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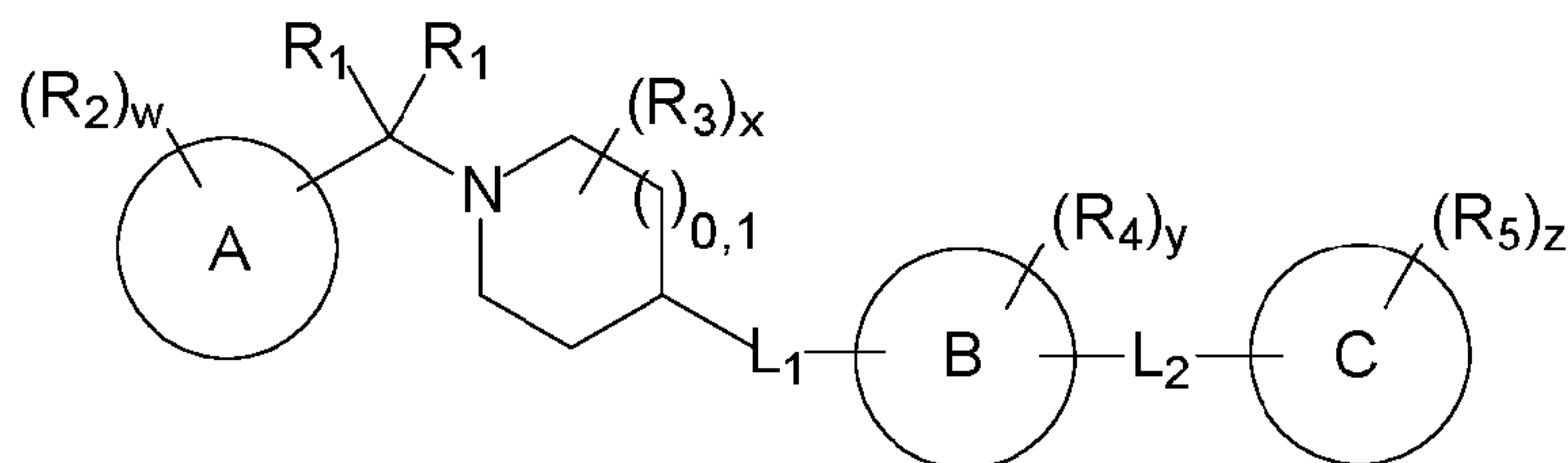
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(54) Titre : DERIVES DE N-[2-(1-BENZYLPIPERIDIN-4-YL)ETHYL]-4-(PYRAZIN-2-YL)-PIPERAZINE-1-CARBOXAMIDE
ET COMPOSES APPARENTES EN TANT QU'ANTAGONISTES DU RECEPTEUR MUSCARINIQUE 4 (M4) POUR
LE TRAITEMENT DE MALADIES NEUROLOGIQUES
(54) Title: N-[2-(1-BENZYLPIPERIDIN-4-YL)ETHYL]-4-(PYRAZIN-2-YL)-PIPERAZINE-1-CARBOXAMIDE DERIVATIVES
AND RELATED COMPOUNDS AS MUSCARINIC RECEPTOR 4 (M4) ANTAGONISTS FOR TREATING
NEUROLOGICAL DISEASES



(I)

(57) Abrégé/Abstract:

Provided herein are small molecule compounds of the following formula (I): or a stereoisomer, tautomer, solvate, ester or pharmaceutically acceptable salt thereof, wherein A, B, C, Li, L 2, Ri, R 2, R 3, R 4, R 5, w, x, y and z are as defined herein. Methods for treating diseases/ disorders by antagonizing muscarinic receptors, including specifically antagonizing muscarinic receptor 4 (M4), are also disclosed. Such diseases/disorders are e.g. neurological diseases/disorders such as e.g. Alzheimer's Disease, Lewy Body Dementia and the cognitive deficits associated with schizophrenia, Parkinson's Disease, drug induced Parkinsonism, dyskinesias, dystonia, chorea, levodopa induced dyskinesia, cerebral palsy, progressive supranuclear palsy, and Huntington's disease. Preferred compounds are e.g. N-[2-(1-benzylpiperidin-4-yl)ethyl]-4- (pyrazin-2-yl)-piperazine-1-carboxamide derivatives and related compounds wherein the pyrazine has been replaced by e.g. pyridazine, pyrimidine, pyridine or phenyl.

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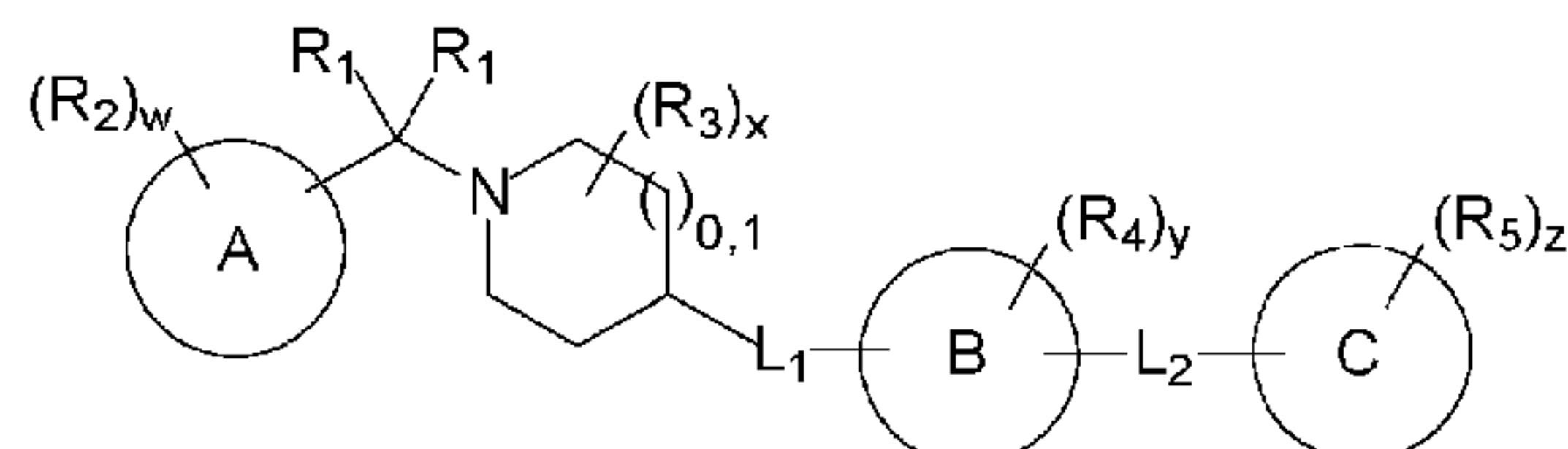
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(54) Title: N-[2-(1-BENZYLPIPERIDIN-4-YL)ETHYL]-4-(PYRAZIN-2-YL)-PIPERAZINE-1-CARBOXAMIDE DERIVATIVES AND RELATED COMPOUNDS AS MUSCARINIC RECEPTOR 4 (M4) ANTAGONISTS FOR TREATING NEUROLOGICAL DISEASES



(I)

(57) Abstract: Provided herein are small molecule compounds of the following formula (I): or a stereoisomer, tautomer, solvate, ester or pharmaceutically acceptable salt thereof, wherein A, B, C, L₁, L₂, R₁, R₂, R₃, R₄, R₅, w, x, y and z are as defined herein. Methods for treating diseases/ disorders by antagonizing muscarinic receptors, including specifically antagonizing muscarinic receptor 4 (M4), are also disclosed. Such diseases/disorders are e.g. neurological diseases/disorders such as e.g. Alzheimer's Disease, Lewy Body Dementia and the cognitive deficits associated with schizophrenia, Parkinson's Disease, drug induced Parkinsonism, dyskinesias, dystonia, chorea, levodopa induced dyskinesia, cerebral palsy, progressive supranuclear palsy, and Huntington's disease. Preferred compounds are e.g. N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(pyrazin-2-yl)-piperazine-1-carboxamide derivatives and related compounds wherein the pyrazine has been replaced by e.g. pyridazine, pyrimidine, pyridine or phenyl.



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N-[2-(1-BENZYLPIPERIDIN-4-YL)ETHYL]-4-(PYRAZIN-2-YL)-PIPERAZINE-1-CARBOXAMIDE DERIVATIVES AND RELATED COMPOUNDS AS MUSCARINIC RECEPTOR 4 (M4) ANTAGONISTS FOR TREATING NEUROLOGICAL DISEASES

BACKGROUND

Technical Field

Compounds are provided herein that selectively antagonize muscarinic
5 receptors, in particular muscarinic receptor 4 (M4), as well as methods for treating diseases and/or disorders that would benefit from the same.

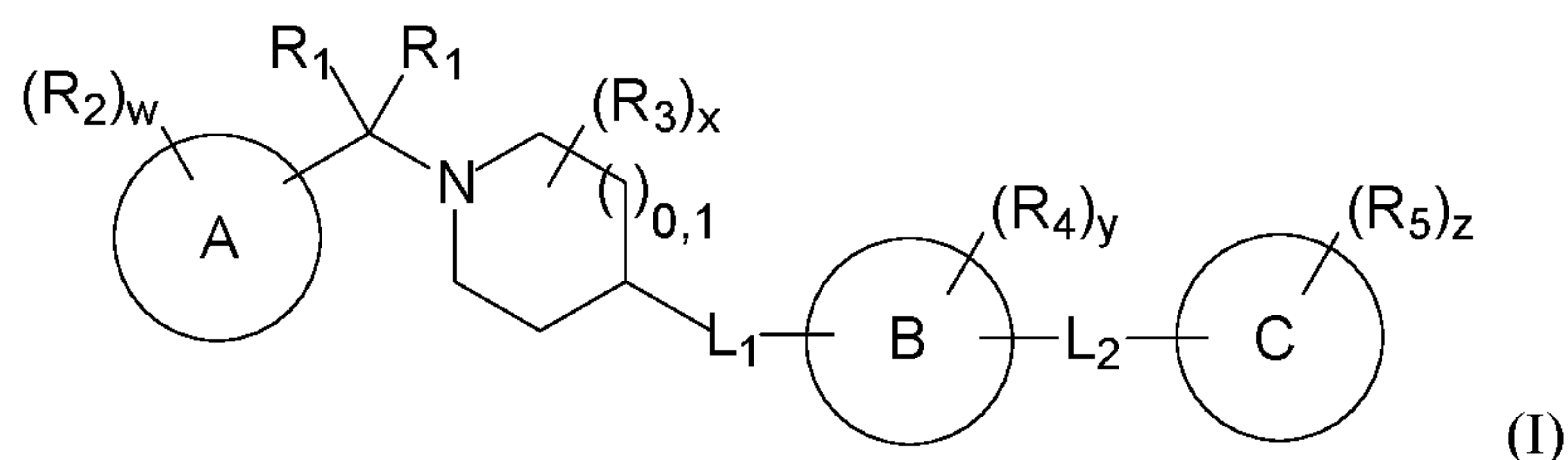
Description of the Related Art

Muscarinic acetylcholine receptors are autonomic receptors that form G protein-receptor complexes in the cell membranes of certain neurons and other cell
10 types (*e.g.*, endothelial cells of blood vessels). Muscarinic receptors are located postsynaptically at the parasympathetic neuroeffector junction, from where the receptors function to increase or decrease the activity of the effector cells. Extrapyrimal symptoms are observed in patients treated with antipsychotic therapeutics and in patients who have neuroleptic malignant syndrome, brain damage
15 (*e.g.*, athetotic cerebral palsy), encephalitis, and meningitis. Drugs other than antipsychotics also cause extrapyramidal symptoms, for example antidopaminergic drugs (*e.g.*, the antiemetic metoclopramide and the antidepressant amoxapine) and selective serotonin reuptake inhibitors (SSR*), which indirectly decrease dopamine. Conditions associated with extrapyramidal symptoms include acute dystonic reactions,
20 akathisia, pseudoparkinsonism, and tardive dyskinesia. Extrapyrimal symptoms caused by antipsychotic therapeutics are being treated with anticholinergic drugs that lack selectivity for any of the five muscarinic receptor subtypes (*see, e.g.*, Erosa-Rivero et al., *Neuropharmacology* 81:176-87 (2014)). Because anticholinergic drugs that effect multiple muscarinic receptors may cause distinct and in certain instances
25 opposing effects, therapeutics that exhibit selectivity for particular receptors are desired.

BRIEF SUMMARY

Provided herein are compounds that antagonize muscarinic receptors. In particular embodiments, compounds are provided that selectively antagonize muscarinic receptor 4 (M4). Such compounds are useful in the treatment of a number of diseases and/or disorders, particularly neurological conditions, diseases, and disorders including cognitive disorders such as Alzheimer's Disease, Lewy Body Dementia and the cognitive deficits associated with schizophrenia. In other embodiments, methods are provided for treating or preventing movement disorders which may include Parkinson's Disease, drug induced Parkinsonism, dyskinesias, dystonia, chorea, levodopa induced dyskinesia, cerebral palsy and progressive supranuclear palsy, and Huntington's disease, particularly chorea associated with Huntington's disease.

In one embodiment, compounds are provided having the structure of formula (I):



or a stereoisomer, tautomer, solvate, ester, prodrug, or pharmaceutically acceptable salt thereof, wherein A, B, C, L₁, L₂, R₁, R₂, R₃, R₄, R₅, w, x, y and z are as defined below. More specific embodiments are also described within Tables 1-14, as well as the more specific formulas noted herein below.

In another embodiment, pharmaceutical compositions are provided comprising a compound of formula (I), including one or more of the specific compounds described herein, and at least one pharmaceutically acceptable excipient. The compounds, as well as the pharmaceutical compositions comprising the compounds, may be used for antagonizing a muscarinic receptor, such as muscarinic receptor 4 (M4). In certain embodiments, the compound is a selective M4 antagonist.

These and other embodiments will be apparent upon reference to the following detailed description. To this end, various references are set forth herein that describe in more detail certain background information, procedures, compounds and compositions, and are each hereby incorporated by reference in their entirety.

5 DETAILED DESCRIPTION

In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to
10 avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising,” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” In addition, the term “comprising” (and related terms such as “comprise” or “comprises”
15 or “having” or “including”) is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may “consist of” or “consist essentially of” the described features. Headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed embodiments.

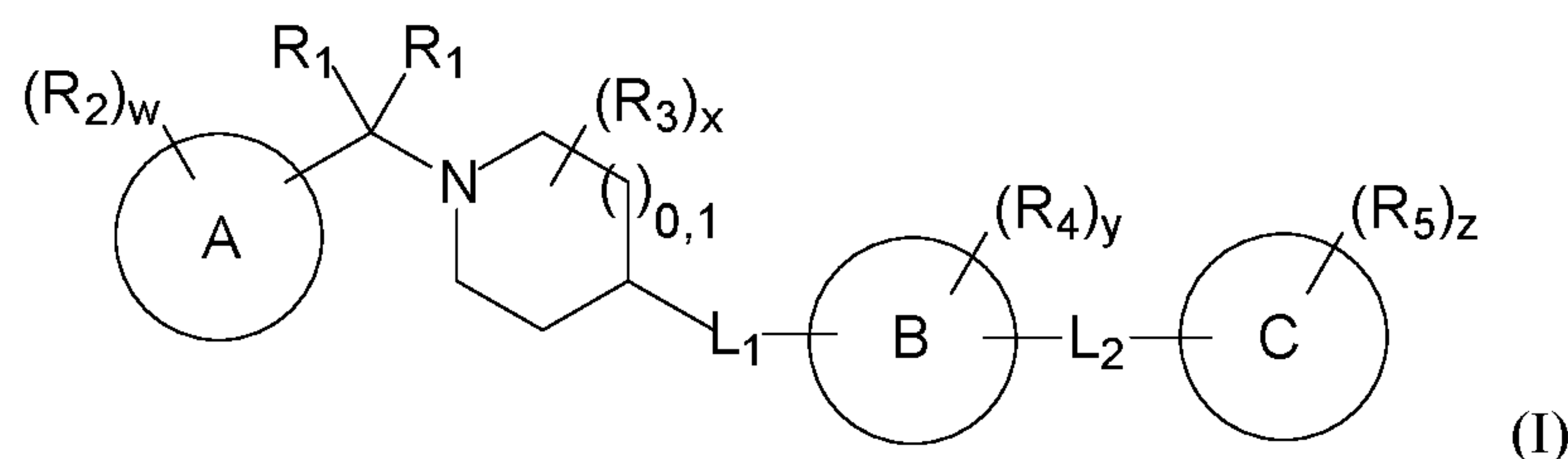
20 Reference throughout this specification to “one embodiment” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an embodiment” in various places throughout this specification are not necessarily all referring to the same
25 embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

Also, as used in this specification and the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the content clearly dictates otherwise. Thus, for example, reference to “a non-human animal” may refer to one or

more non-human animals, or a plurality of such animals, and reference to “a cell” or “the cell” includes reference to one or more cells and equivalents thereof (*e.g.*, plurality of cells) known to those skilled in the art, and so forth. When steps of a method are described or claimed, and the steps are described as occurring in a particular order, the description of a first step occurring (or being performed) “prior to” (*i.e.*, before) a second step has the same meaning if rewritten to state that the second step occurs (or is performed) “subsequent” to the first step. The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated number or numerical range. It should also be noted that the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise. The term, “at least one,” for example, when referring to at least one compound or to at least one composition, has the same meaning and understanding as the term, “one or more.”

Provided herein are compounds useful for treating diseases and/or disorders treatable by antagonizing one or more muscarinic receptors. In particular embodiments, compounds are provided that are selective for muscarinic receptor 4 (M4) (also referred herein as the M4 receptor).

Provided herein are compounds having a structure of the following formula (I):



or a stereoisomer, tautomer, solvate, ester, prodrug, or pharmaceutically acceptable salt thereof, wherein:

- A, B and C are each independently a carbocycle or heterocycle;
 R_1 is, at each occurrence, H, C_{1-4} alkyl, $C(=O)OC_{1-4}$ alkyl or aryl;

R_2 , R_3 , R_4 and R_5 are each independently -OH, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -C≡N, -C(=O)NH₂, halo, C₁₋₄alkyl, C₁₋₄alkylOH, C₁₋₄haloalkyl, C₁₋₄alkoxy or C₁₋₄haloalkoxy;

w, x, y and z are each independently 0, 1, 2 or 3;

5 L_1 is a heteroalkylene linker having at least one N, O or S heteroatom, and wherein the heteroalkylene may be a straight chain or cyclized and optionally substituted with oxo, -OH, C₁₋₄alkyl or C₁₋₄alkoxy; and

L_2 is an optional linker that is not present or, when present, is -O(CH₂)_m- where m is 0 or 1.

10 In one embodiment of formula (I), R_1 is H at both occurrences.

In one embodiment of formula (I), one R_1 is H and the other R_1 is methyl.

In one embodiment of formula (I), R_1 is methyl at both occurrences.

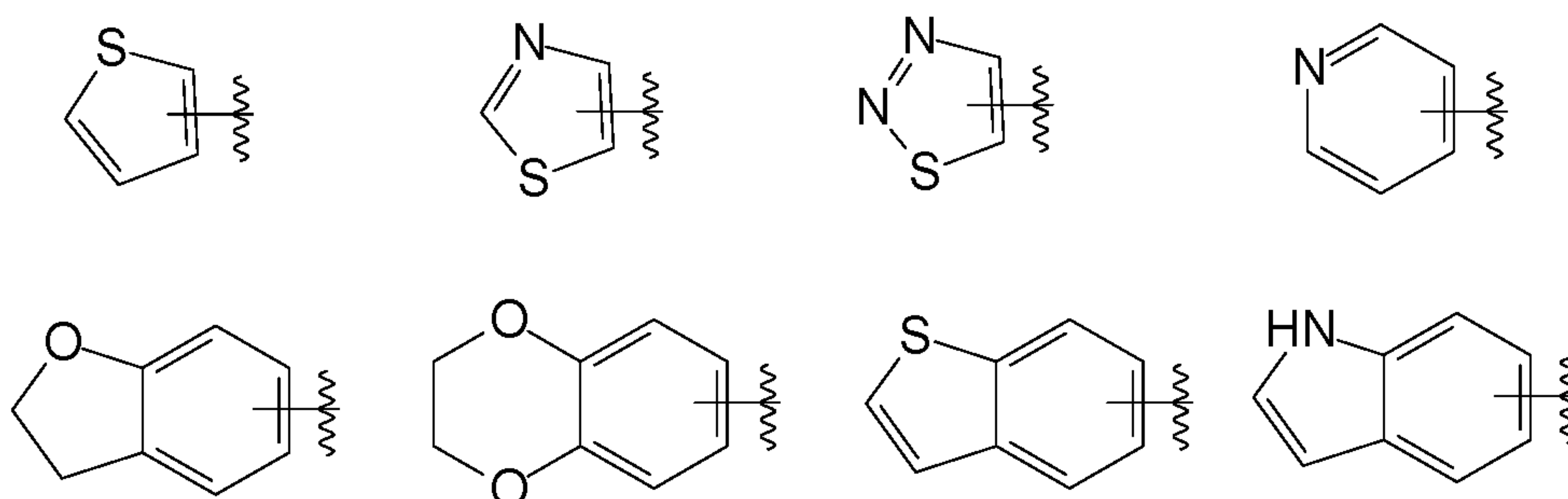
In one embodiment of formula (I), A is a non-aromatic carbocycle, and
15 more specifically cyclohexyl.

In one embodiment of formula (I), A is an aromatic carbocycle, and more specifically aryl.

In one embodiment of formula (I), A is phenyl or naphthyl.

In one embodiment of formula (I), A is phenyl.

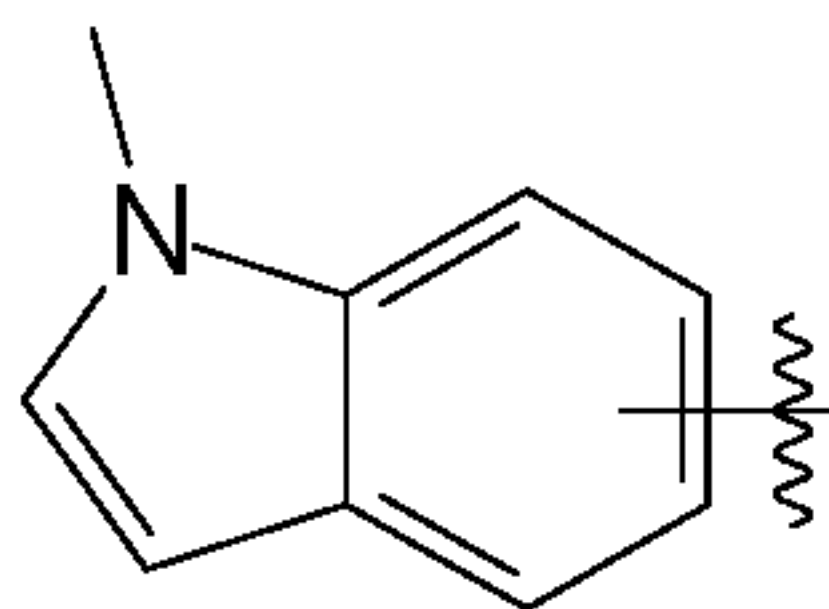
20 In one embodiment of formula (I), A is an aromatic heterocycle, and more specifically one of the following:



In one embodiment of formula (I), w is 0 and R_2 is not present.

In one embodiment of formula (I), w is 1, 2 or 3, and R_2 is at each
25 occurrence -OH, -C≡N, halo, or C₁₋₄alkyl.

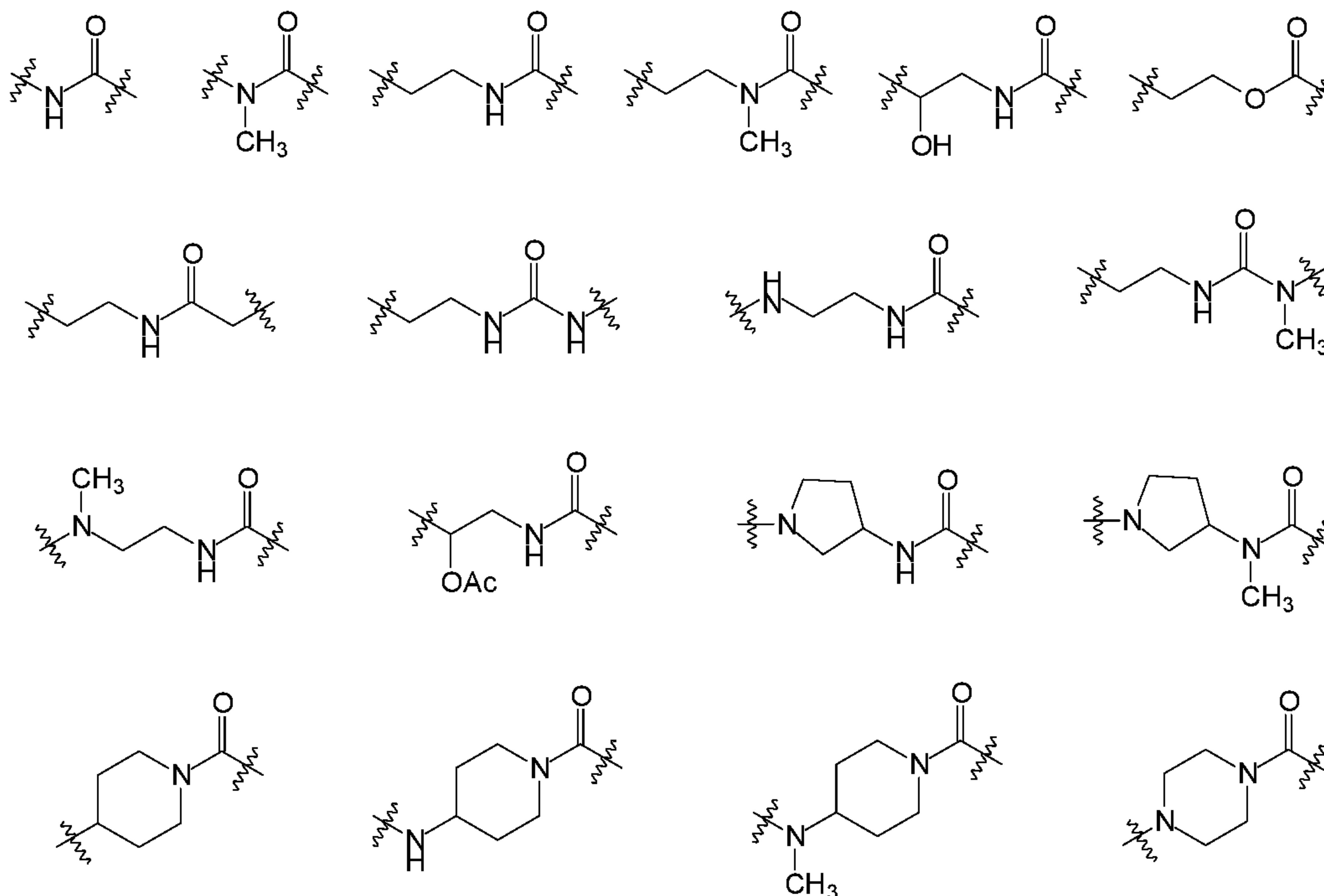
In one embodiment, compounds are provided of formula (I) wherein $-A(R_2)_w$ is:



In one embodiment of formula (I), x is 0 and R_3 is not present.

5 In one embodiment of formula (I), x is 1 or 2 and R_3 is at each occurrence $-OH$ or $C_{1-4}alkyl-OH$.

In one embodiment of formula (I), L_1 is a heteroalkylene linker having at least one N or O heteroatom, and wherein the heteroalkylene may be a straight chain or cyclized and optionally substituted with oxo, $-OH$, $C_{1-4}alkyl$ or $C_{1-4}alkoxy$, and more
10 specifically one of the following:



In one embodiment of formula (I), B is a non-aromatic carbocycle, and more specifically cyclohexyl.

In one embodiment of formula (I), B is an aromatic carbocycle, and more
15 specifically aryl.

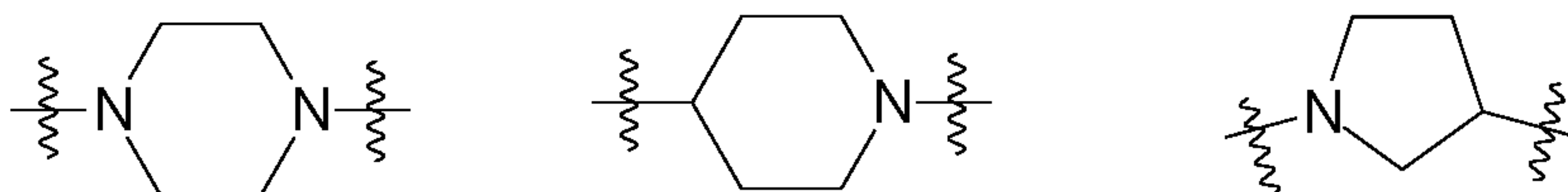
In one embodiment of formula (I), B is phenyl or naphthyl.

In one embodiment of formula (I), B is phenyl.

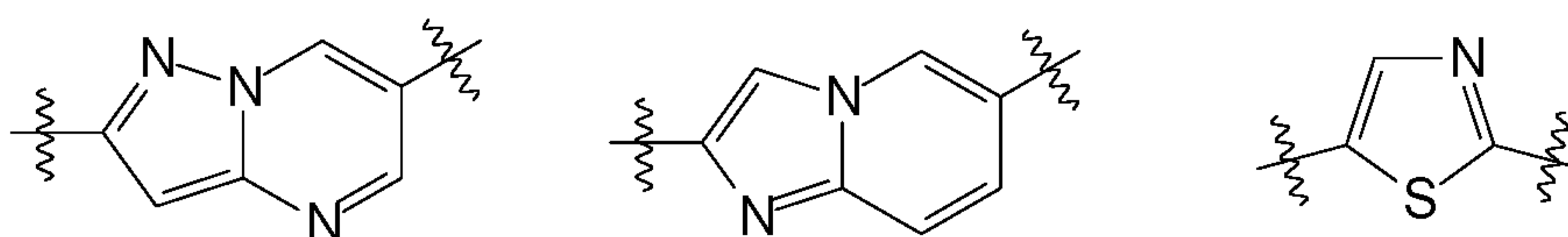
In one embodiment of formula (I), B is a non-aromatic heterocycle.

In one embodiment of formula (I), B is piperaziny, piperadiny or pyrrolidiny, and more specifically one of the following:

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In one embodiment of formula (I), B an aromatic heterocycle, and more specifically

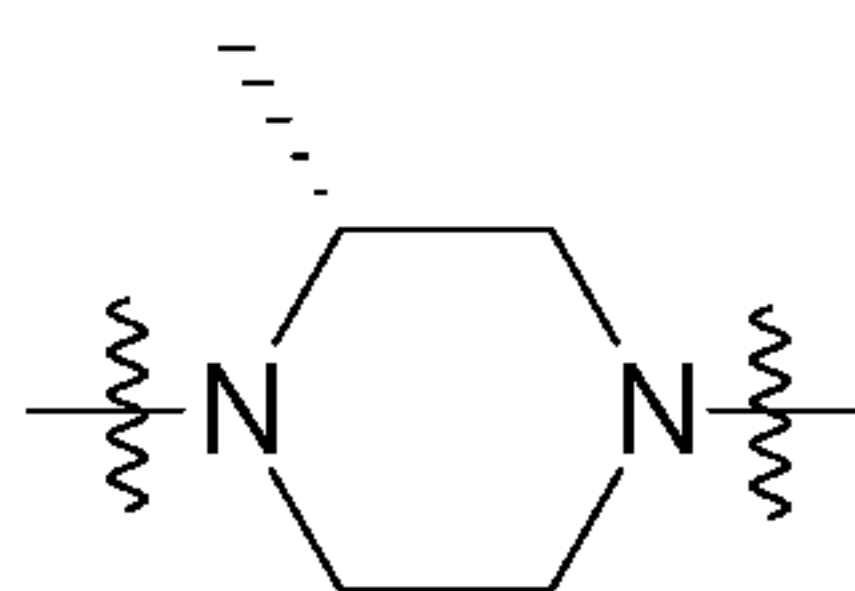


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In one embodiment of formula (I), y is 0 and R₄ is not present.

In one embodiment of formula (I), y is 1 and R₄ is methyl.

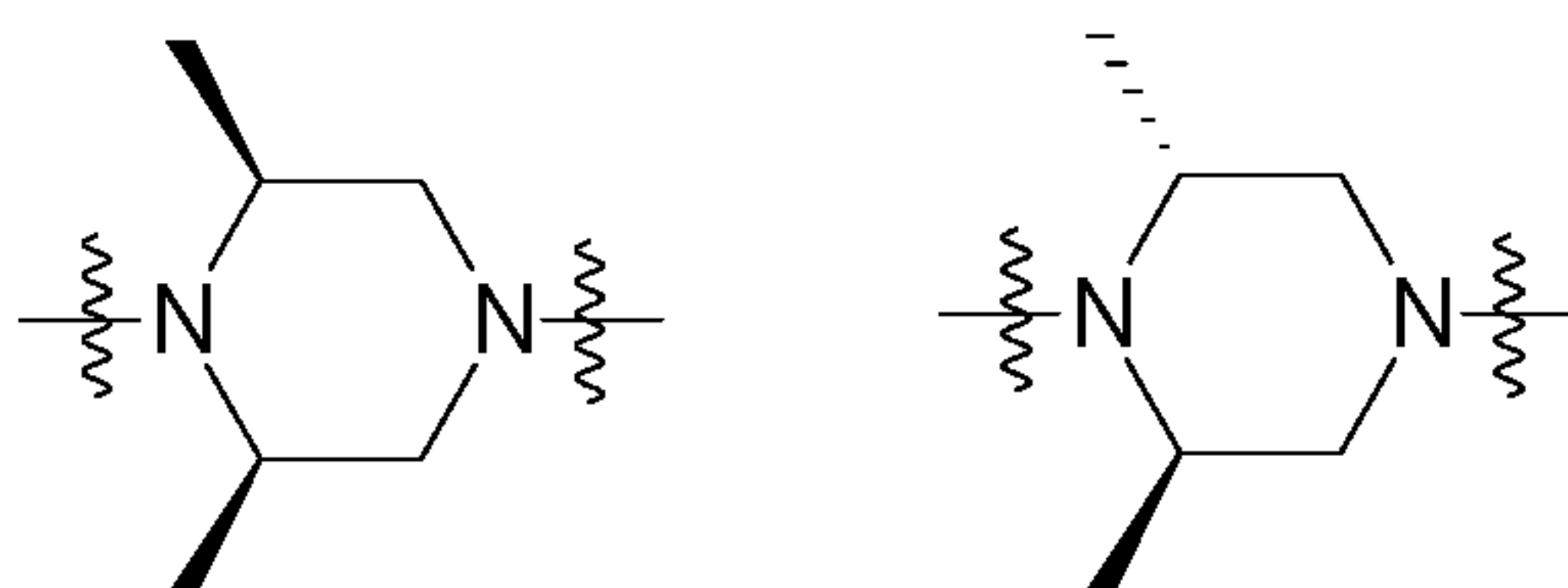
In one embodiment of formula (I), B is piperaziny, y is 1 and R₄ is methyl and, in a more specific embodiment, such moiety has the following structure:



15

In one embodiment of formula (I), y is 2 and R₄ at both occurrences is methyl.

In one embodiment of formula (I), B is piperaziny, y is 2 and R₄ at both occurrences is methyl and, in a more specific embodiment, such moiety has one of the following structures:



20

In one embodiment of formula (I), L₂ is not present.

In one embodiment of formula (I), L_2 is $-O-$

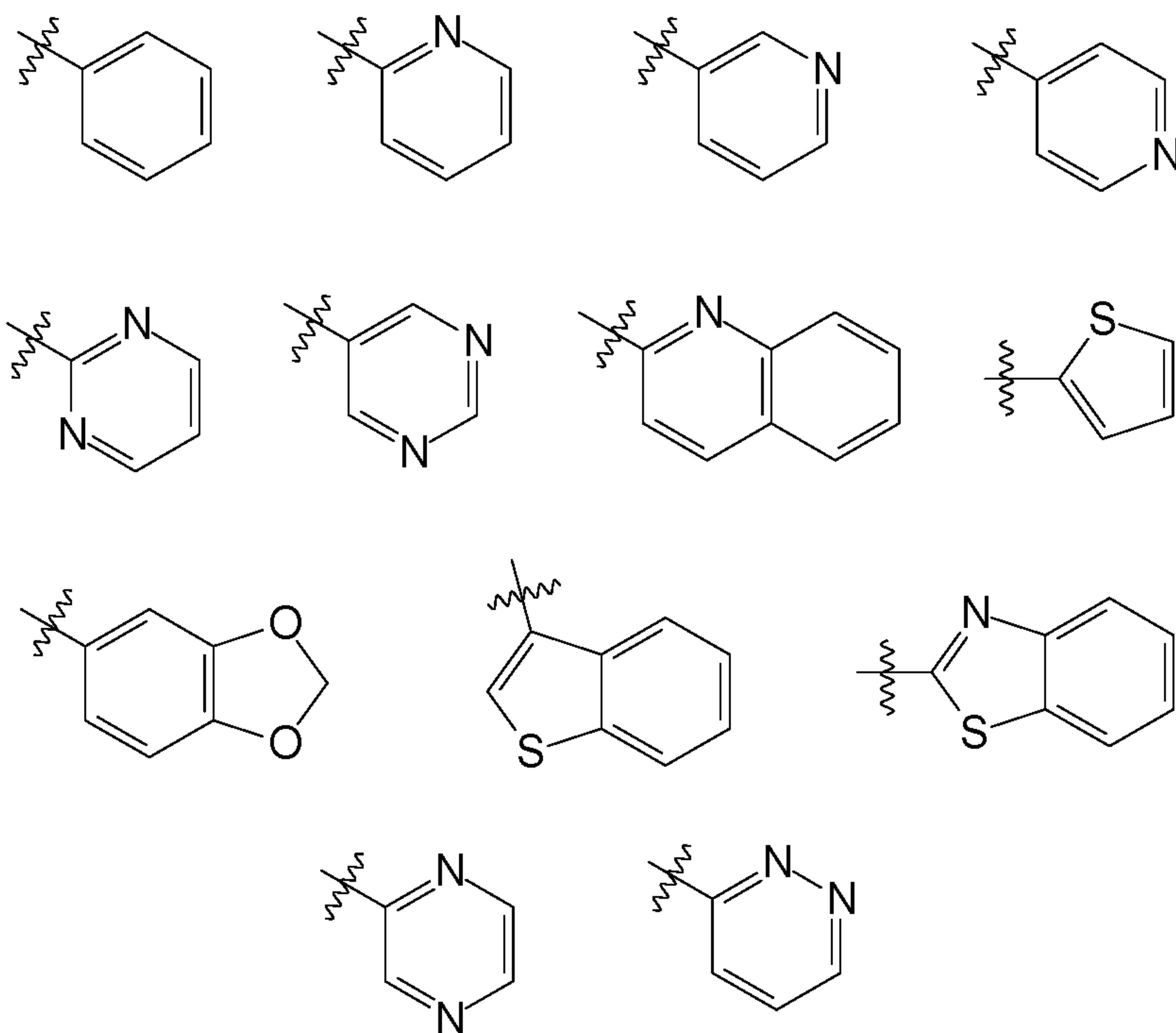
In one embodiment of formula (I), L_2 is $-OCH_2-$.

In one embodiment of formula (I), C is an aromatic 5-12 membered carbocycle or heterocycle.

5 In one embodiment of formula (I), C is an aromatic carbocycle, and more specifically aryl.

In one embodiment of formula (I), C is phenyl.

In one embodiment of formula (I), C is an aromatic heterocycle, and more specifically one of the following:

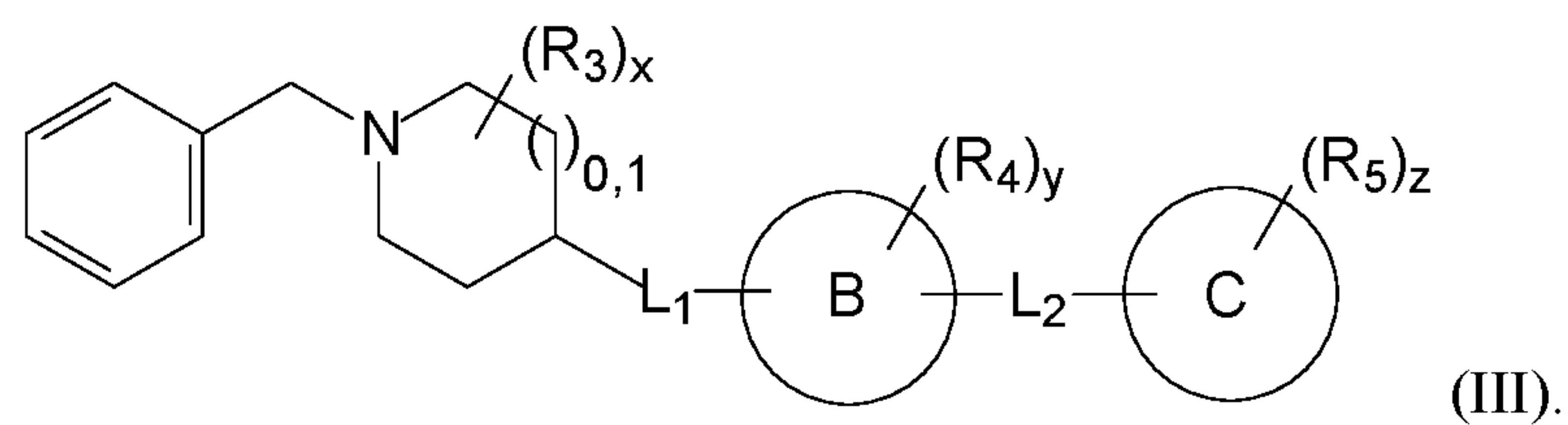
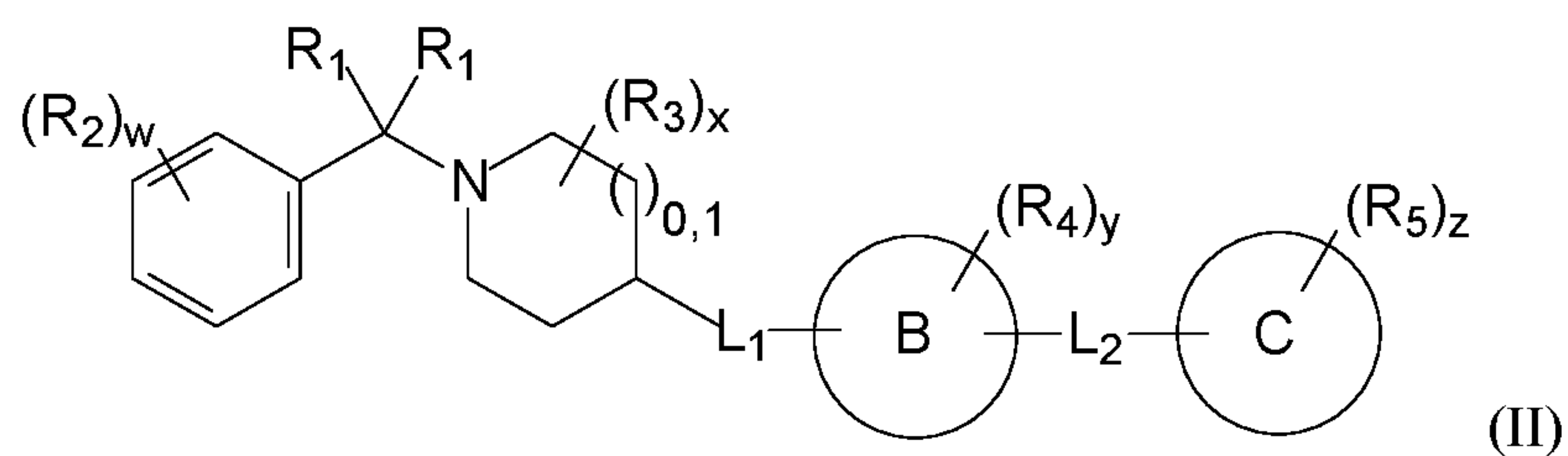


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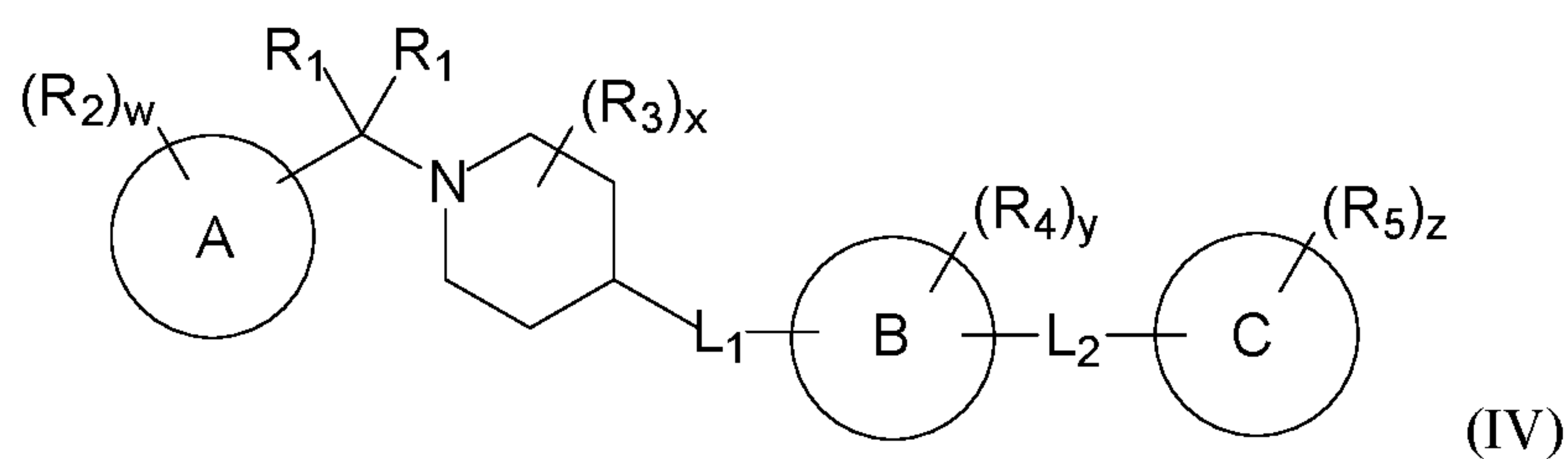
In one embodiment of formula (I), z is 0 and R_5 is not present.

In one embodiment of formula (I), z is 1, 2 or 3, and each occurrence of R_5 is independently $-OH$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, $-C\equiv N$, halo, $C_{1-4}alkyl$,
 15 $C_{1-4}alkyl-OH$, $C_{1-4}haloalkyl$, $C_{1-4}alkoxy$ or $C_{1-4}haloalkoxy$.

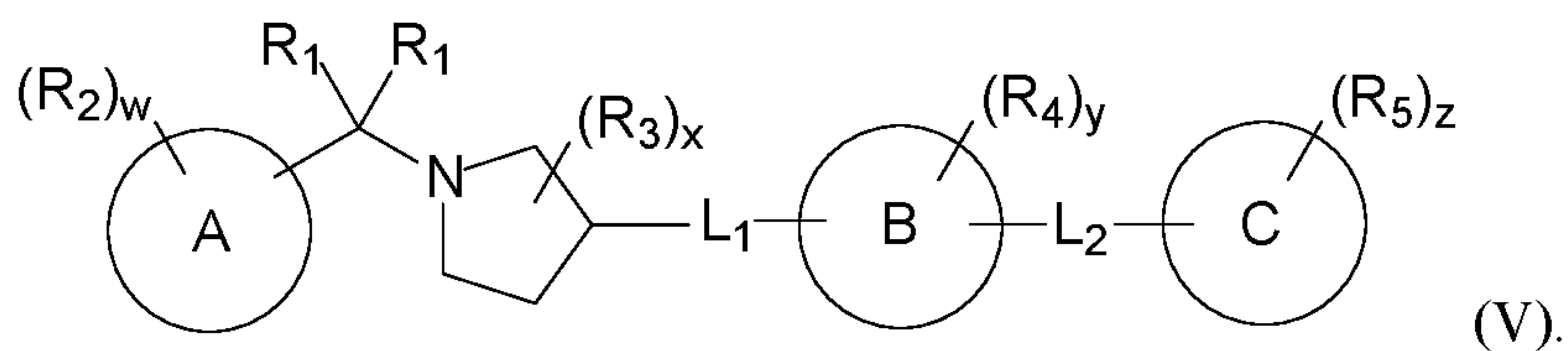
In one embodiment of formula (I), compounds are provided having a structure of the following formula (II) or (III):



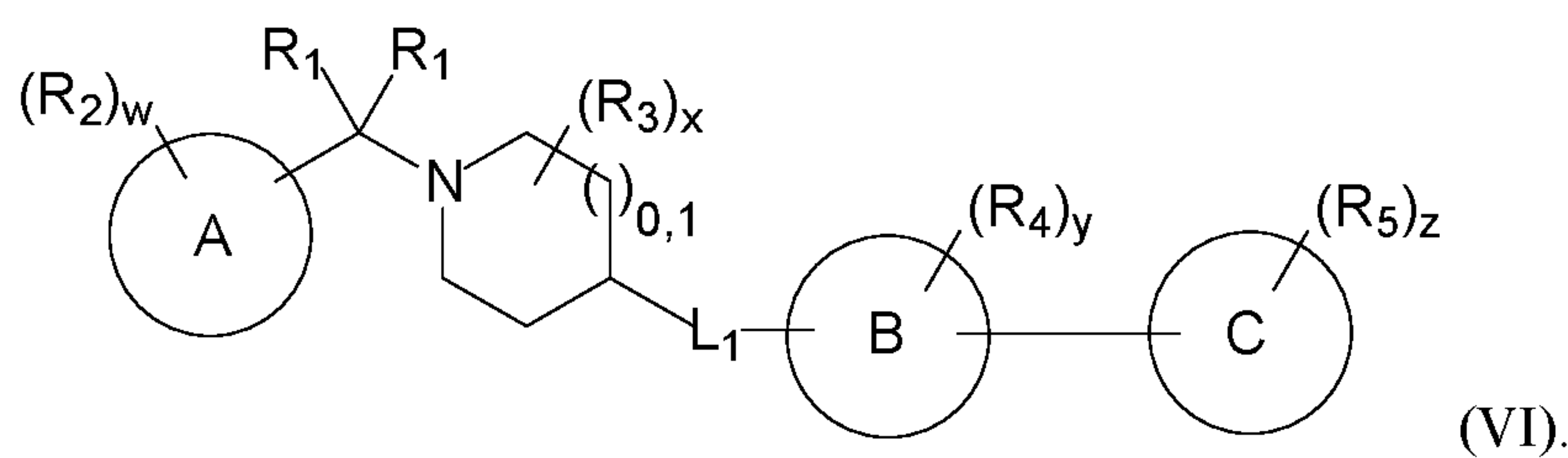
In one embodiment of formula (I), compounds are provided having a structure of the following formula (IV) or (V):



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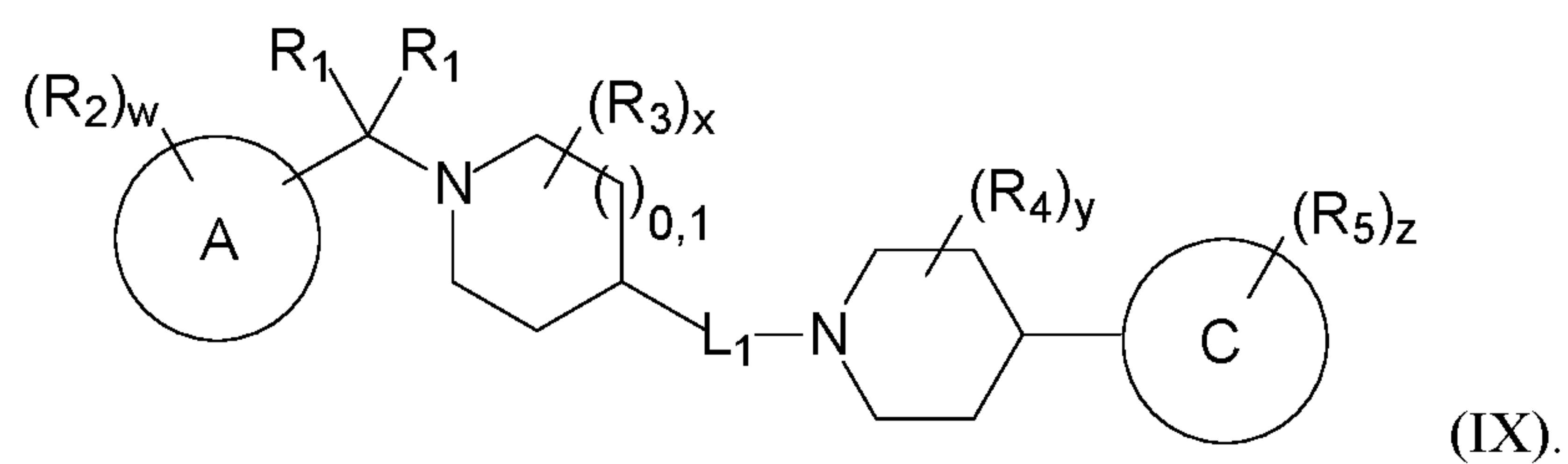
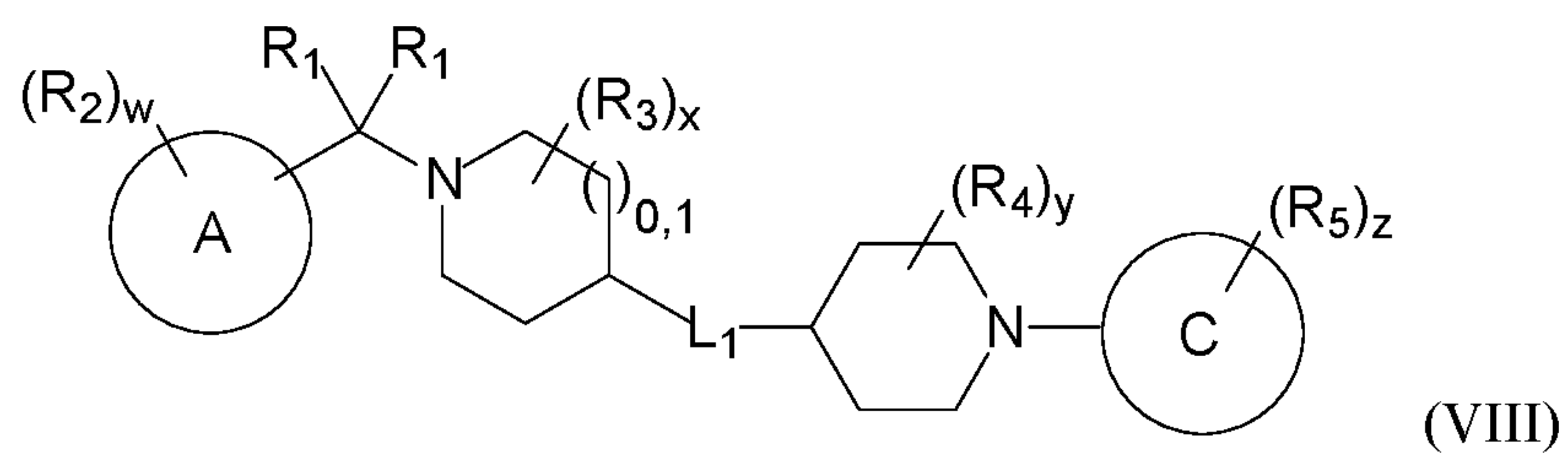
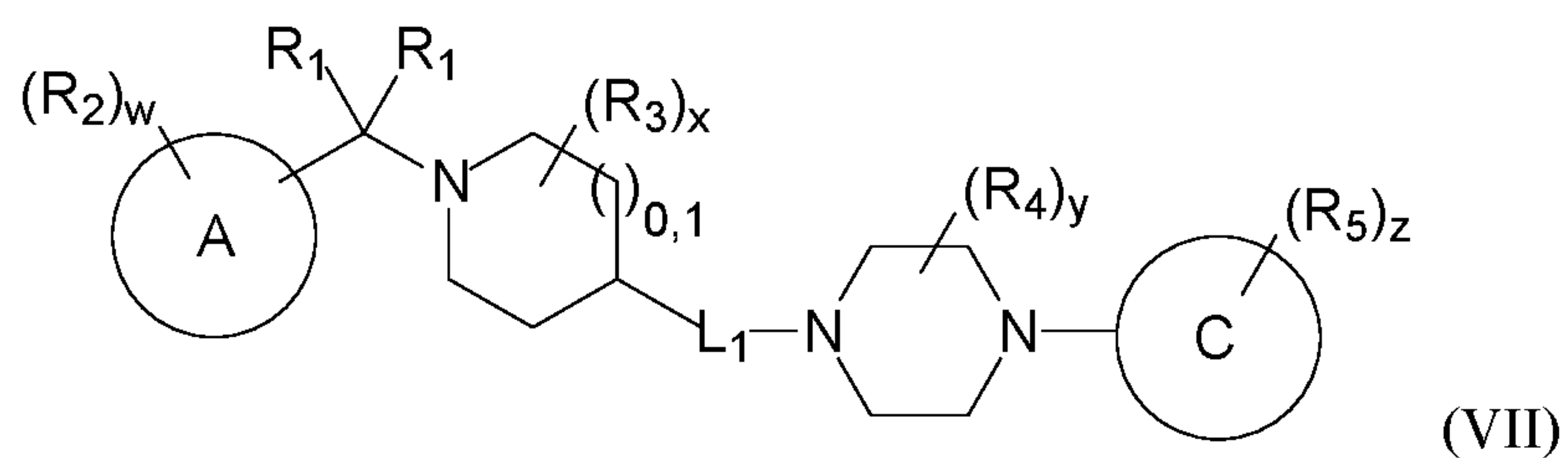


In one embodiment of formula (I), compounds are provided having a structure of the following formula (VI):

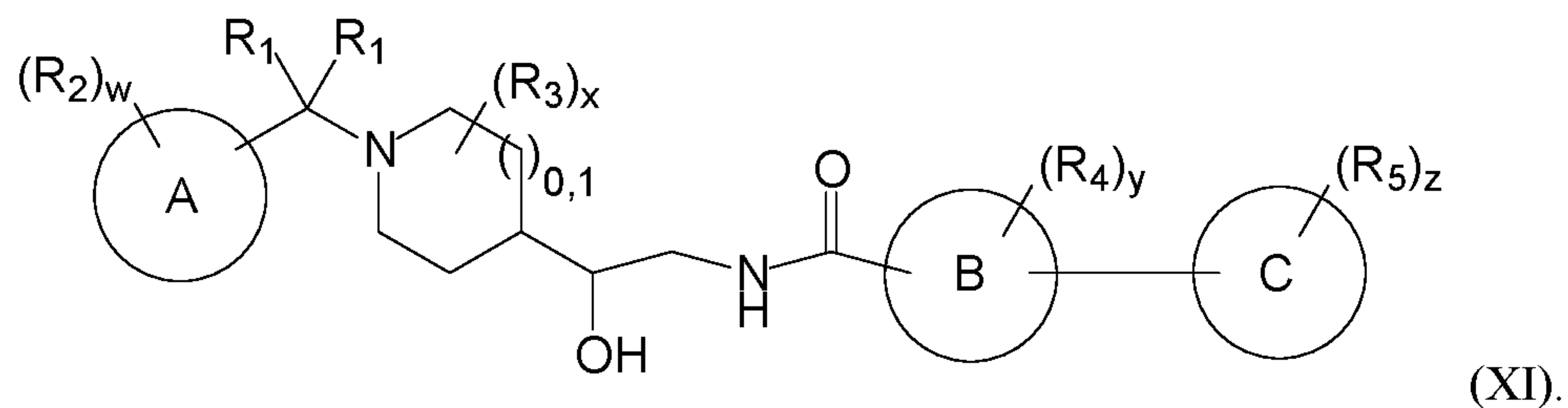
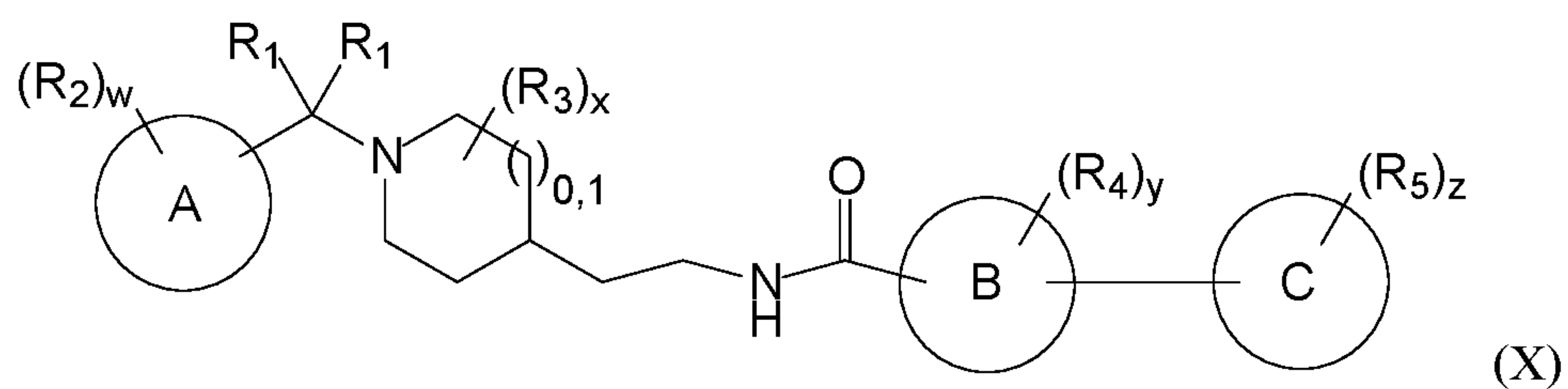


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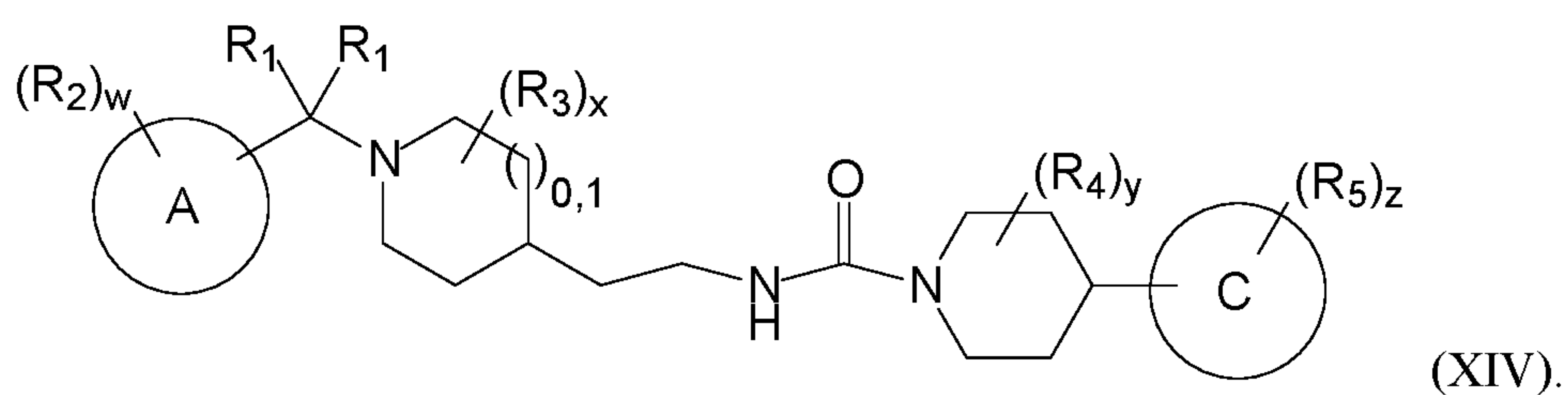
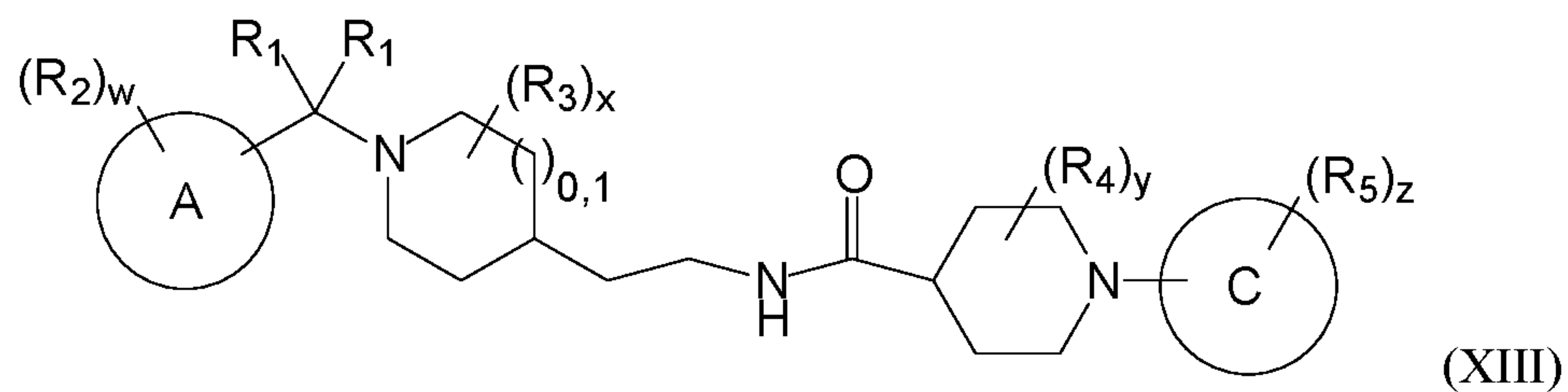
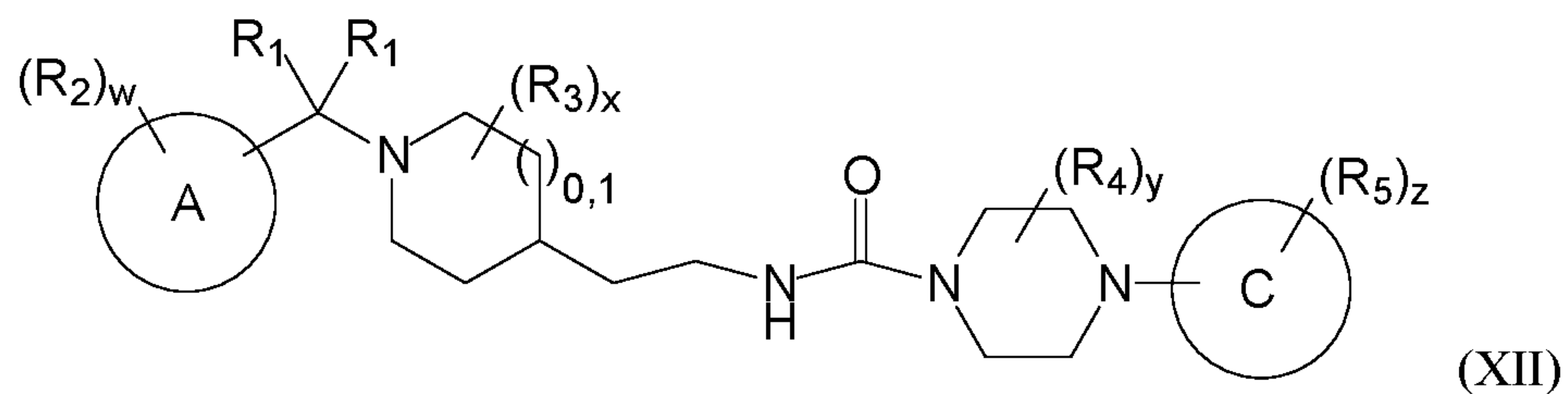
In one embodiment of formula (I), compounds are provided having a structure of the following formula (VII), (VIII) or (IX):



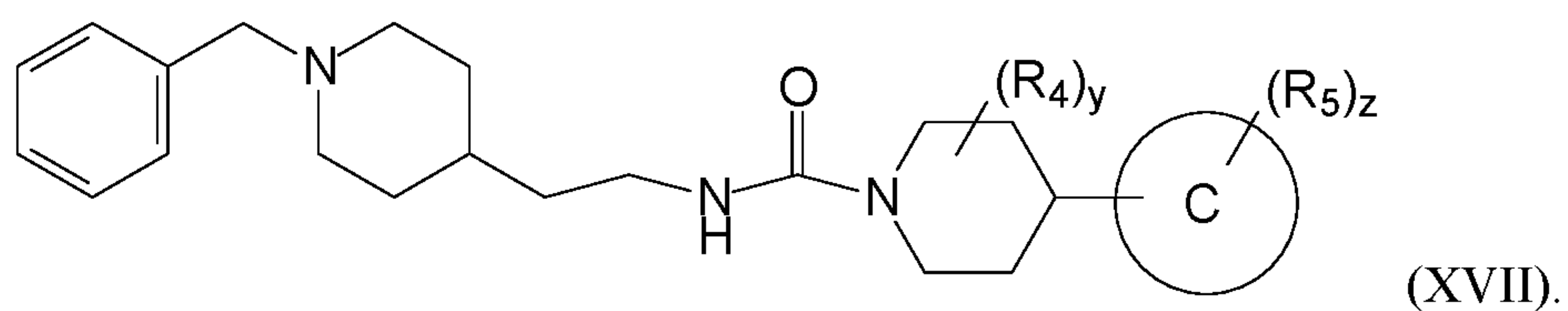
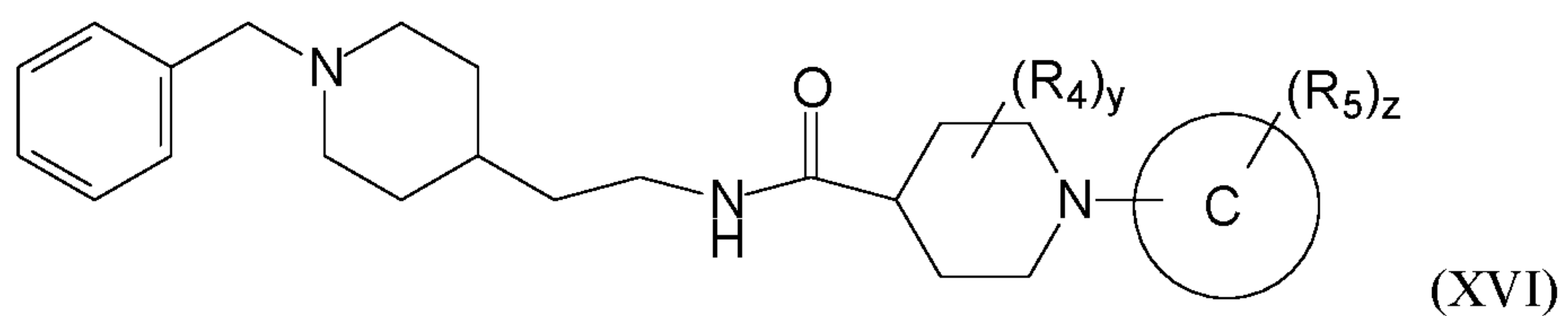
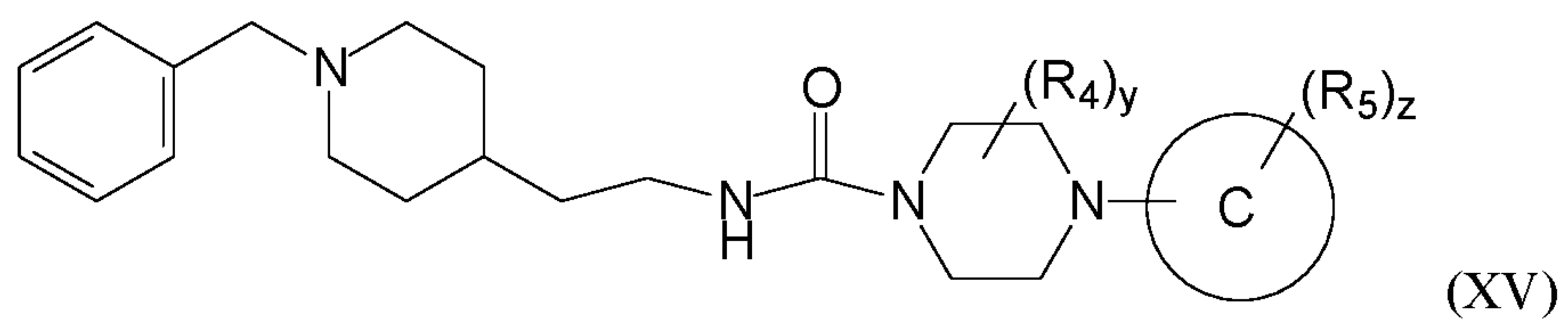
In one embodiment of formula (I), compounds are provided having a
 5 structure of the following formula (X) or (XI):



In one embodiment of formula (I), compounds are provided having a
 structure of the following formula (XII), (XIII) or (XIV):



In one embodiment of formula (I), compounds are provided having a
 5 structure of the following formula (XV), (XVI) or (XVII):

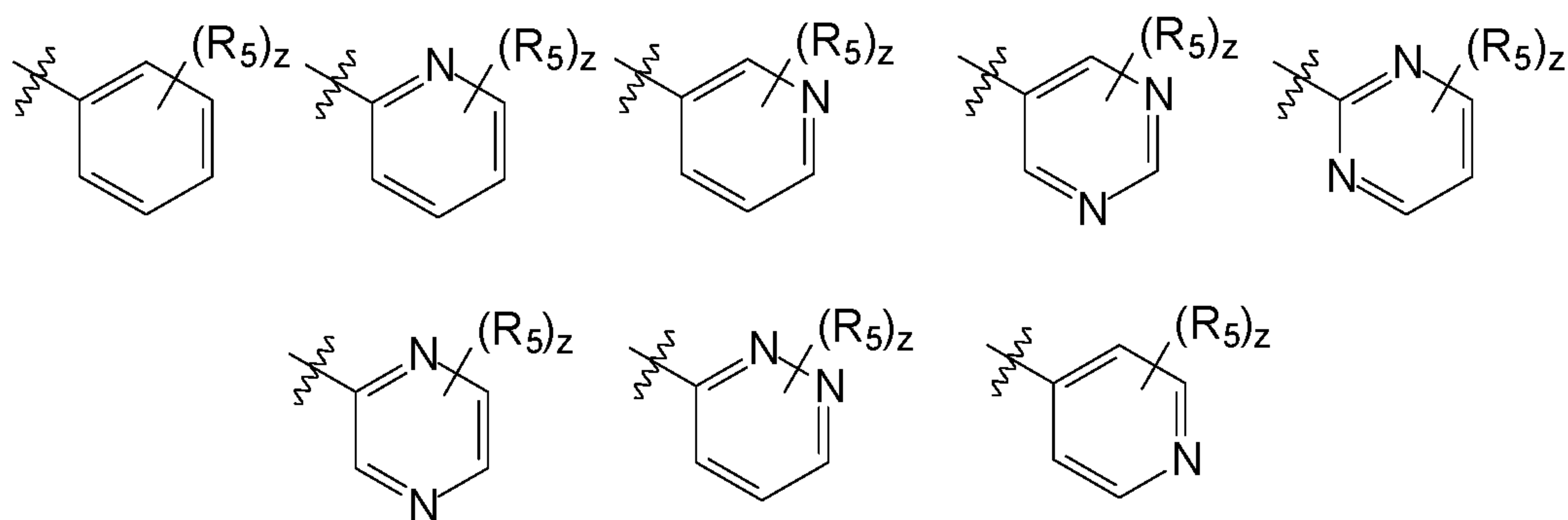


In one embodiment, compounds are provided of formula (XV), (XVI) or
 10 (XVII) wherein y is 0.

In one embodiment, compounds are provided of formula (XV), (XVI) or (XVII) wherein y is 1 or 2, and R₄ is at each occurrence C₁₋₄alkyl.

In one embodiment, compounds are provided of formula (XV), (XVI) or (XVII) wherein y is 1 or 2, and R₄ is at each occurrence methyl.

5 In one embodiment, compounds are provided of formula (XV), (XVI) or (XVII) wherein -C(R₅)_z is one of the following:



10 In one embodiment of the -C(R₅)_z groups noted immediately above, z is 0 and R₅ is not present.

In one embodiment of the -C(R₅)_z groups noted immediately above, z is 1, 2 or 3, and each occurrence of R₅ is independently -OH, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -C≡N, halo, C₁₋₄alkyl, C₁₋₄alkyl-OH, C₁₋₄haloalkyl, C₁₋₄alkoxy or C₁₋₄haloalkoxy.

15 In one embodiment, a compound of formula (I) is one or more of the following compounds (with cal. ion m/z listed in parentheses):

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyrazin-2-yl)-2,6-dimethylpiperazine-1-carboxamide (462.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(6-cyanopyridazin-3-yl)-2,6-dimethylpiperazine-1-carboxamide (462.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-cyanopyrimidin-5-yl)-2,6-dimethylpiperazine-1-carboxamide (462.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyanophenyl)-2,6-dimethylpiperazine-1-carboxamide (460.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyridin-2-yl)-2,6-dimethylpiperazine-1-carboxamide (461.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyano-4-

methoxypyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide (492.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-chloropyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide (471.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-chloropyrazin-2-yl)-2,6-dimethylpiperazine-1-carboxamide (471.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(6-chloropyridazin-3-yl)-2,6-dimethylpiperazine-1-carboxamide (471.3);

(2R,6R)-4-(4-amino-5-chloropyrimidin-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide (486.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(6-chloropyridin-3-yl)-2,6-dimethylpiperazine-1-carboxamide (470.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[6-(trifluoromethyl)pyridazin-3-yl]piperazine-1-carboxamide 505.3

(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-methoxypyrimidin-2-yl)-2-methylpiperazine-1-carboxamide (453.3);

(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-methoxypyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide (467.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-methoxypyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide (467.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-methoxypyrazin-2-yl)-2,6-dimethylpiperazine-1-carboxamide (467.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(6-methoxypyridazin-3-yl)-2,6-dimethylpiperazine-1-carboxamide (467.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-methoxypyrimidin-5-yl)-2,6-dimethylpiperazine-1-carboxamide (467.3);

(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-(difluoromethoxy)pyrimidin-2-yl]-2-methylpiperazine-1-carboxamide (489.3);

(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-(difluoromethoxy)pyrimidin-2-yl]-2,6-dimethylpiperazine-1-carboxamide (503.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-(difluoromethoxy)pyrimidin-2-yl]-2,6-dimethylpiperazine-1-carboxamide (503.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-(difluoromethoxy)pyrazin-2-yl]-2,6-dimethylpiperazine-1-carboxamide (503.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[6-(difluoromethoxy)pyridazin-3-yl]-2,6-dimethylpiperazine-1-carboxamide (503.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[2-(difluoromethoxy)pyrimidin-5-yl]-2,6-dimethylpiperazine-1-carboxamide (503.3);

(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[5-

(trifluoromethoxy)pyrimidin-2-yl]piperazine-1-carboxamide (507.3);

(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[5-(trifluoromethoxy)pyrimidin-2-yl]piperazine-1-carboxamide (521.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[5-(trifluoromethoxy)pyrimidin-2-yl]piperazine-1-carboxamide (521.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[5-(trifluoromethoxy)pyrazin-2-yl]piperazine-1-carboxamide (521.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[6-(trifluoromethoxy)pyridazin-3-yl]piperazine-1-carboxamide (521.3);

(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[2-(trifluoromethoxy)pyrimidin-5-yl]piperazine-1-carboxamide (521.3);

N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-methoxypyrimidin-2-yl)piperazine-1-carboxamide (439.3);

N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-(difluoromethoxy)pyrimidin-2-yl]piperazine-1-carboxamide (475.3); and

N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-(trifluoromethoxy)pyrimidin-2-yl]piperazine-1-carboxamide (492.2).

In even more specific embodiments, specific compounds of formula I are as listed in Tables 1-19 herein.

In other embodiments, pharmaceutical compositions are provided that comprise a compound of Formula I, including one or more of the specific compounds described herein (*see, e.g.*, Tables 1-19), and at least one pharmaceutically acceptable excipient.

In another embodiment, a method is provided for antagonizing a muscarinic receptor in a cell comprising contacting the cell and a compound of Formula I, including specific compounds described herein, for a time sufficient and under appropriate conditions to permit interaction between the cell and the compound. In certain embodiments, the cell is in a subject who is in need of treatment with a compound disclosed herein. For example, the subject may have or be at risk for developing a neurological disease, condition, or disorder including cognitive and movement neurological diseases, conditions, and disorders. In certain embodiments, methods are provided for preventing (*i.e.*, reducing the likelihood of occurrence of) or treating Alzheimer's Disease, Lewy Body Dementia and the cognitive deficits associated with schizophrenia; Parkinson's Disease, drug induced Parkinsonism,

dyskinesias, dystonia, chorea, levodopa induced dyskinesia, cerebral palsy and progressive supranuclear palsy, and Huntington's disease, including chorea associate with Huntington's disease. A person skilled in the medical or neurological art will readily appreciate that many of the aforementioned neurological diseases have both
5 cognitive deficits and movement deficiencies or difficulties associated with them.

As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated.

Certain chemical groups named herein are preceded by a shorthand notation indicating the total number of carbon atoms that are to be found in the
10 indicated chemical group. For example; C₁-C₄alkyl describes an alkyl group, as defined below, having a total of 1 to 4 carbon atoms, and C₄-C₁₂cycloalkylalkyl describes a cycloalkylalkyl group, as defined below, having a total of 4 to 12 carbon atoms. The total number of carbons in the shorthand notation does not include carbons that may exist in substituents of the group described. For example, the following terms have the
15 meaning indicated.

"C₁-C₆alkyl" refers to an alkyl radical as defined below containing one to six carbon atoms. The C₁-C₆alkyl radical may be optionally substituted as defined below for an alkyl group. "C₁-C₄alkyl" refers to an alkyl radical as defined below containing one to four carbon atoms. The C₁-C₄alkyl radical may be optionally
20 substituted as defined below for an alkyl group.

"C₂-C₄alkenyl" refers to an alkenyl radical as defined below containing two to six carbon atoms. The C₂-C₁₂alkenyl radical may be optionally substituted as defined below for an alkenyl group.

"C₂-C₆alkynyl" refers to an alkynyl radical as defined below containing
25 two to six carbon atoms. The C₂-C₁₂alkynyl radical may be optionally substituted as defined below for an alkenyl group.

"C₁-C₄alkoxy" refers to an alkoxy radical as defined below containing one to twelve carbon atoms. The alkyl part of the C₁-C₄alkoxy radical may be optionally substituted as defined below for an alkyl group.

"C₂-C₆alkoxyalkyl" refers to an alkoxyalkyl radical as defined below containing two to six carbon atoms. Each alkyl part of the C₂-C₆alkoxyalkyl radical may be optionally substituted as defined below for an alkyl group.

"C₇-C₁₂aralkyl" refers to an aralkyl group as defined below containing
 5 seven to twelve carbon atoms. The aryl part of the C₇-C₁₂aralkyl radical may be optionally substituted as described below for an aryl group. The alkyl part of the C₇-C₁₂aralkyl radical may be optionally substituted as defined below for an alkyl group.

"C₇-C₁₂aralkenyl" refers to an aralkenyl group as defined below containing seven to twelve carbon atoms. The aryl part of the C₇-C₁₂aralkenyl radical
 10 may be optionally substituted as described below for an aryl group. The alkenyl part of the C₇-C₁₂aralkenyl radical may be optionally substituted as defined below for an alkenyl group.

"C₃-C₁₂cycloalkyl" refers to a cycloalkyl radical as defined below having three to twelve carbon atoms. The C₃-C₁₂cycloalkyl radical may be optionally
 15 substituted as defined below for a cycloalkyl group.

"C₄-C₁₂cycloalkylalkyl" refers to a cycloalkylalkyl radical as defined below having four to twelve carbon atoms. The C₄-C₁₂cycloalkylalkyl radical may be optionally substituted as defined below for a cycloalkylalkyl group.

In addition to the foregoing, as used in the specification and appended
 20 claims, unless specified to the contrary, the following terms have the meaning indicated:

"Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to twelve carbon atoms, one to eight carbon atoms, or one to six carbon
 25 atoms, or one to four carbon atoms, and which is attached to the rest of the molecule by a single bond, *e.g.*, methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl), *n*-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, and the like.

"Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one double
 30 bond, having from two to twelve carbon atoms, preferably two to eight carbon atoms

and which is attached to the rest of the molecule by a single bond, *e.g.*, ethenyl, prop-1-enyl, but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like.

"Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms or from one to four carbon atoms, *e.g.*, methylene, ethylene, propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain.

"Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to twelve carbon atoms, *e.g.*, ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain.

"Carbocyclyl" refers to a stable 3- to 18-membered aromatic or non-aromatic ring radical which consists of 3 to 18 carbon atoms. Unless stated otherwise specifically in the specification, the carbocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems, and may be partially or fully saturated. Non-aromatic carbocyclyl radicals include cycloalkyl, while aromatic carbocyclyl radicals include aryl.

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which may include fused or bridged ring systems, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic radicals include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and

cyclooctyl. Polycyclic radicals include, for example, adamantyl, norbornyl, decalanyl, 7,7-dimethyl-bicyclo-[2.2.1]heptanyl, and the like.

"Aryl" refers to a hydrocarbon ring system radical comprising hydrogen, 6 to 18 carbon atoms and at least one aromatic ring. The aryl radical may be a
 5 monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. In one embodiment, aryl
 10 is phenyl or naphthyl, and in another embodiment is phenyl.

"Heterocyclyl" refers to a stable 3- to 18-membered aromatic or non-aromatic ring radical which consists of two to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical may be
 15 a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclyl radical may be partially or fully saturated. Examples of aromatic heterocyclyl radicals are listed below in the definition of heteroaryls (*i.e.*, heteroaryl
 20 being a subset of heterocyclyl). Examples of non-aromatic heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolanyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholanyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl,
 25 pyrazolidinyl, pyrazolopyrimidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trioxanyl, trithianyl, triazinanyl, tetrahydropyranyl, thiomorpholanyl, thiamorpholanyl, 1-oxo-thiomorpholanyl, and 1,1-dioxo-thiomorpholanyl.

"Heteroaryl" refers to a 5- to 14-membered ring system radical comprising hydrogen atoms, one to thirteen carbon atoms, one to six heteroatoms
 30 selected from the group consisting of nitrogen, oxygen and sulfur, and at least one

aromatic ring. For purposes of this invention, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized.

5 Examples include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiaazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl),

10 benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl, benzoxazolinonyl, benzimidazolthionyl, carbazolyl, cinnolynyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolynyl, isoindolynyl, isoquinolyl, indolizynyl, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-

15 oxidopyrazinyl, 1-oxidopyridazinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, pteridinonyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyridinonyl, pyrazinyl, pyrimidinyl, pyrimidinonyl, pyridazinyl, pyrrolyl, pyrido[2,3-*d*]pyrimidinonyl, quinazolinyl, quinazolinonyl, quinoxalinyl, quinoxalinonyl, quinolynyl, isoquinolynyl, tetrahydroquinolynyl, thiazolyl, thiadiazolyl,

20 thieno[3,2-*d*]pyrimidin-4-onyl, thieno[2,3-*d*]pyrimidin-4-onyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl).

Unless stated otherwise specifically in the specification, each of alkyl, alkenyl, alkylene, alkenylene, carbocyclyl, cycloalkyl, aryl, heterocyclyl and heteroaryl as defined above may be optionally substituted by one or more substituents selected

25 from the group consisting of alkyl, alkenyl, halo, haloalkyl, haloalkenyl, cyano, oxo, thioxo, nitro, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl,

heteroarylalkyl, $-R^{41}-OR^{40}$, $-R^{41}-OC(O)-R^{40}$, $-R^{41}-N(R^{40})_2$, $-R^{41}-C(O)R^{40}$, $-R^{41}-C(O)OR^{40}$, $-R^{41}-C(O)N(R^{40})_2$, $-R^{41}-N(R^{40})C(O)OR^{42}$, $-R^{41}-N(R^{40})C(O)R^{42}$, $-R^{41}-N(R^{40})S(O)_tR^{42}$

30 (where *t* is 1 to 2), $-R^{41}-N=C(OR^{40})R^{40}$, $-R^{41}-S(O)_tOR^{42}$ (where *t* is 1 to

2), $-R^{41}-S(O)_pR^{42}$ (where p is 0 to 2), and $-R^{41}-S(O)_tN(R^{40})_2$ (where t is 1 to 2) where each R^{40} is independently hydrogen, alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl; each R^{41} is independently a direct bond or a straight or branched
 5 alkylene or alkenylene chain; and each R^{42} is alkyl, alkenyl, haloalkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclalkyl, heteroaryl or heteroarylalkyl.

"Amino" refers to the $-NH_2$ radical.

"Cyano" refers to the $-CN$ radical.

10 "Hydroxy" refers to the $-OH$ radical.

"Nitro" refers to the $-NO_2$ radical.

"Oxo" refers to the $=O$ substituent.

"Thioxo" refers to the $=S$ substituent.

"Trifluoromethyl" refers to the $-CF_3$ radical.

15 "Trifluoromethoxy" refers to the $-OCF_3$ radical.

"Acyl" refers to a radical $-C(O)R$, wherein R is alkyl, aralkyl, carbocyclyl, aryl, heteroaryl, or heterocyclyl, as defined herein. When R is methyl, the acyl group is also referred to as acetyl.

"Heteroalkylene" or "heteroalkylene chain" refers to a straight or
 20 branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting of carbon and hydrogen and at least one heteroatom selected from N, O, and S.

"Alkoxy" refers to a radical of the formula $-OR_a$ where R_a is an alkyl, or haloalkyl radical as defined above containing one to six carbon atoms. Representative
 25 alkoxy groups include methoxy and ethoxy. Unless stated otherwise specifically in the specification, an alkoxy group may be optionally substituted. An alkoxy that is substituted with halo may be called herein a haloalkoxy, which includes for example trifluoromethoxy, trichloromethoxy and the like.

"Heteroalkenylene" or "heteroalkenylene chain" refers to a straight or
 30 branched divalent hydrocarbon chain linking the rest of the molecule to a radical group,

consisting of carbon and hydrogen and at least one heteroatom selected from N, O, and S.

"Aralkyl" refers to a radical of the formula $-R_b-R_c$ where R_b is an alkylene chain as defined above and R_c is one or more aryl radicals as defined above, for example, benzyl, diphenylmethyl and the like. The alkylene chain part of the aralkyl radical may be optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical may be optionally substituted as described above for an aryl group.

"Cycloalkylalkyl" refers to a radical of the formula $-R_bR_g$ where R_b is an alkylene chain as defined above and R_g is a cycloalkyl radical as defined above. The alkylene chain and the cycloalkyl radical may be optionally substituted as defined above.

"Fused" refers to any ring system described herein which is fused to an existing ring structure in the compounds of the invention. When the fused ring system is a heterocyclyl or a heteroaryl, any carbon in the existing ring structure which becomes part of the fused ring system may be replaced with a nitrogen.

"Halo" refers to bromo, chloro, fluoro or iodo.

"Haloalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like. The alkyl part of the haloalkyl radical may be optionally substituted as defined above for an alkyl group.

"Haloalkenyl" refers to an alkenyl radical, as defined above, that is substituted by one or more halo radicals, as defined above. The alkenyl part of the haloalkyl radical may be optionally substituted as defined above for an alkenyl group.

"Haloalkoxy" refers to an alkoxy radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethoxy, difluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy, 3-bromo-2-fluoropropoxy, and the like. The alkoxy part of the haloalkoxy radical may be optionally substituted as defined above for an alkoxy group.

"N-heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen. An N-heterocyclyl radical may be optionally substituted as described above for heterocyclyl radicals.

"Heterocyclylalkyl" refers to a radical of the formula $-R_bR_h$ where R_b is an alkylene chain as defined above and R_h is a heterocyclyl radical as defined above, and if the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl may be attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical may be optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkyl radical may be optionally substituted as defined above for a heterocyclyl group.

"N-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An N-heteroaryl radical may be optionally substituted as described above for heteroaryl radicals.

"Heteroarylalkyl" refers to a radical of the formula $-R_bR_i$ where R_b is an alkylene chain as defined above and R_i is a heteroaryl radical as defined above. The heteroaryl part of the heteroarylalkyl radical may be optionally substituted as defined above for a heteroaryl group. The alkylene chain part of the heteroarylalkyl radical may be optionally substituted as defined above for an alkylene chain.

"Hydroxyalkyl" refers to a radical of the formula $-R_bOH$ where R_b is an alkylene chain as defined above. The -OH group can be attached to any carbon in the alkylene chain. The alkylene chain part of the heteroarylalkyl radical may additionally be optionally substituted as defined above for an alkylene chain.

The compounds described herein may generally be used as the free acid or free base. Alternatively, the compounds may be used in the form of acid or base addition salts. Acid addition salts of the free amino compounds may be prepared by methods well known in the art, and may be formed from organic and inorganic acids. Suitable organic acids include maleic, fumaric, benzoic, ascorbic, succinic, methanesulfonic, acetic, trifluoroacetic, oxalic, propionic, tartaric, salicylic, citric,

gluconic, lactic, mandelic, cinnamic, aspartic, stearic, palmitic, glycolic, glutamic, and benzenesulfonic acids. Suitable inorganic acids include hydrochloric, hydrobromic, sulfuric, phosphoric, and nitric acids. Base addition salts included those salts that form with the carboxylate anion and include salts formed with organic and inorganic cations
5 such as those chosen from the alkali and alkaline earth metals (for example, lithium, sodium, potassium, magnesium, barium and calcium), as well as the ammonium ion and substituted derivatives thereof (for example, dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, and the like). Thus, the term “pharmaceutically acceptable salt” of the compounds described herein is intended to encompass any and all
10 acceptable salt forms.

Compounds described herein may sometimes be depicted as an anionic species. One of ordinary skill in the art will recognize that the compounds exist with an equimolar ratio of cation. For instance, the compounds can exist in the fully protonated form, or in the form of a salt such as sodium, potassium, ammonium or in combination
15 with any inorganic base as described above. When more than one anionic species is depicted, each anionic species may independently exist as either the protonated species or as the salt species.

With regard to stereoisomers, the compounds described herein may have one or more chiral (or asymmetric) centers and may thus give rise to enantiomers,
20 diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both *E* and *Z* geometric isomers (*e.g.*, *cis* or *trans*). Likewise, unless otherwise indicated, all possible isomers, as well as their
25 racemic and optically pure forms, and all tautomeric forms are also intended to be included. It is therefore contemplated that various stereoisomers and mixtures thereof include “enantiomers,” which refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. Thus, the compounds may occur in any isomeric form, including racemates, racemic mixtures, and as individual
30 enantiomers or diastereomers.

Furthermore, some of the crystalline forms of the compounds may exist as polymorphs, which are contemplated herein. In addition, some of the compounds may also form solvates with water or other organic solvents. Such solvates are similarly included within the scope of the compounds described herein.

5 As one of skill in the art would appreciate, any of the aforementioned compounds may incorporate radioactive isotopes. Accordingly, also contemplated is use of isotopically-labeled compounds identical to those described herein, wherein one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes
10 that can be incorporated into these compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F , and ^{36}Cl , respectively. Certain isotopically-labeled compounds, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are also useful in drug or substrate tissue distribution assays.
15 Tritiated hydrogen (^3H) and carbon-14 (^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Substitution with heavier isotopes such as deuterium (^2H) can provide certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dose requirements and, therefore, may be preferred in some circumstances. To this end, reference to an
20 element, such as hydrogen (H) or carbon (C), is intended to encompass all isotopes of the same. Thus, reference to H encompasses ^1H (protium), ^2H (deuterium) and ^3H (tritium), and reference to C encompasses ^{12}C , ^{13}C and ^{14}C . For example, compounds of formula (I) wherein both R_1 groups are ^2H (deuterium) are encompassed within the scope of this invention by reference to R_1 being, in one embodiment, hydrogen (H).
25 Isotopically-labeled compounds can generally be prepared by performing procedures routinely practiced in the art.

“Prodrug” is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term “prodrug” refers to a metabolic precursor of a compound described
30 herein that is pharmaceutically acceptable. A prodrug may be inactive when administered

to a subject in need thereof, but is converted *in vivo* to an active compound as described herein. Prodrugs are typically rapidly transformed *in vivo* to yield the parent compound described herein, for example, by hydrolysis in blood. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism
5 (see, e.g., Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein.

10 The term "prodrug" is also meant to include any covalently bonded carriers which release the active compound as described herein *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound described herein may be prepared by modifying functional groups present in the compound described herein in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to
15 the parent compound described herein. Prodrugs include compounds described herein wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, ester and amide derivatives of hydroxy, carboxy, mercapto or amino
20 functional groups in the compounds described herein and the like.

In general, the compounds used in the reactions described herein may be made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" may be obtained from
25 standard commercial sources including Acros Organics (Pittsburgh PA), Aldrich Chemical (Milwaukee WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park UK), Avocado Research (Lancashire U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester PA), Crescent Chemical Co. (Hauppauge NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester
30 NY), Fisher Scientific Co. (Pittsburgh PA), Fisons Chemicals (Leicestershire UK),

Frontier Scientific (Logan UT), ICN Biomedicals, Inc. (Costa Mesa CA), Key Organics (Cornwall U.K.), Lancaster Synthesis (Windham NH), Maybridge Chemical Co. Ltd. (Cornwall U.K.), Parish Chemical Co. (Orem UT), Pfaltz & Bauer, Inc. (Waterbury CN), Polyorganix (Houston TX), Pierce Chemical Co. (Rockford IL), Riedel de Haen AG
5 (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland OR), Trans World Chemicals, Inc. (Rockville MD), and Wako Chemicals USA, Inc. (Richmond VA).

Methods known to one of ordinary skill in the art may be identified through various reference books and databases. Suitable reference books and treatise that
10 detail the synthesis of reactants useful in the preparation of compounds of the present disclosure, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc.
15 Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds of the present disclosure, or provide references to articles
20 that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional
25 Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Quin,
30 L.D. et al. "A Guide to Organophosphorus Chemistry" (2000) Wiley-Interscience,

ISBN: 0-471-31824-8; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" 5 (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

Specific and analogous reactants may also be identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical 10 Society, which are available in most public and university libraries, as well as through on-line databases (the American Chemical Society, Washington, D.C., may be contacted for more details). Chemicals that are known but not commercially available in catalogs may be prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A 15 reference for the preparation and selection of pharmaceutical salts of the present disclosure is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts," *Verlag Helvetica Chimica Acta*, Zurich, 2002.

Compound Synthesis

Detailed compound synthesis methods are described herein in the 20 Examples. A person having ordinary skill in the chemical art would be able to make a compound of Formula I, including specific compounds described herein, by these methods or similar methods or other methods practiced by a person skilled in the art. In general, starting components may be obtained from commercial sources.

Methods of Treatment

25 Methods are provided herein for treating or preventing (*i.e.*, reducing the likelihood of occurrence of neurological condition, disease or disorder including but not limited to Alzheimer's Disease, Lewy Body Dementia and the cognitive deficits associated with schizophrenia; Parkinson's Disease, drug induced Parkinsonism,

dyskinesias, dystonia, chorea, levodopa induced dyskinesia, cerebral palsy and progressive supranuclear palsy, and Huntington's disease, including chorea associate with Huntington's disease. While some of these diseases are considered cognitive disorders (*e.g.*, Alzheimer's disease), and other diseases are considered neurological
5 movement diseases/disorders, several have both cognitive and movement deficiencies or conditions associated with them (*e.g.*, Parkinson's disease, Huntington's disease).

The effectiveness of a muscarinic receptor antagonist, such as a selective M4 antagonist, with respect to treating a neurological condition, disease or disorder described herein can readily be determined by a person skilled in the medical and
10 clinical arts. One or any combination of diagnostic methods appropriate for the particular disease or disorder, which methods are well known to a person skilled in the art, including physical examination, patient self-assessment, assessment and monitoring of clinical symptoms, performance of analytical tests and methods, including clinical laboratory tests, physical tests, and exploratory surgery, for example, may be used for
15 monitoring the health status of the subject and the effectiveness of the inhibitor. The effects of the methods of treatment described herein can be analyzed using techniques known in the art, such as comparing symptoms of patients suffering from or at risk of a particular disease or disorder that have received the pharmaceutical composition comprising an antagonist with those of patients who were not treated with the inhibitor
20 or who received a placebo treatment.

As understood by a person skilled in the medical art, the terms, "treat" and "treatment," refer to medical management of a disease, disorder, or condition of a subject (*i.e.*, patient) (*see, e.g.*, Stedman's Medical Dictionary). In general, an appropriate dose and treatment regimen provide the M4 antagonist in an amount
25 sufficient to provide therapeutic and/or prophylactic benefit. Therapeutic benefit for subjects to whom the M4 antagonist compound(s) described herein are administered, includes, for example, an improved clinical outcome, wherein the object is to prevent or slow or retard (lessen) an undesired physiological change associated with the disease, or to prevent or slow or retard (lessen) the expansion or severity of such disease. As
30 discussed herein, effectiveness of the one or more M4 antagonists may include

beneficial or desired clinical results that comprise, but are not limited to, abatement, lessening, or alleviation of symptoms that result from or are associated with the disease to be treated; decreased occurrence of symptoms; improved quality of life; longer disease-free status (*i.e.*, decreasing the likelihood or the propensity that a subject will
5 present symptoms on the basis of which a diagnosis of a disease is made); diminishment of extent of disease; stabilized (*i.e.*, not worsening) state of disease; delay or slowing of disease progression; amelioration or palliation of the disease state; and remission (whether partial or total), whether detectable or undetectable; and/or overall survival.

“Treatment” can also mean prolonging survival when compared to
10 expected survival if a subject were not receiving treatment. Subjects in need of treatment include those who already have the disease or disorder as well as subjects prone to have or at risk of developing the disease or disorder, and those in which the disease, condition, or disorder is to be prevented (*i.e.*, decreasing the likelihood of occurrence or recurrence of the disease or disorder).

15 A subject (*i.e.*, patient, individual) in need of treatment with an M4 antagonist as described herein may be a human or may be a non-human primate or other animal (*i.e.*, veterinary use) who has developed symptoms of a hyperkinetic disease or disorder or who is at risk for developing a hyperkinetic disease or disorder. Non-human animals that may be treated include mammals, for example, non-human primates (*e.g.*,
20 monkey, chimpanzee, gorilla, and the like), rodents (*e.g.*, rats, mice, gerbils, hamsters, ferrets, rabbits), lagomorphs, swine (*e.g.*, pig, miniature pig), equine, canine, feline, bovine, elephants, bears and other domestic, farm, and zoo animals.

Pharmaceutical Compositions

The present disclosure further provides for pharmaceutical compositions
25 comprising any one of the M4 antagonist compounds described herein (a compound of Formula I, including specific compounds described herein) and a pharmaceutically acceptable excipient for use in the methods for treating hyperkinetic disorders. A pharmaceutically acceptable excipient is a physiologically and pharmaceutically suitable non-toxic and inactive material or ingredient that does not interfere with the

activity of the active ingredient; an excipient also may be called a carrier. The formulation methods and excipients described herein are exemplary and are in no way limiting. Pharmaceutically acceptable excipients are well known in the pharmaceutical art and described, for example, in Rowe *et al.*, Handbook of Pharmaceutical Excipients: A Comprehensive Guide to Uses, Properties, and Safety, 5th Ed., 2006, and in Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)). Exemplary pharmaceutically acceptable excipients include sterile saline and phosphate buffered saline at physiological pH. Preservatives, stabilizers, dyes, buffers, and the like may be provided in the pharmaceutical composition. In addition, antioxidants and suspending agents may also be used.

For compositions formulated as liquid solutions, acceptable carriers and/or diluents include saline and sterile water, and may optionally include antioxidants, buffers, bacteriostats and other common additives. The compositions can also be formulated as pills, capsules, granules, or tablets which contain, in addition to an M4 antagonist, diluents, dispersing and surface active agents, binders, and lubricants. One skilled in this art may further formulate the M4 antagonist in an appropriate manner, and in accordance with accepted practices, such as those disclosed in *Remington, supra*.

Methods of administration include systemic administration of an M4 antagonist described herein, preferably in the form of a pharmaceutical composition as discussed above. As used herein, systemic administration includes oral and parenteral methods of administration. For oral administration, suitable pharmaceutical compositions include powders, granules, pills, tablets, and capsules as well as liquids, syrups, suspensions, and emulsions. These compositions may also include flavorants, preservatives, suspending, thickening and emulsifying agents, and other pharmaceutically acceptable additives. For parental administration, the compounds of the present invention can be prepared in aqueous injection solutions which may contain, in addition to the M4 antagonist, buffers, antioxidants, bacteriostats, and other additives commonly employed in such solutions.

As described herein optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose of the M4 antagonist may depend upon the body mass, weight, blood volume, or other individual characteristics of the subject. For example, a person skilled in the medical art can consider the subject's condition, that is, stage of the disease, severity of symptoms caused by the disease, general health status, as well as age, gender, and weight, and other factors apparent to a person skilled in the medical art. In general, the amount of a compound described herein, that is present in a dose ranges from about 0.1 mg to about 2 mg per kg weight of the subject. In certain embodiments, a daily dose is about 10 - 150 mg. The use of the minimum dose that is sufficient to provide effective therapy is usually preferred. Subjects may generally be monitored for therapeutic effectiveness by clinical evaluation and using assays suitable for the condition being treated or prevented, which methods will be familiar to those having ordinary skill in the art and are described herein. The level of a compound that is administered to a subject may be monitored by determining the level of the compound in a biological fluid, for example, in the blood, blood fraction (*e.g.*, plasma, serum), and/or in the urine, and/or other biological sample from the subject. Any method practiced in the art to detect the compound may be used to measure the level of compound during the course of a therapeutic regimen.

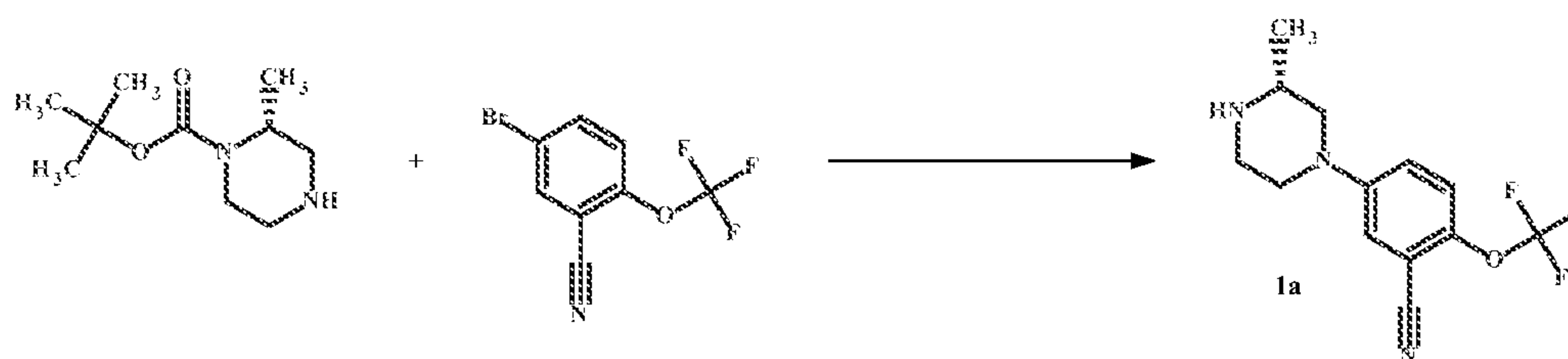
Pharmaceutical composition comprising an M4 antagonist may formulated for timed release (also called extended release, sustained release, controlled release, or slow release). Such compositions may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain the compound dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Excipients for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release, and the nature of the condition to be treated or prevented.

The pharmaceutical compositions described herein that comprise at least one of the M4 antagonist compounds described herein may be administered to a subject in need by any one of several routes that effectively deliver an effective amount of the compound. Such administrative routes include, for example, oral, parenteral (*e.g.*,
 5 subcutaneous, intravenous, intramuscular, intrasternal, intracavernous), enteral, rectal, intranasal, buccal, sublingual, intramuscular, and transdermal.

Kits with unit doses of one or more of the compounds described herein, usually in oral or injectable doses, are provided. Such kits may include a container containing the unit dose, an informational package insert describing the use and
 10 attendant benefits of the drugs in treating pathological condition of interest, and optionally an appliance or device for delivery of the composition.

EXAMPLES

EXAMPLE 1



15 Step 1A: 5-[(3R)-3-methylpiperazin-1-yl]-2-(trifluoromethoxy)benzonitrile

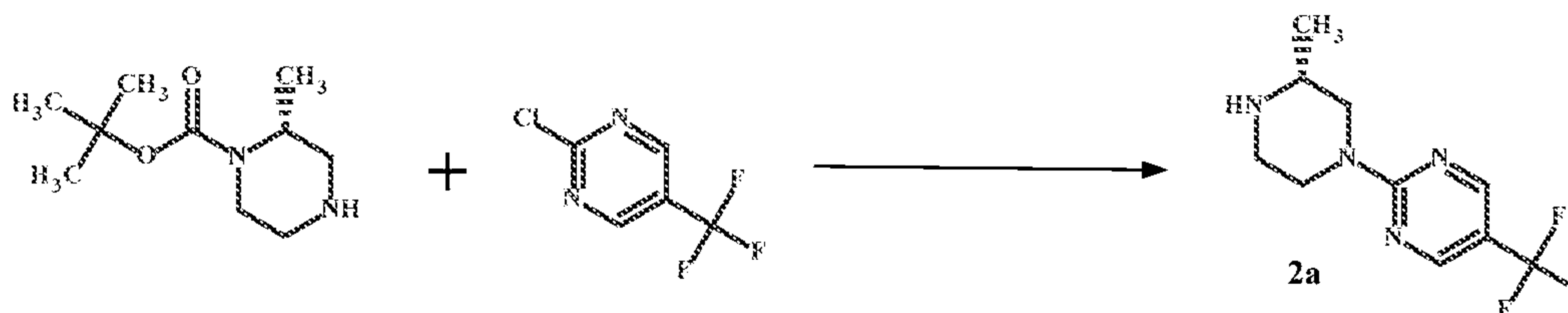
To a solution of tert-butyl (2R)-2-methylpiperazine-1-carboxylate (5.0 g, 25 mmol, 1.0 eq) and 5-bromo-2-(trifluoromethoxy)benzonitrile (3.8 mL, 25 mmol, 1 eq) in toluene (100 mL) was added sodium tert-butoxide (7.2 g, 75 mmol, 3.0 eq), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.6 g, 2.5 mmol, 0.10 eq), and
 20 lastly tris(dibenzylideneacetone)dipalladium(0) (2.3 g, 2.5 mmol, 0.10 eq), and the reaction mixture heated to 100 °C overnight. The resulting dark reaction mixture was cooled, passed thru a pad of celite, and concentrated *in vacuo*. Silica gel column (80 g) was dry loaded and run using an increasing gradient of EtOAc (0-50%) in hexanes over

25 min. The chromatographed material was dissolved in dioxane (40 mL) and treated with a solution of 4M HCl in dioxane (10 mL). The resulting thick suspension was concentrated, dissolved in MeOH, and made basic with the addition of MP-carbonate. Following removal of the resin and concentration of the filtrate, the free base of 5-
 5 [(3R)-3-methylpiperazin-1-yl]-2-(trifluoromethoxy)benzonitrile **1a** (5.2 g, 18 mmol, 72% over two steps) was isolated as an orange oil.

In general, this reaction is completed with stirring overnight, however if necessary, additional acid equivalents and/or gentle heat (50 °C) can be used to push the reaction.

10 Other compounds made using the above synthetic scheme include:
 1-(3,4-difluorophenyl)piperazine **1b**;
 3-(piperazin-1-yl)benzonitrile **1c**;
 2-fluoro-5-(piperazin-1-yl)benzonitrile **1d**;
 3-fluoro-5-(piperazin-1-yl)benzonitrile **1e**;
 15 1-[4-(trifluoromethoxy)phenyl]piperazine **1f**;
 1-[3-(trifluoromethoxy)phenyl]piperazine **1g**;
 1-(3,4,5-trifluorophenyl)piperazine **1h**;
 (3R)-3-methyl-1-[4-(trifluoromethyl)phenyl]piperazine **1i**;
 2-fluoro-5-[(3R)-3-methylpiperazin-1-yl]benzonitrile **1j**;
 20 3-fluoro-5-[(3R)-3-methylpiperazin-1-yl]benzonitrile **1k**;
 (3R)-3-methyl-1-(3,4,5-trifluorophenyl)piperazine **1l**;
 (3R)-3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]piperazine **1m**;
 (3R)-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-3-methylpiperazine
1n;
 25 (3R)-3-methyl-1-[5-(trifluoromethoxy)pyridin-2-yl]piperazine **1o**; and
 (3R)-3-methyl-1-[6-(trifluoromethoxy)pyridin-3-yl]piperazine **1p**.

EXAMPLE 2



STEP 2A: 2-[(3R)-3-METHYLPIPERAZIN-1-YL]-5-(TRIFLUOROMETHYL)PYRIMIDINE

To a solution of tert-butyl (2R)-2-methylpiperazine-1-carboxylate (2.2 g, 11.0 mmol, 1.0 eq) and 2-chloro-5-(trifluoromethyl)pyrimidine (2.0 g, 11.0 mmol, 1.0 eq) in 1-methyl-2-pyrrolidone (NMP, 10 mL) was added *N,N*-diisopropylethylamine (5.7 mL, 44.0 mmol, 4.0 eq) and the reaction mixture heated to 100 °C for 1 hr. The reaction mixture was cooled, diluted heavily with EtOAc, and washed repeatedly with brine (5x). The organic layer was dried over Na₂SO₄ and concentrated. Silica gel column (80 g) was loaded using methylene chloride and run using an increasing gradient of EtOAc (5-90%) in hexanes over 20 min. The chromatographed material was dissolved in dioxane (25 mL) and treated with a solution of 4M HCl in dioxane (6 mL). The resulting thick white suspension was concentrated, dissolved in MeOH, and made basic with the addition of MP-carbonate. Following removal of the resin and concentration of the filtrate, the free base of 2-[(3R)-3-methylpiperazin-1-yl]-5-(trifluoromethyl)pyrimidine **2a** (1.9 g, 7.6 mmol, 69% over two steps) was isolated as a white solid.

In general, this reaction is completed with stirring overnight, however if necessary, additional acid equivalents and/or gentle heat (50 °C) can be used to push the reaction.

Other compounds made using the above synthetic scheme include:

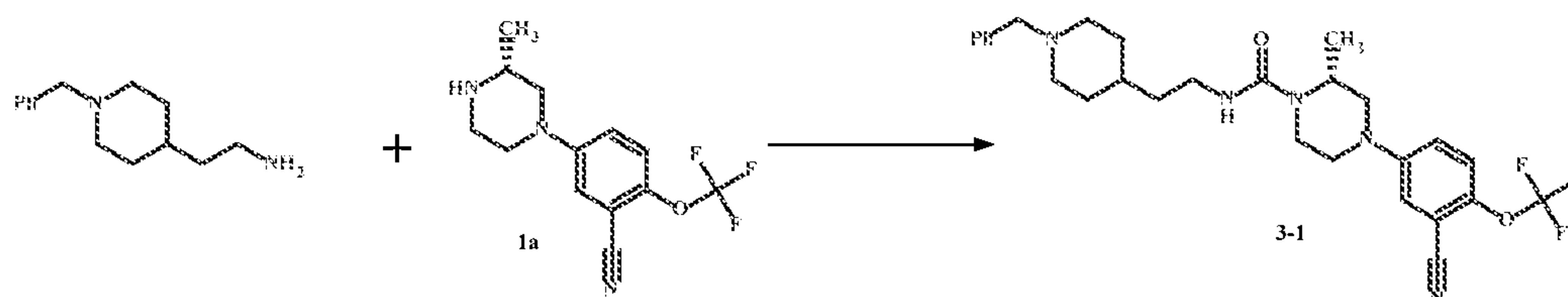
4-(dimethylamino)-2-[(3R)-3-methylpiperazin-1-yl]pyrimidine-5-carbonitrile **2b**;

2-[(1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl]pyrimidine-5-carbonitrile **2c**;

2-[(3R)-3-methylpiperazin-1-yl]-5-(trifluoromethyl)pyrimidin-4-amine **2d**;

- 2-[(3R)-3-methylpiperazin-1-yl]pyrimidine-5-carbonitrile **2e**;
 2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]pyrimidine-5-carbonitrile **2f**;
 2-{2,5-diazabicyclo[2.2.2]octan-2-yl}pyrimidine-5-carbonitrile **2g**;
 2-{2,6-diazaspiro[3.3]heptan-2-yl}pyrimidine-5-carbonitrile **2h**;
 2-{3,6-diazabicyclo[3.1.1]heptan-3-yl}pyrimidine-5-carbonitrile **2i**;
 2-{3,8-diazabicyclo[3.2.1]octan-3-yl}pyrimidine-5-carbonitrile **2j**;
 5-chloro-2-[(3R)-3-methylpiperazin-1-yl]pyrimidine **2k**;
 5-chloro-2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]pyrimidine **2l**;
 6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-5-fluoropyridine-3-carbonitrile
 10 **2m**; and
 6-[(3R,5S)-3,5-dimethylpiperazin-1-yl]pyridine-3-carbonitrile **2n**.

EXAMPLE 3



Step 3A: (2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-cyano-4-
 15 (trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide

Triphosgene (2.1 g, 7.2 mmol, 0.40 eq) was dissolved in methylene chloride (50 mL) and a solution of 5-[(3R)-3-methylpiperazin-1-yl]-2-(trifluoromethoxy)benzonitrile **1a** (5.2 g, 18 mmol, 1.0 eq) and *N,N*-diisopropylethylamine (6.0 mL, 36 mmol, 2.0 eq) in methylene chloride (50 mL) was added dropwise at room temperature. Once the addition was complete, the reaction mixture was stirred for 10 min before a solution of 2-(1-benzylpiperidin-4-yl)ethan-1-amine (4.8 g, 22 mmol, 1.2 eq) and *N,N*-diisopropylethylamine (6.0 mL, 36 mmol, 2.0 eq) in methylene chloride (50 mL) was added and stirred at room temperature for an additional 1 hr. Then, the reaction was diluted further with methylene chloride and
 25 washed with sat. NH_4Cl followed by sat. NaHCO_3 . The combined organic layers were

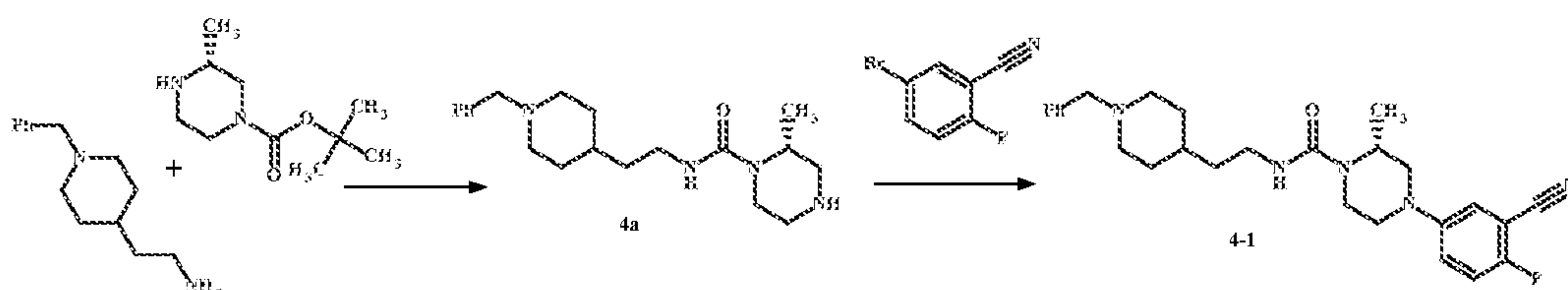
dried over Na₂SO₄ and concentrated *in vacuo*. Silica gel column (80 g) was loaded using methylene chloride and run with an increasing gradient of MeOH (0-20%) in methylene chloride over 20 min to provide (2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-cyano-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide **3-1** (5.2 g, 9.8 mmol, 54%) as an orange oil. The table below provides the observed (Obs) ion m/z ratio for **3-1** (first compound listed in Table 1) and other compounds that were made according to the procedure as described in this example.

Table 1

Cpd. No.	Compound Name	Obs Ion (m/z)
3-1	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-cyano-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	530.2
3-2	(1S)-1-(1-benzylpiperidin-4-yl)-2- {[(2R)-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carbonyl]amino} ethyl acetate	522.25
3-3	(2R)-N-[(2S)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-4-(3-cyano-4-fluorophenyl)-N,2-dimethylpiperazine-1-carboxamide	494.2
3-4	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-4-fluorophenyl)-N,2-dimethylpiperazine-1-carboxamide	478.2
3-5	(2R)-N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-4-[3-cyano-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	546.2
3-6	(2R)-N-[(2S)-2-(1-benzylpiperidin-4-yl)-2-methoxyethyl]-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carboxamide	494.2
3-7	(2R)-4-[3-cyano-4-(trifluoromethoxy)phenyl]-N-(2-{1-[(4-iodophenyl)methyl]piperidin-4-yl}ethyl)-2-methylpiperazine-1-carboxamide	656.1
3-8	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[6-(trifluoromethoxy)pyridin-3-yl]piperazine-1-carboxamide	506.2
3-9	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	491.2
3-10	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-2-methylpiperazine-1-carboxamide	508.2
3-11	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-5-fluorophenyl)-2-methylpiperazine-1-carboxamide	464.2

Cpd. No.	Compound Name	Obs Ion (m/z)
3-12	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	475.2
3-13	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[5-(trifluoromethoxy)pyridin-2-yl]piperazine-1-carboxamide	506.2
3-14	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	490.2
3-15	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyanopyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	448.2
3-16	(2R)-N-[(2R)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	491.2
3-17	(2R)-N-{2-[1-benzyl-3-(hydroxymethyl)piperidin-4-yl]ethyl}-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	505.2
3-18	(2R)-N-[(2S)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carboxamide	480.2
3-19	N-{2-[1-benzyl-3-(hydroxymethyl)piperidin-4-yl]ethyl}-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	491.2
3-20	(2R)-N-{2-[1-benzyl-4-(hydroxymethyl)piperidin-4-yl]ethyl}-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	505.2
3-21	(2R)-N-[(2S)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-4-[3-cyano-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	546.2
3-22	(2R)-N-[(2S)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	491.2
3-23	(2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyridin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	461.1

EXAMPLE 4



Step 4A: (2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methylpiperazine-1-carboxamide

Triphosgene (1.2 g, 4.0 mmol, 0.40 eq) was dissolved in methylene chloride (20 mL) and a solution of tert-butyl (3R)-3-methylpiperazine-1-carboxylate (2.0 g, 10 mmol, 1.0 eq) and *N,N*-diisopropylethylamine (1.6 mL, 10 mmol, 1.0 eq) in methylene chloride (30 mL) was added dropwise at room temperature. Once complete, the reaction mixture was stirred for 10 min before a solution of 2-(1-benzylpiperidin-4-yl)ethan-1-amine (2.6 g, 12 mmol, 1.2 eq) and *N,N*-diisopropylethylamine (1.6 mL, 10 mmol, 1.0 eq) in methylene chloride (30 mL) was added. Stirring at room temperature, the reaction was complete within 1 hr. The reaction mixture was diluted further with methylene chloride and washed with sat. NH_4Cl followed by sat. NaHCO_3 . The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column (40 g) was loaded using methylene chloride and run with an increasing gradient of MeOH (0-25%) in methylene chloride over 20 min. The chromatographed material was dissolved in dioxane (40 mL) and treated with a solution of 4M HCl in dioxane (5 mL). In general, this reaction is completed with stirring overnight, however if necessary, additional acid equivalents and/or gentle heat (50 °C) can be used to push the reaction. The resulting light yellow suspension was concentrated, dissolved in MeOH, and made basic with the addition of MP-carbonate.

Following removal of the resin and concentration of the filtrate, the free base of (2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methylpiperazine-1-carboxamide **4a** (2.0 g, 5.8 mmol, 58% over two steps) was isolated as a yellow oil. (2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide **4b** was made according to the same procedure, but with appropriately modified starting materials.

Step 4B: (2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carboxamide

To a solution of (2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methylpiperazine-1-carboxamide **4a** (20 mg, 0.06 mmol, 1.0 eq) and 5-bromo-2-fluorobenzonitrile (12 mg, 0.06 mmol, 1.0 eq) in 1:1 dioxane:toluene (1 mL) was added

sodium *tert*-butoxide (17 mg, 0.18 mmol, 3.0 eq), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (3.7 mg, 0.006 mmol, 0.10 eq), and lastly tris(dibenzylideneacetone)-dipalladium(0) (5.5 mg, 0.006 mmol, 0.10 eq), and the reaction mixture stirred vigorously at 100 °C overnight. The resulting dark suspension was cooled, passed
 5 through an HPLC filter and concentrated *in vacuo*. The crude material was treated with 1.5 mL of MeOH, passed through an additional HPLC filter (leaving any precipitate behind), and submitted for directly for preparative chromatography yielding (2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carboxamide **4-1**. The table below provides the observed (Obs) ion m/z ratio for **4-1**
 10 (first compound listed in Table 2) and other compounds that were made according to the procedure as described in this example.

Table 2

Cpd. No.	Compound Name	Obs Ion (m/z)
4-1	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carboxamide	464.2
4-2	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-methoxypyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	453.3
4-4	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-3-methylphenyl)-2-methylpiperazine-1-carboxamide	460.3
4-5	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	489.2
4-6	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-2-methylpiperazine-1-carboxamide	501.2
4-8	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide	452.3
4-9	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(6-methylpyridin-3-yl)piperazine-1-carboxamide	436.3

Cpd. No.	Compound Name	Obs Ion (m/z)
4-10	(2S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	505.2
4-11	(2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chloro-6-cyanopyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	496.2
4-12	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[4-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	490.2
4-13	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-fluoro-4-methylphenyl)-2-methylpiperazine-1-carboxamide	453.3
4-14	(2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyanopyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	462.2
4-15	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3,4-difluorophenyl)-2-methylpiperazine-1-carboxamide	457.2
4-16	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[3-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	505.2
4-17	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	475.2
4-18	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-4-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	505.2
4-19	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-fluoro-6-methylpyridin-2-yl)-2-methylpiperazine-1-carboxamide	454.2
4-20	(2S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carboxamide	464.2
4-21	(2S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-cyano-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	530.2
4-22	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-fluoro-4-(trifluoromethoxy)phenyl]-3-methylpiperazine-1-carboxamide	523.2
4-23	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyridin-3-yl)-2-methylpiperazine-1-carboxamide	447.2

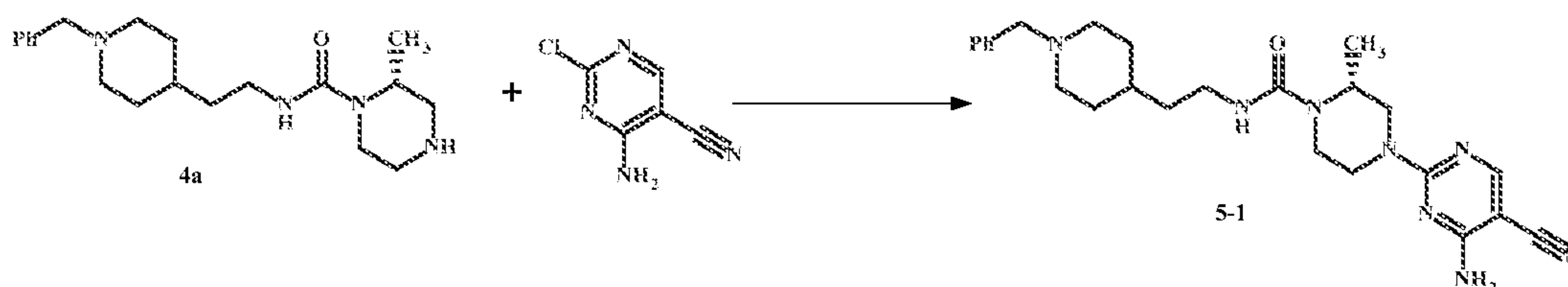
Cpd. No.	Compound Name	Obs Ion (m/z)
4-24	(2S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	475.2
4-25	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyanophenyl)-2-methylpiperazine-1-carboxamide	446.2
4-26	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyano-4-methoxypyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	478.2
4-27	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-fluoro-4-methoxypyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	471.2
4-28	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-cyano-4-(dimethylamino)pyrimidin-2-yl]-2-methylpiperazine-1-carboxamide	491.4
4-28	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-4-methoxyphenyl)-2-methylpiperazine-1-carboxamide	476.3
4-30	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-fluorophenyl)-2-methylpiperazine-1-carboxamide	439.2
4-31	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyridin-2-yl)-2-methylpiperazine-1-carboxamide	447.2
4-33	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2,4-difluorophenyl)-2-methylpiperazine-1-carboxamide	457.2
4-34	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[6-(trifluoromethyl)pyridin-3-yl]piperazine-1-carboxamide	490.3
4-35	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(6-fluoropyridin-3-yl)-2-methylpiperazine-1-carboxamide	440.2
4-36	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(2,4,5-trifluorophenyl)piperazine-1-carboxamide	475.2
4-37	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2,3-difluorophenyl)-2-methylpiperazine-1-carboxamide	457.2
4-38	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4,6-dicyanopyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	473.2

Cpd. No.	Compound Name	Obs Ion (m/z)
4-39	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-5-methoxyphenyl)-2-methylpiperazine-1-carboxamide	476.3
4-40	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(quinolin-3-yl)piperazine-1-carboxamide	472.3
4-41	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-fluoropyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	441.3
4-43	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-2-fluorophenyl)-2-methylpiperazine-1-carboxamide	464.3
4-44	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanothiophen-2-yl)-2-methylpiperazine-1-carboxamide	452.2
4-45	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2,5-difluorophenyl)-2-methylpiperazine-1-carboxamide	457.2
4-46	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-fluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide	440.2
4-47	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-phenylpiperazine-1-carboxamide	421.3
4-48	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3,5-difluoropyridin-2-yl)-2-methylpiperazine-1-carboxamide	458.2
4-49	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-fluorophenyl)-2-methylpiperazine-1-carboxamide	439.2
4-50	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbonyl}-3-methylpiperazin-1-yl]-6-methyl-N-(propan-2-yl)pyrimidine-4-carboxamide	522.2
4-51	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(6-methoxypyridin-2-yl)-2-methylpiperazine-1-carboxamide	452.3
4-52	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-chloro-4,5-difluorophenyl)-2-methylpiperazine-1-carboxamide	491.2
4-53	(2S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-fluoro-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	523.2

Cpd. No.	Compound Name	Obs Ion (m/z)
4-54	(2S,6R)-4-(4-amino-5-cyanopyrimidin-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide	477.3
4-55	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-5-fluoropyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	466.2
4-56	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-methoxyphenyl)-3-methylpiperazine-1-carboxamide	451.3
4-60	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3,5-difluoro-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	541.2
4-61	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-fluoropyridin-3-yl)-2-methylpiperazine-1-carboxamide	440.2
4-62	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(pyridin-2-yl)piperazine-1-carboxamide	422.2
4-63	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(5-methylpyridin-3-yl)piperazine-1-carboxamide	436.3
4-64	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(pyrimidin-2-yl)piperazine-1-carboxamide	423.2
4-68	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyanophenyl)-2-methylpiperazine-1-carboxamide	446.2
4-69	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyano-4-methoxypyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	492.2
4-70	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-fluoro-4-methoxyphenyl)-2-methylpiperazine-1-carboxamide	469.3
4-71	(3S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	475.2
4-72	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3,5-difluorophenyl)-2-methylpiperazine-1-carboxamide	457.25
4-73	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[2-fluoro-4-(trifluoromethyl)phenyl]-2-methylpiperazine-1-carboxamide	507.2

Cpd. No.	Compound Name	Obs Ion (m/z)
4-74	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	461.3
4-75	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4,6-dicyanopyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	473.2
4-76	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	475.2
4-77	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	476.1
4-78	(2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyano-3-fluoropyridin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	479.2
4-79	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	491.17
4-80	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-cyanopyrimidin-5-yl)-2-methylpiperazine-1-carboxamide	448.15

EXAMPLE 5



Step 5A: (2R)-4-(4-amino-5-cyanopyrimidin-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methylpiperazine-1-carboxamide

To a solution of (2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methylpiperazine-1-carboxamide **4a** (0.20 g, 0.58 mmol, 1.0 eq) and 4-amino-2-chloropyrimidine-5-carbonitrile (0.90 g, 0.58 mmol, 1.0 eq) in NMP (2 mL) was added *N,N*-diisopropylethylamine (0.38 mL, 2.3 mmol, 4.0 eq) and the reaction mixture

heated to 100 °C for 1 hr. In some cases, lower temperatures or longer reaction times were used. The reaction mixture was cooled, diluted heavily with EtOAc, and washed repeatedly with brine (3x). The organic layer was dried over Na₂SO₄ and concentrated. Silica gel column (24 g) was loaded using methylene chloride and run using an increasing gradient of MeOH (0-20%) in methylene chloride over 20 min to provide (2R)-4-(4-amino-5-cyanopyrimidin-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methylpiperazine-1-carboxamide **5-1** (0.14 g, 0.31 mmol, 53%) as an off-white foam. The table below provides the observed (Obs) ion m/z ratio for **5-1** (first compound listed in Table 3) and other compounds that were made according to the procedure as described in this example.

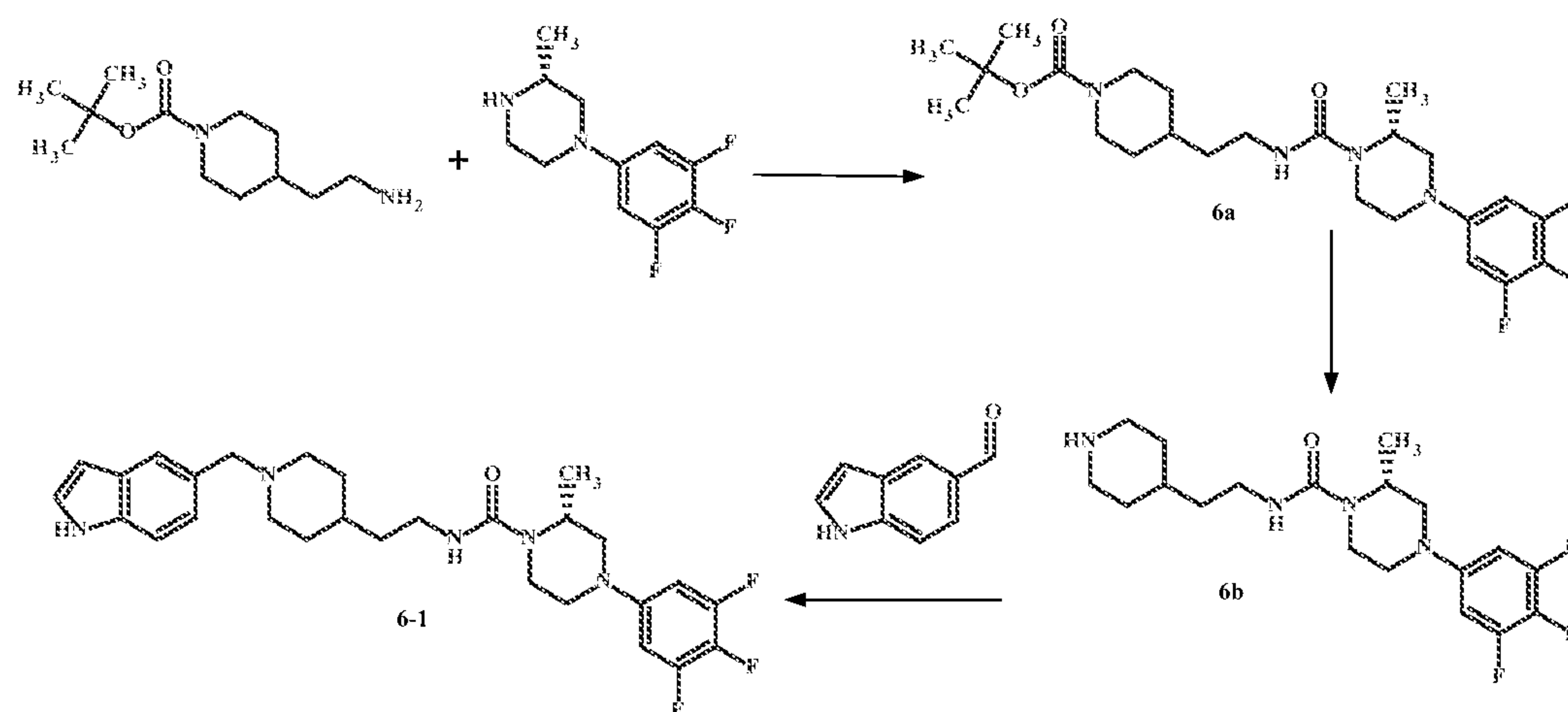
Table 3

Cpd. No.	Compound Name	Obs Ion (m/z)
5-1	(2R)-4-(4-amino-5-cyanopyrimidin-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methylpiperazine-1-carboxamide	463.2
5-2	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]pyrimidine-5-carboxylic acid	467.2
5-3	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4,5-dichloropyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	491.1
5-4	(2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-{5-cyano-4-[(2,2,2-trifluoroethyl)amino]pyrimidin-2-yl}-2,6-dimethylpiperazine-1-carboxamide	559.2
5-5	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chloro-6-cyanopyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	482.2
5-6	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(trifluoropyrimidin-2-yl)piperazine-1-carboxamide	477.2
5-7	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-{5-cyano-4-[(2,2,2-trifluoroethyl)amino]pyrimidin-2-yl}-2-methylpiperazine-1-carboxamide	545.2
5-8	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[4-	491.2

Cpd. No.	Compound Name	Obs Ion (m/z)
	(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	
5-9	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chloro-5-fluoropyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	475.2
5-10	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-bromo-4-chloropyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	537.1
5-11	methyl 2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-6-chloropyrimidine-4-carboxylate	515.1
5-12	methyl 2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-6-methylpyrimidine-4-carboxylate	495.2
5-13	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	448.3
5-14	(2S,6R)-4-(4-amino-5-cyanopyrimidin-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide	477.3
5-15	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-cyano-4-(dimethylamino)pyrimidin-2-yl]-2-methylpiperazine-1-carboxamide	491.4
5-16	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyano-4-methoxypyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	478.2
5-17	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyano-4-methoxypyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	492.2
5-18	(2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-chloropyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	471.2
5-19	(2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-fluoropyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	455.25
5-20	(2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	462.3
5-21	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-cyano-4-(methylamino)pyrimidin-2-yl]-2,6-dimethylpiperazine-1-carboxamide	491.3

Cpd. No.	Compound Name	Obs Ion (m/z)
5-22	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-chloropyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	457.2
5-23	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-cyano-4-(methylamino)pyrimidin-2-yl]-2-methylpiperazine-1-carboxamide	477.2
5-24	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	477.15
5-25	(3S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyrimidin-2-yl)-3-(hydroxymethyl)piperazine-1-carboxamide	464.2
5-26	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyrimidin-2-yl)-2-(hydroxymethyl)piperazine-1-carboxamide	464.2
5-27	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	505.1
5-28	(2R,6S)-4-[4-amino-5-(trifluoromethyl)pyrimidin-2-yl]-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide	520.1
5-29	(2R)-4-[4-amino-5-(trifluoromethyl)pyrimidin-2-yl]-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methylpiperazine-1-carboxamide	506.1
5-30	4-[4-amino-5-(trifluoromethyl)pyrimidin-2-yl]-N-[2-(1-benzylpiperidin-4-yl)ethyl]piperazine-1-carboxamide	492.1
5-31	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-bromopyrimidin-2-yl)-2-methylpiperazine-1-carboxamide	501.2
5-32	(2R)-4-(4-amino-5-chloropyrimidin-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methylpiperazine-1-carboxamide	472.0
5-33	4-(4-amino-5-chloropyrimidin-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]piperazine-1-carboxamide	458.0
5-34	4-(4-amino-5-fluoropyrimidin-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]piperazine-1-carboxamide	442.0

EXAMPLE 6



Step 6A: (2R)-2-methyl-N-[2-(piperidin-4-yl)ethyl]-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide

- 5 Triphosgene (1.3 g, 4.4 mmol, 0.40 eq) was dissolved in methylene chloride (30 mL) and a solution of (3R)-3-methyl-1-(3,4,5-trifluorophenyl)piperazine **11** (2.5 g, 11 mmol, 1.0 eq) and *N,N*-diisopropylethylamine (3.6 mL, 22 mmol, 2.0 eq) in methylene chloride (30 mL) was added dropwise at room temperature. Once the addition was complete, the reaction mixture was stirred for 10 min before a solution of
- 10 tert-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (2.9 g, 13 mmol, 1.2 eq) and *N,N*-diisopropylethylamine (3.6 mL, 22 mmol, 2.0 eq) in methylene chloride (30 mL) was added. Stirring at room temperature, the reaction was complete within 1 hr. The reaction mixture was diluted further with methylene chloride and washed with sat. NH_4Cl followed by sat. NaHCO_3 . The combined organic layers were dried over
- 15 Na_2SO_4 , concentrated *in vacuo*, and loaded onto a silica gel column (40 g). Elution with an increasing gradient of EtOAc (0-100%) in hexanes over 25 min yielded tert-butyl
- 4-(2-{[(2R)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carbonyl]amino}ethyl)piperidine-1-carboxylate **6a**. This chromatographed material was dissolved in dioxane (60 mL) and treated with a solution of 4M HCl in dioxane (10
- 20 mL). After stirring overnight, the resulting light yellow suspension was concentrated, dissolved in MeOH, and made basic with the addition of MP-carbonate.

Following removal of the resin and concentration of the filtrate, the free base of (2R)-2-methyl-N-[2-(piperidin-4-yl)ethyl]-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide **6b** (2.2 g, 5.8 mmol, 53% over two steps) was isolated as a brown foam. (2S,6R)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-[2-(piperidin-4-yl)ethyl]piperazine-1-carboxamide **6c** was made according to the same procedure, but with appropriately modified starting materials.

Step 6B: (2R)-N-{2-[1-(1H-indol-5-ylmethyl)piperidin-4-yl]ethyl}-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide

To NMP solutions of (2R)-2-methyl-N-[2-(piperidin-4-yl)ethyl]-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide **6b** (0.05 mL, 0.50 M, 1 eq) and 1H-indole-5-carbaldehyde (0.05 mL, 0.50 M, 1 eq) was added an ethanolic solution of borane-pyridine complex (0.10 mL, 0.50 M, 2 eq) followed by acetic acid (5 µL) and the mixture stirred at RT overnight. The reaction mixture was diluted to a total volume of 1 mL using MeOH and submitted directly for preparative chromatography yielding (2R)-N-{2-[1-(1H-indol-5-ylmethyl)piperidin-4-yl]ethyl}-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide **6-1**. The table below provides the observed (Obs) ion m/z ratio for **6-1** (first compound listed in Table 4) and other compounds that were made according to the procedure as described in this example.

Table 4

Cpd. No.	Compound Name	Obs Ion (m/z)
6-1	(2R)-N-{2-[1-(1H-indol-5-ylmethyl)piperidin-4-yl]ethyl}-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	514.2
6-2	(2R)-N-(2-{1-[(4-cyanophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	500.2
6-3	(2R)-N-{2-[1-(2,3-dihydro-1-benzofuran-7-ylmethyl)piperidin-4-yl]ethyl}-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	517.2
6-4	(2R)-N-(2-{1-[(4-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	493.2

Cpd. No.	Compound Name	Obs Ion (m/z)
6-5	(2R)-N-(2-{1-[(2-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	493.2
6-6	(2R)-N-{2-[1-(cyclohexylmethyl)piperidin-4-yl]ethyl}-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	481.3
6-7	(2R)-2-methyl-N-{2-[1-(pyridin-2-ylmethyl)piperidin-4-yl]ethyl}-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	476.2
6-8	(2R)-2-methyl-N-{2-[1-(1,2,3-thiadiazol-4-ylmethyl)piperidin-4-yl]ethyl}-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	483.2
6-9	(2R)-N-{2-[1-(2,3-dihydro-1,4-benzodioxin-6-ylmethyl)piperidin-4-yl]ethyl}-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	533.2
6-10	(2R)-N-(2-{1-[(3-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	493.2
6-11	1-(5-cyanopyridin-2-yl)-N-{2-[1-(1H-indol-5-ylmethyl)piperidin-4-yl]ethyl}piperidine-4-carboxamide	471.3
6-12	(2R)-2-methyl-N-(2-{1-[(2-methyl-1,3-thiazol-4-yl)methyl]piperidin-4-yl}ethyl)-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	496.2
6-13	(2R)-N-[2-(1-{[2-(difluoromethoxy)phenyl]methyl}piperidin-4-yl)ethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	541.2
6-14	(2R)-2-methyl-N-{2-[1-(1-phenylethyl)piperidin-4-yl]ethyl}-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	489.2
6-15	4-(benzyloxy)-N-(2-{1-[(4-fluorophenyl)methyl]piperidin-4-yl}ethyl)benzamide	447.6
6-16	(2R)-N-(2-{1-[(4-carbamoylphenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	518.17
6-17	(2R)-N-(2-{1-[(2,3-difluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	511.2
6-18	(2R)-N-(2-{1-[(3-cyanophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	500.2
6-19	(2R)-2-methyl-N-(2-{1-[(5-methyl-1,3,4-oxadiazol-2-yl)(phenyl)methyl]piperidin-4-yl}ethyl)-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	557.2
6-20	(2R)-2-methyl-N-[2-(1-{[3-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)ethyl]-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	559.2

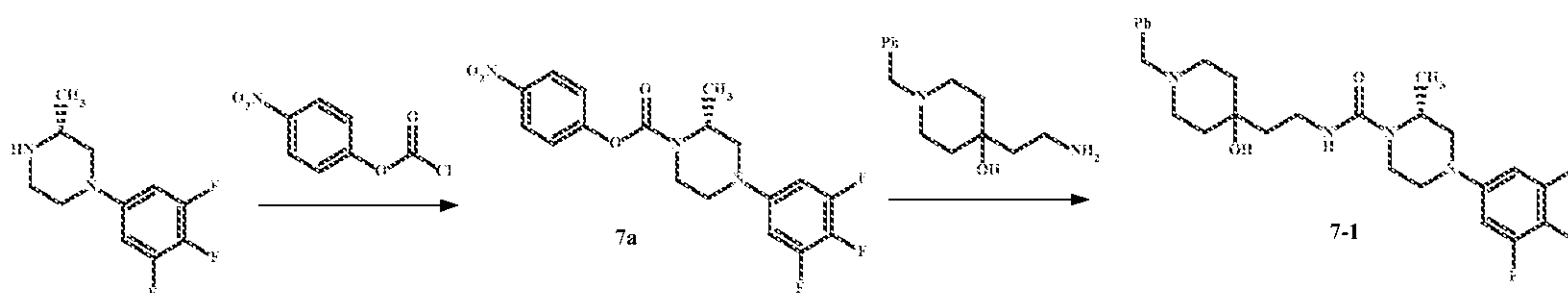
Cpd. No.	Compound Name	Obs Ion (m/z)
6-21	(2R)-2-methyl-N-[2-(1-{[2-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)ethyl]-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	559.2
6-22	(2R)-2-methyl-4-(3,4,5-trifluorophenyl)-N-(2-{1-[(2,3,4-trifluorophenyl)methyl]piperidin-4-yl}ethyl)piperazine-1-carboxamide	529.1
6-23	(2R)-N-(2-{1-[(3,5-difluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	511.2
6-24	(2R)-2-methyl-N-[2-(1-{[4-(trifluoromethoxy)phenyl]methyl}piperidin-4-yl)ethyl]-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	559.2
6-25	(2R)-N-(2-{1-[(2,5-difluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	511.2
6-26	(2R)-2-methyl-N-{2-[1-(thiophen-2-ylmethyl)piperidin-4-yl]ethyl}-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	481.2
6-27	(2R)-N-(2-{1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	491.2
6-28	(2R)-N-(2-{1-[(2,6-difluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	511.2
6-29	(2R)-N-(2-{1-[(2-cyanophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	500.2
6-30	(2R)-N-(2-{1-[(4-cyano-2-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	518.1
6-31	(2R)-2-methyl-N-{2-[1-(pyridin-4-ylmethyl)piperidin-4-yl]ethyl}-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	492.2
6-32	(2R)-2-methyl-N-{2-[1-(pyridin-3-ylmethyl)piperidin-4-yl]ethyl}-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	492.2
6-33	(2R)-2-methyl-N-{2-[1-(pyridin-2-ylmethyl)piperidin-4-yl]ethyl}-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	492.2
6-34	(2R)-N-(2-{1-[(2-cyanophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	516.1
6-35	(2R)-2-methyl-N-(2-{1-[(2-methylphenyl)methyl]piperidin-4-yl}ethyl)-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	505.2

Cpd. No.	Compound Name	Obs Ion (m/z)
6-36	(2R)-N-(2-{1-[(3-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	509.1
6-37	(2R)-N-(2-{1-[(4-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	509.1
6-38	(2R)-N-(2-{1-[(2-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	509.2
6-39	(2R)-2-methyl-N-{2-[1-(pyrimidin-5-ylmethyl)piperidin-4-yl]ethyl}-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	492.3
6-40	(2R)-N-(2-{1-[(3-cyanophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	516.1
6-41	(2R)-N-(2-{1-[(4-cyanophenyl)methyl]piperidin-4-yl}ethyl)-2-methyl-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	516.1
6-42	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-(2-{1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-2,6-dimethylpiperazine-1-carboxamide	478.1
6-43	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-[2-(1-{[4-(dimethylamino)phenyl]methyl}piperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide	505.1
6-44	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-{2-[1-(2-phenylethyl)piperidin-4-yl]ethyl}piperazine-1-carboxamide	476.0
6-45	(2R,6S)-N-(2-{1-[(4-cyanophenyl)methyl]piperidin-4-yl}ethyl)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	487.0
6-46	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-(2-{1-[(3-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2,6-dimethylpiperazine-1-carboxamide	480.1
6-47	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-{2-[1-(1H-indol-5-ylmethyl)-piperidin-4-yl]ethyl}-2,6-dimethylpiperazine-1-carboxamide	501.0
6-48	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-(2-{1-[(4-fluorophenyl)methyl]-piperidin-4-yl}ethyl)-2,6-dimethylpiperazine-1-carboxamide	480.0

Cpd. No.	Compound Name	Obs Ion (m/z)
6-49	(2R,6S)-N-(2-{1-[(4-hydroxy-3-methylphenyl)methyl]piperidin-4-yl}ethyl)-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	535.1
6-50	(2R,6S)-N-{2-[1-(1H-indol-5-ylmethyl)piperidin-4-yl]ethyl}-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	544.1
6-51	(2R,6S)-N-(2-{1-[(3-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	523.1
6-52	(2R,6S)-N-(2-{1-[(2-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	523.0
6-53	(2R,6S)-N-[2-(1-{[4-(dimethylamino)phenyl]methyl}piperidin-4-yl)ethyl]-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	548.1
6-54	(2R,6S)-N-(2-{1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	521.1
6-55	(2R,6S)-N-(2-{1-[(4-fluorophenyl)methyl]piperidin-4-yl}ethyl)-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	523.1
6-56	(2R,6S)-2,6-dimethyl-N-{2-[1-(2-phenylethyl)piperidin-4-yl]ethyl}-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	519.1
6-57	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-(2-{1-[(4-hydroxy-3-methylphenyl)methyl]piperidin-4-yl}ethyl)-2,6-dimethylpiperazine-1-carboxamide	492.0
6-58	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-{2-[1-(pyrimidin-2-ylmethyl)piperidin-4-yl]ethyl}piperazine-1-carboxamide	464.1
6-59	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-(2-{1-[(3-methoxyphenyl)methyl]piperidin-4-yl}ethyl)-2,6-dimethylpiperazine-1-carboxamide	492.1
6-60	(2R,6S)-N-{2-[1-(1-benzofuran-5-ylmethyl)piperidin-4-yl]ethyl}-4-(5-cyanopyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	502.0
6-61	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-{2-[1-(pyridin-3-ylmethyl)piperidin-4-yl]ethyl}piperazine-1-carboxamide	463.1

Cpd. No.	Compound Name	Obs Ion (m/z)
6-62	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-{2-[1-(pyridin-4-ylmethyl)piperidin-4-yl]ethyl} piperazine-1-carboxamide	463.1
6-63	(4-{[4-(2-{[(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethylpiperazine-1-carbonyl]amino}ethyl)piperidin-1-yl]methyl} phenyl)boronic acid	506.1
6-64	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-(2-{1-[(2-fluoropyridin-3-yl)methyl]piperidin-4-yl}ethyl)-2,6-dimethylpiperazine-1-carboxamide	481.1
6-65	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-(2-{1-[(4-methoxyphenyl)-methyl]piperidin-4-yl}ethyl)-2,6-dimethylpiperazine-1-carboxamide	492.1
6-66	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-(2-{1-[(1-methyl-1H-1,2,3-benzotriazol-5-yl)methyl]piperidin-4-yl}ethyl)piperazine-1-carboxamide	517.0
6-67	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-(2-{1-[(2-methoxyphenyl)-methyl]piperidin-4-yl}ethyl)-2,6-dimethylpiperazine-1-carboxamide	492.0

EXAMPLE 7



Step 7A: (2R)-N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide

A solution of (3R)-3-methyl-1-(3,4,5-trifluorophenyl)piperazine **11** (0.30 g, 1.3 mmol, 1.0 eq) and triethylamine (0.34 mL, 2.6 mmol, 2.0 eq) in methylene chloride (20 mL) was prepared and cooled to 0 °C. Then, 4-nitrophenyl chloroformate (0.29 g, 1.4 mmol, 1.1 eq) was added dropwise and the mixture stirred for 10 min at 0 °C before removing the ice bath and stirring for an additional 15 min. The reaction

mixture was diluted with methylene chloride, washed with sat. NH_4Cl , dried over Na_2SO_4 and concentrated *in vacuo*. Purification on a silica gel column (12 g) using an increasing gradient of MeOH (0-10%) in methylene chloride provided (2R)-N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide **7a** (0.40 g, 1.0 mmol, 78%) as a yellow oil.

Step 7B: (3R)-3-methyl-1-(3,4,5-trifluorophenyl)piperazine 4-(2-aminoethyl)-1-benzylpiperidin-4-ol

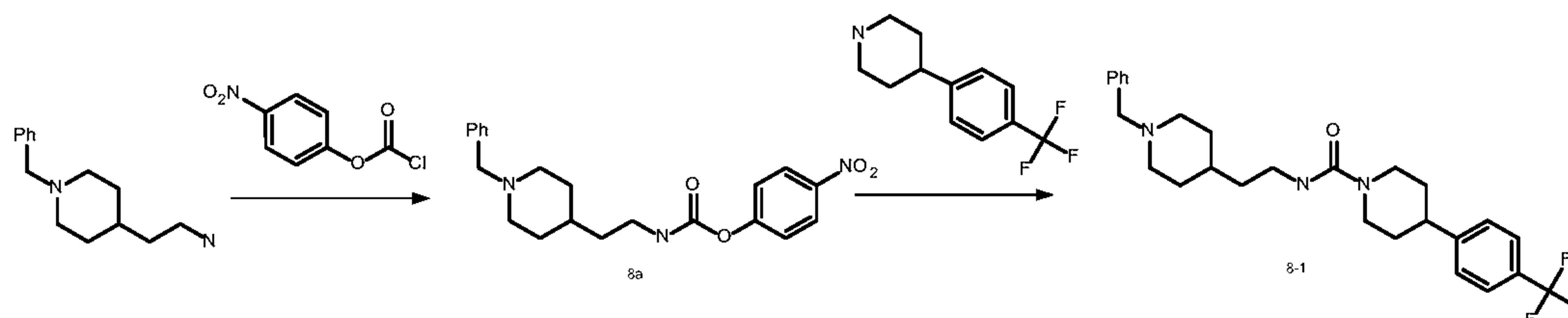
To NMP solutions of (2R)-N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide **7a** (0.05 mL, 0.50 M, 1.0 eq) and 4-(2-aminoethyl)-1-benzylpiperidin-4-ol **14b** (0.05 mL, 0.50 M, 1.0 eq) was added a NMP solution of triethylamine (0.05 mL, 2.0 M, 4.0 eq) and the mixture stirred at RT overnight. The reaction was diluted to a total volume of 1 mL using MeOH and submitted directly for preparative chromatography yielding (3R)-3-methyl-1-(3,4,5-trifluorophenyl)piperazine 4-(2-aminoethyl)-1-benzylpiperidin-4-ol **7-1**. The table below provides the observed (Obs) ion m/z ratio for **7-1** (first compound listed in Table 5) and other compounds that were made according to the procedure as described in this example.

Table 5

Cpd. No.	Compound Name	Obs Ion (m/z)
7-1	(2R)-N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	491.2
7-2	(2R)-N-{2-[1-benzyl-4-(hydroxymethyl)piperidin-4-yl]ethyl}-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carboxamide	494.2
7-3	(2R)-N-[2-(4-benzylpiperazin-1-yl)ethyl]-4-[3-cyano-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	531.2
7-4	(2R)-N-[(2R)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-4-(3-cyano-5-fluorophenyl)-2-methylpiperazine-1-carboxamide	480.3
7-5	(2R)-N-{2-[(3S)-1-benzylpyrrolidin-3-yl]ethyl}-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	461.2

Cpd. No.	Compound Name	Obs Ion (m/z)
7-6	(2R)-N-[2-(4-benzylpiperazin-1-yl)ethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	476.2
7-7	(2R)-N-[2-(4-benzyl-4-hydroxypiperidin-1-yl)ethyl]-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	491.2
7-8	(2R)-N-{2-[(3S)-1-benzylpyrrolidin-3-yl]ethyl}-4-(3-cyano-5-fluorophenyl)-2-methylpiperazine-1-carboxamide	450.2
7-9	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-(difluoromethyl)-4-fluorophenyl]-2-methylpiperazine-1-carboxamide	489.2
7-10	(2R)-N-[(2R)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-4-[3-cyano-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	546.2
7-11	(2R)-N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carboxamide	480.2
7-12	(2R)-N-[(2R)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-4-(3-cyano-4-fluorophenyl)-2-methylpiperazine-1-carboxamide	480.2
7-13	(2R)-N-(2-{[(3R,5R)-1-benzyl-5-(hydroxymethyl)pyrrolidin-3-yl](methyl)amino}ethyl)-2-methyl-4-(3,4,5-trifluorophenyl)piperazine-1-carboxamide	520.2

EXAMPLE 8

Step 8A: 4-Nitrophenyl N-[2-(1-benzylpiperidin-4-yl)ethyl]carbamate

5 A solution of 2-(1-benzylpiperidin-4-yl)ethan-1-amine (0.50 g, 2.3 mmol, 1.0 eq) in methylene chloride (10 mL) was prepared and added dropwise to a cooled methylene chloride solution (10 mL, 0 °C) of 4-nitrophenyl chloroformate (0.51 g, 2.5 mmol, 1.1 eq) and triethylamine (0.64 mL, 4.6 mmol, 2.0 eq). The reaction mixture was diluted further with methylene chloride, washed with sat. NH₄Cl, dried

over MgSO₄ and concentrated *in vacuo*. Silica gel column was loaded using methylene chloride and run with an increasing gradient of MeOH (0-10%) in methylene chloride to provide 4-nitrophenyl N-[2-(1-benzylpiperidin-4-yl)ethyl]carbamate **8a** (0.51 g, 1.0 mmol, 57%) as a yellow oil. Phenyl N-[2-(1-benzylpiperidin-4-yl)ethyl]carbamate **8b** was made according to the same procedure, but with appropriately modified starting materials.

Step 8B: N-[2-(1-Benzylpiperidin-4-yl)ethyl]-4-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide

To a NMP solution of 4-nitrophenyl N-[2-(1-benzylpiperidin-4-yl)ethyl]carbamate **8a** (0.05 mL, 0.50 M, 1 eq) and 4-(4-trifluoromethylphenyl)piperidine (0.05 mL, 0.50 M, 1 eq) was added a NMP solution of triethylamine (0.05 mL, 2.0 M, 4 eq) and the mixture stirred at RT overnight. The reaction was diluted to a total volume of 1 mL using MeOH and submitted directly for preparative chromatography which yielded N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide **8-1**. The table below provides the observed (Obs) ion m/z ratio for **8-1** (first compound listed in Table 6) and other compounds that were made according to the procedure as described in this example.

Table 6

Cpd. No.	Compound Name	Obs Ion (m/z)
8-1	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-(trifluoromethyl)phenyl]piperidine-1-carboxamide	474.3
8-2	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	491.3
8-3	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-(trifluoromethyl)phenyl]piperidine-1-carboxamide	474.3
8-4	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chlorophenyl)piperidine-1-carboxamide	440.3

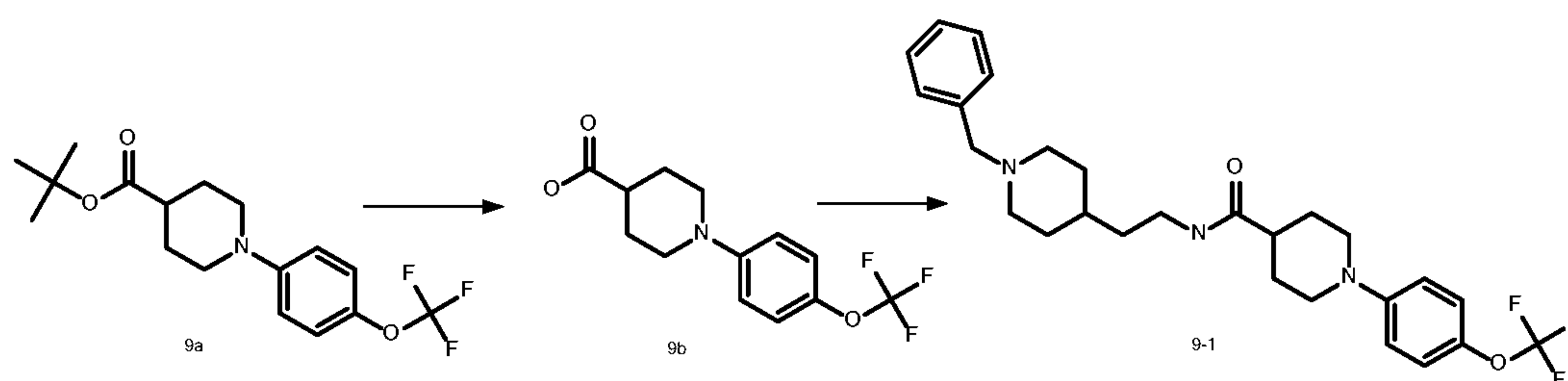
Cpd. No.	Compound Name	Obs Ion (m/z)
8-5	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-methoxyphenyl)piperidine-1-carboxamide	436.1
8-6	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-methoxyphenyl)piperidine-1-carboxamide	436.1
8-7	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chloro-2-cyanophenyl)piperazine-1-carboxamide	466.2
8-8	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxamide	491.3
8-9	1-[2-(1-benzylpiperidin-4-yl)ethyl]-3-[1-(5-bromopyridin-2-yl)pyrrolidin-3-yl]-3-methylurea	500.2
8-10	4-(1-benzothiophen-3-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]piperidine-1-carboxamide	462.4
8-11	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-chlorophenyl)piperazine-1-carboxamide	441.4
8-12	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[2-cyano-4-(trifluoromethyl)phenyl]piperazine-1-carboxamide	500.2
8-13	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chlorophenyl)piperazine-1-carboxamide	441.3
8-14	4-(1,3-benzothiazol-2-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]piperidine-1-carboxamide	463.4
8-15	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperazine-1-carboxamide	510.1
8-16	1-[2-(1-benzylpiperidin-4-yl)ethyl]-3-{1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]pyrrolidin-3-yl}-3-methylurea	524.2
8-17	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-(trifluoromethyl)phenyl]piperazine-1-carboxamide	475.3
8-18	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-5-fluorophenyl)piperazine-1-carboxamide	450.23

Cpd. No.	Compound Name	Obs Ion (m/z)
8-19	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-hydroxy-4-[3-(trifluoromethyl)phenyl]piperidine-1-carboxamide	490.4
8-20	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-fluorophenyl)piperidine-1-carboxamide	424.2
8-21	1-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-3-{1-[4-(trifluoromethyl)phenyl]pyrrolidin-3-yl}urea	489.3
8-22	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-4-fluorophenyl)piperazine-1-carboxamide	450.3
8-23	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chlorophenyl)-4-hydroxypiperidine-1-carboxamide	456.2
8-24	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-methoxyphenyl)piperidine-1-carboxamide	436.1
8-25	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyanophenyl)piperazine-1-carboxamide	432.3
8-26	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-fluorophenyl)piperidine-1-carboxamide	424.1
8-27	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyanophenyl)piperazine-1-carboxamide	432.7
8-28	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-hydroxyphenyl)piperazine-1-carboxamide	423.4
8-29	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(pyrimidin-2-yl)piperazine-1-carboxamide	409.3
8-30	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(1H-indol-3-yl)piperidine-1-carboxamide	445.1
8-31	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[3-(propan-2-yl)-1,2,4-oxadiazol-5-yl]piperidine-1-carboxamide	440.2
8-32	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-fluorophenyl)piperidine-1-carboxamide	424.1

Cpd. No.	Compound Name	Obs Ion (m/z)
8-33	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-cyano-4-phenylpiperidine-1-carboxamide	431.1
8-34	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-fluorophenyl)piperazine-1-carboxamide	425.3
8-35	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-fluorophenyl)piperazine-1-carboxamide	425.45
8-36	4-(4-acetylphenyl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]piperazine-1-carboxamide	449.2
8-37	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-ethylpiperazin-1-yl)piperidine-1-carboxamide	442.4
8-38	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-phenylpiperidine-1-carboxamide	406.3
8-39	1-[2-(1-benzylpiperidin-4-yl)ethyl]-3-[1-(4-fluorophenyl)piperidin-4-yl]urea	439.4
8-40	3-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[1-(3-cyanophenyl)piperidin-4-yl]urea	446.3
8-41	3-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(4-phenoxyphenyl)urea	430.2
8-42	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-hydroxy-4-(2-methoxyphenyl)piperidine-1-carboxamide	452.2
8-43	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[2-(hydroxymethyl)-4-methylphenyl]piperazine-1-carboxamide	451.2
8-44	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-oxo-1,2,3,4-tetrahydroquinazolin-3-yl)piperidine-1-carboxamide	476.2
8-45	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyridin-2-yl)piperazine-1-carboxamide	433.5
8-46	4-(1H-1,2,3-benzotriazol-1-yl)-N-[2-(1-benzylpiperidin-4-yl)ethyl]piperidine-1-carboxamide	447.2

Cpd. No.	Compound Name	Obs Ion (m/z)
8-47	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-chloropyridin-2-yl)piperazine-1-carboxamide	442.3
8-48	N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-(5-cyanopyrimidin-2-yl)-3,8-diazabicyclo[3.2.1]octane-8-carboxamide	460.0

EXAMPLE 9

Step 9A: 1-[4-(Trifluoromethoxy)phenyl]piperidine-4-carboxylic acid

5 To a solution of tert-butyl piperidine-4-carboxylate (1.6 g, 8.7 mmol, 1.0 eq) and 1-iodo-4-(trifluoromethoxy)benzene (2.5 g, 8.7 mmol, 1.0 eq) in toluene (100 mL) was added sodium *tert*-butoxide (2.5 g, 25 mmol, 3.0 eq), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (0.54 g, 0.87 mmol, 0.10 eq), and lastly tris(dibenzylideneacetone)-dipalladium(0) (0.80 g, 0.87 mmol, 0.10 eq), and the

10 reaction mixture heated to 100 °C overnight. The resulting dark reaction mixture was cooled, passed thru a pad of celite, and concentrated *in vacuo*. Silica gel column (40 g) was dry loaded and run using an increasing gradient of EtOAc (0-50%) in hexanes over 25 min yielding tert-butyl 1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxylate **9a**. The chromatographed material **9a** was dissolved in 20% TFA in methylene chloride (50

15 mL) and heated to 60 °C overnight. Following concentration, solid material was obtained by precipitation from hexanes and ether. The resulting white solid was collected by vacuum filtration to provide 1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxylic acid **9b** (1.5 g, 5.2 mmol, 60% over two steps).

Step 9B: N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide

To a solution of acid **9b** (0.30 g, 1.0 mmol, 1.0 eq) and 2-(1-benzylpiperidin-4-yl)ethan-1-amine (0.26 g, 1.2 mmol, 1.2 eq) in methylene chloride (5 mL) was added triethylamine (0.41 mL, 3.0 mmol, 3.0 eq) followed by HATU (0.46 g, 1.2 mmol, 1.2 eq) and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with sat. NH₄Cl and extracted with methylene chloride. The combined organic layers were dried over MgSO₄ and concentrated. A silica gel column was loaded using methylene chloride and run using an increasing gradient of MeOH (0-20%) in methylene chloride over 20 min to provide N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide **9-1** (0.39 g, 0.80 mmol, 80%). The table below provides the observed (Obs) ion m/z ratio for **9-1** (first compound listed in Table 7) and other compounds that were made according to the procedure as described in this example.

15

Table 7

Cpd. No.	Compound Name	Obs Ion (m/z)
9-1	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	490.3
9-2	N-(1-benzylpiperidin-4-yl)-N-cyclopropyl-4-phenylbenzamide	411.3
9-3	N-[2-(1-benzylpiperidin-4-yl)ethyl]-N-(2-hydroxyethyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	534.3
9-4	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(4-chlorophenyl)-4-methyl-1,3-thiazole-5-carboxamide	454.1
9-5	(2R)-N-[(2S)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-4-(3-cyano-5-fluorophenyl)-2-methylpiperazine-1-carboxamide	480.2
9-6	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-fluoro-4-[4-(trifluoromethoxy)phenyl]benzamide	501.2

Cpd. No.	Compound Name	Obs Ion (m/z)
9-7	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-(trifluoromethoxy)phenyl]benzamide	483.15
9-8	N-[2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	506.2
9-9	N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-1-[3-fluoro-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	524.2
9-10	(2R)-N-{2-[(3S)-1-benzylpyrrolidin-3-yl]ethyl}-4-[3-cyano-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	516.2
9-11	N-{2-[1-benzyl-4-(hydroxymethyl)piperidin-4-yl]ethyl}-1-[3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	520.2
9-12	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chlorophenyl)-2-fluorobenzamide	451.2
9-13	N-{2-[1-benzyl-4-(hydroxymethyl)piperidin-4-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	520.3
9-14	methyl 4-(4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}phenyl)benzoate	457.25
9-15	N-[(2R)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-1-(3-cyano-4-fluorophenyl)piperidine-4-carboxamide	465.2
9-16	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-(trifluoromethyl)phenyl]benzamide	467.3
9-17	N-(2-{[(3S)-1-benzylpyrrolidin-3-yl](methyl)amino}ethyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	505.3
9-18	4-chloro-3-(3-cyanoquinolin-2-yl)-N-[(3R)-1-cyclohexylpyrrolidin-3-yl]-N-methylbenzamide	473.2
9-19	N-[2-(4-benzyl-4-hydroxypiperidin-1-yl)ethyl]-2-[4-(trifluoromethoxy)phenyl]imidazo[1,2-a]pyridine-7-carboxamide	539.2
9-20	N-{2-[(3R)-1-benzylpyrrolidin-3-yl]ethyl}-4-chloro-3-(4-chloro-6-methylpyridin-3-yl)benzamide	468.1

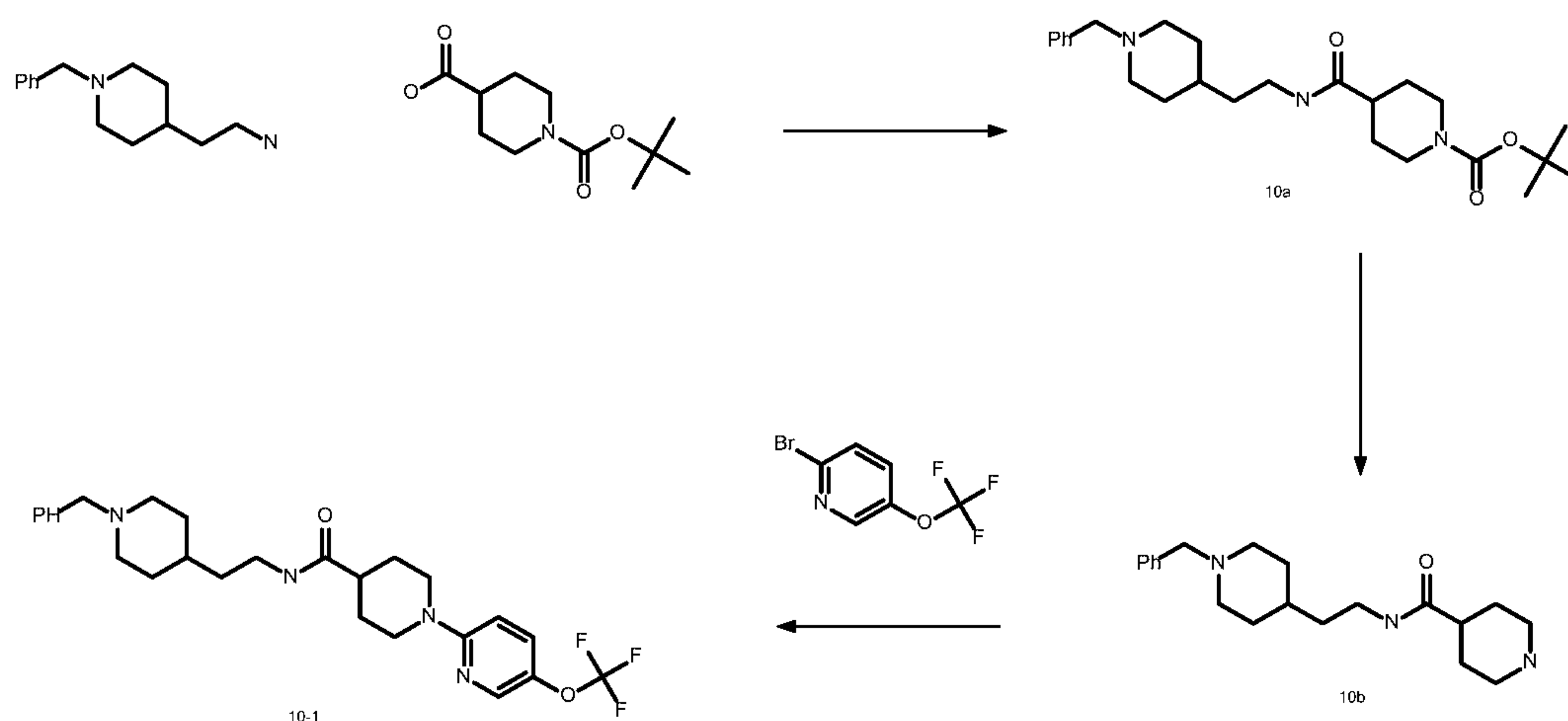
Cpd. No.	Compound Name	Obs Ion (m/z)
9-21	1-(1-benzylpiperidin-4-yl)-4-{1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidine-4-carbonyl}piperazine	550.2
9-22	N-(2-{[(3R)-1-benzylpyrrolidin-3-yl](methyl)amino}ethyl)-1-[3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	505.3
9-23	N-[1-(1-benzylpiperidin-4-yl)pyrrolidin-3-yl]-N-methyl-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	545.3
9-24	N-{2-[1-benzyl-4-(hydroxymethyl)piperidin-4-yl]ethyl}-1-(3-cyano-4-fluorophenyl)piperidine-4-carboxamide	479.2
9-25	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-[4-(trifluoromethoxy)phenyl]imidazo[1,2-a]pyridine-7-carboxamide	523.2
9-26	N-(2-{[(3R)-1-benzylpyrrolidin-3-yl](methyl)amino}ethyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	505.3
9-27	N-[2-(1-benzyl-3-hydroxypiperidin-4-yl)ethyl]-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	506.2
9-28	N-(2-{[(3R)-1-benzylpyrrolidin-3-yl]amino}ethyl)-1-[3-fluoro-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	509.2
9-29	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(4-cyanophenyl)piperidine-4-carboxamide	431.5
9-30	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyanophenyl)benzamide	424.3
9-31	N-(2-{[(3S)-1-benzylpyrrolidin-3-yl](methyl)amino}ethyl)-1-[3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	505.3
9-32	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazole-5-carboxamide	488.2
9-33	N-[(3R)-1-benzylpyrrolidin-3-yl]-N-methyl-1-{1-[4-(trifluoromethoxy)phenyl]piperidine-4-carbonyl}piperidin-4-amine	545.3
9-34	N-[2-(1-benzylpiperidin-4-yl)ethyl]-N-methyl-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	504.3

Cpd. No.	Compound Name	Obs Ion (m/z)
9-35	N-(2-{[1-benzyl-4-(hydroxymethyl)pyrrolidin-3-yl](methyl)amino}ethyl)-1-[3-fluoro-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	553.3
9-36	3-(1-benzylpiperidin-4-yl)-N-{1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}propanamide	490.2
9-37	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-bromopyrimidin-2-yl)piperidine-4-carboxamide	488.1
9-38	N-(2-{[(3R)-1-benzylpyrrolidin-3-yl](methyl)amino}ethyl)-4-phenylbenzamide	414.2
9-39	N-(2-{[(3R)-1-benzylpyrrolidin-3-yl](methyl)amino}ethyl)-4-[4-(trifluoromethoxy)phenyl]benzamide	498.3
9-40	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-fluoro-4-(4-methylphenyl)benzamide	431.25
9-41	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-fluorophenyl)benzamide	417.3
9-42	1-benzyl-1-methyl-4-[2-(N-methyl-1-{1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}formamido)ethyl]piperidin-1-ium	518.3
9-43	2-[4-(benzyloxy)phenyl]-N-[2-(1-benzylpiperidin-4-yl)ethyl]acetamide	443.3
9-44	N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-1-(3-cyano-4-fluorophenyl)piperidine-4-carboxamide	465.2
9-45	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2,6-dioxo-1,3-dipropyl-2,3,6,9-tetrahydro-1H-purin-8-yl)benzamide	557.3
9-46	N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-1-[3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	506.2
9-47	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-cyanopyridin-2-yl)piperidine-4-carboxamide	432.3

Cpd. No.	Compound Name	Obs Ion (m/z)
9-48	N-(1-benzylpiperidin-4-yl)-N-cyclopropyl-2-[4-(trifluoromethoxy)phenyl]imidazo[1,2-a]pyridine-7-carboxamide	535.2
9-49	N-{2-[(3S)-1-benzylpyrrolidin-3-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	476.3
9-50	3-(1-benzylpiperidin-4-yl)-N-{1-[3-(trifluoromethoxy)phenyl]piperidin-4-yl}propanamide	490.2
9-51	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(4-methoxyphenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	484.25
9-52	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(4-methylpyridin-2-yl)piperidine-4-carboxamide	421.3
9-53	N-(1-benzylpiperidin-4-yl)-N-cyclopropyl-4-(thiophen-2-yl)benzamide	417.2
9-54	N-(2-{[(3R)-1-benzylpyrrolidin-3-yl]amino}ethyl)-1-[3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	491.2
9-55	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(thiophen-2-yl)benzamide	405.2
9-56	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[(trifluoromethyl)sulfanyl]benzamide	423.1
9-57	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(6-fluoropyridin-3-yl)-4-methyl-1,3-thiazole-5-carboxamide	438.1
9-58	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]-N-cyclopropylpiperidine-4-carboxamide	549.2
9-59	N-[2-(1-benzylpiperidin-4-yl)ethyl]-5-(4-methoxyphenyl)-7-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-2-carboxamide	538.2
9-60	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-chloro-3-(3-cyanoquinolin-2-yl)benzamide	509.2
9-61	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2,4-dichlorophenyl)-5-methyl-1H-imidazole-4-carboxamide	471

Cpd. No.	Compound Name	Obs Ion (m/z)
9-62	N-{2-[1-benzyl-3-(hydroxymethyl)piperidin-4-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	520.2
9-63	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxamide	509.2
9-64	N-{2-[1-benzyl-4-(hydroxymethyl)piperidin-4-yl]ethyl}-1-[3-fluoro-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	538.2
9-65	N-[(1-benzylpiperidin-4-yl)methyl]-1-[3-chloro-5-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxamide	495.1
9-66	N-{2-[(3R)-1-benzylpyrrolidin-3-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	476.2
9-67	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-chloro-3-(4-chloro-6-methylpyridin-3-yl)benzamide	482.2
9-68	N-[2-(4-benzylpiperidin-1-yl)ethyl]-2-[4-(trifluoromethoxy)phenyl]imidazo[1,2-a]pyridine-7-carboxamide	523.1
9-69	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-hydroxyphenyl)benzamide	415.05
9-70	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-(trifluoromethoxy)phenyl]benzamide	483.15
9-71	N-[2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	506.2
9-72	N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-1-[3-fluoro-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	524.2
9-73	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3-cyano-4-fluorophenyl)piperidine-4-carboxamide	449.3
9-74	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-cyanopyridin-2-yl)-2-methyl-1H-imidazole-4-carboxamide	429.1
9-75	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-cyanopyridin-2-yl)-1H-imidazole-4-carboxamide	415.1

EXAMPLE 10

Step 10A: N-[2-(1-benzylpiperidin-4-yl)ethyl]piperidine-4-carboxamide

To a solution of 1-[(tert-butoxy)carbonyl]piperidine-4-carboxylic acid (2.0 g, 8.7 mmol, 1.0 eq) and 2-(1-benzylpiperidin-4-yl)ethan-1-amine (2.2 g, 9.6 mmol, 1.1 eq) in methylene chloride (20 mL) was added triethylamine (4.3 mL, 26.1 mmol, 3.0 eq) followed by HATU (4.0 g, 10.4 mmol, 1.2 eq) and the reaction stirred at room temperature overnight. The reaction mixture was diluted with saturated NH_4Cl and extracted with methylene chloride. The combined organic layers were dried over MgSO_4 and concentrated. A silica gel column was loaded using methylene chloride and run using an increasing gradient of MeOH (0-10%) in methylene chloride over 20 min yielding tert-butyl 4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}piperidine-1-carboxylate **10a**. A portion of the chromatographed **10a** (1.0 g, 2.3 mmol) was dissolved in 20% TFA in methylene chloride (5 mL) and heated to 50 °C overnight. The reaction mixture was concentrated, dissolved in MeOH, and made basic with the addition of MP-carbonate. Following removal of the resin and concentration of the filtrate, the free base of N-[2-(1-benzylpiperidin-4-yl)ethyl]piperidine-4-carboxamide **10b** (0.62 g, 1.9 mmol, 83%) was isolated as a yellow oil.

(3R,4R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methylpiperidine-4-carboxamide **10c** was synthesized following the same overall procedure.

Step 10B: N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[5-(trifluoromethoxy)pyridin-2-yl]piperidine-4-carboxamide

To a solution of **10b** (20 mg, 0.06 mmol, 1.0 eq) and 2-bromo-5-(trifluoromethoxy)pyridine (14 mg, 0.06 mmol, 1.0 eq) in toluene (1 mL) was added sodium tert-butoxide (17 mg, 0.18 mmol, 3.0 eq), racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (3.7 mg, 0.006 mmol, 0.10 eq), and lastly tris(dibenzylideneacetone)-dipalladium(0) (5.5 mg, 0.006 mmol, 0.10 eq), and the reaction mixture stirred vigorously at 100 °C overnight. The resulting dark suspension was cooled, passed through an HPLC filter and concentrated. Then, the crude material was treated with 1.5 mL of MeOH, passed through an additional HPLC filter (leaving any precipitate behind), and submitted for directly for preparative chromatography yielding N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[5-(trifluoromethoxy)pyridin-2-yl]piperidine-4-carboxamide **10-1**. The table below provides the observed (Obs) ion m/z ratio for **10-1** (first compound listed in Table 8) and other compounds that were made according to the procedure as described in this example.

Table 8

Cpd. No.	Compound Name	Obs Ion (m/z)
10-1	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[5-(trifluoromethoxy)pyridin-2-yl]piperidine-4-carboxamide	491.2
10-2	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3-cyano-4-methoxyphenyl)piperidine-4-carboxamide	461.3
10-3	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-phenylpiperidine-4-carboxamide	406.3
10-4	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-methyl-1-[2-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	504.2
10-5	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)piperidine-4-carboxamide	486.3
10-6	N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-1-[4-	504.25

Cpd. No.	Compound Name	Obs Ion (m/z)
	(trifluoromethoxy)phenyl]piperidine-4-carboxamide	
10-7	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3,4,5-trifluorophenyl)piperidine-4-carboxamide	460.3
10-8	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-fluoro-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	508.5
10-9	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-(trifluoromethyl)phenyl]piperidine-4-carboxamide	474.3
10-10	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-methoxy-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	520.3
10-11	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-fluoro-3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	508.3
10-12	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[2-fluoro-4-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	523.2
10-13	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-cyano-3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	515.2
10-14	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3-cyano-5-fluorophenyl)piperidine-4-carboxamide	449.3
10-15	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-cyanopyridin-3-yl)piperidine-4-carboxamide	432.3
10-16	N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-1-[2-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	504.2
10-17	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-fluoro-1-[2-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	508.2
10-18	N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-1-[3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	504.2
10-19	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	490.4
10-20	N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-1-[3-cyano-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	531.2

Cpd. No.	Compound Name	Obs Ion (m/z)
10-21	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3,4-difluorophenyl)piperidine-4-carboxamide	442.2
10-22	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3,5-difluorophenyl)piperidine-4-carboxamide	442.3
10-23	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-cyano-5-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	515.2
10-24	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[5-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxamide	475.3
10-25	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-methyl-1-[3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	504.2
10-26	2-(1-benzylpiperidin-4-yl)-N-({1-[3-(trifluoromethoxy)phenyl]piperidin-4-yl} methyl)acetamide	490.2
10-27	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(6-chloropyridin-3-yl)piperidine-4-carboxamide	441.2
10-28	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-methoxypyridin-2-yl)piperidine-4-carboxamide	437.2
10-29	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-methoxy-5-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	520.3
10-30	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-(trifluoromethyl)pyrimidin-2-yl]piperidine-4-carboxamide	476.3
10-31	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-methyl-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	504.2
10-32	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxamide	475.2
10-33	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-methoxy-3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	520.2
10-34	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[6-(trifluoromethoxy)pyridin-3-yl]piperidine-4-carboxamide	491.2

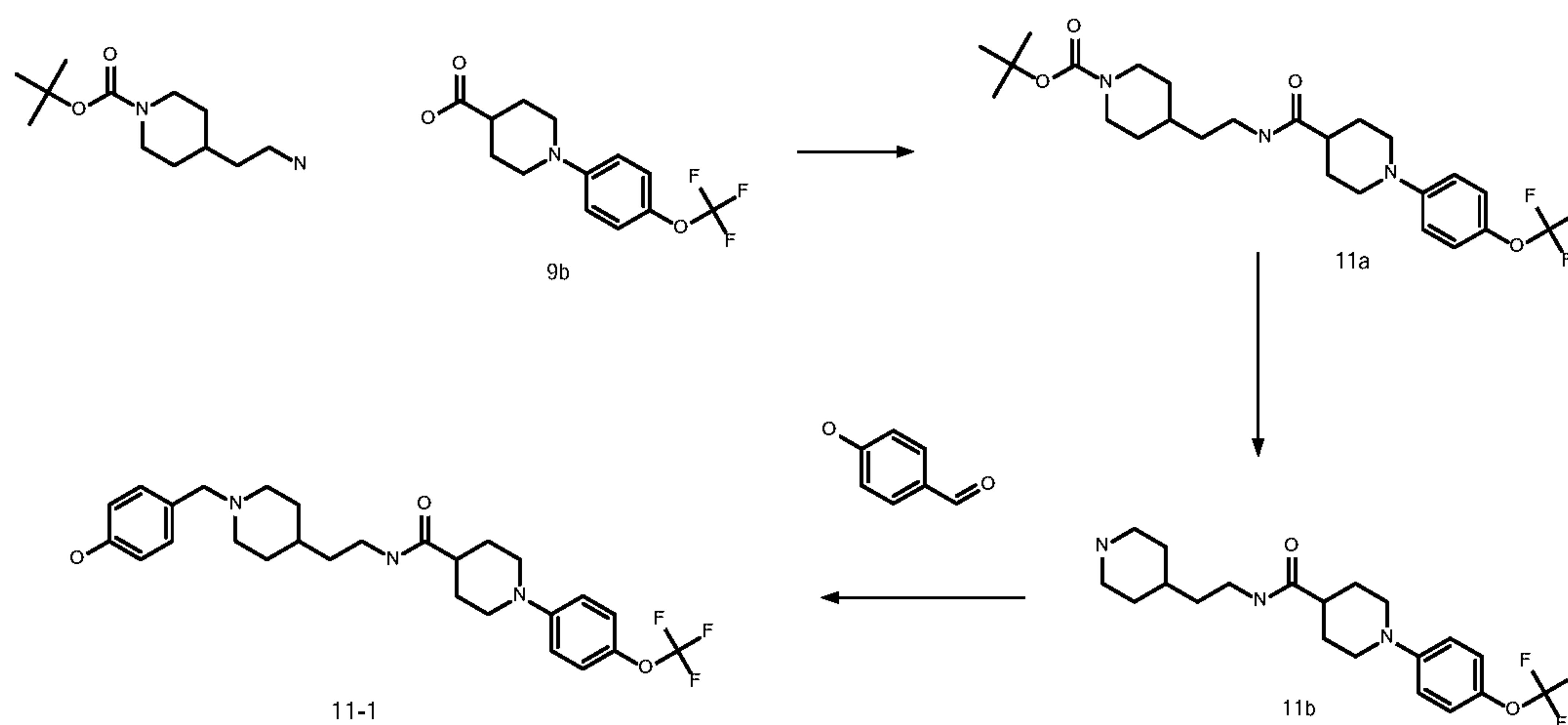
Cpd. No.	Compound Name	Obs Ion (m/z)
10-35	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(4-fluorophenyl)piperidine-4-carboxamide	424.3
10-36	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-cyano-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidine-4-carboxamide	531.2
10-37	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[2-fluoro-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	508.2
10-38	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-methoxy-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	520.2
10-39	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3-fluoro-4-methoxyphenyl)piperidine-4-carboxamide	454.4
10-40	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-hydroxy-1-(3,4,5-trifluorophenyl)piperidine-4-carboxamide	476.3
10-41	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-fluoro-4-(trifluoromethoxy)phenyl]-4-hydroxypiperidine-4-carboxamide	524.2
10-42	N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	504.25
10-43	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3,4,5-trifluorophenyl)piperidine-4-carboxamide	460.3
10-44	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-fluoro-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	508.5
10-45	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(2,2-difluoro-2H-1,3-benzodioxol-4-yl)piperidine-4-carboxamide	486.3
10-46	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-cyano-5-(trifluoromethoxy)phenyl]-4-hydroxypiperidine-4-carboxamide	531.2
10-47	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-methoxy-1-[4-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxamide	505.2
10-48	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-methoxy-1-[5-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxamide	505.2

Cpd. No.	Compound Name	Obs Ion (m/z)
10-49	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-(trifluoromethoxy)phenyl]pyrrolidine-3-carboxamide	476.15
10-50	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(4-cyano-2-fluorophenyl)piperidine-4-carboxamide	449.3
10-51	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3-cyano-4-fluorophenyl)-4-hydroxypiperidine-4-carboxamide	465.25
10-52	(3S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-(trifluoromethoxy)phenyl]pyrrolidine-3-carboxamide	476.2
10-53	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3-methoxyphenyl)piperidine-4-carboxamide	436.3
10-54	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3-cyano-5-methoxyphenyl)piperidine-4-carboxamide	461.6
10-55	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-fluoro-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	508.2
10-56	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-methyl-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	504.3
10-57	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-cyano-4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	515.2
10-58	N-[(2S)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-1-(3-cyano-4-fluorophenyl)piperidine-4-carboxamide	465.2
10-59	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(2-fluorophenyl)piperidine-4-carboxamide	424.3
10-60	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(4-methoxyphenyl)piperidine-4-carboxamide	436.35
10-61	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-hydroxy-1-[5-(trifluoromethoxy)pyridin-2-yl]piperidine-4-carboxamide	507.2
10-62	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-hydroxy-1-[3-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	506.2

Cpd. No.	Compound Name	Obs Ion (m/z)
10-63	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-methoxy-1-[5-(trifluoromethoxy)pyridin-2-yl]piperidine-4-carboxamide	521.2
10-64	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(2,5-difluorophenyl)-4-hydroxypiperidine-4-carboxamide	458.2
10-65	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3-methanesulfonylphenyl)piperidine-4-carboxamide	484.3
10-66	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(4-cyanopyridin-2-yl)piperidine-4-carboxamide	432.3
10-67	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(2-cyanophenyl)piperidine-4-carboxamide	431.25
10-68	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[6-(trifluoromethyl)pyridin-3-yl]piperidine-4-carboxamide	475.3
10-69	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(2-cyano-4-fluorophenyl)piperidine-4-carboxamide	449.4
10-70	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[2-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	490.2
10-71	(3S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-(trifluoromethoxy)phenyl]pyrrolidine-3-carboxamide	476.2
10-72	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-(trifluoromethoxy)phenyl]pyrrolidine-3-carboxamide	476.25
10-73	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-fluoropyridin-2-yl)piperidine-4-carboxamide	425.3
10-74	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(4,6-dimethylpyrimidin-2-yl)piperidine-4-carboxamide	436.4
10-75	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-methoxy-1-[2-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	520.2
10-76	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[4-(difluoromethoxy)phenyl]piperidine-4-carboxamide	472.3

Cpd. No.	Compound Name	Obs Ion (m/z)
10-77	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(3-cyanophenyl)piperidine-4-carboxamide	431.3
10-78	N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(4-cyano-3-fluorophenyl)piperidine-4-carboxamide	449.4
10-79	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-cyanopyridin-2-yl)-3-methylpiperidine-4-carboxamide	446.2
10-80	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-1-[5-(trifluoromethyl)pyridin-2-yl]piperidine-4-carboxamide	489.2
10-81	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-[3-fluoro-5-(trifluoromethyl)pyridin-2-yl]-3-methylpiperidine-4-carboxamide	507.15

EXAMPLE 11



Step 11A: N-[2-(piperidin-4-yl)ethyl]-1-[4-(trifluoromethoxy)phenyl]piperidine-4-
5 carboxamide

To a solution of 1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxylic acid **9b** (0.30 g, 1.0 mmol, 1.0 eq) and tert-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (0.27 g, 1.2 mmol, 1.2 eq) in methylene chloride (5 mL) was added

triethylamine (0.41 mL, 3.0 mmol, 3.0 eq) followed by HATU (0.46 g, 1.2 mmol, 1.2 eq) and the reaction was stirred at room temperature overnight. The reaction mixture was diluted with sat. NH₄Cl and extracted with methylene chloride. The combined organic layers were dried over MgSO₄ and concentrated. A silica gel column was loaded using methylene chloride and run using an increasing gradient of MeOH (0-5%) in methylene chloride over 20 min yielding tert-butyl 4-[2-({1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}formamido)ethyl]-piperidine-1-carboxylate **11a**. The chromatographed **11a** was dissolved in 20% TFA in methylene chloride (5 mL) and heated to 50 °C overnight. The reaction mixture was concentrated, dissolved in MeOH, and made basic with the addition of MP-carbonate. Following removal of the resin and concentration of the filtrate, the free base of N-[2-(piperidin-4-yl)ethyl]-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide **11b** was isolated as a foam.

Step 11B: N-(2-{1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide

To NMP solutions of **11b** (0.05 mL, 0.50 M, 1 eq) and 4-hydroxybenzaldehyde (0.05 mL, 0.50 M, 1 eq) was added an ethanolic solution of borane-pyridine complex (0.10 mL, 0.50 M, 2 eq) followed by acetic acid (5 µL) and the mixture stirred at RT overnight. The reaction was diluted to a total volume of 1 mL using MeOH and submitted directly for preparative chromatography yielding N-(2-{1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide **11-1**. The table below provides the observed (Obs) ion m/z ratio for **11-1** (first compound listed in Table 9) and other compounds that were made according to the procedure as described in this example.

Table 9

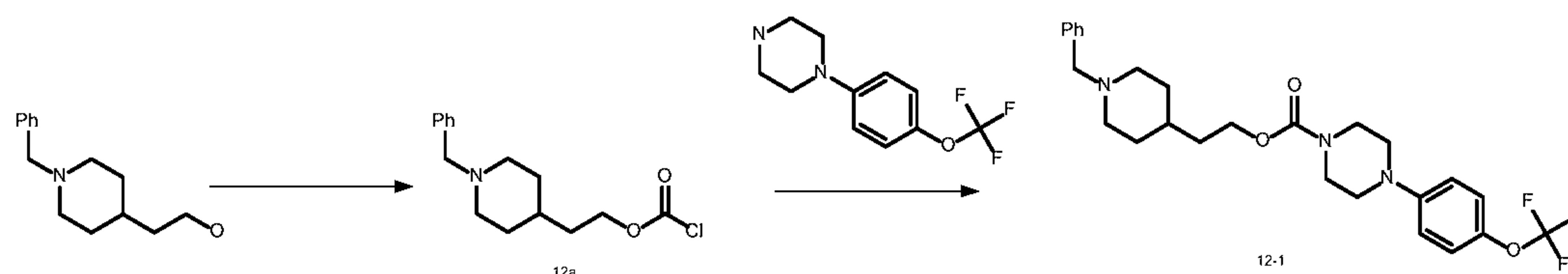
Cpd. No.	Compound Name	Obs Ion (m/z)
11-1	N-(2-{1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	506.2

Cpd. No.	Compound Name	Obs Ion (m/z)
11-2	N-(2-{1-[(2-fluoropyridin-3-yl)methyl]piperidin-4-yl}ethyl)-4-phenoxybenzamide	434.3
11-3	4-(benzyloxy)-N-(2-{1-[(2-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)benzamide	445.2
11-4	N-(2-{1-[(2-methyl-1,3-thiazol-4-yl)methyl]piperidin-4-yl}ethyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	511.2
11-5	N-(2-{1-[(2-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-4-phenoxybenzamide	431.2
11-6	methyl 2-phenyl-2-{4-[2-({1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl}formamido)ethyl]piperidin-1-yl}acetate	548.2
11-7	4-(benzyloxy)-N-{2-[1-(2,3-dihydro-1,4-benzodioxin-5-yl)methyl]piperidin-4-yl}ethyl}benzamide	487.2
11-8	1-(5-cyanopyridin-2-yl)-N-{2-[1-(cyclohexylmethyl)piperidin-4-yl]ethyl}piperidine-4-carboxamide	438.2
11-9	4-(benzyloxy)-N-(2-{1-[(2-hydroxy-3-methoxyphenyl)methyl]piperidin-4-yl}ethyl)benzamide	475.2
11-10	N-(2-{1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-4-phenoxybenzamide	498.2
11-11	N-{2-[1-(1,2,3-thiadiazol-4-yl)methyl]piperidin-4-yl}ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	520.3
11-12	N-{2-[1-(2-hydroxy-1-phenylethyl)piperidin-4-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	448.3
11-13	N-(2-{1-[(3-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-4-phenoxybenzamide	431
11-14	4-(benzyloxy)-N-{2-[1-(1-phenylethyl)piperidin-4-yl]ethyl}benzamide	443.3
11-15	N-(2-{1-[(1-methyl-1H-pyrrol-2-yl)methyl]piperidin-4-yl}ethyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	493.3

Cpd. No.	Compound Name	Obs Ion (m/z)
11-16	1-(5-cyanopyridin-2-yl)-N-{2-[1-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)piperidin-4-yl]ethyl}piperidine-4-carboxamide	490.2
11-17	1-(5-cyanopyridin-2-yl)-N-(2-{1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)piperidine-4-carboxamide	448.3
11-18	N-{2-[1-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)piperidin-4-yl]ethyl}-4-phenoxybenzamide	473.3
11-19	N-{2-[1-(3-methylbutyl)piperidin-4-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	430.1
11-20	4-(benzyloxy)-N-{2-[1-(pyridin-3-ylmethyl)piperidin-4-yl]ethyl}benzamide	433.4
11-21	N-{2-[1-(cyclohexylmethyl)piperidin-4-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	496.3
11-22	N-{2-[1-(1H-indol-5-ylmethyl)piperidin-4-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	529.2
11-23	N-{2-[1-(cyclohexylmethyl)piperidin-4-yl]-2-hydroxyethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	512.3
11-24	4-(benzyloxy)-N-(2-{1-[(3-fluorophenyl)methyl]piperidin-4-yl}ethyl)benzamide	446.9
11-25	1-(5-cyanopyridin-2-yl)-N-(2-{1-[(2-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)piperidine-4-carboxamide	448.3
11-26	1-(5-cyanopyridin-2-yl)-N-(2-{1-[(2-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)piperidine-4-carboxamide	447.5
11-27	N-{2-[1-(2,2-dimethylpropyl)piperidin-4-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	435.3
11-28	4-phenoxy-N-{2-[1-(3-phenylpropyl)piperidin-4-yl]ethyl}benzamide	431.2

Cpd. No.	Compound Name	Obs Ion (m/z)
11-29	N-{2-[1-(2,3-dihydro-1-benzofuran-7-ylmethyl)piperidin-4-yl]ethyl}-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	532.2
11-30	N-(2-{1-[(6-methoxypyridin-2-yl)methyl]piperidin-4-yl}ethyl)-1-[4-(trifluoromethoxy)phenyl]piperidine-4-carboxamide	521.1

Example 12



Step 12A: 2-(1-Benzylpiperidin-4-yl)ethyl chloroformate

5 A solution of 2-(1-benzylpiperidin-4-yl)ethan-1-ol (0.50 g, 2.3 mmol, 1.0 eq) and triphosgene (0.81 g, 2.7 mmol, 1.2 eq) in anhydrous THF (7 mL) was prepared and cooled to 0 °C. Then, pyridine (0.27 g, 3.4 mmol, 1.5 eq) was added dropwise upon which a precipitate formed. After stirring for 20 min, the resulting suspension was filtered and concentrated to provide 2-(1-benzylpiperidin-4-yl)ethyl chloroformate **12a** (0.40 g, 1.4 mmol, 62%) as an oil.

Step 12B: 2-(1-benzylpiperidin-4-yl)ethyl 4-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxylate

To a solution of 1-[4-(trifluoromethoxy)phenyl]piperazine **1f** (0.10 g, 0.41 mmol, 1.0 eq) and **12a** (0.13 g, 0.45 mmol, 1.1 eq) in methylene chloride (3 mL) was added triethylamine (0.17 mL, 1.2 mmol, 3.0 eq) and the reaction mixture stirred at RT. After 10 min, the reaction mixture was diluted with methylene chloride, washed with sat. NH₄Cl, dried over MgSO₄ and concentrated. A silica gel column was loaded using methylene chloride and run using an increasing gradient of MeOH (0-15%) in

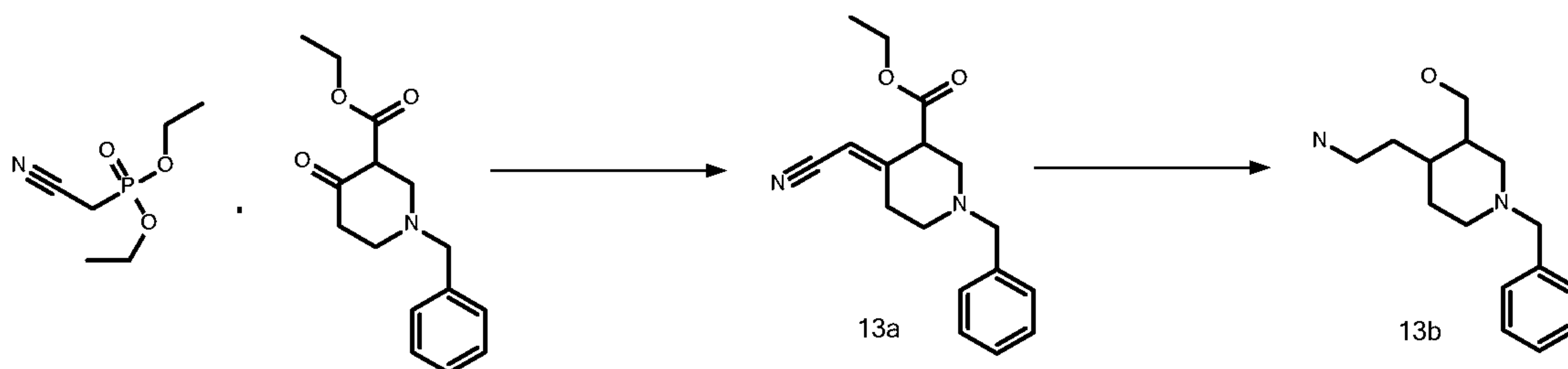
methylene chloride over 20 min to provide 2-(1-benzylpiperidin-4-yl)ethyl 4-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxylate **12-1** (0.15 g, 0.31 mmol, 75%) as a foam. The table below provides the observed (Obs) ion m/z ratio for **12-1** (first compound listed in Table 10) and other compounds that were made according to the

5 procedure as described in this example.

Table 10

Cpd. No.	Compound Name	Obs Ion (m/z)
12-1	2-(1-benzylpiperidin-4-yl)ethyl 4-[4-(trifluoromethoxy)phenyl]piperazine-1-carboxylate	492.2
12-2	2-(1-benzylpiperidin-4-yl)ethyl 4-(3-cyanophenyl)piperazine-1-carboxylate	433.25
12-3	2-(1-benzylpiperidin-4-yl)ethyl 4-(4-fluorophenyl)piperazine-1-carboxylate	426.3
12-4	2-(1-benzylpiperidin-4-yl)ethyl 4-[3-(trifluoromethoxy)phenyl]piperazine-1-carboxylate	492.7
12-5	2-(1-benzylpiperidin-4-yl)ethyl N-[1-(3-cyanophenyl)piperidin-4-yl]carbamate	447.3
12-6	2-(1-benzylpiperidin-4-yl)ethyl N-[1-(4-fluorophenyl)piperidin-4-yl]carbamate	440.3
12-7	2-(1-benzylpiperidin-4-yl)ethyl 4-hydroxy-4-phenylpiperidine-1-carboxylate	423.1
12-8	2-(1-benzylpiperidin-4-yl)ethyl 4-phenylpiperidine-1-carboxylate	407.2
12-9	2-(1-benzylpiperidin-4-yl)ethyl 4-(3-cyano-5-fluorophenyl)piperazine-1-carboxylate	451.2
12-10	2-(1-benzylpiperidin-4-yl)ethyl 4-(3-cyano-4-fluorophenyl)piperazine-1-carboxylate	451.3
12-11	2-(1-benzylpiperidin-4-yl)ethyl N-{1-[4-(trifluoromethoxy)phenyl]piperidin-4-yl} carbamate	506.2
12-12	2-(1-benzylpiperidin-4-yl)ethyl 4-(3,4,5-trifluorophenyl)piperazine-1-carboxylate	462.2

EXAMPLE 13



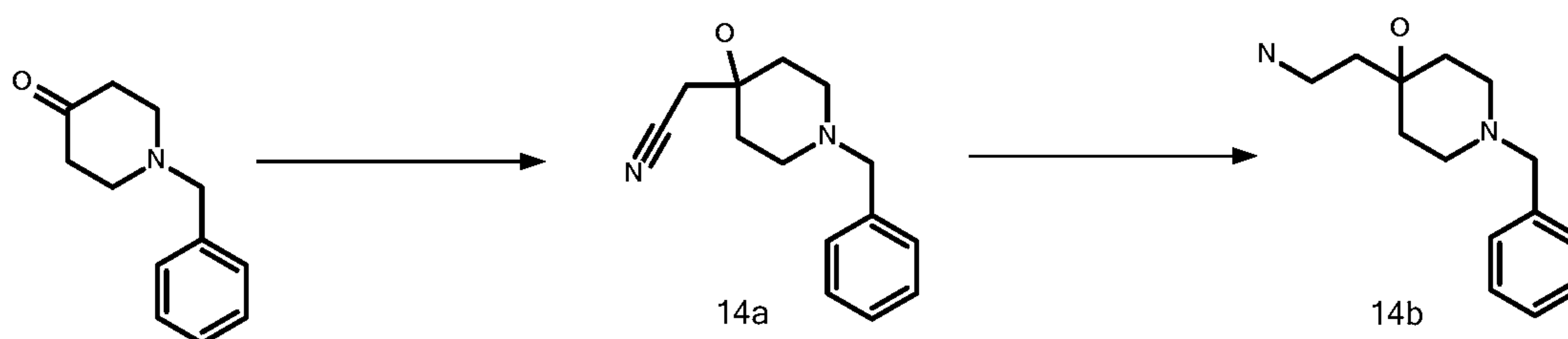
Step 13A: Ethyl (4E)-1-benzyl-4-(cyanomethylidene)piperidine-3-carboxylate

To a solution of diethyl cyanomethylphosphonate (0.5 g, 2.8 mmol, 1.2 eq) in anhydrous THF (5 mL) was added K_2CO_3 (0.4 g, 2.8 mmol, 1.2 eq) and the mixture was stirred at room temp for 15 min, then heated to reflux for 20 min. The mixture was cooled and ethyl 1-benzyl-4-oxopiperidine-3-carboxylate (0.6 g, 2.3 mmol, 1.0 eq) was added and refluxed for 12 hours. The mixture was cooled, diluted with EtOAc (10 mL) and washed with sat. $NaHCO_3$. The organic layer was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by via ISCO chromatography with an increasing gradient from 0% to 60% EtOAc in hexanes. Two peaks were combined as they will merge on reduction to a racemic mixture to give ethyl (4E)-1-benzyl-4-(cyanomethylidene)piperidine-3-carboxylate **13a** (0.4 g, 1.4 mmol, 50% yield).

Step 13B: [4-(2-aminoethyl)-1-benzylpiperidin-3-yl]methanol

(4E)-1-benzyl-4-(cyanomethylidene)piperidine-3-carboxylate (0.4 g, 1.4 mmol, 1.0 eq) was dissolved in anhydrous THF (10 mL) and LAH (0.14 g, 4.23 mmol, 3.0 eq) was added and the mixture stirred for one hour. The reaction was quenched with H_2O (0.5 mL) and diluted with EtOAc and filtered. The organic layer was concentrated to give [4-(2-aminoethyl)-1-benzylpiperidin-3-yl]methanol **13b** (0.35 g, 1.4 mmol, 100% yield).

EXAMPLE 14

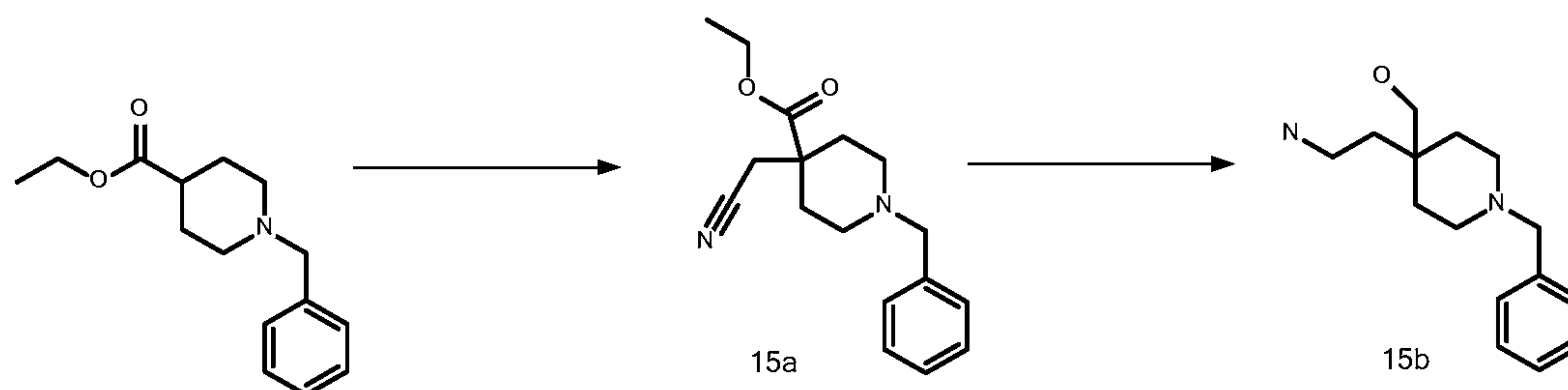
Step 14A: 2-(1-benzyl-4-hydroxypiperidin-4-yl)acetonitrile

n-BuLi (2 M in pentane, 7.3 mL, 1.1 eq) was added dropwise to solution
 5 of MeCN (0.76 mL) in THF (6 mL) at -78 °C and stirred 20 minutes. Next, a solution
 of 1-benzylpiperidine-4-one (2.5 g, 13.2 mmol, 1.0 eq) in 4 mL THF was added
 dropwise at -78 °C. The reaction mixture was warmed to room temperature slowly
 overnight. The mixture was diluted with EtOAc and extracted from water. The crude
 product was purified via ISCO silica chromatography eluting with a gradient of 0% to
 10 50% (80-18-2 CHCl₃/MeOH/NH₃) in DCM to give 2-(1-benzyl-4-hydroxypiperidin-4-yl)
 acetonitrile **14a** (2.6 g, 11.4 mmol) in a 86% yield.

Step 14B: 4-(2-aminoethyl)-1-benzylpiperidin-4-ol

2-(1-Benzyl-4-hydroxypiperidin-4-yl)acetonitrile **14a** (2.6 g, 11.4 mmol,
 1.0 eq) was dissolved in anhydrous THF (30 mL) and LAH (1.1 g, 28 mmol, 2.5 eq)
 15 was added. The reaction mixture was stirred at room temp for 30 min then slowly
 quenched with water and excess EtOAc. The reaction was filtered through celite and
 concentrated to give 4-(2-aminoethyl)-1-benzylpiperidin-4-ol **14b** (1.9 g, 7.9 mmol) in
 a 72% yield.

EXAMPLE 15

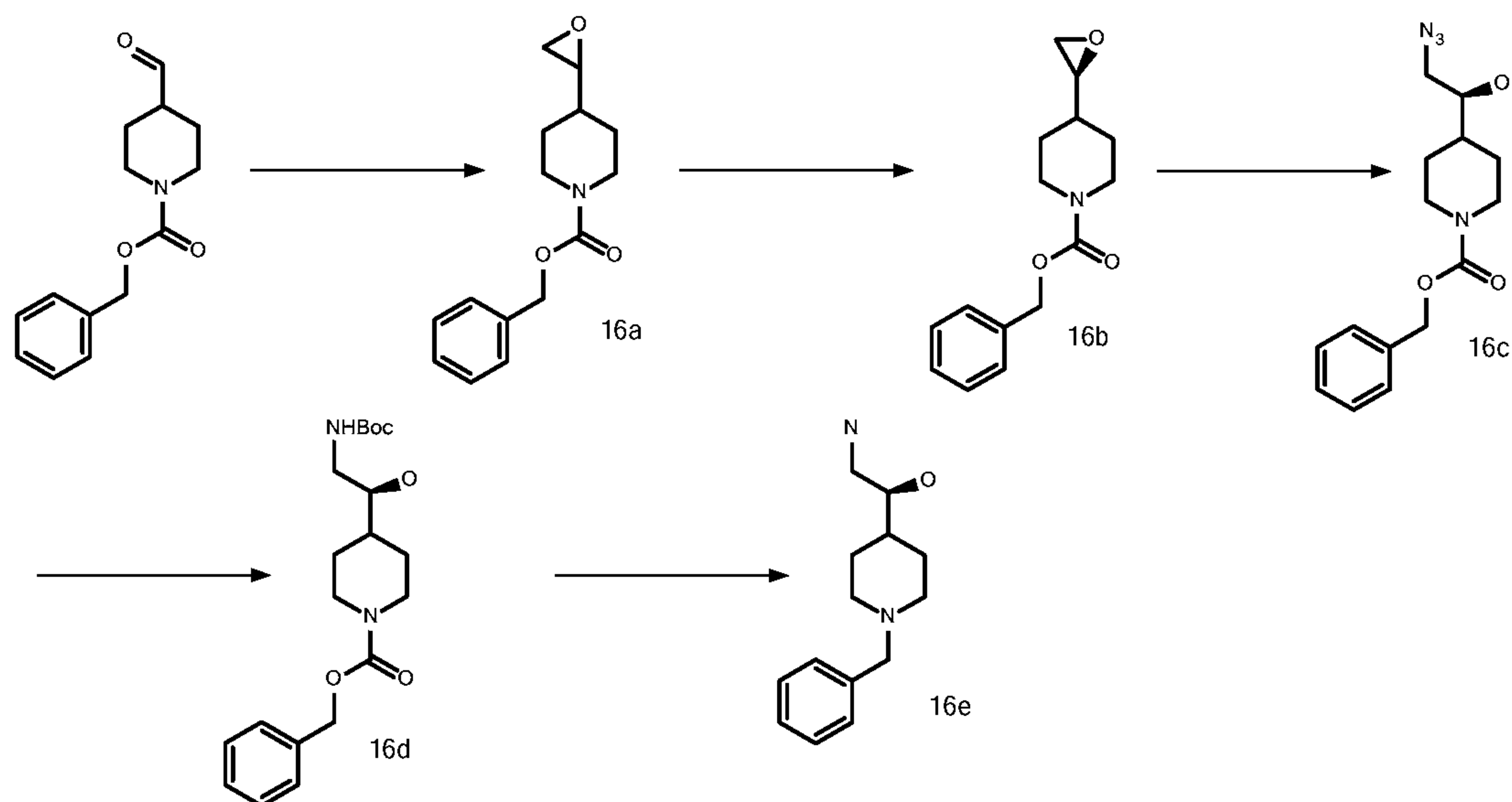
Step 15A: Ethyl 1-benzyl-4-(cyanomethyl)piperidine-4-carboxylate

Ethyl 1-benzylpiperidine-4-carboxylate (2.0 g, 8.1 mmol, 1.0 eq) was dissolved in anhydrous THF (20 mL) and cooled to -78 °C. Next, LDA (2.0M in THF, 8.1 mL, 2.0 eq) was added dropwise and stirred for one hour at -78 °C. A solution of bromoacetonitrile (1.9 g, 16.2 mmol, 2.0 eq) in THF (10 mL) was added dropwise at -78 °C and stirred at this temperature for 3 hours then warmed to room temperature. The reaction mixture was diluted with EtOAc and washed with sat. NH₄Cl and brine. The organic layer was dried over MgSO₄, filtered and concentrated. The crude product was purified via ISCO silica chromatography eluting with an increasing gradient of EtOAc (0% to 100%) in hexanes to give ethyl 1-benzyl-4-(cyanomethyl)piperidine-4-carboxylate **15a** (1.3 g, 4.5 mmol) in a 56% yield.

Step 15B: [4-(2-Aminoethyl)-1-benzylpiperidin-4-yl]methanol

Ethyl 1-benzyl-4-(cyanomethyl)piperidine-4-carboxylate **15a** (0.9 g, 3.1 mmol, 1.0 eq) was dissolved in anhydrous THF (10 mL) and LAH (0.21 g, 6.3 mmol, 2.0 eq) was added. The mixture was stirred at room temp for 30 min then slowly quenched with water and excess EtOAc. The reaction was filtered through celite and concentrated to give [4-(2-aminoethyl)-1-benzylpiperidin-4-yl]methanol **15b** (0.77 g, 3.1 mmol) in a quantitative yield.

EXAMPLE 16

Step 16A: Benzyl 4-(oxiran-2-yl)piperidine-1-carboxylate

Trimethylsulfoxonium iodide (13.5 g, 60.7 mmol, 1.5 eq) was added in two portions to a solution of NaH (1.5 g, 60.7 mmol, 1.5 eq) in anhydrous DMSO (15 mL). This mixture was stirred for one hour at room temp. Then a solution of benzyl 4-formylpiperidine-1-carboxylate (10.0 g, 40.4 mmol, 1.0 eq) in anhydrous DMSO (20 mL) was added and the mixture stirred two hours. The reaction was poured into water and extracted twice with Et₂O. The organic layer was dried over MgSO₄, filtered, and concentrated. The crude product was purified on ISCO with 0% to 70% EtOAC in hexanes to give benzyl 4-(oxiran-2-yl)piperidine-1-carboxylate **16a** as a clear oil (6.8 g, 26.1 mmol) in a 65% yield.

Step 16B: Benzyl 4-[(2S)-oxiran-2-yl]piperidine-1-carboxylate

(*S,S*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) [88264-84-8] (0.40 g, 0.65 mmol, 0.02 eq) was dissolved in toluene (10 mL) and acetic acid (0.07 mL, 1.3 mmol, 0.04 eq) was added and the mixture stirred for one hour. The mixture was then concentrated and dried on a high vacuum to give a solid. Benzyl 4-(oxiran-2-yl)piperidine-1-carboxylate **16a** (6.8 g,

26.1 mmol, 1.0 eq) was dissolved in anhydrous THF (15mL) and the catalyst dissolved in minimal anhydrous THF was added and cooled to 0 °C and water (0.26 mL, 14.6 mmol, 0.6 eq) was added dropwise. The reaction slowly warmed to room temperature and stirred overnight. LCMS showed slow reaction so additional water (0.05 mL, 2.8 mmol, 0.1 eq) was added and the reaction was stirred overnight. The reaction mixture was concentrated and purified by ISCO column chromatography eluting with a gradient of 0% to 70% EtOAc in hexanes. Benzyl 4-[(2S)-oxiran-2-yl]piperidine-1-carboxylate **16b** (3.4 g, 12.9 mmol) was determined to be 99% ee by chiral chromatography compared to the racemic mixture.

10 Step 16C: Benzyl 4-[(1S)-2-azido-1-hydroxyethyl]piperidine-1-carboxylate

Benzyl 4-[(2S)-oxiran-2-yl]piperidine-1-carboxylate **16b** (3.4 g, 12.9 mmol, 1.0 eq) was dissolved in EtOH (9 mL) and water (1 mL) and sodium azide (1.7 g, 25.8 mmol, 2.0 eq) and ammonium chloride (1.4 g, 25.8 mmol, 2.0 eq) were added. The reaction mixture was heated to 55 °C and stirred overnight. EtOH was removed *in vacuo* and the reaction mixture was diluted with DCM and extracted from sat. NaHCO₃. The organic layer was dried over MgSO₄, filtered and concentrated to give benzyl 4-[(1S)-2-azido-1-hydroxyethyl]piperidine-1-carboxylate **16c** (3.9 g, 12.7 mmol) in 98% yield.

20 Step 16D: Benzyl 4-[(1S)-2-{[(tert-butoxy)carbonyl]amino}-1-hydroxyethyl]-piperidine-1-carboxylate

Benzyl 4-[(1S)-2-azido-1-hydroxyethyl]piperidine-1-carboxylate **16c** (3.9 g, 12.7 mmol, 1.0 eq) was dissolved in anhydrous MeOH (100 mL) then dichloronickel hexahydrate (3.0 g, 12.7 mmol, 1.0 eq) and NaBH₄ (0.96 g, 25.4 mmol, 2.0 eq) were added and the mixture stirred for one hour. MeOH was removed *in vacuo* and the product was redissolved in DCM, filtered through celite and concentrated. The crude product was then redissolved in DCM (100 mL) and triethylamine (5.3 mL, 38.1 mmol, 3.0 eq) and di-tert-butyl dicarbonate (5.5 g, 25.4 mmol, 3.0 eq) were added and the reaction was stirred overnight. An additional 0.2 equiv of TEA and di-tert-butyl

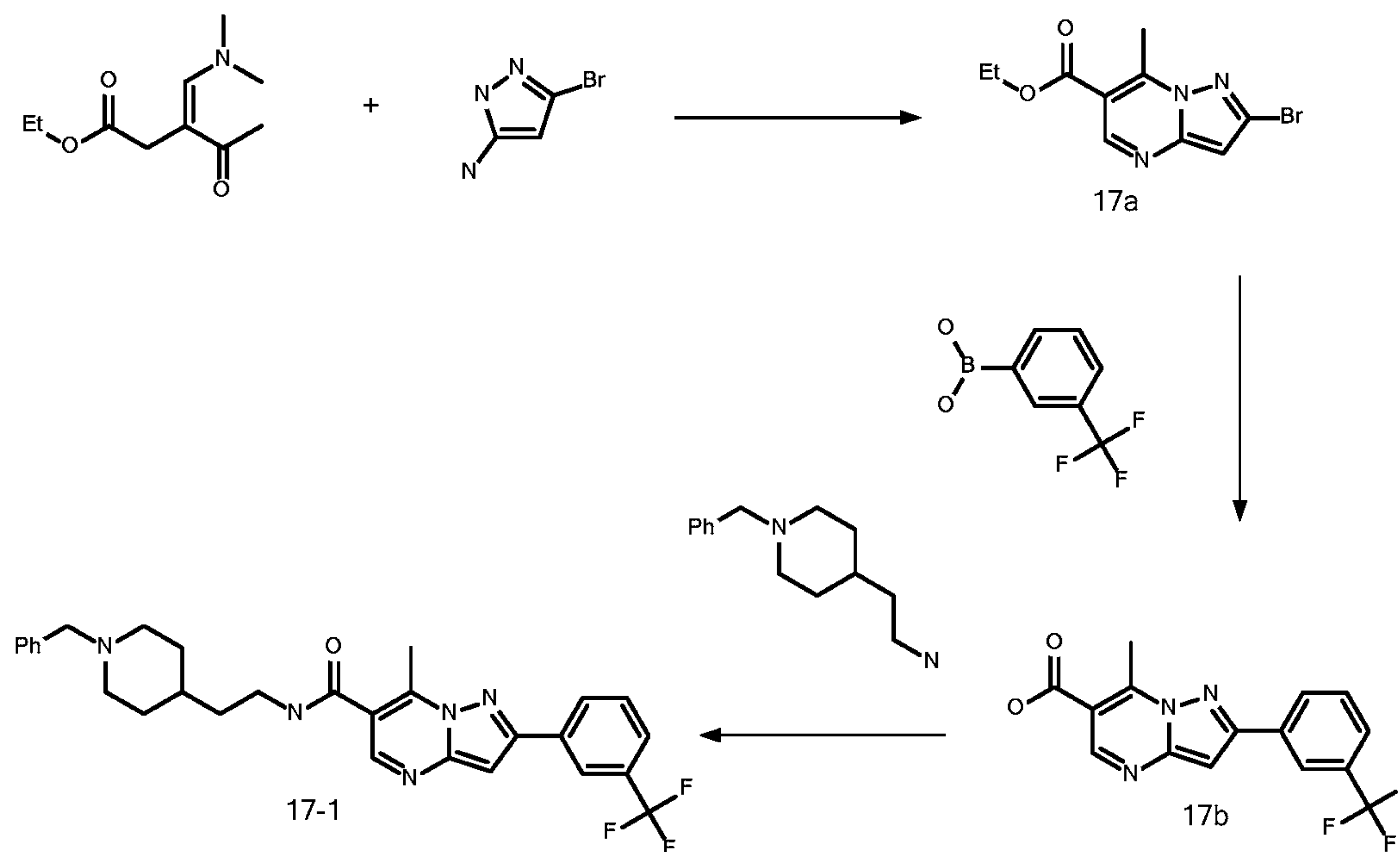
dicarbonate were added along with MeOH (10 mL) for solubility and reaction stirred for one hour. Solvent was removed *in vacuo* and crude product redissolved in DCM and washed with sat. NH₄Cl. The organic layer was dried over MgSO₄, filtered and concentrated. The crude product was purified by ISCO column chromatography elution
5 with a 0% to 100% of EtOAc in hexanes to afford benzyl 4-[(1S)-2-{[(tert-butoxy)carbonyl]amino}-1-hydroxyethyl]piperidine-1-carboxylate **16d** (3.98 g, 10.5 mmol) in a 83% yield.

Step 16E: (1S)-2-amino-1-(1-benzylpiperidin-4-yl)ethan-1-ol

Benzyl 4-[(1S)-2-{[(tert-butoxy)carbonyl]amino}-1-
10 hydroxyethyl]piperidine-1-carboxylate **16d** (3.98 g, 10.5 mmol, 1.1 eq) was dissolved in MeOH and 10% Pd/C was added. The sealed vessel was purged with H₂ and the reaction was stirred one hour. The reaction was filtered through celite and concentrated to afford the crude amine which was used without further purification. The crude amine (2.4 g, 9.8 mmol, 1.0 eq) was dissolved in EtOH (75 mL) and acetic acid (0.55
15 mL, 10.5 mmol, 1.1 eq) and benzaldehyde (1.6 mL, 15.8 mmol, 1.6 eq) were added followed by sodium cyanoborohydride (1.0 g, 15.8 mmol, 1.6 eq) and the reaction was stirred for 2 hours. Additional benzaldehyde (1.0 mL, 8.0 mmol) was added and reaction complete after one hour of stirring. The reaction mixture was quenched with water and MeOH was removed *in vacuo*. The reaction mixture was redissolved in
20 DCM and extracted with sat. NaHCO₃ (2X). The organic layer was dried over MgSO₄ and filtered and concentrated. The crude product was purified by ISCO column chromatography eluting with a gradient of MeOH from 0% to 30% in DCM to yield the benzyl protected amine (3.1 g, 9.3 mmol) in a 95% yield. Next, the benzylamine (3.1 g, 9.3 mmol, 1.0 eq) was dissolved in DCM (50 mL) and TFA (10 mL) was added and the
25 reaction mixture was stirred for one hour. The reaction mixture was concentrated and redissolved in MeOH and MP-carbonate resin was added until the solution was basic. The reaction was filtered and concentrated to afford (1S)-2-amino-1-(1-benzylpiperidin-4-yl)ethan-1-ol **16e** (2.1 g, 9.0 mmol) in a 97% yield.

(1R)-2-Amino-1-(1-benzylpiperidin-4-yl)ethan-1-ol **16f** was synthesized following the same overall procedure but using (*R,R*)-(+)-*N,N'*-Bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) in Step 16B.

EXAMPLE 17



5

Step 17A: Ethyl 2-bromo-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxylate

A solution of 3-bromo-1H-pyrazol-5-amine (4.2 g, 26 mmol, 1.0 eq) and ethyl (3Z)-3-[(dimethylamino)methylidene]-4-oxopentanoate (4.9 g, 26 mmol, 1.0 eq) in ethanol (300 mL) was prepared and heated to reflux for 2 hrs. The reaction mixture was concentrated. Silica gel column was loaded using methylene chloride and run using an increasing gradient of MeOH (0-5%) in methylene chloride over 20 min to provide ethyl 2-bromo-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxylate **17a** (6.0 g, 21 mmol, 81%) as a white solid.

Step 17B: 7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid

To a solution of ethyl 2-bromo-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxylate **17a** (2.0 g, 7.0 mmol, 1.0 eq) in anhydrous dioxane (45 mL) was added [3-(trifluoromethyl)phenyl]boronic acid (2.0 g, 10 mmol, 1.5 eq) followed by aq. K₂CO₃ (7 mL, 22.5 mmol, 3.2 eq) and the resulting solution purged with nitrogen for 10 min. Then, [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II) (0.52 g, 0.70 mmol, 0.1 eq) was added and the reaction heated to 90 °C overnight. The resulting dark reaction mixture was cooled, diluted heavily with EtOAc, and washed with brine. The organic layer was washed again with brine, dried over Na₂SO₄, and concentrated. Silica gel column (80 g) was loaded using methylene chloride and run using an increasing gradient of EtOAc (5-95%) in hexanes over 20 min. The chromatographed material was then suspended in MeOH (50 mL) and treated with an aq. solution of 1 M LiOH (5 mL). After stirring at RT overnight, the dark orange suspension was concentrated and the resulting solid re-dissolved in water. Then, the suspension was made acidic with careful addition of 6 M HCl. The precipitate was collected and dried to provide 7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid **17b** (1.6 g, 4.9 mmol, 70% over two steps) as a tan solid.

Step 17C: N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide

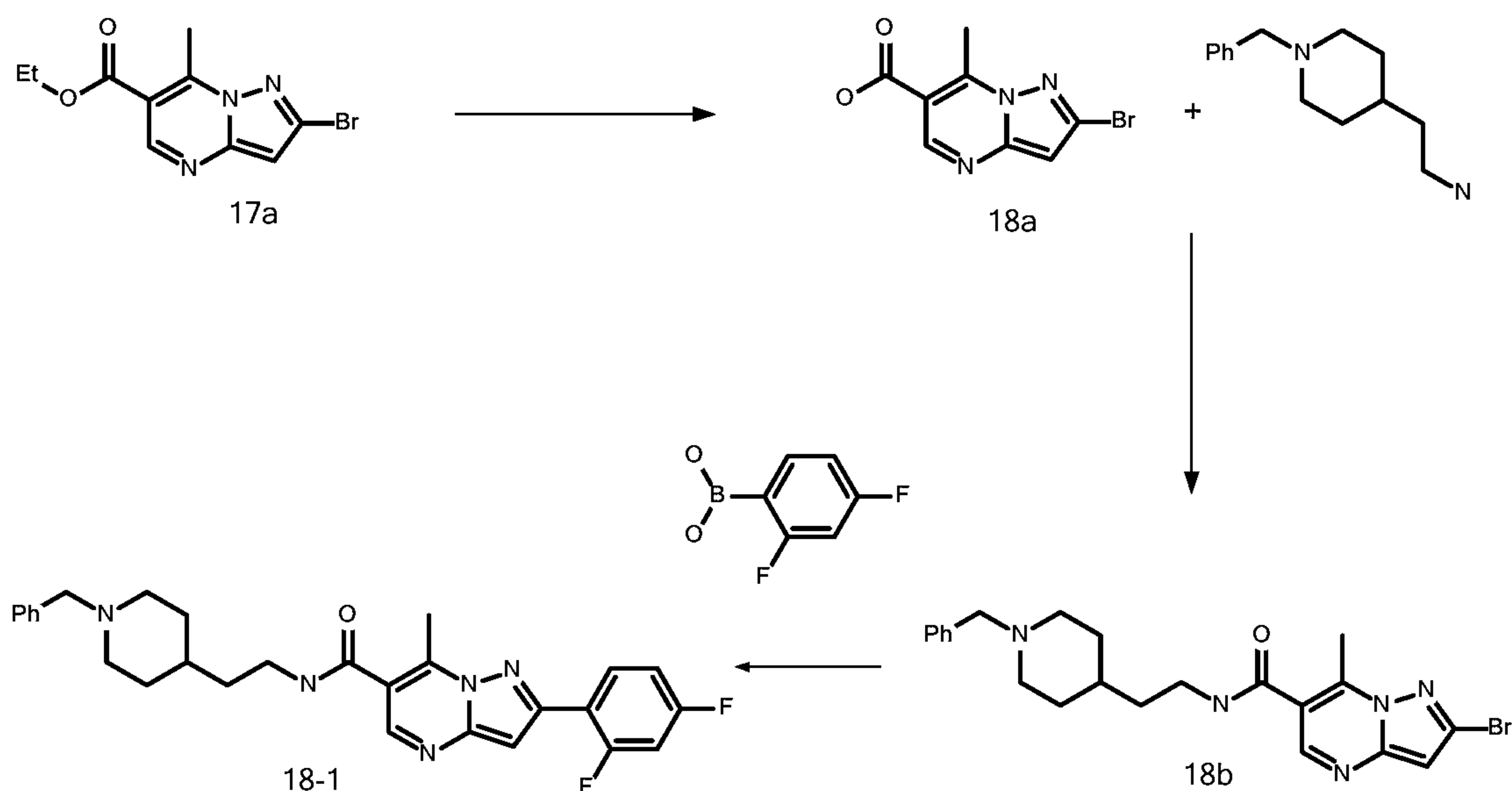
To a solution of 7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo-[1,5-a]pyrimidine-6-carboxylic acid **17b** (1.6 g, 4.9 mmol, 1.0 eq) and 2-(1-benzylpiperidin-4-yl)ethan-1-amine (1.1 g, 4.9 mmol, 1.0 eq) in NMP (20 mL) was added triethylamine (2.7 mL, 20 mmol, 4.0 eq) followed by HATU (1.9 g, 4.9 mmol, 1.0 eq) and the reaction stirred at room temperature overnight. The resulting dark reaction mixture was diluted heavily with EtOAc and washed repeatedly with brine. During the course of the extraction, a large amount of orange precipitate formed; thus after evaporating all organic solvent, the aqueous layers were left to sit overnight. Then, all precipitate was collected by vacuum filtration and washed with water. Silica gel column (120 g) was

dry loaded and run using MeOH (0-20%) in DCM over 25 min to provide N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide **17-1** (1.5 g, 2.9 mmol, 59%) as an off-white solid. The table below provides the observed (Obs) ion m/z ratio for **17-1** (first compound listed in Table 11) and other compounds that were made according to the procedure as described in this example.

Table 11

Cpd. No.	Compound Name	Obs Ion (m/z)
17-1	N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	522.2
17-2	N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6-carboxamide	454.2
17-3	N-[2-(1-benzyl-4-hydroxypiperidin-4-yl)ethyl]-7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	538.14
17-4	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(4-chlorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	488.2
17-5	N-[(2S)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	538.1
17-6	N-[(2R)-2-(1-benzylpiperidin-4-yl)-2-hydroxyethyl]-7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	538.1
17-7	N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-(thiophen-2-yl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	460.3
17-8	N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	522.2

EXAMPLE 18



Step 18A: N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-bromo-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide

- 5 To a solution of ethyl 2-bromo-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxylate **17a** (1.0 g, 3.6 mmol, 1.0 eq) in THF/water (4:1) was added solid NaOH (0.21 g, 5.3 mmol, 1.5 eq). After stirring at RT overnight, the organic solvent was concentrated and the remaining aqueous phase made acidic with careful addition of 6 M HCl. The resulting precipitate was collected and dried to provide 2-bromo-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid **18a**. A portion of this material (0.70 g, 2.7 mmol, 1.0 eq) together with 2-(1-benzylpiperidin-4-yl)ethan-1-amine (0.90 g, 4.1 mmol, 1.5 eq) in methylene chloride/DMF 2:1 (15 mL) was treated with triethylamine (1.5 mL, 11 mmol, 4.0 eq) and HATU (1.4 g, 3.6 mmol, 1.0 eq) and stirred at RT overnight. The reaction mixture was diluted with methylene chloride, washed with sat. NH₄Cl, dried over MgSO₄ and concentrated. Silica gel column was loaded using methylene chloride and run using an increasing gradient of MeOH (0-20%) in methylene chloride over 20 min to provide N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-bromo-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide **18b** (1.1 g, 2.6 mmol, 94%).

Step 18B: N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2,4-difluorophenyl)-7-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide

To an NMP solution of N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-bromo-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide **18b** (0.20 mL, 0.13 M, 1.0 eq) was added a spatula tip of (2,4-difluorophenyl)boronic acid followed by aq. K₃PO₄ (0.05 mL, 1.5 M, 2.9 eq). Then, a generous spatula tip of PS-Pd(PPh₃) was added and the reaction mixture heated to 90 °C. In general, this reaction and others of its kind are complete within 2 hrs, however additional PS-Pd(PPh₃) and/or longer reaction times can be used to push the coupling. The resulting dark suspension was cooled, passed through an HPLC filter, diluted to 1 mL using MeOH, and submitted for directly for preparative chromatography to yield N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2,4-difluorophenyl)-7-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide **18-1**. The table below provides the observed (Obs) ion m/z ratio for **18-1** (first compound listed in Table 12) and other compounds that were made according to the procedure as described in this example.

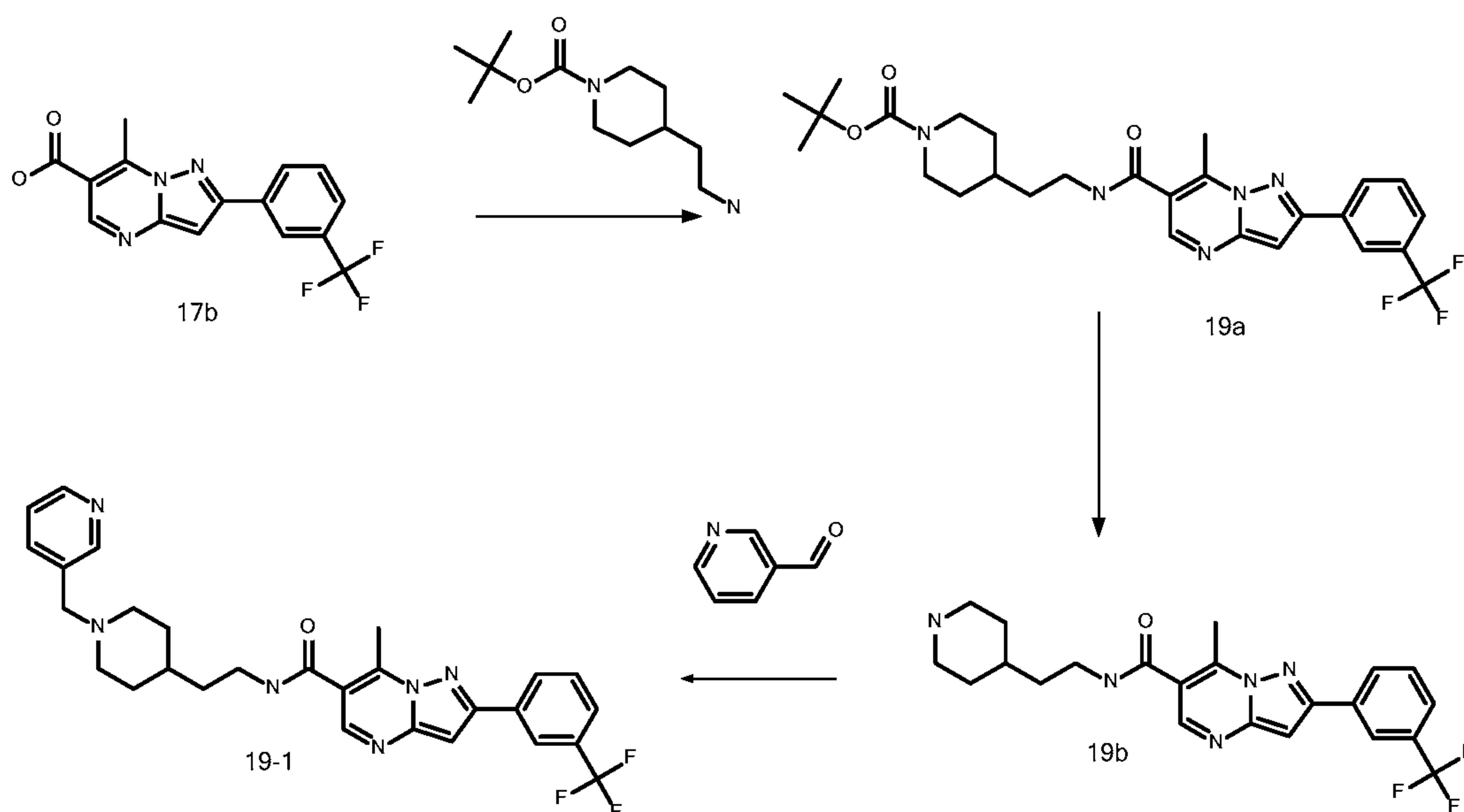
Table 12

Cpd. No.	Compound Name	Obs Ion (m/z)
18-1	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2,4-difluorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	490.15
18-2	N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-(pyridin-2-yl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	456.0
18-3	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(4-cyanophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	479.2
18-4	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(4-fluorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	472.2
18-5	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(3,5-difluorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	490.2
18-6	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(3-fluorophenyl)-7-	472.2

Cpd. No.	Compound Name	Obs Ion (m/z)
	methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	
18-7	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2,3-difluorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	490.2
18-8	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(3-cyanophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	479.1
18-9	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2-methoxyphenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	484.2
18-10	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2,5-difluorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	490.15
18-11	N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-[2-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	522.1
18-12	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(4-cyano-3-fluorophenyl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	497.2
18-13	N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-[4-(trifluoromethoxy)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	538.2
18-14	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2-methoxypyridin-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	485.3
18-15	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(6-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	473.1
18-16	N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-[3-(trifluoromethoxy)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	538.1
18-17	N-[2-(1-benzylpiperidin-4-yl)ethyl]-7-methyl-2-(3,4,5-trifluorophenyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	508.1
18-18	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2-fluoropyridin-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	473.2

Cpd. No.	Compound Name	Obs Ion (m/z)
18-19	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(6-methoxy-4-methylpyridin-3-yl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	499.2
18-20	N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-(2-fluoropyridin-4-yl)-7-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	473.2

EXAMPLE 19



Step 19A: 7-methyl-N-[2-(piperidin-4-yl)ethyl]-2-[3-

5 (trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide

To a solution of 7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxylic acid **17b** (0.09 g, 0.27 mmol, 1.0 eq) and tert-butyl 4-(2-aminoethyl)piperidine-1-carboxylate (0.07 g, 0.32 mmol, 1.2 eq) in methylene chloride was added triethylamine (0.11 mL, 0.81 mmol, 3.0 eq) followed by HATU (0.12 g, 0.32 mmol, 1.2 eq) and the reaction stirred at room temperature overnight. The reaction mixture diluted with sat. NH₄Cl and extracted with methylene chloride. The combined

organic layers were dried over MgSO_4 and concentrated. Silica gel column was loaded using methylene chloride and run using an increasing gradient of MeOH (0-10%) in methylene chloride yielding tert-butyl 4-[2-({7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl}formamido)ethyl]piperidine-1-carboxylate **19a**. The chromatographed **19a** was dissolved in 20% TFA in methylene chloride and stirred at RT overnight. The reaction mixture was concentrated, dissolved in MeOH, and made basic with the addition of MP-carbonate. Following removal of the resin and concentration of the filtrate, the free base of 7-methyl-N-[2-(piperidin-4-yl)ethyl]-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide **19b** (0.08 g, 0.19 mmol, 70% over two steps) was isolated as an oil.

Step 19B: 7-methyl-N-{2-[1-(pyridin-3-ylmethyl)piperidin-4-yl]ethyl}-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide

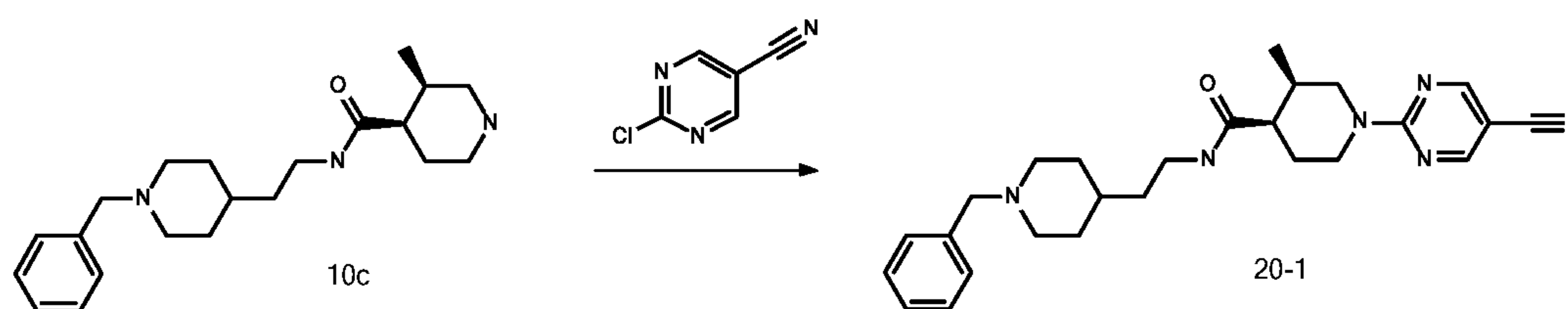
To NMP solutions of 7-methyl-N-[2-(piperidin-4-yl)ethyl]-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide **19b** (0.05 mL, 0.50 M, 1 eq) and pyridine-3-carbaldehyde (0.05 mL, 0.50 M, 1 eq) was added an ethanolic solution of borane-pyridine complex (0.10 mL, 0.50 M, 2 eq) followed by acetic acid (5 μL) and the mixture stirred at RT overnight. The reaction was diluted to a total volume of 1 mL using MeOH and submitted directly for preparative chromatography yielding 7-methyl-N-{2-[1-(pyridin-3-ylmethyl)piperidin-4-yl]ethyl}-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide **19-1**. The table below provides the observed (Obs) ion m/z ratio for **19-1** (first compound listed in Table 13) and other compounds that were made according to the procedure as described in this example.

Table 13

Cpd. No.	Compound Name	Obs Ion (m/z)
19-1	7-methyl-N-{2-[1-(pyridin-3-ylmethyl)piperidin-4-yl]ethyl}-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	523.1

Cpd. No.	Compound Name	Obs Ion (m/z)
19-2	N-{2-[1-(2,3-dihydro-1,4-benzodioxin-5-ylmethyl)piperidin-4-yl]ethyl}-7-methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6-carboxamide	512.2
19-3	N-{2-[1-(cyclohexylmethyl)piperidin-4-yl]ethyl}-7-methyl-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	528.2
19-4	N-(2-{1-[(2-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-7-methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6-carboxamide	470.1
19-5	7-methyl-N-{2-[1-(pyridin-4-ylmethyl)piperidin-4-yl]ethyl}-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	523.2
19-6	7-methyl-N-{2-[1-(pyridin-2-ylmethyl)piperidin-4-yl]ethyl}-2-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	523.2
19-7	N-(2-{1-[(3-methoxyphenyl)methyl]piperidin-4-yl}ethyl)-7-methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6-carboxamide	484.3
19-8	N-(2-{1-[(4-hydroxyphenyl)methyl]piperidin-4-yl}ethyl)-7-methyl-2-phenylpyrazolo[1,5-a]pyrimidine-6-carboxamide	470.2

Example 20



Step 20A: (3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-cyanopyrimidin-2-yl)-3-methylpiperidine-4-carboxamide

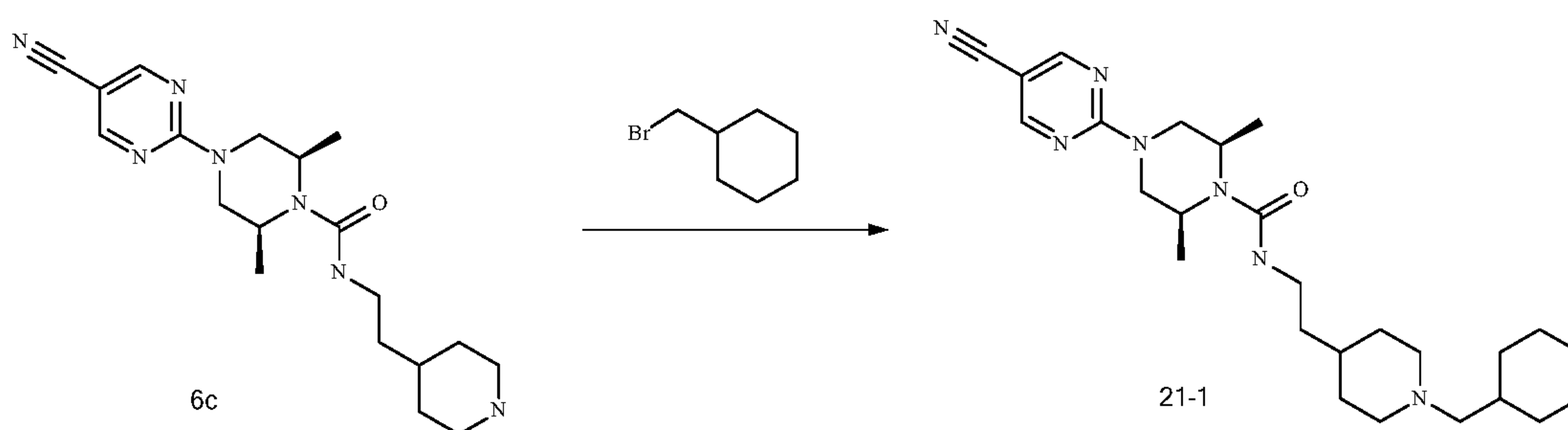
To NMP solutions of (3R,4R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methylpiperidine-4-carboxamide **10c** (0.05 mL, 0.50 M, 1 eq) and 2-chloro-5-cyanopyrimidine (0.025 mmol, 1 eq) was added a NMP solution of trimethylamine (0.100 mL, 1.0 M, 4 eq) and the mixture stirred at 100 °C overnight. The reaction was

diluted to a total volume of 1 mL using MeOH and submitted directly for preparative chromatography yielding (3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-cyanopyrimidin-2-yl)-3-methylpiperidine-4-carboxamide **20-1**. The table below provides the observed (Obs) ion m/z ratio for **20-1** (first compound listed in Table 13) and other compounds that were made according to the procedure as described in this example.

Table 14

Cpd. No.	Compound Name	Obs Ion (m/z)
20-1	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-cyanopyrimidin-2-yl)-3-methylpiperidine-4-carboxamide	447.2
20-2	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-3-methyl-1-[5-(trifluoromethyl)pyrimidin-2-yl]piperidine-4-carboxamide	490.14
20-3	(3R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-1-(5-chloropyrimidin-2-yl)-3-methylpiperidine-4-carboxamide	456.1

EXAMPLE 21



10 Step 21A: (2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-[2-[1-(cyclohexylmethyl)piperidin-4-yl]ethyl]-2,6-dimethylpiperazine-1-carboxamide

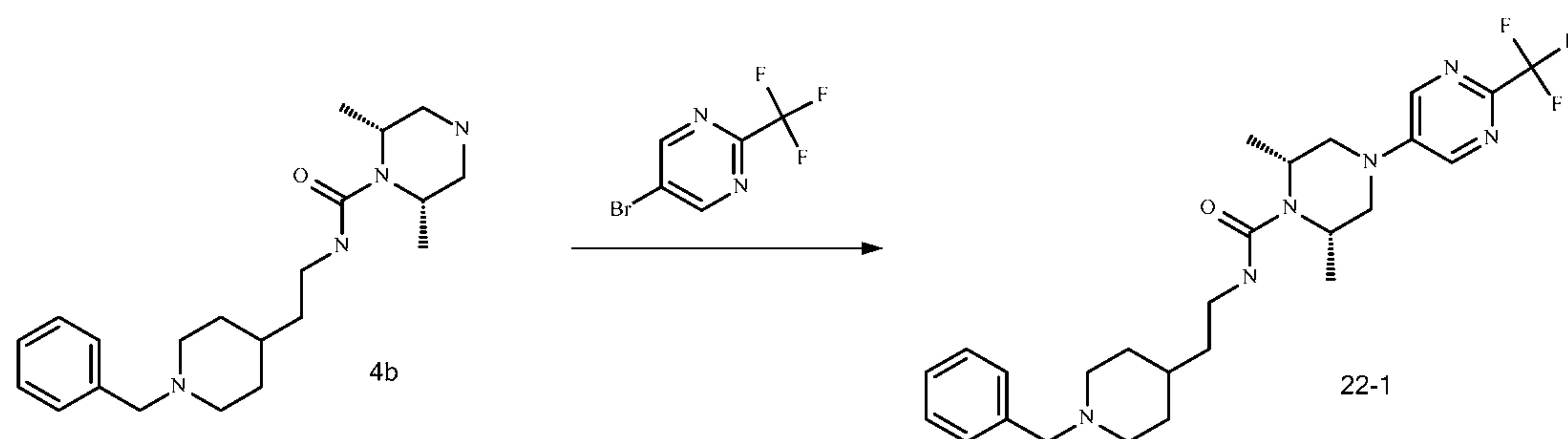
To NMP solutions of (2S,6R)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-[2-(piperidin-4-yl)ethyl]piperazine-1-carboxamide **6c** (0.20 mL, 0.12 M, 1.0 eq) and *N,N*-diisopropylethylamine (0.05 mL, 0.5 M, 4.0 eq) was added
 15 (bromomethyl)cyclohexane (4.4 mg, 0.025 mmol, 1.0 eq) and the reaction mixture

heated at 50 °C overnight. The reaction mixture was diluted to a total volume of 1 mL using MeOH and submitted directly for preparative chromatography yielding (2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-{2-[1-(cyclohexylmethyl)piperidin-4-yl]ethyl}-2,6-dimethylpiperazine-1-carboxamide **21-1**. The table below provides the observed (Obs) ion m/z ratio for **21-1** (first compound listed in Table 15) and other compounds that were made according to the procedure as described in this example.

Table 15

Cpd.No.	Compound Name	Obs Ion (m/z)
21-1	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-{2-[1-(cyclohexylmethyl)piperidin-4-yl]ethyl}-2,6-dimethylpiperazine-1-carboxamide	468.1
21-2	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-(2-{1-[α,α - ² H-benzyl]piperidin-4-yl}ethyl)piperazine-1-carboxamide	469.1
21-3	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-{2-[1-(pyridin-2-ylmethyl)piperidin-4-yl]ethyl}piperazine-1-carboxamide	463.1
21-4	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-{2-[1-(2,3-dihydro-1H-inden-2-yl)piperidin-4-yl]ethyl}-2,6-dimethylpiperazine-1-carboxamide	488.1
21-5	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-{2-[1-(cyclobutylmethyl)piperidin-4-yl]ethyl}-2,6-dimethylpiperazine-1-carboxamide	440.4
21-6	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-{2-[1-(2-methylpropyl)piperidin-4-yl]ethyl}piperazine-1-carboxamide	428.1
21-7	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-(2-{1-[2-(trimethylsilyl)ethyl]piperidin-4-yl}ethyl)piperazine-1-carboxamide	472.1
21-8	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-{2-[1-(3-methylbutyl)piperidin-4-yl]ethyl}piperazine-1-carboxamide	442.1
21-9	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-{2-[1-(oxan-	470.1

Cpd.No.	Compound Name	Obs Ion (m/z)
	2-ylmethyl)piperidin-4-yl]ethyl} piperazine-1-carboxamide	
21-10	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-(2-{1-[(3-methyloxetan-3-yl)methyl]piperidin-4-yl}ethyl)piperazine-1-carboxamide	456.1
21-11	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-N-(2-{1-[(1,1-dioxo-1-thian-3-yl)methyl]piperidin-4-yl}ethyl)-2,6-dimethylpiperazine-1-carboxamide	518.1
21-12	(2R,6S)-N-[2-(1-{bicyclo[1.1.1]pentan-1-ylmethyl} piperidin-4-yl)ethyl]-4-(5-cyanopyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	452.1
21-13	(2R,6S)-N-{2-[1-(cuban-1-ylmethyl)piperidin-4-yl]ethyl}-4-(5-cyanopyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	488.1
21-14	(2R)-2-methyl-N-(2-{1-[α,α - ² H-benzyl]piperidin-4-yl}ethyl)-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	493.1
21-15	(2R,6S)-4-(5-cyanopyrimidin-2-yl)-2,6-dimethyl-N-(2-{1-[α,α - ² H-benzyl]piperidin-4-yl}ethyl)piperazine-1-carboxamide	464.2
21-16	(2R)-4-[4-amino-5-(trifluoromethyl)pyrimidin-2-yl]-2-methyl-N-(2-{1-[α,α - ² H-benzyl]piperidin-4-yl}ethyl)piperazine-1-carboxamide	507.3
21-17	(2R)-4-[4-amino-5-(trifluoromethyl)pyrimidin-2-yl]-2-methyl-N-(2-{1-[α,α - ² H-benzyl]piperidin-4-yl}ethyl)piperazine-1-carboxamide	512.3

Example 22

Step 22A: (2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide

- 5 To a solid mixture of (2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide **4b** (15 mg, 0.04 mmol, 1.0 eq), 5-bromo-2-(trifluoromethyl)pyrimidine (9.4 mg, 0.04 mmol, 1.0 eq), sodium *tert*-butoxide (11 mg, 0.12 mmol, 3.0 eq), and lastly bis(tri-*tert*-butylphosphine)palladium(0) (3.1 mg, 0.006 mmol, 0.15 eq) was added dioxane (1 mL) and reaction mixture stirred vigorously at 50
- 10 °C overnight. The resulting dark suspension was cooled, passed through an HPLC filter and concentrated *in vacuo*. The crude material was treated with 1.5 mL of MeOH, passed through an additional HPLC filter (leaving any precipitate behind), and purified by preparative chromatography yielding (2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide **22-1**.
- 15 The table below provides the observed (Obs) ion *m/z* ratio for **22-1** (first compound listed in Table 16) and other compounds that were made according to the procedure as described in this example. For some less reactive halides, methanesulfonato(2-di-*t*-butylphosphino-2',4',6'-tri-*i*-propyl-1,1'-biphenyl)(2'-amino-1,1'-biphenyl-2-yl) palladium (II) was used in place of bis(tri-*tert*-butylphosphine)palladium(0). These
- 20 reactions were carried out at 100°C for 1-2 hrs.

Table 16

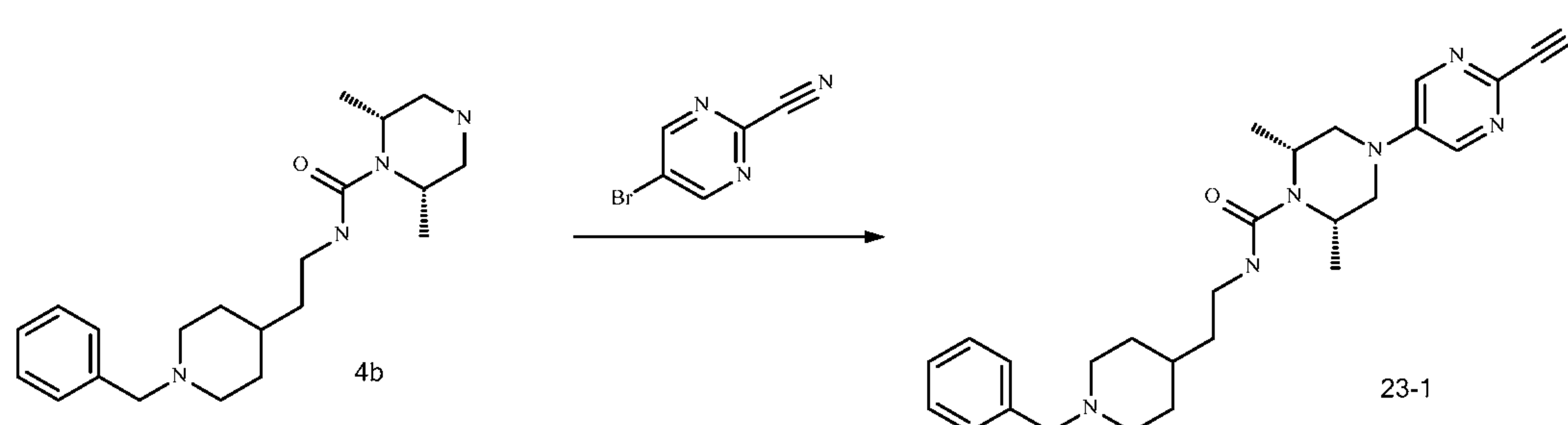
Cpd.N o.	Compound Name	Obs Ion (<i>m/z</i>)
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Cpd.No.	Compound Name	Obs Ion (m/z)
22-1	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	505.1
22-2	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyanophenyl)-2,6-dimethylpiperazine-1-carboxamide	460.1
22-3	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-2-fluorophenyl)-2,6-dimethylpiperazine-1-carboxamide	478.1
22-4	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-3-fluorophenyl)-2,6-dimethylpiperazine-1-carboxamide	478.1
22-5	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3,5-difluoropyridin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	472.1
22-6	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-(2,4,5-trifluorophenyl)piperazine-1-carboxamide	489.2
22-7	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-chloro-4,5-difluorophenyl)-2,6-dimethylpiperazine-1-carboxamide	505.1
22-8	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(6-chloro-5-fluoropyridin-3-yl)-2,6-dimethylpiperazine-1-carboxamide	488.0
22-9	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-3,5-difluorophenyl)-2,6-dimethylpiperazine-1-carboxamide	496.1
22-10	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-2,5-difluorophenyl)-2-methylpiperazine-1-carboxamide	482.1
22-11	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(6-chloropyridin-3-yl)-2-methylpiperazine-1-carboxamide	456.1
22-12	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-3,5-difluorophenyl)-2-methylpiperazine-1-carboxamide	482.1
22-13	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chloro-3,5-difluorophenyl)-2-methylpiperazine-1-carboxamide	491.1
22-14	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-chloro-3-fluorophenyl)-2-methylpiperazine-1-carboxamide	473.1

Cpd.No.	Compound Name	Obs Ion (m/z)
22-15	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-3-fluorophenyl)-2-methylpiperazine-1-carboxamide	464.1
22-16	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-methoxypyridin-4-yl)-2-methylpiperazine-1-carboxamide	452.1
22-17	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-cyano-3-(trifluoromethoxy)phenyl]-2-methylpiperazine-1-carboxamide	530.1
22-18	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-fluoropyridin-4-yl)-2-methylpiperazine-1-carboxamide	440.1
22-19	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-(pyrimidin-5-yl)piperazine-1-carboxamide	423.1
22-20	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-methoxypyrimidin-5-yl)-2-methylpiperazine-1-carboxamide	453.0
22-21	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[2-(dimethylamino)pyrimidin-5-yl]-2-methylpiperazine-1-carboxamide	466.3
22-22	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[5-(trifluoromethyl)pyrazin-2-yl]piperazine-1-carboxamide	491.1
22-23	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[5-(trifluoromethyl)pyrazin-2-yl]piperazine-1-carboxamide	505.1
22-24	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(3-cyano-4-methoxyphenyl)-2,6-dimethylpiperazine-1-carboxamide	490.1
22-25	N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[5-(trifluoromethyl)pyrazin-2-yl]piperazine-1-carboxamide	476.9
22-26	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-cyano-3-(dimethylamino)phenyl]-2-methylpiperazine-1-carboxamide	489.1
22-27	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyrazin-2-yl)-2-methylpiperazine-1-carboxamide	448.1
22-28	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-3-methoxyphenyl)-2-methylpiperazine-1-carboxamide	476.0

Cpd.No.	Compound Name	Obs Ion (m/z)
22-29	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2-methyl-4-[2-(trifluoromethyl)pyridin-4-yl]piperazine-1-carboxamide	490.0
22-30	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2,6-difluoropyridin-4-yl)-2-methylpiperazine-1-carboxamide	458.1
22-31	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-[4-cyano-3-(trifluoromethyl)phenyl]-2-methylpiperazine-1-carboxamide	514.1
22-32	(2R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(4-cyano-3-fluoro-5-methoxyphenyl)-2-methylpiperazine-1-carboxamide	494.1

EXAMPLE 23



Step 23A: (2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-cyanopyrimidin-5-yl)-2,6-dimethylpiperazine-1-carboxamide

To a solid mixture of (2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide **4b** (30 mg, 0.08 mmol, 1.0 eq), 5-bromopyrimidine-2-carbonitrile (22 mg, 0.12 mmol, 1.5 eq) and cesium carbonate (39 mg, 0.12 mmol, 1.5 eq) was added NMP (1 mL) and reaction mixture stirred at 45 °C over the weekend.

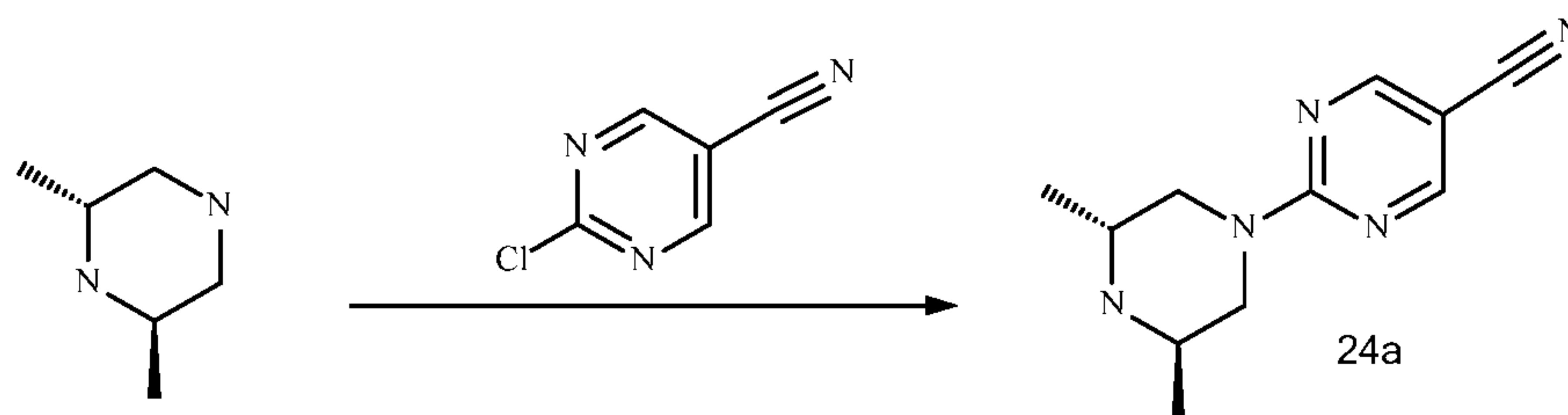
The resulting suspension was cooled, passed through an HPLC filter diluting to 1 mL with MeOH and submitted for directly for preparative chromatography yielding (2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-cyanopyrimidin-5-yl)-2,6-dimethylpiperazine-1-carboxamide **23-1**. The table below provides the observed (Obs)

ion m/z ratio for **23-1** (first compound listed in Table 17) and other compounds that were made according to the procedure as described in this example.

Table 17

Cpd. No.	Compound Name	Obs Ion (m/z)
23-1	(2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(2-cyanopyrimidin-5-yl)-2,6-dimethylpiperazine-1-carboxamide	462.2
23-2	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyrazin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	462.1
23-3	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(6-cyanopyridazin-3-yl)-2,6-dimethylpiperazine-1-carboxamide	462.1

EXAMPLE 24



Step 24A: 2-[(3R,5R)-3,5-dimethylpiperazin-1-yl]pyrimidine-5-carbonitrile

To a suspension of (2R,6R)-2,6-dimethylpiperazine dihydrochloride (0.250 g, 1.34 mmol, 1.0 eq) and 2-chloropyrimidine-5-carbonitrile (0.187 g, 1.34 mmol, 1.0 eq) in acetonitrile (5 mL) was added triethylamine (0.93 mL, 6.7 mmol, 5.0 eq) and reaction mixture stirred at room temperature overnight. The resulting suspension was filtered to remove triethylamine hydrochloride and concentrated to yield 2-[(3R,5R)-3,5-dimethylpiperazin-1-yl]pyrimidine-5-carbonitrile **24a** as an orange solid. The crude material was carried to Example 26 without further purification.

Other compounds made using the above synthetic scheme include:

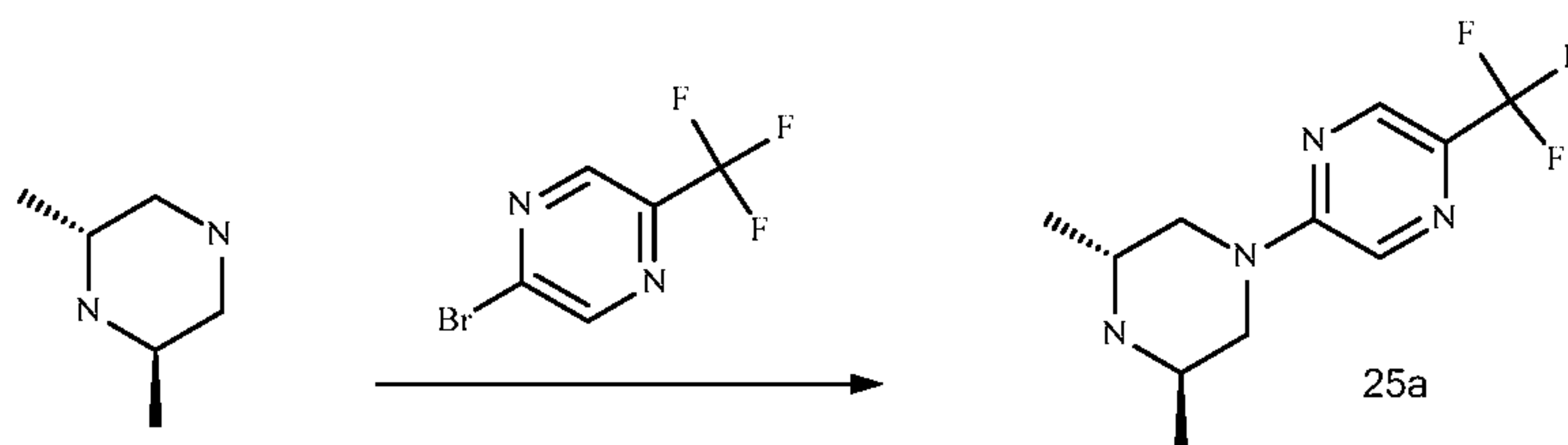
2-[(3R,5R)-3,5-dimethylpiperazin-1-yl]-5-(trifluoromethyl)pyrimidin-4-amine **24b**;

2-[(3R,5R)-3,5-dimethylpiperazin-1-yl]-5-(trifluoromethyl)pyrimidine

24c; and

2-[(3S,5S)-3,5-dimethylpiperazin-1-yl]pyrimidine-5-carbonitrile **24d**.

EXAMPLE 25



5

Step 25A: 2-[(3R,5R)-3,5-dimethylpiperazin-1-yl]-5-(trifluoromethyl)pyrazine

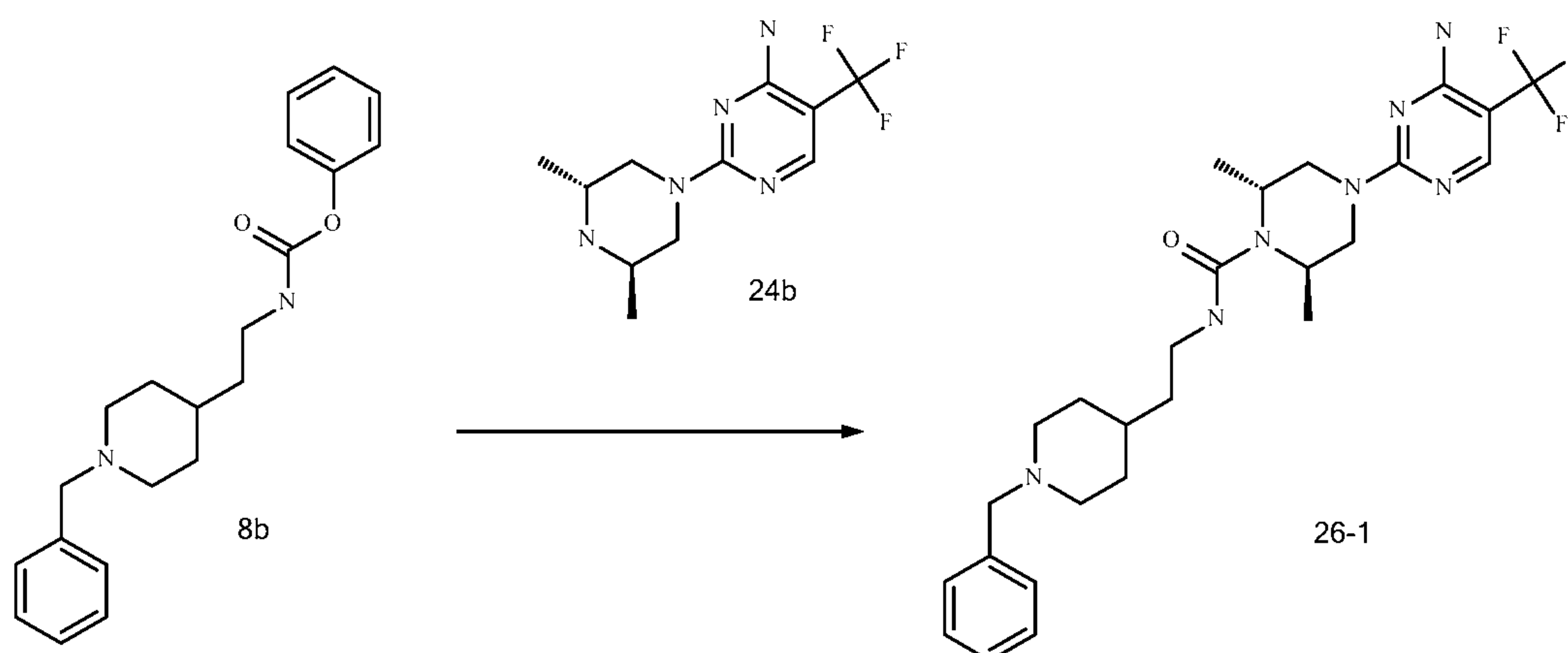
To a solid mixture of (2R,6R)-2,6-dimethylpiperazine dihydrochloride (0.08 g, 0.44 mmol, 1.0 eq), sodium *tert*-butoxide (0.21 g, 2.2 mmol, 5.0 eq) and bis(*tert*-butylphosphine)palladium(0) (34 mg, 0.07 mmol, 0.15 eq) was added dioxane (4 mL) followed by 2-bromo-5-(trifluoromethyl)pyrazine (0.10 g, 0.44 mmol, 1.0 eq) and the reaction mixture stirred at 50°C overnight. The resulting suspension was filtered thru a pad of celite using EtOAc and concentrated. Silica gel column (24 g) was loaded using methylene chloride and run using an increasing gradient of MeOH (0-20%) in methylene chloride over 25 min. Following concentration of the product eluents, 2-[(3R,5R)-3,5-dimethylpiperazin-1-yl]-5-(trifluoromethyl)pyrazine **25a** (0.09 g, 0.33 mmol, 75%) was isolated as a yellow oil. The purified material was carried to Example 26.

15

5-[(3R,5R)-3,5-dimethylpiperazin-1-yl]-2-(trifluoromethyl)pyrimidine

25b was made in a similar fashion.

EXAMPLE 26



Step 26A: (2R,6R)-4-[4-amino-5-(trifluoromethyl)pyrimidin-2-yl]-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide

5 To a solution of phenyl N-[2-(1-benzylpiperidin-4-yl)ethyl]carbamate **8b** (15 mg, 0.04 mmol, 1.0 eq) and crude 2-[(3R,5R)-3,5-dimethylpiperazin-1-yl]-5-(trifluoromethyl)pyrimidin-4-amine **24b** (22 mg, 0.08 mmol, 2.0 eq) in NMP (0.50 mL) was added triethylamine (0.02 mL, 0.16 mmol, 4.0 eq) and reaction mixture stirred at 100°C overnight. The reaction mixture was filtered and diluted to a total volume of 1
10 mL using MeOH and submitted directly for preparative chromatography yielding

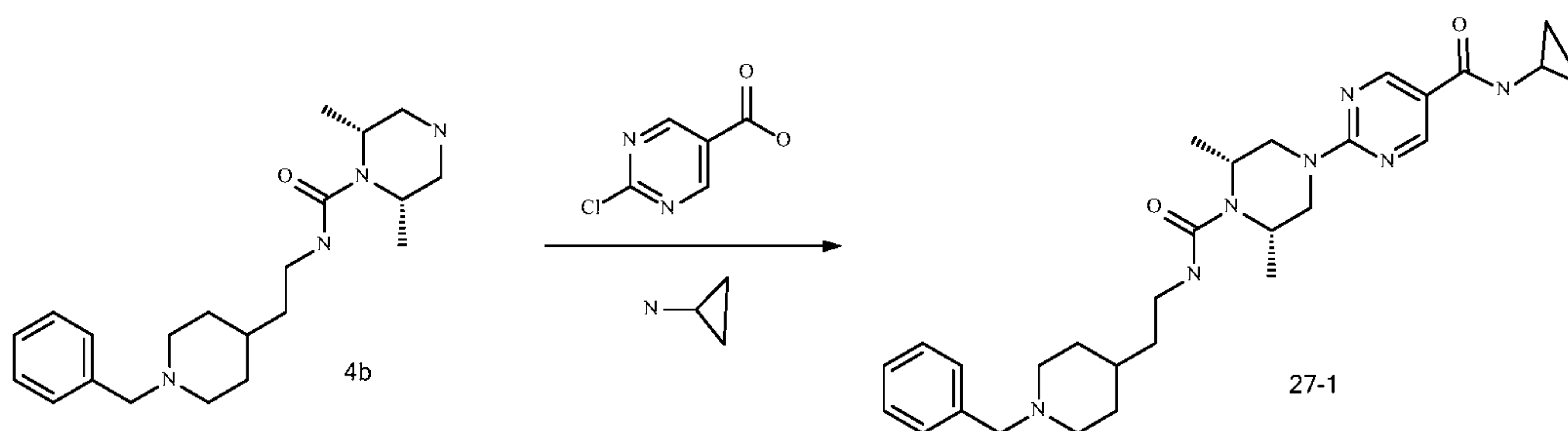
(2R,6R)-4-[4-amino-5-(trifluoromethyl)pyrimidin-2-yl]-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide **26-1**. The table below provides the observed (Obs) ion m/z ratio for **26-1** (first compound listed in Table 18) and other compounds that were made according to the procedure as described
15 in this example.

Table 18

Cpd. No.	Compound Name	Obs Ion (m/z)
26-1	(2R,6R)-4-[4-amino-5-(trifluoromethyl)pyrimidin-2-yl]-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide	520.1
26-2	(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyrimidin-	462.1

	2-yl)-2,6-dimethylpiperazine-1-carboxamide	
26-3	(2S,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-4-(5-cyanopyrimidin-2-yl)-2,6-dimethylpiperazine-1-carboxamide	462.1
26-4	(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[5-(trifluoromethyl)pyrazin-2-yl]piperazine-1-carboxamide	505.1
26-5	(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[5-(trifluoromethyl)pyrimidin-2-yl]piperazine-1-carboxamide	505.0
26-6	(2R,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[2-(trifluoromethyl)pyrimidin-5-yl]piperazine-1-carboxamide	505.05

EXAMPLE 27



Step 27A: 2-[(3R,5S)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3,5-dimethylpiperazin-1-yl]-N-cyclopropylpyrimidine-5-carboxamide

5 To a 0.5 M NMP solution of (2S,6R)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethylpiperazine-1-carboxamide **4b** (1.0 mL, 0.50 mmol, 1.0 eq) and triethylamine (0.28 mL, 2.0 mmol, 4 eq) was added 2-chloropyrimidine-5-carboxylic acid (79 mg, 0.50 mmol, 1.0 eq) and the reaction mixture stirred at 50 °C overnight. Then, a 75 µL aliquot was treated with NMP solutions of cyclopropylamine (0.10 mL, 0.5 M, 1.3 eq), triethylamine (0.10 mL, 2.0 M, 5.2 eq) and HATU (0.10 mL, 0.5 M, 1.3 eq) and again stirred at 50 °C overnight. The reaction mixture was passed through an HPLC filter diluting to 1 mL with MeOH and purified by preparative chromatography yielding 2-[(3R,5S)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3,5-dimethylpiperazin-1-yl]-N-cyclopropylpyrimidine-5-carboxamide **27-1**. The table

15 below provides the observed (Obs) ion m/z ratio for **27-1** (first compound listed in

Table 19) and other compounds that were made according to the procedure as described in this example.

Table 19

Cpd. No.	Compound Name	Obs Ion (m/z)
27-1	2-[(3R,5S)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3,5-dimethylpiperazin-1-yl]-N-cyclopropylpyrimidine-5-carboxamide	520.1
27-2	(2R,6S)-N-[2-(1-benzylpiperidin-4-yl)ethyl]-2,6-dimethyl-4-[5-(pyrrolidine-1-carbonyl)pyrimidin-2-yl]piperazine-1-carboxamide	534.1
27-3	2-[(3R,5S)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3,5-dimethylpiperazin-1-yl]-N-methyl-N-(propan-2-yl)pyrimidine-5-carboxamide	536.2
27-4	2-[(3R,5S)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3,5-dimethylpiperazin-1-yl]-N-(prop-2-en-1-yl)pyrimidine-5-carboxamide	520.2
27-5	2-[(3R,5S)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3,5-dimethylpiperazin-1-yl]-N-(cyclopropylmethyl)pyrimidine-5-carboxamide	534.2
27-6	2-[(3R,5S)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3,5-dimethylpiperazin-1-yl]-N-cyclobutylpyrimidine-5-carboxamide	534.1
27-7	2-[(3R,5S)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3,5-dimethylpiperazin-1-yl]-N-(2-fluoroethyl)pyrimidine-5-carboxamide	526.1
27-8	2-[(3R,5S)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3,5-dimethylpiperazin-1-yl]-N-(butan-2-yl)pyrimidine-5-carboxamide	536.2
27-9	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-N-ethyl-N-methylpyrimidine-5-carboxamide	508.3
27-10	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-N-methylpyrimidine-5-carboxamide	480.3
27-11	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-6-methyl-N-(2-methylpropyl)pyrimidine-4-	536.3

Cpd. No.	Compound Name	Obs Ion (m/z)
	carboxamide	
27-12	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-N-(2-methylpropyl)pyrimidine-5-carboxamide	522.3
27-13	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-6-methyl-N-(propan-2-yl)pyrimidine-4-carboxamide	522.2
27-14	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-N-cyclopropyl-6-methylpyrimidine-4-carboxamide	520.3
27-15	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-N-(propan-2-yl)pyrimidine-5-carboxamide	508.3
27-16	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-N-ethylpyrimidine-5-carboxamide	494.2
27-17	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-N,N-dimethylpyrimidine-5-carboxamide	494.2
27-18	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-N-ethyl-N,6-dimethylpyrimidine-4-carboxamide	522.3
27-19	2-[(3R)-4-{[2-(1-benzylpiperidin-4-yl)ethyl]carbamoyl}-3-methylpiperazin-1-yl]-N-ethyl-6-methylpyrimidine-4-carboxamide	508.3

BIOLOGY EXAMPLES

Binding assay

Binding affinity (K_i) of compounds was measured by inhibition of radioligand binding to membranes from CHO cells expressing human M1, M2, M3, M4 and M5 receptors. Membranes were prepared by nitrogen cavitation and differential centrifugation as previously described (Hoare et al., Mol. Pharmacol. 2003 Mar; 63(3): 751-65). The radioligand employed was tritiated N-methylscopolamine, used at a

concentration of 1.5 nM. A dose-response of twelve concentrations of compound was used, ranging from 10 μ M to 32 pM. The assay buffer was 50 mM HEPES, 100 mM NaCl, 5 mM MgCl₂, 1 mM ethylenediaminetetraacetic acid, pH-adjusted to pH 7.4. Membranes, radioligand and compound were incubated together for 90 minutes at 37 °C, in a total volume of 150 μ l in a 96-well plate. Receptor-bound radioligand was then collected by harvesting the assay over glass fiber filters pretreated with polyethylenimine to trap the cell membranes, using rapid vacuum filtration. Harvesting and radioactivity counting was conducted as previously described (*see, e.g., Hoare et al., Mol. Pharmacol.* 2003 63(3):751-65); Erratum at *Mol. Pharmacol.* 2005 Jul; 68(1): 260).

Binding affinities of all the exemplified compounds, which are described in the examples and listed in the tables above, are less than 1 μ M against the M4 receptor. More specifically, specificity for the M4 receptor for each of the compounds listed in Table 20 is as follows: (1) “+” means the compound had a Ki against the M4 receptor of less than 1 μ M (1,000 nM) but greater or equal to 100 nM; (2) “++” means the compound had a Ki against the M4 receptor of less than 100 nM but greater or equal to 10 nM; and (3) “+++” means that the compound had a Ki against the M4 receptor of less than 10 nM.

Table 20

Cpd. No.	Ki
3-1	+++
3-2	++
3-3	+
3-4	+
3-5	+++
3-6	++
3-7	++
3-8	+++
3-9	+++
3-10	+++
3-11	+++
3-12	+++
3-13	+++
3-14	+++

Cpd. No.	Ki
3-15	++
3-16	+++
3-17	+++
3-18	+++
3-19	+++
3-20	++
3-21	+++
3-22	+++
3-23	+++
4-1	+++
4-2	+
4-4	+
4-5	+++
4-6	+++

Cpd. No.	Ki
4-8	+
4-9	+
4-10	+++
4-11	+++
4-12	+++
4-13	+++
4-14	+++
4-15	+++
4-16	+++
4-17	+++
4-18	+++
4-19	+++
4-20	+++
4-21	+++

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Cpd. No.	Ki
4-22	+++
4-23	+
4-24	++
4-25	++
4-26	++
4-27	++
4-28	++
4-28	++
4-30	++
4-31	++
4-33	++
4-34	++
4-35	++
4-36	++
4-37	++
4-38	++
4-39	++
4-40	++
4-41	++
4-43	++
4-44	++
4-45	++
4-46	++
4-47	++
4-48	++
4-49	+
4-51	+
4-52	+++
4-53	+++
4-54	+++
4-55	+
4-56	+
4-60	+++
4-61	+
4-62	+
4-63	+
4-64	+
4-68	+++
4-69	++
4-70	++
4-71	+++
4-72	+++
4-73	+++
4-74	++
4-75	++

Cpd. No.	Ki
4-76	+++
4-77	+++
4-78	++
4-79	+++
4-80	+++
5-1	+++
5-2	+
5-3	+
5-4	++
5-5	+++
5-6	++
5-7	++
5-8	+++
5-9	+
5-10	+
5-11	+
5-12	+
5-13	++
5-14	+++
5-15	++
5-16	++
5-17	+++
5-18	+++
5-19	++
5-20	+++
5-21	+
5-22	+++
5-23	+++
5-24	+++
5-25	+
5-26	+
5-27	+++
5-28	+++
5-29	+++
5-30	+++
5-31	+++
5-32	+++
5-33	++
5-34	+
6-1	+++
6-2	+
6-3	+++
6-4	+++
6-5	++
6-6	++

Cpd. No.	Ki
6-7	++
6-8	++
6-9	++
6-10	++
6-11	++
6-12	++
6-13	++
6-14	++
6-15	++
6-16	++
6-17	++
6-18	++
6-19	+
6-20	+
6-21	+
6-22	+
6-23	+
6-24	+
6-25	+
6-26	+++
6-27	+++
6-28	+
6-29	+
6-30	+
6-31	+
6-32	++
6-33	+
6-34	+
6-35	+++
6-36	+++
6-37	+++
6-38	++
6-39	+
6-40	+++
6-41	++
6-42	+++
6-43	++
6-44	+
6-45	+
6-46	+++
6-47	+++
6-48	+++
6-49	+
6-50	+++
6-51	++

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Cpd. No.	Ki
6-52	++
6-53	++
6-54	++
6-55	++
6-56	++
6-57	++
6-58	+
6-59	++
6-60	++
6-61	+
6-62	+
6-63	+
6-64	+
6-65	++
6-66	+
6-67	++
7-1	+++
7-2	++
7-3	++
7-4	++
7-5	+
7-6	+
7-7	+
7-8	+
7-9	+++
7-10	+++
7-11	+++
7-12	+++
7-13	+
8-1	+++
8-2	++
8-3	++
8-4	++
8-5	+
8-6	+
8-7	+
8-8	++
8-9	++
8-10	++
8-11	++
8-12	++
8-13	++
8-14	++
8-15	++
8-16	++

Cpd. No.	Ki
8-17	++
8-18	++
8-19	++
8-20	+
8-21	+
8-22	+
8-23	+
8-24	+
8-25	+
8-26	+
8-27	+
8-28	+
8-29	+
8-30	+
8-31	+
8-32	+
8-33	+
8-34	+
8-35	+
8-36	+
8-37	+
8-38	+
8-39	+
8-40	+
8-41	+
8-42	+
8-43	+
8-44	+
8-45	+
8-46	+
8-47	+
8-48	+++
9-1	+++
9-2	+
9-3	+
9-4	+
9-5	+++
9-6	+++
9-7	+++
9-8	+++
9-9	+++
9-10	+++
9-11	++
9-12	++
9-13	++

Cpd. No.	Ki
9-14	++
9-15	++
9-16	++
9-17	++
9-18	+
9-19	+
9-20	+
9-21	++
9-22	++
9-23	++
9-24	++
9-25	++
9-26	++
9-27	++
9-28	++
9-29	++
9-30	++
9-31	++
9-32	++
9-33	++
9-34	+
9-35	+
9-36	+
9-37	+
9-38	+
9-39	++
9-40	++
9-41	++
9-42	+
9-43	+
9-44	++
9-45	++
9-46	++
9-47	+
9-48	+
9-49	+
9-50	+
9-51	+
9-52	+
9-53	+
9-54	+
9-55	+
9-56	+
9-57	+
9-58	+

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Cpd. No.	Ki
9-59	+
9-60	+
9-61	+
9-62	+++
9-63	+++
9-64	+++
9-65	+
9-66	+
9-67	+
9-68	+
9-69	+
9-70	+++
9-71	+++
9-72	+++
9-73	+++
9-74	+
9-75	+
10-1	++
10-2	+
10-3	+
10-4	+
10-5	+++
10-6	+++
10-7	+++
10-8	+++
10-9	+++
10-10	+++
10-11	+++
10-12	+++
10-13	+++
10-14	+++
10-15	+
10-16	+
10-17	+
10-18	+++
10-19	+++
10-20	+++
10-21	+++
10-22	+++
10-23	+++
10-24	++
10-25	++
10-26	+
10-27	+
10-28	+

Cpd. No.	Ki
10-29	++
10-30	++
10-31	++
10-32	++
10-33	++
10-34	++
10-35	++
10-36	++
10-37	++
10-38	++
10-39	++
10-40	++
10-41	++
10-42	+++
10-43	+++
10-44	+++
10-45	++
10-46	++
10-47	++
10-48	+
10-49	+
10-50	+
10-51	+
10-52	+
10-53	+
10-54	+++
10-55	++
10-56	+++
10-57	+++
10-58	+++
10-59	+
10-60	+
10-61	+
10-62	+
10-63	+
10-64	+
10-65	+
10-66	+
10-67	+
10-68	+
10-69	+
10-70	+
10-71	+
10-72	+
10-73	+

Cpd. No.	Ki
10-74	+
10-75	+
10-76	++
10-77	++
10-78	++
10-79	+++
10-80	+++
10-81	+++
11-1	++
11-2	++
11-3	++
11-4	+
11-5	+
11-6	++
11-7	++
11-8	+
11-9	+
11-10	+
11-11	+
11-12	+
11-13	+
11-14	+
11-15	+
11-16	+
11-17	+
11-18	+
11-19	+
11-20	+
11-21	+
11-22	+
11-23	+
11-24	+
11-25	+
11-26	+
11-27	+
11-28	+
11-29	+
11-30	+
12-1	++
12-2	+
12-3	+
12-4	++
12-5	+
12-6	+
12-7	+

Cpd. No.	Ki
12-8	+
12-9	+
12-10	+
12-11	++
12-12	++
17-1	+++
17-2	+
17-3	+++
17-4	++
17-5	+++
17-6	+++
17-7	+
17-8	++
18-1	+++
18-2	+
18-3	+
18-4	+++
18-5	+++
18-6	++
18-7	++
18-8	++
18-9	++
18-10	++
18-11	++
18-12	++
18-13	++
18-14	++
18-15	+
18-16	+++
18-17	+++
18-18	+
18-19	+
18-20	++
19-1	+
19-2	++
19-3	+
19-4	+
19-5	+
19-6	+
19-7	+
19-8	+

Cpd. No.	Ki
20-1	++
20-2	+++
20-3	+++
21-1	++
21-2	+++
21-3	+
21-4	++
21-5	+
21-6	+
21-7	+++
21-8	+
21-9	+
21-10	+
21-11	+
21-12	+
21-13	++
21-14	+++
21-15	+++
21-16	+++
21-17	+++
22-1	++
22-2	+++
22-3	+++
22-4	+++
22-5	+++
22-6	++
22-7	+++
22-8	+++
22-9	+++
22-10	+++
22-11	++
22-12	+++
22-13	+++
22-14	+++
22-15	+++
22-16	++
22-17	+++
22-18	++
22-19	++
22-20	NT
22-21	NT

Cpd. No.	Ki
22-22	+++
22-23	+++
22-24	+++
22-25	+++
22-26	++
22-27	++
22-28	++
22-29	++
22-30	+++
22-31	+++
22-32	+++
23-1	+
23-2	++
23-3	++
26-1	+++
26-2	+++
26-3	+
26-4	+++
26-5	+++
26-6	+++
27-1	++
27-2	+
27-3	+
27-4	+
27-5	+
27-6	+
27-7	+
27-8	+
27-9	+
27-10	+
27-11	++
27-12	++
27-13	+
27-14	+
27-15	+
27-16	+
27-17	+
27-18	+
27-19	+

For the compounds of Table 20 above with Ki values against the M4 receptor of less than 10 nM (*i.e.*, the “+++” compounds), their selectivity over the M1,

M2, M3 and M5 receptors are set forth in Table 21 below. In Table 21, activity is expressed as follows: (1) “+++” means the compound had a Ki against the noted receptor of less than 10 nM; (2) “++” means the compound had a Ki against the noted receptor of less than 100 nM but greater than or equal to 10 nM; (3) “+” means the compound had a Ki against the noted receptor of less than 1 μ M (1,000 nM) but greater or equal to 100 nM; and (4) “-” means the compound had a Ki against the noted receptor of 1 μ M (1,000 nM) or greater or that activity was not detected against the noted receptor. (“NT” in Table 21 means that the compound was not tested against the muscarinic receptor noted.)

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Table 21

Cpd No	M1	M2	M3	M5	Cpd No	M1	M2	M3	M5
3-1	+	++	-	-	4-19	+	+	-	-
3-5	-	+	-	-	4-20	+	++	-	-
3-8	+	++	+	-	4-21	+	++	+	-
3-9	+	++	+	-	4-22	-	+	-	+
3-10	+	++	+	-	4-52	+	++	+	-
3-11	-	+	-	-	4-53	+	++	+	+
3-12	+	++	-	-	4-54	+	+	-	-
3-13	+	+	-	-	4-60	+	++	+	+
3-14	+	++	-	-	4-68	+	+	-	-
3-16	-	-	-	-	4-71	+	+	-	-
3-17	-	+	-	-	4-72	+	+	NT	-
3-18	-	-	-	-	4-73	+	++	+	-
3-19	-	+	-	-	4-76	-	+	-	-
3-21	-	+	-	-	4-77	+	++	-	-
3-22	-	+	-	-	4-79	+	++	-	-
3-23	-	+	-	-	4-80	+	+	-	-
4-1	+	+	-	-	5-1	-	+	-	-
4-5	+	++	-	-	5-5	+	+	-	-
4-6	+	++	NT	-	5-8	-	++	+	-
4-10	+	++	+	+	5-14	+	+	-	-
4-11	+	++	-	-	5-17	+	+	+	-
4-12	+	++	+	-	5-18	-	++	-	-
4-13	-	+	-	-	5-20	-	+	-	-
4-14	-	+	NT	-	5-22	+	++	-	-
4-15	+	+	-	-	5-23	+	++	-	-
4-16	+	+	NT	-	5-24	+	++	-	-
4-17	-	+	-	-	5-27	+	+	-	-
4-18	-	+	-	-	5-28	+	+	-	-

Cpd No	M1	M2	M3	M5
5-29	-	+	-	-
5-30	-	+	-	-
5-31	++	+++	++	+
5-32	-	++	-	-
6-1	+	+++	+	+
6-3	+	++	+	-
6-4	+	+	-	-
6-26	+	++	-	-
6-27	+	++	+	-
6-35	+	++	+	-
6-36	+	+	-	-
6-37	+	++	-	-
6-40	+	++	+	-
6-42	-	++	+	-
6-46	-	+++	-	-
6-47	+	+++	+	+
6-48	-	++	-	-
6-50	+	++	+	-
7-1	-	-	-	-
7-9	+	+	-	-
7-10	-	+	-	-
7-11	-	-	-	-
7-12	-	-	-	-
8-1	+	+	+	+
8-48	++	+++	+	+
9-1	-	+	-	-
9-5	-	-	-	-
9-6	+	++	+	+
9-7	+	+	-	-
9-8	-	+	-	-
9-9	+	+	-	-
9-10	+	+	+	-
9-62	+	+	-	-
9-63	++	+++	++	+
9-64	+	+	-	-
9-70	+	+	-	-
9-71	-	+	-	-
9-72	+	+	-	-
9-73	-	+	-	-
10-5	+	++	-	-
10-6	+	+	-	-
10-7	-	+	-	-
10-8	-	+	-	-
10-9	-	+	-	-
10-10	+	+	-	-

Cpd No	M1	M2	M3	M5
10-11	+	+	-	-
10-12	+	++	+	+
10-13	+	+	-	-
10-14	-	+	-	-
10-18	-	+	-	-
10-19	+	+	-	-
10-20	-	+	-	-
10-21	-	+	-	-
10-22	-	+	-	-
10-23	+	++	-	-
10-42	+	+	-	-
10-43	-	+	-	-
10-44	-	+	-	-
10-54	+	++	-	-
10-56	+	++	+	-
10-57	+	++	-	-
10-58	-	-	-	-
10-79	+	++	-	+
10-80	++	++	+	+
10-81	++	++	++	+
17-1	-	+	-	-
17-3	+	+	-	-
17-5	+	++	-	-
17-6	-	+	-	-
18-1	-	++	-	-
18-4	+	+	-	-
18-5	-	+	-	-
18-16	-	+	-	-
18-17	-	+	-	-
20-2	++	++	++	+
20-3	+	+	+	-
21-2	-	+	-	-
21-7	++	+++	++	+
21-14	+	++	+	-
21-15	-	+	-	-
21-16	++	+++	++	+
21-17	++	+++	++	+
22-2	-	+	-	-
22-3	-	+	-	-
22-4	-	++	-	-
22-5	+	++	-	+
22-7	+	++	+	+
22-8	+	++	-	-
22-9	+	++	-	-
22-10	-	+	-	-

Cpd No	M1	M2	M3	M5
22-12	-	++	-	+
22-13	+	++	+	+
22-14	+	++	+	+
22-15	+	++	-	+
22-17	+	++	-	+
22-22	+	++	-	-
22-23	+	+++	+	+
22-24	+	++	-	-

Cpd No	M1	M2	M3	M5
22-25	-	++	-	-
22-30	+	++	-	-
22-31	++	++	-	+
22-32	+	+	-	+
26-1	+	++	-	-
26-2	-	+	-	-
26-4	-	+	-	-
26-6	++	++	+	+

Functional assay

Functional antagonism of acetylcholine responses were evaluated using a ^{35}S -GTP γ S binding assay. Acetylcholine binding to the muscarinic receptors activates G-proteins. Activation of G-proteins can be determined by their binding of the radiolabeled GTP analogue ^{35}S -GTP γ S. In the assay, acetylcholine stimulates the binding of ^{35}S -GTP γ S to G-proteins associated with cell membranes, and the incorporated ^{35}S -GTP γ S can be collected by harvesting the membranes. Antagonist activity of the compounds was determined as the IC₅₀ for inhibition of the acetylcholine response. The assay buffer used was 50 mM HEPES, 100 mM NaCl, 5 mM MgCl₂, 1 mM ethylenediaminetetraacetic acid, pH-adjusted to pH 7.4. Acetylcholine, compound (a dose-response of twelve concentrations ranging from 10 μM to 32 pM) and membranes from CHO cells expressing M4 or M2 receptors were incubated together in 150 μl buffer for 30 minutes at 30°C in a 96-well plate. ^{35}S -GTP γ S was then added, to a final concentration of 0.2 nM and a final volume of 175 μl . Twenty minutes later, membranes were harvested by rapid vacuum filtration onto non-treated glass fiber filters, as previously described (*see, e.g., Hoare et al., Mol. Pharmacol.* 2003 63(3):751-65); Erratum at *Mol. Pharmacol.* 2005 Jul; 68(1): 260). The concentration of acetylcholine used was that which stimulated 80% of the maximal response (3 μM for the M4 receptor, 1 μM for M2). Many of the compounds described above have been evaluated in the functional assay.

Electrophysiology Assay

Adult (>8 weeks) female Lister hooded rats (Harlan, UK) were killed by decapitation and the brain was removed and placed into ice-cold oxygenated sucrose Krebs' medium containing (mM): sucrose 202, KCl 2, KH₂PO₄ 1.25, MgSO₄ 10, CaCl₂ 0.5, NaHCO₃ 26, glucose 10. The brain was hemisected along the midline and 300 μ M parasagittal slices were prepared with an oscillating microtome (Integraslice; Campden Instruments Ltd., Loughborough, UK). Slices were then transferred to a recovery chamber at room temperature containing oxygenated Krebs' solution (mM): NaCl 124, KCl 2, KH₂PO₄ 1.25, MgSO₄ 1, CaCl₂ 2, NaHCO₃ 26, glucose 10. Following at least 1 hour of recovery, individual slices were transferred to an interface recording chamber where they were perfused with Krebs' solution (33 °C). Extracellular field potential recordings were made with an Axoprobe 1A amplifier (Axon Instruments Ltd., USA) via a Krebs'-filled glass micropipette (resistance 2-5 M Ω) positioned in the stratum radiatum of the CA1, digitized (10kHz) via a CED1401 interface and stored on a computer with Spike2 software (Cambridge Electronic Design Ltd., Cambridge, UK). Field excitatory postsynaptic potential (fEPSP) responses were evoked (pair of 0.02ms pulses, separated by 40 ms; applied every 10s; adjusted to approximately 60% of the maximal spike-free response) by a bipolar stimulating electrode positioned in the stratum radiatum near the CA3-CA1 border.

The cholinergic agonist carbachol (aza-acetylcholine, resistant to degradation by acetylcholinesterase) was used to stimulate muscarinic receptors. The M1 muscarinic receptor was blocked using 5 μ M VU0255035, a selective M1 antagonist. The resulting inhibitory signal was primarily M4-mediated, based on its sensitivity to the M4 activator VU010010. The effect of M4 antagonists on this M4-mediated inhibition of fEPSPs was measured by adding M4 compound 20 minutes prior to application of carbachol.

6-OHDA Surgical Lesion and Behavioral Testing Procedures

6-OHDA Lesion protocol: Male Sprague-Dawley rats were anesthetized with isoflurane and placed into the stereotaxic frame. Thirty minutes prior the injection

of 6-OHDA, rats received desipramine (15 mg/kg, i.p.) to prevent the entry of the toxin into the noradrenergic cells. A unilateral lesion was induced by injections of 6-OHDA (8 µg/4 µl/site/rat; flow rate 1 µl/min; dissolved in 0.9% NaCl with 0.02% ascorbic acid) or vehicle into the left and right medial forebrain bundle at the following
5 coordinates: AP -4.4. mm; L ±1.2 mm; V -7.8 mm relative to Bregma (Paxinos and Watson, 2007). The rats were allowed to recover for 14 days and were then tested for locomotor activity induced by novelty (placing the rat in a new cage, 30 min) and for contraversive (contralateral) rotational behavior induced by apomorphine (0.2 mg/kg, s.c.).

10 Experimental animal selection criteria: Only the rats with activity higher than 5 turns/min following apomorphine treatment were enrolled in the study; rats not fulfilling the criteria were excluded from the study (typically 20%). Turning activity was then recorded for each group once per week for four consecutive weeks.

Locomotor Activity

15 Young adult male, Sprague-Dawley rats (240-250g) were purchased from Charles River Laboratories and assessed in the Open Field (Kinder Scientific, CA) task during the light hours of a 12:12 L:D cycle and were tested under bright light conditions. Animals were allowed to acclimate to the facility for at least one week prior to use. On the day of testing, animals were acclimated to the test room for at least 1
20 hour and were then treated orally with the Neurocrine compound and placed into the test chamber 30 minutes later. Animals were allowed to freely ambulate for 60 minutes. Measurements taken included, but were not limited to, total horizontal and vertical beam breaks.

The various embodiments described above can be combined to provide
25 further embodiments. All U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications, and non-patent publications referred to in this specification and/or listed in the Application Data Sheet are incorporated herein by reference in their entirety. Aspects of the embodiments can be

modified, if necessary to employ concepts of the various patents, applications and publications to provide yet further embodiments.

The disclosures of U.S. provisional patent application Serial No. 62/252,179, filed November 6, 2015, and U.S. provisional patent application Serial No. 5 62/275,708, filed June 1, 2016, are incorporated herein by reference in their entirety.

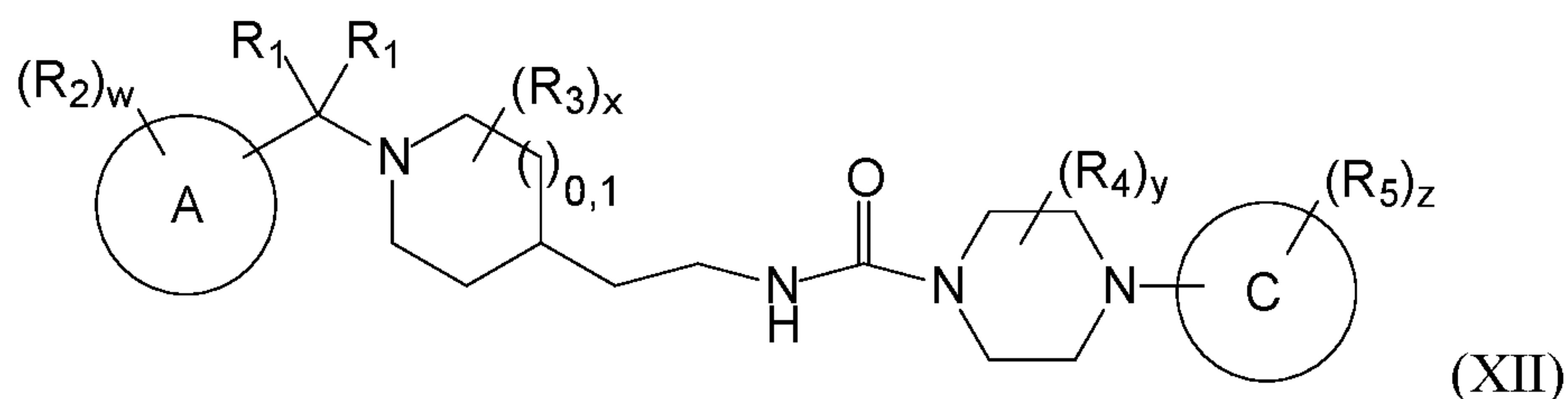
These and other changes can be made to the embodiments in light of the above-detailed description. In general, in the following claims, the terms used should not be construed to limit the claims to the specific embodiments disclosed in the specification and the claims, but should be construed to include all possible 10 embodiments along with the full scope of equivalents to which such claims are entitled. Accordingly, the claims are not limited by the disclosure.

AMENDED CLAIMS

received by the International Bureau on 16 February 2017

We claim the following:

1. A compound having the structure of the following formula (XII):



or a stereoisomer, tautomer, solvate, ester, prodrug, or pharmaceutically acceptable salt thereof, wherein:

A and C are each independently a carbocyclyl or heterocyclyl;

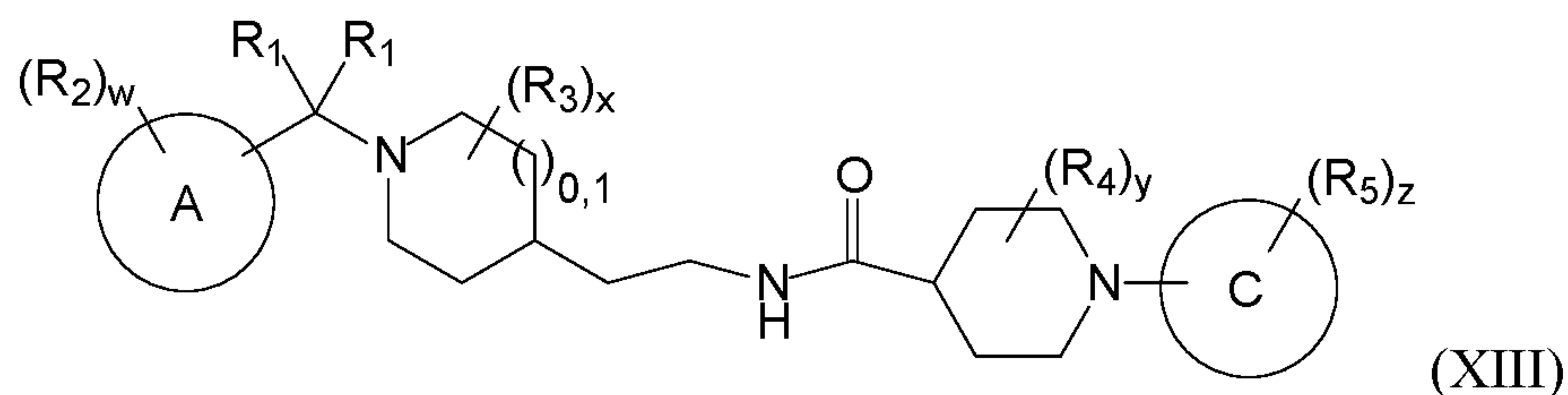
R₁ is, at each occurrence, H, C₁₋₄alkyl, C(=O)OC₁₋₄alkyl or aryl;

R₂, R₃, R₄ and R₅ are each independently -OH, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -C≡N, -C(=O)NH₂, halo, C₁₋₄alkyl, C₁₋₄alkyl-OH, C₁₋₄haloalkyl, C₁₋₄alkoxy or C₁₋₄haloalkoxy; and

w, x, y and z are each independently 0, 1, 2 or 3;

or

a compound having the structure of the following formula (XIII):



or a stereoisomer, tautomer, solvate, ester, prodrug, or pharmaceutically acceptable salt thereof, wherein:

A and C are each independently a carbocyclyl or heterocyclyl;

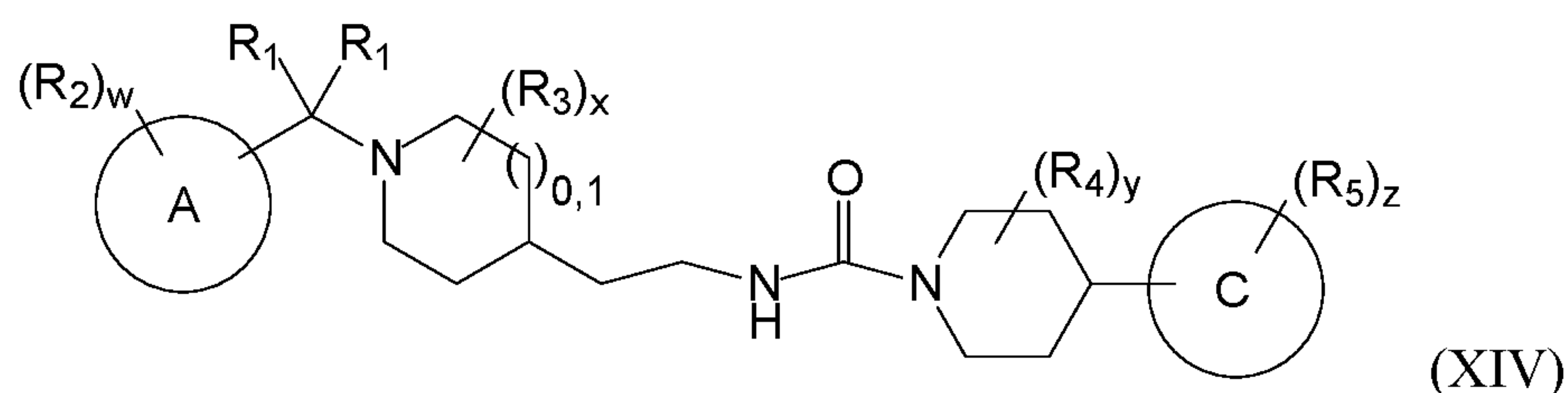
R₁ is, at each occurrence, H, C₁₋₄alkyl, C(=O)OC₁₋₄alkyl or aryl;

R_2 , R_3 , R_4 and R_5 are each independently $-OH$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, $-C\equiv N$, $-C(=O)NH_2$, halo, $C_{1-4}alkyl$, $C_{1-4}alkyl-OH$, $C_{1-4}haloalkyl$, $C_{1-4}alkoxy$ or $C_{1-4}haloalkoxy$; and

w , x , y and z are each independently 0, 1, 2 or 3, wherein at least one of y or z is 1, 2 or 3;

or

a compound having the structure of the following formula (XIV):



or a stereoisomer, tautomer, solvate, ester, prodrug, or pharmaceutically acceptable salt thereof, wherein:

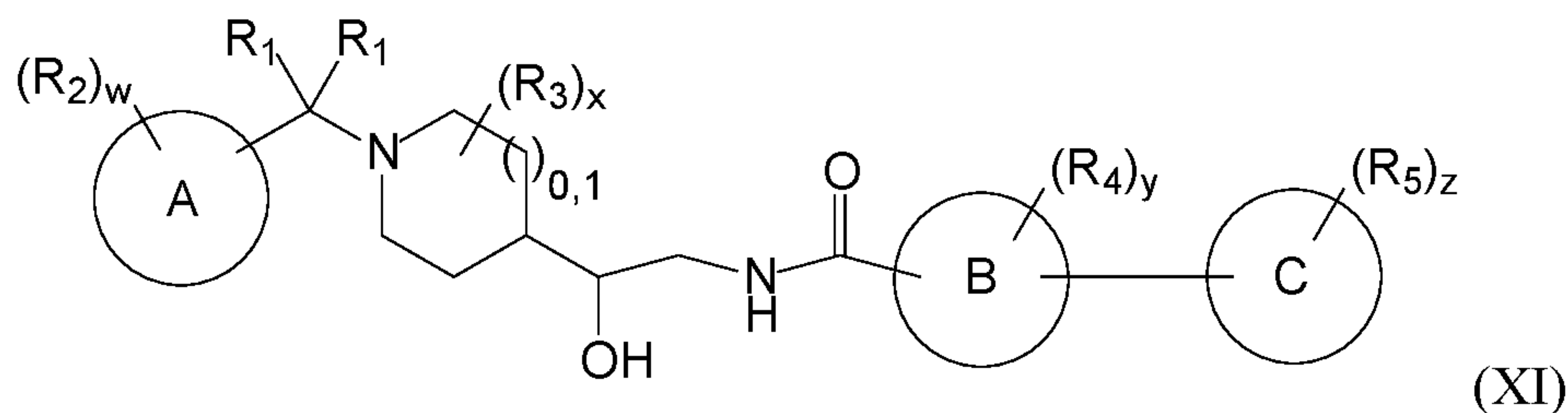
A and C are each independently a carbocyclyl or heterocyclyl;

R_1 is, at each occurrence, H , $C_{1-4}alkyl$, $C(=O)OC_{1-4}alkyl$ or aryl;

R_2 , R_3 , R_4 and R_5 are each independently $-OH$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, $-C\equiv N$, $-C(=O)NH_2$, halo, $C_{1-4}alkyl$, $C_{1-4}alkyl-OH$, $C_{1-4}haloalkyl$, $C_{1-4}alkoxy$ or $C_{1-4}haloalkoxy$; and

w , x , y and z are each independently 0, 1, 2 or 3.

2. A compound having the structure of the following formula (XI):



or a stereoisomer, tautomer, solvate, ester, prodrug, or pharmaceutically acceptable salt thereof, wherein:

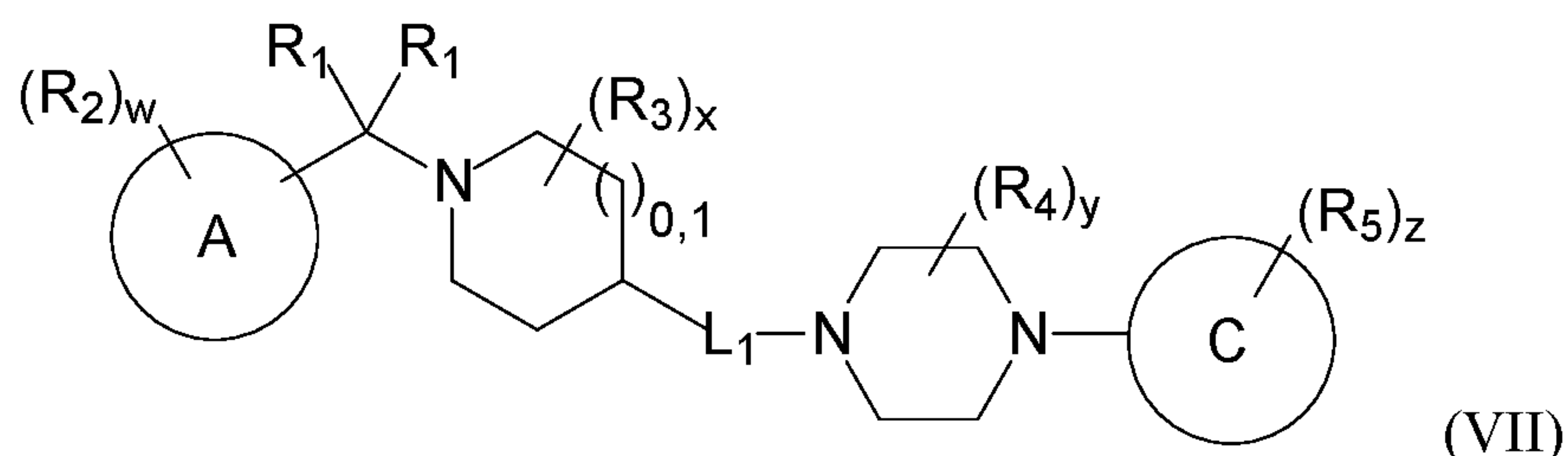
A , B and C are each independently a carbocyclyl or heterocyclyl;

R_1 is, at each occurrence, H, C_{1-4} alkyl, $C(=O)OC_{1-4}$ alkyl or aryl;

R_2 , R_3 , R_4 and R_5 are each independently $-OH$, $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl) $_2$, $-C\equiv N$, $-C(=O)NH_2$, halo, C_{1-4} alkyl, C_{1-4} alkyl- OH , C_{1-4} haloalkyl, C_{1-4} alkoxy or C_{1-4} haloalkoxy; and

w, x, y and z are each independently 0, 1, 2 or 3.

3. A compound having the structure of the following formula (VII):



or a stereoisomer, tautomer, solvate, ester, prodrug, or pharmaceutically acceptable salt thereof, wherein:

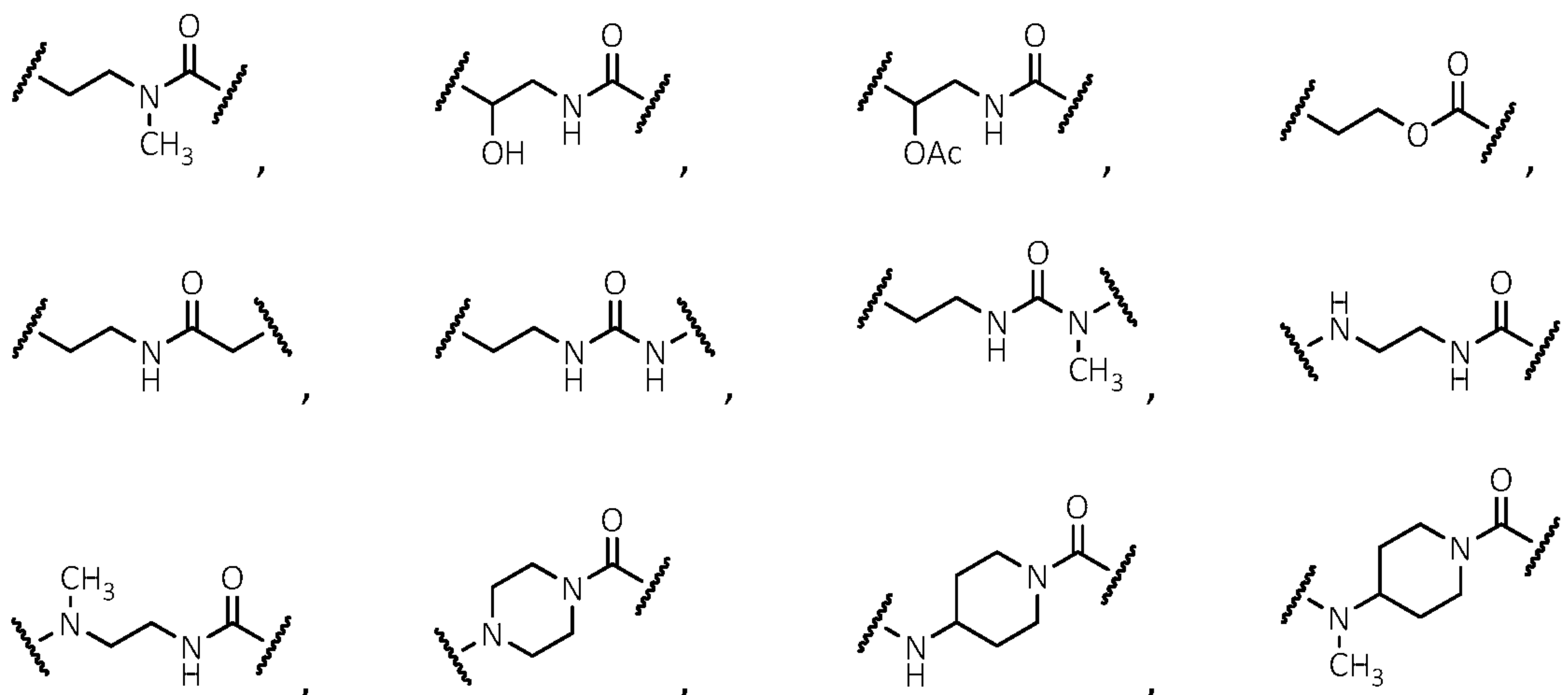
A and C are each independently a carbocyclyl or heterocyclyl;

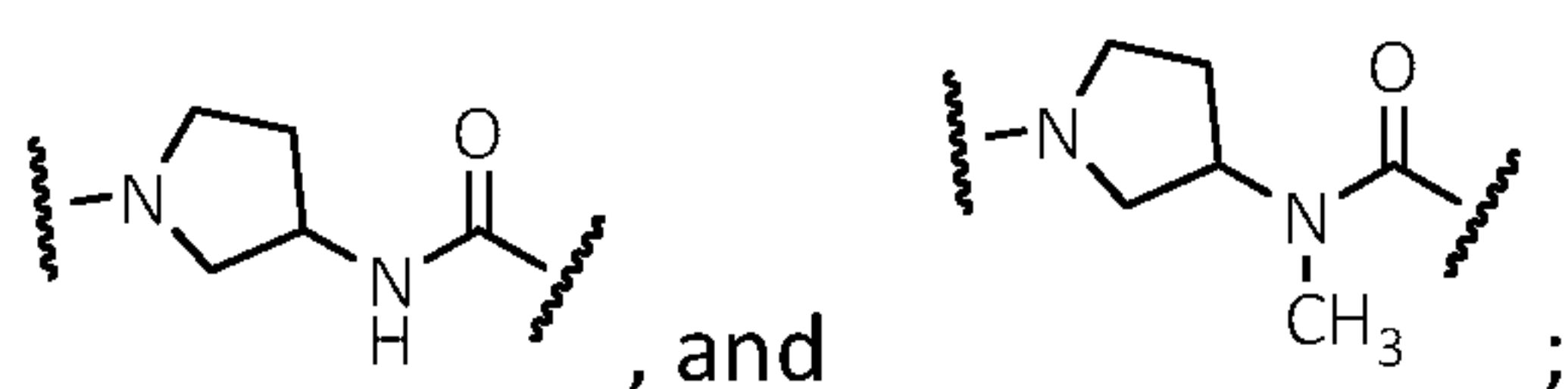
R_1 is, at each occurrence, H, C_{1-4} alkyl, $C(=O)OC_{1-4}$ alkyl or aryl;

R_2 , R_3 , R_4 and R_5 are each independently $-OH$, $-NH_2$, $-NH(C_{1-4}$ alkyl), $-N(C_{1-4}$ alkyl) $_2$, $-C\equiv N$, $-C(=O)NH_2$, halo, C_{1-4} alkyl, C_{1-4} alkyl- OH , C_{1-4} haloalkyl, C_{1-4} alkoxy or C_{1-4} haloalkoxy;

w, x, y and z are each independently 0, 1, 2 or 3; and

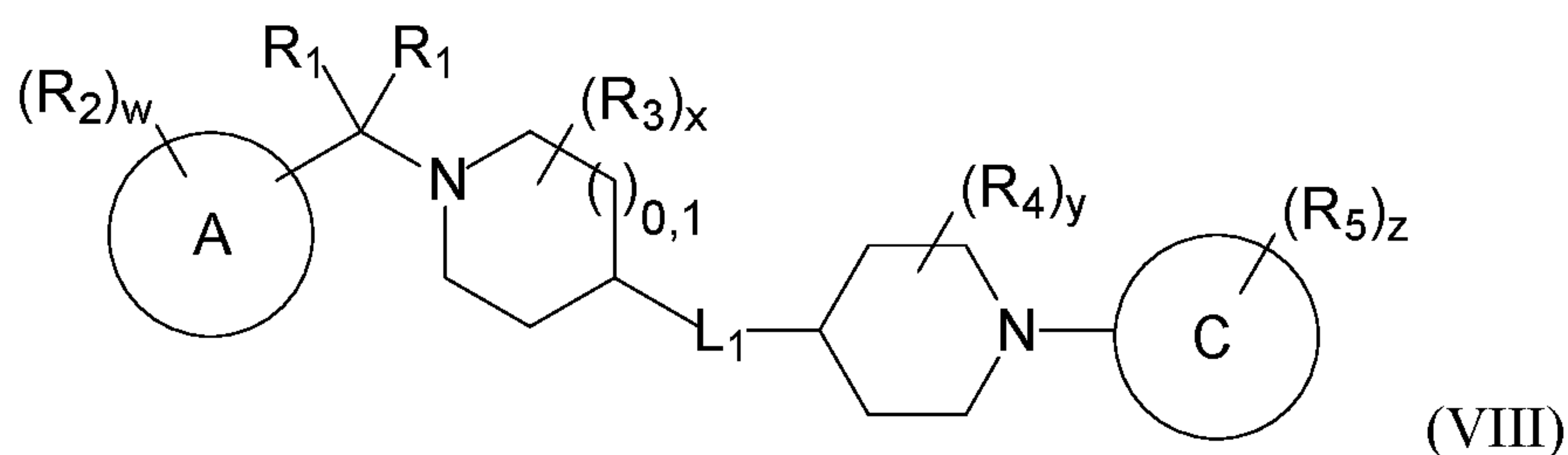
L_1 is one of the following:





or

a compound having the structure of the following formula (VIII):



or a stereoisomer, tautomer, solvate, ester, prodrug, or pharmaceutically acceptable salt thereof, wherein:

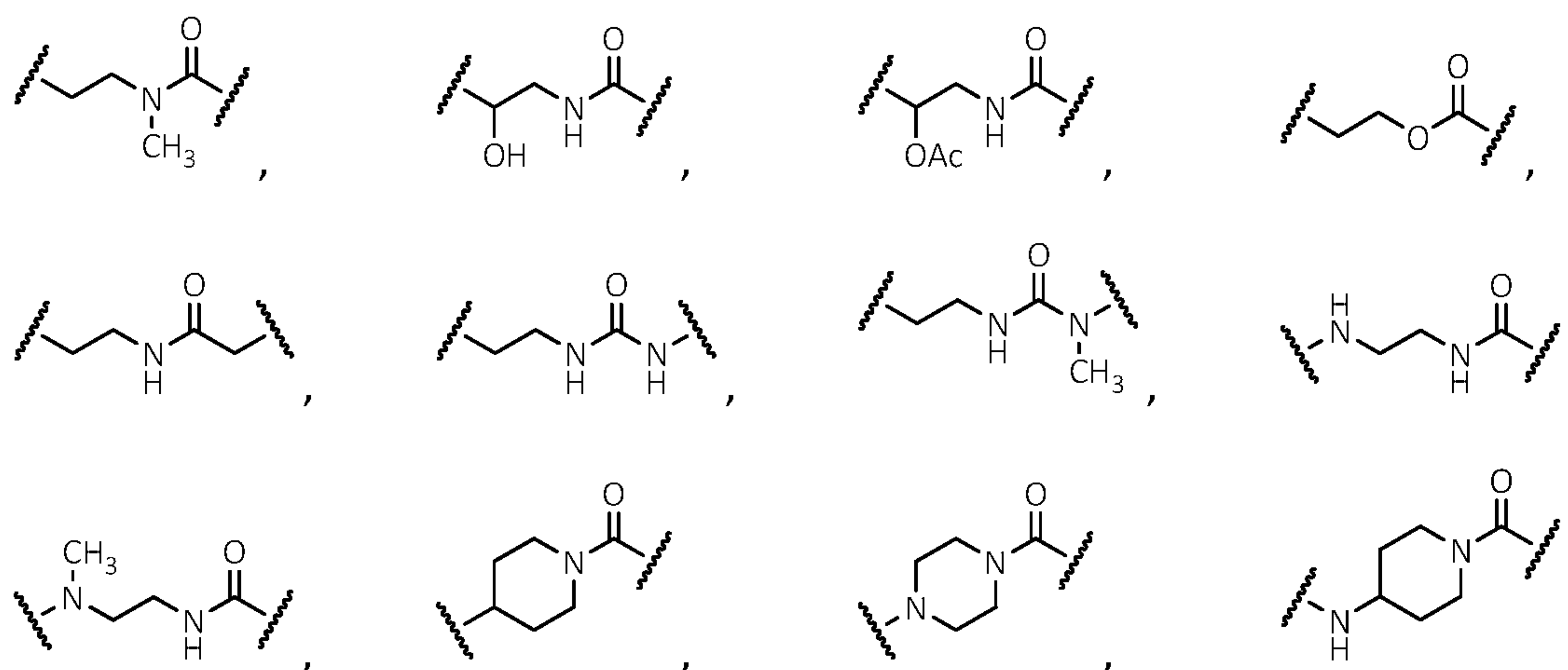
A and C are each independently a carbocyclyl or heterocyclyl;

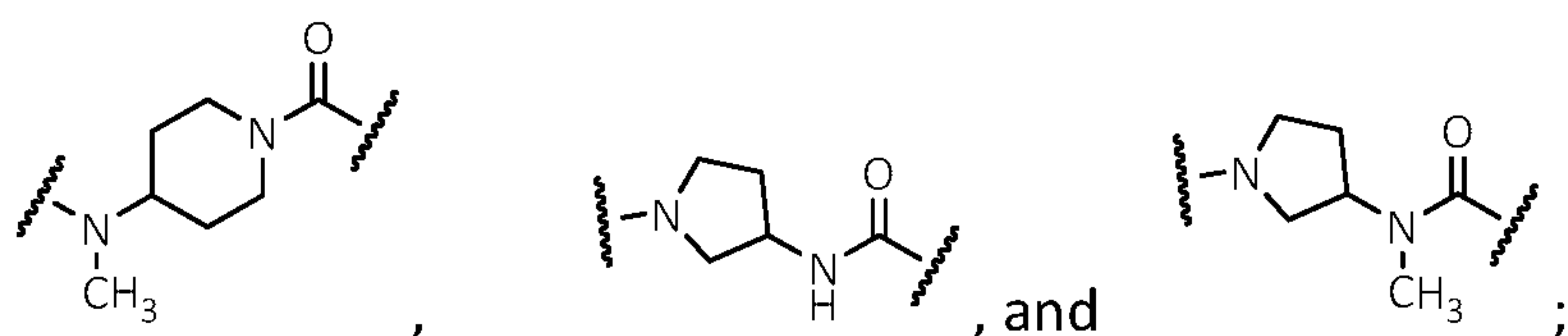
R₁ is, at each occurrence, H, C₁₋₄alkyl, C(=O)OC₁₋₄alkyl or aryl;

R₂, R₃, R₄ and R₅ are each independently -OH, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -C≡N, -C(=O)NH₂, halo, C₁₋₄alkyl, C₁₋₄alkyl-OH, C₁₋₄haloalkyl, C₁₋₄alkoxy or C₁₋₄haloalkoxy;

w, x, y and z are each independently 0, 1, 2 or 3; and

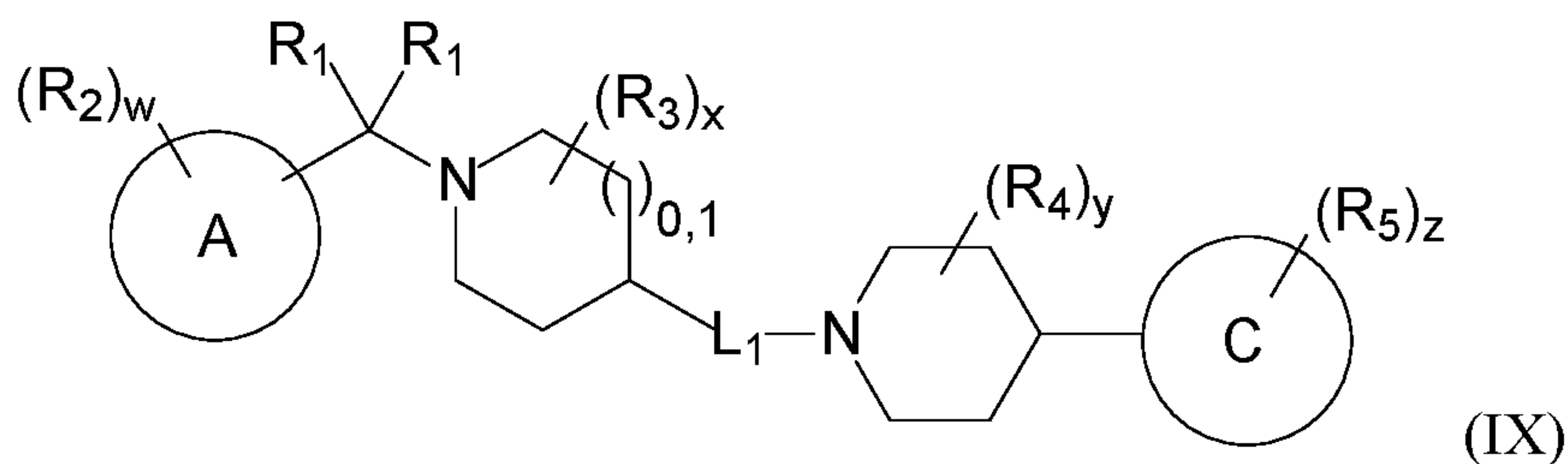
L₁ is one of the following:





or

a compound having the structure of the following formula (IX):



or a stereoisomer, tautomer, solvate, ester, prodrug, or pharmaceutically acceptable salt thereof, wherein:

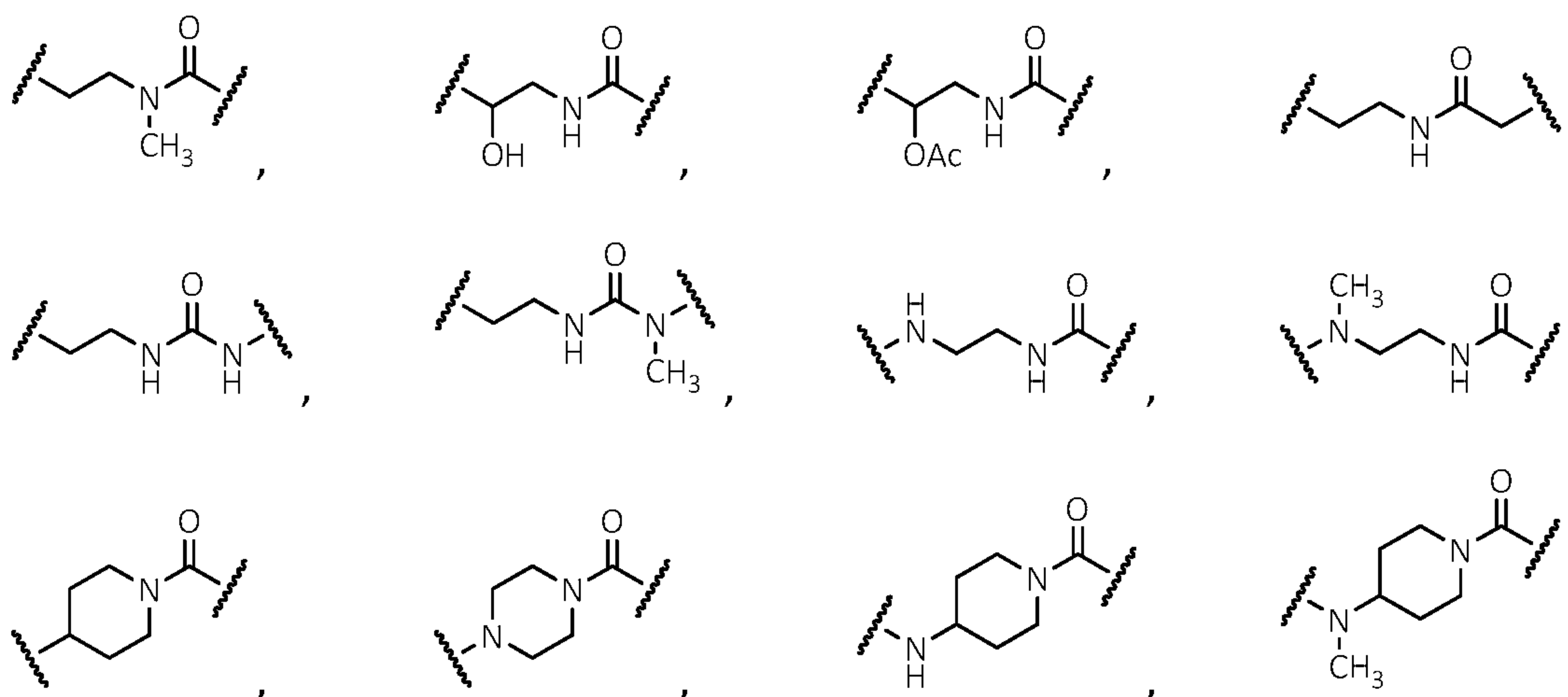
A and C are each independently a carbocyclyl or heterocyclyl;

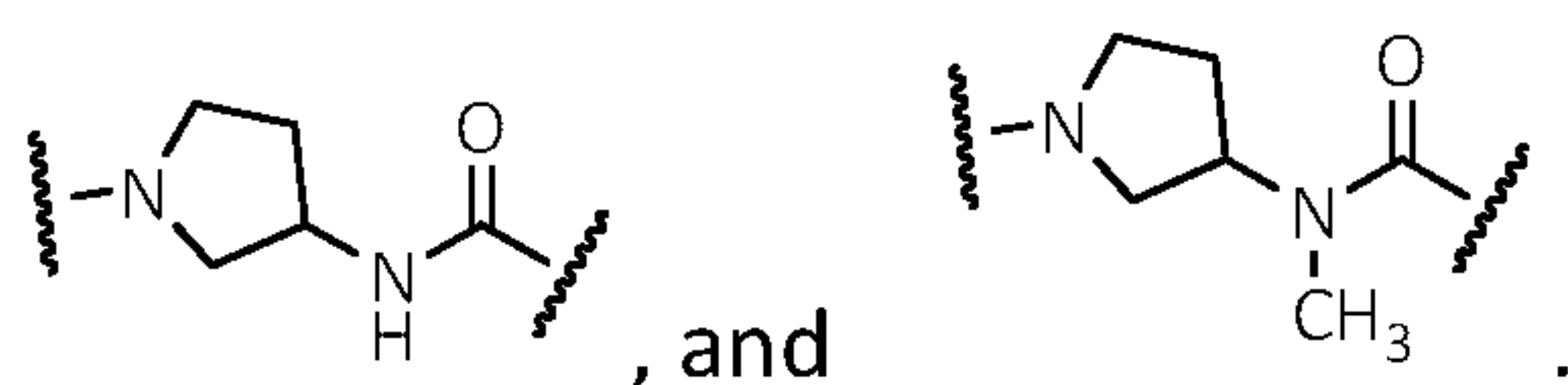
R₁ is, at each occurrence, H, C₁₋₄alkyl, C(=O)OC₁₋₄alkyl or aryl;

R₂, R₃, R₄ and R₅ are each independently -OH, -NH₂, -NH(C₁₋₄alkyl), -N(C₁₋₄alkyl)₂, -C≡N, -C(=O)NH₂, halo, C₁₋₄alkyl, C₁₋₄alkyl-OH, C₁₋₄haloalkyl, C₁₋₄alkoxy or C₁₋₄haloalkoxy;

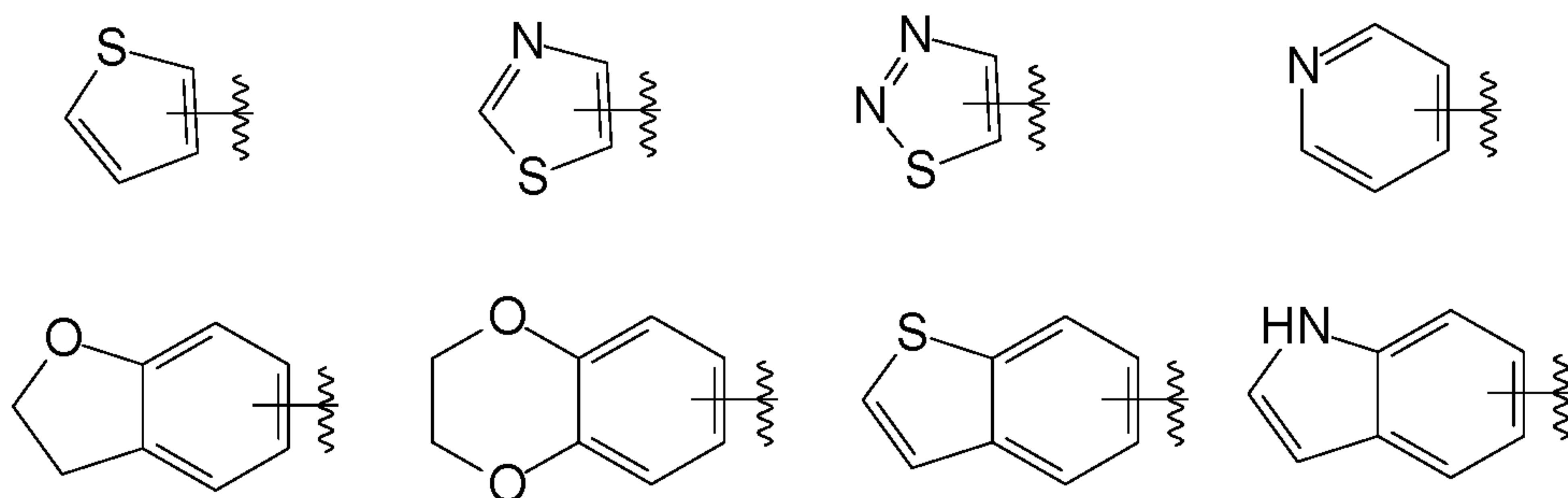
w, x, y and z are each independently 0, 1, 2 or 3; and

L₁ is one of the following:





4. The compound of any one of claims 1–3, wherein R_1 is H at both occurrences.
5. The compound of any one of claims 1–3, wherein one R_1 is H and the other R_1 is methyl.
6. The compound of any one of claims 1–3, wherein R_1 is methyl at both occurrences.
7. The compound of any one of claims 1–3, where A is a non-aromatic carbocycle.
8. The compound of claim 7, wherein A is cyclohexyl.
9. The compound of any one of claims 1–3, wherein A is an aromatic carbocycle.
10. The compound of claim 9, wherein A is aryl.
11. The compound of claim 10, wherein A is phenyl or naphthyl.
12. The compound of claim 11, wherein A is phenyl.
13. The compound of any one of claims 1–3, wherein A is an aromatic heterocycle.
14. The compound of claim 13, wherein A is one of the following:



15. The compound of any one of claims 1–3, wherein w is 0 and R_2 is not present.

16. The compound of any one of claims 1–3, wherein w is 1, 2 or 3, and R_2 is at each occurrence -OH, $-C\equiv N$, halo or C_{1-4} alkyl.

17. The compound of any one of claims 1–3, wherein x is 0 and R_3 is not present.

18. The compound of any one of claims 1–3, wherein x is 1 or 2 and R_3 is at each occurrence -OH or C_{1-4} alkyl-OH.

19. The compound of claim 2, wherein B is a non-aromatic carbocycle.

20. The compound of claim 19, wherein B is cyclohexyl.

21. The compound of claim 2, wherein B is an aromatic carbocycle.

22. The compound of claim 21, wherein B is aryl.

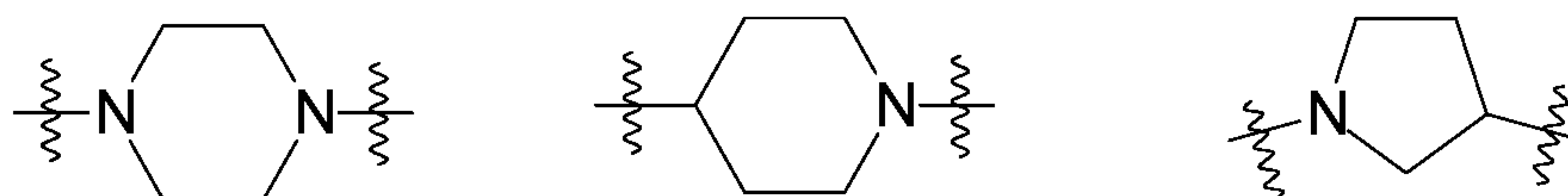
23. The compound of claim 22, wherein B is phenyl or naphthyl.

24. The compound of claim 23, wherein B is phenyl.

25. The compound of claim 2, wherein B is a non-aromatic heterocycle.

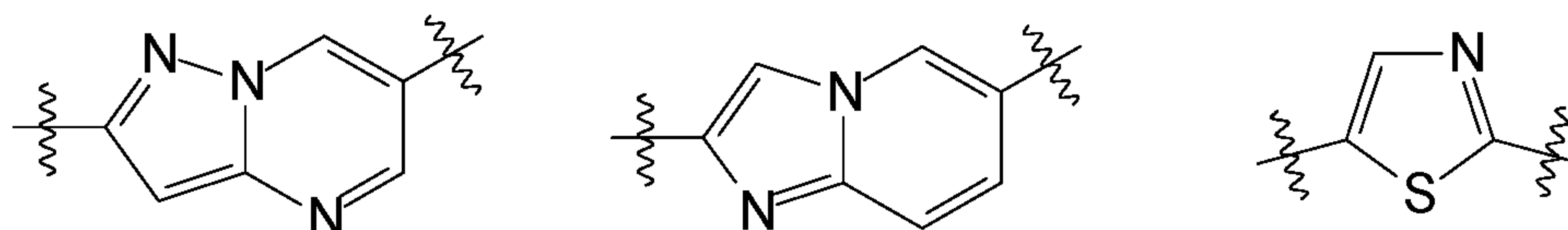
26. The compound of claim 25, wherein B is piperziny, piperdiny or pyrrolidiny.

27. The compound of claim 26, wherein B is one of the following:



28. The compound of claim 2, wherein B is an aromatic heterocycle.

29. The compound of claim 28, wherein B is one of the following:



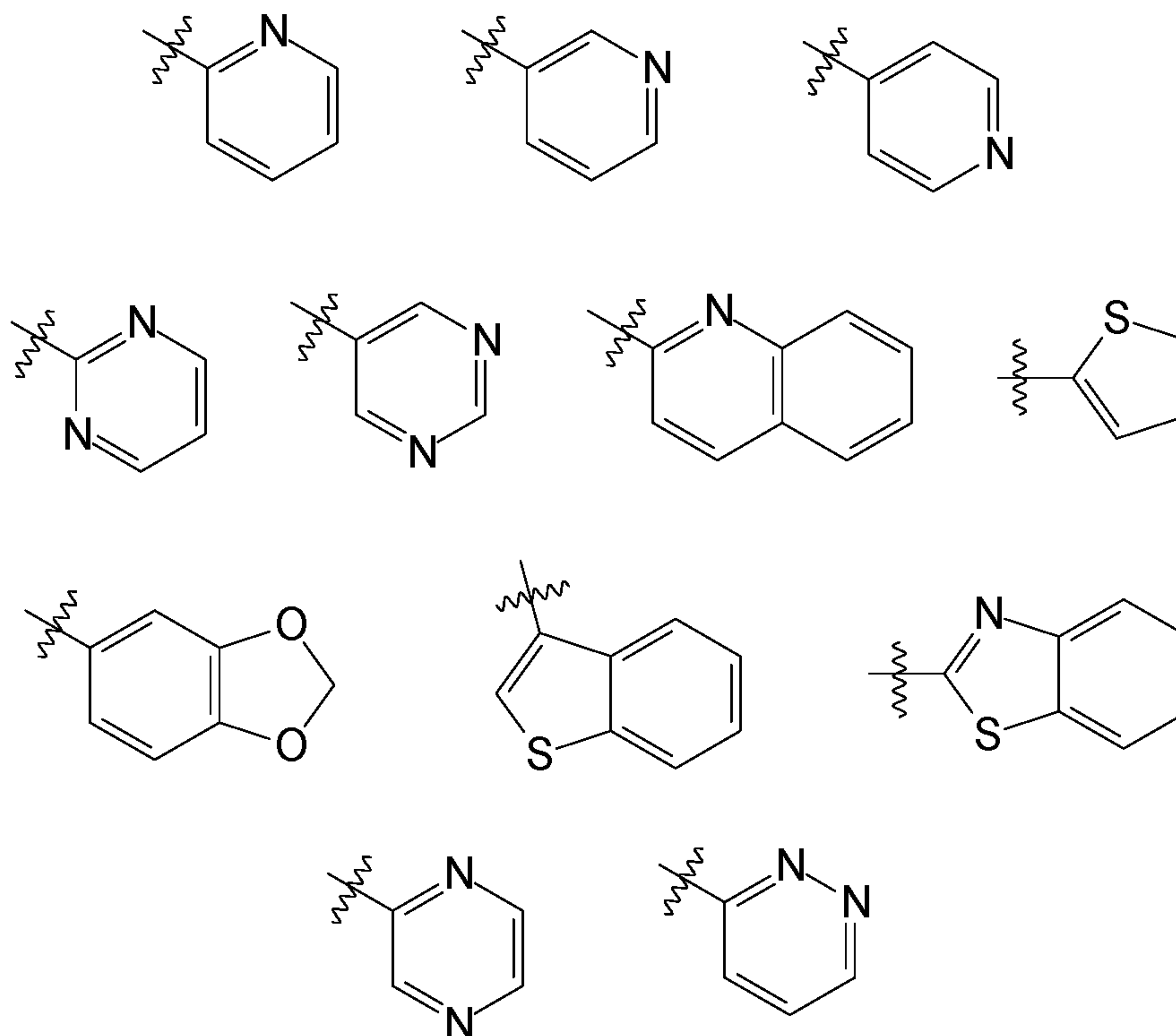
30. The compound of any one of claims 1–3, wherein y is 0 and R₄ is not present.

31. The compound of any one of claims 1–3, wherein y is 1 and R₄ is methyl.

32. The compound of any one of claims 1–3, wherein y is 2 and R₄ at both occurrences is methyl.

33. The compound of any one of claims 1–3, wherein C is an aromatic carbocycle or heterocycle.

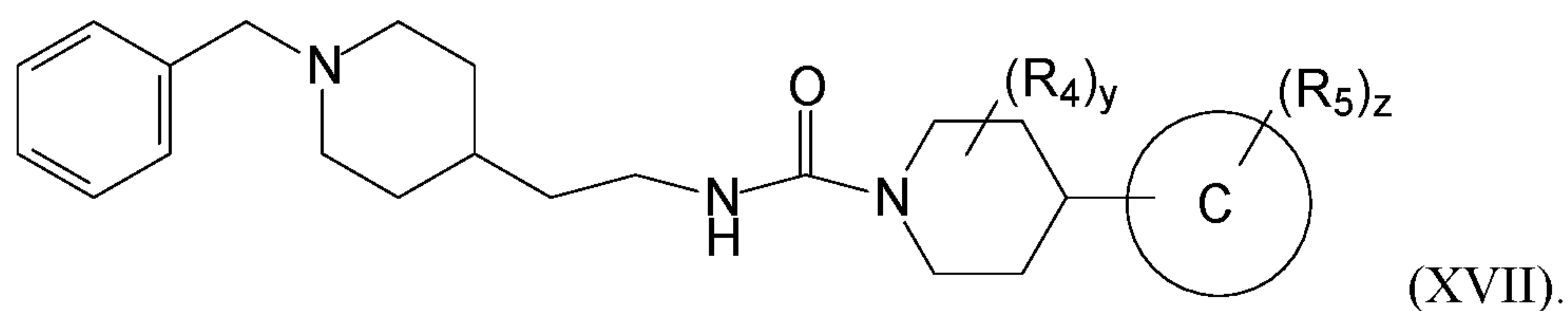
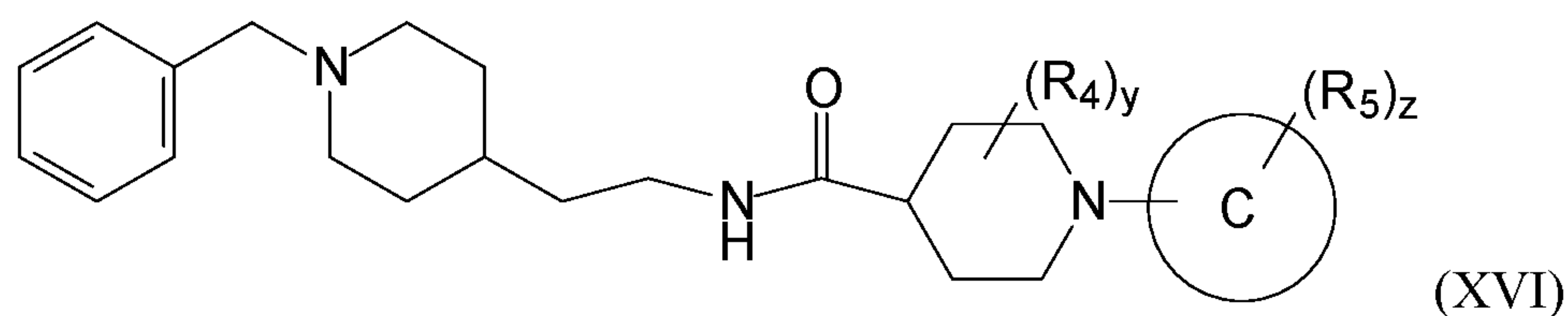
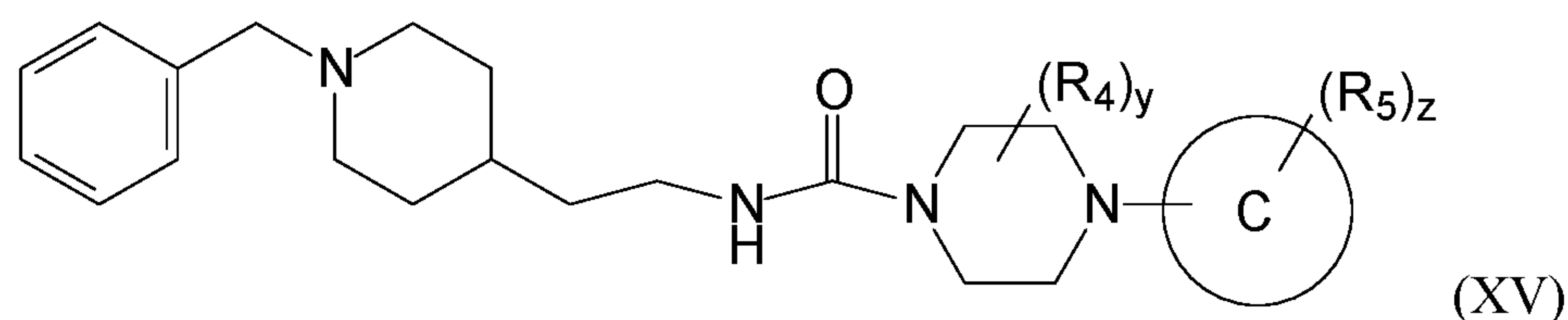
34. The compound of claim 33, wherein C is an aromatic carbocycle.
35. The compound of claim 34, wherein C is aryl.
36. The compound of claim 35, wherein C is phenyl.
37. The compound of any one of claims 1–3, wherein C is an aromatic heterocycle.
38. The compound of claim 37, wherein C is one of the following:



39. The compound of any one of claims 1–3, wherein z is 0 and R₅ is not present.

40. The compound of any one of claims 1–3, wherein z is 1, 2 or 3, and each occurrence of R_5 is independently $-OH$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, $-C\equiv N$, halo, $C_{1-4}alkyl$, $C_{1-4}alkyl-OH$, $C_{1-4}haloalkyl$, $C_{1-4}alkoxy$ or $C_{1-4}haloalkoxy$.

41. The compound of claim 1, wherein the compound has a structure of one of the following formulas (XV) through (XVII):

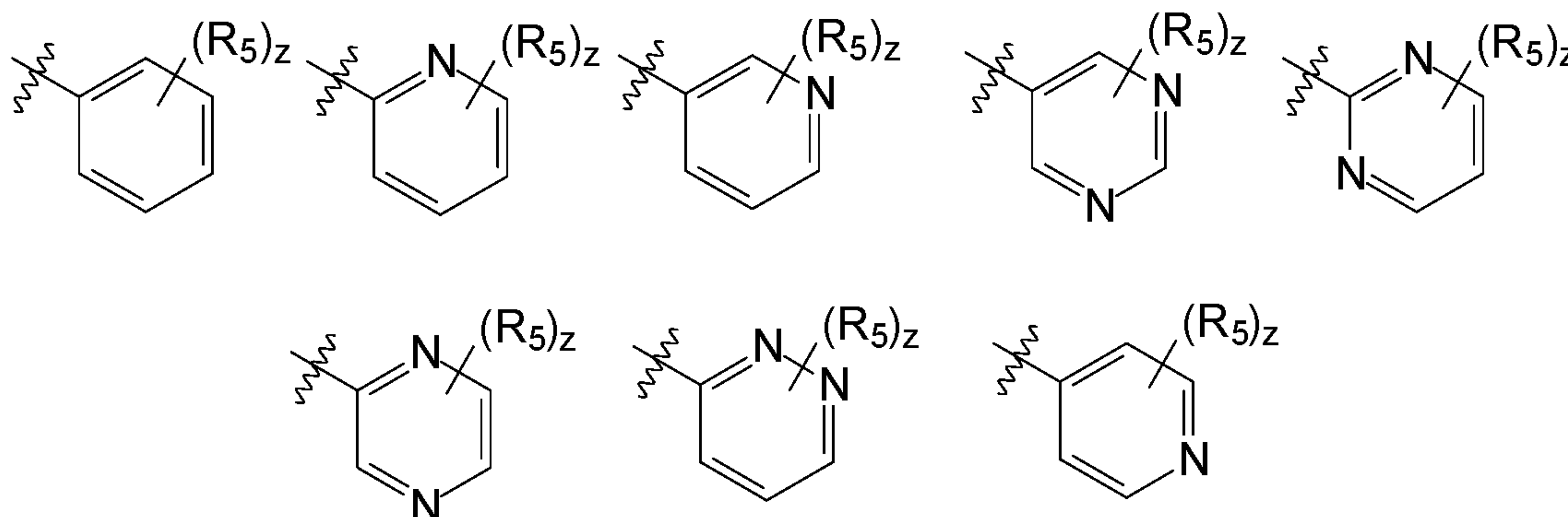


42. The compound of claim 41, wherein the compound has a structure of formula (XV) or (XVII), wherein y is 0.

43. The compound of claim 41, wherein the compound has a structure of formula (XV), (XVI) or (XVII), wherein y is 1 or 2 and R_4 is at each occurrence $C_{1-4}alkyl$.

44. The compound of claim 41, wherein the compound has a structure of formula (XV), (XVI) or (XVII), wherein y is 1 or 2 and R_4 is at each occurrence methyl.

45. The compound of claim 41, wherein the compound has a structure of formula (XV), (XVI) or (XVII), wherein $C(R_5)_z$ is one of the following:



46. The compound of claim 45, wherein z is 0 and R_5 is not present.

47. The compound of claim 45, wherein z is 1, 2 or 3, and each occurrence of R_5 is independently $-OH$, $-NH_2$, $-NH(C_{1-4}alkyl)$, $-N(C_{1-4}alkyl)_2$, $-C\equiv N$, halo, $C_{1-4}alkyl$, $C_{1-4}alkyl-OH$, $C_{1-4}haloalkyl$, $C_{1-4}alkoxy$ or $C_{1-4}haloalkoxy$.

48. The compound of claim 4, wherein R_1 is ^1H at both occurrences.

49. The compound of claim 4, wherein R_1 is ^2H at both occurrences.

50. A compound having the structure of one of the compounds listed in any one of Tables 1-14.

51. A pharmaceutical composition comprising a compound of any one of claims 1-50 and at least one pharmaceutically acceptable excipient.

52. A method for antagonizing a muscarinic receptor of a cell comprising contacting the cell with the compound of any one of claims 1-50.

53. The method of claim 52, wherein the muscarinic receptor is muscarinic receptor 4.

54. The method of claim 53, wherein the compound selectively antagonizes muscarinic receptor 4 (M4).

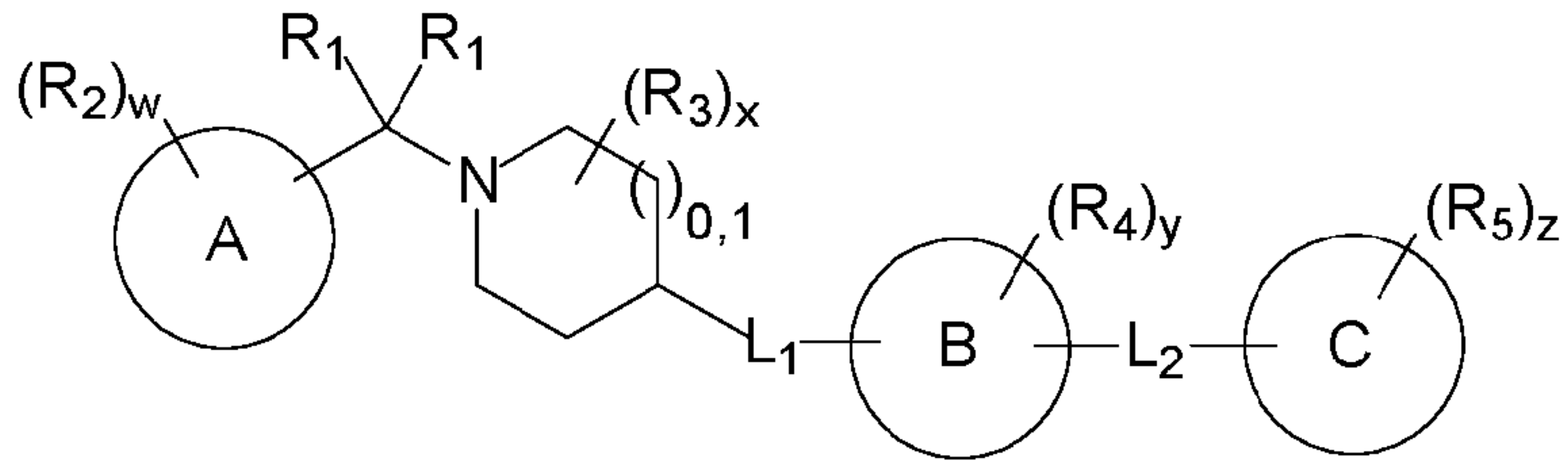
55. The method of any one of claims 52–54 wherein the cell is comprised within a subject who is in need of treatment with the compound.

56. The method of claim 55 wherein the subject has a neurological disease or disorder.

57. A method for treating or preventing a neurological disease or disorder comprising administering the pharmaceutical composition of claim 51.

58. The method of claim 57 wherein the neurological disease or disorder is any one of Alzheimer's Disease, Lewy Body Dementia and the cognitive deficits associated with schizophrenia; Parkinson's Disease, drug induced Parkinsonism, dyskinesias, dystonia, chorea, levodopa induced dyskinesia, cerebral palsy, progressive supranuclear palsy, and Huntington's disease.

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