.30 (s, 2H), 2.22 (s, 1H), 1.51-1.16 (m, 6H), 1.12-0.97 (m, 2H), 0.92-0.83 (m, 3H), 0.77-0.66 (m, 3H)</td>
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<td>23</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.60 (s, 1H), 8.06 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 1.6 Hz, 1H), 7.79 (s, 1H), 7.50 (br s, 1H), 7.32-7.31 (m, 2H), 7.20-7.06 (m, 3.5H), 6.83 (d, J = 7.5 Hz, 0.5H), 4.65 (br s, 1H), 4.13-4.11 (m, 1H), 4.08-4.05 (m, 1H), 3.96-3.92 (m, 1H), 3.87-3.82 (m, 1H), 3.77 (br s, 1H), 3.63-3.35 (m, 3H), 3.22-3.08 (m, 2H), 3.03-3.00 (m, 1H), 2.97 (s, 1H), 2.83-2.80 (m, 1H), 2.73 (br s, 1H), 2.26 (s, 2H), 2.22 (s, 1H), 2.16-2.09 (m, 1H), 2.04-1.93 (m, 2H), 1.85-1.78 (m, 1H), 1.49-1.43 (m, 1H), 1.39-1.34 (m, 2H), 1.31-1.18 (m, 4H), 1.09-0.99 (m, 2H), 0.90-0.84 (m, 3H), 0.73 (t, J = 7.2 Hz, 2H), 0.68 (t, J = 7.4 Hz, 1H)</td>
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<td>24</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.56 (s, 1H), 8.07-8.04 (m, 1H), 7.94-7.91 (m, 1H), 7.88-7.86 (m, 2H), 7.81 (d, J = 9.0 Hz, 2H), 7.51-7.48 (m, 1H), 7.32 (d, J = 2.3 Hz, 1H), 7.26 (dd, J = 8.9, 2.4 Hz, 1H), 7.21-7.07 (m, 2.5H), 6.64 (d, J = 7.5 Hz, 0.5H), 4.74 (dt, J = 12.1, 6.1 Hz, 2H), 4.41 (s, 1H), 3.81 (br s, 1H), 3.64 (br s, 1H), 3.45 (br s, 1H), 3.13 (br s, 1H), 3.03-2.99 (m, 1.5H), 2.83 (br s, 1.5H), 2.28 (s, 2H), 2.24 (s, 1H), 1.48-1.43 (m, 1H), 1.40-1.35 (m, 7H), 1.29-1.17 (m, 6H), 1.10-0.98 (m, 1H), 0.91-0.84 (m, 3H), 0.74 (t, J = 7.3 Hz, 2H), 0.68 (t, J = 7.4 Hz, 1H)</td>
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<td>Ex. No.</td>
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<td>25</td>
<td>(1:1 CD$_3$OD:CDCl$_3$) δ 8.51 (s, 1H), 8.17 (dd, $J = 8.3$, 2.0 Hz, 1H), 8.08 (d, $J = 1.8$ Hz, 1H), 7.91-7.88 (m, 1H), 7.85-7.82 (m, 1H), 7.78 (d, $J = 9.0$ Hz, 1H), 7.40 (dd, $J = 8.3$, 2.3, 1H), 7.36 (d, $J = 2.3$ Hz, 1H), 7.29-7.34 (m, 3H), 7.20-7.07 (m, 3.5H), 6.97-6.92 (m, 3H), 6.86 (d, $J = 7.5$ Hz, 0.5H), 4.78 (br s, 1H), 4.45 (dd, $J = 6.0$, 3.3 Hz, 2H), 4.39-4.37 (m, 2H), 3.63 (br s, 1H), 3.53-3.42 (m, 2H), 3.22-3.10 (m, 2H), 3.01 (br s, 1.5H), 2.83 (br s, 1.5H), 2.27 (s, 2H), 2.23 (s, 1H), 1.48-1.43 (m, 1H), 1.40-1.34 (m, 2H), 1.31-1.17 (m, 4H), 1.12-0.99 (m, 2H), 0.91-0.85 (m, 3H), 0.74 (t, $J = 7.3$ Hz, 2H), 0.67 (t, $J = 7.3$ Hz, 1H)</td>
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<td>26</td>
<td>(CD$_3$OD) δ 9.14 (s, 1H), 8.22-7.94 (m, 6H), 7.77-7.51 (m, 5H), 7.31-7.02 (m, 4.5H), 6.89-6.87 (m, 0.5H), 5.45 (s, 2H), 4.53 (br s, 2H), 4.01-3.83 (m, 3H), 3.73-3.39 (m, 4H), 3.23-3.08 (m, 1H), 3.03 (br s, 1H), 2.92-2.62 (m, 2H), 2.33 (s, 2H), 2.27 (s, 1H), 1.57-1.19 (m, 6H), 1.16-1.01 (m, 2H), 0.93 (td, $J = 16.2$, 7.3 Hz, 3H), 0.83-0.58 (m, 3H)</td>
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<td>27</td>
<td>(CD$_3$OD) δ 9.20 (s, 1H), 8.22-7.95 (m, 4H), 7.77-7.59 (m, 3H), 7.29-7.07 (m, 4.5H), 6.90-6.88 (m, 0.5H), 4.77-4.65 (m, 2H), 4.56 (d, $J = 2.0$ Hz, 2H), 4.05 (br s, 4H), 3.96-3.85 (m, 2H), 3.75-3.48 (m, 4H), 3.39-3.33 (m, 4H), 3.23-2.99 (m, 2H), 3.00-2.72 (m, 2H), 2.32 (s, 2H), 2.27(s, 1H), 1.59-1.21 (m, 6H), 1.19-1.02 (m, 2H), 0.96 (ddd, $J = 14.6$, 7.3, 7.2 Hz, 3H), 0.86-0.67 (m, 3H)</td>
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<td>28</td>
<td>(1:1 CD$_3$OD:CDCl$_3$) δ 8.58 (s, 1H), 8.07 (dt, $J = 8.4$, 2.0 Hz, 1H), 7.94-7.93 (m, 1H), 7.89 (s, 2H), 7.82 (d, $J = 8.9$ Hz, 1H), 7.50-7.47 (m, 1H), 7.36-7.32 (m, 2H), 7.21-7.07 (m, 3.5H), 6.65 (d, $J = 7.5$ Hz, 0.5H), 4.77 (br s, 1H), 4.42 (s, 1H), 4.27-4.25 (m, 2H), 3.84-3.82 (m, 2H), 3.60 (br s, 1H), 3.53-3.38 (m, 5H), 3.25-3.10 (m, 2H), 3.02 (br s, 1.5H), 2.84 (br s, 1.5H), 2.29 (s, 2H), 2.24 (s, 1H), 1.50-1.44 (m, 1H), 1.40-1.34 (m, 1H), 1.32-1.20 (m, 5H), 1.12-0.99 (m, 2H), 0.91-0.85 (m, 3H), 0.74 (t, $J = 7.4$ Hz, 2H), 0.68 (t, $J = 7.4$ Hz, 1H)</td>
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<tr>
<td>Ex. No.</td>
<td>$^1$H NMR (2:1 mixture of amide rotamers)</td>
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<td>29</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.55 (s, 1H), 8.08-8.05 (m, 1H), 7.95 (t, $J = 4.8$ Hz, 2H), 7.81 (dd, $J = 8.7$, 1.6 Hz, 1H), 7.72 (t, $J = 9.0$ Hz, 1H), 7.65 (s, 1H), 7.35 (dd, $J = 8.8$, 2.3 Hz, 1H), 7.20-7.07 (m, 3.5H), 6.99 (d, $J = 7.5$ Hz, 0.5H), 4.71 (br s, 1H), 4.58 (br s, 1H), 4.33 (br s, 1H), 3.91 (s, 3H), 3.49 (br s, 2H), 3.12 (br s, 1H), 2.97-2.94 (m, 1.5H), 2.77-2.74 (m, 1.5H), 2.22 (s, 2H), 2.18 (s, 1H), 1.42-1.34 (m, 1H), 1.30-1.12 (m, 6H), 1.04-0.92 (m, 2H), 0.87-0.81 (m, 3H), 0.68 (t, $J = 7.3$ Hz, 2H), 0.61 (t, $J = 7.3$ Hz, 1H)</td>
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<td>30</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.58 (s, 1H), 8.08-8.05 (m, 1H), 7.93-7.92 (m, 1H), 7.90-7.88 (m, 2H), 7.82 (d, $J = 8.9$ Hz, 1H), 7.50-7.48 (m, 1H), 7.36-7.33 (m, 2H), 7.21-7.08 (m, 3.5H), 6.85 (d, $J = 7.5$ Hz, 0.5H), 4.78 (br s, 1H), 4.66 (br s, 1H), 4.42 (s, 1H), 4.27-4.25 (m, 2H), 3.88-3.86 (m, 2H), 3.63 (q, $J = 7.1$ Hz, 2H), 3.45 (br s, 2H), 3.16 (br s, 2H), 3.02 (br s, 1.5H), 2.84 (br s, 1.5H), 2.29 (s, 2H), 2.24 (s, 1H), 1.50-1.44 (m, 1H), 1.40-1.34 (m, 2H), 1.32-1.20 (m, 7H), 1.12-0.99 (m, 2H), 0.91-0.85 (m, 3H), 0.74 (t, $J = 7.4$ Hz, 2H), 0.68 (t, $J = 7.2$ Hz, 1H)</td>
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<td>31</td>
<td>(CD$_2$OD) δ 9.08 (d, $J = 1.8$ Hz, 1H), 8.53 (d, $J = 9.0$ Hz, 1H), 8.31-8.10 (m, 2H), 8.09-7.98 (m, 1H), 7.98-7.84 (m, 1H), 7.73 (t, $J = 7.8$ Hz, 1H), 7.39-7.05 (m, 4.5H), 6.91-6.89 (m, 0.5H), 4.58 (br s, 2H), 3.80-3.43 (m, 4H), 3.21-3.00 (m, 2H), 2.95 (s, 6H), 2.84-2.60 (m, 2H), 2.33 (s, 2H), 2.28 (s, 1H), 1.61-1.22 (m, 6H), 1.21-1.02 (m, 2H), 0.96 (td, $J = 16.7$, 7.3 Hz, 3H), 0.86-0.62 (m, 3H)</td>
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<td>32</td>
<td>(CD$_2$OD) δ 9.07 (d, $J = 1.5$ Hz, 1H), 8.22 (dd, $J = 8.4$, 1.8 Hz, 1H), 8.17-7.92 (m, 3H), 7.66-7.55 (m, 3H), 7.32-7.06 (m, 4.5H), 6.91-6.89 (m, 0.5H), 4.74-4.51 (m, 2H), 4.42 (t, $J = 5.3$ Hz, 2H), 4.11-3.87 (m, 4H), 3.80-3.38 (m, 10H), 3.29-3.01 (m, 2H), 3.01-2.71 (m, 2H), 2.57-2.44 (m, 2H), 2.32 (s, 2H), 2.26 (s, 1H), 1.61-1.23 (m, 6H), 1.08 (br s, 2H), 1.01-0.88 (m, 3H), 0.87-0.68 (m, 3H)</td>
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<tr>
<td>Ex. No.</td>
<td>¹H NMR (2:1 mixture of amide rotamers)</td>
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<td>33</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.44 (s, 1H), 8.18-8.15 (m, 1H), 8.05 (d, J = 1.8 Hz, 1H), 7.94 (s, 1H), 7.90-7.87 (m, 2H), 7.73 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.24-7.06 (m, 4.5H), 6.84 (d, J = 7.7 Hz, 0.5H), 4.75 (br s, 1H), 4.43 (s, 1H), 4.32 (t, J = 4.1 Hz, 2H), 3.86-3.84 (m, 4H), 3.65-3.40 (m, 3H), 3.26 (br s, 2H), 3.04 (br s, 4H), 2.82 (br s, 2H), 2.74 (br s, 2H), 2.27 (s, 2H), 2.22 (s, 1H), 1.51-1.43 (m, 1H), 1.40-1.34 (m, 2H), 1.32-1.20 (m, 6H), 1.10-0.99 (m, 2H), 0.91-0.85 (m, 3H), 0.74 (t, J = 7.3 Hz, 2H), 0.68 (t, J = 7.4 Hz, 1H)</td>
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<td>34</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.46 (s, 1H), 8.28-8.24 (m, 1H), 8.16-8.14 (m, 1H), 7.95 (s, 1H), 7.86-7.80 (m, 2H), 7.72 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.19-7.06 (m, 4.5H), 6.86 (d, J = 7.7 Hz, 0.5H), 4.76 (br s, 1H), 4.46 (s, 1H), 4.19 (br s, 2H), 3.89-3.83 (m, 4H), 3.63-3.43 (m, 3H), 3.13 (br s, 6H), 2.83 (br s, 2H), 2.75 (br s, 2H), 2.28 (s, 2H), 2.24 (s, 1H), 2.09-2.02 (m, 2H), 1.52-1.45 (m, 1H), 1.42-1.35 (m, 2H), 1.33-1.22 (m, 4H), 1.11-1.00 (m, 2H), 0.92-0.85 (m, 3H), 0.75 (t, J = 7.4 Hz, 2H), 0.69 (t, J = 7.4 Hz, 1H)</td>
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<td>35</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.54 (s, 1H), 8.13-8.10 (m, 1H), 7.98 (t, J = 2.1 Hz, 1H), 7.88 (s, 2H), 7.80 (d, J = 9.0 Hz, 1H), 7.46 (dd, J = 8.4, 2.6 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.24 (dd, J = 9.0, 2.4 Hz, 1H), 7.19-7.07 (m, 3.5H), 6.85 (d, J = 7.5 Hz, 0.5H), 4.75 (br s, 1H), 4.43 (s, 1H), 4.15 (t, J = 6.0 Hz, 2H), 3.81 (br s, 1H), 3.62-3.40 (m, 4H), 3.24-3.13 (m, 4H), 3.04-3.02 (m, 2H), 2.92 (br s, 2H), 2.86-2.74 (m, 7H), 2.28 (s, 2H), 2.23 (s, 1H), 2.06 (ddd, J = 13.4, 6.6, 6.4 Hz, 2H), 1.51-1.43 (m, 1H), 1.40-1.34 (m, 2H), 1.32-1.20 (m, 4H), 1.11-0.99 (m, 2H), 0.91-0.85 (m, 3H), 0.74 (t, J = 7.3 Hz, 2H), 0.68 (t, J = 7.3 Hz, 1H)</td>
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<td>36</td>
<td>(DMSO-d₆) δ 8.62, (s, 1H), 8.10-8.07 (m, 1H), 7.96-7.93 (m, 3H), 7.86 (d, J = 9.0 Hz, 1H), 7.49-7.46 (m, 1H), 7.35 (dd, J = 9.0, 2.6 Hz, 1H), 7.26 (d, J = 1.3 Hz, 2H), 7.21-7.06 (m, 5.5H), 6.85 (d, J = 7.5 Hz, 0.5H), 5.39 (s, 2H), 4.77 (br s, 1H), 4.43 (s, 1H), 3.87 (s, 3H), 3.62 (br s, 1H), 3.15 (br s, 1H), 3.04-3.00 (m, 1.5H), 2.82 (br s, 1.5H), 2.63 (s, 3H), 2.28 (s, 2H), 2.24 (s, 1H), 1.51-1.43 (m, 1H), 1.40-1.34 (m, 2H), 1.32-1.17 (m, 4H), 1.11-0.99 (m, 2H), 0.91-0.84 (m, 3H), 0.74 (t, J = 7.4 Hz, 2H), 0.68 (t, J = 7.3 Hz, 1H)</td>
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</table>
| Ex. No. | ¥H NMR  
(2:1 mixture of amide rotamers) |
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<td>37</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.54 (s, 1H), 8.15 (dd, J = 8.4, 2.0 Hz, 1H), 8.05 (s, 1H), 7.94-7.91 (m, 1H), 7.88-7.80 (m, 2H), 7.46 (br s, 1H), 7.42 (dd, J = 8.4 Hz, 1H), 7.31-7.26 (m, 1H), 7.21-7.07 (m, 3.5H), 6.86 (d, J = 7.5 Hz, 0.5H), 5.05 (br s, 1H), 4.78 (br s, 1H), 4.45 (s, 1H), 4.40 (dd, J = 11.4, 3.7 Hz, 1H), 4.30-4.25 (m, 1H), 3.90-3.86 (m, 1H), 3.81 (br s, 1H), 3.64 (br s, 2H), 3.51-3.39 (m, 3H), 3.24-3.10 (m, 2H), 3.03 (br s, 1H), 2.94 (d, J = 7.3 Hz, 4H), 2.82 (br s, 1.5H), 2.22 (s, 2H), 2.38 (s, 1H), 1.50 (d, J = 6.8 Hz, 1H), 1.47-1.43 (m, 1H), 1.40 (d, J = 5.9 Hz, 1H), 1.38-1.34 (m, 2H), 1.33-1.18 (m, 4H), 1.11-0.99 (m, 2H), 0.92-0.85 (m, 3H), 0.74 (t, J = 7.4 Hz, 2H), 0.68 (t, J = 7.3 Hz, 1H)</td>
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<td>38</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.60 (s, 1H), 8.07 (dt, J = 8.4, 2.2 Hz, 1H), 7.94-7.84 (m, 4H), 7.52-7.49 (m, 1H), 7.39 (d, J = 2.2 Hz, 1H), 7.21-7.07 (m, 3.5H), 6.85 (d, J = 7.5 Hz, 0.5H), 4.93 (br s, 1H), 4.77 (br s, 1H), 4.42 (s, 1H), 4.26 (br s, 1H), 3.72 (br s, 2H), 3.56 (br s, 3H), 3.41 (br s, 1H), 3.17 (br s, 3H), 3.04-3.00 (m, 1.5H), 2.92 (s, 3H), 2.84 (br s, 1.5H), 2.29 (s, 2H), 2.24 (s, 1H), 2.14 (br s, 3H), 1.94 (br s, 2H), 1.51-1.43 (m, 1H), 1.37 (br s, 2H), 1.33-1.19 (m, 4H), 1.12-0.99 (m, 2H), 0.91-0.85 (m, 3H), 0.74 (t, J = 7.4 Hz, 2H), 0.68 (t, J = 7.4 Hz, 1H)</td>
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<td>39</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.44 (s, 1H), 8.26-8.22 (m, 1H), 8.14-8.12 (m, 1H), 7.87-7.84 (m, 1H), 7.80-7.79 (m, 1H), 7.71 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.19-7.06 (m, 5.5H), 6.85 (d, J = 7.5 Hz, 0.5H), 4.76 (br s, 1H), 4.46 (s, 1H), 4.19 (br s, 2H), 3.96-3.93 (m, 2H), 3.81 (br s, 1H), 3.65 (br s, 2H), 3.53 (br s, 1H), 3.42 (br s, 1H), 3.29-3.26 (m, 2H), 3.05-3.03 (m, 1.5H), 2.91 (s, 3H), 2.82 (br s, 1.5H), 2.27 (s, 2H), 2.23 (s, 1H), 2.14-2.08 (m, 2H), 1.50-1.44 (m, 1H), 1.38 (br s, 2H), 1.32-1.19 (m, 4H), 1.10-1.00 (m, 2H), 0.91-0.85 (m, 3H), 0.74 (t, J = 7.4 Hz, 2H), 0.69 (t, J = 7.4 Hz, 1H)</td>
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<tr>
<td>Ex. No.</td>
<td>¹H NMR (2:1 mixture of amide rotamers)</td>
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<td>40</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.49 (s, 1H), 8.21 (d, J = 7.5 Hz, 1H), 8.10 (br s, 1H), 7.87-7.82 (m, 2H), 7.75 (d, J = 9.3 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.20-7.07 (m, 5.5H), 6.85 (d, J = 7.8 Hz, 0.5H), 4.77 (br s, 1H), 4.45 (s, 1H), 4.00 (s, 2H), 3.81-3.60 (m, 3H), 3.52 (br s, 1H), 3.37-3.34 (m, 2H), 3.25-3.13 (m, 3H), 3.05-3.03 (m, 1.5H), 2.90 (br s, 1H), 2.83 (br s, 1.5H), 2.28 (s, 2H), 2.23 (s, 1H), 2.19-2.05 (m, 6H), 1.50-1.44 (m, 1H), 1.40-1.36 (m, 3H), 1.32-1.19 (m, 5H), 1.11-1.00 (m, 2H), 0.91-0.85 (m, 3H), 0.74 (t, J = 7.4 Hz, 2H), 0.69 (t, J = 7.4 Hz, 1H)</td>
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<td>41</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.48 (s, 1H), 8.22 (t, J = 7.1 Hz, 1H), 8.12 (d, J = 5.5 Hz, 1H), 7.88-7.81 (m, 2H), 7.74 (d, J = 9.4 Hz, 1H), 7.43-7.39 (m, 2H), 7.22-7.07 (m, 5.5H), 6.85 (d, J = 7.5 Hz, 0.5H), 4.79 (br s, 1H), 4.45 (s, 1H), 3.96 (s, 2H), 3.72-3.50 (m, 4H), 3.26-3.23 (m, 2H), 3.17-3.13 (m, 2H), 3.07-3.03 (m, 1H), 3.01-2.97 (m, 1H), 2.94-2.81 (m, 3H), 2.27 (s, 2H), 2.23 (s, 1H), 2.16 (br s, 2H), 1.92-1.83 (m, 4H), 1.53-1.44 (m, 2H), 1.39-1.36 (m, 3H), 1.33-1.21 (m, 5H), 1.11-1.00 (m, 2H), 0.94-0.85 (m, 3H), 0.74 (t, J = 7.4 Hz, 2H), 0.69 (t, J = 7.4 Hz, 1H)</td>
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<td>42</td>
<td>(CDCl₃) δ 8.60 (s, 1H), 8.51 (d, J = 5.0 Hz, 2H), 8.03-7.97 (m, 2H), 7.92 (d, J = 8.1 Hz, 1H), 7.81-7.78 (m, 1H), 7.75-7.71 (m, 1H), 7.24-7.02 (m, 8.5H), 6.76 (br s, 0.5H), 4.66 (s, 1H), 4.28 (s, 1H), 4.03 (br s, 2H), 3.71 (br s, 1H), 3.42 (br s, 2H), 3.08 (br s, 1H), 2.96 (s, 1H), 2.89 (s, 1H), 2.84-2.73 (m, 3.5H), 2.62 (br s, 0.5H), 2.17 (s, 3H), 2.16-2.08 (m, 2H), 1.55-1.49 (m, 0.5H), 1.47-1.41 (m, 1.5H), 1.35-1.24 (m, 5H), 1.10-1.02 (m, 2H), 0.94-0.88 (m, 3H), 0.75 (t, J = 7.4 Hz, 1.5H), 0.71 (t, J = 7.4 Hz, 1.5H)</td>
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<td>43</td>
<td>(CD₃OD) δ 9.11 (d, J = 1.8 Hz, 1H), 8.51 (d, J = 9.0 Hz, 1H), 8.30 (dd, J = 9.0, 1.8 Hz, 1H), 8.11 (dd, J = 8.4, 1.8 Hz, 1H), 8.02-8.01 (m, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.66 (t, J = 8.0 Hz, 1H), 7.24-7.07 (m, 3.5H), 6.91 (d, J = 7.5 Hz, 0.5H), 4.91 (br s, 1H), 4.54 (br s, 1H), 3.96 (br s, 1H), 3.69 (br s, 1H), 3.01 (br s, 1H), 2.89-2.77 (m, 2H), 2.66 (br s, 1H), 2.33 (s, 2H), 2.28 (s, 1H), 1.53-1.45 (m, 2H), 1.39-1.17 (m, 5H), 1.12-0.99 (m, 3H), 0.94 (t, J = 7.3 Hz, 1H), 0.89 (t, J = 7.3 Hz, 2H), 0.76 (t, J = 7.4 Hz, 2H), 0.68 (t, J = 7.4 Hz, 1H)</td>
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<tr>
<td>Ex. No.</td>
<td>$^1$H NMR (2:1 mixture of amide rotamers)</td>
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<td>44</td>
<td>(CDCl$_3$) δ 9.16-9.15 (m, 1H), 8.47 (d, $J = 8.8$ Hz, 1H), 8.35 (dd, $J = 9.0$, 1.8 Hz, 1H), 8.02 (d, $J = 7.9$ Hz, 1H), 7.92-7.88 (m, 1H), 7.69-7.62 (m, 2H), 7.24-7.08 (m, 4.5H), 6.82 (d, $J = 7.7$ Hz, 0.5H), 4.76 (br s, 2H), 4.33 (s, 1H), 3.97 (br s, 1H), 3.50 (br s, 2H), 3.20 (br s, 2H), 2.87 (br s, 1H), 2.64 (br s, 1H), 2.17 (s, 2H), 2.16 (s, 1H), 1.61-1.53 (m, 1H), 1.50-1.41 (m, 2H), 1.39-1.24 (m, 4H), 1.14-1.01 (m, 2H), 0.95-0.90 (m, 3H), 0.79-0.74 (m, 3H)</td>
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<td>53</td>
<td>(CD$_2$OD) δ 8.12 (dd, $J = 8.3$, 1.8 Hz, 1H), 8.03-8.02 (m, 1H), 7.74 (dd, $J = 8.3$, 1.8 Hz, 1H), 7.64-7.59 (m, 2H), 7.24-7.10 (m, 3.5H), 6.94 (d, $J = 7.3$ Hz, 0.5H), 6.46 (d, $J = 8.3$ Hz, 1H), 4.75-4.55 (m, 2H), 4.16-3.65 (m, 2H), 3.53 (t, $J = 8.5$ Hz, 2H), 3.29-3.23 (m, 2H), 3.20-2.65 (m, 6H), 2.34 (s, 2H), 2.29 (s, 1H), 1.50-0.99 (m, 13H), 0.95-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.70-0.66 (m, 1H)</td>
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<td>54</td>
<td>(CD$_2$OD) δ 8.38 (d, $J = 1.7$ Hz, 1H), 8.12-8.10 (m, 1H), 8.02-8.01 (m, 1H), 7.81 (dd, $J = 8.6$ Hz, 1.7 Hz, 1H), 7.62-7.58 (m, 1H), 7.51 (d, $J = 8.9$ Hz, 1H), 7.39 (d, $J = 3.1$ Hz, 1H), 7.22-7.09 (m, 3.5H), 6.91 (d, $J = 7.5$ Hz, 0.5H), 6.63 (d, $J = 2.2$ Hz, 1H), 4.75-4.45 (m, 2H), 3.90-3.40 (m, 2H), 3.12-2.55 (m, 4H), 2.32 (s, 2H), 2.27 (s, 1H), 1.53-0.99 (m, 10H), 0.94-0.87 (m, 3H), 0.76 (t, $J = 7.4$ Hz, 2H), 0.68 (t, $J = 7.4$ Hz, 1H)</td>
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<td>55</td>
<td>(CD$_2$OD) δ 8.25 (br s, 1H), 8.14-8.11 (m, 1H), 8.02-8.01 (m, 1H), 7.91 (s, 1H), 7.88 (d, $J = 8.9$ Hz, 1H), 7.64-7.61 (m, 1H), 7.24-7.10 (m, 3.5H), 6.92 (d, $J = 7.5$ Hz, 0.5H), 4.75-4.40 (m, 2H), 4.27 (t, $J = 8.3$ Hz, 2H), 3.95-3.40 (m, 3H), 3.27 (t, $J = 8.3$ Hz, 2H), 3.20-2.55 (m, 6H), 2.33 (s, 2H), 2.28 (s, 1H), 1.89-1.70 (m, 5H), 1.55-0.99 (m, 13H), 0.94-0.88 (m, 3H), 0.77 (t, $J = 7.4$ Hz, 2H), 0.69 (t, $J = 7.4$ Hz, 1H)</td>
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<td>56</td>
<td>(CD$_2$OD) δ 8.34 (d, $J = 1.4$ Hz, 1H), 8.16-8.13 (m, 1H), 8.05-8.04 (m, 1H), 7.84 (dd, $J = 8.7$, 1.8 Hz, 1H), 7.58-7.55 (m, 1H), 7.52 (d, $J = 8.9$ Hz, 1H), 7.37 (d, $J = 3.3$ Hz, 1H), 7.23-7.09 (m, 3.5H), 6.92 (d, $J = 7.5$ Hz, 0.5H), 6.61 (d, $J = 2.8$ Hz, 1H), 4.75-4.48 (m, 2H), 4.27 (q, $J = 7.2$ Hz, 2H), 3.80-3.40 (m, 2H), 3.12-2.55 (m, 4H), 2.32 (s, 2H), 2.27 (s, 1H), 1.51-0.98 (m, 13H), 0.94-0.88 (m, 3H), 0.76 (t, $J = 7.4$ Hz, 2H), 0.71-0.67 (m, 1H)</td>
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<td>Ex. No.</td>
<td>¹H NMR (2:1 mixture of amide rotamers)</td>
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<td>57</td>
<td>(CD₃OD) δ 8.06 (dd, J = 8.4, 2.0 Hz, 1H), 7.97-7.95 (m, 1H), 7.74 (dd, J = 8.5, 1.9 Hz, 1H), 7.69-7.65 (m, 1H), 7.61-7.59 (m, 1H), 7.35-7.0 (m, 3.5H), 6.93 (d, J = 7.5 Hz, 0.5H), 6.42 (d, J = 8.6 Hz, 1H), 4.85-4.40 (m, 2H), 3.61 (t, J = 8.7 Hz, 2H), 3.07-2.97 (m, 4H), 3.16-2.55 (m, 4H), 2.34 (s, 2H), 2.29 (s, 1H), 1.79-1.67 (m, 7H), 1.53-1.00 (m, 16H), 0.95-0.87 (m, 3H), 0.77 (t, J = 7.3 Hz, 2H), 0.69 (t, J = 7.3 Hz, 1H)</td>
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<td>58</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.18-8.15 (m, 1H), 8.06 (d, J = 1.5 Hz, 1H), 7.94 (s, 1H), 7.67-7.66 (m, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.43-7.40 (m, 3H), 7.19-7.09 (m, 4.5H), 6.89-6.87 (m, 0.5H), 4.85-4.50 (m, 2H), 4.11 (t, J = 8.3 Hz, 2H), 3.70-3.50 (m, 2H), 3.24-3.19 (m, 2H), 3.15-2.70 (m, 4H), 2.28 (s, 2H), 2.23 (s, 1H), 1.50-0.99 (m, 10H), 0.92-0.85 (m, 3H), 0.75 (t, J = 7.3 Hz, 2H), 0.69 (t, J = 7.4 Hz, 1H)</td>
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<td>59</td>
<td>(CD₃OD) δ 8.06 (dd, J = 8.4, 2.0 Hz, 1H), 7.97-7.95 (m, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.71-7.66 (m, 2H), 7.49-7.47 (m, 2H), 7.27-7.09 (m, 4.5H), 6.93 (d, J = 7.5 Hz, 0.5H), 6.55 (d, J = 8.4 Hz, 1H), 4.85-4.40 (m, 2H), 4.42 (s, 2H), 4.10-3.50 (m, 2H), 3.57 (t, J = 8.6 Hz, 2H), 3.09 (t, J = 8.6 Hz, 2H), 3.16-2.55 (m, 4H), 2.34 (s, 2H), 2.29 (s, 1H), 1.52-0.99 (m, 10H), 0.95-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.68 (m, 1H)</td>
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<td>60</td>
<td>(CD₃OD) δ 8.79 (d, J = 1.3 Hz, 1H), 8.07 (dd, J = 8.4, 2.0 Hz, 1H), 7.97-7.96 (m, 1H), 7.82 (dd, J = 7.8, 1.7 Hz, 1H), 7.70-7.66 (m, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.25-7.09 (m, 3.5H), 6.93 (d, J = 7.7 Hz, 0.5H), 4.90-4.80 (m, 1H), 4.65-4.50 (m, 2H), 4.21 (t, J = 8.5 Hz, 2H), 4.10-3.40 (m, 3H), 3.28-2.50 (m, 4H), 2.34 (s, 2H), 2.29 (s, 1H), 2.24 (s, 3H), 1.51-0.99 (m, 10H), 0.95-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.67 (m, 1H)</td>
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<td>61</td>
<td>(CD₃OD) δ 8.07 (dd, J = 8.4, 2.2 Hz, 1H), 7.97-7.95 (m, 1H), 7.77 (dd, J = 8.5, 1.9 Hz, 1H), 7.70-7.66 (m, 2H), 7.35-7.09 (m, 8.5H), 6.93 (d, J = 7.3 Hz, 0.5H), 6.56 (d, J = 8.6 Hz, 1H), 4.85-4.40 (m, 2H), 4.43 (s, 2H), 4.10-3.50 (m, 2H), 3.56 (t, J = 8.7 Hz, 2H), 3.07 (t, J = 8.7 Hz, 2H), 3.15-2.55 (m, 4H), 2.34 (s, 2H), 2.29 (s, 1H), 1.52-1.00 (m, 10H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.68 (m, 1H)</td>
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<tr>
<td>Ex. No.</td>
<td>$^1$H NMR (2:1 mixture of amide rotamers)</td>
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<td>62</td>
<td>(CD$_3$OD) δ 8.07 (dd, $J = 8.4$, 2.2 Hz, 1H), 7.97-7.96 (m, 1H), 7.78 (dd, $J = 8.5$, 1.9 Hz, 1H), 7.70-7.66 (m, 2H), 7.26-7.09 (m, 6.5H), 6.93 (d, $J = 7.5$ Hz, 0.5H), 6.55 (d, $J = 8.6$ Hz, 1H), 4.85-4.40 (m, 2H), 4.41 (s, 2H), 4.10-3.50 (m, 2H), 3.57 (t, $J = 8.7$ Hz, 2H), 3.09 (t, $J = 8.6$ Hz, 2H), 3.15-2.55 (m, 4H), 2.34 (s, 2H), 2.30 (s, 1H), 1.52-0.99 (m, 10H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.68 (m, 1H)</td>
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<td>63</td>
<td>(CD$_3$OD) δ 8.08 (dd, $J = 8.4$, 2.2 Hz, 1H), 7.98-7.96 (m, 1H), 7.71-7.67 (m, 1H), 7.32 (dd, $J = 7.6$, 1.7 Hz, 1H), 7.25-7.23-7.09 (m, 4.5H), 7.08 (d, $J = 1.8$ Hz, 1H), 6.93 (d, $J = 7.3$ Hz, 0.5H), 4.85-4.40 (m, 2H), 4.16-3.50 (m, 2H), 3.48-3.44 (m, 2H), 3.23 (q, $J = 7.3$ Hz, 2H), 3.12-2.55 (m, 4H), 3.01 (t, $J = 8.5$ Hz, 2H), 2.34 (s, 2H), 2.29 (s, 1H), 1.52-0.99 (m, 13H), 0.95-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.67 (m, 1H)</td>
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<td>64</td>
<td>(CD$_3$OD) δ 8.26 (d, $J = 7.5$ Hz, 1H), 8.07 (dd, $J = 8.4$, 2.2 Hz, 1H), 7.97-7.95 (m, 2H), 7.92 (d, $J = 8.8$ Hz, 1H), 7.70-7.67 (m, 1H), 7.49-7.47 (m, 2H), 7.25-7.10 (m, 4.5H), 6.92 (d, $J = 7.5$ Hz, 0.5H), 4.80-4.40 (m, 2H), 4.33-4.27 (m, 4H), 3.92 (s, 2H), 3.60-3.35 (m, 2H), 3.15-2.60 (m, 4H), 2.34 (s, 2H), 2.29 (s, 1H), 1.52-0.99 (m, 10H), 0.95-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.67 (m, 1H)</td>
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<tr>
<td>65</td>
<td>(CD$_3$OD) δ 8.07 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.97-7.95 (m, 1H), 7.74-7.66 (m, 2H), 7.63 (br s, 1H), 7.44 (d, $J = 2.0$ Hz, 1H), 7.40-7.38 (m, 1H), 7.23-7.10 (m, 4.5H), 6.93 (d, $J = 7.3$ Hz, 0.5H), 6.40-6.37 (m, 1H), 4.80-4.40 (m, 2H), 4.10-3.55 (m, 2H), 3.59 (t, $J = 8.7$ Hz, 2H), 3.51-3.47 (m, 2H), 3.50-3.40 (m, 2H), 3.03 (t, $J = 8.8$ Hz, 2H), 2.89 (t, $J = 7.2$ Hz, 2H), 3.10-2.60 (m, 2H), 2.34 (s, 2H), 2.29 (s, 1H), 1.52-0.98 (m, 10H), 0.95-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.67 (m, 1H)</td>
</tr>
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<td>66</td>
<td>(CD$_3$OD) δ 8.23-8.21 (m, 1H), 8.08 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.98-7.96 (m, 2H), 7.92 (d, $J = 8.6$ Hz, 1H), 7.68 (t, $J = 7.7$ Hz, 1H), 7.47 (d, $J = 7.3$ Hz, 2H), 7.32-7.10 (m, 6.5H), 6.93-6.91 (m, 0.5H), 4.70-4.50 (m, 2H), 4.28 (t, $J = 8.6$ Hz, 2H), 3.97 (s, 2H), 3.70-3.40 (m, 4H), 3.10-2.65 (m, 4H), 2.34 (s, 2H), 2.29 (s, 1H), 1.52-1.00 (m, 10H), 0.95-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.67 (m, 1H)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>$^1$H NMR (2:1 mixture of amide rotamers)</td>
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</tr>
<tr>
<td>67</td>
<td>(CD$_3$OD) δ 8.07 (dd, J = 8.4, 2.0 Hz, 1H), 7.97-7.95 (m, 1H), 7.73-7.66 (m, 2H), 7.59 (br s, 1H), 7.37-7.34 (m, 2H), 7.26-7.09 (m, 6.5H), 6.90 (d, J = 7.5 Hz, 0.5H), 6.31 (d, J = 8.6 Hz, 1H), 4.60-4.40 (m, 2H), 4.00-3.55 (m, 2H), 3.60 (t, J = 8.7 Hz, 2H), 3.49-3.45 (m, 2H), 3.18 (t, J = 6.8 Hz, 2H), 2.95 (t, J = 8.7 Hz, 2H), 3.00-2.60 (m, 4H), 2.34 (s, 2H), 2.29 (s, 1H), 1.51-0.99 (m, 10H), 0.95-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.67 (m, 1H)</td>
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<tr>
<td>68</td>
<td>(CD$_3$OD) δ 8.45 (d, J = 1.8 Hz, 1H), 8.05 (dd, J = 8.4, 2.0 Hz, 1H), 7.95-7.93 (m, 1H), 7.87 (dd, J = 8.8, 1.8 Hz, 1H), 7.68-7.64 (m, 1H), 7.4-7.52 (m, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.33-7.02 (m, 4.5H), 6.90 (d, J = 7.3 Hz, 0.5H), 6.77 (d, J = 3.1 Hz, 1H), 5.47 (s, 2H), 4.65-4.50 (m, 2H), 4.10-3.50 (m, 2H), 3.45-2.60 (m, 4H), 2.33 (s, 2H), 2.28 (s, 1H), 1.50-0.99 (m, 10H), 0.95-0.87 (m, 3H), 0.78-0.74 (m, 2H), 0.70-0.66 (m, 1H)</td>
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<td>69</td>
<td>(CD$_3$OD) δ 8.35 (d, J = 1.8 Hz, 1H), 8.07 (dd, J = 8.4, 2.0 Hz, 1H), 7.97-7.96 (m, 1H), 7.81-7.78 (m, 2H), 7.71-7.66 (m, 2H), 7.44 (d, J = 8.4 Hz, 1H), 7.23-7.09 (m, 3.5H), 6.93 (d, J = 7.3 Hz, 0.5H), 6.61 (d, J = 8.4 Hz, 1H), 4.70-4.55 (m, 2H), 4.48 (s, 2H), 4.00-3.40 (m, 2H), 3.57 (t, J = 8.6 Hz, 2H), 3.15-2.95 (m, 4H), 2.90-2.55 (m, 2H), 2.34 (s, 2H), 2.29 (s, 1H), 1.51-1.00 (m, 10H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.68 (m, 1H)</td>
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<td>70</td>
<td>(CD$_3$OD) δ 8.07 (dd, J = 8.4, 2.0 Hz, 1H), 7.97-7.95 (m, 1H), 7.79-7.77 (m, 1H), 7.69-7.66 (m, 2H), 7.49 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 7.21-7.10 (m, 4.5H), 7.00 (d, J = 8.1 Hz, 1H), 6.94-6.93 (m, 0.5H), 6.63 (d, J = 8.6 Hz, 1H), 6.39-6.38 (m, 1H), 4.60-4.50 (m, 2H), 4.54 (s, 2H), 3.75 (s, 3H), 3.78-3.60 (m, 3H), 3.56 (t, J = 8.7 Hz, 2H), 3.05 (t, J = 8.5 Hz, 2H), 3.08-2.70 (m, 3H), 2.34 (s, 2H), 2.29 (s, 1H), 1.55-1.00 (m, 10H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.70 (t, J = 7.4 Hz, 1H)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>(^1)H NMR</td>
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<tr>
<td></td>
<td>(2:1 mixture of amide rotamers)</td>
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<tr>
<td>71</td>
<td>(CD(_3)OD) δ 8.15-8.12 (m, 1H), 8.04-8.03 (m, 1H), 7.71 (d, (J = 7.9) Hz, 1H), 7.34-7.33 (m, 1H), 7.28 (s, 1H), 7.25-7.10 (m, 3.5H), 6.95 (d, (J = 7.5) Hz, 0.5H), 4.95-4.50 (m, 2H), 3.95-3.55 (m, 2H), 3.50 (t, (J = 8.5) Hz, 2H), 3.26 (q, (J = 7.2) Hz, 2H), 3.25-3.20 (m, 2H), 3.02 (t, (J = 8.5) Hz, 2H), 2.95-2.70 (m, 2H), 2.36 (s, 2H), 2.31 (s, 1H), 1.52-1.01 (m, 13H), 0.95-0.87 (m, 3H), 0.79-0.76 (m, 2H), 0.70 (t, (J = 7.4) Hz, 1H)</td>
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<td>72</td>
<td>(DMSO-d(_6)) δ 8.10-8.06 (m, 2H), 7.62-7.60 (m, 2H), 7.36 (dd, (J = 8.3, 1.9) Hz, 1H), 7.24-7.23 (m, 1H), 7.20-7.08 (m, 4.5H), 6.99 (d, (J = 7.3) Hz, 0.5H), 6.95 (s, 1H), 4.36 (s, 2H), 3.55-3.24 (m, 8H), 3.01-2.97 (m, 2H), 2.70 (br s, 2H), 2.24 (s, 2H), 2.19 (s, 1H), 1.42-0.90 (m, 10H), 0.88-0.82 (m, 3H), 0.70-0.62 (m, 3H)</td>
</tr>
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<td>73</td>
<td>(CD(_3)OD) δ 8.06 (dd, (J = 8.4, 2.2) Hz, 1H), 7.96-7.95 (m, 1H), 7.80 (d, (J = 8.4) Hz, 1H), 7.73 (s, 1H), 7.70-7.60 (m, 1H), 7.51 (s, 1H), 7.48 (d, (J = 8.1) Hz, 1H), 7.28-7.09 (m, 4.5H), 6.93 (d, (J = 7.5) Hz, 0.5H), 6.48 (d, (J = 8.6) Hz, 1H), 4.70-4.40 (m, 4H), 3.69 (s, 3H), 3.59-3.48 (m, 2H), 3.30-3.22 (m, 2H), 3.20-2.65 (m, 5H), 2.34 (s, 2H), 2.29 (s, 1H), 1.61-1.00 (m, 10H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H) 0.69 (t, (J = 7.4) Hz, 1H)</td>
</tr>
<tr>
<td>74</td>
<td>(CD(_3)OD) δ 8.07 (dd, (J = 8.4, 2.0) Hz, 1H), 7.98-7.96 (m, 1H), 7.94-7.92 (m, 2H), 7.71-7.67 (m, 1H), 7.25-7.10 (m, 4.5H), 6.93 (d, (J = 7.5) Hz, 0.5H), 4.88-4.48 (m, 4H), 4.02 (t, (J = 8.4) Hz, 2H), 3.74-3.72 (m, 4H), 3.45-3.43 (m, 4H), 3.16 (t, (J = 8.4) Hz, 2H), 3.10-2.60 (m, 4H), 2.34 (s, 2H), 2.29 (s, 1H), 1.55-0.98 (m, 10H), 0.95-0.87 (m, 3H), 0.77 (t, (J = 7.3) Hz, 2H), 0.69 (t, (J = 7.3) Hz, 1H)</td>
</tr>
<tr>
<td>75</td>
<td>(CD(_3)OD) δ 8.31 (d, (J = 8.6) Hz, 1H), 8.08 (dd, (J = 8.5, 2.1) Hz, 1H), 8.01-7.96 (m, 3H), 7.70 (d, (J = 8.4) Hz, 1H), 7.24-7.10 (m, 3.5H), 6.93 (d, (J = 7.5) Hz, 0.5H), 4.90-4.50 (m, 2H), 4.38 (s, 2H), 4.18 (t, (J = 8.6) Hz, 2H), 4.00-3.95 (m, 6H), 3.70-3.36 (m, 8H), 3.38 (t, (J = 8.5) Hz, 2H), 3.25-2.60 (m, 2H), 2.34 (s, 2H), 2.29 (s, 1H), 1.49-1.00 (m, 8H), 0.96-0.87 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.68 (m, 1H)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>H NMR (2:1 mixture of amide rotamers)</td>
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<tr>
<td>76</td>
<td>(CD$_3$OD) δ 8.08 (dd, J = 8.4, 2.9 Hz, 1H), 7.99-7.97 (m, 1H), 7.88 (d, J = 1.8 Hz, 1H), 7.71-7.67 (m, 1H), 7.58 (d, J = 1.3 Hz, 1H), 7.25-7.09 (m, 3.5H), 6.94 (d, J = 7.3 Hz, 0.5H), 4.60-4.50 (m, 2H), 3.85-3.68 (m, 1H), 3.76 (q, J = 7.0 Hz, 2H), 3.69 (t, J = 9.0 Hz, 2H), 3.65-3.43 (m, 2H), 3.15-3.00 (m, 2H), 3.07-2.80 (m, 2H), 2.66 (s, 2H), 2.35 (s, 2H), 2.30 (s, 1H), 1.55-1.00 (m, 12H), 0.95-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.71-0.67 (m, 1H)</td>
</tr>
<tr>
<td>77</td>
<td>(CD$_3$OD) δ 8.06 (dd, J = 8.4, 2.0 Hz, 1H), 7.96-7.94 (m, 1H), 7.87-7.85 (m, 1H), 7.75 (br s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.24-7.05 (m, 3.5H), 6.93 (d, J = 7.7 Hz, 0.5H), 6.73 (d, J = 8.6 Hz, 1H), 5.00-4.60 (m, 2H), 4.10-3.80 (m, 2H), 3.65-3.60 (m, 6H), 3.52-3.45 (m, 8H), 3.15-2.87 (m, 6H), 2.34 (s, 2H), 2.29 (s, 1H), 1.49-0.96 (m, 10H), 0.96-0.88 (m, 3H), 0.79-0.75 (m, 2H), 0.69 (t, J = 7.3 Hz, 1H)</td>
</tr>
<tr>
<td>78</td>
<td>(1:1 CD$_3$OD:CDCl$_3$) δ 8.39 (d, J = 2.2 Hz, 1H), 8.13-8.11 (m, 1H), 8.02-7.94 (m, 2H), 7.84 (dd, J = 8.6, 2.5 Hz, 2H), 7.47-7.45 (m, 1H), 7.20-7.08 (m, 4.5H), 6.88-6.86 (m, 1.5H), 4.60-4.40 (m, 2H), 4.18 (t, J = 8.3 Hz, 2H), 3.80 (t, J = 4.7 Hz, 6H), 3.22 (t, J = 8.2 Hz, 2H), 3.20-2.98 (m, 4H), 2.87-2.84 (m, 6H), 2.64 (s, 3H), 2.29 (s, 2H), 2.24 (s, 1H), 1.49-1.03 (m, 9H), 0.91-0.85 (m, 3H), 0.75 (t, J = 7.4 Hz, 2H), 0.69 (t, J = 7.4 Hz, 1H)</td>
</tr>
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<td>79</td>
<td>(CD$_3$OD) δ 8.53-8.50 (m, 1H), 8.15 (d, J = 1.8 Hz, 1H), 8.08-8.05 (m, 1H), 8.02-8.00 (m, 2H), 7.87 (s, 1H), 7.84-7.80 (m, 1H), 7.24-7.10 (m, 3.5H), 7.03 (d, J = 6.6 Hz, 0.5H), 4.71-4.60 (m, 1H), 4.10-3.50 (m, 3H), 3.20-2.80 (m, 4H), 2.43 (s, 2H), 2.38 (s, 1H), 1.55-1.05 (m, 10H), 0.97-0.88 (m, 3H), 0.82-0.78 (m, 2H), 0.75-0.72 (m, 1H)</td>
</tr>
<tr>
<td>80</td>
<td>(CD$_3$OD) δ 8.31 (d, J = 1.8 Hz, 1H), 8.08-8.05 (m, 1H), 7.97-7.94 (m, 2H), 7.69-7.65 (m, 2H), 7.59 (s, 1H), 7.24-7.07 (m, 3.5H), 6.91 (d, J = 7.5 Hz, 0.5H), 4.70-4.45 (m, 2H), 4.31 (q, J = 7.3 Hz, 2H), 4.10-3.40 (m, 2H), 3.20-3.00 (m, 2H), 2.90-2.60 (m, 2H), 2.33 (s, 2H), 2.28 (s, 1H), 1.60-0.98 (m, 13H), 0.95-0.87 (m, 3H), 0.78-0.74 (m, 2H), 0.68 (t, J = 7.3 Hz, 1H)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>¹H NMR (2:1 mixture of amide rotamers)</td>
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<tr>
<td>81</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.23 (d, J = 8.4 Hz, 1H), 8.09-8.06 (m, 1H), 7.95-7.89 (m, 3H), 7.52-7.49 (m, 1H), 7.20-7.10 (m, 3.5H), 6.87 (d, J = 7.5 Hz, 0.5H), 4.20-4.10 (m, 4H), 4.00-3.85 (m, 6H), 3.55-3.43 (m, 2H), 3.30-3.28 (m, 6H), 3.10-2.95 (m, 4H), 2.91-2.89 (m, 2H), 2.30 (s, 2H), 2.25 (s, 1H), 1.46-0.92 (m, 10H), 0.92-0.85 (m, 3H), 0.75 (t, J = 7.4 Hz, 2H), 0.69 (t, J = 7.3 Hz, 1H)</td>
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<td>82</td>
<td>(CD₃OD) δ 8.43 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.4, 2.0 Hz, 1H), 7.95-7.92 (m, 2H), 7.70-7.66 (m, 2H), 7.49 (d, J = 3.3 Hz, 1H), 7.25-7.08 (m, 3.5H), 6.91 (d, J = 7.5 Hz, 0.5H), 6.75 (d, J = 3.3 Hz, 1H), 4.93 (br s, 1H), 4.64-4.47 (m, 2H), 4.41 (t, J = 6.6 Hz, 2H), 4.00 (br s, 2H), 3.68 (br s, 2H), 3.42 (br s, 2H), 3.16-3.12 (m, 4H), 3.01 (br s, 2H), 2.78 (br s, 1H), 2.33-2.28 (m, 5H), 1.53-1.45 (m, 1H), 1.39-1.19 (m, 6H), 1.12-0.98 (m, 3H), 0.93 (t, J = 7.4 Hz, 1.5H), 0.89 (t, J = 7.3 Hz, 1.5H), 0.76 (t, J = 7.3 Hz, 1.5H), 0.69 (t, J = 7.4 Hz, 1.5H)</td>
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<td>83</td>
<td>(CD₃OD) δ 8.37 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.4, 2.0 Hz, 1H), 7.97-7.94 (m, 2H), 7.69-7.65 (m, 2H), 7.55 (s, 1H), 7.24-7.08 (m, 3.5H), 6.91 (d, J = 7.7 Hz, 0.5H), 4.92 (br s, 1H), 4.63-4.46 (m, 2H), 4.28 (q, J = 7.3 Hz, 2H), 4.02 (br s, 1H), 3.68 (br s, 1H), 3.58-3.41 (m, 2H), 3.01 (br s, 1H), 2.65 (br s, 1H), 2.33 (s, 2H), 2.28 (s, 1H), 1.52-1.43 (m, 4H), 1.39-1.18 (m, 6H), 1.12-0.98 (m, 2H), 0.93 (t, J = 7.4 Hz, 1H), 0.89 (t, J = 7.2 Hz, 2H), 0.76 (t, J = 7.3 Hz, 2H), 0.68 (t, J = 7.3 Hz, 1H)</td>
</tr>
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<td>84</td>
<td>(CD₃OD) δ 8.18 (d, J = 1.8 Hz, 1H), 8.07 (d, J = 2.2 Hz, 0.5H), 8.05 (d, J = 2.2 Hz, 0.5H), 7.97-7.94 (m, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.65-7.62 (m, 2H), 7.24-7.07 (m, 3.5H), 6.90 (d, J = 7.3 Hz, 0.5H), 4.93 (br s, 1H), 4.62-4.45 (m, 2H), 4.32 (q, J = 7.3 Hz, 2H), 4.01 (br s, 1H), 3.69 (br s, 1H), 3.59-3.42 (m, 2H), 3.00 (br s, 1H), 2.66 (br s, 1H), 2.33 (s, 2H), 2.28 (s, 1H), 1.52-1.43 (m, 4H), 1.39-1.16 (m, 6H), 1.13-0.98 (m, 2H), 0.93 (t, J = 7.4 Hz, 1H), 0.89 (t, J = 7.3 Hz, 2H), 0.76 (t, J = 7.4 Hz, 2H), 0.68 (t, J = 7.4 Hz, 1H)</td>
</tr>
</tbody>
</table>
### Ex. No. 85

**$^1$H NMR**

(2:1 mixture of amide rotamers)

(CD$_3$OD) δ 8.27 (d, $J = 1.8$ Hz, 1H), 8.12 (d, $J = 1.8$ Hz, 1H), 8.10 (d, $J = 2.2$ Hz, 0.5H), 8.08 (d, $J = 2.2$ Hz, 0.5H), 7.99-7.98 (m, 1H), 7.68 (t, $J = 8.4$ Hz, 1H), 7.64 (s, 1H), 7.24-7.07 (m, 3.5H), 6.92 (d, $J = 7.3$ Hz, 0.5H), 4.95 (br s, 1H), 4.69 (q, $J = 7.3$ Hz, 2H), 4.61-4.48 (m, 2H), 4.03 (br s, 1H), 3.69 (br s, 1H), 3.55 (br s, 1H), 3.43 (br s, 1H), 3.00 (br s, 1H), 2.66 (br s, 1H), 2.34 (s, 2H), 2.29 (s, 1H), 1.52-1.45 (m, 4H), 1.39-1.17 (m, 6H), 1.12-0.99 (m, 2H), 0.93 (t, $J = 7.4$ Hz, 1H), 0.89 (t, $J = 7.3$ Hz, 2H), 0.76 (t, $J = 7.3$ Hz, 2H), 0.68 (t, $J = 7.3$ Hz, 1H)

### Ex. No. 108

**$^1$H NMR**

(mixture of amide rotamers)

(CD$_3$OD) δ 8.63-8.53 (m, 1H), 8.35-7.86 (m, 6H), 7.63-7.50 (m, 3H), 7.32-7.11 (m, 3H), 7.05-6.92 (m, 1H), 5.42-5.19 (m, 0.5H), 4.69-4.24 (m, 2H), 3.54-3.33 (m, 3.5H), 3.18-2.65 (m, 10H), 2.56-2.51 (m, 0.5H), 2.49-2.40 (m, 0.5H), 2.26 (br s, 3H), 1.65-0.74 (m, 12.5H), 0.63-0.51 (m, 1.5H)

(CD$_3$OD) δ 8.65-8.54 (m, 1H), 8.33-8.15 (m, 2H), 8.10-7.88 (m, 4H), 7.59 (br s, 3H), 7.30-7.07 (m, 3.5H), 7.01-6.84 (m, 0.5H), 5.29-5.11 (m, 1H), 4.66-4.49 (m, 1H), 4.32-4.07 (m, 1H), 3.92-3.68 (m, 3H), 3.57-3.34 (m, 3H), 3.27-2.57 (m, 8.5H), 2.50-2.38 (m, 0.5H), 2.34-2.20 (m, 4H), 1.66-0.61 (m, 14H)

(DMSO-d$_6$) δ 8.54-8.41 (m, 1H), 8.32-8.24 (m, 0.5H), 8.16-8.03 (m, 1.5H), 7.96 (d, $J = 4.8$ Hz, 3.5H), 7.68-7.50 (m, 2.5H), 7.3 -7.00 (m, 4.5H), 6.98-6.92 (m, 0.5H), 5.27-4.91 (m, 1.5H), 4.65-4.50 (m, 0.5H), 4.45-4.32 (m, 1H), 3.98-2.64 (m, 13H), 2.27-2.16 (m, 1H), 2.09 (s, 2H), 2.02-0.61 (m, 16H), 0.57-0.45 (m, 2H)

### Ex. No. 111

(1:1 CD$_3$OD:CDCl$_3$) δ 8.64-8.56 (m, 1H), 8.38-8.00 (m, 3H), 7.98-7.92 (m, 1H), 7.91-7.82 (m, 2H), 7.58-7.51 (m, 3.5H), 7.30-7.07 (m, 3H), 6.98-6.87 (m, 0.5H), 5.43-5.12 (m, 0.5H), 4.91-4.74 (m, 0.5H), 4.37-4.19 (m, 0.5H), 3.73-2.57 (m, 13.5H), 2.35-2.18 (m, 3H), 2.15-1.79 (m, 4H), 1.67-0.70 (m, 13H), 0.62-0.49 (m, 1H)
<table>
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<tr>
<th>Ex. No.</th>
<th>$^1$H NMR (mixture of amide rotamers)</th>
</tr>
</thead>
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<tr>
<td>112</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.55 (d, $J = 7.7$ Hz, 1H), 8.41-8.30 (m, 1H), 8.26-8.18 (m, 1H), 8.02 (td, $J = 2.0$, 8.6 Hz, 1H), 7.95 (d, $J = 7.0$ Hz, 1H), 7.92-7.82 (m, 2H), 7.56-7.48 (m, 2H), 7.38 (dd, $J = 8.4$, 15.0 Hz, 1H), 7.24-7.03 (m, 3.5H), 6.94 (d, $J = 6.2$ Hz, 0.5H), 5.26 (d, $J = 18.5$ Hz, 0.5H), 5.21-5.12 (m, 0.5H), 4.56-4.45 (m, 1.5H), 4.27-4.09 (m, 1.5H), 3.49-2.93 (m, 4.5H), 2.90-2.77 (m, 4H), 2.74-2.52 (m, 4H), 2.46-2.31 (m, 2H), 2.27 (s, 1.5H), 2.24 (s, 1.5H), 1.39-0.92 (m, 8H), 0.92-0.84 (m, 3H), 0.76-0.70 (m, 1.5H), 0.66 (t, $J = 7.3$ Hz, 1.5H)</td>
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<tr>
<td>113</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.67-8.58 (m, 1H), 8.33-7.82 (m, 6.5H), 7.64-7.38 (m, 2H), 7.31-7.07 (m, 3.5H), 7.03-6.90 (m, 1H), 5.32-5.12 (m, 0.5H), 4.81-4.66 (m, 1H), 4.50-4.35 (m, 1H), 3.68-2.82 (m, 17H), 2.78-2.54 (m, 1H), 2.40-2.34 (m, 0.5H), 2.33-2.22 (m, 3H), 1.64-0.69 (m, 13H), 0.66-0.54 (m, 1H)</td>
</tr>
<tr>
<td>114</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.64-8.53 (m, 1H), 8.36-8.13 (m, 2H), 8.08-8.00 (m, 1H), 8.00-7.81 (m, 3H), 7.56-7.39 (m, 3.5H), 7.30-7.08 (m, 3H), 6.98 (d, $J = 7.3$ Hz, 0.5H), 5.29-5.10 (m, 0.5H), 4.80-4.66 (m, 0.5H), 4.48-4.35 (m, 0.5H), 4.34-4.09 (m, 0.5H), 3.84-3.58 (m, 1.5H), 3.76-2.64 (s, 14.5H), 2.33-2.20 (m, 3H), 1.68-0.54 (m, 14H)</td>
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<tr>
<td>115</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.58 (d, $J = 8.6$ Hz, 1H), 8.44-8.35 (m, 1H), 8.23 (ddd, $J = 2.0$, 8.4, 14.3 Hz, 1H), 8.08-8.03 (m, 1H), 8.02-7.96 (m, 1H), 7.95-7.87 (m, 2H), 7.63-7.53 (m, 1.55H), 7.43 (d, $J = 8.4$ Hz, 0.5H), 7.39 (d, $J = 8.4$ Hz, 0.5H), 7.29-7.07 (m, 4H), 6.98 (d, $J = 6.4$ Hz, 0.5H), 5.32-5.18 (m, 0.5H), 4.55-4.51 (m, 1H), 4.28-4.13 (m, 0.5H), 3.95-3.72 (m, 2H), 3.42-2.97 (m, 14.5H), 2.95-2.82 (m, 0.5H), 2.79-2.56 (m, 2.5H), 2.52-2.32 (m, 1.5H), 2.30 (s, 2H), 2.27 (s, 1H), 1.36-0.86 (m, 10.5H), 0.79-0.74 (m, 1.5H), 0.72-0.67 (m, 2H)</td>
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<td>116</td>
<td>(1:1 CD$_2$OD:CDCl$_3$) δ 8.60-8.48 (m, 1H), 8.37-8.32 (m, 1.5H), 8.20 (br s, 0.5H), 8.07-7.81 (m, 4H), 7.59-7.53 (m, 2H), 7.39 (d, $J = 8.6$ Hz, 1H), 7.25-7.01 (m, 3.5H), 6.94 (d, $J = 7.7$ Hz, 0.5H), 5.42 (d, $J = 18.0$ Hz, 1H), 5.26-5.12 (m, 0.5H), 4.50-4.42 (m, 1H), 4.18 (d, $J = 18.0$ Hz, 1H), 3.75-3.56 (m, 3H), 3.51-3.20 (m, 4.5H), 3.16-3.04 (m, 1.5H), 3.01-2.85 (m, 2.5H), 2.80 (s, 4.5H), 2.50 (d, $J = 16.3$ Hz, 0.5H), 2.34-2.24 (m, 3H), 2.21-2.10 (m, 1H), 1.44-0.71 (m, 13H), 0.67-0.59 (m, 0.5H)</td>
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<tr>
<td>Ex. No.</td>
<td>¹H NMR (mixture of amide rotamers)</td>
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<tr>
<td>117</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.65 (br s, 1H), 8.34 (s, 0.5H), 8.16 (br s, 0.5H), 8.11-7.80 (m, 4.5H), 7.65-7.52 (m, 3H), 7.46-7.34 (m, 1H), 7.32-6.96 (m, 8H), 6.83 (d, J = 6.9 Hz, 0.5H), 5.23 (d, J = 17.8 Hz, 0.5H), 4.41-4.29 (m, 1.5H), 4.23 (d, J = 17.8 Hz, 2H), 3.68-3.14 (m, 8.5H), 3.12-2.88 (m, 2.5H), 2.63 (d, J = 0.8 Hz, 0.5H), 2.53 (d, J = 16.1 Hz, 0.5H), 2.26 (s, 2H), 2.23 (s, 1H), 1.57 - 0.82 (m, 11.5H), 0.72 (t, J = 7.4 Hz, 2H), 0.64 (br s, 0.5H)</td>
</tr>
<tr>
<td>118</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.55 (d, J = 7.7 Hz, 1H), 8.41-8.30 (m, 1H), 8.26-8.18 (m, 1H), 8.02 (td, J = 2.0, 8.6 Hz, 1H), 7.95 (d, J = 7.0 Hz, 1H), 7.92-7.82 (m, 2H), 7.56-7.48 (m, 2H), 7.38 (dd, J = 8.4, 15.0 Hz, 1H), 7.24-7.03 (m, 3.5H), 6.94 (d, J = 6.2 Hz, 0.5H), 5.26 (d, J = 18.5 Hz, 0.5H), 5.21-5.12 (m, 0.5H), 4.56-4.45 (m, 1.5H), 4.27-4.09 (m, 1.5H), 3.49-2.93 (m, 4.5H), 2.90-2.77 (m, 4H), 2.74-2.52 (m, 4H), 2.46-2.31 (m, 2H), 2.27 (s, 1.5H), 2.24 (s, 1.5H), 1.39-0.92 (m, 8H), 0.92-0.84 (m, 3H), 0.76-0.70 (m, 1.5H), 0.66 (t, J = 7.3 Hz, 1.5H)</td>
</tr>
<tr>
<td>126</td>
<td>(1:1 CD₃OD:CDCl₃) δ 8.70 (s, 1H), 8.12-7.98 (m, 4H), 7.96-7.89 (m, 2H), 7.71-7.59 (m, 2H), 7.55-7.45 (m, 1H), 7.39-6.98 (m, 6H), 6.94-6.76 (m, 1H), 4.80-4.67 (m, 1H), 4.45-4.18 (m, 2H), 3.77-3.35 (m, 3H), 3.26-2.97 (m, 2H), 2.84-2.66 (m, 2H), 2.30 (s, 1H), 2.25 (d, J = 3.3 Hz, 1.5H), 2.18 (s, 0.5H), 1.46-0.93 (m, 4H), 0.89-0.80 (m, 1.5H), 0.71 (t, J = 7.4 Hz, 1H), 0.65 (t, J = 7.4 Hz, 0.5H)</td>
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<tr>
<td>127</td>
<td>(DMSO-d₆) δ 8.69 (s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.6 Hz, 1H), 8.12-8.02 (m, 2.5H), 8.01-7.92 (m, 2H), 7.80-7.65 (m, 2.5H), 7.51-7.44 (m, 0.5H), 7.38 (d, J = 8.0 Hz, 0.5H), 7.32 (d, J = 8.3 Hz, 0.5H), 7.24-6.91 (m, 5H), 6.87-6.79 (m, 0.5H), 4.69-4.48 (m, 1.5H), 4.30 (br s, 0.5H), 3.64-3.43 (m, 3.5H), 3.22-2.97 (m, 2H), 2.95-2.53 (m, 4H), 2.45-2.31 (m, 0.5H), 2.21 (s, 2H), 2.18-2.13 (m, 1H), 1.43-0.80 (m, 6H), 0.66 (t, J = 7.4 Hz, 0.5H), 0.59 (t, J = 7.4 Hz, 0.5H)</td>
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<tr>
<td>Ex. No.</td>
<td>[1^H\text{NMR}] (mixture of amide rotamers)</td>
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<td>128</td>
<td>( (1:1 \text{CD}_3\text{OD}:\text{CDCl}_3 \delta 8.71 (s, 1H), 8.08-8.03 (m, 3H), 8.01-7.99 (m, 1H), 7.94-7.92 (m, 2H), 7.68-7.61 (m, 2H), 7.53-7.48 (m, 1H), 7.21-7.06 (m, 3.5H), 6.84 (t, J = 7.6 Hz, 0.5H), 4.83 (br s, 1H), 4.42 (br s, 1H), 4.04-3.88 (br s, 1H), 3.61 (br s, 1H), 3.49 (br s, 2H), 3.22 (br s, 1H), 3.10-3.07 (m, 0.5H), 3.00 (br s, 0.5H), 2.82-2.69 (m, 2H), 2.29-2.22 (m, 3H), 2.14-2.05 (m, 1H), 1.88 (br s, 1H), 1.78-1.72 (m, 1H), 1.69-1.63 (m, 1H), 1.58-1.52 (m, 1H), 1.44-1.34 (m, 1H), 1.31-1.16 (m, 2H), 1.09-0.98 (m, 1H), 0.92-0.66 (m, 3H) )</td>
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<td>129</td>
<td>( (1:1 \text{CD}_3\text{OD}:\text{CDCl}_3 \delta 8.70 (s, 1H), 8.09 (dd, J = 8.3, 1.9 Hz, 1H), 8.06-8.03 (m, 2H), 8.02-7.99 (m, 1H), 7.97-7.92 (m, 2H), 7.68-7.61 (m, 2H), 7.53-7.48 (m, 1H), 7.22-7.06 (m, 3.5H), 6.84 (t, J = 7.8 Hz, 0.5H), 4.43 (br s, 1H), 4.24 (br s, 0.5H), 4.12 (br s, 0.5H), 3.67-3.58 (m, 1H), 3.53 (br s, 1H), 3.25 (br s, 1H), 3.14-3.11 (m, 1H), 2.77-2.72 (m, 2H), 2.37 (br s, 1H), 2.29 (s, 1.5H), 2.21 (s, 1.5H), 2.19-2.05 (m, 2H), 1.95-1.85 (m, 1.5H), 1.81-1.68 (m, 1.5H), 1.60-1.54 (m, 1H), 1.40 (br s, 1H) )</td>
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<tr>
<td>130</td>
<td>( (1:1 \text{CD}_3\text{OD}:\text{CDCl}_3 \delta 8.71 (d, J = 2.9 Hz, 1H), 8.10-8.07 (m, 1H), 8.05-7.98 (m, 3H), 7.97-7.92 (m, 2H), 7.68-7.60 (m, 2H), 7.51-7.47 (m, 1H), 7.21-7.07 (m, 3.5H), 6.84 (t, J = 7.5 Hz, 0.5H), 4.70 (br s, 1H), 4.45-4.39 (m, 2H), 4.23 (br s, 1H), 3.59 (br s, 1H), 3.53-3.50 (m, 1H), 3.27 (br s, 2H), 2.82 (br s, 1H), 2.73-2.70 (m, 1H), 2.39 (br s, 2H), 2.27 (s, 1.5H), 2.20 (s, 1.5H), 1.91 (br s, 2H) )</td>
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<td>131</td>
<td>( (1:1 \text{CD}_3\text{OD}:\text{CDCl}_3 \delta 8.57 (br s, 1H), 8.26-8.18 (m, 1H), 8.14-8.07 (m, 1H), 8.06-7.99 (m, 1H), 7.98-7.93 (m, 1H), 7.91-7.79 (m, 2H), 7.66-7.47 (m, 3.5H), 7.43-7.33 (m, 1H), 7.22-6.98 (m, 4H), 6.91-6.84 (m, 0.5H), 6.82-6.70 (m, 1.5H), 6.65 (d, J = 5.8 Hz, 0.5H), 6.56-6.49 (m, 1H), 4.54-4.13 (m, 6.5H), 3.69-3.39 (m, 2H), 3.26-3.04 (m, 1H), 2.83-2.72 (m, 1.5H), 2.31-2.15 (m, 3H), 1.49-1.12 (m, 8.5H), 0.99-0.78 (m, 3H), 0.69 (t, J = 7.3 Hz, 1H), 0.62 (t, J = 7.3 Hz, 0.5H) )</td>
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<td>132</td>
<td>( (1:1 \text{CD}_3\text{OD}:\text{CDCl}_3 \delta 8.60 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 8.10-7.84 (m, 5H), 7.65-7.50 (m, 3H), 7.46-6.68 (m, 11.5H), 6.60 (br s, 0.5H), 4.55-4.14 (m, 4.5H), 3.74-3.44 (m, 2H), 3.04-2.92 (m, 1H), 2.83-2.67 (m, 2.5H), 2.31-2.15 (m, 3H), 1.44-0.79 (m, 5.5H), 0.70 (t, J = 7.3 Hz, 1H), 0.63 (t, J = 7.3 Hz, 0.5H) )</td>
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<td>Ex. No.</td>
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<td>133</td>
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<td>(1:1 CD$_3$OD:CDC1$_3$) δ 8.62 (br s, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.08-7.79 (m, 4.5H), 7.66-7.51 (m, 3H), 7.42 (d, J = 7.9 Hz, 1H), 7.21-6.96 (m, 4H), 6.93-6.78 (m, 2H), 6.74-6.59 (m, 1.5H), 4.50-4.13 (m, 3H), 3.97-3.46 (m, 3.5H), 3.23-3.03 (m, 1H), 2.79-2.61 (m, 1.5H), 2.33-2.08 (m, 3H), 1.81-1.61 (m, 2H), 1.54-1.13 (m, 6H), 1.04-0.79 (m, 5H), 0.74-0.60 (m, 1H)</td>
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<td>134</td>
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<td>(1:1 CD$_3$OD:CDC1$_3$) δ 8.71 (s, 1H), 8.11-7.92 (m, 5H), 7.72-7.65 (m, 2H), 7.46 (br s, 1H), 7.35 (br s, 1H), 7.21-6.93 (m, 6H), 6.62 (br s, 1H), 4.72 (br s, 0.5H), 4.46 (br s, 0.5H), 4.33 (br s, 0.5H), 4.13 (br s, 0.5H), 3.92 (br s, 1H), 3.64 (br s, 1H), 3.48 (br s, 2H), 3.08 (br s, 0.5H), 2.95 (br s, 0.5H), 2.81 (br s, 1H), 2.12 (s, 3H), 1.45-1.21 (m, 4H), 0.92-0.82 (m, 3H)</td>
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<td>135</td>
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<td>(1:1 CD$_3$OD:CDC1$_3$) δ 8.70 (s, 1H), 8.08-7.97 (m, 4H), 7.96-7.87 (m, 2H), 7.69-7.58 (m, 2H), 7.52-7.45 (m, 1H), 7.26-7.01 (m, 6.5H), 6.95 (s, 0.5H), 6.90-6.81 (m, 1H), 4.72-4.19 (m, 3.5H), 3.97 (br s, 0.5H), 3.73-3.66 (m, 1H), 3.45 (d, J = 1.4 Hz, 2H), 3.25-3.00 (m, 1H), 2.78 (d, J = 5.5 Hz, 2H), 2.32-2.15 (m, 3H), 1.44-0.93 (m, 4H), 0.88-0.80 (m, 1.5H), 0.70 (t, J = 7.4 Hz, 1H), 0.64 (t, J = 7.4 Hz, 0.5H)</td>
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<td>136</td>
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<td>(1:1 CD$_3$OD:CDC1$_3$) δ 8.70 (s, 1H), 8.10-7.97 (m, 4H), 7.96-7.88 (m, 2H), 7.69-7.58 (m, 2H), 7.54-7.44 (m, 1H), 7.25-6.99 (m, 6.5H), 6.92 (dd, J = 3.6, 8.3 Hz, 1H), 6.84 (t, J = 6.7 Hz, 0.5H), 4.80 (br s, 1H), 4.50-4.17 (m, 2.5H), 3.99 (br s, 0.5H), 3.76-3.36 (m, 2.5H), 3.17 (br s, 1H), 2.81-2.65 (m, 2.5H), 2.33-2.16 (m, 3H), 1.47-0.93 (m, 3.5H), 0.84 (q, J = 7.5 Hz, 2H), 0.70 (t, J = 7.4 Hz, 1H), 0.65 (t, J = 7.4 Hz, 0.5H)</td>
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<td>137</td>
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<td>(1:1 CD$_3$OD:CDC1$_3$) δ 8.71 (s, 1H), 8.10-7.97 (m, 4H), 7.98-7.85 (m, 2H), 7.73-7.59 (m, 2H), 7.45-7.23 (m, 1H), 7.21-7.11 (m, 3.5H), 7.11-6.96 (m, 2.5H), 6.91-6.77 (m, 3H), 6.71 (d, J = 8.0 Hz, 1H), 6.59 (s, 2H), 4.23 (br s, 1H), 3.88 (br s, 2H), 3.60 (br s, 1H), 3.45 (dd, J = 3.3, 1.7 Hz, 1H), 3.08-2.97 (m, 1H), 2.91-2.73 (m, 2H), 2.17 (s, 2H), 2.07 (s, 1H), 1.50-1.17 (m, 4H), 0.96-0.78 (m, 3H)</td>
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<td>138</td>
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<td>(1:1 CD$_3$OD:CDC1$_3$) δ 8.62 (s, 1H), 8.17-7.85 (m, 6H), 7.63-7.50 (m, 2H), 7.35-7.21 (m, 2H), 7.17-7.09 (m, 4H), 6.94-6.81 (m, 3.5H), 6.78-6.70 (m, 2H), 6.63-6.51 (m, 1.5H), 4.28 (br s, 1H), 3.89 (br s, 2H), 3.65-3.40 (m, 2H), 3.08-2.95 (m, 1H), 2.92-2.76 (m, 2H), 2.20 (s, 2H), 2.05 (s, 1H), 1.50-1.19 (m, 4H), 0.91-0.79 (m, 3H)</td>
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<tr>
<td>Ex. No.</td>
<td>(^1^H) NMR (mixture of amide rotamers)</td>
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<tr>
<td>139</td>
<td>(1:1 CD(_2)OD:CDCl(_3)) δ 8.70 (s, 1H), 8.14-7.87 (m, 6H), 7.77-7.34 (m, 5.5H), 7.22-6.95 (m, 4.5H), 6.89-6.72 (m, 1H), 6.42-6.29 (m, 1H), 4.53-4.35 (m, 2H), 3.72 (s, 2H), 3.63-3.56 (m, 3H), 3.50-3.35 (m, 2H), 3.19-3.03 (m, 2H), 2.77-2.62 (m, 2H), 2.31 (s, 2H), 2.14 (s, 1H), 1.40-1.06 (m, 3H), 1.04-0.90 (m, 1H), 0.82-0.60 (m, 3H)</td>
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<td>140</td>
<td>(1:1 CD(_2)OD:CDCl(_3)) δ 8.64 (br s, 1H), 8.13-7.84 (m, 6H), 7.68-7.48 (m, 5H), 7.28-7.06 (m, 4.5H), 6.51-6.40 (m, 0.5H), 4.52-4.40 (m, 2H), 3.83-3.71 (m, 3H), 3.66 (br s, 3H), 3.63-3.50 (m, 2H), 3.17-3.13 (m, 2H), 2.89-2.75 (m, 2H), 2.08 (s, 1H), 2.06 (s, 2H), 1.48-1.38 (m, 2H), 1.35-1.27 (m, 2H), 0.95-0.74 (m, 3H)</td>
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<td>141</td>
<td>(1:1 CD(_2)OD:CDCl(_3)) δ 8.70 (br s, 1H), 8.12-7.82 (m, 6H), 7.79-7.57 (m, 2H), 7.26 (dd, J = 19.0, 8.3 Hz, 1H), 7.20-7.08 (m, 5H), 6.95-6.76 (m, 1H), 6.66-6.57 (m, 1H), 6.50 (d, J = 8.8 Hz, 1H), 4.71 (br s, 1H), 4.41 (br s, 1H), 4.25 (br s, 1H), 3.82 (br s, 2H), 3.73-3.61 (m, 1H), 3.50-3.39 (m, 1H), 2.08 (s, 2H), 2.06 (s, 1H), 2.81-2.69 (m, 2H), 1.50-1.25 (m, 4H), 1.28-1.13 (m, 6H), 0.92-0.79 (m, 3H)</td>
</tr>
<tr>
<td>142</td>
<td>(1:1 CD(_2)OD:CDCl(_3)) δ 8.65 (s, 1H), 8.16-7.84 (m, 8H), 7.70-7.48 (m, 4H), 7.26-6.85 (m, 4H), 4.78-4.51 (m, 2H), 4.34-3.90 (m, 2H), 3.76-3.41 (m, 2H), 2.94-2.75 (m, 2H), 2.21 (br s, 2H), 2.11 (br s, 4H), 1.45 - 1.33 (m, 2H), 1.29-1.19 (m, 2H), 0.95-0.68 (m, 3H)</td>
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<td>143</td>
<td>(1:1 CD(_2)OD:CDCl(_3)) δ 8.69 (s, 1H), 8.09-7.77 (m, 7H), 7.75-7.56 (m, 2H), 7.51-7.21 (m, 8H), 7.20-6.74 (m, 5H), 4.72 (br s, 1H), 4.22 (br s, 1H), 4.03 (br s, 1H), 3.89 (br s, 1H), 3.66-3.42 (m, 2H), 2.75 (br s, 2H), 2.10 (s, 1H), 2.07 (s, 2H), 1.55-1.39 (m, 2H), 1.35-1.17 (m, 2H), 0.95-0.76 (m, 3H)</td>
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<tr>
<td>144</td>
<td>(1:1 CD(_2)OD:CDCl(_3)) δ 8.66 (br s, 1H), 8.13-7.84 (m, 6H), 7.68-7.48 (m, 4H), 7.30-7.12 (m, 4H), 6.95-6.80 (m, 1H), 6.66 (d, J = 8.6 Hz, 1H), 6.53 (d, J = 8.6 Hz, 1H), 4.25 (br s, 1H), 4.07 (br s, 1H), 3.88-3.68 (m, 3H), 3.65-3.50 (m, 3H), 3.35 (br s, 1H), 3.01-2.70 (m, 2H), 2.10 (s, 1H), 2.07 (s, 2H), 1.52-1.16 (m, 4H), 0.95-0.74 (m, 3H)</td>
</tr>
<tr>
<td>145</td>
<td>(1:1 CD(_2)OD:CDCl(_3)) δ 8.65 (s, 1H), 8.15-7.85 (m, 6H), 7.69-7.49 (m, 4H), 7.32-7.06 (m, 4H), 7.04-6.79 (m, 1H), 6.65-6.25 (m, 2H), 4.34-4.05 (m, 2H), 3.84-3.67 (m, 4H), 3.68-3.57 (m, 3H), 2.93-2.72 (m, 2H), 2.09 (s, 1H), 2.08 (s, 2H), 1.51-1.14 (m, 4H), 0.96-0.72 (m, 3H)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>(^1)H NMR (mixture of amide rotamers)</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>146</td>
<td>((1:1 \text{ CD}_3\text{OD}:\text{CDCl}_3) \delta 8.63 (s, 1H), 8.10-7.85 (m, 5H), 7.68-7.47 (m, 5H), 7.34-6.88 (m, 6H), 6.70 (br s, 0.5H), 6.44 (br s, 0.5H), 4.50-4.16 (m, 2H), 3.98-3.75 (m, 2H), 3.43-3.23 (m, 2H), 2.83-2.75 (m, 2H), 2.05 (s, 1H), 2.04 (s, 2H), 1.55-1.25 (m, 4H), 1.23-1.05 (m, 9H), 0.90-0.75 (m, 3H))</td>
</tr>
<tr>
<td>147</td>
<td>((1:1 \text{ CD}_3\text{OD}:\text{CDCl}_3) \delta 8.62 (s, 1H), 8.16-7.82 (m, 6H), 7.66-7.51 (m, 5H), 7.44-7.20 (m, 6H), 7.17-6.65 (m, 5H), 4.19 (br s, 2H), 3.83 (br s, 2H), 3.55 (br s, 2H), 2.91-2.67 (m, 2H), 2.09 (s, 1H), 2.07 (s, 2H), 1.57-1.22 (m, 4H), 0.90-0.78 (m, 3H))</td>
</tr>
<tr>
<td>148</td>
<td>((1:1 \text{ CD}_3\text{OD}:\text{CDCl}_3) \delta 8.71-8.57 (m, 1H), 8.17-7.79 (m, 6H), 7.68-7.44 (m, 5H), 7.26-6.99 (m, 5H), 6.93-6.80 (m, 1H), 4.36-4.12 (m, 2H), 3.94-3.79 (m, 2H), 3.68-3.60 (m, 1H), 3.53-3.38 (m, 1H), 2.88-2.76 (m, 2H), 2.16-1.91 (m, 3H), 1.54-1.06 (m, 13H), 0.96-0.74 (m, 3H))</td>
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<tr>
<td>149</td>
<td>((\text{DMSO-d}_6) \delta 8.69 (s, 1H), 8.39-7.89 (m, 6H), 7.86-7.62 (m, 3H), 7.51 (br s, 1H), 7.28-7.09 (m, 4H), 6.75-6.13 (m, 2H), 4.44 (br s, 1H), 4.32-4.00 (m, 5H), 3.84-3.27 (m, 4H), 2.92-2.71 (m, 2H), 2.24-1.97 (br s, 3H), 1.38-1.02 (m, 4H), 0.96-0.56 (m, 3H))</td>
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<tr>
<td>150</td>
<td>((1:1 \text{ CD}_3\text{OD}:\text{CDCl}_3) \delta 8.69 (s, 1H), 8.13-7.80 (m, 6H), 7.74-7.53 (m, 3H), 7.35-7.06 (m, 4H), 7.01-6.76 (m, 2H), 6.66-6.21 (m, 2H), 4.79 (br s, 1H), 4.38 (br s, 2H), 3.88-3.61 (m, 2H), 3.53 (br s, 1H), 3.28-3.14 (m, 1H), 2.95-2.74 (m, 2H), 2.08 (br s, 3H), 1.54-1.10 (m, 10H), 0.95-0.76 (m, 3H))</td>
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<tr>
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<td>((1:1 \text{ CD}_3\text{OD}:\text{CDCl}_3) \delta 8.61 (d, J = 4.2 Hz, 1H), 8.22-8.10 (m, 1H), 8.08-7.82 (m, 5H), 7.82-7.51 (m, 5H), 7.50-7.27 (m, 5H), 7.19-6.72 (m, 4H), 4.57-4.42 (m, 2H), 4.29 (br s, 2H), 3.65-3.35 (m, 4H), 2.78-2.65 (m, 2H), 2.24 (s, 2H), 2.16 (s, 1H), 1.50-0.94 (m, 4H), 0.93-0.58 (m, 3H))</td>
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<td>152</td>
<td>((\text{CDCl}_3) \delta 9.25-9.05 (m, 2H), 8.50-8.40 (m, 1H), 8.36-8.20 (m, 1H), 7.96-7.74 (m, 3H), 7.65-7.55 (m, 1H), 7.40-6.81 (m, 14H), 4.30 (br s, 1H), 4.10 (br s, 1H), 3.97-3.76 (m, 2H), 3.53-3.35 (m, 1H), 3.28-3.16 (m, 1H), 2.83 (br s, 1H), 2.70-2.55 (m, 1H), 2.07 (s, 1H), 2.05 (br s, 2H), 1.55-1.22 (m, 4H), 0.95-0.77 (m, 3H))</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>$^1$H NMR (mixture of amide rotamers)</td>
</tr>
<tr>
<td>--------</td>
<td>-------------------------------------</td>
</tr>
<tr>
<td>153</td>
<td>(CDCl$_3$) $\delta$ 9.40-9.11 (m, 1H), 8.76 (d, $J = 3.1$ Hz, 1H), 8.11-7.76 (m, 5H), 7.74-7.54 (m, 2H), 7.44-6.80 (m, 13H), 4.28 (br s, 1H), 4.10 (br s, 1H), 3.87 (br s, 2H), 3.47 (br s, 1H), 3.26 (br s, 1H), 2.85-2.67 (m, 1H), 2.61 (br s, 1H), 2.06 (br s, 1H), 2.04 (br s, 2H), 1.76-1.43 (m, 3H), 1.42-1.16 (m, 1H), 0.93-0.70 (m, 3H)</td>
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<td>154</td>
<td>(1:1 CD$_3$OD:CDCl$_3$) $\delta$ 8.61 (s, 1H), 8.20-7.80 (m, 6H), 7.72 (d, $J = 8.1$ Hz, 1H), 7.61-7.48 (m, 3H), 7.22-7.08 (m, 5H), 6.98 (d, $J = 8.6$ Hz, 1H), 6.74 (br s, 1H), 4.39-4.09 (m, 2H), 3.98-3.77 (m, 5H), 3.50 (br s, 2H), 2.86-2.76 (m, 2H), 2.11 (s, 1H), 2.09 (s, 2H), 1.46-1.10 (m, 4H), 0.91-0.70 (m, 3H)</td>
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<td>155</td>
<td>(1:1 CD$_3$OD:CDCl$_3$) $\delta$ 8.61 (s, 1H), 8.20-7.80 (m, 6H), 7.72 (d, $J = 8.1$ Hz, 1H), 7.61-7.48 (m, 3H), 7.22-7.08 (m, 5H), 6.98 (d, $J = 8.6$ Hz, 1H), 6.74 (br s, 1H), 4.39-4.09 (m, 2H), 3.98-3.77 (m, 5H), 3.50 (br s, 2H), 2.86-2.76 (m, 2H), 2.11 (s, 1H), 2.09 (s, 2H), 1.46-1.10 (m, 4H), 0.91-0.70 (m, 3H)</td>
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<td>241</td>
<td>(DMSO-$d_6$) $\delta$ 8.74 (s, 1H), 8.31 (d, $J = 8$ Hz, 1H), 8.21 (d, $J = 8$ Hz, 1H), 8.15 (d, $J = 8$ Hz, 1H), 8.10-8.03 (m, 3H), 7.86-7.74 (m, 2H), 7.69-6.97 (m, 14H), 4.89-4.10 (m, 4H), 3.28-3.22 (m, 2H), 2.78-2.44 (m, 4H), 1.18-0.98 (m, 4H), 0.65-0.60 (m, 3H)</td>
</tr>
<tr>
<td>242</td>
<td>(1:1 CD$_3$OD:CDCl$_3$) $\delta$ 8.68 (s, 1H), 8.09-7.97 (m, 5H), 7.92 (d, $J = 8$ Hz, 1H), 7.65-7.58 (m, 2H), 7.37-6.96 (m, 12.5H), 6.89-6.88 (m, 0.5H), 4.53-4.23 (m, 4H), 3.38-3.15 (m, 2H), 2.81-2.47 (m, 4H), 1.06-0.87 (m, 4H), 0.56-0.54 (m, 3H)</td>
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<td>243</td>
<td>(CD$_3$OD) $\delta$ 8.73 (s, 1H), 8.12-7.98 (m, 6H), 7.73-7.66 (m, 2H), 7.63-6.94 (m, 13H), 4.62-4.18 (m, 4H), 3.65-3.17 (m, 2H), 2.79-2.45 (m, 4H), 1.31-0.91 (m, 4H), 0.65-0.58 (m, 3H)</td>
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<tr>
<td>244</td>
<td>(1:1 CD$_3$OD:CDCl$_3$) $\delta$ 8.73 (s, 1H), 8.23-8.03 (m, 4H), 7.96-7.91 (m, 2H), 7.70-7.62 (m, 2H), 7.45-6.80 (m, 9H), 4.50-4.22 (m, 4H), 4.03-4.00 (m, 2H), 3.28-3.17 (m, 2H), 2.83-2.40 (m, 4H), 1.83-1.76 (m, 2H), 1.56-1.49 (m, 2H), 1.02-0.87 (m, 7H), 0.55-0.52 (m, 3H)</td>
</tr>
<tr>
<td>Ex. No.</td>
<td>(^1^H) NMR (mixture of amide rotamers)</td>
</tr>
<tr>
<td>---------</td>
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</tr>
<tr>
<td>245</td>
<td>(CD(_2)OD) (\delta) 8.66 (s, 1H), 8.17-7.95 (m, 6H), 7.69-7.59 (m, 2H), 7.47-6.82 (m, 9H), 4.74-4.20 (m, 6H), 3.82-3.79 (m, 2H), 2.92-2.90 (m, 2H), 2.82-2.54 (m, 4H), 1.04-0.88 (m, 4H), 0.65-0.52 (m, 3H)</td>
</tr>
<tr>
<td>246</td>
<td>(CD(_2)OD) (\delta) 8.69 (s, 1H), 8.12-7.96 (m, 6H), 7.69-7.61 (m, 2H), 7.43-6.84 (m, 9H), 6.11-6.02 (m, 1H), 5.44-5.39 (m, 1H), 5.29-5.25 (m, 1H), 4.72-4.16 (m, 8H), 2.90-2.41 (m, 4H), 1.10-0.96 (m, 4H), 0.54-0.52 (m, 3H)</td>
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<td>247</td>
<td>(CD(_2)OD) (\delta) 8.67 (s, 1H), 8.12-7.97 (m, 6H), 7.81-7.61 (m, 7H), 7.48-7.37 (m, 4H), 7.25-7.04 (m, 4.5H), 6.94-6.93 (m, 0.5H), 4.75-4.22 (m, 6H), 2.90-2.42 (m, 4H), 1.21-0.89 (m, 4H), 0.58-0.54 (m, 3H)</td>
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<tr>
<td>248</td>
<td>(CD(_2)OD) (\delta) 9.10 (s, 1H), 8.21-8.14 (m, 2H), 8.05-7.97 (m, 3H), 7.81-7.78 (m, 1H), 7.68-7.64 (m, 1H), 7.51-7.38 (m, 3H), 7.22-7.01 (m, 9.5H), 6.82-6.81 (m, 0.5H), 4.51-3.47 (m, 6H), 2.81-2.48 (m, 4H), 1.17-0.89 (m, 7H), 0.62 (t, (J = 6) Hz, 3H)</td>
</tr>
<tr>
<td>249</td>
<td>(CD(_2)OD) (\delta) 8.18-8.17 (m, 1H), 8.13 (s, 1H), 7.57-7.39 (m, 4H), 7.22-7.02 (m, 8.5H), 6.86-6.85 (m, 0.5H), 4.56-3.58 (m, 6H), 3.42-3.40 (m, 2H), 2.81-2.48 (m, 4H), 1.42-1.38 (m, 3H), 1.19-1.04 (m, 7H), 0.64 (t, (J = 6) Hz, 3H)</td>
</tr>
<tr>
<td>250</td>
<td>(CD(_2)OD) (\delta) 8.18-8.17 (m, 1H), 8.13 (s, 1H), 7.50-7.49 (m, 4H), 7.22-7.02 (m, 8.5H), 6.85-6.84 (m, 0.5H), 4.56-3.80 (m, 6H), 3.41-3.40 (m, 2H), 2.79-2.53 (m, 4H), 1.90-1.85 (m, 2H), 1.51-1.36 (m, 4H), 1.19-1.03 (m, 7H), 0.94 (t, (J = 8) Hz, 3H), 0.65 (t, (J = 6) Hz, 3H)</td>
</tr>
<tr>
<td>251</td>
<td>(CDCl(_3)) (\delta) 9.15 (s, 1H), 8.48-8.35 (m, 2H), 7.92-7.84 (m, 2H), 7.49-6.77 (m, 16H), 4.90-4.80 (m, 0.5H), 4.55-4.45 (m, 0.5H), 4.36-3.95 (m, 3H), 3.52-3.32 (m, 2H), 2.80-2.49 (m, 4H), 1.33-0.87 (m, 7H), 0.60-0.56 (m, 3H)</td>
</tr>
<tr>
<td>252</td>
<td>(CD(_2)OD) (\delta) 8.19-7.98 (m, 6H), 7.80 (d, (J = 8) Hz, 1H), 7.66 (t, (J = 8) Hz, 1H), 7.57-7.37 (m, 2H), 7.23-6.87 (m, 11H), 4.61-4.21 (m, 4H), 3.62-3.19 (m, 2H), 2.84-2.55 (m, 4H), 1.20-0.91 (m, 4H), 0.62-0.57 (m, 3H)</td>
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<tr>
<td>253</td>
<td>(CD(_2)OD) (\delta) 8.14-8.02 (m, 2H), 7.43-7.39 (m, 2H), 7.24-7.00 (m, 10.5H), 6.92-6.91 (m, 0.5H), 4.78-4.10 (m, 6H), 3.57 (q, (J = 4) Hz, 2H), 2.87-2.50 (m, 4H), 1.40 (t, (J = 4) Hz, 3H), 1.14-0.92 (m, 4H), 0.65-0.60 (m, 3H)</td>
</tr>
</tbody>
</table>
BIOLOGICAL ASSAYS

[00765] The pharmacological properties of the compounds of this invention may be confirmed by a number of biological assays. The exemplified biological assays, which follow, have been carried out with compounds of the invention and/or salts thereof.

[00766] In general, compounds of the present invention inhibit at least one of the following pro-survival proteins: Bc1xl and/or Bcl-2.

**Bc1xl**/Bim Fluorescence Resonance Energy Transfer Assay (FRET)

[00767] The assays were performed in black flat-bottom 384-well plates. The final assay volume was 55 μL prepared from additions of Biotin-Bcl-xl (Bc1xl: GENBANK® Accession No. Q07817), fluoresceinated 18-mer BIM peptide (N³⁴-YYANFEDGIRLEQAIWI-[FAM]) (SEQ ID NO: 1), Streptavidin-Terbium FRET detection reagent, and test compounds in assay buffer consisting of 20 mM Sodium Phosphate, 1mM EDTA, 50 mM NaCl, and 0.05% Pluronic Acid. The reaction was incubated at room temperature for 60 minutes. After 60 minutes, 5 μL of Streptavidin-Terbium FRET detection reagent (Perkin Elmer) was added to the reaction mixture and incubated at room temperature in the dark for 30 mins. The FRET signal generated by the reaction was detected on the Envision Plate Reader. Inhibition data were calculated from FRET values generated by the no protein control reactions for 100% inhibition and vehicle-only reactions for 0% inhibition. The final concentration of reagents in the assay was 10 nM Bc1xl, 5 nM fluoresceinated 18-mer BIM peptide, 5 nM Streptavidin-

<table>
<thead>
<tr>
<th>Ex. No.</th>
<th>1H NMR (mixture of amide rotamers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>254</td>
<td>(CD3OD) δ 8.13-8.07 (m, 2H), 7.45-7.38 (m, 2H), 7.24-7.01 (m, 10.5H), 6.92-6.91 (m, 0.5H), 4.78-4.10 (m, 6H), 3.56 (q, J = 4 Hz, 2H), 2.90-2.50 (m, 4H), 1.91-1.84 (m, 2H), 1.51-1.46 (m, 2H), 1.43-1.38 (m, 2H), 1.13-1.02 (m, 4H), 0.94 (t, J = 4 Hz, 3H), 0.68-0.62 (m, 3H)</td>
</tr>
<tr>
<td>255</td>
<td>(1:1 CD3OD:CDCl3) δ 9.09 (s, 1H), 8.44 (d, J = 8 Hz, 1H), 8.31 (t, J = 8 Hz, 1H), 8.13-7.98 (m, 2H), 7.85 (d, J = 8 Hz, 1H), 7.61-7.56 (m, 2H), 7.41-7.31 (m, 2H), 7.20-6.82 (m, 10H), 4.61-4.16 (m, 4H), 3.38-3.15 (m, 2H), 2.86-2.49 (m, 4H), 1.07-0.85 (m, 4H), 0.60-0.53 (m, 3H)</td>
</tr>
</tbody>
</table>
Terbium FRET detection reagent, and 1% DMSO. Dose response curves were generated to determine the concentration required inhibiting 50% of kinase activity (IC$_{50}$).

Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at eleven concentrations. IC$_{50}$ values were derived by non-linear regression analysis.

**Bcl-2 / Bim Fluorescence Polarization Assay (FPA)**

The assays were performed in black flat-bottom 384-well plates. The final assay volume was 50 µl prepared from additions of Gst-Bcl-2 (Bcl-2: GENBANK® Accession No. P10415), fluoresceinated 18-mer BIM peptide (NH$_2$-YYANFEDGIRRLEQAIWI-[FAM]) (SEQ ID NO: 1), and test compounds in assay buffer consisting of 20 mM Sodium Phosphate, 1mM EDTA, 50 mM NaCl, and 0.05% Pluronic Acid. The reaction was incubated at room temperature for 60 minutes and fluorescence polarization of the reaction was detected on the LJL Plate Reader. Inhibition data were calculated from mP values generated by the no protein control reactions for 100% inhibition and vehicle-only reactions for 0% inhibition. The final concentrations of reagents in the assay were 4.9 nM BCL-2, 5 nM fluoresceinated 18-mer BIM peptide and 1% DMSO. Dose response curves were generated to determine the concentration required inhibiting 50% of kinase activity (IC$_{50}$). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at eleven concentrations. IC$_{50}$ values were derived by non-linear regression analysis.

Table 3 below lists the Bcl-2 IC$_{50}$ and Bcl-XL IC$_{50}$ values for the following examples of this invention measured in the assays described hereinabove. The compounds of the present invention, as exemplified by the following examples, showed Bcl-2 IC$_{50}$ and Bcl-XL values of less than 5 µM and 10 µM, respectively.

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Bcl-2 IC$_{50}$ Value (µM)</th>
<th>Bcl-XL IC$_{50}$ Value (µM)</th>
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<tr>
<td>2</td>
<td>0.20</td>
<td>0.03</td>
</tr>
<tr>
<td>5</td>
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<tr>
<td>Example No.</td>
<td>Bcl-2 IC&lt;sub&gt;50&lt;/sub&gt; Value (µM)</td>
<td>Bcl-x&lt;sub&gt;L&lt;/sub&gt; IC&lt;sub&gt;50&lt;/sub&gt; Value (µM)</td>
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<tr>
<td>------------</td>
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</tr>
<tr>
<td>7</td>
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<td>0.04</td>
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<tr>
<td>Example No.</td>
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<td>Bcl-x$<em>L$ IC$</em>{50}$ Value (µM)</td>
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What is claimed is:

1. A compound of Formula (I)

or a pharmaceutically acceptable salt thereof, wherein:

W is:

(a) naphthalenyl or isoquinolinyl, each substituted with zero to 3 substituents independently selected from -OH, -CN, halo, -N0₂, -C(0)OH, -C(0)O(C₁₋₄ alkyl), -S(0)₂(C₁₋₄ alkyl), -S(CH₂)₁₋₃C(0)OH, -S(CH₂)₁₋₃NH₂, d₋₄ alkoxy,

(b) each substituted with zero to 3 substituents independently selected from halo, C₁₋₄ alkyl, C(0)(C₁₋₄ alkyl), C(0)(CH₂)i₋₃Rx, -C(0)(CH₂)i₋₃S(phenyl), -C(0)(CH₂)i₋₃S(phenyl), C₂₋₄ alkenyl, and/or morpholinyl; or

Q is:
(c) Ci-6 alkyl or -(CH₂)₃(trimethylsilyl), provided that W is each Rₐ is independently C₃-6 cycloalkyl, phenyl, chlorophenyl, difluorophenyl, dichlorophenyl, benzoic acid, methyl benzoate, methylsulfonylphenyl, pyridinyl, chloropyridinyl, furanyl, pyrrolidinyl, piperidinyl, morpholinyl, (morpholinoethoxy)pyridinyl, N-methylpyrrolidinyl, N-methylpiperazinyl, N-methyl-IH-imidazolyl, 1-methyl-IH-indolyl, or N-(2-hydroxyethyl)piperazinyl;

G is:
(a) -N(C₁₋₄ alkyl)₂; or
(b) a bicyclic heterocyclyl selected from:

wherein said bicyclic heterocyclyl is substituted with zero to 3 substituents independently selected from: halo, C₁₋₄ alkyl, C₁₋₄ fluoroalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ alkoxy, -(CH₂)₀₋₃C(0)OH, -(CH₂)₁₋₃N(CH₃)₂, -(CH₂)₁₋₃N(CH₃)(C₁₋₄ hydroxyalkyl), -(CH₂)₁₋₃N(CH₃)((CH₂)₁₋₃OCH₃), -(CH₂)₁₋₃O(CH₂)₁₋₃N(C₁₋₄ alkyl)₂, -(CH₂)₁₋₃O(CH₂)₁₋₃OH, -(CH₂)₁₋₃O(CH₂)₁₋₃(C₁₋₄ alkyl), -(CH₂)₁₋₃O(CH₂)₁₋₃O(phenyl), -(CH₂)₁₋₃O(CH₂)₁₋₃CH₃, -(CH₂)₁₋₃Rₓ,
-(CH₂)₀₋₃N(CH₃)₂, -(CH₂)₀₋₃N(CH₃)((CH₂)₁₋₃O(C₁₋₄ alkyl),

R₁₆ is H, halo, Ci₋₆ alkyl, -CF₃, Ci₋₄ hydroxyalkyl, -(CH₂)₀₋₃O(CH₂)₁₋₃O(Ci₋₄ alkyl), -(CH₂)₀₋₃O(CH₂)₁₋₃O(Ci₋₄ hydroxyalkyl), -(CH₂)₀₋₃C(O)OH, -(CH₂)₀₋₃N(C₁₋₄ alkyl)₂, -(CH₂)₀₋₃C(O)NH(d₋₄ alkyl), -(CH₂)₁₋₃Rₓ, -(CH₂)₀₋₃C(O)NH₂, -(CH₂)₀₋₃C(O)NH(O)₂(C₃₋₆ cycloalkyl), -(CH₂)₁₋₃OC(O)(Rₓ), or -(CH₂)₀₋₃OC(O)NH(CH₂)₁₋₃Rₓ;

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R_{1b} is H, C_{i-4} alkyl, -CF_{3}, C_{i-4} hydroxyalkyl, -(CH_{2})_{1-3}0(C_{i-4} alkyl), -(CH_{2})_{1-3}0(C_{i-4} hydroxyalkyl), -(CH_{2})_{0-3}C(O)OH, -(CH_{2})_{0-3}N(d-4 alkyl)_{2}, -(CH_{2})_{0-3}C(O)NH(d-4 alkyl), -(CH_{2})_{1-3}Rx, -(CH_{2})_{0-3}OC(O)N_{2}(C_{i-6} cycloalkyl), -(CH_{2})_{1-3}OC(O)R_{x}, or -(CH_{2})_{0-3}OC(O)NH(CH_{2})_{1-3}R_{x};

5 R_{2} is:
(a) H, Cl, Br, d-3 hydroxyalkyl, -(CH_{2})_{0-3}C(O)OH, or -(CH_{2})_{0-3}N(CH_{3})_{2}; or
(b) phenyl substituted with zero to 2 substituents independently selected from d-4 alkyl, -(CH_{2})_{0-3}OH, -O(CH_{3})_{0-3}CH_{3}, -O(CH_{2})_{1-3}OH,
-0(CH_{2})_{1-3}CH(OH)(CH_{2})_{1-2}OH, -0(d-4 alkenyl), -OR_{x}, -C(0)0(d_4 alkyl), and/or phenyl;

10 R_{2a} is:
(a) H, Ci-3 hydroxyalkyl, -(CH_{2})_{0-3}C(O)OH, or -(CH_{2})_{0-3}N(CH_{3})_{2}; or
(b) phenyl substituted with zero to 2 substituents independently selected from d-4 alkyl, -(CH_{2})_{0-3}OH, -O(CH_{3})_{0-3}CH_{3}, -O(CH_{2})_{1-3}OH,
-0(CH_{2})_{1-2}CH(OH)(CH_{2})_{1-2}OH, -0(d-4 alkenyl), -OR_{x}, -C(0)0(d_4 alkyl), and/or phenyl;

15 one of R_{2b} and R_{2c} is H and the other of R_{3/4} and R_{2a} is R_{2};
R_{3} is -(CH_{2})_{1-3}OH, -C(0)OH, -C(0)0(C_{i-4} alkyl), -C(0)NR_{a}R_{b}, or -NR_{a}R_{b};
R_{4} is H, Ci-6 alkyl, or d-4 fluoroalkyl; and

20 R_{b} is
(a) Ci-6 alkyl, d-4 fluoroalkyl, -(CH_{2})_{i-3}C(0)OH, -(CH_{2})_{i-3}C(0)0(Ci-4 alkyl),
-(CH_{2})_{i-3}(d-6 cycloalkyl), -CH_{2}(naphthalenyl), -(CH_{2})_{1-3}0(0) NHOH(C_{i-4} hydroxyalkyl), -(CH_{2})_{1-3}0(0) NHOH(C_{i-4} hydroxyalkyl), or
-(CH_{2})_{1-3}C(0)NH(CH_{2})_{1-3}R_{x};

25 (b) -(CH_{2})_{1-2}(phenyl) wherein said phenyl is substituted with zero to 2 substituents independently selected from Cl, I, d-4 alkyl, d-4 alkoxy, -(CH_{2})_{0-3}C(O)OH,
-C(0)0(C_{i-4} alkyl), -(CH_{2})_{1-4}C(0)0(C_{i-4} alkyl), phenyl, halophenyl, halophenoxy, phenyl acetic acid, and/or -(CH_{2})_{i-3}C(0)R_{x}; or

(c) 

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or Rₐ and Rₕ together with the nitrogen atom to which they are attached, form a pyrrolidinyl ring substituted with zero to 1 substituent selected from C₄₋₉ alkyl or -(CH₂)₁₋₃(phenyl).

5 2. The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein:

Q is:

(a) naphthalenyl substituted with zero to 3 substituents independently selected from -OH, -CN, Cl, Br, I, -NO₂, -N(CH₃)₂, -C(0)OH, -C(0)OCH₂CH₃, -S(O)₂CH₂CH₃,

Cl-3 alkoxy, -OCH(CH₃)CH₂N(CH₃)₂, -O(CH₂)₃N(CH₃)₂, -OCH₂(phenyl),

-OCH₂(dichlorophenyl), -OCH₂(benzoic acid), -OCH₂(methyl benzoate),

-OCH₂(methylsulfonylphenyl), -OCH₂(furanyl),

-OCH₂(N-methyl-1H-imidazolyl), -O(CH₂)₂(N-methylpyrrolidinyl),

-0(CH₂)₂₂₃(morpholinyl), -0(CH₂)₂₃(pyrrolidinyl), -0(CH₂)₂₃(piperidinyl),

0(CH₂)₂₃(N-methylpiperazinyl), -0(CH₂)₂₃(pyridinyl), -OCH₂CH₂OH,

-OCH₂CH₂O(C₆H₅ alky), -OCH₂CH₂O(phenyl), -C(0)N(CH₃)₂,

-C(0)(N-methylpiperazinyl), -C(0)(morpholinyl), and/or

-NHC(0)(dichlorophenyl);

(b) isoquinolinyl substituted with -OCH₂CH₂(morpholinyl), -SCH₂CH₂NH₂, or

20 -SCH₂(C(0)OH;

(c) H, H, or or each substituted with zero to 3 substituents independently selected from Cl, Br, I, -CH₂CH₃, -CH₂(cyclohexyl),

-CH₂(phenyl), -CH₂(difluorophenyl), -(CH₂)₁₋₂(dichlorophenyl),

-CH₂(chloropyrimidinyl), -CH₂(1-methyl-1H-indolyl), -(CH₂)₁₋₃(morpholinyl),

25 -C(0)(cyclohexyl), -C(0)(dichlorophenyl), -C(0)(morpholinyl),

-C(0)((morpholinooethoxy)pyridinyl), -C(0)OCH₃, -C(0)CH₂(2)(dichlorophenyl),

-C(0)(CH₂)₁₋₂(morpholinyl), -C(0)CH₂S(phenyl), -CH₂CH₂S(phenyl),

-CH=CHCH₃, -CH=CHCH₂CH₃, and/or morpholinyl; or
ethyl, pentyl, or -CH₂CH₂(trimethylsilyl)), provided that W is
G is:
(a) -N(CH₃)₂; or
(b) a bicyclic heterocyclyl selected from:

![Chemical structures]

wherein said bicyclic heterocyclyl is substituted with zero to 2 substituents independently selected from: Br, -CH₃, -CF₃, -CH₂OH, -CH₂NH₂, -CH₂N₃,
-CH₂N(CH₃)(CH₂CH₂OH), -CH₂N(CH₃)(CH₂CH₂OCH₃),
-CH₂OCH₂CH₂N(CH₃)₂, -CH₂OCH₂CH₂OH, -CH₂OCH₂CH₂O(phenyl),
-CH₂OCH₂CH₂CH₂OCH₃, -CH₂(pyrrolidinyl), -CH₂(N-methyl piperazinyl),
-CH₂/N-(2-hydroxyethyl)piperazinyl), -CH₂(morpholinyl), -OCH₃, -C(O)OH,
-(CH₂)₁⁻⁴N(CH₃)₂, -N(CH₃)(CH₂CH₂OCH₃).

R₁ᵦ is H, Cl, Br, -CH₃, butyl, -CF₃, -(CH₂)₂OH, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OH,
-CH₂C(0)OH, -(CH₂)₂N(CH₃)₂, -CH₂C(0)NHCH₃, -(CH₂)₁⁻³(phenyl),
-(CH₂)₁⁻⁴(morpholinyl), -(CH₂)₁⁻⁴(N-methyl piperazinyl), -(CH₂)₂O(0)NH₂,
-CH₂C(0)NHS(0) (cyclopropyl), -(CH₂)₂OC(0)₁⁻⁴N-methyl piperazinyl), or
-(CH₂)₂OC(0)NH(CH₂)₂(N-methyl piperazinyl);

Rᵦb is H, -CH₃, butyl, -CF₃, -(CH₂)₂OH, -CH₂CH₂OCH₃, -CH₂CH₂OCH₂CH₂OH,
-CH₂C(0)OH, -(CH₂)₂N(CH₃)₂, -CH₂C(0)NHCH₃, -(CH₂)₁⁻³(phenyl),
-(CH₂)₁⁻⁴(morpholinyl), -(CH₂)₁⁻⁴(N-methyl piperazinyl), -(CH₂)₂OC(0)NH₂.
-CH₂C(0)NHS(0)₂(cyclopropyl), -(CH₂)₂OC(0)⁻N(-methyl piperazinyl), or
-(CH₂)₂OC(0)NH(CH₂)₂(N-methyl piperazinyl);

R₂ is:
(a) H, Cl, Br, C₁₋₃ hydroxyalkyl, -(CH₂)₂C(0)OH, or -(CH₂)₃N(CH₃)₂; or
(b) phenyl substituted with zero to 1 substituent selected from propyl, -(CH₂)₀₋₂OH,
-0(CH₃)₀₋₂CH₃, -0(CH₂)₂OH, -OCH₂CH(OH)CH₂OH, -C(0)OH,
-OCH₂CH=CH₂, -O(phenyl), -O(chlorophenyl), -C(0)OCH₃, or phenyl;

R₂a is:
(a) H, C₁₋₃ hydroxyalkyl, -(CH₂)₂C(0)OH, or -(CH₂)₃N(CH₃)₂; or
(b) phenyl substituted with zero to 1 substituent selected from propyl, -(CH₂)₀₋₂OH,
-0(CH₃)₀₋₂CH₃, -0(CH₂)₂OH, -OCH₂CH(OH)CH₂OH, -C(0)OH,
-OCH₂CH=CH₂, -O(phenyl), -O(chlorophenyl), -C(0)OCH₃, or phenyl;

R₂b is:
(a) C₁₋₅ alkyl, C₁₋₄ fluoroalkyl, -(CH₂)₂C(0)OH, -(CH₂)₃C(0)(butyl),
-CH₂(cyclopropyl), -CH₂(naphthalenyl), -(CH₂)₂C(0)NHCH(Cl₋₂ hydroxyalkyl)₂, 
-(CH₂)₂C(0)NHCH(CH₂OH)₃, or -(CH₂)₂C(0)NHCH₂(N-methyl piperazinyl);
(b) -(CH₂)₀₋₂(phenyl) wherein said phenyl is substituted with zero to 2 substituents
independently selected from Cl, I, C₁₋₄ alkyl, C₁₋₄ alkoxy, -(CH₂)₀₋₂C(O)OH,
-C(0)OCH₃, -CH₂C(O)OCH₂CH₃, phenyl, chlorophenyl, fluorophenoxy,
chlorophenoxy, phenyl acetic acid, and/or -(CH₂)₂C(0)(piperidinyl carboxylic acid); or

(c) or R₂ and Rb together with the nitrogen atom to which they are attached, form a
pyrrolidinyl ring substituted with zero to 1 substituent selected from propyl or
-CH₂CH₂(phenyl).

3. The compound according to any one of claims 1 to 2 or a pharmaceutically
acceptable salt thereof, wherein:
W is:

4. The compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein:

\[ R_2 R_3 N \]

W is:

4. The compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein:

\[ R_2 R_3 N \]

W is:

Q is

(a) naphthalenyl substituted with zero to 3 substituents independently selected from

- OH, -CN, Cl, Br, I, -NO_2, -N(CH_3)_2, -C(0)OH, -C(0)OCH_2CH_3, -S(0)_2CH_2CH_3,

C_1-3 alkoxy, -OCH(CH_3)_2N(CH_3)_2, -0(CH_2)3N(CH_3)_2, -OCH_2(phenyl),

-OCH_2(dichlorophenyl), -OCH_2(benzoic acid), -OCH_2(methyl benzoate),

-OCH_2(methylsulfonylphenyl), -OCH_2(furanyl),

-OCH_2(N-methyl-1H-imidazolyl), -0(CH_2)3(N-methylpyrroldinyl),

-0(CH_2)2(morpholinyl), -0(CH_2)3(pyrrolidinyl), -0(CH_2)3(piperidinyl),

0(CH_2)5(N-methyl piperazinyl), -0(CH_2)3(pyridinyl), -0(CH_2)2OH,

-0(CH_2)2O(Ci-2 alkyl), -0(CH_2)2O(phenyl), -C(0)N(CH_3)_2,

-C(0)(N-methylpipperazine), -C(0)(morpholinyl), and/or

-NHC(0)(dichlorophenyl);

(b) isoquinolinyl substituted with -OCH_2CH_2(morpholinyl), -SCH_2CH_2NH_2, or

-SCH_2C(0)OH; or

(c) each substituted with zero to 3 substituents independently selected from Cl, Br, I, -CH_2CH_3, -CH_2(cyclohexyl),

-CH_2(phenyl), -CH_2(difluorophenyl), -(CH_2)2-2(dichlorophenyl),

-CH_2(chloropyridinyl), -CH_2(1-methyl-1H-indolyl), -(CH_2)i-2(morpholinyl),

-C(0)(cyclohexyl), -C(0)(dichlorophenyl), -C(0)(morpholinyl),

-C(0)((morpholinoethoxy)pyridinyl), -C(0)OCH_3, -C(0)CH_2(dichlorophenyl),

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-C(0)(CH₂)₂(S(morpholinyl)), -C(0)CH₂S(phenyl), -CH₂CH₂S(phenyl),
-CH=CHCH₃, -CH=CHCH₂CH₃, and/or morpholinyl;

G is a bicyclic heterocyclyl selected from:

wherein said bicyclic heterocyclyl is substituted with zero to 2 substituents independently selected from: Br, -CH₃, -CF₃, -CH₂OH, -CH₂NH₂, -CH₂N(CH₃)(CH₂CH₂OH),
-CH₂N(CH₃)(CH₂CH₂OCH₃), -CH₂OCH₂CH₂N(CH₃)₂, -CH₂0(CH₂)₂OH,
-CH₂0(CH₂)₂0(phenyl), -CH₂0(CH₂)₃OCH₃, -CH₂(pyrrolidinyl), -CH₂(N-methyl piperazinyl), -CH₂(N-(2-hydroxyethyl)piperazinyl), -CH₂(morpholinyl), -OCH₃,
-C(0)OH, -(CH₂)₀₋₁N(CH₃)₂, -N(CH₃)(CH₂CH₂OCH₃),

R₁ is H, -CH₃, -CF₃, -(CH₂)₂OH, -CH₂C(0)OH, -(CH₂)₂OC(0)NH₂,
-(CH₂)₂OC(0)NHS(0)₂(cyclopropyl), -(CH₂)₂OC(0)N-(N-methyl piperazinyl), or
-(CH₂)₂OC(0)NHCH(CH₂)₂;

R₂ is H, Cl, Br, Ci₋₄ hydroxyalkyl, -(CH₂)₃C(0)OH, -(CH₂)₃N(CH₃)₂, or benzoic acid;

R₃ is -N(C₃₋₄alkyl)₂ or -C(0)NRₐRₖ;

Rₐ is H, Ci₋₄ alkyl, or C₃₋₄ fluoroalkyl; and

Rₖ is:

(a) Ci₋₄ alkyl, C₃₋₄ fluoroalkyl, -(CH₂)₂C(0)OH, -(CH₂)₂C(0)(butyl),
-CH₂(naphthalenyl), -(CH₂)₂C(0)NHCH(CH₂)OH₂, -(CH₂)₂C(0)NHC(CH₂)OH₃,
or -(CH₂)₂C(0)NHCH₂CH₂(N-methyl piperazinyl);

(b) -(CH₂)₀₋₂(phenyl) wherein said phenyl is substituted with zero to 2 substituents independently selected from Cl, I, Ci₋₄ alkyl, Ci₋₄ alkoxy, -C(0)OH,

-CH₂(0)OCH₃, -CH₂C(0)OCH₂CH₃, phenyl, chlorophenyl,
fluorophenoxy, chlorophenoxy, phenyl acetic acid, and/or
-(CH₂)₂C(0)(piperidinyl carboxylic acid); or

5. The compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein:

- W is ethyl, pentyl, -(CH₂)₂(trimethylsilyl), or naphthalenyl substituted zero to 2 substituents independently selected from CI and/or Br;

- Q is ethyl, pentyl, -(CH₂)₂(trimethylsilyl), or naphthalenyl substituted zero to 1 substituent selected from -CH₂OH, -CH₂NH₂, or -CH₂N₃;

- R₁a is -CH₃ or butyl;

- R₂a is phenyl substituted with zero to 1 substituent selected from propyl, -OH, -(CH₂)₂OH, -OCH₃, -0(CH₂)₂CH₃, -0(CH₂)₃OH, -OCH₂CH(OH)CH₂OH, -OCH₂CH=CH₂, -O(phenyl), -O(chlorophenyl), C(0)OCH₃, and phenyl; and

- R₃ is -CH₂OH, -C(0)OH, or -C(0)OCH₂CH₃.

6. The compound according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein:

- W is ethyl, pentyl, -(CH₂)₂(trimethylsilyl), or naphthalenyl substituted zero to 1 substituent selected from CI or I.
G is substituted with zero to 1 substituent selected from -CH₂OH or
  -CH₂NH₂;
Rib is H, -CH₃, -(CH₂)₂OH, -(CH₂)i,₂ (phenyl), -(CH₂)₂,₃ (morpholinyl),-
  (CH₂)₂,₃(N-methyl piperazinyl), -(CH₂)₂OCH₃, -(CH₂)₂,₀(CH₂)₂OH,
  -(CH₂)₃N(CH₃)₂, -CH₂C(0)OH, or -CH₂C(0)NHCH₃;
R₂ is H; and
R₃ is -C(0)N(n-butyl)₂.

7. The compound according to any one of claims 1 to 3 or a pharmaceutically
acceptable salt thereof, wherein:

W is ;

Q is naphthalenyl substituted Cl or 1;

R₂ is H; and
R₃ is -C(0)N(n-butyl)₂.

8. The compound according to any one of claims 1 to 2 or a pharmaceutically
acceptable salt thereof, wherein:

W is ,

Q is:
(a) naphthalenyl substituted with zero to 1 substituent selected from Cl; or
substituted with zero to 1 substituent selected from
-CH₂(dichlorophenyl);

\[ \text{G is} \]

\[ \text{R}_1 \text{a is H or Br;} \]
\[ \text{R}_2 \text{b is H;} \]
\[ \text{R}_2 \text{c is H;} \]
\[ \text{R}_3 \text{ is } -\text{N(n-butyl)}_2 \text{ or } -\text{C(\theta )N(n-butyl)}_2. \]

9. The compound according to any one of claims 1 to 2 or a pharmaceutically acceptable salt thereof, wherein:

\[ \text{W is} \]

\[ \text{Q is:} \]
\[ \text{(a)} \text{ naphthalenyl substituted with zero to 1 substituent selected from } \text{Cl or I;} \text{ or} \]

\[ \text{(b)} \text{ substituted with zero to 1 substituent selected from } -\text{CH}_2\text{CH}_3 \text{ or} \]

\[ -\text{CH}_2(\text{dichlorophenyl}); \]

\[ \text{G is:} \]
\[ \text{(a)} -\text{N(CH)}_2; \]
\[ \text{(b)} \text{ substituted with zero to 1 substituent selected from } -\text{CF}_3, \]

\[ -\text{CH}_2\text{OH, or } -\text{CH}_2\text{NH}_2; \text{ or} \]
R\textsubscript{ia} is H, Cl, Br, -CH\textsubscript{3}, or -C(0)OCH\textsubscript{2}CH\textsubscript{3};
R\textsubscript{2} is H;
R\textsubscript{3} is -NR\textsubscript{a}R\textsubscript{b};
R\textsubscript{a} is C\textsubscript{2}-5 alkyl; and
R\textsubscript{b} is C\textsubscript{2}-5 alkyl, -CH\textsubscript{2}(cyclopropyl), or -CH\textsubscript{2}(dichlorophenyl);
or R\textsubscript{a} and R\textsubscript{b} together with the nitrogen atom to which they are attached, form a
pyrrolidinyl ring substituted with zero to 1 substituent selected from propyl or
-CH\textsubscript{2}CH\textsubscript{2}(phenyl).

10. A pharmaceutical composition, comprising: a pharmaceutically acceptable
carrier and a compound of any one of claims 1 to 9 or pharmaceutically acceptable salts thereof.

11. Use of a compound of any one of claims 1 to 9 or pharmaceutically acceptable salts thereof, in the manufacture of a medicament for treatment of cancer.

12. A compound of any one of claims 1 to 9 or pharmaceutically acceptable salts thereof, for use in therapy in treating cancer.
A. CLASSIFICATION OF SUBJECT MATTER

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B. MINIMUM DOCUMENTATION SEARCHED

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2008/024337 A2 (INFINITY DISCOVERY INC [US]; CASTRO ALFREDO C [US]; DEPEW KRISTOPHER M) 28 February 2008 (2008-02-28) page 1, line 24 - page 1, line 28; claims; examples</td>
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Further documents are listed in the continuation of Box C. X See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search: 5 July 2012

Date of mailing of the international search report: 18/07/2012

Name and mailing address of the ISA/Authorized officer:

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Schmid, Arnold
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